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Brief Title: Pembrolizumab in Metastatic Anal Cancer

Full Title: A Multicenter Phase 2 Clinical Trial of Pembrolizumab in Metastatic Anal Cancer

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TITLE: A Multicenter Phase 2 Clinical Trial of Pembrolizumab in Metastatic Anal Cancer

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

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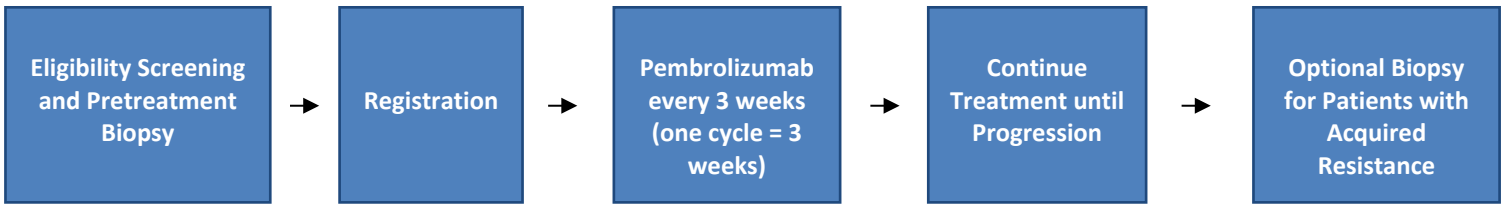
SCHEMA


Eligibility Screening and Pretreatment Biopsy
Registration
Pembrolizumab every 3 weeks (one cycle = 3 weeks)
Continue Treatment until Progression
Optional Biopsy for Patients with Acquired Resistance

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1. TRIAL SUMMARY

Abbreviated Title	Phase 2 Clinical Trial of Pembrolizumab in Metastatic Anal Cancer
Trial Phase	Phase 2
Clinical Indication	Anal cancer
Trial Type	Open label phase 2 study
Type of control	Historical control
Route of administration	Intravenous
Trial Blinding	Non-blinded
Treatment Groups	One
Number of trial subjects	32
Estimated enrollment period	18 months
Estimated duration of trial	36 months
Duration of Participation	36 months

2. TRIAL DESIGN

2.1 Trial Design

This is a multicenter, open label, single arm phase 2 clinical trial of pembrolizumab in metastatic anal cancer. Metastatic anal cancer patients who have progressed on a prior regimen of platinum and 5-FU-based chemotherapy are eligible to participate. All 32 patients enrolled on the study will receive pembrolizumab administered every three weeks.

Patients will continue on the trial until they suffer intolerable toxicity or are found to have disease progression by RECIST criteria (RECIST version 1.1). Given the possibility of a delayed tumor response, patients will be allowed to continue on the trial until there is disease progression on two successive imaging studies (Wolchok et al., 2009). Toxicity will be graded according to CTCAE 4.0. Optional post-treatment biopsies will be performed on patients who initially respond to pembrolizumab and then develop acquired resistance.

3. OBJECTIVE(S) & HYPOTHESIS(ES)

3.1 Primary Objective(s) & Hypothesis(es)

(1) **Objective:**

Evaluate the response rate, by RECIST 1.1, of pembrolizumab in metastatic anal cancer patients.

Hypothesis:

- Pembrolizumab will show a response rate of ≥20% in metastatic anal cancer patients

3.2 Secondary Objectives & Hypotheses

(1) **Objective**:

Evaluate the response rate, by RECIST 1.1, of pembrolizumab in metastatic anal cancer patients who are PD-L1 positive.

Hypothesis:

- Pembrolizumab will have anti-cancer activity in PD-L1 positive metastatic anal cancer.

(2) **Objective**:

Evaluate the durability of pembrolizumab response in PD-L1 positive metastatic anal cancer patients by measuring median overall survival and median progression free survival

Hypothesis:

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

(3) **Objective**

Evaluate the safety and tolerability of pembrolizumab administered every three weeks, in metastatic anal cancer.

Hypothesis:

- Pembrolizumab every 3 weeks will be well tolerated in the metastatic anal cancer patient population.

3.3 Exploratory Objective

(1) **Objective:**

Evaluate relationship between response rate, by RECIST 1.1, 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.

4. BACKGROUND & RATIONALE

4.1 Background

Metastatic anal cancer is an incurable malignancy that has limited therapeutic options. NCCN guidelines recommend cisplatin and 5-FU as first line therapy based several cases series demonstrating the activity of this regimen (Dewdney and Rao, 2012; Faivre et al., 1999). Beyond

first line cisplatin and 5-FU, NCCN guidelines make no recommendations for subsequent lines of therapy as "no other regimens have shown to be effective (Benson et al., 2012)."

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 (Hodi et al., 2010; Robert et al., 2011). 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 (Brahmer et al., 2010; Hamid et al., 2013; Robert et al.; Topalian et al., 2014). 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 (Ott et al., 2013; Topalian et al., 2014). 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 (Robert et al.). Pembrolizumab was generally well tolerated and drug-related grade 3 and 4 toxicity occurred in only 13% of patients (Robert et al.).

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 86% of 31 metastatic anal cancers patients were PD-L1 positive. Interestingly, other HPV associated tumors (head/neck and cervical cancer) also had a very high rate of PD-L1 positivity.

The Dana-Farber experience on this trial (MK-3475-028, NCT02054806) suggests that pembrolizumab is active in patients with refractory metastatic anal cancer. The first anal cancer patient treated at Dana-Farber has had a 59% decrease in her tumor burden after eight cycles of pembrolizumab.

This is a multicenter, open label, single arm phase 2 clinical trial of pembrolizumab in metastatic anal cancer. If this trial demonstrates activity it would open up a new therapeutic opportunity in a disease with very limited options. It is our hope that a demonstration of clinical activity would catalyze the inclusion of pembrolizumab in the NCCN guidelines allowing it to become a standard therapy for this cancer.

4.2 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.

4.3 Rationale

4.3.1 Rationale for the Trial and Selected Subject Population

Metastatic squamous cell carcinoma of the anus is a malignancy with extremely limited treatment options. An ongoing phase 1 trial has shown that pembrolizumab has activity in some metastatic anal cancer patients. This trial is being performed to further characterize pembrolizumab's activity in this disease population.

In July 2017, the trial's eligibility criteria were amended. The requirement that patients receive one line of chemotherapy prior to entering the trial was eliminated. The rationale for this is that a phase 2 clinical trial testing nivolumab in refractory metastatic anal cancer showed an impressive 24% radiological response rate (Morris et al., 2017). The encouraging results from the nivolumab trial has made recruitment to this trial challenging because many patients are receiving off-label PD1 directed therapy in the first line of treatment.

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

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

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

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.

