A phase II study of the anti-PD-1 antibody pembrolizumab in patients with malignant mesothelioma

Study Number: **IRB14-1381**

Coordinating Center: The University of Chicago Medical Center

Co-Principal Investigator: Hedy Lee Kindler, MD
University of Chicago Medical Center
5841 S. Maryland Avenue, MC2115
Chicago, IL 60637
Tel: 773-702-0360
Fax: 773-702-3163
Email: hkindler@medicine.bsd.uchicago.edu

Tanguy Y. Seiwert, MD
University of Chicago Medical Center
5841 S. Maryland Avenue, MC2115
Chicago, IL 60637
Tel: 773-702-2452
Fax: 773-702-3163
Email: tseiwert@medicine.bsd.uchicago.edu

Co-Investigator: Thomas Gajewski, MD, PhD
University of Chicago Medical Center
5841 S. Maryland Avenue, MC 2115
Chicago, IL 60637
Tel: 773-702-4601
Fax: 773-834-0778
Email: tgajewski@medicine.bsd.uchicago.edu

Statistician:
Theodore Karrison, PhD
5841 S. Maryland Avenue, MC 2007
Chicago, IL 60637-1470
Telephone: 773-702-9326
Fax: 773-702-1979
tkarrison@health.bsd.uchicago.edu

Regulatory Coordinator:
Tamika Harris
5841 S. Maryland Ave, MC 1140
Chicago, IL 60637-1470
Telephone: 773-702-4367
Fax: 773-834-5800
tharris@medicine.bsd.uchicago.edu

Responsible Research Nurse:
Buerkley Rose, RN
5841 S. Maryland Avenue, MC 2115
Chicago, IL 60637-1470
Telephone: 773-834-4002
Fax: 773-834-1798
brose@bsd.uchicago.edu

Responsible Data Manager:
Bianca Hill
5841 S. Maryland Avenue, MC 2115
Chicago, IL 60637-1470
Telephone: 773-834-1472
Fax: 773-834-1472
mahmad3@medicine.bsd.uchicago.edu

1.0 TABLE OF CONTENTS

2.0 TRIAL SUMMARY

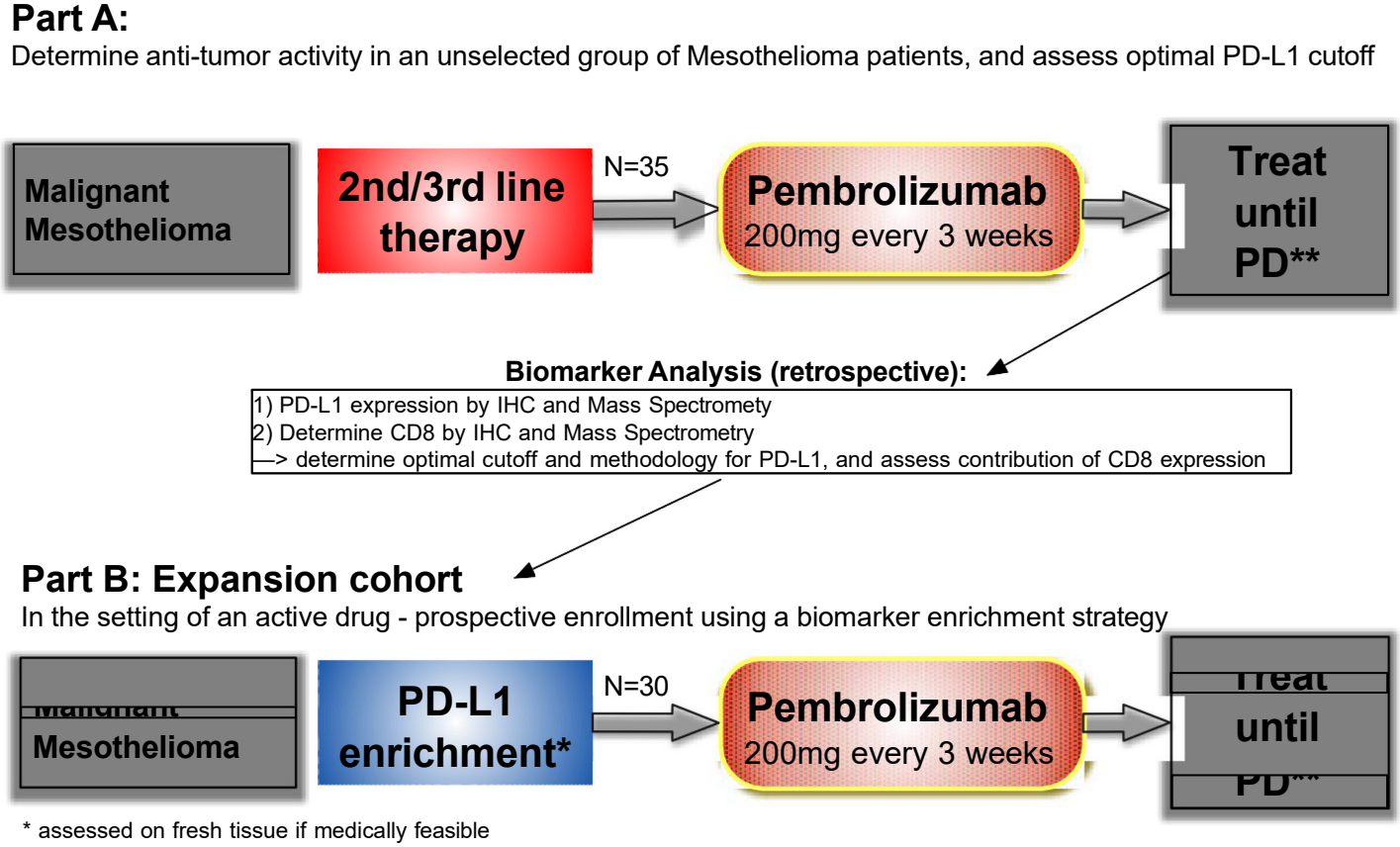
Abbreviated Title	Pembrolizumab in Mesothelioma
Trial Phase	II
Clinical Indication	Mesothelioma
Trial Type	Treatment
Type of control	None
Route of administration	Intravenous
Trial Blinding	None
Treatment Groups	3
Number of trial subjects	36-63
Estimated duration of trial	3 years
Duration of Participation	6 months

3.0 TRIAL DESIGN

3.1 Trial Design

This single institution, single-arm, phase II trial of pembrolizumab in mesothelioma patients will consist of two parts. In part A, n=35 unselected mesothelioma patients will be enrolled and treated with pembrolizumab. Response rates will be assessed and evaluated as a function of PD-L1 expression. If activity is observed and response is related to PD-L1 level, Part B will enroll n=30 patients enriched for high PD-L1 expression.

3.2 Trial Schema



* assessed on fresh tissue if medically feasible

** Treatment beyond PD is allowable under specific circumstance (see respective paragraph in protocol)

*If Part A is successful and activity shown, in Part B PD-L1 pre-screening will be performed using a CLIA approved immunohistochemistry assay, performed centrally via Merck using the proprietary 22C3 antibody. The cutpoint for % positive cells will be determined based on ROC analysis of PD-L1 expression and response from the patients enrolled in part A (and [as feasible] validated in mesothelioma samples from the Keynote 28 study).

In addition a second CLIA assessment will be performed using the OncoplexDx Mass Spectrometry platform for PD-L1 and CD8 expression. These data will be exploratory, and correlated with the more established PD-L1 IHC assay using the 22C3 antibody. *Eligibility of patients for enrollment into Part B will be based on the IHC assay (performed centrally using the Merck (CLIA certified) PD-L1 assay.*

4.0 OBJECTIVES & HYPOTHESES

4.1 Primary Objectives

Objective: (1) To determine the objective response rate of patients with malignant mesothelioma treated with pembrolizumab in A) an unselected patient population, as well as B) in a PD-L1 positive population (should the trial proceed to Part B, and PD-L1 expression correlate with improved efficacy).

Objective: (2) To determine the optimal threshold for PD-L1 expression using the 22C3 antibody based IHC assay in correlation to tumor response.

4.2 Secondary Objectives

(1) **Objective**: To determine the progression-free survival of patients with malignant mesothelioma in A) an unselected patient population and B) a PD-L1 positive population when treated with pembrolizumab.

(2) **Objective**: To determine the overall survival of patients with malignant mesothelioma in A) an unselected patient population and B) a PD-L1 positive population when treated with pembrolizumab.

(3) **Objective**: To determine the disease control rate (CR + PR + SD) of patients with malignant mesothelioma who are treated with pembrolizumab in A) an unselected patient population and B) a PD-L1 positive population.

(4) **Objective**: To determine toxicity in patients with malignant mesothelioma who are treated with pembrolizumab.

(5) **Objective**: To determine percentage of patients with mesothelioma who have PD-L1 tumor expression, and the distribution of PD-L1 expression (percent positivity of tumor cells / stroma staining).

4.3 Exploratory Objectives

(1) To characterize the T-cell inflamed phenotype in mesothelioma patients via presence of CD8 tumor infiltrating lymphocytes (TILs) and/or use of a gene expression signature (Nanostring).*

(2) To evaluate other immune escape mechanisms including IDO expression, Tregs (FOXP3 expression), MDSCs and other checkpoints by immunohistochemistry (or other methods e.g. Flow Cytometry (also see 4)).*

(3) To determine PD-L1 expression by mass spectrometry and correlate with tumor response, PD-L1 expression by IHC, and the T-cell inflamed phenotype.*

(4) To determine the immune cell populations present in fresh tumor (when available), via tumor digests and mass spectrometry-based flow cytometric analysis (e.g. using CyTOF) in a multiplex fashion in patients with fresh tumor tissue.*

(5) To characterize the T-cell receptor repertoire of TILs compared to circulating T-cells in mesothelioma patients with available fresh frozen tissue (spectrotyping, T-cell repertoire sequencing (e.g. using the Adaptive platform))*

(6) To develop a radiomics-based method to quantify acute immunotherapy-induced pneumonitis and automatically identify patients with pneumonitis based on quantifiable changes in a patient's CT scans.

* As available fresh biopsy tissues (or alternatively/concurrently circulating T-cells) will be assessed for baseline status or treatment effects.

4.4 Hypotheses

(1) Clinical:

Pembrolizumab will induce objective responses in malignant mesothelioma, and responses will correlate with higher PD-L1 expression levels.

(2) Translational:

We will further characterize the Immune Escape Phenotype and the PD-L1 expression pattern in malignant mesothelioma and define their relationship to tumor responsiveness in this disease.

5.0 BACKGROUND & RATIONALE

5.1 Background

5.1.1 Pharmaceutical and Therapeutic Background

The importance of intact immune surveillance in controlling outgrowth of neoplastic transformation has been known for decades (Disis 2010). Accumulating evidence shows a correlation between tumor-infiltrating lymphocytes (TILs) in cancer tissue and favorable prognosis in various malignancies (Dong 2002; Sharpe 2002; Brown 2003; Francisco 2010; Thomson 2007). In particular, the presence of CD8+ T-cells and the ratio of CD8+ effector T-cells / FoxP3+ regulatory T-cells seems to correlate with improved prognosis and long-term survival in many solid tumors.

The PD-1 receptor-ligand interaction is a major pathway hijacked by tumors to suppress immune control. The normal function of PD-1, expressed on the cell surface of activated T-cells under healthy conditions, is to down-modulate unwanted or excessive immune responses, including autoimmune reactions. PD-1 (encoded by the gene Pdcd1) is an Ig superfamily member related to CD28 and CTLA-4, which has been shown to negatively regulate antigen receptor signaling upon engagement of its ligands (PD-L1 and/or PD-L2) (Talmadge 2007; Usubütün 1998). The structure of murine PD-1 has been resolved (Al-Shibli 2008). 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 that are involved in the CD3 T-cell signaling cascade (Talmadge 2007; Deschoolmeester 2010; Diez 1998; Galon 2006). 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 (Hiraoka 2010; Nobili 2008). PD-1 was shown to be expressed on activated lymphocytes including peripheral CD4+ and CD8+ T-cells, B-cells, regulatory T cells (T regs) and Natural Killer cells (Hodi 2010; Kloor 2009). Expression has also been shown during thymic development on CD4-CD8- (double negative) T-cells as well as subsets of macrophages and dendritic cells (Hillen 2008). 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 (Lee 2008; Leffers 2009; Nishimura 2000; Hiraoka 2010). 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 (Hiraoka 2010). 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) (Liotta 2010). This suggests that the PD-1/PD-L1 pathway plays a critical role in tumor immune evasion and should be considered as an attractive target for therapeutic intervention.

Pembrolizumab (previously known as SCH 900475, 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.

5.1.2 Preclinical and Clinical Trial Data

Refer to the Package Insert for Preclinical and Clinical data.

5.2 Rationale

5.2.1 Rationale for the Trial and Selected Subject Population

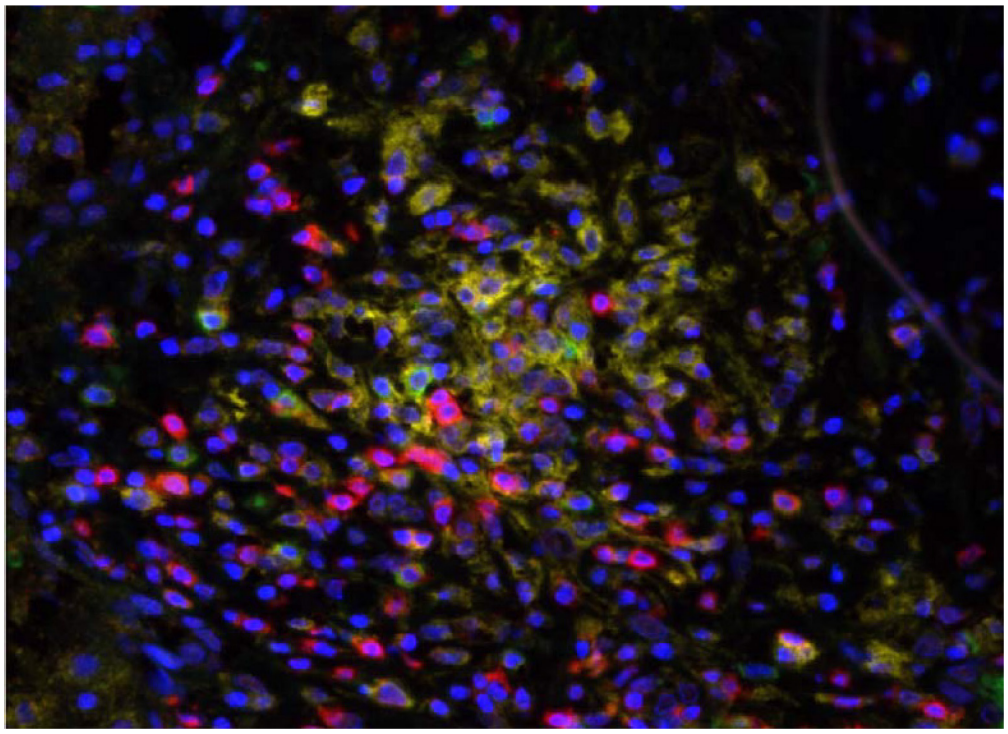
Malignant mesothelioma (MM) is a devastating illness that affects approximately 3000 patients annually in the US (Ray 2009). Most patients present with advanced disease; their treatment is generally limited to systemic chemotherapy (Campbell 2011). Pemetrexed plus cisplatin has become the standard front-line regimen due to the results of a pivotal randomized phase III trial in which the combination was superior to single-agent cisplatin measured by response rate (RR) (41 vs. 17%, $p<0.001$), time-to-progression (TTP) (5.7 vs. 3.9 months), and median overall survival (OS) (12.1 vs. 9.3 months, $p=0.02$) (Vogelzang 2003). Nearly all MM patients progress during or after first-line pemetrexed-based treatment. These patients are generally still healthy at the time of disease progression, and are able to receive further therapy. Since there are no approved treatment options for previously-treated MM patients, this setting is an ideal place to evaluate novel agents.

PD-1/PD-L1 is an immune checkpoint that was recently found to mediate immune evasion in a wide spectrum of tumors including malignant melanoma, squamous cell carcinoma of the lung, adenocarcinoma of the lung, and renal cell carcinoma. While the normal function of PD-1 is to counteract excessive immune responses directed against normal tissues, various types of cancer have manipulated this function by up-regulating the natural ligand of PD-1, PD-L1 to evade immune recognition. The critical role of this pathway became evident with the promising recent results of clinical trials of PD-1/PD-L1 inhibitors, such as pembrolizumab/MK-3475 (Hamid 2013), nivolumab (Wolchok 2013), and MPDL3280A (Powderly 2013). PD-1/PD-L1 checkpoint blockers have not been evaluated for MM.

In an analysis presented at ASCO 2014 (Kindler and Seiwert 2014), we analyzed gene expression data on 44 MM (Gordon 2005), applied a melanoma-derived signature of T-cell inflammation (Harlin 2009), and analyzed other immune response related genes. We identified that **32% malignant mesotheliomas showed high CD8 gene expression,** and **a T-cell inflamed phenotype** analogous to melanoma was present in multiple MM tumors.

