Status Page

PROTOCOL 16-293

Closed to New Accrual

Closure Effective Date: 10/11/2018
No new subjects may be enrolled in the study as described above.
Any questions regarding this closure should be directed to the study's Principal Investigator

NCI Protocol #: NCT02971956

DF/HCC Protocol #: 16-293

TITLE: A Phase II Study of Pembrolizumab in Refractory Advanced Esophageal Cancer

Coordinating Center: Dana-Farber Cancer Center

Principal Investigator (PI): Peter C. Enzinger MD
Dana-Farber Cancer Institute
Peter_Enzinger@dfci.harvard.edu

Other Investigators:

Justin Gainor, MD
Massachusetts General Hospital
JGainor@partners.org

Eirini Pectasides, MD
Beth Israel Deaconess Medical Center
epectasi@bidmc.harvard.edu

Statistician: Hui Zheng, PhD
Massachusetts General Hospital
HZheng1@partners.org

Study Coordinator: Bridget Fitzpatrick
Dana-Farber Cancer Institute
Bridget_Fitzpatrick@dfci.harvard.edu

Agent(s): Pembrolizumab **(**MK-3475) (NSC 776864)

IND #: 130810
IND Sponsor: Peter Enzinger, MD

Protocol Version Date: 02/26/2019

SCHEMA

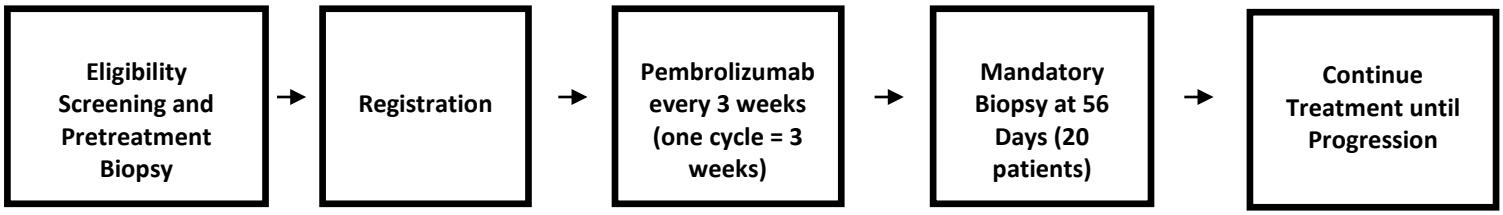
Eligibility Screening and Pretreatment Biopsy
Registration
Pembrolizumab every 3 weeks (one cycle = 3 weeks)
Mandatory Biopsy at 56 Days (20 patients)
Continue Treatment until Progression

TABLE OF CONTENTS

1. TRIAL DESIGN

1.1 Trial Design

This is an open label, single arm phase 2 clinical trial of pembrolizumab in advanced, refractory esophageal cancer. Advanced esophageal cancer patients who have progressed on a prior regimen are eligible to participate. All 50 patients enrolled on the study will receive pembrolizumab 200 mg administered every three weeks.

Patients will continue on the trial until they suffer intolerable toxicity or are found to have disease progression by Immune-related Response Evaluation Criteria In Solid Tumors (irRECIST). [19] Toxicity will be graded according to CTCAE 4.0. Mandatory day 56 (+/- 5 days) tumor biopsies will be performed on 20 patients and optional post-treatment tumor biopsies will be performed on patients who initially respond to pembrolizumab and then develop acquired resistance.

2. OBJECTIVE(S) & HYPOTHESIS(ES)

2.1 Primary Objective(s) & Hypothesis(es)

(1) **Objective:**
Evaluate the response rate, by irRECIST, of pembrolizumab in refractory, advanced esophageal adenocarcinoma patients.

Hypothesis:
- Pembrolizumab will show a response rate of ≥ 10% in refractory, advanced esophageal adenocarcinoma patients

2.2 Secondary Objective(s) & Hypothesis(es)

(1) **Objective**:
Evaluate the response rate, by irRECIST, of pembrolizumab in refractory, advanced esophageal adenocarcinoma patients who are PD-L1 positive and negative.

Hypothesis:
- Pembrolizumab will have anti-cancer activity in both PD-L1 positive and negative refractory, advanced esophageal cancer.

(2) **Objective**:
Evaluate the Progression-free Survival (PFS) and Overall Survival (OS) as measured by the Method of Kaplan and Meier in patients with refractory, advanced esophageal adenocarcinoma.

Hypothesis:
- Pembrolizumab will have similar PFS and OS as seen in the KEYNOTE-059 study.

(3) Objective
Evaluate the durability of pembrolizumab response in advanced esophageal cancer patients by measuring median overall survival and median progression free survival.

Hypothesis:
- The response to pembrolizumab in metastatic esophageal cancer will be durable and will significantly increase progression free survival.

(4) **Objective**
Evaluate the safety and tolerability of pembrolizumab 200 mg, administered every three weeks, in advanced esophageal cancer.

Hypothesis:
- Pembrolizumab 200mg every 3 weeks will be well tolerated in the advanced esophageal cancer patient population.

2.3 Exploratory Objective

(1) **Objective:**
Evaluate relationship between response rate, by irRECIST, and potential predictive biomarkers.

Hypothesis:
- Molecular analysis of pre-treatment tumor biopsy samples as well as serially collected PBMCs and plasma samples will enable us to identify biomarkers predictive of pembrolizumab response.

(2) **Objective:**
Evaluate the response rate, by irRECIST, of pembrolizumab in refractory, advanced, Western esophageal squamous cell carcinoma patients.

Hypothesis:
- Pembrolizumab will show activity in refractory, advanced, Western esophageal squamous cell carcinoma patients.

3. BACKGROUND & RATIONALE

3.1 Background

Esophageal cancer is one of the most rapidly increasing cancers in the United States. In 2014, it is predicted that 18,170 cases will be diagnosed and 15,450 patients will die of this disease. [1]

Globally, esophageal cancer was diagnosed in 482,300 persons and 406,800 individuals died of this cancer in 2008.[2] Therapy remains inadequate, as these numbers show, and few definitive trials have been conducted in esophageal cancer specifically. Based on a few large randomized trials that have included esophageal cancer in addition to gastroesophageal junction cancer and gastric cancer, it is believed that esophageal cancer responds similarly to standard chemotherapy as these lower GI malignancy sites.[3] Thus, the standard of care is a platinum-fluoropyrimidine doublet (+ trastuzumab for HER2/neu positive tumors) upfront and recently, 2nd line therapy has become established in this disease through a sequence of 3 trails, Cougar 02, REGARD, and RAINBOW, as the combination of Paclitaxel and Ramucirumab.[4-6] There are, however, no other established lines of therapy beyond this and the treatment algorithm remains wide open to additional new effective drugs in this disease.

Recently, immunotherapies directed against the immune checkpoint molecules CTLA-4 and PD-1 have shown very great promise in the treatment of metastatic melanoma. Ipilimumab, a fully humanized antibody directed against CTLA-4, was FDA approved for the treatment of melanoma after two randomized phase 3 clinical trials showed a significant survival benefit.[7,8] Monoclonal antibodies directed against PD-1, pembrolizumab and nivolumab, have also shown promising results in metastatic melanoma, non-small cell lung cancer, and renal cancer.[9-12] Importantly, in melanoma the majority of responses to both CTLA-4 and PD-1 directed-therapies appear to be durable and last for greater than one year.[12,13] Pembrolizumab was granted FDA approval in 2014 on the basis of a phase 1 clinical trial expansion cohort of 173 patients with refractory metastatic melanoma (Robert et al.). Refractory melanoma patients receiving pembrolizumab had an overall response rate of 26% and 88% of the responding patients were still benefitting from the drug after 6 months.[7] Pembrolizumab was generally well tolerated and drug-related grade 3 and 4 toxicity occurred in only 13% of patients.

A large, multicenter phase 1 clinical trial testing pembrolizumab in several disease cohorts is currently underway (MK-3475-028, NCT02054806). This trial is molecularly prescreening patients for PD-L1 positivity. Preliminary data generated by this prescreening effort showed that 33% of 89 metastatic esophageal cancers patients were PD-L1 positive.

3.2 Pharmaceutical and Therapeutic Background

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

The PD-1 receptor-ligand interaction is a major pathway hijacked by tumors to suppress immune control. The normal function of PD-1, expressed on the cell surface of activated T-cells under healthy conditions, is to down-modulate unwanted or excessive immune responses, including autoimmune reactions. PD-1 (encoded by the gene Pdcd1) is an Ig superfamily member related to CD28 and CTLA-4 which has been shown to negatively regulate antigen receptor signaling upon

engagement of its ligands (PD-L1 and/or PD-L2). The structure of murine PD-1 has been resolved. PD-1 and family members are type I transmembrane glycoproteins containing an Ig Variable-type (V-type) domain responsible for ligand binding and a cytoplasmic tail which is responsible for the binding of signaling molecules. The cytoplasmic tail of PD-1 contains 2 tyrosine-based signaling motifs, an immunoreceptor tyrosine-based inhibition motif (ITIM) and an immunoreceptor tyrosine-based switch motif (ITSM). Following T-cell stimulation, PD-1 recruits the tyrosine phosphatases SHP-1 and SHP-2 to the ITSM motif within its cytoplasmic tail, leading to the dephosphorylation of effector molecules such as CD3ζ, PKCθ and ZAP70 which are involved in the CD3 T-cell signaling cascade. The mechanism by which PD-1 down modulates T-cell responses is similar to, but distinct from that of CTLA-4 as both molecules regulate an overlapping set of signaling proteins. PD-1 was shown to be expressed on activated lymphocytes including peripheral CD4+ and CD8+ T-cells, B-cells, T regs and Natural Killer cells. Expression has also been shown during thymic development on CD4-CD8- (double negative) T-cells as well as subsets of macrophages and dendritic cells. The ligands for PD-1 (PD-L1 and PD-L2) are constitutively expressed or can be induced in a variety of cell types, including non-hematopoietic tissues as well as in various tumors . Both ligands are type I transmembrane receptors containing both IgV- and IgC-like domains in the extracellular region and contain short cytoplasmic regions with no known signaling motifs. Binding of either PD-1 ligand to PD-1 inhibits T-cell activation triggered through the T-cell receptor. PD-L1 is expressed at low levels on various non-hematopoietic tissues, most notably on vascular endothelium, whereas PD-L2 protein is only detectably expressed on antigen-presenting cells found in lymphoid tissue or chronic inflammatory environments. PD-L2 is thought to control immune T-cell activation in lymphoid organs, whereas PD-L1 serves to dampen unwarranted T-cell function in peripheral tissues. Although healthy organs express little (if any) PD-L1, a variety of cancers were demonstrated to express abundant levels of this T-cell inhibitor. PD-1 has been suggested to regulate tumor-specific T-cell expansion in subjects with melanoma (MEL). This suggests that the PD-1/PD-L1 pathway plays a critical role in tumor immune evasion and should be considered as an attractive target for therapeutic intervention.

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

3.3 Rationale

3.3.1 Rationale for the Trial and Selected Subject Population

Data on the expression and prognostic impact of PD-L1 and PD-L2 in human esophageal cancer is limited. One study by Ohigashi and colleagues sought to define the clinical significance PD-L1 and PD-L2 expression after esophagectomy.[14] They evaluated 41 esophagectomy patients by real-time quantitative PCR, using newly generated monoclonal antibodies that recognize human PD-L1 (MIH1) and PD-L2 (MIH18). They demonstrated that PD-L positive patients had a significantly poorer prognosis than negative patients. This was more pronounced in advanced

stage tumors. Multivariate analysis indicated that PD-L status was an independent prognostic factor. Although there was no significant correlation between PD-L1 expression and tumor-infiltrating T lymphocytes. PD-L2 expression was inversely correlated with tumor-infiltrating CD8+ Tcells.