5. PARTICIPANT SELECTION

5.1 Eligibility Criteria

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

1. Participants must have metastatic or locally advanced incurable anal cancer that has been histologically confirmed. Patients with locally advanced anal cancer must have had cancer recurrence after chemoradiation and must be unresectable.

2. There is no limit to the number of prior therapies.

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

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

5. Have measurable disease based on RECIST 1.1.

6. Be willing to provide tissue from a newly obtained core or excisional biopsy of a tumor lesion. *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.*

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

8. Demonstrate adequate organ function as defined in

   Table 1, all screening labs must be performed within 10 days of treatment initiation. Labs must meet eligibility criteria within 4 days of Cycle 1 Day 1.

Table 1 Adequate Organ Function Laboratory Values

System	Laboratory Value
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 **OR** Measured or calculated[a] creatinine clearance (GFR can also be used in place of creatinine or CrCl)	≤1.5 X upper limit of normal (ULN) **OR** ≥60 mL/min for subject with creatinine levels > 1.5 X institutional ULN
Hepatic	
Serum total bilirubin	≤ 1.5 X ULN **OR**
	Direct bilirubin ≤ ULN for subjects with total bilirubin levels > 1.5 ULN
AST (SGOT) and ALT (SGPT)	≤ 2.5 X ULN **OR** ≤ 5 X ULN for subjects with liver metastases
Albumin	≥2.8 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
[a]Creatinine clearance should be calculated per institutional standard.	

12. 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.

13. 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 7.4). Subjects of childbearing potential are those who have not been surgically sterilized or have not been free from menses for > 1 year.

14. 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.

5.2 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. HIV+ positive patients are eligible if their CD4+ count ≥ 300/μL and they have an undetectable viral load. In addition, they must be currently receiving Highly Active Antiretroviral Therapy (HAART) and be under the care of an Infectious Diseases specialist.

16. Patients with hepatitis B and hepatitis C must be under the care of viral hepatitis expert consultant. Patients with hepatitis B are required to be treated with anti-HBV treatment (e.g., entecavir). Patients with hepatitis C need to have received prior and/or ongoing hepatitis C treatment.

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.

5.3 Inclusion of Women and Minorities

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

6. REGISTRATION PROCEDURES

6.1 General Guidelines for DF/HCC and DF/PCC 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.

6.2 Registration Process for DF/HCC and DF/PCC Institutions

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

6.3 General Guidelines for Other Investigative Sites

Eligible participants will be entered on study centrally at Dana-Farber Cancer Institute by the Study Coordinator. All sites should call the Study Coordinator at 617-632-6316 when a potential patient is identified to confirm the study status and enrollment availability. Following registration, participants should begin protocol therapy within 5 days. Issues that would cause treatment delays should be discussed with the Overall PI. If a participant does not receive protocol therapy following registration, the participant's registration on the study must be canceled. The Study Coordinator should be notified of cancellations as soon as possible.

6.4 Registration Process for Other Investigative Sites

To register a participant, the following documents should be completed by the research nurse or data manager and faxed or e-mailed to the Study Coordinator (617-582-7988 or mailto:KatherineA_Metayer@dfci.harvard.edu):

- Copy of pathology report confirming diagnosis, laboratory results and baseline imaging report
- Signed participant consent form
- HIPAA authorization form
- Eligibility Checklist

The research nurse or data manager at the participating site will then call or e-mail the Study Coordinator to verify eligibility. To complete the registration process, the Coordinator will follow DF/HCC Standard Operating Procedure for Human Subject Research Titled *Subject Protocol Registration* (SOP #: REGIST-101) and register the participant on the protocol. The coordinator will fax or e-mail the participant study number, and if applicable the dose treatment level, to the participating site. The coordinator will also call the research nurse or data manager at the participating site and verbally confirm registration

7. TREATMENT PLAN

7.1 Trial Treatment

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

Table 2 Trial Treatment

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

7.1.1 **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 12). 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 (Appendix G).

7.2 Pre-Treatment Criteria

Pembrolizumab must be withheld for severe or life-threatening drug-related toxicities. Please see section 8.1 (Table 3) for specific instructions.

7.3 Concomitant Medications/Vaccinations (allowed & prohibited)

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

7.3.1 **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 9.8.1.2.

7.3.2 **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
- 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.

7.4 Diet/Activity/Other Considerations

7.4.1 **Diet**

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

7.4.2 **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 9.7-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.

7.4.3 **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 9.7.

7.4.4 **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.

7.5 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 on two successive imaging studies

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 9.0
- 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 12.1.1.1.

- Administrative reasons

The End of Treatment and Follow-up visit procedures are listed in Section 12 (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 9.8). 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 12.1.1.1.

A ODQ Treatment Ended/Off Study Form will be filled out when a participant is removed from protocol therapy. This form can be found on the ODQ website or obtained from the ODQ registration staff.

7.6 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.

7.7 Duration of Follow Up

After removal from protocol therapy, participants will be followed until death, lost to follow-up, or study closure, whichever occurs first. Participants removed from protocol therapy for unacceptable adverse event(s) will be followed until resolution or stabilization of the adverse event.

7.8 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 Centralized Subject Registrations, the research team submits a completed Off Treatment/Off Study form to ODQ when a participant comes off study. This form can be found on the ODQ website or obtained from the ODQ registration staff.

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

8. DOSING DELAYS/DOSE MODIFICATIONS

8.1 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 8.2.1 and Events of Clinical Interest Guidance Document for supportive care guidelines, including use of corticosteroids. Refer to Appendix B for more information on Events of Clinical Interest.

Table 3 Dose Modification Guidelines for Drug-Related Adverse Events

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

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

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

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

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

8.2 Rescue Medications & Supportive Care

8.2.1 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 8.1 for dose modification. Refer to Appendix B for more information on Events of Clinical Interest.

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: 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:	**Stop Infusion.** Additional appropriate medical therapy may include but is not limited to: IV fluids Antihistamines NSAIDS Acetaminophen Narcotics Oxygen Pressors	No subsequent dosing

NCI CTCAE Grade	Treatment	Premedication at subsequent dosing
Life-threatening; pressor or ventilatory support indicated	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.		

9. ADVERSE EVENTS: LIST AND REPORTING REQUIREMENTS

9.1 Expedited Adverse Event Reporting

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

9.1.2 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 30 days of the last dose of treatment on the local institutional SAE form.

9.1.3 For multi-institution studies where a DF/HCC investigator is serving as the Overall Principal Investigator, each participating institution **must** abide by the reporting requirements set by the DF/HCC. This applies to any medical event equivalent to an unexpected grade 2 or 3 with a possible, probable or definite attribution, unexpected grade 4 toxicities, and grade 5 (death) regardless of study phase or attribution.

9.1.4 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.