We evaluated MM tumor tissues from patients by multi-color immunohistochemistry (IHC), staining for CD68 (macrophages), CD8 (tumor infiltrating lymphocytes), and **PD-L1** (immune checkpoint, MTA: Lieping Chen, Clone 5H1). **We observed PDL1 expression in 75% of MM tumors tested**, which was **2-3+ in 37.5%**, and 1+ in 37.5%. Patchy higher level PDL1 expression was observed in stromal or CD68 cells located close to CD8+ cells. CD8 tumor infiltrating lymphocytes (TILs) were present in all epithelial tumors. Prominent CD68 infiltration was seen in all tumors. An example of immunohistochemistry is given below.

Thus, we identified high PD-L1 expression, a CD8 infiltrative pattern with a T-cell inflamed expression and presence of PD-1-PD-L1 immune checkpoints in a fraction of malignant mesotheliomas (**approximately 1/3 of MM tumors**) similar to the phenotype found in other tumors such as melanoma that benefit from immune checkpoint blockade. We therefore propose to investigate PD-1 checkpoint blockade in this subset of MM.



Malignant Mesothelioma (IHC):

PD-1

PD-L1

(Cell Signaling E1L3N)

While PD-L1 expression correlates with responsiveness to anti-PD-1 agents (Topalian 2013) **it has been consistently reported for such agents that some patients with PD-L1 negative tumors still respond to therapy**. The hypotheses are that PD-L1 expression is heterogeneous, and that one biopsy may not be representative for PD-L1 expression overall. Furthermore PD-L1 expression is dynamic and may change over time, e.g. a one-year old biopsy may no longer be representative of the current immune environment of the tumor. It is also possible that the current detection methodologies are suboptimal and that new approaches, including mass spectrometry, or gene expression signature approaches will prove more reliable. Henceforth many trials include PD-L1 negative tumors. In our study we will

evaluate all patients initially and then enrich for PD-L1 expression if an association between PD-L1 and tumor response to treatment is found. See schema Section 3.2.

5.2.2 Rationale for Dose Selection/Regimen/Modification

The dose regimen of 200 mg Q3W of pembrolizumab is planned for all urothelial cancer trials. Available PK results in subjects with melanoma, NSCLC, and other solid tumor types support a lack of meaningful difference in PK exposures obtained at a given dose among tumor types. An open-label Phase 1 trial (PN001) in melanoma subjects is being conducted to evaluate the safety and clinical activity of single agent pembrolizumab. The dose escalation portion of this trial evaluated three dose levels, 1 mg/kg, 3 mg/kg, and 10 mg/kg, administered every 2 weeks (Q2W) in subjects with advanced solid tumors. All three dose levels were well tolerated and no dose-limiting toxicities were observed. This first in human study of pembrolizumab showed evidence of target engagement and objective evidence of tumor size reduction at all dose levels (1 mg/kg, 3 mg/kg and 10 mg/kg Q2W). No maximum tolerated dose (MTD) has been identified.

In KEYNOTE-001, two randomized cohort evaluations of melanoma subjects receiving pembrolizumab at a dose of 2 mg/kg versus 10 mg/kg Q3W have been completed. The clinical efficacy and safety data demonstrate a lack of clinically important differences in efficacy response or safety profile at these doses. For example, in Cohort B2, advanced melanoma subjects who had received prior ipilimumab therapy were randomized to receive pembrolizumab at 2 mg/kg versus 10 mg/kg Q3W. The overall response rate (ORR) was 26% (21/81) in the 2mg/kg group and 26% (25/79) in the 10 mg/kg group (full analysis set (FAS)). The proportion of subjects with drug-related adverse events (AEs), grade 3-5 drug-related AEs, serious drug-related AEs, death or discontinuation due to an AE was comparable between groups or lower in the 10 mg/kg group.

Available pharmacokinetic results in subjects with melanoma, NSCLC, and other solid tumor types support a lack of meaningful difference in pharmacokinetic exposures obtained at a given dose among tumor types. Population PK analysis has been performed and has confirmed the expectation that intrinsic factors do not affect exposure to pembrolizumab to a clinically meaningful extent. Taken together, these data support the use of lower doses (with similar exposure to 2 mg/kg Q3W) in all solid tumor indications. 2 mg/kg Q3W is being evaluated in NSCLC in PN001, Cohort F30 and PN010, and 200 mg Q3W is being evaluated in head and neck cancer in PN012, which are expected to provide additional data supporting the dose selection.

Selection of 200 mg as the appropriate dose for a switch to fixed dosing is based on simulation results indicating that 200 mg will provide exposures that are reasonably consistent with those obtained with 2 mg/kg dose and importantly will maintain individual patient exposures within the range established in melanoma as associated with maximal clinical response. A population PK model, which characterized the influence of body weight and other patient covariates on exposure, has been developed using available data from 476 subjects from PN001. The distribution of exposures from the 200 mg fixed dose are predicted to considerably overlap those obtained with the 2 mg/kg dose, with some tendency

for individual values to range slightly higher with the 200 mg fixed dose. The slight increase in PK variability predicted for the fixed dose relative to weight-based dosing is not expected to be clinically important given that the range of individual exposures is well contained within the range of exposures shown in the melanoma studies of 2 and 10 mg/kg to provide similar efficacy and safety. 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 tumor types and indication settings.

5.2.3 Rationale for Endpoints

Tumor response is a surrogate marker of benefit from immune therapies that has been used for studies with pembrolizumab and other immune therapies. Response is considered a reliable marker of benefit for malignant mesothelioma and correlates with a survival benefit (e.g. Vogelzang 2003).

Immunotherapeutic agents such as pembrolizumab may produce antitumor effects by potentiating endogenous cancer-specific immune responses, which may be functionally anergic. 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.

Therefore, response criteria will be used with the following adaptation (Byrne 2004):
If 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 (except if the patient is felt to have clinical improvement). In determining whether or not the tumor burden has increased or decreased, investigators should consider all target lesions as well as non-target lesions.

5.2.4 Optional continuation of treatment beyond Progression

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 e.g. until repeat imaging is obtained a minimum of 4 weeks later. This decision should be based on the clinical judgment of the subject's overall clinical condition, including performance status, clinical symptoms, and laboratory data (Please see Section 6.5 for details and exact criteria). 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 or atypical patterns of benefit. Please see Section 6.5 for details and exact criteria.

6.0 METHODOLOGY

6.1 Entry Criteria / Eligibility

6.1.1 Diagnosis/Condition for Entry into the Trial

1. Histologically or cytologically confirmed pleural or peritoneal malignant mesothelioma, epithelial, sarcomatoid, or biphasic subtypes.

2. Disease progression on or after pemetrexed and cis- or carboplatin (unless 5. applies).

3. For Part B – PD-L1 selection should a PD-L1 expression threshold have been defined in Part A.

4. No more than 2 prior lines of cytotoxic therapy, which should have included pemetrexed and a platinum.

6.1.2 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 for the trial.

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

3. Have measurable disease based on RECIST 1.1 for peritoneal mesothelioma, and modified RECIST for pleural mesothelioma (Byrne et al 2004).

4. Have provided tissue from an archival tissue sample or newly obtained core or excisional biopsy of a tumor lesion. While 20 unstained slides or a tumor block are preferred, at least 14 unstained slides are requested for analysis. PI approval for a lower number of slides is acceptable.

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

6. Demonstrate adequate organ function as defined in Table 1, all screening labs should be performed within 14 days of treatment initiation.

Table 1 Adequate Organ Function Laboratory Values

System	Laboratory Value
Hematological	
Absolute neutrophil count (ANC)	≥1,500 /mcL
Platelets	≥100,000 / mcL
Hemoglobin	≥9 g/dL
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** ≥50 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
Coagulation	
International Normalized Ratio (INR) or Prothrombin Time (PT) Activated Partial Thromboplastin Time (aPTT)	≤1.5 X ULN unless subject is receiving anticoagulant therapy as long as PT or PTT is within therapeutic range of intended use of anticoagulants ≤1.5 X ULN unless subject is receiving anticoagulant therapy as long as PT or PTT is within therapeutic range of intended use of anticoagulants
[a] Creatinine clearance should be calculated per institutional standard.	

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

8. Female subjects of childbearing potential should be willing to use 2 methods of birth control or be surgically sterile, or abstain from heterosexual activity for the course of the study through 120 days after the last dose of study medication (Please also see Section 6.9.2). Subjects of childbearing potential are those who have not been surgically sterilized or have not been free from menses for > 1 year.

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

6.1.3 Subject Exclusion Criteria

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

1. Is currently participating in or has participated in a study of an investigational agent or using an investigational device within 2 weeks (4 weeks for monoclonal antibodies) of the first dose of treatment

2. Side effects from prior treatment have not resolved to ≤ grade 1 (or baseline due to previously administered agent/pre-existing conditions).

3. 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.

4. Has had a prior monoclonal antibody 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.

5. 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.

6. Has a known additional malignancy that is progressing or requires active treatment. Exceptions include basal cell carcinoma of the skin, squamous cell carcinoma of the skin, in situ cervical cancer, or other indolent cancers which either have undergone curative-intent therapy or inactive (i.e. not expected to limit life expectancy or interfere with therapy).

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

8. Has an active autoimmune disease requiring systemic treatment within the past 3 months or a documented history of clinically severe autoimmune disease, or a syndrome that requires systemic steroids or immunosuppressive agents. Subjects with vitiligo or resolved childhood asthma/atopy would be an exception to this rule. Subjects that require intermittent use of bronchodilators or local steroid injections would not be excluded from the study. Subjects with hypothyroidism stable on hormone replacement or Sjorgen's syndrome will not be excluded from the study.

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

10. Has evidence of interstitial lung disease.

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, anti-PD-L2, anti-CD137, or anti-Cytotoxic T-lymphocyte-associated antigen-4 (CTLA-4) antibody (including ipilimumab or any other antibody or drug specifically targeting T-cell co-stimulation or checkpoint pathways).

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 prior to the first dose of trial treatment.

6.2 Trial Treatments

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

Table 2 Trial Treatment

Drug	Dose/Potency	Dose Frequency	Route of Administration	Regimen/Treatment Period	Use
pembrolizumab	200 mg	Every 21 days	IV infusion	single agent/ongoing for period of treatment benefit	Experimental
The pembrolizumab dosing interval may be increased due to toxicity as described in Section 5.2.1.2.					

6.2.1 Dose Selection/Modification

6.2.1.1 Dose Selection

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

The dose amount required to prepare the pembrolizumab infusion solution will be a flat dose of 200mg. Details on the preparation and administration will be provided by the drug manufacturer on delivery of pembrolizumab.

6.2.1.2 Dose Modification

Pembrolizumab will be withheld for drug-related Grade 4 hematologic toxicities, non-hematological toxicity ≥ Grade 3 including laboratory abnormalities, and severe or life-threatening AEs as per Table 3 below.

Table 3: Dose modification guidelines for drug-related adverse events.

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

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

In case toxicity does not resolve to Grade 0-1 within 12 weeks after last infusion, trial treatment should be discontinued after consultation with the PI. With PI agreement, subjects with a laboratory adverse event still at Grade 2 after 12 weeks may continue treatment in the trial only if asymptomatic and controlled. For information on the management of adverse events, see Section 13.3.

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

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

General instructions:

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

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

AST / ALT elevation or Increased bilirubin	Grade 2	Withhold	• Administer corticosteroids (initial dose of 0.5- 1 mg/kg prednisone or equivalent) followed by taper	• Monitor with liver function tests (consider weekly or more frequently until liver enzyme value returned to baseline or is stable
	Grade 3 or 4	Permanently discontinue	• Administer corticosteroids (initial dose of 1-2 mg/kg prednisone or equivalent) followed by taper	
Type 1 diabetes mellitus (T1DM) or Hyperglycemia	Newly onset T1DM or Grade 3 or 4 hyperglycemia associated with evidence of β-cell failure	Withhold	• Initiate insulin replacement therapy for participants with T1DM • Administer anti-hyperglycemic in participants with hyperglycemia	• Monitor participants for hyperglycemia or other signs and symptoms of diabetes.
Hypophysitis	Grade 2	Withhold	• Administer corticosteroids and initiate hormonal replacements as clinically indicated.	• Monitor for signs and symptoms of hypophysitis (including hypopituitarism and adrenal insufficiency)
	Grade 3 or 4	Withhold or permanently discontinue[1]		
Hyperthyroidism	Grade 2	Continue	• Treat with non-selective beta-blockers (eg, propranolol) or thionamides as appropriate	• Monitor for signs and symptoms of thyroid disorders.
	Grade 3 or 4	Withhold or permanently discontinue[1]		
Hypothyroidism	Grade 2-4	Continue	• Initiate thyroid replacement hormones (eg, levothyroxine or liothyroinine) per standard of care	• Monitor for signs and symptoms of thyroid disorders.
Nephritis and Renal dysfunction	Grade 2	Withhold	• Administer corticosteroids (prednisone 1-2 mg/kg or equivalent) followed by taper.	• Monitor changes of renal function
	Grade 3 or 4	Permanently discontinue		
Myocarditis	Grade 1 or 2	Withhold	• Based on severity of AE administer corticosteroids	• Ensure adequate evaluation to confirm etiology and/or exclude other causes

	Grade 3 or 4	Permanently discontinue		
All other immune-related AEs	Intolerable/ persistent Grade 2	Withhold	• Based on type and severity of AE administer corticosteroids	• Ensure adequate evaluation to confirm etiology and/or exclude other causes
	Grade 3	Withhold or discontinue based on the type of event. Events that require discontinuation include and not limited to: Gullain-Barre Syndrome, encephalitis		
	Grade 4 or recurrent Grade 3	Permanently discontinue		

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

NOTE:

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

6.2.2 Timing of Dose Administration

Trial treatment should be administered on Day 1 of each cycle after all procedures/assessments have been completed as detailed on the Trial Flow Chart (Section 7.0). Trial treatment may be administered up to 3 days before or after the scheduled Day 1 of each cycle due to administrative reasons.

All trial treatments will be administered on an outpatient basis.

Pembrolizumab will be administered as a 30 minute IV infusion (treatment cycle intervals may be increased due to toxicity as described in Section 6.2.1.2). Every effort should be made to target infusion timing to be as close to 30 minutes as possible. However, given the variability of infusion pumps, a window of -5 minutes and +10 minutes is permitted (i.e., infusion time is 30 minutes: -5 min/+10 min).

The specific instructions for pembrolizumab dose calculation, reconstitution, preparation of the infusion fluid, and administration will be provided by the Drug Manufacturer in conjunction with pembrolizumab.

6.2.3 Trial Blinding/Masking

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

6.3 Randomization or Treatment Allocation

There will be no randomization. For Part A all patients that meet eligibility criteria will be enrolled. For Part B PD-L1 expression pre-screening will be performed using a CLIA approved immunohistochemistry assay, performed centrally via a commercial provider using the proprietary 22C3 antibody. Estimated turnaround time will be 1-2 weeks. Results will be classified based on prior data (Part A +/- data for Mesothelioma patients from the Keynote 28 study) into above or below the optimal threshold, and patients with tumor PD-L1 expression equal or above the threshold will be eligible to enroll in Part B (See Schema Section 3.2):

6.4 Transition from Part A to Part B

If Part A meets efficacy criteria outline in the statistical section, determination of correlation of PD-L1 expression with response and optimal threshold will be performed. Such a threshold would be employed as a selection criterion for Part B. Should no correlation be present or no clinically reasonable threshold be identifiable, the protocol ideally after discussion with the drug manufacturer (Merck) may proceed to part B without a threshold, or an alternative biomarker for enrichment may be implemented if mutually agreed and felt to be clinically reasonable and/or superior to PD-L1 expression.

6.5 Optional continuation of treatment beyond progression

In order to ensure that patients are not exposed to unreasonable risk by continuing a potentially ineffective therapy in spite of disease progression, the following procedures are put into place:

In subjects who have initial evidence of radiological PD, there is the option to continue a subject on study treatment until repeat imaging is obtained a minimum of 4 weeks later or beyond. A supplemental consent form is available and required for this purpose and it is at the discretion of the treating physician whether to consider continuing pembrolizumab therapy.

This decision should be based on the clinical judgment of the subject's overall clinical condition, including performance status, clinical symptoms, and laboratory data.

Subjects may receive treatment if they have signed the supplemental consent form and are clinically stable as defined by the following criteria:

- Absence of signs and symptoms indicating disease progression
- No decline in ECOG performance status (ECOG 0 or 1 required)
- Absence of rapid progression of disease
- Absence of progressive tumor at critical anatomical sites (e.g., cord compression, development or worsening of brain metastases, respiratory failure from tumor compression, etc.) requiring urgent alternative medical intervention
- Demonstrate adequate organ function as defined in Table 1 (section 6.1.2)

Patients must have signed the supplemental consent form for continuation of therapy beyond progression. Treatment beyond initial evidence of tumor progression is not the standard of care, although commonly used in trials with PD-1 and PD-L1 inhibitors. The supplemental consent form outlines the potential risks of continuing therapy (namely further worsening of the disease), and lists alternative treatment options, namely participation in another clinical trial, off label use of chemotherapy, or comfort care, as no other FDA approved agents are available after prior failure of methotrexate/platinum.

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. Supportive retrospective central review of all imaging time-points will be performed for this study using modified RECIST criteria for mesothelioma (Byrne et al 2004).