Until recently, there was limited clinical experience with immune checkpoints inhibitor in gastroesophageal cancer. A phase 2 trial of tremelimumab, a CTLA4 inhibitor, in metastatic gastric cancer showed a low overall response rate but did have one patient who had a durable, over 2.5 years, partial response.[15]

Recently, the gastric cancer results of Keynote- 012 were presented at GI Cancers Symposium in San Francisco, California by Muro and colleagues.[16] This Merck phase 2 clinical trial screened 162 patients with recurrent of metastatic adenocarcinoma of the stomach or GE junction and found that 65 (40%) were PD-L1 positive. PD-L1 expression was assessed in archival tumor samples using a prototype IHC assay and the 22C3 antibody. Patients with PD-L1 staining in the stroma or in $\geq$ 1% of tumor cells were eligible for enrollment. Of these 65 patients, 39 patients received Pembrolizumab at 10mg/kg every 2 weeks. Nine (23%) had received $\leq$ 1 prior therapy and 26 (67%) had received two or more prior therapies for metastatic disease. The treatment was well tolerated and grade 3-5 adverse events occurred in only 4 patients (10%), including grade 3 decreased appetite, grade 3 fatigue, grade 5 hypoxia, grade 3 peripheral sensory neuropathy and grade 4 pneumonitis. Best overall response by investigator review (N=39) was 33% (95%CI: 19.1-50.2) with 13 partial responses, 5 stable disease, and 21 progressive disease. Best overall response by central review (N=36) was 22% (95% CI: 10.1-39.2) with 8 partial responses, 5 stable disease, and 19 progressive disease. Overall, 53.1% of patients showed at least some improvement from baseline in the measurement of their tumor size by central review. Of the patients with response, 10 have had responses of 24 weeks or longer and many responses are ongoing. Six month progression-free survival is 24% and median overall survival has not yet been reached. A trend toward an association between higher levels of PD-L1 expression and response, progression-free survival, and overall survival was observed.

A second study in esophageal carcinoma, the Keynote -028 study, was recently presented by Doi and colleagues at the ASCO conference in Chicago, IL on May 31st, 2015.[17] This study screened 83 patients for PD-L1. Of these, 37 were deemed PD-L1 positive by the same criteria used in Keynote -012. Of these, 23 patients (17 with squamous cell carcinoma and 5 with adenocarcinoma and 1 with mucoepidermoid carcinoma) were enrolled. Two patients (8.7%) had one prior therapy for advanced disease, nine patients (39.1%) had two prior therapies for advanced disease, and 11 (47.8%) had three or more prior lines of therapy for advanced disease. Treatment-related adverse events occurred in only four (17.4%) patients, including one decreased lymphocyte count, one decreased appetite, one liver disorder, and one pruritic rash. There were no treatment-related deaths or discontinuations due to treatment-related adverse events. Pembrolizumab-specific toxicity included 2 patients with grade 2 hypothyroidism and 2 patients with grade 2 adrenal insufficiency, neither requiring pembrolizumab discontinuation. Of 23 patients, a partial response rate was documented in 30% (95% CI: 13.2-52.9) of patients by investigator review. Five of 17 squamous cell carcinoma patients had a major response and two of five adenocarcinoma patients had a major response. Overall, 52.2% of patients showed a

decrease in target lesion burden. To date, responses have been 24 weeks or longer in 7 patients, including 2 adenocarcinoma patients. The median time to response was 16 weeks and the median duration of response was 40 weeks.

Data from KEYNOTE -059 (DFCI Protocol 15-073) have recently become available to co-authors and is embargoed (strictly confidential) until the presentation at the ASCO Meeting on June 4th, 2017. A manuscript has been submitted to Lancet. KEYNOTE – 059 enrolled 259 patients with measurable gastric and gastroesophageal junction adenocarcinoma with disease progression after at least 2 prior lines of treatment. Patients received 200mg of pembrolizumab every 3 weeks. Primary endpoint was objective response rate by RECIST 1.1. Important points of this study relevant to this protocol are: 1) the study enrolled 259 patients, of whom 51.4% were gastroesophageal junction cancers; 2) the study enrolled both PD-L1 positive and negative patients, of whom 42.1% were PD-L1 negative; 3) Objective response was 15.5% for PD-L1 positive patients and 6.4% for PD-L1 negative patients; 4) Patients with PD-L1 negative tumors who received pembrolizumab as a third-line treatment for metastatic disease had an objective response rate of 8.6% with 3.4% achieving complete response; 5) Median duration of response was 16.3 months in PD-L1 positive patients and 6.9 months in PD-L1 negative patients.

This trial is being performed to further characterize pembrolizumab's activity in esophageal carcinoma, particularly in the esophageal adenocarcinoma population that is less common in East Asia (with only 5 patients reported in the Keynote -028 study). However, we would also like to perform an exploratory analysis of North American squamous cell carcinoma patients, which may have a different pathophysiology from East Asian patients. This is based on the fact that North American squamous cell carcinoma patients are HPV negative [18] and these patients typically do not have the other risk factors seen in East Asia.

3.3.2 **Rationale for Dose Selection/Regimen/Modification**

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

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

A population pharmacokinetic analysis has been performed using serum concentration time data from 476 patients. Within the resulting population PK model, clearance and volume parameters of

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

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

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

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

4. PARTICIPANT SELECTION

4.1 Eligibility Criteria

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

1. Histologically confirmed, measurable, unresectable adenocarcinoma or squamous cell carcinoma of the esophagus. For the purposes of this study, undifferentiated carcinomas or adenosquamous carcinomas will be categorized as adenocarcinomas.

2. The primary tumor must originate in the esophagus. Tumors that involve the GE junction must meet Sievert Type 1 criteria: "Adenocarcinoma of the distal oesophagus which usually arises from an area with specialized intestinal metaplasia of the oesophagus (i.e. Barrett's oesophagus) and which may infiltrate the oesophagogastric junction from above." For the purposes of this protocol, this will be interpreted as: greater than 50% of the tumor must be above the GE junction or, alternatively, the tumor must involve the GE junction and arise in the setting of biopsy-documented Barrett's esophagus (specialized intestinal metaplasia).

3. Patients must have received at least one prior therapy for unresectable disease. Patients with recurrence within 6 months of completion of neoadjuvant or adjuvant therapy may be considered as having received one prior therapy for unresectable disease.

4. Be willing and able to provide written informed consent for the trial.

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

6. Have measurable disease based on irRECIST.

7. Be willing to provide tissue from a newly obtained biopsy of a tumor lesion, most commonly an EGD biopsy from the esophagus. Newly-obtained is defined as a specimen obtained up to 6 weeks (42 days) prior to initiation of treatment on Day 1. Subjects for whom newly-obtained samples cannot be provided (e.g. inaccessible or subject safety concern) may submit an archived specimen only upon agreement from the Sponsor. Please note, patients may not initiate therapy until the biopsy specimen is received at the Dana-Farber Cancer Institute.

8. The first 15 patients with adenocarcinoma will be offered an optional tumor biopsy (typically EGD biopsy) at 8 weeks. Starting with adenocarcinoma patient #16, patients must have an accessible tumor and must agree to tumor biopsy at 8 weeks; this will continue to be mandatory until a total of 20 patients have undergone biopsy at 8 weeks.

9. Have a performance status of 0 or 1 on the ECOG Performance Scale (Appendix A).

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

11. Female subjects of childbearing potential must be willing to use 2 methods of birth control or be surgically sterile, or abstain from heterosexual activity for the course of the study through 120 days after the last dose of study medication (Reference Section 6.3.2). Subjects of childbearing potential are those who have not been surgically sterilized or have not been free from menses for > 1 year.

12. Male subjects must 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.

13. Demonstrate adequate organ function as defined below, all screening labs should be performed within 10 days of treatment initiation.

    Hematological
    - Absolute neutrophil count (ANC) ≥1,500 /mcL
    - Platelets ≥80,000 / mcL
    - Hemoglobin ≥8.5 g/dL or ≥5.6 mmol/L

    Renal
    - Serum creatinine ≤1.5 X upper limit of normal (ULN) **OR** Measured creatinine clearance ≥60 mL/min for subject with creatinine levels > 1.5 X institutional ULN (GFR can also be used in place of creatinine or CrCL) Creatinine clearance should be calculated per institutional standard.

    Hepatic
    - Serum total bilirubin ≤ 1.5 X ULN **OR** Direct bilirubin ≤ ULN for subjects with total bilirubin levels > 1.5 ULN
    - AST (SGOT) ≤ 2.5 X ULN **OR** ≤ 5 X ULN for subjects with liver metastases
    - ALT (SGPT) ≤ 2.5 X ULN **OR** ≤ 5 X ULN for subjects with liver metastases
    - Albumin ≥ 2.8 mg/dL

    Coagulation
    - International Normalized Ratio (INR) **OR** Prothrombin Time (PT) ≤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
    - 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

4.2 Subject Exclusion Criteria

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

1. 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. Subjects requiring systemic steroids are excluded from the trial. The use of physiologic doses of corticosteroids may be approved after discussion with the sponsor.
2. Has a known history of active TB (Bacillus Tuberculosis)
3. Hypersensitivity to pembrolizumab or any of its excipients.
4. Has had a prior anti-cancer monoclonal antibody (mAb) within 4 weeks prior to study Day 1 or who has not recovered (i.e., ≤ Grade 1 or at baseline) from adverse events due to agents administered more than 4 weeks earlier.

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 and alopecia are an exception to this criterion and may qualify for the study.

    - Note: If subject received major surgery, they must wait ≥ 3 weeks prior to starting study treatment. 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 or squamous cell carcinoma of the skin that has undergone potentially curative therapy or in situ cervical cancer.

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. This exception does not include carcinomatous meningitis which is excluded regardless of clinical stability.

8. Has active autoimmune disease that has required systemic treatment in the past 2 years (i.e. with use of disease modifying agents, corticosteroids or immunosuppressive drugs). Replacement therapy (eg., thyroxine, insulin, or physiologic corticosteroid replacement therapy for adrenal or pituitary insufficiency, etc.) is not considered a form of systemic treatment.
9. Has an active infection requiring systemic therapy.
10. Patients that require supplemental oxygen are excluded.
11. Has a history or current evidence of any condition, therapy, or laboratory abnormality that might confound the results of the trial, interfere with the subject's participation for the full duration of the trial, or is not in the best interest of the subject to participate, in the opinion of the treating investigator.
12. Has known psychiatric or substance abuse disorders that would interfere with cooperation with the requirements of the trial.
13. Is pregnant or breastfeeding, or expecting to conceive or father children within the projected duration of the trial, starting with the pre-screening or screening visit through 120 days after the last dose of trial treatment.
14. Has received prior therapy with an anti-PD-1, anti-PD-L1, or anti-PD-L2 agent.
15. Has a known history of Human Immunodeficiency Virus (HIV) (HIV 1/2 antibodies).

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

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

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

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

4.3 Inclusion of Women and Minorities

Both men and women of all races and ethnic groups are eligible for this trial.

5. REGISTRATION PROCEDURES

5.1 General Guidelines for DF/HCC Institutions

Institutions will register eligible participants in the Clinical Trials Management System (CTMS) OnCore. Registrations must occur prior to the initiation of protocol therapy. Any participant not registered to the protocol before protocol therapy begins will be considered ineligible and registration will be denied.

An investigator will confirm eligibility criteria and a member of the study team will complete the protocol-specific eligibility checklist.

Following registration, participants may begin protocol therapy. Issues that would cause treatment delays should be discussed with the Overall Principal Investigator (PI). If a participant does not receive protocol therapy following registration, the participant's registration on the study must be canceled. Registration cancellations must be made in OnCore as soon as possible.

5.2 Registration Process for DF/HCC Institutions

DF/HCC Standard Operating Procedure for Human Subject Research Titled *Subject Protocol Registration* (SOP #: REGIST-101) must be followed.

6. TREATMENT PLAN

6.1 Trial Treatment

The treatment to be used in this trial is outlined below in Table 1. Treatment must begin within 5

days of registration.

Table 1 Trial Treatment

Drug	Dose/Potency	Dose Frequency	Route of Administration	Regimen/Treatment Period	Use
Pembrolizumab	200 mg	Q3W	IV infusion	Day 1 of each 3-week cycle	Experimental

6.1.1 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 11). 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 200 mg will be administered as a 30-minute IV infusion every 3 weeks. Sites should make every effort to target infusion timing to be as close to 30 minutes as possible. However, given the variability of infusion pumps from site to site, a window of -5 minutes and +10 minutes is permitted (i.e., infusion time is 30 minutes: -5 min/+10 min).

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

6.2 Concomitant Medications/Vaccinations

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

6.2.1 Acceptable Concomitant Medications

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

All concomitant medications received within 28 days before the first dose of trial treatment and 30 days after the last dose of trial treatment should be recorded. Concomitant medications administered after 30 days after the last dose of trial treatment should be recorded for SAEs and Events of Clinical Interest (ECIs) as defined in Section 8.3.1.1.