Other investigative sites will report AEs to their respective IRB according to the local IRB's policies and procedures in reporting adverse events. A copy of the submitted institutional AE form should be forwarded to the Overall PI within the timeframes detailed in the table below.

Attribution	DF/HCC Reportable AEs				
	Gr. 2 & 3 AE Expected	**Gr. 2 & 3 AE Unexpected**	**Gr. 4 AE Expected**	**Gr. 4 AE Unexpected**	**Gr. 5 AE Expected or Unexpected**
Unrelated Unlikely	Not required	Not required	5 calendar days#	5 calendar days	24 hours*
Possible Probable Definite	Not required	5 calendar days	5 calendar days#	5 calendar days	24 hours*
# If listed in protocol as expected and not requiring expedited reporting, event does not need to be reported.					
* For participants enrolled and actively participating in the study ***or*** for AEs occurring within 30 days of the last intervention, the AE should be reported within 1 business day of learning of the event.					

The Overall PI will submit AE reports from outside institutions to the DFCI OHRS according to DFCI IRB policies and procedures in reporting adverse events.

9.2 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.

9.3 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.

9.4 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.**

9.5 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 90 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 9.8.

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

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

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

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

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

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

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

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

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

9.8.1.1 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 a new cancer (that is not a condition of the study);
- Is associated with an overdose;
- Is an other important medical event

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

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

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

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

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

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

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

9.8.1.2 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 9.6 - 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 B 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.

9.8.2 **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.)	

10. 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 Appendix B.

10.1 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

10.2 Packaging and Labeling Information

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

10.3 Clinical Supplies Disclosure

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

10.4 Storage and Handling Requirements

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

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

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

10.5 Ordering

Investigative sites will order and acquire Pembrolizumab directly from Merck per Appendix F, Section 4 (Data and Safety Monitoring Plan).

10.6 Returns and Reconciliation

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

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

11. BIOMARKER, CORRELATIVE, AND SPECIAL STUDIES

11.1 Biomarker Studies

11.1.1 Pre-treatment Tumor Biopsies

All patients with tumors that can be safely biopsied are required to undergo a pretreatment biopsy. Biopsy tissues will be collected and fixed by 10% neutral buffered formalin overnight, dehydrated and paraffin embedded. The paraffin blocks should be sent to the Coordinating Center at the

following address:

Katherine Metayer
Gastrointestinal Cancer Center
Dana-Farber Cancer Institute
450 Brookline Avenue, Dana 1B-16
Boston, MA 02215
Ph: 617-632-6746

Please alert the Coordinating Center via email and provide a tracking number for the shipment: KatherineA_Metayer@dfci.harvard.edu

This fresh pretreatment tumor biopsy will allow us to analyze immunohistochemically the tumor and surrounding immune-infiltrate for PD-L1, PD-L2 and PD1 expression. Since human papillomavirus (HPV) infection is strongly associated with anal cancer, we will also utilize immunohistochemistry to evaluate p16 expression, a well-established surrogate marker of HPV infection (Alemany et al., 2015; Serup-Hansen et al., 2014).

For patients treated at Dana-Farber Cancer Institute (DFCI), we will also use this biopsy to perform additional immune characterization. Biopsy tissues will be collected and fixed by 10% neutral buffered formalin overnight, dehydrated and paraffin embedded. Four-micrometer-thick sections will be cut. The paraffin blocks and unstained slides will be stored at room temperature. In collaboration with the Core laboratory at Dana-Farber Cancer Institute, we will utilize digital spatial profiling (assessing IHC biomarkers and RNA expression patterns) of the tumor samples to assess the tumor microenvironment. By analyzing the differences between responding and resistant patients, this will help us to better understand mechanisms of sensitivity and resistance to pembrolizumab.

11.1.2 **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 (for the initial collection this can occur either at screening or prior to treatment on C1D1). Following cycle 3, PBMCs will be collected on day 1 of every other treatment cycle. PBMCs will also be collected, if possible, on the visit when the patient is taken off the trial. Leftover specimens will be banked for future use by the Coordinating Center.

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

Peripheral Blood Mononuclear Cell (PBMC) Specimens:
Samples will be drawn by an experienced phlebotomist or research nurse. Blood samples may be drawn either peripherally or via central line. Each site will be responsible for ordering their own laboratory supplies and shipping materials for the specimens. Shipping costs and supplies will be covered by the protocol budget. Specimens will be stored at the participating site until shipping arrangements have been made to the Coordinating Center.

Approximately 5-7 ml of blood for PBMC specimens will be collected in heparin treated (green top) tubes. Samples will be collected prior to the administration of pembrolizumab on Day 1 of the first three cycles. Following Cycle 3, samples will be collected on Day 1 of every other treatment cycle.

Instructions for PBMC Specimens:

1. Spin green-cap tubes (heparin treated tubes) at 1500 rpm for 10 min.
2. Aspirate 2 ml plasma/tube and aliquot into 4 tubes (Corning, 430488)
3. Pour all blood from green cap tubes into a 50 ml conical tube with maximum amount of 25 ml.
4. Dilute blood 1:1 with PBS. e. Add 12 ml ficoll-paque (Cat# 17-1440-03; GE Healthcare) per a 50 ml conical tube.
5. Slowly and gently layer the diluted blood on the ficoll-paque of the tube with maximum 35 ml.
6. Centrifuge the tube at 1900 rpm for 20 min at room temperature with slow acceleration (#3) and deceleration (#3) in a Sorvall Legend centrifuge.

7. Aspirate the PBMC layer between upper part (diluted plasma) and middle part (ficoll-paque) and transferring into a 50 ml conical tube. The lower part is composed of red blood cells.
8. Dilute the collected PBMC at least 1:2 with PBS
9. Centrifuge the tube at 1500 rpm for 5 min at room temperature.
10. Wash PBMC pellet with PBS once.
11. Store the 5 × 106 cells/cryo vial in 300-500 µl of Fetal Bovine Serum plus 15% DMSO
12. Samples will be frozen at -70C until shipment is arranged to the Coordinating Center.

Samples will be shipped to the Coordinating Center at the following address:

Katherine Metayer
Gastrointestinal Cancer Center
Dana-Farber Cancer Institute
450 Brookline Avenue, Dana 1B-16
Boston, MA 02215
Ph: 617-632-6316

All PBMC Cryovials will be labeled as follows:

- Protocol Number
- Subject Initials and Study ID #
- Date of Collection
- Contents: PBMC or Plasma

Please alert the Coordinating Center via email and provide a tracking number for the shipment: KatherineA_Metayer@dfci.harvard.edu

11.1.3 **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 on day 1 of every other treatment cycle. A plasma sample will also be collected, if possible, on the visit when the patient is taken off the trial. Plasma will be frozen and later analyzed.