In addition some patterns of benefit may not be captured by traditional assessment of progressive disease (e.g. oscillating patterns of tumor shrinkage and regression have been

observed in patients on PD-1/PD-L1 agents (Chen et al, CRI meeting 2014). In patients deemed to have clinical benefit/symptomatic improvement (and fulfillment of all of the above criteria), further continuation of therapy can be approved by the PI.

6.6 Stratification

No stratification will be done.

6.7 Concomitant Medications/Vaccinations (allowed & prohibited)

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

6.7.1 Acceptable Concomitant Medications / Radiation

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

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

Radiation for selected tumor lesions/tumors may be administered concurrently with pembrolizumab treatment, e.g. for progressive lesions causing symptoms such as pain.

6.7.2 Prohibited Concomitant Medications

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

- Anti-cancer 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 after consultation with the PI.
- Live vaccines within 30 days prior to the first dose of trial treatment and while participating in the trial. Examples of live vaccines include, but are not limited to, the following: measles, mumps, rubella, chicken pox, yellow fever, rabies, BCG, and typhoid (oral) vaccine. Seasonal influenza vaccines for injection are generally killed virus vaccines and are allowed; however intranasal influenza vaccines (e.g. Flu-Mist®) are live attenuated vaccines, and are not allowed.

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

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.

6.8 Rescue Medications & Supportive Care

6.8.1 Supportive Care Guidelines

Subjects should receive appropriate supportive care measures as deemed necessary by the treating investigator including but not limited to the items outlined the appendix 13.3.16 Events of Clinical Interest (ECI) Guidance Section of this protocol.

6.9 Diet/Activity/Other Considerations

6.9.1 Diet

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

6.9.2 Contraception

Pembrolizumab may have adverse effects on a fetus in utero. Furthermore, it is not known if pembrolizumab has transient adverse effects on the composition of sperm. 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. Subjects of childbearing potential are those who have not been surgically sterilized or have not been free from menses for > 1 year.

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 8.2.2-Reporting of Pregnancy and Lactation 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.

6.9.3 Use in Pregnancy

If a subject inadvertently becomes pregnant while on treatment with pembrolizumab, the subject will immediately be removed from the study. The site will contact the subject at least monthly and document the subject's status until the pregnancy has been completed or terminated. The outcome of the pregnancy will be reported to Merck without delay and within 24 hours if the outcome is a serious adverse experience (e.g., death, abortion, congenital anomaly, or other disabling or life-threatening complication to the mother or newborn). The study investigator will make every effort to obtain permission to follow the outcome of the pregnancy and report the condition of the fetus or newborn to Merck. If a male subject impregnates his female partner the study personnel at the site must be informed immediately and the pregnancy reported to Merck and followed as described above and in Section 8.2.2.

6.9.4 Use in Nursing Women

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

6.10 Subject Withdrawal/Discontinuation Criteria

Subjects may withdraw consent at any time for any reason or be dropped from the trial at the discretion of the investigator should any untoward effect occur. In addition, a subject may be withdrawn by the investigator or the Drug Manufacturer 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 8.1.4 – 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 6.5.

  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 6.5
- Unacceptable adverse experiences (See Section 13)
- Intercurrent illness that prevents further administration of treatment
- Investigator's decision to withdraw the subject
- The subject has a confirmed positive serum pregnancy test
- Noncompliance with trial treatment or procedure requirements
- The subject is lost to follow-up
- Completed 24 months of treatment with pembrolizumab

  Note: 24 months of study medication is calculated from the date of first dose. Subjects who stop pembrolizumab after 24 months may be eligible for up to one year of additional study treatment if they progress after stopping study treatment provided they meet the requirements detailed in Section 8.1.5.2.1.
- Administrative reasons

The End of Treatment and Follow-up visit procedures are listed in Section 7 (Protocol Flow Chart) and Section 8.1.5 (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 8.2.3.1). Subjects who discontinue for reasons other than progressive disease will have post-treatment follow-up for disease and clinical evaluation until disease progression, initiating a non-study cancer treatment, withdrawing study 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.

Procedures for currently enrolled patients with a history of pneumonitis

Subjects who are currently enrolled and have a history of pneumonitis may either discontinue pembrolizumab or continue dosing with pembrolizumab at the discretion of the treating physician after discussion of the safety information and informed consent.

6.11 Subject Replacement Strategy

Additional subjects may be enrolled 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. Patients will be considered evaluable if they have received any treatment with pembrolizumab.

6.12 Clinical Criteria for Early Trial Termination

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

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

2. Poor adherence to protocol and regulatory requirements

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

4. Plans to modify 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.

6.13 Correlative Analysis and Methodology

6.13.1 Archival tissue

Previously obtained or fresh frozen tissue is acceptable. For FFPE tissue 14 to 20, 5 micron slides are requested. Slides will be stored in the HTRC pathology core at the University of Chicago. If possible additional slides will be requested using OncoPlexDx compatible slides (see OncoPlex Dx general instructions on their website for further details).

Predefined Analyses include:

1) Staining for PD-L1 by IHC using the 22C3 antibody via a commercial provider in a CLIA laboratory

2) PD-L1 and CD8 determination via OncoPlexDx in a CLIA environment

3) Multiplex staining (one or several slides) for multiple immune markers including IDO, PD-L1, CD8, FOXP3; additional staining may be performed for additional markers. Additional markers will be analyzed

6.13.2 Fresh tumor biopsies

If clinically indicated tissue from a biopsy will also be banked using the UCCCC# 9571 banking protocol. The following clinical situations should be considered for obtaining additional tissue for banking purposes and biomarker analysis as outlined below:

1. Baseline biopsy e.g. indicated diagnostically

2. Possible tumor flare should be considered for biopsy to assess immune cell infiltration

3. Tumor progression – especially after prior benefit from therapy to rule out pseudoprogression and identify possible mechanisms of resistance using the methodologies described in this section.

4. Other clinically appropriate scenarios – e.g. assessment of residual tumor may be considered for biopsy.

6.13.3 TCR sequencing

TCR sequencing analysis will be performed using the Adaptive commercial platform or collaborative work at the University of Chicago in Dr. Yusuke Nakamura's lab. Fresh Frozen tumor tissue will be used preferentially (but FFPE compliant technology is in testing and samples will be collected as a backup on all patients). Specific information for sample preparation is available via the Adaptive Website (Adaptive Biotechnologies, Seattle WA http://www.adaptivebiotech.com/technology/).

6.13.4 Nanostring Analysis

From 3-5 FFPE slides RNA will be extracted using the Qiagen RNA/DNA FFPE kit and protocol. A Nanostring probeset including ca 20-150 immune and other marker related probes will used using the Nanostring (Seattle) standard ordering and analysis process. The

Nanostring nCounter available in the White lab at the University of Chicago will be used. Alternatively FFPE based RNAseq libraries may be constructed using the Illumina FFPE RNA access protocol. The Seiwert lab is experienced with both the Nanostring and FFPE RNAseq process and additional details are available on request. These are exploratory analyses and laboratory protocols are constantly updated.

6.13.5 Tumor DNA analysis

Exome or more focused panel sequencing (e.g. Foundation One) will be performed on the majority of tumor samples for an exploratory analysis of correlation of genetic aberrations, immune phenotype and tumor response.

6.13.6 Germline DNA analysis

Blood will be obtained from all patients enrolled in the study for pharmacogenomic evaluation. Investigation of the relevant polymorphisms will take place in germline DNA extracted from peripheral whole blood (10 ml) collected in plastic EDTA (lavender top) vacutainers (BD catalog#366643). Blood samples after necessary processing in the CTRC (pathology) should be stored at -80°C. Samples should be labeled with protocol number, patient initials, patient registration number, and the date and time of draw.

DNA extraction for genotyping will be performed according to commercially available DNA isolation kits, such as Puregene (Gentra Systems, Inc., Minneapolis, MN). Samples ideally should be collected prior to initiation of therapy; however, sample collections missed at the initiation of therapy still **can be collected at any time**, as genotype is not expected to change. Genotyping for the selected variants will be performed based on previously published methods for the variants of interest.

Specifically we aim to perform SNP genotyping to evaluate candidate SNPs related to immune function that were recently discovered (unpublished work). These SNP candidates will be first confirmed in the upcoming TCGA Mesothelioma cohort and their relation to immune markers. If successful this will be done for all patients on this study and correlated with the immune phenotype. This work will be done in collaboration with Dr. Thomas Gajewski.

6.13.7 Flow Cytometric Analysis of Tumor Digests

Fresh tumor samples (as available) will be digested using a protocol for tumor digestion employing the Miltenyi GentleMACS system available in the HIM Core facility. Single cell

suspension will be stored for subsequent FACS/CyTOF multiplex immune marker analysis. Markers include those listed above as well as additional immune markers and are subject to change. Please refer to the detailed sample processing instruction/protocol which will be updated as appropriate and is therefore not included in the protocol as several parameters are still being optimized.

6.13.8 Flow Cytometric Analysis of PBMCs

Blood samples will be obtained at baseline and after cycle 3 using 2 (two) lavender- (EDTA) (or alternatively green- (sodium heparin)) tubes. Processing will occur in the HIM core facility following standard protocol for processing and storage of cell suspensions for later analysis by flow cytometry. Subsequent FACS/CyTOF multiplex immune marker analysis will be performed. Markers include those listed above as well as additional immune markers and are subject to change.

Section 6.13.9 Radiomics

The medical record numbers (MRN) for the 65 Mesothelioma patients receiving Pembrolizumab along with their pneumonitis status and scan date will be acquired and forwarded to HIRO. These data will be collected by HIRO and anonymized such that the research team will be provided with the patient scans without any patient-identifying information. HIRO will assign a case-identifying number to each patient in order to label all scans for each patient. Protected patient health information will be stored in password-protected files, and anonymization will comply with the Privacy Rule by removing all 18 private identifiers.

The anonymized patient scans acquired at various time points throughout treatment will used by the research team to classify patients with and without immunotherapy-induced pneumonitis using quantitative texture features extracted from various regions throughout the images of the lungs. The lungs will be segmented, and two-dimensional regions of interest (ROI) will be randomly placed throughout the lungs in each axial slice of the baseline scan acquired prior to immunotherapy treatment. A maximum of ten 32x32-pixel ROIs will be placed in each axial slice of the baseline scans where no two ROIs overlap. Each ROI in the baseline scan will then be matched to the corresponding anatomical location in the followup scans using the vector map acquired from deformable registration. The pixel information from each ROI will be extracted and used to calculate various classifications of radiomics texture features, which describe the patterns in pixel intensity and spatial relationships of pixels within the ROIs. The change in feature values between time points will be calculated, and linear regression analysis will be used to determine if texture feature change is significantly related to pneumonitis status. Then, receiver operating characteristic (ROC) curve analysis will be used to evaluate the classification performance of regression modeling relating changes in texture features to pneumonitis status.

7.0 TRIAL FLOW CHART

7.1 Study Flow Chart

Trial Period:	**Screening Phase**		**Treatment Cycles***								**End of Treat-ment**	**Post-Treatment**		
							To be repeated beyond 8 cycles **							
Treatment Cycle/Title:	Pre-screening (Visit 1)	Main Study Screening (Visit 2)	1	2	3	4	5	6	7	8	Discontinuation (D/C)	Safety Follow-up(+/- 1 week)	Follow Up Visits (+/- 1 week)	Survival Follow-Up(+/- 2 weeks)
Scheduling Window (Days):		-28 to -1		± 3	± 3	± 3	± 3	± 3	± 3	± 3	At time of D/C	30 days post D/C	Every 8 weeks post D/C	Every 12 weeks
Administrative Procedures														
Informed Consent	X													
Inclusion/Exclusion Criteria	X	X												
Demographics and Medical History#	X	X												
Prior and Concomitant Medication Review	X	X	X	X	X	X	X	X	X	X	X			
Trial Treatment Administration			X	X	X	X	X	X	X	X				
Post-study anticancer therapy status											X			
Survival Status											X	X	X	X
Clinical Procedures/Assessments														
Review Adverse Events			X	X	X	X	X	X**	X	X**	X			
Full Physical Examination		X	X	X	X	X	X	X**	X	X**	X	X	X	
Vital Signs and Weight		X	X	X	X	X	X	X	X	X	X	X	X	
ECOG Performance Status		X	X	X	X	X	X	X**	X	X**	X	X	X	
Laboratory Procedures/Assessments: analysis performed by LOCAL laboratory														

Trial Period:	**Screening Phase**		**Treatment Cycles***								**End of Treat-ment**	**Post-Treatment**		
							To be repeated beyond 8 cycles **							
Treatment Cycle/Title:	Pre-screening (Visit 1)	Main Study Screening (Visit 2)	1	2	3	4	5	6	7	8	Discontinuation (D/C)	Safety Follow-up(+/- 1 week)	Follow Up Visits (+/- 1 week)	Survival Follow-Up(+/- 2 weeks)
Scheduling Window (Days):		-28 to -1		± 3	± 3	± 3	± 3	± 3	± 3	± 3	At time of D/C	30 days post D/C	Every 8 weeks post D/C	Every 12 weeks
For Women of childbearing potential - Pregnancy Test – (continued) Urine or Serum β-HCG (also see Table 9, page 37)		X												
PT/INR and aPTT		X												
CBC with Differential		X	X	X	X	X	X	X	X	X	X	X	X	
Comprehensive Serum Chemistry Panel		X	X	X	X	X	X	X	X	X	X	X	X	
Urinalysis		X												
T3, FT4 and TSH		X					X				X			
Efficacy Measurements														
Tumor Imaging (every 9 weeks = 3 cycles)		X				X			X				X	
Tumor Biopsies/Archival Tissue Collection/Correlative Studies Blood														
Archival (or Newly Obtained) Tissue Collection (typically FFPE, ≥14 5micron slides to be collected, see 6.13.1 for additional details)	X													
Fresh Tumor Biopsies (optional) – to	X[1]													

Trial Period:	**Screening Phase**		**Treatment Cycles***								**End of Treat-ment**	**Post-Treatment**		
							To be repeated beyond 8 cycles **							
Treatment Cycle/Title:	Pre-screening (Visit 1)	Main Study Screening (Visit 2)	1	2	3	4	5	6	7	8	Discontinuation (D/C)	Safety Follow-up(+/- 1 week)	Follow Up Visits (+/- 1 week)	Survival Follow-Up(+/- 2 weeks)
Scheduling Window (Days):		-28 to -1		± 3	± 3	± 3	± 3	± 3	± 3	± 3	At time of D/C	30 days post D/C	Every 8 weeks post D/C	Every 12 weeks
be obtained if biopsy is clinically justified														
Correlative Studies Blood Collection including a) germline DNA collection and b) Flow analysis (See Sections 6.13.6-7)		X[2]			X[3]									

Laboratory tests for screening or potentially a Second Treatment Course (see Section 8.1.5.2.1) should be performed within 14 days prior to the first dose of treatment. After Cycle 1, pre-dose laboratory procedures can be conducted up to 72 hours prior to dosing.
** Treatment cycle length = 21 days*

*** After cycle 8, as clinically appropriate ECOG performance status, physical exam, and adverse event recording interval may be increased to every other cycle (=every 6 weeks).*

 # This includes history of asbestos exposure (see Appendix 5—Mesothelioma Program Exposure History Form)

1. If clinically indicated tissue from a biopsy will also be banked using the UCCCC# 9571 banking protocol. The following clinical situations should be considered for obtaining additional tissue for banking purposes and biomarker analysis as outlined below (also see section 6.13.2:.

a) Baseline biopsy e.g. indicated diagnostically, b) Possible tumor flare should be considered for biopsy to assess immune cell infiltration, c) Tumor progression – especially after prior benefit from therapy to rule out pseudoprogression and identify possible mechanisms of resistance using the methodologies described in this section. d) Other clinically appropriate

Trial Period:	**Screening Phase**		**Treatment Cycles***								**End of Treat-ment**	**Post-Treatment**		
							To be repeated beyond 8 cycles **							
Treatment Cycle/Title:	Pre-screening (Visit 1)	Main Study Screening (Visit 2)	1	2	3	4	5	6	7	8	Discontinuation (D/C)	Safety Follow-up(+/- 1 week)	Follow Up Visits (+/- 1 week)	Survival Follow-Up(+/- 2 weeks)
Scheduling Window (Days):		-28 to -1		± 3	± 3	± 3	± 3	± 3	± 3	± 3	At time of D/C	30 days post D/C	Every 8 weeks post D/C	Every 12 weeks

scenarios – e.g. assessment of residual tumor may be considered for biopsy.

2. -- 2 + 2 Purple top tubes (see section 6.13.7-8), blood volume, processing etc will follow HTRC SOPs

3. -- 2 Purple top tubes (see section 6.13.7-8), blood volume, processing etc will follow HTRC SOPs

8.0 TRIAL PROCEDURES

8.1 Trial Procedures

The Trial Flow Chart - Section 7.0 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 investigator and/or Merck for reasons related to subject safety. In some cases, such evaluation/testing may be potentially sensitive in nature (e.g., HIV, Hepatitis C, etc.), and thus local regulations may require that additional informed consent be obtained from the subject. In these cases, such evaluations/testing will be performed in accordance with those regulations.

8.1.1 Administrative Procedures

8.1.1.1 Informed Consent

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

8.1.1.1.1 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.