6.2.2 **Prohibited Concomitant Medications**

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

- Antineoplastic systemic chemotherapy or biological therapy
- Immunotherapy not specified in this protocol
- Chemotherapy not specified in this protocol
- Intranasal influenza vaccines
- Investigational agents other than pembrolizumab
- Radiation therapy
  Note: Radiation therapy to a symptomatic solitary lesion or to the brain may be allowed at the investigator's discretion.
- Live vaccines within 30 days prior to the first dose of trial treatment and while participating in the trial. Examples of live vaccines include, but are not limited to, the following: measles, mumps, rubella, varicella/zoster, yellow fever, rabies, BCG, and typhoid vaccine.
- Systemic glucocorticoids for any purpose other than to modulate symptoms from an event of clinical interest of suspected immunologic etiology. The use of physiologic doses of corticosteroids may be approved after consultation with the Sponsor.

Subjects who, in the assessment by the investigator, require the use of any of the aforementioned treatments for clinical management should be removed from the trial. Subjects may receive other medications that the investigator deems to be medically necessary.
The Exclusion Criteria describes other medications which are prohibited in this trial.
There are no prohibited therapies during the Post-Treatment Follow-up Phase.

6.3 Diet/Activity/Other Considerations

6.3.1 **Diet**

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

6.3.2 **Contraception**

Pembrolizumab may have adverse effects on a fetus in utero. Furthermore, it is not known if pembrolizumab has transient adverse effects on the composition of sperm. Non-pregnant, non-breast-feeding women may be enrolled if they are willing to use 2 methods of birth control or are

considered highly unlikely to conceive. Highly unlikely to conceive is defined as 1) surgically sterilized, or 2) postmenopausal (a woman who is ≥45 years of age and has not had menses for greater than 1 year will be considered postmenopausal), or 3) not heterosexually active for the duration of the study. The two birth control methods can be either two barrier methods or a barrier method plus a hormonal method to prevent pregnancy. Subjects should start using birth control from study Visit 1 throughout the study period up to 120 days after the last dose of study therapy.

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

Subjects should be informed that taking the study medication may involve unknown risks to the fetus (unborn baby) if pregnancy were to occur during the study. In order to participate in the study they must adhere to the contraception requirement (described above) for the duration of the study and during the follow-up period defined in section 8.2-Reporting of Pregnancy and Lactation to the Sponsor and to Merck. If there is any question that a subject will not reliably comply with the requirements for contraception, that subject should not be entered into the study.

6.3.3 **Use in Pregnancy**

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

The study investigator will make every effort to obtain permission to follow the outcome of the pregnancy and report the condition of the fetus or newborn to the Sponsor. If a male subject impregnates his female partner, the study personnel at the site must be informed immediately and the pregnancy reported to the Sponsor and to Merck and followed as described above and in Section 8.2.

6.3.4 **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.

6.4 Criteria for Taking a Participant Off Protocol Therapy

Subjects may withdraw consent at any time for any reason or be dropped from the trial at the

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

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

- The subject or legal representative (such as a parent or legal guardian) withdraws consent.
- Confirmed radiographic disease progression
  Note: A subject may be granted an exception to continue on treatment with confirmed radiographic progression if clinically stable or clinically improved
- Unacceptable adverse experiences as described in Section 7.1
- Intercurrent illness that prevents further administration of treatment
- Investigator's decision to withdraw the subject
- The subject has a confirmed positive serum pregnancy test
- Noncompliance with trial treatment or procedure requirements
- The subject is lost to follow-up
- Completed 24 months of uninterrupted treatment with pembrolizumab or 35 administrations of study medication, whichever is later.
  Note: 24 months of study medication is calculated from the date of first dose. Subjects who stop pembrolizumab after 24 months may be eligible for up to one year of additional study treatment if they progress after stopping study treatment provided they meet the requirements detailed in Section 11.1.1.1.
- Administrative reasons

The End of Treatment and Follow-up visit procedures are listed in Section 11 (Protocol Flow Chart). After the end of treatment, each subject will be followed for 30 days for adverse event monitoring (serious adverse events will be collected for 90 days after the end of treatment as described in Section 8.9). Subjects who discontinue for reasons other than progressive disease will have post-treatment follow-up for disease status until disease progression, initiating a non-study cancer treatment, withdrawing consent or becoming lost to follow-up. After documented disease progression each subject will be followed by telephone for overall survival until death, withdrawal of consent, or the end of the study, whichever occurs first.

Discontinuation of Study Therapy after CR

Discontinuation of treatment may be considered for subjects who have attained a confirmed CR that have been treated for at least 24 weeks with pembrolizumab and had at least two treatments with pembrolizumab beyond the date when the initial CR was declared. Subjects who then experience radiographic disease progression may be eligible for up to one year of additional treatment with pembrolizumab via the Second Course Phase at the discretion of the investigator if no cancer treatment was administered since the last dose of pembrolizumab, the subject meets the safety parameters listed in the Inclusion/Exclusion criteria, and the trial is open. Subjects will resume therapy at the same dose and schedule at the time of initial discontinuation. Additional details are provided in Section 11.1.1.1.

6.5 Clinical Criteria for Early Trial Termination

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

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

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

6.6 Duration of Follow Up

Participants will be followed until 30 days after last study treatment or death, whichever occurs later. Participants removed from protocol therapy for unacceptable adverse event(s) will be followed until resolution or stabilization of the adverse event.

6.7 Criteria for Taking a Participant Off Study

Participants will be removed from study when any of the following criteria apply:

- Lost to follow-up
- Withdrawal of consent for data submission
- Death

The reason for taking a participant off study, and the date the participant was removed, must be documented in the case report form (CRF).

For Decentralized Subject Registrations, the research team updates the relevant Off Treatment/Off Study information in OnCore.

7. DOSING DELAYS/DOSE MODIFICATIONS

7.1 Dose Modification

Adverse events (both non-serious and serious) associated with pembrolizumab exposure may represent an immunologic etiology. These adverse events may occur shortly after the first dose or several months after the last dose of treatment. Pembrolizumab must be withheld for drug-related toxicities and severe or life-threatening AEs as per Table 3 below. See Section 7.2.1 and Events

of Clinical Interest Guidance Document for supportive care guidelines, including use of corticosteroids. Please also refer to the Events of Clinical Interest Guidance Document (Appendix B).

Table 3 Dose Modification and Toxicity Management Guidelines for Immune-Related Adverse Events 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
	Grade 4	Permanently discontinue		

				substituted via IV infusion.
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	Grade 2	Withhold	• Administer corticosteroids	• Monitor changes of renal function

dysfunction	Grade 3 or 4	Permanently discontinue	(prednisone 1-2 mg/kg or equivalent) followed by taper.	
Myocarditis	Grade 1 or 2	Withhold	• Based on severity of AE administer corticosteroids	• Ensure adequate evaluation to confirm etiology and/or exclude other causes
	Grade 3 or 4	Permanently discontinue		
All other immune-related AEs	Intolerable/ persistent Grade 2	Withhold	• Based on type and severity of AE administer corticosteroids	• Ensure adequate evaluation to confirm etiology and/or exclude other causes
	Grade 3	Withhold or discontinue based on the type of event. Events that require discontinuation include and not limited to: Gullain-Barre Syndrome, encephalitis		
	Grade 4 or recurrent Grade 3	Permanently discontinue		

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

NOTE:

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

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

7.2 Rescue Medications & Supportive Care

7.2.1 Supportive Care Guidelines

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

Note: if after the evaluation the event is determined not to be related, the investigator is instructed to follow the ECI reporting guidance but does not need to follow the treatment guidance (as outlined in the ECI guidance document). Refer to Section 7.1 for dose modification.

It may be necessary to perform conditional procedures such as bronchoscopy, endoscopy, or skin photography as part of evaluation of the event. Suggested conditional procedures, as appropriate, can be found in the ECI guidance document.

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

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

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

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

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

- **Hyperthyroidism or Hypothyroidism**:
  Thyroid disorders can occur at any time during treatment. Monitor patients for changes in thyroid function (at the start of treatment, periodically during treatment, and as indicated based on clinical evaluation) and for clinical signs and symptoms of thyroid disorders.
  - **Grade 2** hyperthyroidism events (and **Grade 3-4** hypothyroidism):
    - In hyperthyroidism, non-selective beta-blockers (e.g. propranolol) are suggested as initial therapy.
    - In hypothyroidism, thyroid hormone replacement therapy, with levothyroxine or liothyroinine, is indicated per standard of care.
  - **Grade 3-4** hyperthyroidism
    - Treat with an initial dose of IV corticosteroid followed by oral corticosteroids. When symptoms improve to Grade 1 or less, steroid taper

should be started and continued over no less than 4 weeks. Replacement of appropriate hormones may be required as the steroid dose is tapered.

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

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

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

  Table 4 below shows treatment guidelines for subjects who experience an infusion reaction associated with administration of pembrolizumab (MK-3475).

Table 4 Infusion Reaction Treatment Guidelines

NCI CTCAE Grade	Treatment	Premedication at subsequent dosing
Grade 1 Mild reaction; infusion interruption not indicated; intervention not indicated	Increase monitoring of vital signs as medically indicated until the subject is deemed medically stable in the opinion of the investigator.	None
Grade 2 Requires infusion interruption but responds promptly to symptomatic treatment (e.g., antihistamines, NSAIDS, narcotics, IV fluids); prophylactic medications indicated for < =24 hrs	**Stop Infusion and monitor symptoms.** Additional appropriate medical therapy may include but is not limited to: IV fluids Antihistamines NSAIDS Acetaminophen Narcotics Increase monitoring of vital signs as medically indicated until the subject is deemed medically stable in the opinion of the investigator. If symptoms resolve within one hour of stopping drug infusion, the infusion may be restarted at 50% of the original infusion rate (e.g., from 100 mL/hr to 50 mL/hr). Otherwise dosing will be held until symptoms resolve and the subject should be premedicated for the next scheduled dose. **Subjects who develop Grade 2 toxicity despite adequate premedication should be permanently discontinued from further trial treatment administration.**	Subject may be premedicated 1.5h (± 30 minutes) prior to infusion of pembrolizumab (MK-3475) with: Diphenhydramine 50 mg po (or equivalent dose of antihistamine). Acetaminophen 500-1000 mg po (or equivalent dose of antipyretic).
Grades 3 or 4 Grade 3:	**Stop Infusion.** Additional appropriate medical therapy may	No subsequent dosing

NCI CTCAE Grade	Treatment	Premedication at subsequent dosing
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 ventilator support indicated	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.**	
Appropriate resuscitation equipment should be available in the room and a physician readily available during the period of drug administration.		

8. ADVERSE EVENTS: LIST AND REPORTING REQUIREMENTS

Adverse event (AE) monitoring and reporting is a routine part of every clinical trial. The following list of reported and/or potential AEs (Section 9.1) and the characteristics of an observed AE (Section 9.2) will determine whether the event requires expedited reporting **in addition** to routine reporting.

8.1 Adverse Event Characteristics

- **CTCAE term (AE description) and grade:** The descriptions and grading scales found in the revised NCI Common Terminology Criteria for Adverse Events (CTCAE) version 4.0 will be utilized for AE reporting. All appropriate treatment areas should have access to a copy of the CTCAE version 4.0. A copy of the CTCAE version 4.0 can be downloaded from the CTEP web site http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm.

- **For expedited reporting purposes only:**
  - AEs for the agent(s) that are listed above should be reported only if the adverse event varies in nature, intensity or frequency from the expected toxicity information which is provided.
  - Other AEs for the protocol that do not require expedited reporting are outlined in the next section (Expedited Adverse Event Reporting) under the sub-heading of Protocol-Specific Expedited Adverse Event Reporting Exclusions.

- **Attribution** of the AE:
  - Definite – The AE *is clearly related* to the study treatment.
  - Probable – The AE *is likely related* to the study treatment.
  - Possible – The AE *may be related* to the study treatment.

- Unlikely – The AE *is doubtfully related* to the study treatment.
- Unrelated – The AE *is clearly NOT related* to the study treatment.

8.2 Expedited Adverse Event Reporting

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

8.2.2 Investigators **must** report to the Overall PI any serious adverse event (SAE) that occurs after the initial dose of study treatment, during treatment, or within 90 days of the last dose of treatment or 30 days of starting a new treatment (whichever is earlier), on the local institutional SAE form.