We will analyze the serial plasma samples with markers of circulating tumor-tissue-modified HPV DNA (Naveris NavDx assay). We will use these data to correlate with recurrence of disease and to correlate with tumor response to pembrolizumab. These experiments will help us establish whether a liquid biopsy can predict responsiveness or the response kinetics to pembrolizumab.

If a sufficient volume of sample remains, in batches by DFCI's immune-oncology core laboratory (led by Dr. Steve Hodi), we will analyze a panel of cytokines and chemokines 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.

Plasma Specimens:
Samples will be drawn by an experienced phlebotomist or research nurse. Blood samples may be drawn either peripherally or via central line. Each site will be responsible for ordering their own laboratory supplies and shipping materials for the specimens. Shipping costs and supplies will be covered by the protocol budget. Specimens will be stored at the participating site until shipping arrangements have been made to the Coordinating Center.

Approximately 5-7 ml of blood for plasma-based studies will be collected in EDTA (purple top) tubes. Samples will be collected prior to the administration of pembrolizumab on Day 1 of the first three cycles. Following Cycle 3, samples will be collected on Day 1 of every other treatment cycle.

Instructions for Plasma Specimens:
Invert tube several times to assure complete mixing of anticoagulant (EDTA) and immediately centrifuge in a clinical centrifuge at 3,000 r.p.m. for 10 minutes at room temperature. Plasma should be aspirated without disturbing cells, aliquoted in 3 cryogenic vials, and frozen at –70C until shipment is arranged to the coordinating center.

All Plasma Cryovials will be labeled as follows:

- Protocol Number
- Subject Initials and Study ID #
- Date of Collection
- Contents: PBMC or Plasma

Samples will be shipped to the Coordinating Center at the following address:

Katherine Metayer
Gastrointestinal Cancer Center
Dana-Farber Cancer Institute
450 Brookline Avenue, Dana 1B-16
Boston, MA 02215
Ph: 617-632-6316

Please alert the Coordinating Center via email and provide a tracking number for the shipment: KatherineA_Metayer@dfci.harvard.edu

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

Patients that develop acquired resistance to pembrolizumab will be encouraged to undergo an optional post-treatment biopsy. This biopsy will allow us to study mechanisms of resistance to pembrolizumab. To do this, we utilize the immune characterization techniques described above.

Biopsy tissues will be collected and fixed by 10% neutral buffered formalin overnight, dehydrated

and paraffin embedded. The paraffin blocks should be sent to the Coordinating Center at the following address:

Katherine Metayer
Gastrointestinal Cancer Center
Dana-Farber Cancer Institute
450 Brookline Avenue, Dana 1B-16
Boston, MA 02215
Ph: 617-632-6316

Please alert the Coordinating Center via email and provide a tracking number for the shipment: KatherineA_Metayer@dfci.harvard.edu

12. STUDY CALENDAR AND VISIT REQUIREMENTS

Trial Period:	**Screening Phase**	**Treatment Cycles**									**End of Treatment**	**Post-Treatment**
Treatment Cycle/Title:	Main Study Screening (Visit 2)	1	2	3	4	To be repeated beyond 8 cycles: 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[g]											
Demographics and Medical History	X											
Prior and Concomitant Medication Review	X	X (to be reviewed throughout treatment period)										
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	X [l]
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[e]	X[i]	X[i]	X[i]	X[i]	X[i]	X[i]	X[i]	X[i]	X[i]		X[i]	
PT/INR and aPTT	X[h]											
CBC with Differential	X[h]	X	X	X	X	X	X	X	X			
Comprehensive Serum Chemistry Panel[f]	X[h]	X	X	X	X	X	X	X	X			
Urinalysis	X[h]											
T3, FT4 and TSH	X[h]		X		X		X		X[a]			
HIV and Hepatitis Testing	X											
Efficacy Measurements												
Tumor Imaging	X[b]			X			X[c]					
Tumor Biopsies/Archival Tissue Collection/Correlative Studies Blood												
Archival or Newly Obtained Tissue Collection [j]	X									X[d]		
Correlative Studies Blood Collection	X[m]	X	X	X		X		X[k]		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:. After cycle 12, restaging scans can be performed every 3-4 cycles at the discretion of the treating investigator.
d: Patients that initially responded to pembrolizumab can undergo an optional tumor biopsy at the end of the trial
e: Only for women of child-bearing potential
f: Albumin, alkaline phosphatase, total bilirubin, bicarbonate, BUN, calcium, chloride, creatinine, glucose, potassium, total protein, SGOT [AST], SGPT [ALT], sodium.
g: Labs must meet eligibility criteria sometime between day -4 and day 1 of the trial
h: Labs for screening are to be performed within 10 days prior to the first dose of trial treatment
i: For women of reproductive potential, a serum pregnancy test should 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: Tissue may be obtained up to 6 weeks (42 days) prior to initiation of treatment on Day 1. If a newly obtained sample cannot be provided (e.g. inaccessible or subject safety concern), an archival specimen may be submitted upon agreement from the Sponsor.
k: After Cycle 3, Correlative Studies Blood Collection will take place every other cycle.
l: Adverse events to be reported until 90 days post-treatment

m: Baseline correlative blood can be collected either during screening or pre-dose on C1D1

12.1 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.

12.1.1.1 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 RECIST 1.1, and
    - Was treated for at least 24 weeks with pembrolizumab before discontinuing therapy
    - Received at least two treatments with pembrolizumab beyond the date when the initial CR was declared

OR

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

AND

- Experienced an investigator-determined confirmed radiographic disease progression after stopping their initial treatment with pembrolizumab
- Did not receive any anti-cancer treatment since the last dose of pembrolizumab
- Has a performance status of 0 or 1 on the ECOG Performance Scale
- Demonstrates adequate organ function as detailed in Section 5.1
- 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 12 – Trial Flow Chart.

13. MEASUREMENT OF EFFECT

13.1 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 7. After cycle 12, restaging scans can be performed every 3-4 cycles at the discretion of the treating investigator.

Response and progression will be evaluated in this study using the new international criteria proposed by the Response Evaluation Criteria in Solid Tumors (RECIST) guideline (version 1.1) [*Eur J Ca* 45:228-247, 2009]. Changes in the largest diameter (unidimensional measurement) of the tumor lesions and the shortest diameter in the case of malignant lymph nodes are used in the RECIST criteria.

13.1.1 **Definitions**

Evaluable for Target Disease response. Only those participants who have measurable disease present at baseline, have received at least one cycle of therapy, and have had their disease re-evaluated will be considered evaluable for target disease response. These participants will have their response classified according to the definitions stated below. (Note: Participants who exhibit objective disease progression prior to the end of cycle 1 will also be considered evaluable.)