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

8.1.1.2 Inclusion/Exclusion Criteria

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

8.1.1.3 Subject Identification Card

No Subject Identification Cards will be issued as part of this trial.

8.1.1.4 Medical History

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

8.1.1.5 Prior and Concomitant Medications Review

8.1.1.5.1 Prior Medications

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

8.1.1.5.2 Concomitant Medications

The investigator or qualified designee will record medication, if any, taken by the subject during the trial. All medications related to reportable SAEs and ECIs should be recorded as defined in Section 8.2.

8.1.1.6 Disease Details and Treatments

8.1.1.6.1 Disease Details

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

8.1.1.6.2 Prior Treatment Details

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

8.1.1.6.3 Subsequent Anti-Cancer Therapy Status

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

8.1.1.7 Assignment of Screening Number

All consented subjects will be given a unique screening number that will be used to identify the subject for all procedures that occur prior to treatment allocation and for Part B PD-L1 prescreening. Each subject will be assigned only one screening number. Screening numbers must not be re-used for different subjects. Any subject who is screened multiple times will retain the original screening number assigned at the initial screening visit.

8.1.1.8 Assignment of Randomization Number

No randomization will be performed and no randomization numbers will be performed. However patients in part B will be enrolled based on their PD-L1 expression level.

Once a screening number is assigned to a subject, it can never be re-assigned to another subject.

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

Interruptions from the protocol specified treatment plan for greater than 12 weeks between MK-3475/pembrolizumab doses due to toxicity require consultation between the investigator and the PI 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 conjunction with the delivery of pembrolizumab/MK-3475.

8.1.2 Clinical Procedures/Assessments

8.1.2.1 Adverse Event (AE) Monitoring

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

All AEs of unknown etiology associated with pembrolizumab exposure should be evaluated to determine if it is possibly an event of clinical interest (ECI) of a potentially immunologic etiology (irAE). See the separate guidance document at the end of this protocol regarding the identification, evaluation and management of AEs of a potential immunological etiology.

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

8.1.2.2 Full Physical Exam

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

8.1.2.3 Directed Physical Exam

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

8.1.2.4 Vital Signs

The investigator or qualified designee will take vital signs at screening, prior to the administration of each dose of trial treatment and at treatment discontinuation as specified in the Trial Flow Chart (Section 7.0). Vital signs should include temperature, pulse, respiratory rate, weight and blood pressure. Height will be measured at screening only.

8.1.2.5 Eastern Cooperative Oncology Group (ECOG) Performance Scale

The investigator or qualified designee will assess ECOG status (see Section 13.1) at screening, prior to the administration of each dose of trial treatment and discontinuation of trial treatment as specified in the Trial Flow Chart. After Cycle 8 assessment of ECOG status will be performed every other cycle in conjunction with a physical exam (see Section 7).

8.1.2.6 Tumor Imaging and Assessment of Disease

CT scans or comparable transactional imaging will be obtained every 9 weeks (=3 treatment cycles).

Response will be assessed using mesothelioma response criteria/modified RECIST (Byrne 2004), as is common practice for mesothelioma trials, as RECIST criteria do not adequately capture treatment benefit.

8.1.2.7 Tumor Tissue Collection and Correlative Studies Blood Sampling

Tumor tissue (archival or fresh) will be obtained prior to study initiation and is required for enrollment on study (see eligibility criteria, Section 6.1).

If feasible/indicated a second, fresh biopsy during/after therapy may be done to better assess treatment effect – e.g. to confirm tumor flare/tumor progression and will be evaluated change in immune cell infiltrates.

8.1.3 Laboratory Procedures/Assessments

Details regarding specific laboratory procedures/assessments to be performed in this trial are provided below. The total amount of blood/tissue to be drawn/collected over the course of the trial (from pre-trial to post-trial visits), including approximate blood/tissue volumes drawn/collected by visit and by sample type per subject can be confirmed by the PI upon request.

8.1.3.1 Laboratory Safety Evaluations (Hematology, Chemistry and Urinalysis)

Laboratory tests for hematology, chemistry, urinalysis, and others are specified in the Flow Chart (Table) in Section 7.

Table 9 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	Carbon Dioxide	Microscopic exam *(If abnormal)*	Total thriiodothyronine (T3)
Absolute Neutrophil Count	*(CO_2 or biocarbonate)*	results are noted	Free tyroxine (T4)
	Calcium	Urine pregnancy test †	Thyroid stimulating hormone (TSH)
	Chloride		Blood for correlative studies
	Glucose		
	Potassium		
	Sodium		
	Total Bilirubin		
	Direct Bilirubin *(If total bilirubin is elevated above the upper limit of normal)*		
	Total protein		
	Blood Urea Nitrogen		

† Perform on women of childbearing potential only. If urine pregnancy results cannot be confirmed as negative, a serum pregnancy test will be required.
If indicated additional laboratory test may be drawn as indicated – e.g. FSH/LH/testosterone

Laboratory tests for screening or entry into the Second Treatment Course (=Re-initiation of therapy see Section 8.1.5.2.1) should be performed within 14 days prior to the first dose of treatment. After Cycle 1, pre-dose laboratory procedures can be conducted up to 72 hours prior to dosing. Results must be reviewed by the investigator or qualified designee and found to be acceptable prior to each dose of trial treatment.

8.1.3.2 Pharmacokinetic/Pharmacodynamic Evaluations

8.1.3.2.1 Blood Collection for Serum pembrolizumab

Sample collection, storage and shipment instructions will follow institutional standards at the University of Chicago following the Pathology and Tissue bank SOPs.

8.1.3.2.2 Blood Collection for Anti-pembrolizumab Antibodies

Sample collection, storage and shipment instructions for blood samples will follow institutional standards at the University of Chicago following the Pathology and Tissue bank SOPs.

8.1.4 Other Procedures

8.1.4.1 Withdrawal/Discontinuation

When a subject discontinues/withdraws prior to trial completion, all applicable activities scheduled for the final trial visit should be performed at the time of discontinuation. Any adverse events which are present at the time of discontinuation/withdrawal should be followed in accordance with the safety requirements outlined in Section 8.2 - Assessing and Recording Adverse Events. 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 8.1.5.2.1. After discontinuing treatment following assessment of CR, these subjects should return to the site for a Safety Follow-up Visit (described in Section 8.1.5.3.1) and then proceed to the Follow-Up Period of the study (described in Section 8.1.5.4).

8.1.4.2 Blinding/Unblinding

Not applicable, this is an open label study

8.1.5 Visit Requirements

Visit requirements are outlined in Section 7.0 - Trial Flow Chart. Specific procedure-related details are provided above in Section 8.1 - Trial Procedures.

8.1.5.1 Screening

The screening period is 28 days during which for Part B - PD-L1 testing of tumor tissue, and laboratory, and imaging studies prior to treatment initiation must be completed. See Flow Chart, Section 7.0 for further details.

8.1.5.1.1 Screening Period

During the 28 days prior to enrollment, potential subjects will be evaluated to determine that they fulfill the entry requirements as set forth - See Flow Chart, Section 7.0

8.1.5.2 Treatment Period

8.1.5.2.1 Re-initiation of therapy after treatment interruption (Retreatment / Second Treatment Course)

Subjects are allowed to stop pembrolizumab with SD or better if the below conditions are met. Such patients may be eligible for up to one year of additional pembrolizumab therapy if they progress after stopping pembrolizumab (Second Treatment Course). This is only available if the study remains open and the subject meets the following conditions:

Either

a. Stopped initial treatment with pembrolizumab after attaining an investigator determined confirmed CR
b. Was treated for at least 24 weeks with pembrolizumab before discontinuing therapy
c. Received at least two treatments with pembrolizumab beyond the date when the initial CR was declared

OR

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

AND

a. Experienced an investigator-determined confirmed radiographic disease progression after stopping their initial treatment with pembrolizumab
b. Did not receive any anti-cancer treatment since the last dose of pembrolizumab
c. Has a performance status of 0 or 1 on the ECOG Performance Scale
d. Demonstrates adequate organ function as detailed in Section 6.1.2
e. Female subject of childbearing potential should have a negative urine or serum pregnancy test within 72 hours prior to receiving retreatment with study medication.
f. 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 (please see Section 6.9.2 for details).
g. 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.
h. 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 frequency as when they last received pembrolizumab. Treatment will be administered for up to one additional year.
Visit requirements are to follow the same schema as outlined for the initial treatment course (see Section 7.0 – Trial Flow Chart), and screening prior to study initiation should also be analogous).

(For information regarding treatment beyond progression see Section 6.5).

8.1.5.3 Post-Treatment Visits

See Flow Chart, Section 7.0

8.1.5.3.1 Safety Follow-Up Visit

The mandatory Safety Follow-Up Visit should be conducted approximately 30 days after the last dose of trial treatment or before the initiation of a new anti-cancer treatment, whichever comes first. All AEs that occur prior to the Safety Follow-Up Visit should be recorded. Subjects with an AE of Grade > 1 will be followed until the resolution of the AE to Grade 0-1 or until the beginning of a new anti-neoplastic therapy, whichever occurs first. SAEs that occur within 90 days of the end of treatment or before initiation of a new anti-cancer treatment should also be followed and recorded.

8.1.5.4 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 8 weeks (56 ± 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 8.1.5.2.1. Information regarding post-study anti-neoplastic treatment will be collected if new treatment is initiated.

Subjects who are eligible to receive retreatment with pembrolizumab according to the criteria in Section 8.1.5.2.1 will continue follow-up as scheduled, but data will be recorded separately under a Second Treatment Course Section.

8.1.5.4.1 Survival Follow-up

Once a subject experiences confirmed disease progression or starts a new anti-cancer therapy, the subject moves into the survival follow-up phase and should be contacted by telephone every 12 weeks to assess for survival status until death, withdrawal of consent, or the end of the study, or 3 years after study patient enrollment, whichever occurs first.

8.2 Assessing and Recording Adverse Events

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

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, onset of menses or menopause occurring at a physiologically appropriate time.

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

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

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

All adverse events will be recorded from the time of treatment initiation 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 8.2.3.1.

8.2.1 Definition of an Overdose for This Protocol and Reporting of Overdose to Merck

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

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

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

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

8.2.2 Reporting of Pregnancy and Lactation 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 Merck Global Safety. (Attn: Worldwide Product Safety; FAX 215 993-1220)

8.2.3 Immediate Reporting of Adverse Events to Merck

8.2.3.1 Serious Adverse Events

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

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

Refer to Table 10 (Section 8.2.4) for additional details regarding each of the above criteria.

Progression of the cancer under study is not considered an adverse event.

Any serious adverse event, or follow up to a serious adverse event, including death due to any cause other than progression of the cancer under study that occurs to any subject from

the time the consent is signed through 90 days following cessation of treatment, or the initiation of new anti-cancer therapy, whichever is earlier, whether or not related to Merck product, must be reported within 24 hours to Merck Global Safety from the time the investigator was notified. Death due to radiographic or clinical disease progression is not a reportable SAE within 90 days of last treatment dose window.

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

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

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

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

Unexpected events are serious adverse events not listed at the observed specificity or severity in the protocol, informed consent, or FDA-approved package insert. An event is considered unexpected if it is listed as occurring within the class of drugs or otherwise expected from the drug's pharmacological properties but which has not been previously observed with this specific investigational agent. Unexpected events will be reported to the University of Chicago IRB according to their policies and procedures.

8.2.3.2 Events of Clinical Interest

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

Events of clinical interest for this trial include:

1. An overdose of Merck product, as defined in Section 8.2.1 - Definition of an Overdose for This Protocol and Reporting of Overdose to the Drug Manufacturer, that is not associated with clinical symptoms or abnormal laboratory results.

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

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

an additional evaluation for an underlying etiology. The guidance for assessment and follow up of these criteria can be found in the appendix.

3. In the event a subject develops any of the following AEs, a detailed narrative of the event should be reported as an Event of Clinical Interest (ECI) to Merck Global Safety within 2 working days of the event:

    a. Grade ≥ 3 diarrhea
    b. Grade ≥ 3 colitis
    c. Grade ≥ 2 pneumonitis
    d. Grade ≥ 3 hypo- or hyperthyroidism

4. A separate, more detailed guidance document is available under 13.3 (Appendix 13.3) "Immune related Adverse Event Guidance / Events of Clinical Interest Guidance." This document provides guidance regarding identification, evaluation and management of ECIs and irAEs. Additional ECIs are identified in this guidance document and also need to be reported to Merck Global Safety within 2 working days of the event.

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

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

8.2.4 Evaluating Adverse Events

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

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

Table 10 Evaluating Adverse Events

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

V4.0 CTCAE Grading	**Grade 1**	**Mild; asymptomatic or mid symptoms; clinical or diagnostic observations only; intervention not indicated.**
	Grade 2	**Moderate; minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental ADL.**
	Grade 3	**Severe or medically significant but not immediately life-threatening; hospitalization or prolongation or hospitalization indicated; disabling; limiting self-care ADL.**
	Grade 4	**Life threatening consequences; urgent intervention indicated.**
	Grade 5	**Death related to AE**
Seriousness	A serious adverse event is any adverse event occurring at any dose or during any use of Merck product that:	
	†**Results in death**; or	
	†**Is life threatening; or** places the subject, in the view of the investigator, at immediate risk of death from the event as it occurred (Note: This does not include an adverse event that, had it occurred in a more severe form, might have caused death.); or	
	†**Results in a persistent or significant disability/incapacity** (substantial disruption of one's ability to conduct normal life functions); or	
	†**Results in or prolongs an existing inpatient hospitalization** (hospitalization is defined as an inpatient admission, regardless of length of stay, even if the hospitalization is a precautionary measure for continued observation. (Note: Hospitalization [including hospitalization for an elective procedure] for a preexisting condition which has not worsened does not constitute a serious adverse event.); or	
	†**Is a congenital anomaly/birth defect** (in offspring of subject taking the product regardless of time to diagnosis);or	
	Is a new **cancer;** (that is not a condition of the study) **or**	
	Is an overdose (whether accidental or intentional). Any adverse event associated with an overdose is considered a serious adverse event. An overdose that is not associated with an adverse event is considered a non-serious event of clinical interest and must be reported within 24 hours.	
	Other important medical events that may not result in death, not be life threatening, or not require hospitalization may be considered a serious adverse event when, based upon appropriate medical judgment, the event may jeopardize the subject and may require medical or surgical intervention to prevent one of the outcomes listed previously (designated above by a †).	
Duration	Record the start and stop dates of the adverse event. If less than 1 day, indicate the appropriate length of time and units	
Action taken	Did the adverse event cause the Merck product to be discontinued?	
Relationship to test drug	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?
	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 PRINCIPAL INVESTIGATOR AS PER DOSE MODIFICATION GUIDELINES IN THE PROTOCOL.
	Consistency with Trial Treatment Profile	Is the clinical/pathological presentation of the AE consistent with previous knowledge regarding the Merck product or drug class pharmacology or toxicology?
The assessment of relationship will be reported on the case report forms /worksheets by an investigator who is a qualified physician according to his/her best clinical judgment, including consideration of the above elements.		
Record one of the following		**Use the following scale of criteria as guidance (not all criteria must be present to be indicative of a Merck product relationship).**
Yes, there is a reasonable possibility of Merck product relationship.		There is evidence of exposure to the Merck product. The temporal sequence of the AE onset relative to the administration of the Merck product is reasonable. The AE is more likely explained by the Merck product than by another cause.
No, there is not a reasonable possibility Merck product relationship		Subject did not receive the Merck product OR temporal sequence of the AE onset relative to administration of the Merck product is not reasonable OR there is another obvious cause of the AE. (Also entered for a subject with overdose without an associated AE.)

8.2.5 Drug Manufacturer Responsibility for Reporting Adverse Events

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

8.2.6 SAE Reporting to the University of Chicago Comprehensive Cancer Center

All serious adverse events (as defined in section 8.2.3.1) and all adverse events of clinical interest (as defined in section 8.2.3.2) occurring on this study require expedited reporting to the University of Chicago Comprehensive Cancer Center (UCCCC). The responsible Research Nurse or other designated individual should report the SAE to the UCCCC according to standard operating procedures by the end of the business day when s/he becomes aware of the event. Events occurring after business hours should be reported to the UCCCC by 12pm (noon) the next business day.

All unexpected adverse reactions must be reported to the IND holder so that the University of Chicago CCTO can inform the FDA. The responsible Research Nurse or other designated individual at the treating site should provide a complete written report using the FDA MedWatch 3500A form. The completed form should be sent to the CCTO at qaccto@bsd.uchicago.edu within the specified timelines below regardless of whether all information regarding the event is available. If applicable, a follow-up report should be provided to the CCTO if additional information on the event becomes available.

Fatal or Life-threatening Events: within 4 calendar days from treating investigator knowledge of the event

All Other Reportable Events: within 10 calendar days of treating investigator knowledge of the event

All serious adverse events should also be reported to the local IRB of record according to their policies and procedures.

9.0 STATISTICAL ANALYSIS PLAN

9.1 Statistical Analysis Plan Summary

9.1.1 Hypotheses

(1) Clinical:

Pembrolizumab will induce objective responses in malignant mesothelioma, and responses will correlate with higher PD-L1 expression levels.