8.2.3 DF/HCC Expedited Reporting Guidelines

Investigative sites within DF/HCC will report AEs directly to the DFCI Office for Human Research Studies (OHRS) per the DFCI IRB reporting policy.

8.3 Expedited Reporting to the Food and Drug Administration (FDA)

The Overall PI, as study sponsor, will be responsible for all communications with the FDA. The Overall PI will report to the FDA, regardless of the site of occurrence, any serious adverse event that meets the FDA's criteria for expedited reporting following the reporting requirements and timelines set by the FDA.

8.4 Expedited Reporting to Hospital Risk Management

Participating investigators will report to their local Risk Management office any participant safety reports or sentinel events that require reporting according to institutional policy.

8.5 Routine Adverse Event Reporting

All Adverse Events **must** be reported in routine study data submissions to the Overall PI on the toxicity case report forms. **AEs reported through expedited processes (e.g., reported to the IRB, FDA, etc.) must also be reported in routine study data submissions.**

8.6 Definition of an Adverse Event and Reporting of Adverse Events to Merck

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

and/or intensity) of a preexisting condition that is temporally associated with the use of the Merck's product is also an adverse event.

Changes resulting from normal growth and development that do not vary significantly in frequency or severity from expected levels are not to be considered adverse events. Examples of this may include, but are not limited to, teething, typical crying in infants and children and onset of menses or menopause occurring at a physiologically appropriate time.
Merck product includes any pharmaceutical product, biological product, device, diagnostic agent or protocol-specified procedure, whether investigational (including placebo or active comparator medication) or marketed, manufactured by, licensed by, provided by or distributed by Merck for human use.

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

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

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

All adverse events will be recorded from the time the consent form is signed through 30 days following cessation of treatment and at each examination on the Adverse Event case report forms/worksheets. The reporting timeframe for adverse events meeting any serious criteria is described in Section 8.

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

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

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

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

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

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

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

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

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

8.9.1.1 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 an other important medical event

- **Note**: In addition to the above criteria, adverse events meeting either of the below criteria, although not serious per ICH definition, are reportable to the Merck in the same timeframe as SAEs to meet certain local requirements. Therefore, these events are considered serious by Merck for collection purposes.
    - Is a new cancer (that is not a condition of the study);
    - Is associated with an overdose.

Refer to Table 6 for additional details regarding each of the above criteria.

For the time period beginning when the consent form is signed until treatment allocation/randomization, any serious adverse event, or follow up to a serious adverse event, including death due to any cause other than progression of the cancer under study (reference Section 8.9.1.3 for additional details) that occurs to any subject must be reported within 24 hours to the Sponsor and within 2 working days to Merck Global Safety if it causes the subject to be excluded from the trial, or is the result of a protocol-specified intervention, including but not limited to washout or discontinuation of usual therapy, diet, placebo treatment or a procedure.

For the time period beginning at treatment allocation/randomization through 90 days following cessation of treatment, or 30 days following cessation of treatment if the subject initiates new anticancer therapy, whichever is earlier, any 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 (reference Section 8.9.1.3 for additional details), whether or not related to the Merck product, must be reported within 24 hours to the Sponsor and within 2 working days to Merck Global Safety.

Additionally, any serious adverse event, considered by an investigator who is a qualified physician to be related to Merck product that is brought to the attention of the investigator at any time following consent through the end of the specified safety follow-up period specified in the paragraph above, or at any time outside of the time period specified in the previous paragraph also must be reported immediately to the Sponsor and to Merck Global Safety.

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

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

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

8.9.1.2 Events of Clinical Interest

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

1. An overdose of Merck product, as defined in Section 8.1 - Definition of an Overdose for This Protocol and Reporting of Overdose to the Sponsor, that is not associated with clinical symptoms or abnormal laboratory results.

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

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

3. Additional adverse events:
A separate guidance document has been provided entitled "Event of Clinical Interest Guidance Document" (previously entitled, "Event of Clinical Interest and Immune-Related Adverse Event Guidance Document"). This document can be found in Appendix 4 and provides guidance regarding identification, evaluation and management of ECIs and irAEs.

ECIs (both non-serious and serious adverse events) identified in this guidance document from the date of first dose through 90 days following cessation of treatment, or 30 days after the initiation of a new anticancer therapy, whichever is earlier, need to be reported within 24 hours to the Sponsor and within 2 working days to Merck Global Safety. (Attn: Worldwide Product Safety; FAX 215 993-1220), regardless of attribution to study treatment, consistent with standard SAE reporting guidelines.

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.

8.9.1.3 **Protocol-Specific Exceptions to Serious Adverse Event Reporting**

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

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

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

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

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

8.9.2 **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 6 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?

		Is the time of onset of the AE compatible with a drug-induced effect (applies to trials with investigational medicinal product)?
	Likely Cause	Is the AE not reasonably explained by another etiology such as underlying disease, other drug(s)/vaccine(s), or other host or environmental factors

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

9. PHARMACEUTICAL INFORMATION

A list of the adverse events and potential risks associated with the investigational or other agents administered in this study can be found in Section 7.

9.1 Investigational Product

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

Clinical Supplies will be provided by Merck as summarized in Table 7.

Table 7 Product Descriptions

Product Name & Potency	Dosage Form
Pembrolizumab 50 mg	Lyophilized Powder for Injection
Pembrolizumab 100 mg/ 4mL	Solution for Injection

9.2 Packaging and Labeling Information

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

9.3 Clinical Supplies Disclosure

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

9.4 Storage and Handling Requirements

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

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

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

9.5 Ordering

Participating Institutions will order their own investigational agent (Pembrolizumab) directly from Merck using the Drug Supply Request Form. Please allow for 3 weeks for drug to arrive after the order is submitted. The Participating Institution will ensure that the pharmacy will be able to receive and store the agent according to state and federal guidelines. The IRB should be kept informed of who will supply the agent (i.e., Merck pharmaceuticals Inc.) so that any regulatory responsibilities can be met in a timely fashion.

9.6 Returns and Reconciliation

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

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

10. BIOMARKER, CORRELATIVE, AND SPECIAL STUDIES

10.1 Biomarker Studies

10.1.1 Pre-treatment Tumor Biopsies

Through the biopsies of pre-treatment disease, we will test hypotheses regarding predictors of response to PD-1 inhibition based upon the inflammatory state of the tumor. At this time, our understanding of the etiology of response and de novo resistance to these drugs are still emerging. However, increasing evidence points to the potential for a 6-10 gene mRNA expression signature of interferon γ-related genes as predictive. This signature was recently identified in melanoma samples as being significantly associated with response to pembrolizumab [20]. A recent assessment of pembrolizumab activity in PD-L1 positive advanced stomach and gastroesophageal junction tumors [21] also showed a trend between an interferon γ gene signature and response to pembrolizumab (P= 0.07).

Based upon pre-clinical research within the Bass laboratory at Dana-Farber, the estimated prevalence of the interferon γ-gene signature in an unselected group of esophageal adenocarcinoma is 43% (unpublished data). Based upon these preliminary data, we anticipate this signature being significantly more prevalent in responders than non-responders. Assuming that we are unable to get good quality biopsies for RNA extraction in 75% of patients (small biopsies, technical problems with RNA extraction), we anticipate that we will have 30 samples of baseline tumors prior to treatment with PD-1 inhibitor. With n=30, we have > 90% power to detect a difference between 40% vs. 70% in the prevalence of interferon γ-gene signature the using one sided test with 5% type 1 error.

All patients with tumors that can be safely biopsied are required to undergo a pretreatment biopsy. For patients with a primary tumor intact, this will typically be an endoscopic biopsy of the primary tumor. Among other studies (below), the fresh pretreatment tumor biopsy will allow us to analyze immunohistochemically the tumor and surrounding immune-infiltrate for PD-L1, PD-L2 and PD1 expression.

Biopsy tissues will be collected and fixed by 10% neutral buffered formalin overnight, dehydrated and paraffin embedded. The paraffin blocks will be stored at room temperature. IHC staining for immunological markers will be performed in the Center for Immuno-Oncology Pathology Core at Dana-Farber/Harvard Cancer Center Specialized Histopathology Core.

PD-L1 testing will be performed by QualTek Molecular Laboratories. Biopsies tissues must be sent to the Dana-Farber Cancer Institute study team as soon as possible. DFCI study team

will prepare batch shipments of tissue to QualTek for testing.

The tissue samples should be sent to the following address:

Bridget Fitzpatrick
Gastrointestinal Cancer Center
Dana-Farber Cancer Institute
450 Brookline Avenue, DA1B16
Boston, MA 02215
Ph: 617-632-6565

Please alert the Study Coordinator via email and provide a tracking number for the shipment: Bridget_Fitzpatrick@dfci.harvard.edu

We will also collect additional pre-treatment tissue to attempt immune cell characterization in collaboration with the Belfer Center for Applied Science. Biopsy tissue will be placed immediately into DMEM+10%FBS, placed on ice and delivered immediately to the Belfer Center for disaggregation and flow cytometry characterization to define the specific cellular composition of the CD3+ immune cell population (e.g. percent of cells which are CD4, CD8, FOXP3, CD45RO, CD45RA, CXCR7, CD19-positive), the presence of T-cell exhaustion markers (e.g. PD-1, LAG3, TIM3), the composition of the myeloid population (macrophages, MDSCs) and for flow cytometric evidence of PD-L1 and/or PD-L2 on the EPCAM-positive cell population. If material is available, additional material will be stored for possible later gene expression profiling.

If sufficient cell material is available from pre-treatment biopsies, these may be utilized as part of ongoing cancer modeling whereby residual tumor is utilized for generation of in vitro cultures and/or implantation into immunocompromised mice for xenograft generation.

Furthermore, additional testing of samples will be done to explore genomic sequencing, RNA expression patterns, and somatic alterations with existing next generation testing, for example, OncoPanel.

10.1.2 **Analysis of Circulating Peripheral Blood Mononuclear Cells (PBMCs):**

We will isolate PBMCs at initiation of pembrolizumab therapy and at serial time points during pembrolizumab therapy. PBMCs will be isolated prior to the administration of pembrolizumab on day 1 of the first three cycles. Following cycle 3, PBMCs will be collected at the time of restaging. PBMCs will also be collected, if possible, on the visit when the patient is taken off the trial.

Blood samples collected at Massachusetts General Hospital and Beth Israel Deaconess Medical Center will be delivered to the Dana-Farber Cancer Institute. All samples will be processed and stored by the DFCI Hodi Lab.

PBMCs will be processed and frozen for later batched flow cytometric analysis. Peripheral blood mononuclear cells (PBMCs) will be collected from whole blood to assess immune cell populations. Surface staining with a panel of antibodies (CD3, CD4, CD8, CD25, FoxP3, CD11c, CD83, CD86, CD56) and intracytoplasmatic cytokine staining, followed by flow cytometry will be performed in order to identify different T cell populations, their activation status, and the production of different cytokines as well as other immune cell populations as described below:

		FITC	PE	ECD	PE-Cy5	PE-Cy7
1	**Treg (1); intracellular**	FoxP3	CTLA-4	CD3	CD25	CD4
2	**T, B, monocyte, NK,NKT**	CD19	CD56	CD14	CD45	CD3
3	**T cell subset**	CD8	TCRγδ	CD4	TCRαβ	CD3
4	**CD4 T cell naïve memory**	CCR7	CD57	CD45RO	CD28	CD4
5	**CD8 T cell naïve memory**	CCR7	CD57	CD45RO	CD28	CD8
6	**Myeloid DC**	Lineage (CD3,CD14, CD16,CD19,CD56)	CD86	HLA-DR	CD11c	CD45
7	**Plasmacytoid DC**	Lineage (CD3,CD14, CD16,CD19,CD56)	CD86	HLA-DR	CD45	CD123
8	**PD1-ICOS**	ICOS	PD-1	CD3	CD8	CD4
9	**41BB-OX40**	CD3	4-1BB	CD8	OX-40	CD4
10	**CD127 Treg**	CD3	CD127	CD25	CD27	CD4
11	**NK,NKT**	CD16	NKG2D	CD3	CD56	CD8
12	**BDCA.DC**	BDCA-2	BDCA-1	CD14,CD19	BDCA-3	CD45

10.1.3 **Analysis of Circulating Immune Markers:**

In parallel to PBMC isolation, we will also collect plasma at multiple time points through the course of pembrolizumab therapy. Plasma samples will be isolated prior to the administration of pembrolizumab on day 1 of the first three cycles. Following cycle 3, plasma samples will be collected at the time of restaging. A plasma sample will also be collected, if possible, on the visit when the patient is taken off the trial.