Evaluable Non-Target Disease Response. Participants who have lesions present at baseline that are evaluable but do not meet the definitions of measurable disease, have received at least one cycle of therapy, and have had their disease re-evaluated will be considered evaluable for non-target disease. The response assessment is based on the presence, absence, or unequivocal progression of the lesions.

13.1.2 **Disease Parameters**

Measurable disease. Measurable lesions are defined as those that can be accurately

measured in at least one dimension (longest diameter to be recorded) as ≥ 20 mm by chest x-ray or ≥10 mm with CT scan, MRI, or calipers by clinical exam. All tumor measurements must be recorded in millimeters (or decimal fractions of centimeters).

Note: Tumor lesions that are situated in a previously irradiated area might or might not be considered measurable.

Malignant lymph nodes. To be considered pathologically enlarged and measurable, a lymph node must be ≥15 mm in short axis when assessed by CT scan (CT scan slice thickness recommended to be no greater than 5 mm). At baseline and in follow-up, only the short axis will be measured and followed.

Non-measurable disease. All other lesions (or sites of disease), including small lesions (longest diameter <10 mm or pathological lymph nodes with ≥10 to <15 mm short axis), are considered non-measurable disease. Bone lesions, leptomeningeal disease, ascites, pleural/pericardial effusions, lymphangitis cutis/pulmonitis, inflammatory breast disease, abdominal masses (not followed by CT or MRI), and cystic lesions are all considered non-measurable.

Note: Cystic lesions that meet the criteria for radiographically defined simple cysts should not be considered as malignant lesions (neither measurable nor non-measurable) since they are, by definition, simple cysts.

'Cystic lesions' thought to represent cystic metastases can be considered as measurable lesions, if they meet the definition of measurability described above. However, if non-cystic lesions are present in the same participant, these are preferred for selection as target lesions.

Target lesions. All measurable lesions up to a maximum of 2 lesions per organ and 5 lesions in total, representative of all involved organs, should be identified as **target lesions** and recorded and measured at baseline. Target lesions should be selected on the basis of their size (lesions with the longest diameter), be representative of all involved organs, but in addition should be those that lend themselves to reproducible repeated measurements. It may be the case that, on occasion, the largest lesion does not lend itself to reproducible measurement in which circumstance the next largest lesion which can be measured reproducibly should be selected. A sum of the diameters (longest for non-nodal lesions, short axis for nodal lesions) for all target lesions will be calculated and reported as the baseline sum diameters. If lymph nodes are to be included in the sum, then only the short axis is added into the sum. The baseline sum diameters will be used as reference to further characterize any objective tumor regression in the measurable dimension of the disease.

Non-target lesions. All other lesions (or sites of disease) including any measurable lesions over and above the 5 target lesions should be identified as **non-target lesions** and should also be recorded at baseline. Measurements of these lesions are not required, but the presence, absence, or in rare cases unequivocal progression of each should be noted throughout follow up.

13.1.3 **Methods for Evaluation of Disease**

All measurements should be taken and recorded in metric notation using a ruler, calipers, or a digital measurement tool. All baseline evaluations should be performed as closely as possible to the beginning of treatment and never more than 4 weeks before the beginning of the treatment.

The same method of assessment and the same technique should be used to characterize each identified and reported lesion at baseline and during follow-up. Imaging-based evaluation is preferred to evaluation by clinical examination unless the lesion(s) being followed cannot be imaged but are assessable by clinical exam.

Clinical lesions. Clinical lesions will only be considered measurable when they are superficial (*e.g.*, skin nodules and palpable lymph nodes) and ≥10 mm in diameter as assessed using calipers (*e.g.*, skin nodules). In the case of skin lesions, documentation by color photography, including a ruler to estimate the size of the lesion, is recommended.

Chest x-ray. Lesions on chest x-ray are acceptable as measurable lesions when they are clearly defined and surrounded by aerated lung; however, CT is preferable.

Conventional CT and MRI. This guideline has defined measurability of lesions on CT scan based on the assumption that CT thickness is 5mm or less. If CT scans have slice thickness greater than 5 mm, the minimum size of a measurable lesion should be twice the slice thickness. MRI is also acceptable in certain situations (*e.g.* for body scans).

Use of MRI remains a complex issue. MRI has excellent contrast, spatial, and temporal resolution; however, there are many image acquisition variables involved in MRI, which greatly impact image quality, lesion conspicuity, and measurement. Furthermore, the availability of MRI is variable globally. As with CT, if an MRI is performed, the technical specifications of the scanning sequences used should be optimized for the evaluation of the type and site of disease. Furthermore, as with CT, the modality used at follow-up should be the same as was used at baseline and the lesions should be measured/assessed on the same pulse sequence. It is beyond the scope of the RECIST guidelines to prescribe specific MRI pulse sequence parameters for all scanners, body parts, and diseases. Ideally, the same type of scanner should be used and the image acquisition protocol should be followed as closely as possible to prior scans. Body scans should be performed with breath-hold scanning techniques, if possible.

FDG-PET. While FDG-PET response assessments need additional study, it is sometimes reasonable to incorporate the use of FDG-PET scanning to complement CT scanning in assessment of progression (particularly possible 'new' disease). New lesions on the basis of FDG-PET imaging can be identified according to the following algorithm:

(a) Negative FDG-PET at baseline, with a positive FDG-PET at follow-up is a sign of PD based on a new lesion.

(b) No FDG-PET at baseline and a positive FDG-PET at follow-up: If the positive FDG-PET at follow-up corresponds to a new site of disease confirmed by CT, this is PD. If the positive FDG-PET at follow-up is not confirmed as a new site of disease on CT, additional follow-up CT scans are needed to determine if there is truly progression occurring at that site (if so, the date of PD will be the date of the initial abnormal FDG-

PET scan). If the positive FDG-PET at follow-up corresponds to a pre-existing site of disease on CT that is not progressing on the basis of the anatomic images, this is not PD.

(c) FDG-PET may be used to upgrade a response to a CR in a manner similar to a biopsy in cases where a residual radiographic abnormality is thought to represent fibrosis or scarring. The use of FDG-PET in this circumstance should be prospectively described in the protocol and supported by disease-specific medical literature for the indication. However, it must be acknowledged that both approaches may lead to false positive CR due to limitations of FDG-PET and biopsy resolution/sensitivity.

Note: A 'positive' FDG-PET scan lesion means one which is FDG avid with an uptake greater than twice that of the surrounding tissue on the attenuation corrected image.

PET-CT. At present, the low dose or attenuation correction CT portion of a combined PET-CT is not always of optimal diagnostic CT quality for use with RECIST measurements. However, if the site can document that the CT performed as part of a PET-CT is of identical diagnostic quality to a diagnostic CT (with IV and oral contrast), then the CT portion of the PET-CT can be used for RECIST measurements and can be used interchangeably with conventional CT in accurately measuring cancer lesions over time. Note, however, that the PET portion of the CT introduces additional data which may bias an investigator if it is not routinely or serially performed.