(2) Translational:

We will further characterize the Immune Escape Phenotype and the PD-L1 expression pattern in malignant mesothelioma and define their relationship to tumor responsiveness in this disease.

9.2 Primary Objectives

Objective (1): To determine the objective response rate of patients with malignant mesothelioma treated with pembrolizumab in A. an unselected patient population, as well as B. in a PD-L1 positive population (should the trial proceeds to Part B, and PD-L1 expression correlate with improved efficacy).

Objective (2): To determine the optimal threshold for PD-L1 expression using the 22C3 antibody based IHC assay in correlation to tumor response

9.3 Secondary Objectives

(1) **Objective**: To determine the progression-free survival of patients with malignant mesothelioma in A) an unselected patient population and B) a PD-L1 positive population when treated with pembrolizumab.

(2) **Objective**: To determine the overall survival of patients with malignant mesothelioma in A). an unselected patient population and B) a PD-L1 positive population when treated with pembrolizumab.

(3) **Objective**: To determine the disease control rate (CR + PR + SD) of patients with malignant mesothelioma who are treated with pembrolizumab in A). an unselected patient population and B) a PD-L1 positive population.

(4) **Objective**: To determine toxicity in patients with malignant mesothelioma who are treated with pembrolizumab.

(5) **Objective**: To determine percentage of patients with mesothelioma who have PD-L1 tumor expression, and the distribution of PD-L1 expression (percent positivity of tumor cells / stroma staining).

9.4 Exploratory Objectives

(1) To characterize the T-cell inflamed phenotype in mesothelioma patients using via presence of of CD8 tumor infiltrating lymphocytes (TILs) and/or use of a gene expression signature (Nanostring).*

(2) To evaluate other immune escape mechanisms including IDO expression, Tregs (FOXP3 expression), MDSCs and other checkpoints by immunohistochemistry (or other methods e.g. Flow Cytometry (also see 4)).*

(3) To determine PD-L1 expression by mass spectrometry and correlate with tumor response, PD-L1 expression by IHC, and the T-cell inflamed phenotype.*

(4) To determine the immune cell populations present in fresh tumor (when available), via tumor digests and mass spectrometry-based flow cytometric analysis (e.g. using CyTOF) in a multiplex fashion in patients with fresh tumor tissue.*

(5) To characterize the T-cell receptor repertoire of TILs compared to circulating T-cells in mesothelioma patients with available fresh frozen tissue (spectrotyping, T-cell repertoire sequencing (e.g. using the Adaptive platform))*

* As available fresh biopsy tissues (or alternatively/concurrently circulating T-cells) will be assessed for baseline status or treatment effects.

9.5 Statistical Analysis Plan

Primary Objective

Clinical and pathologic response rates will be determined and 90% confidence intervals obtained using the exact binomial distribution.

A single stage binomial design will be used for Part A and also separately for Part B. If Part A is successful, Part B (with PD-L1 pre-selection) will be pursued to answer a follow-up question (efficacy in a pre-selection population).

Part A:

The null hypothesis that the true response rate is 2% [p_0] will be tested against a one-sided alternative of 12% [p_A]. 35 patients will be accrued. If there are ≤2 responses in these 35 patients the null hypothesis will be accepted. The null hypothesis will be rejected if 3 or more responses are observed in 35 patients. This design yields a type I error rate of 0.1 and power of 80% when the true response rate is 12%.

A response rate of 12% would be considered clinically meaningful for MM in the absence of alternative treatment options in the $2^{nd}/3^{rd}$ line setting and further development of pembrolizumab would proceed for malignant mesothelioma in this setting. The disease control rate (CR+PR+SD) and 90% confidence interval will also be determined.

If Part A efficacy is met a second cohort (Part B) will be opened.

Part B:

Based on the results from Part A - we will use the Youden Index (Youden 1950; Fluss et al., 2005) methodology to determine the optimal threshold for PD-L1 expression in correlation with tumor response, and if a correlation is identified we will use this threshold for Part B. The Youden index is the maximum value of the sum of sensitivity (here the proportion of responders with a PD-L1 expression level above a given cutpoint) and specificity (proportion of non-responders below the cutpoint) (minus one) over all threshold values (scored 0-100% for the 22C3 antibody based IHC assay) of the biomarker. Since we anticipate only about 4 responders in part A, the threshold will also be assessed/validated in a second cohort of Mesothelioma patients from the Keynote 28 study as available. The overall ability of PD-L1 to predict response will be assessed using the area under the ROC curve (AUC). If the area is significantly greater than 0.5, we will proceed to part B using the optimum cutpoint as determined from the Youden index. Our sample size of n= 35 patients will provide 80% power if the true AUC is 0.81, based on a one-sided test at the alpha=0.10 significance level (Hanley and McNeil, 1983). Should no statistically significant correlation be identified alternative biomarkers will be assessed as possible candidates and the study will proceed to part B as an expansion cohort without pre-screening.

For part B the null hypothesis that the true response rate (in a PD-L1 preselected population is 10% [p_0] will be tested against a one-sided alternative of 25% [p_A]. 30 patients will be accrued. If there are fewer than 6 responses in these 30 the null hypothesis will be accepted. The null hypothesis will be rejected if 6 or more responses are observed in 30 patients. This design yields a type I error rate of 0.1 and power of 80% when the true response rate is 25%.

A response rate of 25% would be considered clinically very meaningful for MM and suggest that development of pembrolizumab in such a PD-L1 preselected population would potentially be competitive with upfront or 2nd line chemotherapy.

Secondary Objectives

Survival Outcomes: Kaplan-Meier (1958) curves will be generated for overall (OS) and progression free survival (PFS); the latter endpoint will be defined as the time from enrollment until disease progression or death from any cause. Median OS and PFS will be estimated along with 90% confidence intervals using the method of Brookmeyer and Crowley (1982). Duration of response will be determined as the time from response until disease progression or death among the subset of patients who respond, and estimated by Kaplan-Meier. The disease control rate (CR+PR+SD) and 90% confidence interval will also be determined.

Toxicity: Toxicities will be summarized in tabular form by type and severity and incidence rates generated.

Exploratory Objectives

Statistical analysis for the correlative studies will be primarily descriptive in nature and summarized in tabular form. Data from Parts A and B of the trial may be pooled for these analyses. Specifically:

→ CD8 tumor infiltrating lymphocytes (TILs) will be assessed by % of tumor showing infiltration. CD8 levels will be correlated with PD-L1 expression using Pearson or Spearman rank correlation coefficients.

→ T-cell inflamed phenotype will be determined using the signature by (Harlin 2005), and previously used for MM (Kindler and Seiwert ASCO 2014).

→ Other immune escape mechanisms including MDSCs and other checkpoints will be assessed by immunohistochemistry (0 - 3+) or flow cytometry counting the number and percentage of positive cells. Levels will be correlated with PD-L1 expression and other biomarkers.

→ PD-L1 expression by mass spectrometry (Collaboration of Dr. Seiwert with – Oncoplex Dx) and correlation with PD-L1 expression by IHC as well as tumor response, and the T-cell inflamed phenotype will be performed. Multivariate logistic regression will be performed to determine whether these biomarkers or combinations of biomarkers are predictive of response. Exact logistic regression models (Hirji et al., 1987) will be fit given the small number of responders expected (4 from part A and 7-8 from part B).

→ Mass spectrometry-based flow cytometric analysis (CyTOF) will be descriptive based on number and percentage of certain cell populations.

→ Analysis of T-cell receptor repertoire from TILs will be descriptive looking for presence or absence of oligoclonal T-cell population. Spectrotyping will be used as a screening tool.

10.0 LABELING, PACKAGING, STORAGE AND RETURN OF CLINICAL SUPPLIES

10.1 Drug 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 drug product in accordance with the protocol and any applicable laws and regulations.

Clinical Supplies will be provided by Merck as summarized in Table 11.

Table 11 Product Descriptions

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

10.2 Packaging and Labeling Information

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

10.3 Clinical Supplies Disclosure

This trial is open-label; therefore, the subject, the trial site personnel, the Drug Manufacturer 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.

10.4 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.

10.5 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.

11.0 ADMINISTRATIVE AND REGULATORY DETAILS

11.1 Confidentiality

Individual patient medical information obtained as a result of this study is considered confidential and disclosure to third parties is prohibited with the exceptions noted below. Patient confidentiality will be ensured by using patient identification code/pre-screening numbers.

Treatment data may be given to the patient's personal physician or to other appropriate medical personnel responsible for the patient's welfare. Data generated as a result of the study need to be available for inspection on request by the participating physicians, the Drug Manufacturer's representatives, by the IRB and the regulatory authorities.

11.2 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) and will be implemented following institutional standards.

11.3 Compliance with Law, Audit and Debarment

The trial will be conducted 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.

11.4 Compliance with Trial Registration and Results Posting Requirements

In accordance with the terms of the Food and Drug Administration Modernization Act (FDAMA) and the Food and Drug Administration Amendments Act (FDAAA), this trial will be submitted to the Clinical Trials Data Bank, http://www.clinicaltrials.gov. Information posted will allow subjects to identify potentially appropriate trials for their disease conditions and pursue participation by calling a central contact number for further information on appropriate trial locations and trial site contact information.

11.5 Quality Management System

The Principal Investigator and study Drug Manufacturer (Merck) will ensure that trial is 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.

A quality assurance audit/inspection of this study may be conducted by regulatory authorities. The quality assurance auditor will have access to all medical records, the investigator's study-related files and correspondence, and the informed consent documentation of this clinical study.

11.6 Data Management

Data management will be provided via the cancer clinical trial infrastructure available at the University of Chicago (eVELOS, etc). It is the responsibility of the investigators to record and verify the accuracy of subject data.

12.0 LIST OF REFERENCES

(1) Al-Shibli KI, Donnem T, Al-Saad S, Persson M, Bremnes RM, Busund L-T. Prognostic effect of epithelial and stromal symphocyte infiltration in non-small cell lung cancer. Clin Cancer Res 2008;14(16):5220-7.

(2) Bellmunt J, Théodore C, Demkov T, Komyakov B, Sengelov L, et al. Phase III Trial of Vinflunine Plus Best Supportive Care Compared With Best Supportive Care Alone After a Platinum-Containing Regimen in Patients With Advanced Transitional Cell Carcinoma of the Urothelial Tract. J Clin Oncol. 2009;27(27):4454

(3) Blum JL, Jones SE, Buzdar AU, LoRusso PM, et al. Multicenter Phase II Study of Capecitabine in Paclitaxel-Refractory Metastatic Breast Cancer. J Clin Oncol 17: 485-493, 1999

(4) Brown JA, Dorfman DM, Ma F-R, Sullivan EL, Munoz O, Wood CR, et al. Blockade of programmed death-1 ligands on dendritic cells enhances T cell activation and cytokine production. J Immunol 2003;170:1257-66.

(5) Brookmeyer R, Crowley J. A confidence interval for the median survival time. Biometrics 1982;38:29-41.

(6) Byrne MJ, Nowak AK. Modified RECIST criteria for assessment of response in malignant pleural mesothelioma. Ann Oncol 2004 Feb; 15(2): 257-260

(7) Campbell N, Kindler HL. Update on malignant pleural mesothelioma. Semin Respir Crit Care Med 2011; 32(1): 102-110.

(8) Clopper C and Pearson ES. The use of confidence or fiducial limits illustrated in the case of the binomial. Biometrika 1934;26:404-413.

(9) Deschoolmeester V, Baay M, Van Marck E, Weyler J, Vermeulen p, Lardon F, et al. Tumor infiltrating lymphocytes: an intriguing player in the survival of colorectal cancer patients. BMC Immunol 2010;11:19.

(10) Diez M, Pollán M, Enriquez JM, Dominguez P, Santana A, Tobaruela E, et al. Histopathologic prognostic score in colorectal adenocarcinomas. Anticancer Res 1998;18:689-94.Disis ML. Immune regulation of cancer. J Clin Oncol 2010; 28(29):4531-8.

(11) Dong H, Strome SE, Salomao DR, Tamura H, Hirano F, Flies DB, et al. Tumor-associated B7-H1 promotes T-cell apoptosis: a potential mechanism of immune evasion. Nat Med 2002;8(8):793-800.

(12) Dudley ME, Wunderlich JR, Yang JC, Sherry RM, Topalian SL, Restifo NP, et al. Adoptive cell transfer therapy following non-myeloablative but lymphodepleting chemotherapy for the treatment of patients with refractory metastatic melanoma. J Clin Oncol 2005;23(10):2346-57.

(13) Eisenhauer EA, Therasse P, Bogaerts J, Schwartz LH, Sargent R, Ford R, et al. New response evaluation criteria in solid tumors: Revised RECIST guideline (version 1.1). Eur J Cancer 2009;45(2):228-47.

(14) Francisco LM, Sage PT, Sharpe AH. The PD-1 pathway in tolerance and autoimmunity. Immunol Rev 2010;236:219-42.

(15) Galon J, Costes A, Sanchez-Cabo F, Kirilovsky A, Mlecnik B, Lagorce-Pagès C, et al. Type, density, and location of immune cells within human colorectal tumors predict clinical outcome. Science 2006;313:1960-4.

(16) Fluss R, Faraggi D, Reise B. Estimation of the Youden index and its associated cutoff point. Biometrical Journal 2005;47:458-72.

(17) Gordon GJ, Rockwell GN, Godfrey PA, Jensen RV, Glickman JN, Yeap BY, Richards WG, Sugarbaker DJ, Bueno R (2005). Validation of genomics-based prognostic tests in malignant pleural mesothelioma. Clin Cancer Res 11:4406-14

(18) Greenwald RJ, Freeman GJ, Sharpe AH. The B7 family revisted. Annu Rev Immunol 2005;23:515-48.

(19) Hamid, O., Robert, C., Daud, A., Hodi, F.S., Hwu, W.-J., Kefford, R., Wolchok, J.D., Hersey, P., Joseph, R.W., Weber, J.S., et al. (2013). Safety and Tumor Responses with Lambrolizumab (Anti-PD-1) in Melanoma. N. Engl. J. Med. 369:134-44

(20) Hanley, JA and McNeil BJ 1983. A Method of Comparing the Areas under Receiver Operating Characteristic Curves Dervied from the Same Cases. Radiology 1983:148, 839-43

(21) Harlin, H. et al. Chemokine expression in melanoma metastases associated with CD8+ T-cell recruitment. Cancer Res. 69, 3077–3085 (2009)

(22) Hillen F, Baeten CIM, van de Winkel A, Creytens D, van der Schaft DWJ, Winnepenninckx V, et al. Leukocyte infiltration and tumor cell plasticity are parameters of aggressiveness in primary cutaneous melanoma. Cancer Immunol Immunother 2008;57:97-106.

(23) Hiraoka N. Tumor-infiltrating lymphocytes and hepatocellular carcinoma: molecular biology. Int J Clin Oncol 2010;15:544-51.Hodi FS, Dranoff G. The biologic importance of tumor-infiltrating lymphocytes. J Cutan Pathol 2010;37(Suppl 1):48-53.

(24) Hirji K F, Mehta CR, and Patel NR. Computing distributions for exact logistic regression. J Am Stat Assoc 1987; 82:1110-17.

(25) Homsi J, Kashani-Sabet M, Messina JL, Daud A. Cutaneous melanoma: prognostic factors. Cancer Control 2005;12(4):223-9.

(26) Hunder NN, Wallen H, Cao J, Hendricks DW, Reilly JZ, Rodmyre R, et al. Treatment of metastatic melanoma with autologous CD4+ T cells against NY-ESO-1. N Engl J Med 2008;358(25):2698-703.

(27) Iannone R, Gergich K, Cong C, Kang P, Daud A, Dronca R, et al. Efficacy and safety of pembrolizumab in patients with advanced melanoma. Pigment Cell Melanoma Res 2012;25:836-903.

(28) Kaplan EL, Meier P. Nonparametric estimation from incomplete observatons. J Am Stat Assoc 1958;53:457-81.

(29) Kloor M. Lymphocyte infiltration and prognosis in colorectal cancer. Lancet 2009;10(840):841.

(30) Lee HE, Chae SW, Lee YJ, Kim MA, Lee HS, Lee BL, et al. Prognostic implications of type and density of tumour-infiltrating lymphocytes in gastric cancer. Br J Cancer 2008;99(10):1704-11.

(31) Leffers N, Gooden MJM, de Jong RA, Hoogeboom B-N, ten Hoor KA, Hollema H, et al. Prognostic significance of tumor-infiltrating T-lymphocytes in primary and metastatic lesions of advanced stage ovarian cancer. Cancer Immunol Immunother 2009;58:449-59.

(32) Liotta F, Gacci M, Frosali F, Querci V, Vittori G, Lapini A, et al. Frequency of regulatory T cells in peripheral blood and in tumour-infiltrating lymphocytes correlates with poor prognosis in renal cell carcinoma. BJU Intern 2010;107:1500-6.

(33) Lyford-Pike S, Peng S, Young GD, et al. Evidence for a role of the PD-1:PD-L1 pathway in immune resistance of HPV-associated head and neck squamous cell carcinoma. Cancer Res 2013;73(2): Published online January 3.