Blood samples collected at Massachusetts General Hospital and Beth Israel Deaconess Medical Center will be delivered to the DFCI Hodi Lab. All samples will be processed and stored by the DFCI Hodi Lab.

Plasma will be frozen and then analyzed in batches by DFCI's immune-oncology core laboratory (led by Dr. Steve Hodi). A panel of cytokines and chemokines will be tested in serum using Luminex cytokine assay. Changes in cytokine production in immune cell subsets as a function of treatment will be determined by ELISA and intracellular cytokine staining. Absolute lymphocyte count (ALC) will be monitored.

10.1.4 **Post-treatment Tumor Biopsies in Patients with Acquired Resistance to Pembrolizumab**

Post-treatment biopsies will be obtained at 56 days (+/- 5days) after the first dose of pembrolizumab. Patients that develop acquired resistance to pembrolizumab will be encouraged to undergo an optional post-treatment biopsy but this is not mandatory. This biopsy will allow us to study mechanisms of resistance to pembrolizumab. To do this, we utilize the immune characterization techniques described above. Furthermore, at time of acquired resistance, additional testing of the sampled tumor may include genomic analysis to identify novel somatic alterations which could contribute to resistance.

Additionally, further testing of samples will be done to explore genomic sequencing, RNA expression patterns, and somatic alterations with existing next generation testing, for example, OncoPanel

The tissue samples should be sent to the following address:

Bridget Fitzpatrick
Gastrointestinal Cancer Center
Dana-Farber Cancer Institute
450 Brookline Avenue, DA1B16
Boston, MA 02215
Ph: 617-632-6565

Please alert the Study Coordinator via email and provide a tracking number for the shipment: Bridget_Fitzpatrick@dfci.harvard.edu

11. STUDY CALENDAR AND VISIT REQUIREMENTS

Trial Period:	**Screening Phase**	**Treatment Cycles**									**End of Treatment**	**Post-Treatment**
						To be repeated beyond 8 cycles						
Treatment Cycle/Title:	Main Study Screening (Visit 2)	1	2	3	4	5	6	7	8	Discon	Safety Follow-up	Survival Follow-Up
Scheduling Window (Days):	-28 to -1		± 3	± 3	± 3	± 3	± 3	± 3	± 3	At time of Discon	30 days post discon	Every 12 weeks
Administrative Procedures												
Informed Consent	X											
Inclusion/Exclusion Criteria	X											
Demographics and Medical History	X											
Prior and Concomitant Medication Review	X											
Trial Treatment Administration		X	X	X	X	X	X	X	X			
Survival Status										X	X	X
Clinical Procedures/Assessments												
Review Adverse Events		X	X	X	X	X	X	X	X	X	X	
Full Physical Examination	X	X	X	X	X	X	X	X	X			
Vital Signs and Weight	X	X	X	X	X	X	X	X	X			
ECOG Performance Status	X	X	X	X	X	X	X	X	X			
Laboratory Procedures/Assessments: analysis performed by LOCAL laboratory												
Pregnancy Test – Urine or Serum *b*-HCG[f]	X[i]											
PT/INR and aPTT	X[h]											
CBC with Differential	X[h]	X[k]	X[k]	X[k]	X[k]	X[k]	X[k]	X[k]	X[k]			
Comprehensive Serum Chemistry Panel[g]	X[h]	X[k]	X[k]	X[k]	X[k]	X[k]	X[k]	X[k]	X[k]			
Urinalysis	X[h]											
T3, FT4 and TSH	X[h]		X		X		X		X[a]			
Efficacy Measurements												
Tumor Imaging	X[b]			X[c]			X[c]					
Tumor Biopsies/Archival Tissue Collection/Correlative Studies Blood												
Archival or Newly Obtained Tissue Collection	X			X[d]						X[e]		
Correlative Studies Blood Collection		X[l]	X	X[j]			X[j]			X		

a: Beyond the 8th cycle TSH can be checked every 2-3 cycles at the treating investigators discretion
b: Baseline scans need to be obtained within 21 days of the start of pembrolizumab
c:. Scans are obtained every 9 weeks (-7 day window), approximately every 3 cycles. After cycle 18, restaging scans can be performed every 4 cycles at the discretion of the treating investigator.
d: For the first 15 adenocarcinoma patients, biopsy at 56 days (+/- 5 days is optional). Starting with adenocarcinoma patient #16, biopsy at 56 days is mandatory until tumor biopsies have been obtained on 20 individuals. Biopsy at 56 days is optional for squamous cell carcinoma patients.
e: All patients that initially responded to pembrolizumab can undergo an optional tumor biopsy on progression of disease at the end of the trial.
f: Only for women of child-bearing potential
g: Albumin, alkaline phosphatase, total bilirubin, bicarbonate, BUN, calcium, chloride, creatinine, glucose, potassium, total protein, SGOT [AST], SGPT [ALT], sodium.

h: Labs for screening are to be performed within 10 days prior to the first dose of trial treatment. Labs do not need to re-meet eligibility criteria if performed within 7 days of C1D1.
i: For women of reproductive potential, a serum pregnancy test must be performed within 72 hours prior to each cycle of trial treatment and 30 days post treatment. Pregnancy tests should be repeated if required by local guidelines.
j: After Cycle 3, Correlative Studies Blood Collection will be collected at the time of restaging.
k: Labs must be reviewed prior to treatment
l: Baseline blood sample can be collected within 7 days prior to C1D1. Must be collected prior to treatment on C1D1.

11.1 Survival Follow-up

Once a subject experiences confirmed disease progression or starts a new anti-cancer therapy, the subject moves into the survival follow-up phase and should be contacted by telephone every 12 weeks to assess for survival status until death, withdrawal of consent, or the end of the study, whichever occurs first, up to a maximum of 5 years.

11.1.1.1 Second Course Phase (Retreatment Period)

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

- **Either**
    - Stopped initial treatment with pembrolizumab after attaining an investigator-determined confirmed CR according to irRECIST, and
        - Was treated for at least 24 weeks with pembrolizumab before discontinuing therapy
        - Received at least two treatments with pembrolizumab beyond the date when the initial CR was declared

OR

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

AND

- Experienced an investigator-determined confirmed radiographic disease progression after stopping their initial treatment with pembrolizumab
- Did not receive any anti-cancer treatment since the last dose of pembrolizumab
- Has a performance status of 0 or 1 on the ECOG Performance Scale
- Demonstrates adequate organ function as detailed in Section 4.1

- Female subject of childbearing potential should have a negative serum or urine pregnancy test within 72 hours prior to receiving retreatment with study medication.

- Female subject of childbearing potential should be willing to use 2 methods of birth control or be surgically sterile, or abstain from heterosexual activity for the course of the study through 120 days after the last dose of study medication (Reference Section 6.3.2). Subjects of child bearing potential are those who have not been surgically sterilized or have been free from menses for > 1 year.

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

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

Subjects who restart treatment will be retreated at the same dose and dose interval as when they last received pembrolizumab. Treatment will be administered for up to one additional year. Visit requirements are outlined in Section 11 – Trial Flow Chart.

12. MEASUREMENT OF EFFECT

12.1 Antitumor Effect – Solid Tumors

For the purposes of this study, participants should be re-evaluated for response every 9 weeks (3 cycles) up to cycle 18. After cycle 18, restaging scans can be performed every 4 cycles at the discretion of the treating investigator.

Response and progression will be evaluated in this study using the new Immune-related Response Evaluation Criteria In Solid Tumors (irRECIST) criteria. [Wolchok et al. Clin Cancer Res 2009;15(23):7412-20] as administered by the Dana-Farber/Harvard Cancer Center Tumor Imaging Metrics Core.[19].

12.1.1 **Duration of Response**

Duration of overall response: The duration of overall response is measured from the time measurement criteria are met for CR or PR (whichever is first recorded) until the first date that recurrent or progressive disease is objectively documented (taking as reference for progressive disease the smallest measurements recorded since the treatment started, or death due to any cause. Participants without events reported are censored at the last disease evaluation).

Duration of overall complete response: The duration of overall CR is measured from the time measurement criteria are first met for CR until the first date that progressive disease is objectively documented, or death due to any cause. Participants without events reported are censored at the last disease evaluation.

Duration of stable disease: Stable disease is measured from the start of the treatment until the criteria for progression are met, taking as reference the smallest measurements recorded since the treatment started, including the baseline measurements.

12.1.2 Progression-Free Survival

Overall Survival: Overall Survival (OS) is defined as the time from registration to death due to any cause, or censored at date last known alive.

Progression-Free Survival: Progression-Free Survival (PFS) is defined as the time from registration to the earlier of progression or death due to any cause. Participants alive without disease progression are censored at date of last disease evaluation.

Time to Progression: Time to Progression (TTP) is defined as the time from registration to progression, or censored at date of last disease evaluation for those without progression reported.

12.1.3 Response Review

Central review of baseline and restaging scans will be performed by the DF/HCC Tumor Imaging Metrics Core.

13. DATA REPORTING / REGULATORY REQUIREMENTS

Adverse event lists, guidelines, and instructions for AE reporting can be found in Section 8.0 (Adverse Events: List and Reporting Requirements).

13.1 Data Reporting

13.1.1 Method

The ODQ will collect, manage, and perform quality checks on the data for this study.

13.1.2 Responsibility for Data Submission

Investigative sites within DF/HCC or DF/PCC are responsible for submitting data and/or data forms to the ODQ according to the schedule set by the ODQ.

13.2 Data Safety Monitoring

The DF/HCC Data and Safety Monitoring Committee (DSMC) will review and monitor toxicity and accrual data from this study. The committee is composed of clinical specialists with experience in oncology and who have no direct relationship with the study. Information that raises any questions about participant safety will be addressed with the Overall PI and study team.

The DSMC will review each protocol up to four times a year or more often if required to review toxicity and accrual data. Information to be provided to the committee may include: up-to-date participant accrual; current dose level information; DLT information; all grade 2 or higher unexpected adverse events that have been reported; summary of all deaths occurring with 30 days of intervention for Phase I or II protocols; for gene therapy protocols, summary of all deaths while being treated and during active follow-up; any response information; audit results, and a summary provided by the study team. Other information (e.g. scans, laboratory values) will be provided upon request.

14. STATISTICAL CONSIDERATIONS

14.1 Study Design/Endpoints

14.1.1 Primary Objective

The primary endpoint of this study is to determine the major response rate (CR + PR) of patients with refractory esophageal adenocarcinoma to pembrolizumab. We expect a response rate of approximately 10-15% for patients with refractory metastatic esophageal adenocarcinoma, similar to what was seen in the Keynote– - 059 study (DFCI Protocol 15-073).

We propose a one-stage study (n=40) including both PD-L1 positive and PD-L1 negative patients. With this sample size, we will have 80% power to reject the null hypothesis that the response rate is 7% or lower if the true response rate is 22% or higher, using a one-sided binomial test with 5% type 1 error. The null hypothesis is rejected if there are 7 or more responses.

We will also perform an exploratory analysis in patients with esophageal squamous cell carcinoma, a cancer that accounts for only approximately 10-20% of the patients seen in our practice. We will enroll no more than 10 patients of this histologic subtype.

Overall survival and progression-free survival will include all evaluable adenocarcinoma patients, will be measured from the date of registration, and will be calculated using the method of Kaplan and Meier.

14.1.2 Analyses of Correlative Endpoints

Subpopulations of PBMCs will be isolated, including but not limited to dendritic cells,

T cells, and B cells. Phenotype changes in these cell populations by flow cytometry will be determined as a function of treatment. These include regulatory and effector immune panels, naïve and memory CD4, CD8 and NK lymphocyte populations. Given its importance in immune regulation and association, we will evaluate Tie-2 expressing monocytes (TEM).

For the analysis of cytokines, chemokines, and immune cell populations from serum or blood, data will be analyzed in longitudinal measurements for all patients. Serum marker levels will be summarized descriptively and graphically. The time course of expression levels will also be summarized graphically by patient and time of disease progression.