MIBG (meta-iodobenzylguanidine).The following is recommended, to assure high quality images are obtained.

Patient preparation: Iodides, usually SSKI (saturated solution of potassium iodide), are administered to reduce thyroidal accumulation of free radioiodine, preferably beginning the day prior to injection and continuing for 3 additional days (4 days total). For infants and children, one drop t.i.d. is sufficient, for adolescents 2 drops t.i.d., and for adults 3 drops t.i.d. Participants and/or parents are asked about exposure to potential interfering agents. If none is noted, an indwelling intravenous line is established. The dose of MIBG is administered by slow intravenous injection over 90 seconds.

Images from the head to the distal lower extremities should be obtained.

I-123MIBG scintigraphy is performed to obtain both planar and tomographic images.

Planar: Anterior and posterior views from the top of the head to the proximal lower extremities are obtained for 10 minutes at 24 hours and occasionally at 48 hours following injection of 10 mCi/1.7 square meters of body surface area (~150 μCi/kg, maximum 10 mCi). Anterior views of the distal lower extremities are adequate. A large field of view dual head gamma camera with low energy collimators is preferred.

SPECT: Most participants receiving I-123 MIBG also undergo SPECT at 24 hours, using a single or multi-headed camera with a low energy collimator. The camera is rotated through 360 degrees, 120 projections at 25 seconds per stop. Data are

reconstructed using filtered back projections with a Butterworth filter and a cut off frequency of 0.2-0.5. SPECT/CT may be performed at institutions with this capacity.

Ultrasound. Ultrasound is not useful in assessment of lesion size and should not be used as a method of measurement. Ultrasound examinations cannot be reproduced in their entirety for independent review at a later data and, because they are operator dependent, it cannot be guaranteed that the same technique and measurements will be taken from one assessment to the next. If new lesions are identified by ultrasound in the course of the study, confirmation by CT or MRI is advised. If there is concern about radiation exposure from CT, MRI may be used instead of CT in selected instances.

Endoscopy, Laparoscopy. The utilization of these techniques for objective tumor evaluation is not advised. However, such techniques may be useful to confirm complete pathological response when biopsies are obtained or to determine relapse in trials where recurrence following complete response (CR) or surgical resection is an endpoint.

Tumor markers. Tumor markers alone cannot be used to assess response. If markers are initially above the upper normal limit, they must normalize for a participant to be considered in complete clinical response. Specific guidelines for both CA-125 response (in recurrent ovarian cancer) and PSA response (in recurrent prostate cancer) have been published [*JNCI* 96:487-488, 2004; *J Clin Oncol* 17, 3461-3467, 1999; *J Clin Oncol* 26:1148-1159, 2008]. In addition, the Gynecologic Cancer Intergroup has developed CA-125 progression criteria which are to be integrated with objective tumor assessment for use in first-line trials in ovarian cancer [*JNCI* 92:1534-1535, 2000].

Cytology, Histology. These techniques can be used to differentiate between partial responses (PR) and complete responses (CR) in rare cases (*e.g.*, residual lesions in tumor types, such as germ cell tumors, where known residual benign tumors can remain).

The cytological confirmation of the neoplastic origin of any effusion that appears or worsens during treatment when the measurable tumor has met criteria for response or stable disease is mandatory to differentiate between response or stable disease (an effusion may be a side effect of the treatment) and progressive disease.

13.1.4 **Response Criteria**

13.1.4.1 **Evaluation of Target Lesions**

Complete Response (CR): Disappearance of all target lesions. Any pathological lymph nodes (whether target or non-target) must have reduction in short axis to <10 mm.

Partial Response (PR): At least a 30% decrease in the sum of the diameters of target lesions, taking as reference the baseline sum diameters.

Progressive Disease (PD): At least a 20% increase in the sum of the diameters of target lesions, taking as reference the smallest sum on study (this includes the baseline sum if that is the smallest on study). In addition to the relative increase of 20%, the sum must

also demonstrate an absolute increase of at least 5 mm. (Note: the appearance of one or more new lesions is also considered progressions).

Stable Disease (SD): Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as reference the smallest sum diameters while on study.

13.1.4.2 Evaluation of Non-Target Lesions

Complete Response (CR): Disappearance of all non-target lesions and normalization of tumor marker level. All lymph nodes must be non-pathological in size (<10 mm short axis).

Note: If tumor markers are initially above the upper normal limit, they must normalize for a patient to be considered in complete clinical response.

Non-CR/Non-PD: Persistence of one or more non-target lesion(s) and/or maintenance of tumor marker level above the normal limits.

Progressive Disease (PD): Appearance of one or more new lesions and/or *unequivocal progression* of existing non-target lesions. *Unequivocal progression* should not normally trump target lesion status. It must be representative of overall disease status change, not a single lesion increase.

Although a clear progression of "non-target" lesions only is exceptional, the opinion of the treating physician should prevail in such circumstances, and the progression status should be confirmed at a later time by the review panel (or Principal Investigator).

13.1.4.3 Evaluation of New Lesions

The finding of a new lesion should be unequivocal (i.e. not due to difference in scanning technique, imaging modality, or findings thought to represent something other than tumor (for example, some 'new' bone lesions may be simply healing or flare of pre-existing lesions). However, a lesion identified on a follow-up scan in an anatomical location that was not scanned at baseline is considered new and will indicate PD. If a new lesion is equivocal (because of small size etc.), follow-up evaluation will clarify if it truly represents new disease and if PD is confirmed, progression should be declared using the date of the initial scan on which the lesion was discovered.

13.1.4.4 Evaluation of Best Overall Response

The best overall response is the best response recorded from the start of the treatment until disease progression/recurrence (taking as reference for progressive disease the smallest measurements recorded since the treatment started). The patient's best response assignment will depend on the achievement of both measurement and confirmation criteria.

For Participants with Measurable Disease (*i.e.*, Target Disease)

Target Lesions	**Non-Target Lesions**	**New Lesions**	**Overall Response**	**Best Overall Response when Confirmation is Required***
CR	CR	No	CR	≥4 wks Confirmation**
CR	Non-CR/Non-PD	No	PR	≥4 wks Confirmation**
CR	Not evaluated	No	PR	
PR	Non-CR/Non-PD/not evaluated	No	PR	
SD	Non-CR/Non-PD/not evaluated	No	SD	Documented at least once ≥4 wks from baseline**
PD	Any	Yes or No	PD	no prior SD, PR or CR
Any	PD***	Yes or No	PD	
Any	Any	Yes	PD	

* See RECIST 1.1 manuscript for further details on what is evidence of a new lesion.
** Only for non-randomized trials with response as primary endpoint.
*** In exceptional circumstances, unequivocal progression in non-target lesions may be accepted as disease progression.