(34) Martin M, Ruiz A, Munoz M, Balil A, Garcia-Mata J, Calvo L, et al. Gemcitabine plus vinorelbine monotherapy in patients with metastatic breast cancer previously treated with anthracyclines and taxanes: final results of the phase III Spanish Breast Cancer Research Group (GEICAM) trial. Lancet Oncol. 2007;8(3):219.

(35) Nishimura H, Honjo T, Minato N. Facilitation of β selection and modification of positive selection in the thymus of PD-1-deficient mice. J Exp Med 2000;191(5):891-7.

(36) Nobili C, Degrate L, Caprotti R, Franciosi C, Leone BE, Trezzi R, et al. Prolonged survival of a patient affected by pancreatic adenocarcinoma with massive

lymphocyte and dendritic cell infiltration after interleukin-2 immunotherapy. Report of a case. Tumori 2008;94:426-30.

(37) Okazaki T, Maeda A, Nishimura H, Kurosaki T, Honjo T. PD-1 immunoreceptor inhibits B cell receptor-mediated signaling by recruiting src homology 2-domain-containing tyrosine phosphatase 2 to phosphotyrosine. PNAS 2001;98(24):13866-71.

(38) Ölcher M, Braun M, Friedrichs N, Rudlowski C, Bercht E, Fimmers R, et al. Foxp3+ cell infiltration and granzyme B+/Foxp3+ cell ratio are associated with outcome in neoadjuvant chemotherapy-treated ovarian carcinoma. Cancer Immunol Immunother 2010;59:909-19

(39) Powderly, J.D., Koeppen, H., Hodi, F.S., Sosman, J.A., Gettinger, S.N., Desai, R., Tabernero, J., Soria, J.-C., Hamid, O., Fine, G.D., et al. (2013). Biomarkers and associations with the clinical activity of PD-L1 blockade in a MPDL3280A study. J. Clin. Oncol. 31. (suppl; abstr 3001)Ropponen KM, Eskelinen MJ, Lipponen PK, Alhava E, Kosma V-M. Prognostic value of tumour-infiltrating lynmphocytes (TILs) in colorectal cancer. J Pathol 1997;182:318-24.

(40) Ray M, Kindler HL. Malignant pleural mesothelioma: an update on biomarkers and treatment. Chest 2009 Sep; 136(3): 888-896.

(41) Sledge GW, Neuberg D, Bernardo P, Ingle JN, Martino S, et al. Phase III Trial of Doxorubicin, Paclitaxel, and the Combination of Doxorubicin and Paclitaxel as Front-Line Chemotherapy for Metastatic Breast Cancer: An Intergroup Trial (E1193). J Clin Oncol. 2003;21(4):588.

(42) Sharpe AH, Freeman GJ. The B7-CD28 superfamily. Nature 2002;2:116-26.

(43) Simon R. Controlled Clinical Trials (1989). 10:1-10

(44) Sweeney CJ, Roth BJ, Kabbinavar FF, Vaughn DJ, Arning M, et al. Phase II Study of Pemetrexed for Second-Line Treatment of Transitional Cell Cancer of the Urothelium. J Clin Oncol. 2006;24(21):3451

(45) Talmadge JE, Donkor M, Scholar E. Inflammatory cell infiltration of tumors: Jekyll or Hyde. Cancer Metastasis Rev 2007;26:373-400.

(46) Thompson RH, Dong H, Lohse CM, Leibovich BC, Blute ML, Cheville JC, et al. PD-1 expressed by tumor-infiltrating immune cells and is associated with poor outcome for patients with renal cell carcinoma. Clin Caner Res 2007;13(6):1757-61.

(47) Topalian SL, Hodi FS, Brahmer JR, Gettinger SN, Smith DC, McDermott DF, et al. Safety, activity, and immune correlates of Anti-PD-1 antibody in cancer. N Engl J Med 2012:doi: 10.1056/NEJMoa1200690.

(48) Usubütün A, Ayhan A, Uygur MC, zen H, klu C, acan S. Prognostic factors in renal cell carcinoma. J Exp Clin Cancer Res 1998;17(1):77-81.Wolchok JD, Hoos A, O'Day S, Weber JS, Hamid O, Lebbe C, et al. Guidelines for the evaluation of immune therapy activity in solid tumors: immune-related response criteria. Clin Cancer Res 2009;15(23):7412-20.

(49) Vogelzang NJ, Rusthoven JJ, Symanowski J, Denham C, Kaukel E, Ruffie P, Gatzemeier U, Boyer M, Emri S, Manegold C, Niyikiza C, Paoletti P. Phase III study of pemetrexed in combination with cisplatin versus cisplatin alone in patients with malignant pleural mesothelioma. J Clin Oncol 2003 Jul 15; 21(14): 2636-2644.

(50) Wolchok, JD, Kluger, H, Callahan, MK, Postow, MA, Rizvi, NA, Lesokhin, AM, Segal, NH, Ariyan, CE, Gordon, R-A, Reed, K, et al. (2013). Nivolumab plus Ipilimumab in Advanced Melanoma. N. Engl. J. Med. 369:122-33

(51) Youden WJ Index for rating diagnostic tests. Cancer. 1950 Jan;3(1):32-5.

13.0 APPENDICES

13.1 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.

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

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

13.3 Immune related Adverse Event Guidance / Events of Clinical Interest Guidance

PEMBROLIZUMAB PROGRAM

(MK-3475)

EVENT OF CLINICAL INTEREST (ECI)

GUIDANCE DOCUMENT

Version 3.0

REVISION HISTORY LOG

Version	Effective Date*	Revision Author	Action
1	08-Aug-2012	Kevin Gergich	Initial Release of guidance document for MK-3475
2	07-June-2013	Marty Huber, Kevin Gergich, Holly Brown	Revised title, formerly was "MK-3475 Immune-Related Adverse Event Identification, Evaluation and Management Guidance Document for Investigators" Revised the format of irAE Guidance document, including layout, font, sectioning, etc. for consistency with Drug Manufacturer Events of Clinical Interest guidance documents. Modified Categories for irAEs: – Replaced GI with Colitis category. – Removed Neurologic category. – Added Renal category. Removed detail in the irAE is part of this protocol or can be requested from the drug manufacturer. Removed details regarding non-MK-3475 compounds. Added ECI reporting guidelines. Included a Table Events of Clinical Interest: Immune-Related Adverse Events that includes the key terms. – Also placed a pull-out quick-review sheet in the Appendix. Updated background, diagnosis and course of treatment details for irAEs.
3		Marty Huber, Kevin Gergich, Holly Brown	Renamed the document: "Pembrolizumab Program (MK-3475) - Events of Clinical Interest (end of this protocol). Introduced generic name: pembrolizumab (MK-3475) and inserted throughout the document. Updated Overview – Section 1 - Clarified the scope of the document and the reporting window for ECIs - Updated Table 1 with medDRA Preferred Terms for adverse events to correspond with reporting of terms to clinical database, rearranged the order, and updated the reporting criteria. - Updated the dose modification/discontinuation section to clarify discontinuation and hold terminology. Updated Section 2 – ECI Reporting Guidelines

			– Clarified that ECIs must be reported to Merck **within 24 hours** regardless of attribution to study treatment or etiology. Updated Section 3 – For All Sections, removed the Course of Action for Grade 1 events. - Section 3.1 Pneumonitis – Moved Pneumonitis to beginning of ECI Section – Updated management guidelines for Grade 2 and Grade 3-4 events - Section 3.2 Colitis: - Updated AE terms and ECI criteria, updated course of action language for clarity - Section 3.3 Endocrine: - Updated ECI criteria and updated course of action language for clarity. - Added subsections for hypophysitis, hyperthyroidism and hypothyroidism to clarify management guidelines. - Section 3.4 Hematologic: - New section added. - Section 3.5: Hepatic: - Updated terms and added additional guidance for reporting of DILI ECI; updated course of action for clarity - Section 3.6 Neurologic: - New section added. - Section 3.7 Ocular: - Changed the name of this section from Eye to Ocular - Added the term “iritis”, updated ECI guidance, and updated course of action language for clarity - Section 3.8 Renal: - Updated section for clarity. - Section 3.9 Skin: - Updated list of terms and added terms for reporting of other skin ECIs; added section 3.9.1: Immediate Evaluation for Potential Skin ECIs - Section 3.10 Other: - Updated list of terms for clarity; revised course of action for clarity.

			- Section 3.11 Infusion Reactions: - New section added. - Section 3.12: Follow-up to Resolution: - New section added. - Section 4: - References updated. - Section 5: - ECI table updated for consistency with Table 1. - Section 6: Appendix 2 – Past Medical History Related to Dermatologic Event: New section added. - Section 7: Appendix 3 – Presentation of the Dermatologic Event: New section added. - Section 8: Appendix 4 – Focused Skin Examination: New section added.

*Ensure that you are using the most current version of this document.

13.3.1 Overview

The purpose of this document is to provide study sites with guidance on the identification and management of Events of Clinical Interest for the MK-3475 (also known as pembrolizumab) program.

Based on the literature review (see ECI reference section 13.3.16), and consideration of mechanism of action of pembrolizumab, potential immune-related adverse events (irAEs) are the primary Event of Clinical Interest (ECI). Immune-related AEs are adverse events associated with the treatment of patients with immunotherapy treatments that appear to be associated with the immune therapy's mechanism of action. Based on these potential irAEs, the Drug Manufacturer has defined a list of specific adverse event terms (ECIs) that are selected adverse experiences that **must be reported to Merck within 24 hours** from the time the Investigator/physician is aware of such an occurrence, regardless of whether or not the investigator/physician considers the event to be related to study drug(s). In addition, these ECIs require additional detailed information to be collected and entered in the study database. ECIs may be identified through spontaneous patient report and / or upon review of subject data. **Table 1** provides the list of terms and reporting requirements for AEs that must be reported as ECIs for MK-3475 protocols. Of note, the requirement for reporting of ECIs applies to all arms, including comparators, of MK-3475 clinical trials

Given that our current list of events of clinical interest is not comprehensive for all potential immune-related events, it is possible that AEs other than those listed in this document may be observed in patients receiving pembrolizumab. Therefore any Grade 3 or higher event that the investigator/physician considers to be immune-related should be reported as an ECI regardless of whether the specific event term is in Table 1 **and reported to Merck within 24 hours** from the time the Investigator/physician is aware of such an occurrence. Adverse events that are both an SAE and an ECI should be reported one time as an SAE only, however the event must be appropriately identified as an ECI as well in in the database.

Table 3: Events of Clinical Interest

Pneumonitis (reported as ECI if ≥ Grade 2)		
Acute interstitial pneumonitis	Interstitial lung disease	Pneumonitis
Colitis (reported as ECI if ≥ Grade 2 or any grade resulting in dose modification or use of systemic steroids to treat the AE)		
Intestinal Obstruction	Colitis	Colitis microscopic
Enterocolitis	Enterocolitis hemorrhagic	Gastrointestinal perforation
Necrotizing colitis	Diarrhea	
Endocrine (reported as ECI if ≥ Grade 3 or ≥ Grade 2 and resulting in dose modification or use of systemic steroids to treat the AE)		
Adrenal Insufficiency	Hyperthyroidism	Hypophysitis
Hypopituitarism	Hypothyroidism	Thyroid disorder
Thyroiditis		
Hematologic (reported as ECI if ≥ Grade 3 or any grade resulting in dose modification or use of systemic		

steroids to treat the AE)		
Autoimmune hemolytic anemia	Aplastic anemia	Thrombotic Thrombocytopenic Purpura (TTP)
Idiopathic (or immune) Thrombocytopenia Purpura (ITP)	Disseminated Intravascular Coagulation (DIC)	Haemolytic Uraemic Syndrome (HUS)
Any Grade 4 anemia regardless of underlying mechanism		
Hepatic (reported as ECI if ≥ Grade 2, or any grade resulting in dose modification or use of systemic steroids to treat the AE**)**		
Hepatitis	Autoimmune hepatitis	Transaminase elevations
Infusion Reactions (reported as ECI for any grade)		
Allergic reaction	Anaphylaxis	Cytokine release syndrome
Serum sickness	Infusion reactions	Infusion-like reactions
Neurologic (reported as ECI for any grade)		
Autoimmune neuropathy	Guillain-Barre syndrome	Demyelinating polyneuropathy
Myasthenic syndrome		
Ocular (report as ECI if ≥ Grade 2 or any grade resulting in dose modification or use of systemic steroids to treat the AE)		
Uveitis	Iritis	
Renal (reported as ECI if ≥ Grade 2)		
Nephritis	Nephritis autoimmune	Renal Failure
Renal failure acute	Creatinine elevations (report as ECI if ≥Grade 3 or any grade resulting in dose modification or use of systemic steroids to treat the AE)	
Skin (reported as ECI for any grade)		
Dermatitis exfoliative	Erythema multiforme	Stevens-Johnson syndrome
Toxic epidermal necrolysis		
Skin (reported as ECI if ≥ Grade 3)		
Pruritus	Rash	Rash generalized
Rash maculo-papular		
Any rash considered clinically significant in the physician's judgment		
Other (reported as ECI for any grade)		
Myocarditis	Pancreatitis	Pericarditis
Any other Grade 3 event which is considered immune-related by the physician		

Each of the events above is described within this guidance paragraph, along with site requirements for reporting these events to the Drug Manufacturer. The information collected should be entered into the narrative field(s) of the Adverse Event module in the database (please note, if narrative entry into the database is not available, please use the narrative text box on the 1727/AER Form). If additional Medical History or Concomitant Medications are reported, the Medical History and Concomitant Medication modules in the database must be updated.

In addition, the guidelines include recommendations on the management of these ECIs. These guidelines are intended to be applied when the physician determines the events to be

related to pembrolizumab. Note: if after the evaluation the event is determined not to be related, the physician is instructed to follow the ECI reporting guidance but does not need to follow the treatment guidance (below). Therefore, these recommendations should be seen as guidelines and the treating physician should exercise individual clinical judgment based on the patient. For any question of dose modification or other treatment options, the specific language in the protocol should be followed. Any questions pertaining to the collection of this information or management of ECIs should be directed to your local Drug Manufacturer contact.

Dose Modification/Discontinuation

The treatment guidance provides specific direction when to hold and/or discontinue pembrolizumab for each immune related adverse event. Of note, when the guidance states to "discontinue" pembrolizumab this is the permanent discontinuation of treatment with pembrolizumab. "Hold" means to stop treating with pembrolizumab but resumption of treatment may be considered assuming the patient meets the criteria for resumption of treatment (see Section 8.1.5.2.1).

13.3.2 ECI Reporting Guidelines

ECIs are selected non-serious and serious adverse experiences that must be reported to Merck **within 24 hours** regardless of attribution to study treatment. The AEs listed in this document and any event that meets the ECI criteria (as noted) in Table 1 or in the respective protocol (event term and Grade) must be reported regardless of physician-determined causality with study medication and whether or not considered immune-related by the physician (unless otherwise specified). Physicians/study coordinators/designated site personnel are required to record these experiences as ECIs on the Adverse Experience electronic Case Report Forms (eCRFs) (or on paper) and to provide supplemental information (such as medical history, concomitant medications, investigations, etc.) about the event.

- Please refer to the Data Entry Guidelines (DEGs) for your protocol.
- Please refer to protocol for details on reporting timelines and reporting of Overdose and Drug Induced Liver Injury (DILI).

13.3.3 ECI Categories and Terms

This section describes the ECI categories and outlines subject management guidelines when an ECI is reported.

13.3.4 Pneumonitis

The following AE terms, if considered ≥ Grade 2, are considered ECIs and should be reported to the Drug Manufacturer within 24 hours of the event:

- Pneumonitis
- Interstitial lung disease
- Acute interstitial pneumonitis

If symptoms indicate possible new or worsening cardiac abnormalities additional testing and/or a cardiology consultation should be considered.

All attempts should be made to rule out other causes such as metastatic disease, bacterial or viral infection**. It is important that patients with a suspected diagnosis of pneumonitis be managed as per the guidance below until treatment-related pneumonitis is excluded. Treatment of both a potential infectious etiology and pneumonitis in parallel may be warranted. Management of the treatment of suspected pneumonitis with steroid treatment should not be delayed for a therapeutic trial of antibiotics.** If an alternative diagnosis is established, the patient does not require management as below; however the AE should be reported regardless of etiology.

Course of Action

Grade 2 events:
- Report as ECI
- Hold pembrolizumab.
- Consider pulmonary consultation with bronchoscopy and biopsy/BAL.
- Consider ID consult
- Conduct an in person evaluation approximately twice per week
- Consider frequent Chest X-ray as part of monitoring
- Treat with systemic corticosteroids at a dose of 1 to 2 mg/kg/day prednisone or equivalent. When symptoms improve to Grade 1 or less, steroid taper should be started and continued over no less than 4 weeks.
- Permanently discontinue for inability to reduce corticosteroid dose to 10 mg or less of prednisone or equivalent per day within 12 weeks.
- Second episode of pneumonitis – discontinue pembrolizumab if upon re-challenge the patient develops a second episode of Grade 2 or higher pneumonitis.