A pretreatment tumor biopsy will be utilized for analysis of tissue biomarkers. Pre-treatment biomarker expression, using appropriate IHC, Aperio scoring, or H-score will be reported and summarized using descriptive methods. We will also summarize descriptively pre-treatment biomarker levels according to response (PD vs. non-PD). For a sample size of 32 patients, formal statistical inference relating pre-treatment biomarker levels to response will be of low power and will be capable of detecting only a strong signal. However, we will explore the prognostic ability of biomarker scoring by retrospectively dividing the patient sample according to PD vs. non-PD.

Pre-treatment immune cell infiltration and biomarker changes will be summarized graphically and using descriptive methods. Immune cell infiltration sub-populations will also be dichotomized into positive and negative at 10% (negative: $< 10\%$, positive: $\geq 10\%$).

15. PUBLICATION PLAN

The results should be made public within 24 months of reaching the end of the study. The end of the study is the time point at which the last data items are to be reported, or after the outcome data are sufficiently mature for analysis, as defined in the section on Sample Size, Accrual Rate and Study Duration. If a report is planned to be published in a peer-reviewed journal, then that initial release may be an abstract that meets the requirements of the International Committee of Medical Journal Editors. A full report of the outcomes should be made public no later than three (3) years after the end of the study.

REFERENCES

1. American Cancer Society. *Cancer Facts & Figures 2014*. Atlanta: American Cancer Society; 2014.
2. American Cancer Society. Global Cancer Facts & Figures *2nd Edition. Atlanta: American Cancer Society; 2011.*
3. Chau I, Norman AR, Cunningham D et al. Multivariate prognostic factor analysis in locally advanced and metastatic esophago-gastric cancer--pooled analysis from three multicenter, randomized, controlled trials using individual patient data. J Clin Oncol. 2004 Jun 15;22(12):2395-403.
4. Ford HE, Marshall A, Janowitz T et al. Docetaxel versus active symptom control for refractory oesophagogastric adenocarcinoma (COUGAR-02): an open-label, phase 3 randomised controlled trial. Lancet Oncol. 2014 Jan;15(1):78-86.
5. Fuchs CS, Tomasek J, Yong CJ et al. Ramucirumab monotherapy for previously treated advanced gastric or gastro-oesophageal junction adenocarcinoma (REGARD): an international, randomised, multicentre, placebo-controlled, phase 3 trial. The Lancet, Volume 383, Issue 9911, Pages 31 - 39, 4 January 2014.
6. Wilke H, Muro K, Van Cutsem E, et al. Ramucirumab plus paclitaxel vers placebo plus paclitaxel in patients with previously treated advanced gastric or gastro-oesophageal junction adenocarcinoma (RAINBOW): a double-blind randomised phase 3 trial. The Lancet Oncology, Volume 15, Issue 11, Pages 1224 - 1235, October 2014.
7. Robert C, Ribas A, Wolchok JD, Hodi FS, Hamid O, Kefford R, Weber JS, Joshua AM, Hwu W-J, Gangadhar TC, Patnaik A, Dronca R, Zarour H, Joseph RW, Boasberg P, Chmielowski B, Mateus C, Postow MA, Gergich K, Elassaiss-Schaap J, Li XN, Iannone R, Ebbinghaus SW, Kang SP, Daud A. Anti-programmed-death-receptor-1 treatment with pembrolizumab in ipilimumab-refractory advanced melanoma: A randomised dose-comparison cohort of a phase 1 trial. *The Lancet*;384:1109-1117.
8. Hodi, F.S., S.J. O'Day, D.F. McDermott, R.W. Weber, J.A. Sosman, J.B. Haanen, R. Gonzalez, C. Robert, D. Schadendorf, J.C. Hassel, W. Akerley, A.J.M. van den Eertwegh, J. Lutzky, P. Lorigan, J.M. Vaubel, G.P. Linette, D. Hogg, C.H. Ottensmeier, C. Lebbé, C. Peschel, I. Quirt, J.I. Clark, J.D. Wolchok, J.S. Weber, J. Tian, M.J. Yellin, G.M. Nichol, A. Hoos, and W.J. Urba. 2010. Improved Survival with Ipilimumab in Patients with Metastatic Melanoma. *New England Journal of Medicine*. 363:711-723.
9. Brahmer, J.R., C.G. Drake, I. Wollner, J.D. Powderly, J. Picus, W.H. Sharfman, E. Stankevich, A. Pons, T.M. Salay, T.L. McMiller, M.M. Gilson, C. Wang, M. Selby, J.M. Taube, R. Anders, L. Chen, A.J. Korman, D.M. Pardoll, I. Lowy, and S.L. Topalian. 2010. Phase I Study of Single-Agent Anti–Programmed Death-1 (MDX-1106) in Refractory Solid Tumors: Safety, Clinical Activity, Pharmacodynamics, and Immunologic Correlates. *Journal of Clinical Oncology*. 28:3167-3175.
10. Hamid, O., C. Robert, A. Daud, F.S. Hodi, W.-J. Hwu, R. Kefford, J.D. Wolchok, P. Hersey, R.W. Joseph, J.S. Weber, R. Dronca, T.C. Gangadhar, A. Patnaik, H. Zarour, A.M. Joshua, K. Gergich, J. Elassaiss-Schaap, A. Algazi, C. Mateus, P. Boasberg, P.C. Tumeh, B. Chmielowski, S.W. Ebbinghaus, X.N. Li, S.P. Kang, and A. Ribas. 2013. Safety and Tumor Responses with Lambrolizumab (Anti–PD-1) in Melanoma. *New England Journal of Medicine*. 369:134-144.

11. Robert, C., L. Thomas, I. Bondarenko, S. O'Day, J. Weber, C. Garbe, C. Lebbe, J.-F. Baurain, A. Testori, J.-J. Grob, N. Davidson, J. Richards, M. Maio, A. Hauschild, W.H. Miller, P. Gascon, M. Lotem, K. Harmankaya, R. Ibrahim, S. Francis, T.-T. Chen, R. Humphrey, A. Hoos, and J.D. Wolchok. 2011. Ipilimumab plus Dacarbazine for Previously Untreated Metastatic Melanoma. *New England Journal of Medicine*. 364:2517-2526.
12. Topalian, S.L., M. Sznol, D.F. McDermott, H.M. Kluger, R.D. Carvajal, W.H. Sharfman, J.R. Brahmer, D.P. Lawrence, M.B. Atkins, J.D. Powderly, P.D. Leming, E.J. Lipson, I. Puzanov, D.C. Smith, J.M. Taube, J.M. Wigginton, G.D. Kollia, A. Gupta, D.M. Pardoll, J.A. Sosman, and F.S. Hodi. 2014. Survival, Durable Tumor Remission, and Long-Term Safety in Patients With Advanced Melanoma Receiving Nivolumab. *Journal of Clinical Oncology*. 32:1020-1030.
13. Ott PA, Hodi FS, Robert C. Ctla-4 and pd-1/pd-l1 blockade: New immunotherapeutic modalities with durable clinical benefit in melanoma patients. *Clinical Cancer Research* 2013;19:5300-5309.
14. Ohigashi Y, Masayuki Sho M, Yamada Y et al. Clinical Significance of Programmed Death-1Ligand-1and Programmed Death-1Ligand-2 Expression in HumanEsophageal CancerClin Cancer Res 2005;11:2947-2953.
15. Ralph C, Elkord E, Burt DJ, O'Dwyer JF, Austin EB, Stern PL, Hawkins RE, Thistlethwaite FC. Modulation of lymphocyte regulation for cancer therapy: A phase ii trial of tremelimumab in advanced gastric and esophageal adenocarcinoma. *Clinical Cancer Research* 2010;16:1662-1672
16. Muro K, Bang Y, Shankaran V, et al. Relationship between PD-L1 expression and clinical outcomes in patients with advanced gastric cancer treated with the anti-PD-1 monoclonal antibody Pembrolizumab (MK-3475) in KEYNOTE-012. Presented by K. Muro at the GI Cancers Symposium in San Francisco, CA on January 16th, 2015.
17. Doi T, Piha-Paul S, Jalal S et al. Pembrolizumab (MK-3475) for patients with advanced esophageal carcinoma: preliminary results from KEYNOTE-028. Presented by T. Doi at the ASCO Symposium in Chicago, IL on March 31st, 2015.
18. Turner JR, Shen LH, Crum CP, Dean PJ, Odze RD. Low prevalence of human papillomavirus infection in esophageal squamous cell carcinomas from North America: analysis by a highly sensitive and specific polymerase chain reaction-based approach. Hum Pathol. 1997 Feb;28(2):174-8.
19. Wolchok, J.D., A. Hoos, S. O'Day, J.S. Weber, O. Hamid, C. Lebbé, M. Maio, M. Binder, O. Bohnsack, G. Nichol, R. Humphrey, and F.S. Hodi. 2009. Guidelines for the Evaluation of Immune Therapy Activity in Solid Tumors: Immune-Related Response Criteria. *Clinical Cancer Research*. 15:7412-7420.
20. Ribas, A, Robert, C, Hodi, S et al. 1Proc Am Soc Clin Oncol. 2015; 33 (abstract 3001.)
21. Muro, K. et al. Pembrolizumab for patients with PD-L1-positive advanced gastric cancer (KEYNOTE-012): a multicentre, open-label, phase 1b trial. Lancet Oncol 17, 717-26 (2016).

APPENDIX A PERFORMANCE STATUS CRITERIA

ECOG Performance Status Scale		**Karnofsky Performance Scale**	
Grade	Descriptions	Percent	Description
0	Normal activity. Fully active, able to carry on all pre-disease performance without restriction.	100	Normal, no complaints, no evidence of disease.
		90	Able to carry on normal activity; minor signs or symptoms of disease.
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).	80	Normal activity with effort; some signs or symptoms of disease.
		70	Cares for self, unable to carry on normal activity or to do active 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.	60	Requires occasional assistance, but is able to care for most of his/her needs.
		50	Requires considerable assistance and frequent medical care.
3	In bed >50% of the time. Capable of only limited self-care, confined to bed or chair more than 50% of waking hours.	40	Disabled, requires special care and assistance.
		30	Severely disabled, hospitalization indicated. Death not imminent.
4	100% bedridden. Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair.	20	Very sick, hospitalization indicated. Death not imminent.
		10	Moribund, fatal processes progressing rapidly.
5	Dead.	0	Dead.

APPENDIX B EVENTS OF CLINICAL INTEREST

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 [1-11], 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 sponsor 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 the database.

Table 2: 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	Hyperglycemia, if ≥Grade 3 and associated with ketosis or metabolic acidosis (DKA)	
Endocrine (reported as ECI)		
Type 1 diabetes mellitus (if new onset)		
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 (ALT and/or AST)
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 document, along with site requirements for reporting these events to the Sponsor. 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 Sponsor 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.

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).

3. ECI CATEGORIES AND TERMS

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

3.1 Pneumonitis

The following AE terms, if considered ≥ Grade 2, are considered ECIs and should be reported to the Sponsor 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.

3.2 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 Sponsor 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 for greater than 3 days, 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 persists for > 1 week):

- 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.

3.3 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 Sponsor 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 2-4 events:

- Report as ECI if appropriate
- Hold pembrolizumab

- Rule out infection and sepsis with appropriate cultures and imaging.
- 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.
- Hypophysitis with clinically significant adrenal insufficiency and hypotension, dehydration, and electrolyte abnormalities (such as hyponatremia and hyperkalemia) constitutes adrenal crisis.
- Consultation with an endocrinologist may be considered.

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 hyperthyroidism, Grade 2-4 hypothyroidism events:

- 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 hyperthyroidism events:
- Report as ECI
- Discontinue pembrolizumab.
- Manage as per Grade 3

Type 1 diabetes mellitus (if new onset) and ≥ Grade 3 Hyperglycemia
The following AE terms are considered ECIs and should be reported to the Sponsor within 24 hours of the event:
- Type I diabetes mellitus (T1DM), if new onset, including diabetic ketoacidosis (DKA)
- Grade 3 or higher hyperglycemia, if associated with ketosis (ketonuria) or metabolic acidosis (DKA).