Note: Participants with a global deterioration of health status requiring discontinuation of treatment without objective evidence of disease progression at that time should be reported as "*symptomatic deterioration."* Every effort should be made to document the objective progression even after discontinuation of treatment.

For Participants with Non-Measurable Disease (*i.e.*, Non-Target Disease)

Non-Target Lesions	**New Lesions**	**Overall Response**
CR	No	CR
Non-CR/non-PD	No	Non-CR/non-PD*
Not all evaluated	No	not evaluated
Unequivocal PD	Yes or No	PD
Any	Yes	PD

* 'Non-CR/non-PD' is preferred over 'stable disease' for non-target disease since SD is increasingly used as an endpoint for assessment of efficacy in some trials so to assign this category when no lesions can be measured is not advised

13.1.5 **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.

13.1.6 **Progression-Free Survival**

Overall Survival: Overall Survival (OS) is defined as the time from randomization (or 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 randomization (or 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 randomization (or registration) to progression, or censored at date of last disease evaluation for those without progression reported.

13.1.7 **Response Review**

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

14. 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).

14.1 Data Reporting

14.1.1 **Method**

The Office of Data Quality (ODQ) will collect, manage, and perform quality checks on the data for this study.

14.1.2 **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.

14.2 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.

14.3 Multicenter Guidelines

This protocol will adhere to the policies and requirements of the DF/HCC Multi-Center Data and Safety Monitoring Plan. The specific responsibilities of the Overall PI, Coordinating Center, and Participating Institutions and the procedures for auditing are presented in Appendix F.

- The Overall PI/Coordinating Center is responsible for distributing all IND Action Letters or Safety Reports to all participating institutions for submission to their individual IRBs for action as required.

- Mechanisms will be in place to ensure quality assurance, protocol compliance, and adverse event reporting at each site.

- Except in very unusual circumstances, each participating institution will order the study agent(s) directly from supplier. A participating site may order the agent(s) only after the initial IRB approval for the site has been forwarded to the Coordinating Center.

15. STATISTICAL CONSIDERATIONS

15.1 Study Design/Endpoints

15.1.1 Primary Objective

This single arm, phase 2 clinical trial is testing the hypothesis that pembrolizumab has clinically meaningful activity in metastatic anal cancer. This multicenter trial will enroll 32 patients with metastatic anal cancer.

An overall response rate of ≥20% would demonstrate clinically meaningful activity in this population. Based on NCCN guidelines, there are no anti-cancer regimens for patients with refractory, metastatic anal cancer (Benson et al., 2012)."

This study has 90% power to differentiate between an unacceptable 5% overall response rate and a desirable overall response rate of 20% using a one-sided binomial test with 10% type 1 error.

15.1.2 **Secondary Objectives**

Progression free survival and overall survival will be determined by the Kaplan-Meier method. Both progression free survival and overall survival will be analyzed with an intention to treat analysis. Overall survival will be calculated as the time from initiating treatment until death, progression free survival as the time until disease progression or death.

Each reported adverse event will be assigned a grade of severity in accordance with the NCI-CTCAE version 4.0 guidelines. All adverse events will be listed. The participant incidence rate of treatment emergent adverse events will be summarized by treatment group and maximum severity (where appropriate) for all adverse events, serious adverse events, adverse events leading to discontinuation of protocol-specified treatment, adverse events leading to discontinuation from the study, and fatal adverse events. These summary tables will also be repeated for treatment-related adverse events.

15.1.3 **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: $\geq 10\%$).

16. 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

Alemany, L., M. Saunier, I. Alvarado-Cabrero, B. Quirós, J. Salmeron, H.-R. Shin, E.C. Pirog, N. Guimerà, G. Hernandez-Suarez, A. Felix, O. Clavero, B. Lloveras, E. Kasamatsu, M.T. Goodman, B.Y. Hernandez, J. Laco, L. Tinoco, D.T. Geraets, C.F. Lynch, V. Mandys, M. Poljak, R. Jach, J. Verge, C. Clavel, C. Ndiaye, J. Klaustermeier, A. Cubilla, X. Castellsagué, I.G. Bravo, M. Pawlita, W.G. Quint, N. Muñoz, F.X. Bosch, S. de Sanjosé, and H.P.V.V.S.G. on behalf of the. 2015. Human papillomavirus DNA prevalence and type distribution in anal carcinomas worldwide. *International Journal of Cancer*. 136:98-107.

Benson, A.B., J.P. Arnoletti, T. Bekaii-Saab, E. Chan, Y.-J. Chen, M.A. Choti, H.S. Cooper, R.A. Dilawari, P.F. Engstrom, P.C. Enzinger, M.G. Fakih, J.W. Fleshman, C.S. Fuchs, J.L. Grem, L.A. Leong, E. Lin, K.S. May, M.F. Mulcahy, K. Murphy, E. Rohren, D.P. Ryan, L. Saltz, S. Sharma, D. Shibata, J.M. Skibber, W. Small, C.T. Sofocleous, A.P. Venook, C. Willett, and D.A. Freedman-Cass. 2012. Anal Carcinoma, Version 2.2012: Featured Updates to the NCCN Guidelines. *Journal of the National Comprehensive Cancer Network*. 10:449-454.

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.

Dewdney, A., and S. Rao. 2012. Metastatic Squamous Cell Carcinoma of the Anus: Time for a Shift in the Treatment Paradigm? *ISRN Oncology*. 2012:6.

Faivre, C., P. Rougier, M. Ducreux, E. Mitry, A. Lusinchi, P. Lasser, D. Elias, and F. Eschwege. 1999. [5-fluorouracile and cisplatinum combination chemotherapy for metastatic squamous-cell anal cancer]. *Bull Cancer*. 86:861-865.

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.

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.

Morris, V.K., Salem, M.E., Nimeiri, H., Igbal, S., Singh, P., Ciombor, K., Polite, B., Deming, D., Chan, E., Wade, J.L., Xiao, L., Bekaii-Saab, T., Vence, L., Blando, J., Mahvash, A., Foo, W.C., Ohaji, C., Pasia, M., Bland, M., Ohinata, A., Rogers, J., Mehdizadeh, A., Banks, K., Lanman, R.,

Wolff, R.A., Streicher, H., Allison, J., Sharma, P., Eng, C. Nivolumab for previously treated unresected metastatic anal cancer (NCI9673): a multicentre, single-arm, phase 2 study. *The Lancet Oncology*. 18:446-453.

Ott, P.A., F.S. Hodi, and C. Robert. 2013. CTLA-4 and PD-1/PD-L1 Blockade: New Immunotherapeutic Modalities with Durable Clinical Benefit in Melanoma Patients. *Clinical Cancer Research*. 19:5300-5309.