Grade 3 and 4 events:
- Report as ECI
- Discontinue pembrolizumab.
- Hospitalize patient
- Bronchoscopy with biopsy and/or BAL is recommended.
- Immediately treat with intravenous steroids (methylprednisolone 125 mg IV). When symptoms improve to Grade 1 or less, a high dose oral steroid (prednisone 1 to 2

mg/kg once per day or dexamethasone 4 mg every 4 hours) taper should be started and continued over no less than 4 weeks.
- If IV steroids followed by high dose oral steroids does not reduce initial symptoms within 48 to 72 hours, treat with additional anti-inflammatory measures. Discontinue additional anti-inflammatory measures upon symptom relief and initiate a prolonged steroid taper over 45 to 60 days. If symptoms worsen during steroid reduction, initiate a retapering of steroids starting at a higher dose of 80 or 100 mg followed by a more prolonged taper and administer additional anti-inflammatory measures, as needed
- Add prophylactic antibiotics for opportunistic infections.

13.3.5 Colitis

The following AE terms, if considered ≥ Grade 2 or resulting in dose modification **or use of systemic steroids to treat the AE**, are considered ECIs and should be reported to the Drug Manufacturer within 24 hours of the event:

- Colitis
- Colitis microscopic
- Enterocolitis
- Enterocolitis hemorrhagic
- Gastrointestinal perforation
- Intestinal obstruction
- Necrotizing colitis
- Diarrhea

All attempts should be made to rule out other causes such as metastatic disease, bacterial or parasitic infection, viral gastroenteritis, or the first manifestation of an inflammatory bowel disease by examination for stool leukocytes, stool cultures, a Clostridium difficile titer and endoscopy. However the AE should be reported regardless of etiology.

Course of Action

Grade 2 Diarrhea/Colitis (4-6 stools/day over baseline, dehydration requiring IV fluids < 24 hours, abdominal pain, mucus or blood in stool):
- Report as ECI
- Hold pembrolizumab.
- Symptomatic Treatment
- For Grade 2 diarrhea that persists >1 week, and for diarrhea with blood and/or mucus,
    - Consider GI consultation and endoscopy to confirm or rule out colitis
    - Administer oral corticosteroids (prednisone 1-2 mg/kg QD or equivalent)
- When symptoms improve to Grade 1 or less, steroid taper should be started and continued over no less than 4 weeks.

- Permanently discontinue for inability to reduce corticosteroid dose to 10 mg or less of prednisone or equivalent per day within 12 weeks.
- If symptoms worsen or persist > 3 days treat as Grade 3

Grade 3 Diarrhea/Colitis (or Grade 2 diarrhea that persist for greater than 3 days):

- Report as ECI
- Hold pembrolizumab.
- Rule out bowel perforation. Imaging with plain films or CT can be useful.
- Recommend consultation with Gastroenterologist and confirmation biopsy with endoscopy.
- Treat with intravenous steroids (methylprednisolone 125 mg) followed by high dose oral steroids (prednisone 1 to 2 mg/kg once per day or dexamethasone 4 mg every 4 hours) When symptoms improve to Grade 1 or less, steroid taper should be started and continued over no less than 4 weeks. Taper over 6 to 8 weeks in patients with diffuse and severe ulceration and/or bleeding.
- Permanently discontinue for inability to reduce corticosteroid dose to 10 mg or less of prednisone or equivalent per day within 12 weeks.
- If IV steroids followed by high dose oral steroids does not reduce initial symptoms within 48 to 72 hours, consider treatment with additional anti-inflammatory measures as described in the literature [5]. Discontinue additional anti-inflammatory measures upon symptom relief and initiate a prolonged steroid taper over 45 to 60 days. If symptoms worsen during steroid reduction, initiate a retapering of steroids starting at a higher dose of 80 or 100 mg followed by a more prolonged taper and administer additional anti-inflammatory measures as needed.

Grade 4 events:

- Report as ECI
- Permanently discontinue pembrolizumab.
- Manage as per Grade 3.

13.3.6 Endocrine

The following AE terms, if considered ≥Grade 3 or if ≥Grade 2 and require holding/discontinuation/ modification of pembrolizumab dosing, are considered ECIs and should be reported to the Drug Manufacturer within 24 hours of the event:

- Adrenal insufficiency
- Hyperthyroidism
- Hypophysitis
- Hypopituitarism
- Hypothyroidism
- Thyroid disorder

– Thyroiditis

All attempts should be made to rule out other causes such as brain metastases, sepsis and/or infection. However the AE should be reported regardless of etiology.

Hypophysitis or other symptomatic endocrinopathy other than hypo- or hyperthyroidism

Grade 2 events:
- Report as ECI if appropriate
- Hold pembrolizumab
- Monitor thyroid function or other hormonal level tests and serum chemistries more frequently until returned to baseline values.
- Pituitary gland imaging should be considered (MRIs with gadolinium and selective cuts of the pituitary can show enlargement or heterogeneity and confirm the diagnosis).
- Treat with prednisone 40 mg p.o. or equivalent per day. 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.
- Permanently discontinue for inability to reduce corticosteroid dose to 10 mg or less of prednisone or equivalent per day within 12 weeks.
- Consultation with an endocrinologist may be considered.

Grade 3 events:
- Report as ECI
- Hold pembrolizumab.
- Endocrine consultation is recommended.
- Rule out infection and sepsis with appropriate cultures and imaging.
- Treat with an initial dose of methylprednisolone 1 to 2 mg/kg intravenously followed by oral prednisone 1 to 2 mg/kg per day. 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.
- Permanently discontinue for inability to reduce corticosteroid dose to 10 mg or less of prednisone or equivalent per day within 12 weeks.
- Hypophysitis with clinically significant adrenal insufficiency and hypotension, dehydration, and electrolyte abnormalities (such as hyponatremia and hyperkalemia) constitutes adrenal crisis.
- Hospitalization and endocrine consultation should be considered.

Grade 4 events:

- Report as ECI
- Discontinue pembrolizumab.
- Manage as per Grade 3

Hyperthyroidism and 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 events (and Grade 3-4 hypothyroidism):

- Report as ECI if appropriate (see Table 1)
- Monitor thyroid function or other hormonal level tests and serum chemistries more frequently until returned to baseline values.
- Thyroid hormone and/or steroid replacement therapy to manage adrenal insufficiency.
- Therapy with pembrolizumab can be continued while treatment for the thyroid disorder is instituted.
- 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.
- Consultation with an endocrinologist may be considered.

Grade 3 hyperthyroidism events:

- Report as ECI
- Hold pembrolizumab.
- Rule out infection and sepsis with appropriate cultures and imaging.
- Treat with an initial dose of methylprednisolone 1 to 2 mg/kg intravenously followed by oral prednisone 1 to 2 mg/kg per day. 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.
- Permanently discontinue for inability to reduce corticosteroid dose to 10 mg or less of prednisone or equivalent per day within 12 weeks.

Grade 4 events:

- Report as ECI
- Discontinue pembrolizumab.
- Manage as per Grade 3

13.3.7 Hematologic

The following AE term, if considered Grade ≥3 or requiring dose modification or use of systemic steroids to treat the AE, are considered an ECI and should be reported to the Drug Manufacturer within 24 hours of the event:

- Autoimmune hemolytic anemia
- Aplastic anemia
- Disseminated Intravascular Coagulation (DIC)
- Haemolytic Uraemic Syndrome (HUS)
- Idiopathic (or immune) Thrombocytopenia Purpura (ITP)
- Thrombotic Thrombocytopenic Purpura (TTP)
- Any Grade 4 anemia regardless of underlying mechanism

All attempts should be made to rule out other causes such as metastases, sepsis and/or infection. Relevant diagnostic studies such as peripheral blood smear, reticulocyte count, LDH, haptoglobin, bone marrow biopsy or Coomb's test, etc., should be considered to confirm the diagnosis. However the AE should be reported regardless of etiology.

Course of Action

Grade 2 events:
- Report as ECI
- Hold pembrolizumab
- Prednisone 1-2 mg/kg daily may be indicated
- Consider Hematology consultation.
  Permanently discontinue for inability to reduce corticosteroid dose to 10 mg or less of prednisone or equivalent per day within 12 weeks.

Grade 3 events:
- Report as ECI
- Hematology consultation.
- Hold pembrolizumab Discontinuation should be considered as per specific protocol guidance.
- Treat with methylprednisolone 125 mg iv or prednisone 1-2 mg/kg p.o. (or equivalent) as appropriate
- Permanently discontinue for inability to reduce corticosteroid dose to 10 mg or less of prednisone or equivalent per day within 12 weeks.

Grade 4 events:
- Report as ECI
- Hematology consultation
- Discontinue pembrolizumab for all solid tumor indications; refer to protocol for hematologic malignancies.

– Treat with methylprednisolone 125 mg iv or prednisone 1-2 mg/kg p.o. (or equivalent) as appropriate

13.3.8 Hepatic

The following AE terms, if considered ≥ Grade 2 or greater (or any grade with dose modification or use of systemic steroids to treat the AE), are considered ECIs and should be reported to the Drug Manufacturer within 24 hours of the event:

– Autoimmune hepatitis
– Hepatitis
– Transaminase elevations

All attempts should be made to rule out other causes such as metastatic disease, infection or other hepatic diseases. However the AE should be reported regardless of etiology.

Drug Induced Liver Injury (DILI)

In addition, the event must be reported as a Drug Induced Liver Injury (DILI) ECI, if the patient meets the laboratory criteria for potential DILI defined as:

- An elevated alanine transaminase (ALT) or aspartate transaminase (AST) lab value that is greater than or equal to three times (3X) the upper limit of normal (ULN) and
- An elevated total bilirubin lab value that is greater than or equal to two times (2X) ULN and
- At the same time, an alkaline phosphatase (ALP) lab value that is less than 2X ULN,
- As a result of within-protocol-specific testing or unscheduled testing.

Note that any hepatic immune ECI meeting DILI criteria should only be reported once as a DILI event.

Course of Action

Grade 2 events:
– Report as ECI
– Hold pembrolizumab when AST or ALT >3.0 to 5.0 times ULN and/or total bilirubin >1.5 to 3.0 times ULN.
– Monitor liver function tests more frequently until returned to baseline values (consider weekly).
    o Treat with 0.5-1 mg/kg/day methylprednisolone or oral equivalent and when LFT returns to grade 1 or baseline, taper steroids over at least 1 month, consider prophylactic antibiotics for opportunistic infections, and resume pembrolizumab per protocol

- Permanently discontinue for inability to reduce corticosteroid dose to 10 mg or less of prednisone or equivalent per day within 12 weeks.
- Permanently discontinue pembrolizumab for patients with liver metastasis who begin treatment with Grade 2 elevation of AST or ALT, and AST or ALT increases ≥50% relative to baseline and lasts ≥1 week.

Grade 3 events:
- Report as ECI
- Discontinue pembrolizumab when AST or ALT >5.0 times ULN and/or total bilirubin >3.0 times ULN.
- Consider appropriate consultation and liver biopsy to establish etiology of hepatic injury, if necessary
- Treat with high-dose intravenous glucocorticosteroids for 24 to 48 hours. When symptoms improve to Grade 1 or less, a steroid taper with dexamethasone 4 mg every 4 hours or prednisone at 1 to 2 mg/kg should be started and continued over no less than 4 weeks.
- If serum transaminase levels do not decrease 48 hours after initiation of systemic steroids, oral mycophenolate mofetil 500 mg every 12 hours may be given. Infliximab is not recommended due to its potential for hepatotoxicity.
- Several courses of steroid tapering may be necessary as symptoms may worsen when the steroid dose is decreased.
- Permanently discontinue for inability to reduce corticosteroid dose to 10 mg or less of prednisone or equivalent per day within 12 weeks.

Grade 4 events:
- Report as ECI
- Permanently discontinue pembrolizumab
- Manage patient as per Grade 3 above

13.3.9 Neurologic

The following AE terms, regardless of grade, are considered ECIs and should be reported to the Drug Manufacturer within 24 hours of the event:

- Autoimmune neuropathy
- Demyelinating polyneuropathy
- Guillain-Barre syndrome
- Myasthenic syndrome

All attempts should be made to rule out other causes such as metastatic disease, other medications or infectious causes. However the AE should be reported regardless of etiology.

Course of Action

Grade 2 events:
- Report as ECI
- Moderate (Grade 2) – consider withholding pembrolizumab.
- Consider treatment with prednisone 1-2 mg/kg p.o. daily as appropriate
- Consider Neurology consultation. Consider biopsy for confirmation of diagnosis.
- Permanently discontinue for inability to reduce corticosteroid dose to 10 mg or less of prednisone or equivalent per day within 12 weeks.

Grade 3 and 4 events:
- Report as ECI
- Discontinue pembrolizumab
- Obtain neurology consultation. Consider biopsy for confirmation of diagnosis
- Treat with systemic corticosteroids at a dose of 1 to 2 mg/kg prednisone or equivalent once per day. If condition worsens consider IVIG or other immunosuppressive therapies as per local guidelines

When symptoms improve to Grade 1 or less, steroid taper should be started and continued over no less than 4 weeks

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13.3.10 Ocular

The following AE terms, if considered Grade ≥2 or requiring dose modification **or use of systemic steroids to treat the AE**, is considered an ECI and should be reported to the Drug Manufacturer within 24 hours of the event:

- Uveitis
- Iritis

All attempts should be made to rule out other causes such as metastatic disease, infection or other ocular disease (e.g. glaucoma or cataracts). However the AE should be reported regardless of etiology.

Course of Action

Grade 2 events:

- Evaluation by an ophthalmologist is strongly recommended.
- Treat with topical steroids such as 1% prednisolone acetate suspension and iridocyclitics.
- Discontinue pembrolizumab as per protocol if symptoms persist despite treatment with topical immunosuppressive therapy.

Grade 3 events:

- Evaluation by an ophthalmologist is strongly recommended
- Hold pembrolizumab and consider permanent discontinuation as per specific protocol guidance.
- Treat with systemic corticosteroids such as prednisone at a dose of 1 to 2 mg/kg per day. When symptoms improve to Grade 1 or less, steroid taper should be started and continued over no less than 4 weeks.
- Permanently discontinue for inability to reduce corticosteroid dose to 10 mg or less of prednisone or equivalent per day within 12 weeks.

Grade 4 events:

- Evaluation by an ophthalmologist is strongly recommended
- Permanently discontinue pembrolizumab.
- Treat with corticosteroids as per Grade 3 above

13.3.11 Renal

The following AEs if ≥ Grade 2 are considered ECIs and should be reported to the Drug Manufacturer within 24 hours of the event:

- Nephritis
- Nephritis autoimmune
- Renal failure
- Renal failure acute

Creatinine elevations ≥ Grade 3 or any grade with dose modification or use of systemic steroids to treat the AE.

All attempts should be made to rule out other causes such as obstructive uropathy, progression of disease, or injury due to other chemotherapy agents. A renal consultation is recommended. However the AE should be reported regardless of etiology.

Course of Action

Grade 2 events:
- Hold pembrolizumab
- Treatment with prednisone 1-2 mg/kg p.o. daily.
- Permanently discontinue for inability to reduce corticosteroid dose to 10 mg or less of prednisone or equivalent per day within 12 weeks.

Grade 3-4 events:
- Discontinue pembrolizumab
- Renal consultation with consideration of ultrasound and/or biopsy as appropriate
- Treat with systemic corticosteroids at a dose of 1 to 2 mg/kg prednisone IV or equivalent once per day.

When symptoms improve to Grade 1 or less, steroid taper should be started and continued over no less than 4 weeks.

13.3.12 Skin

Rash and Pruritus

The following AEs should be considered as ECIs, if ≥ Grade 3 and should be reported to the Drug Manufacturer within 24 hours of the event:

- Pruritus
- Rash
- Rash generalized
- Rash maculo-papular
- In addition to CTCAE Grade 3 rash, any rash that is considered clinically significant, in the physician's judgment, should be treated as an ECI. Clinical significance is left to the physician to determine, and could possibly include rashes such as the following:
  - rash with a duration >2 weeks; OR
  - rash that is >10% body surface area; OR
  - rash that causes significant discomfort not relieved by topical medication or temporary cessation of study drug.

Other Skin ECIs

The following AEs should **always** be reported as ECIs, regardless of grade, and should be reported to the Drug Manufacturer within 24 hours of the event:

- Dermatitis exfoliative
- Erythema multiforme
- Steven's Johnson syndrome
- Toxic epidermal necrolysis

Please note, the AE should be reported regardless of etiology.

Course of Action

Grade 2 events:
- Symptomatic treatment should be given such as topical glucocorticosteroids (e.g., betamethasone 0.1% cream or hydrocortisone 1%) or urea-containing creams in combination with oral anti-pruritics (e.g., diphenhydramine HCl or hydroxyzine HCl).
- Treatment with oral steroids is at physician's discretion for Grade 2 events.

Grade 3 events:
- Hold pembrolizumab.
- Consider Dermatology Consultation and biopsy for confirmation of diagnosis.
- Treatment with oral steroids is recommended, starting with 1 mg/kg prednisone or equivalent once per day or dexamethasone 4 mg four times orally daily. When symptoms improve to Grade 1 or less, steroid taper should be started and continued over no less than 4 weeks.
- Permanently discontinue for inability to reduce corticosteroid dose to 10 mg or less of prednisone or equivalent per day within 12 weeks.

Grade 4 events:
- Permanently discontinue pembrolizumab.
- Dermatology consultation and consideration of biopsy and clinical dermatology photograph.
- Initiate steroids at 1 to 2 mg/kg prednisone or equivalent. When symptoms improve to Grade 1 or less, steroid taper should be started and continued over no less than 4 weeks.