Immune-mediated diabetes may present as new onset of Type 1 diabetes or an abrupt worsening of pre-existing diabetes associated with laboratorial evidence of beta cell failure. All attempts should be made to rule out other causes such as type 2 diabetes mellitus (T2DM), T2DM decompensation, steroid-induced diabetes, physiologic stress-induced diabetes, or poorly controlled pre-existing diabetes (either T1DM or T2DM), but events meeting the above criteria should be reported as ECIs regardless of etiology. The patients may present with hyperglycemia (abrupt onset or abrupt decompensation) with clinical evidence of diabetic ketoacidosis or laboratory evidence of insulin deficiency, such as ketonuria, laboratory evidence of metabolic acidosis, or low or undetected c-peptide.

Course of Action
T1DM should be immediately treated with insulin.

T1DM or Grade 3-4 Hyperglycemia events:
- Report as ECI if appropriate (see Table 1)
- Hold pembrolizumab for new onset Type 1 diabetes mellitus or Grade 3-4 hyperglycemia associated with evidence of beta cell failure, and resume pembrolizumab when patients are clinically and metabolically stable.
- Insulin replacement therapy is recommended for Type I diabetes mellitus and for Grade 3-4 hyperglycemia associated with metabolic acidosis or ketonuria.
- Evaluate patients with serum glucose and a metabolic panel, urine ketones, glycosylated hemoglobin, and C-peptide.
- Consultation with an Endocrinologist is recommended.
- Consider local testing for islet cell antibodies and antibodies to GAD, IA-2, ZnT8, and insulin may be obtained.

3.4 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 Sponsor 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

3.5 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 Sponsor 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).
    - 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

3.6 Neurologic
The following AE terms, regardless of grade, are considered ECIs and should be reported to the Sponsor 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.

3.7 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 Sponsor 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

3.8 Renal

The following AEs if ≥ Grade 2 are considered ECIs and should be reported to the Sponsor 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.

3.9 Skin
Rash and Pruritus
The following AEs should be considered as ECIs, if ≥ Grade 3 and should be reported to the Sponsor 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 Sponsor 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.

1.1.1 3.9.1. Immediate Evaluation for Potential Skin ECIs

A. <u>Photographs</u>:
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 Sponsor may request copies of photographs. The local study contact (e.g., CRA) will provide guidance to the site, if needed.

B. <u>Past Medical History</u>:
Collect past medical history relevant to the event, using the questions in Appendix C (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 D (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 E (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.

3.10 Other
The following AEs, regardless of grade, are considered ECIs and should be reported to the Sponsor 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

3.11 Infusion Reactions

The following AE terms, regardless of grade, are considered ECIs and should be reported to the Sponsor 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).
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		

3.12 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.

4. APPENDIX B 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

APPENDIX C – 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

APPENDIX D – 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

APPENDIX E – 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?
_____

PHARMACY MANUAL

PEMBROLIZUMAB (MK-3475)

KEYNOTE 291

Merck Sharp & Dohme Corp., NJ, USA

SUMMARY OF REVISIONS

The following are a list of revisions to the Pharmacy Manual for pembrolizumab (MK-3475):

Revision Date	Revisions to Document	New Version #:
10-Dec-14	Global change: updated MK-3475 to pembrolizumab	2.0
10-Dec-14	Global change: Inserted header Pembrolizumab (MK-3475) Pharmacy Manual for Investigational Studies	2.0
10-Dec-14	Expanded table of contents	2.0
10-Dec-14	Removed trailing zeros after decimal points	2.0
10-Dec-14	Section 2: Revised footnote 1 in trial treatment table	2.0
10-Dec-14	Section 3.1: Removed text, "The pH is maintained using a 10 mM histidine buffer"	2.0
10-Dec-14	Section 3.2: Added text to emphasize normal saline as preferred diluent Insert cautionary statement regarding drug transport and delivery Inserted text that any deviation from the guidance listed in this manual, must be discussed with sponsor	2.0
10-Dec-14	Section 3.3: Clarified weight based dosing calculation for changes in weight (10% rule) Removed calculation for 200 mg fixed dosing	2.0
10-Dec-14	Section 3.4: Clarified preferred method of dose preparation as volumetric reconstitution Clarified reconstitution technique.	2.0
10-Dec-14	Section 3.6:	2.0

	Inserted text stating infusion rates may differ for infusion reactions Inserted text that entire bag needs to be dosed during infusion Removed text regarding excess volume preparation Added text to document volume administered per DEG instructions	
10-Dec-14	Section 4.2 Added text to emphasize normal saline as preferred diluent Insert cautionary statement regarding drug transport and delivery Inserted text that any deviation from the guidance listed in this manual, must be discussed with sponsor	2.0
10-Dec-14	Section 4.3: Clarified weight based dosing calculation for changes in weight (10% rule) Removed calculation for 200 mg fixed dosing	2.0
10-Dec-14	Section 4.4: Clarified preferred method of dose preparation as volumetric method	2.0
10-Dec-14	Section 4.5: Inserted text stating infusion rates may differ for infusion reactions Inserted text that entire bag needs to be dosed during infusion Removed text regarding excess volume preparation Added text to document volume administered per DEG instructions	2.0

21-Oct-15	Section 2: Text added to footnote 2 for sourcing and recording of lot number, manufacturer, and expiry date.	3.0
21-Oct-15	Section 3.2: Added guidance for collection of the following diluent information (manufacturer, lot, and expiry). Removed the following text, " unless instructed by the sponsor in writing" in the following sentence : Pembrolizumab (MK-3475) SHOULD NOT BE MIXED WITH OTHER DILUENTS unless instructed by the SPONSOR in writing. Added diluted drug product in the following sentence: Sites should follow their SOPs for drug transport and delivery, with all possible effort to minimize agitation of the reconstituted and diluted drug product between the pharmacy and the clinic	3.0
21-Oct-15	Section 3.3: Clarified re-calculation of weight based dosing guidance.	3.0
21-Oct-15	Section 3.5 Additional text added for concentration range requirements.	3.0
21-Oct-15	Section 3.7: Removed chemotherapeutic waste designation for solution remaining in vials that must be discarded.	3.0

21-Oct-15	Section 4.1: Text added about cap color.	3.0
21-Oct-15	Section 4.2: Added guidance for collection of the following diluent information (manufacturer, lot, and expiry).	3.0
21-Oct-15	Section 4.3: Clarified re-calculation of weight based dosing guidance.	3.0
21-Oct-15	Section 4.4: Additional text added for concentration range requirements.	3.0
21-Oct-15	Section 4.5: Added the following text regarding infusion set materials: *Contact Sponsor for materials not listed above	3.0
21-Oct-15	Section 4.6: Added text for discarding used vials.	3.0
28-Feb-17	Section 2.0: Updated footnote in trial treatment table to include SmPC and guidance regarding locally sourced drug.	4.0
28-Feb-17	Section 3.1	4.0

	Added text stating formulation is latex free	
28-Feb-17	Section 3.2 Added rounding guidance. Added guidance on temperature excursions. Clarified 4 hour room temperature time limitation. Updated language around particulates.	4.0
28-Feb-17	Section 3.3 Updated units from lb to kg to align with weight based dosing examples.	4.0
28-Feb-17	Section 3.4 Clarified use of biosafety cabinets. Updated gravimetric dosing guidance. Added statement for use of spikes. Updated text for potential for foaming.	4.0
28-Feb-17	Section 3.5 Deleted duplicate text regarding use of biosafety cabinets. Updated text regarding formation of particulates.	4.0
28-Feb-17	Section 3.6 Added guidance for preparation of placebo.	4.0
28-Feb-17	Section 3.7 Added instructional text that states 250mL volume is only applicable to weight based studies.	4.0
28-Feb-17	Section 3.8	4.0

	Clarified instructions for return of un-used vials.	
28-Feb-17	Section 4.1 Added text stating formulation is latex free. Updated cap color for liquid formulation. Added text regarding overfill volume.	4.0
28-Feb-17	Section 4.2 Added rounding guidance. Added guidance on temperature excursions. Clarified 4 hour room temperature time limitation. Updated language around particulates.	4.0
28-Feb-17	Section 4.3 Updated units from lb to kg to align with weight based dosing examples.	4.0
28-Feb-17	Section 4.4 Clarified use of biosafety cabinets. Updated gravimetric dosing guidance. Added statement for use of spikes. Updated text for potential for foaming.	4.0
28-Feb-17	Section 4.5 Added guidance for preparation of placebo.	4.0
28-Feb-17	Section 4.6 Added instructional text that states 250mL volume is only applicable to weight based studies.	4.0

	Additional text added regarding formation of foam.	
28-Feb-17	Section 4.7 Clarified instructions for return of un-used vials.	4.0
21-Mar-2018	Section 1.0: Added unblinded clinical scientist to contact list Updated CDS title to CS Updated IVRS to IRT throughout document	5.0
21-Mar-2018	Section 3.2 Added text for temperature excursions that temperature data needs to be included in clinical complaint. Clarified for blinded studies that uCRA should be contacted for temperature excursions. Updated the room temperature allowance from 4 hours to 6 hours and clarified fridge time allowance. Clarified the start of room temperature time.	5.0
21-Mar-2018	Section 3.6 Revised flushing statement. Section 3.7 Updated drug destruction instructions.	5.0
21-Mar-2018	Section 4.2 Added text for temperature excursions that temperature data needs to be included in clinical complaint.	5.0

	Clarified for blinded studies that uCRA should be contacted for temperature excursions. Updated the room temperature allowance from 4 hours to 6 hours and clarified fridge time allowance. Clarified the start of room temperature time.	
21-Mar-2018	Section 4.4 Updated room temperature time allowance to 6 hours and clarified cumulative storage time.	5.0
21-Mar 2018	Section 4.5: Revised flushing statement. Section 4.6: Updated drug destruction instructions.	5.0

TABLE OF CONTENTS

Contents

1. Contact List

Merck Sharp & Dohme Corp., NJ, USA (Pharmacy Manual questions only)

For questions regarding the details outlined within this Pharmacy Manual, please contact your clinical scientist (CS)

Waheeda Sirah, Associate Prin. Scientist
Phone: 1-732-594-2230
E-mail: waheeda_sirah@merck.com

2. Trial Treatment

Trial Treatment Table

Drug	Dose/Potency	Dose Frequency	Route of Administration	Regimen/ Treatment Period	Use
pembrolizumab (MK-3475) [1]	2 or 10 mg/kg	Q3W	IV infusion	Day 1 of each cycle[1]	Experimental
[1] Refer to protocol for specific study drug administration sequence for combination studies of pembrolizumab (MK-3475) and chemo/immunotherapy					

3. Drug Preparation – Pembrolizumab (MK-3475) Solution for Infusion

3.1 DRUG PRODUCT

Pembrolizumab (MK-3475) Solution for Infusion, 100 mg/ 4 mL vial

- Pembrolizumab (MK-3475) Solution for Infusion is a sterile, non-pyrogenic aqueous solution supplied in single-use Type I glass vial containing 100 mg/4 mL of pembrolizumab (MK-3475). The product is preservative-free, latex free solution which is essentially free of extraneous particulates.

- Cap color of MK-3475 (Pembrolizumab) 100 mg vials:

    - Both red, salmon, and blue color caps may be used. Though the cap color may be different, the product inside the vial is the same MK-3475 drug product.

- Pembrolizumab (MK-3475) Solution for Infusion vials are filled to a target of 4.25mL (106.25mg) to ensure recovery of 4.0mL (100mg).

3.2 STABILITY AND HANDLING OF DRUG PRODUCT

- **Pembrolizumab (MK-3475) Solution for Infusion, 100 mg/ 4 mL vial**: pembrolizumab (MK-3475) Solution for Infusion vials should be stored at refrigerated conditions 2 – 8 °C (36 - 46 °F) and protected from light.

- To determine whether to report a temperature excursion, the temperature values should be rounded to whole numbers.

- <u>Rounding:</u>

    - Decimal values from 0.1 to 0.4 round down to the nearest whole number

(e.g., 8.3 = 8)
- Decimal values from 0.5 to 0.9 round up to the nearest whole number (e.g., 8.7 = 9)

- Then compare the rounded values to the required temperature range to determine if there's an excursion.
- All temperature excursions, however small, must be reported by the site to the Clinical Complaint Intake mailbox (clinical.complaints.intake@merck.com) for investigation within 1 business day using the Clinical Supply Complaint & GCP Inquiry Form (excel version) and attached temperature data. All Clinical Supply stock that is subject to an investigation must be placed in quarantine and remain unavailable to dispense to patients until disposition has been determined.
- Please note temperature excursions after drug product is prepared are out of scope of the clinical complaint process. Please contact HQ clinical study team for further guidance.

Note: vials should be stored in the original box to ensure the drug product is protected from light.

- Pembrolizumab (MK-3475) infusion solutions should be prepared in **0.9% Sodium Chloride Injection, USP** (normal saline) or regional equivalent or 5% Dextrose Injection, USP (5% dextrose) or regional equivalent and the final concentration of pembrolizumab (MK-3475) in the infusion solutions should be between 1 mg/mL and 10 mg/mL.

- Please note, the preferred diluent is 0.9% Sodium Chloride and 5% dextrose is only permissible if normal saline is not available.

- Local guidelines should be followed for collection of diluent information such as manufacturer, lot and expiry. When the diluent is provided by Merck, the drug accountability log should be used for collection of diluent information.

- Pembrolizumab (MK-3475) SHOULD **NOT** BE MIXED WITH OTHER DILUENTS.

- Pembrolizumab (MK-3475) solutions may be stored at room temperature for a cumulative time of up to 6 hours. The 6 hour countdown begins when the vial is pierced, and includes room temperature storage of admixture solutions in the IV bags and the duration of infusion. (Please note this 6 hour timeframe is to provide a microbial control strategy. The microbial clock only starts when the product stopper is pierced and not when the vial is removed from the refrigerator.)

- In addition, IV bags may be stored under refrigeration at 2 °C to 8 °C (36 °F to 46 °F), total cumulative storage time at room temperature and refrigeration should not exceed 24 hours.

- If refrigerated, allow the IV bags to come to room temperature prior to use.

- Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration. Discard the drug product vial if visible particles are observed.

- Sites should follow their SOPs for drug transport and delivery, with all possible effort to minimize agitation of the drug product between the pharmacy and the clinic

- **DO NOT USE PEMBROLIZUMAB (MK-3475) IF DISCOLORATION IS OBSERVED**.

- **DO NOT SHAKE OR FREEZE THE VIAL(S).**

- **DO NOT ADMINISTER THE PRODUCT AS AN INTRAVENOUS (IV) PUSH OR BOLUS.**

- **DO NOT COMBINE, DILUTE OR ADMINISTER IT AS AN INFUSION WITH OTHER MEDICINAL PRODUCTS.**

- **Any departure from the guidance listed in this manual, must be discussed with sponsor**

3.3 DOSE CALCULATION

Follow directions applicable to the dose level (mg/kg) of the study.

<u>200 mg Fixed Dose</u>

- **2 vials (100 mg/4 mL)**
- **8 mL total**

4.4 PREPARATION OF INFUSION SOLUTION

- Aseptic technique must be strictly observed throughout the preparation procedure

- Use of a biosafety cabinet is preferred since no anti-microbial preservative is present in the product; however, it is not mandatory unless specified by site standard operating procedure.

- Equilibrate required number of pembrolizumab MK-3475 vials to room temperature

- The preferred method of dose preparation is the volumetric method

- Sponsor recommends reconstitution and administration of pembrolizumab (MK-3475) that follows the parameters in this manual, however if use of gravimetric preparation is mandatory due to local site procedures, the following requirements must be satisfied and documented:
    - Draw the required volume up to 4.0 mL (100 mg) of pembrolizumab from each vial
    - Limit the number of punctures of each vial to one

- For gravimetric preparation method using density of pembrolizumab solution, a value of 1.03 g/mL should be used

- Merck does not support methods of preparation of non-Merck agents beyond what is stated in the product literature. Sites should reference the SmPCs or packaging inserts for preparation instructions

- If the site procedures require use of spikes or other closed system transfer devices (CSTDs), please contact sponsor for approval

- Choose a suitable infusion bag size so that the following conditions are met:
    - Concentration of pembrolizumab MK-3475 is between 1 mg/mL and 10 mg/mL
    - The infusion volume to bag capacity ratio should not be less than 0.3. In other words, the bag must be filled to at least 30% of its capacity.

- Choose a suitable infusion bag material. The bag may be empty or it may contain normal saline The following infusion bag materials are compatible with pembrolizumab (MK-3475):

    - PVC plasticized with DEHP

  - Non-PVC (polyolefin)
  - EVA
  - PE lined polyolefin

*Contact Sponsor for materials not listed above

- Calculate the volume of pembrolizumab (MK-3475) and normal saline required to prepare the infusion (admixture) bag

  Volume of pembrolizumab (MK-3475) (mL) = required dose amount (mg) / 25 (mg/mL)

  Volume of normal saline = total infusion volume – volume of pembrolizumab (MK-3475) from above

- If a bag pre-filled with normal saline is being used, remove the excess volume of normal saline using a sterile syringe (Polypropylene, latex-free) attached to a suitable needle. Keep in consideration the excess bag fill volume as well as the volume of pembrolizumab (MK-3475) to be added to the bag to prepare the infusion solution. This helps ensure that the concentration in the bag can be accurately calculated and falls within the acceptable range of 1 mg/mL to 10 mg/mL. If the site would like to proceed without removing excess saline they must ensure that the concentration of MK-3475 would still fall within acceptable range.

- If an empty bag is being used, withdraw the necessary volume of normal saline from another appropriate bag and inject into the empty bag. Keep in consideration the volume of pembrolizumab (MK-3475) to be added to the bag to prepare the infusion solution.

- Withdraw the required volume of pembrolizumab (MK-3475) from the vial(s) (up to 4 mL from each vial) using a sterile syringe attached to a suitable needle. The vial(s) may need to be inverted to remove solution.

  Volume of pembrolizumab (MK-3475) (mL) = required dose amount (mg) / 25 (mg/mL)

  Note: If it is necessary to use several vials, it is advisable to withdraw from several vials into a suitable size single use syringe using a new needle for each vial.

- Add the required pembrolizumab (MK-3475) into the infusion IV bag containing normal saline and gently invert the bag 10-15 times to mix the solution.

- Pembrolizumab (MK-3475) solutions may be stored at room temperature for a cumulative time of up to 6 hours. This includes room temperature storage of admixture solutions in the IV bags and the duration of infusion.

- In addition, IV bags may be stored under refrigeration at 2 °C to 8 °C (36 °F to 46 °F), total cumulative storage time at room temperature and refrigeration should not exceed 24 hours.

- If refrigerated, allow the IV bags to come to room temperature prior to use.

- If the infusion bag is excessively handled or shaken, particulates may form. If this occurs discard the bag and create a new bag taking care not to shake. Please contact your HQ clinical study team if particulates are noticed for further instructions. Be prepared to provide the following information:
    - IV bag manufacture, lot and expiry
    - Target volume of admixture solution in the IV bag (e.g. 100 mL, 200 mL etc.)
    - Amount of drug product (mL or mg) added to the bag
    - Drug product lot
    - Brief description of the nature of visible particles (color, shape, size, numbers etc.).

- **DO NOT FREEZE THE PEMBROLIZUMAB (MK-3475) INFUSION SOLUTION.**

- Discard any unused portion left in the vial as the product contains no preservative

3.5 ADMINISTRATION

- Pembrolizumab (MK-3475) infusions should be administered in 30 minutes, with a window of -5 and +10 minutes, using an infusion pump. A central catheter is not required for infusion; however, if a subject has a central venous catheter in place, it is recommended that it be used for the infusion.

- The following infusion set materials are compatible with (pembrolizumab) MK-3475:

    - PVC Infusion set that is plasticized using DEHP
    - PVC and tri-(2-ethylhexyl) trimellitate (TOTM) infusion set
    - Polyethylene lined PVC infusion set
    - PVC Infusion set that is plasticized using Di-2-ethylhexyl Terephthalate (DEHT)
    - Polyurethane set

    *Contact Sponsor for materials not listed above

- A sterile, non-pyrogenic, low-protein binding 0.2 to 5 µm in-linefilter made of polyethersulfone (PES) must be used during administration to remove any adventitious particles. If the infusion set does not contain 0.2 to 5 µm in-line filter, it is recommended to use 0.2 to 5 µm add-on filter which may contain an extension line (Note: the materials of the extension line and filter should be as mentioned above).

- Attach the infusion line to the pump and prime the line, either with normal saline (at least 25 mL) or with infusion solution as per local SOP, before starting the infusion.

- Infuse pembrolizumab (MK-3475) over approximately 30 minutes, with a window of -5 and +10 minutes, through a peripheral line or indwelling catheter.

- Ensure the entire contents of the bag are dosed and all remaining drug solution in the line is administered through saline flushing.

- Document volume administered according to data entry guidelines.

- *In case of infusion reactions, infusion rate may differ; refer to protocol for specific instructions.*

- Whenever possible, the lowest infusion rate should be used that will allow completion of the infusion within the 30 minutes.

- Maximum rate of infusion should not exceed 6.7 mL/min. through a peripheral line or indwelling catheter.
- However, when it is necessary to infuse a larger volume (i.e. 250 mL), the flow rate may go as high as 10 mL/min (maximum) in order to keep the infusion within the window as defined above.

- **DO NOT CO-ADMINISTER OTHER DRUGS THROUGH THE SAME INFUSION LINE.**

- **UNUSED INFUSION SOLUTION FOR INJECTION SHOULD NOT BE USED FOR ANOTHER INFUSION OF THE SAME SUBJECT OR DIFFERENT SUBJECT.**

- **Caution: Do not shake the vials/bags otherwise this may result in formation of foam. If foam is noticed in either vial or bag, the drug product will need to be discarded. A new preparation should be made, taking care not to shake or agitate the product.**

3.6 RETURN AND DISCARDING OF PEMBROLIZUMAB (MK-3475) VIALS

Unused pembrolizumab (MK-3475) Solution for Infusion vial(s) shall be returned to the designated facility for destruction.

- For US clinical sites, return to the central depot that shipped supplies to the site:
  - Fisher Clinical Services, Return and Destruction Center, 700B Nestle Way, Breinigsville, PA 18031
  - Merck & Co., Inc. 770 Sumneytown Pike B-78A West Point, PA 19486
- For ex-US clinical sites, consult with local Merck subsidiary for facility address.

- Solution remaining in a used vial should be discarded according to your local procedures.

- Any information on the label identifying the subject should be redacted prior to returning the study medication.

DANA-FARBER CANCER INSTITUTE
Nursing Protocol Education Sheet

Protocol Number:	**16-293**
Protocol Name:	A Phase II Study of Pembrolizumab in Refractory Advanced Esophageal Cancer
DFCI Site PI:	Peter Enzinger, MD
DFCI Research Nurse:	Christopher Graham, RN, BSN ; Laura Casadonte, RN, BSN, OCN

Page the DFCI research nurse or DFCI site PI if there are any questions/concerns about the protocol.
Please also refer to ONC 15: Oncology Nursing Protocol Education Policy
***** Remember to check the ALERT PAGE*****

SPECIAL NURSING CONSIDERATIONS UNIQUE TO THIS PROTOCOL

Study Design	• ***Pembrolizumab*** is a potent and highly selective humanized monoclonal antibody (mAb) of the IgG4/kappa isotype designed to directly block the interaction between PD-1 and its ligands, PD-L1 and PD-L2 (Section 3.2) • A cycle is defined as 3 weeks (Section 1.1)
Dose Calc.	• ***Pembrolizumab*** is dosed in mg and is a fixed dose (Section 6.1, Table 2)
Study Drug Administration	Agent *Administration* Guidelines are found in Section 6 • ***Pembrolizumab:*** o Administered via IV infusion over 30 minutes (-5/+10 minutes) on Day 1 of each 3 week cycle (Section 6.1.1) o Required to thaw to room temperature prior to administration (Pharmacy Manual)
Dose Mods & Toxicity	*Criteria to Treat, Dose Modifications/Dosing Delay for Toxicity* are outlined in Section 7 • This protocol uses NCI CTCAE criteria, version 4.0 (Section 8.1)
Con Meds	*Concomitant Therapy* Guidelines are in Section 6.2 • Acceptable concomitant medications can be found in Section 6.2.1 • Prohibited concomitant medications can be found in Section 6.2.2 • *Please review the cited sections for permitted, prohibited, and "use with caution" medications/therapies/foods*
Required Data	*Study Calendar and Assessment Required data* are outlined in Section 11 • **Vital signs:** The time points are in Section 11 • **Biopsies**: The time points are in Section 11
Tips	**All study drugs require documentation of exact administration time.**