13.3.12.1 Immediate Evaluation for Potential Skin ECIs

A. Photographs:

Every attempt should be made to get a photograph of the actual ECI skin lesion or rash as soon as possible**. Obtain appropriate consent for subject photographs if a consent form addendum is required by your IRB/ERC.**

- Take digital photographs of:
  - the head (to assess mucosal or eye involvement),
  - the trunk and extremities, and
  - a close-up of the skin lesion/rash.

- If possible, a ruler should be placed alongside the site of a skin occurrence as a fixed marker of distance.
- The time/date stamp should be set in the 'ON' position for documentation purposes.
- Photographs should be stored with the subject's study records.
- The Drug Manufacturer may request copies of photographs. The local study contact (e.g., CRA) will provide guidance to the site, if needed.

B. Past Medical History:
Collect past medical history relevant to the event, using the questions in Appendix 2 (Past Medical History Related to Dermatologic Event) as a guide. Any preexisting conditions not previously reported (e.g., drug allergy) should be entered into the Medical History eCRF.

C. Presentation of the Event:
Collect information on clinical presentation and potential contributing factors using the questions in Appendix 3 (Presentation of the Dermatologic Event) as a guide. This information should be summarized and entered in narrative format in the AE eCRF. Please use the available free-text fields, such as Signs and Symptoms. Note pertinent negatives where applicable to reflect that the information was collected. Any treatments administered should be entered on the Concomitant Medication eCRF.

D. Vitals Signs and Standard Laboratory Tests:
Measure vital signs (pulse, sitting BP, oral temperature, and respiratory rate) and record on the Vital Signs eCRF. Perform standard laboratory tests (CBC with manual differential and serum chemistry panel, including LFTs).

E. Focused Skin Examination:
Perform a focused skin examination using the questions in Appendix 4 (Focused Skin Examination) as a guide. Information should be summarized and entered on the Adverse Experience eCRF as part of the narrative.

F. Dermatology Consult
Refer the subject to a dermatologist as soon as possible.

- For a **"severe rash"**, the subject must be seen within **1-2 days** of reporting the event.
- For **clinically significant rash**, the subject should be seen within **3-5 days**.

The dermatologist should submit a biopsy sample to a certified dermatopathology laboratory or to a pathologist experienced in reviewing skin specimens.

The site should provide the dermatologist with all relevant case history, including copies of clinical photographs and laboratory test results.

13.3.13 Other

The following AEs, regardless of grade, are considered ECIs and should be reported to the Drug Manufacturer within 24 hours of the event:

- Myocarditis
- Pericarditis
- Pancreatitis
- Any additional Grade 3 or higher event which the physician considers to be immune related

All attempts should be made to rule out other causes. Therapeutic specialists should be consulted as appropriate. However the AE should be reported regardless of etiology.

Course of Action

Grade 2 events or Grade 1 events that do not improve with symptomatic treatment:
- Withhold pembrolizumab.
- Systemic corticosteroids may be indicated.
- Consider biopsy for confirmation of diagnosis.
- If pembrolizumab held and corticosteroid required, manage as per grade 3 below.

Grade 3 events:
- Hold pembrolizumab
- Treat with systemic corticosteroids at a dose of 1 to 2 mg/kg prednisone or equivalent once per day.
- When symptoms improve to Grade 1 or less, steroid taper should be started and continued over no less than 4 weeks.
- Permanently discontinue for inability to reduce corticosteroid dose to 10 mg or less of prednisone or equivalent per day within 12 weeks. Otherwise, pembrolizumab treatment may be restarted and the dose modified as specified in the protocol

Grade 4 events:
- Treat with systemic corticosteroids at a dose of 1 to 2 mg/kg prednisone or equivalent once per day.
- Discontinue pembrolizumab

13.3.14 Infusion Reactions

The following AE terms, regardless of grade, are considered ECIs and should be reported to the Drug Manufacturer within 24 hours of the event:

- Allergic reaction
- Anaphylaxis
- Cytokine release syndrome
- Serum sickness
- Infusion reactions
- Infusion-like reactions

Please note, the AE should be reported regardless of etiology.

Course of Action

Refer to infusion reaction table in the protocol and below.

Infusion Reactions

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.** Additional appropriate medical therapy may include but is not limited to: IV fluids Antihistamines NSAIDS Acetaminophen Narcotics Increase monitoring of vital signs as medically indicated until the subject is deemed medically stable in the opinion of the investigator. If symptoms resolve within one hour of stopping drug infusion, the infusion may be restarted at 50% of the original infusion rate (e.g. from 100 mL/hr to 50 mL/hr). Otherwise dosing will be held until symptoms resolve and the subject should be premedicated for the next scheduled dose. **Subjects who develop Grade 2 toxicity despite adequate premedication should be permanently discontinued from further trial treatment administration.**	Subject may be premedicated 1.5h (± 30 minutes) prior to infusion of pembrolizumab with: Diphenhydramine 50 mg p.o. (or equivalent dose of antihistamine). Acetaminophen 500-1000 mg p.o. (or equivalent dose of antipyretic).

NCI CTCAE Grade	Treatment	Premedication at subsequent dosing
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. For Further information, please refer to the Common Terminology Criteria for Adverse Events v4.0 (CTCAE) at http://ctep.cancer.gov		

13.3.15 Follow-up to Resolution

Subjects should be followed to resolution. The Adverse Experience eCRF should be updated with information regarding duration and clinical course of the event. Information obtained from the consulting specialist, including diagnosis, should be recorded in the appropriate AE fields. Free-text fields should be used to record narrative information:

- Clinical course of the event
- Course of treatment
- Evidence supporting recovery
- Follow-up to the clinical course

Any treatments administered for the event should also be entered in the Concomitant Medication eCRF.

13.3.16 ECI Related References

1. Pardoll DM. The blockade of immune checkpoints in cancer immunotherapy. Nature Reviews Cancer 2012; 12:252-264.

2. Weber JS Practical Management of Immune-Related Adverse Events from Immune Checkpoint Protein Antibodies for the Oncologist. American Society of Clinical Oncology 2012; 1092-9118/10/1-10.

3. Weber JS, Ka¨hler KC, and Hauschild A. Management of Immune-Related Adverse Events and Kinetics of Response With Ipilimumab. J Clin Oncol 30. 2012. http://jco.ascopubs.org/cgi/doi/10.1200/JCO.2012.41.6750.

4. Hodi FS, O'Day SJ, McDermott DF, Weber RW, Sosman JA, et al. Improved Survival with Ipilimumab in Patients with Metastatic Melanoma. N Engl J Med 363:711-723, 2010.

5. Topalian SL, Hodi FS, Brahmer JR, Gettinger SN, Smith DC, McDermott DF, et al. Safety, Activity, and Immune Correlates of Anti-PD-1 Antibody in Cancer. N Engl J Med 2012; 366:2443-2454.

6. Brahmer JR, Tykodi SS, Chow LQM, Hwu WJ, et al. Safety and Activity of Anti–PD-L1 Antibody in Patients with Advanced Cancer. N Engl J Med 2012; 366:2455-2465.

7. Weber J, Thompson JA, Hamid O, et al: A randomized, double-blind, placebo-controlled, phase II study comparing the tolerability and efficacy of ipilimumab administered with or without prophylactic budesonide in patients with unresectable stage III or IV melanoma. Clin Cancer Res 15:5591-5598, 2009.

8. Lemech C and Arkenau HT. Novel Treatments for Metastatic Cutaneous Melanoma and the Management of Emergent Toxicities. Clinical Medicine Insights: Oncology 2012:6 53–66.

9. Phan GQ, Weber JS, and Sondak VK. CTLA-4 Blockade with Monoclonal Antibodies in Patients with Metastatic Cancer: Surgical Issues. Annals of Surgical Oncology 15(11):3014–3021.

10. Bristol-Myers Squibb: YERVOY (ipilimumab): Serious and fatal immune-mediated adverse reactions—YERVOY Risk Evaluation and Mitigation Strategy (REMS). http://www.yervoy.com/hcp/rems.aspx

11. Bristol-Myers Squibb: YERVOY (ipilimumab) prescribing information revised March 2011. http://www.accessdata.fda.gov/drugsatfda_docs/label/2011/125377s0000lbl.pdf

13.3.17 ECI APPENDIX 1 – Events of Clinical Interest (ECI) – Reference Table

Pneumonitis (reported as ECI if ≥ Grade 2)		
Acute interstitial pneumonitis	Interstitial lung disease	Pneumonitis
Colitis (reported as ECI if ≥ Grade 2 or any grade resulting in dose modification or use of systemic steroids to treat the AE)		
Intestinal Obstruction	Colitis	Colitis microscopic
Enterocolitis	Enterocolitis hemorrhagic	Gastrointestinal perforation
Necrotizing colitis	Diarrhea	
Endocrine (reported as ECI if ≥ Grade 3 or ≥ Grade 2 and resulting in dose modification or use of systemic steroids to treat the AE)		
Adrenal Insufficiency	Hyperthyroidism	Hypophysitis
Hypopituitarism	Hypothyroidism	Thyroid disorder
Thyroiditis		
Hematologic (reported as ECI if ≥ Grade 3 or any grade resulting in dose modification or use of systemic steroids to treat the AE)		
Autoimmune hemolytic anemia	Aplastic anemia	Thrombotic Thrombocytopenic Purpura (TTP)
Idiopathic (or immune) Thrombocytopenia Purpura (ITP)	Disseminated Intravascular Coagulation (DIC)	Haemolytic Uraemic Syndrome (HUS)
Any Grade 4 anemia regardless of underlying mechanism		
Hepatic (reported as ECI if ≥ Grade 2, or any grade resulting in dose modification or use of systemic steroids to treat the AE**)**		
Hepatitis	Autoimmune hepatitis	Transaminase elevations
Infusion Reactions (reported as ECI for any grade)		
Allergic reaction	Anaphylaxis	Cytokine release syndrome
Serum sickness	Infusion reactions	Infusion-like reactions
Neurologic (reported as ECI for any grade)		
Autoimmune neuropathy	Guillain-Barre syndrome	Demyelinating polyneuropathy
Myasthenic syndrome		
Ocular (report as ECI if ≥ Grade 2 or any grade resulting in dose modification or use of systemic steroids to treat the AE)		
Uveitis	Iritis	
Renal (reported as ECI if ≥ Grade 2)		
Nephritis	Nephritis autoimmune	Renal Failure
Renal failure acute	Creatinine elevations (report as ECI if ≥Grade 3 or any grade resulting in dose modification or use of systemic steroids to treat the AE)	
Skin (reported as ECI for any grade)		
Dermatitis exfoliative	Erythema multiforme	Stevens-Johnson syndrome
Toxic epidermal necrolysis		
Skin (reported as ECI if ≥ Grade 3)		
Pruritus	Rash	Rash generalized
Rash maculo-papular		

Any rash considered clinically significant in the physician's judgment		
Other (reported as ECI for any grade)		
Myocarditis	Pancreatitis	Pericarditis
Any other Grade 3 event which is considered immune-related by the physician		

13.3.18 ECI APPENDIX 2 – Past Medical History Related to Dermatologic Event

Past Medical History:
Any preexisting conditions not previously reported (e.g., drug allergy) should be entered into the Medical History eCRF.

1. Does the subject have any allergies? □ Yes □ No

If yes, please obtain the following information:

a. Any allergy to drugs (including topical or ophthalmic drugs)? □ Yes □ No

List the drug name(s) and describe the type of allergic response (e.g. rash, anaphylaxis, etc): _____
_____

b. Any allergy to external agents, such as laundry detergents, soaps, poison ivy, nickel, etc.? □ Yes □ No

Describe the agent and type of allergic response: _____
_____

c. Any allergy to food? □ Yes □ No

Describe the food and type of allergic response: _____
_____

d. Any allergy to animals, insects? □ Yes □ No

Describe the allergen and type of allergic response: _____
_____

e. Any other allergy? □ Yes □ No

Describe the allergen and type of allergic response: _____
_____

2. Does the subject have any other history of skin reactions, skin eruptions, or rashes? □ Yes □ No

If so what kind? _____

3. Has the subject ever been treated for a skin condition? □ Yes □ No

If so what kind? _____

4. Is the current finding similar to a past experience? □ Yes □ No

13.3.19 ECI APPENDIX 3 – Presentation of the Dermatologic Event

Presentation of the event:
Collect information on clinical presentation and potential contributing factors. Key information should be summarized and entered on the Adverse Experience eCRF. Any treatments administered should be entered on the Concomitant Medication eCRF.

1. What is the onset time of the skin reaction, skin eruption, or rash relative to dose of study drug? _____
2. Has the subject contacted any known allergens? □ Yes □ No

If so what kind? _____

3. Has the subject contacted new, special, or unusual substances (e.g., new laundry detergents, soap, personal care product, poison ivy, etc.)? □ Yes □ No

If so what kind? _____

4. Has the subject taken any other medication (over the counter, prescription, vitamins, and supplement)? □ Yes □ No

If so what kind? _____

5. Has the subject consumed unaccustomed, special or unusual foods? □ Yes □ No

If so what kind? _____

6. Does the subject have or had in the last few days any illness? □ Yes □ No

If so what kind? _____

7. Has the subject come into contact with any family or house members who are ill? □ Yes □ No

If so who and what? _____

8. Has the subject recently been near children who have a skin reaction, skin eruption, or rash (e.g. *Molluscum Contagiosum*)? □ Yes □ No

9. Has the subject had recent sun exposure? □ Yes □ No

10. For the current rash, have there been any systemic clinical signs? □ Yes □ No

If so what kind? _____

i. Anaphylaxis? □ Yes □ No
ii. Signs of hypotension? □ Yes □ No
iii. Signs of dyspnea? □ Yes □ No
iv. Fever, night sweats, chills? □ Yes □ No

11. For the current rash, has the subject needed subcutaneous epinephrine or other systemic catecholamine therapy? □ Yes □ No

If so what kind? _____

12. For the current rash, has the subject used any other medication, such as inhaled bronchodilators, antihistaminic medication, topical corticosteroid, and/or systemic corticosteroid? □ Yes □ No

List medication(s) and dose(s): _____
_____

13. Is the rash pruritic (itchy)? □ Yes □ No

13.3.20 ECI APPENDIX 4 – Focused Skin Examination

Focused Skin Examination:
Key information should be summarized and entered on the Adverse Experience eCRF.

Primary Skin Lesions Description
Color: _____

General description:

_____
_____

Describe the distribution of skin reaction, skin eruption, or rash on the body:

_____
_____

Is skin reaction, skin eruption, or rash resolving or continuing to spread?

_____
_____

Any associated signs on physical examination? _____

13.3.21 ECI APPENDIX 5 – Asbestos Exposure Checklist

Asbestos Exposure	☐ Yes ☐ No ☐ Unknown	Indicate whether the patient has asbestos exposure prior to the diagnosis of the tumor submitted for TCGA.
Type of Asbestos Exposure	☐ Chrysotile ☐ Crocidolite ☐ Anthophyllite ☐ Actinolite ☐ Amosite ☐ Tremolite ☐ Erionite ☐ Unknown	If the patient had a known exposure to asbestos, indicate the type of asbestos exposure.
Source of First Asbestos Exposure	☐ Occupational ☐ Secondary (paraoccupational-spouse/parent/etc) ☐ Unknown	If the patient had a known exposure to asbestos, indicate the source of the asbestos exposure.
Age at First Asbestos Exposure	_____Years ☐ Unknown	If the patient had known occupational and/or environmental asbestos exposure, indicate the patient's age at their first exposure.
Number of Years of Asbestos Exposure	_____Years ☐ Unknown	If the patient had known occupational and/or environmental asbestos exposure, indicate the number of years of exposure.
Age at Last Asbestos Exposure	_____Years ☐ Unknown	If the patient had a known exposure to asbestos, provide the age at last asbestos exposure.
Primary Occupation	☐ Asbestos Mining ☐ Construction ☐ Automotive ☐ Welding ☐ Unknown	

<table>
<tr><td></td><td colspan="5">☐ Other (please specify)</td><td></td></tr>
<tr><td>Other Primary Occupations</td><td colspan="5">_____</td><td></td></tr>
<tr><td>Years Worked in Industry</td><td colspan="5">_____Years
☐ Unknown</td><td></td></tr>
<tr><td rowspan="7">Family History of Mesothelioma</td><td></td><td>Mesothelioma</td><td>Ocular Melanoma</td><td>Melanoma</td><td>Other (specify)</td><td rowspan="7"></td></tr>
<tr><td>Spouse</td><td></td><td></td><td></td><td></td></tr>
<tr><td>Child</td><td></td><td></td><td></td><td></td></tr>
<tr><td>Parent</td><td></td><td></td><td></td><td></td></tr>
<tr><td>Sibling</td><td></td><td></td><td></td><td></td></tr>
<tr><td>Grandparent</td><td></td><td></td><td></td><td></td></tr>
<tr><td>Unknown</td><td></td><td></td><td></td><td></td></tr>
<tr><td>Other Family History of Cancer</td><td colspan="5">_____</td><td></td></tr>
</table>

Exposure to radiation? Y____ N_____ Unknown_____

Patient Name _____

Signature_____ Date _____