Robert, C., A. Ribas, J.D. Wolchok, F.S. Hodi, O. Hamid, R. Kefford, J.S. Weber, A.M. Joshua, W.-J. Hwu, T.C. Gangadhar, A. Patnaik, R. Dronca, H. Zarour, R.W. Joseph, P. Boasberg, B. Chmielowski, C. Mateus, M.A. Postow, K. Gergich, J. Elassaiss-Schaap, X.N. Li, R. Iannone, S.W. Ebbinghaus, S.P. Kang, and A. Daud. 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.

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.

Serup-Hansen, E., D. Linnemann, W. Skovrider-Ruminski, E. Høgdall, P.F. Geertsen, and H. Havsteen. 2014. Human Papillomavirus Genotyping and p16 Expression As Prognostic Factors for Patients With American Joint Committee on Cancer Stages I to III Carcinoma of the Anal Canal. *Journal of Clinical Oncology*. 32:1812-1817.

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.

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.

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 pembrolizumab (also known as MK-3475) 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 3** provides the list of terms and reporting requirements for AEs that must be reported as ECIs for pembrolizumab protocols. Of note, the requirement for reporting of ECIs applies to all arms, including comparators, of pembrolizumab 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 3 **and reported to Merck within 24 hours** from the time the Investigator/physician is aware of such an occurrence. Adverse events that are both an SAE and an ECI should be reported one time as an SAE only, however the event must be appropriately identified as an ECI as well in in the database.

Table 3: Events of Clinical Interest

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

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– Please refer to protocol for details on reporting timelines and reporting of Overdose and Drug Induced Liver Injury (DILI). Refer to Appendix B, Section 3.5.

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
- 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.

<u>Drug Induced Liver Injury (DILI)</u>
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.

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. 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

5. EVENTS OF CLINICAL INTEREST (ECI) – REFERENCE TABLE

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

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?
_____

APPENDIX F – DF/HCC MULTI-CENTER DATA AND SAFETY MONITORING PLAN

16.1 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).

16.2 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>

    o Decimal values from 0.1 to 0.4 round down to the nearest whole number (e.g., 8.3 = 8)
    o 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**

16.3 3.3 DOSE CALCULATION

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

200 mg Fixed Dose

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

16.4 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

16.5 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.**

16.6 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.

DFCI IRB Protocol #: 16-301

APPENDIX F

Dana-Farber/Harvard Cancer Center
Multi-Center Data and Safety Monitoring Plan

TABLE OF CONTENTS

1. INTRODUCTION

The Dana-Farber/Harvard Cancer Center Multi-Center Data and Safety Monitoring Plan (DF/HCC DSMP) outlines the procedures for conducting a DF/HCC Multi-Center research protocol. The DF/HCC DSMP should serve as a reference for any sites external to DF/HCC that will be participating in the research protocol.

1.1 Purpose

To establish standards that will ensure that a Dana-Farber/Harvard Cancer Center Multi-Center protocol will comply with Federal Regulations, Health Insurance Portability and Accountability Act (HIPAA) requirements and applicable DF/HCC Standard Operating Procedures.

1.2 Multi-Center Data and Safety Monitoring Plan Definitions

DF/HCC Multi-Center Protocol: A research protocol in which one or more outside institutions are collaborating with Dana-Farber/Harvard Cancer Center where a DF/HCC investigator is the sponsor. DF/HCC includes Dana-Farber/Partners Cancer Care (DF/PCC) Network Clinical Trial Affiliates.

Lead Institution: One of the Dana-Farber/Harvard Cancer Center consortium members (Dana-Farber Cancer Institute (DFCI), Massachusetts General Hospital (MGH), Beth Israel Deaconess Medical Center (BIDMC), Boston Children's Hospital (BCH), Brigham and Women's Hospital (BWH)) responsible for the coordination, development, submission, and approval of a protocol as well as its subsequent amendments per the DFCI IRB and applicable regulatory guidelines (CTEP, Food and Drug Administration (FDA), Office of Biotechnology Activities (OBA) etc.). The Lead Institution is typically the home of the DF/HCC Sponsor. The Lead Institution also typically serves as the Coordinating Center for the DF/HCC Multi-Center Protocol.

DF/HCC Sponsor: The person sponsoring the submitted Multi-Center protocol. Within DF/HCC, this person is the Overall Principal Investigator who takes responsibility for initiation, management and conduct of the protocol at all research locations. In applicable protocols, the DF/HCC Sponsor will serve as the single liaison with any regulatory agencies. The DF/HCC Sponsor has ultimate authority over the protocol and is responsible for the conduct of the study at DF/HCC and all Participating Institutions. In most cases the DF/HCC Sponsor is the same person as the DF/HCC Overall Principal Investigator; however, both roles can be filled by two different people.

Participating Institution: An institution that is outside the DF/HCC and DF/PCC consortium that is collaborating with DF/HCC on a protocol where the sponsor is a DF/HCC Investigator. The Participating Institution acknowledges the DF/HCC Sponsor as having the ultimate authority and responsibility for the overall conduct of the study.

Coordinating Center: The entity (i.e. Lead Institution, Medical Monitor, Contract Research Organization (CRO), etc) that provides administrative support to the DF/HCC Sponsor in order that he/she may fulfill the responsibilities outlined in the protocol document and DSMP, and as specified in applicable regulatory guidelines (i.e. CTEP Multi-Center Guidelines). In general, the Lead Institution is the Coordinating Center for the DF/HCC Multi-Center Protocol. Should the DF/HCC Sponsor decide to use a CRO, the CRO will be deemed the Coordinating Center.

DF/HCC Office of Data Quality: A group within DF/HCC responsible for registering human subjects for trials, ensuring high-quality standards are used for data collection and the ongoing management of clinical trials, auditing, and data and safety monitoring. ODQ also coordinates quality assurance efforts related to multi-center clinical research.

2. GENERAL ROLES AND RESPONSIBILITIES

For DF/HCC Multi-Center Protocols, the DF/HCC Sponsor, the Coordinating Center, and the Participating Institutions are expected to adhere to the following general responsibilities:

2.1 DF/HCC Sponsor

The DF/HCC Sponsor, James Cleary, MD, PhD, will accept responsibility for all aspects of conducting a DF/HCC Multi-Center protocol which includes but is not limited to:

- Oversee the coordination, development, submission, and approval of the protocol as well as subsequent amendments.
- Ensure that the investigators, study team members, and Participating Institutions are qualified and appropriately resourced to conduct the protocol.
- Include the Multi-Center Data and Safety Monitoring Plan as an appendix to the protocol.
- Ensure all Participating Institutions are using the correct version of the protocol.
- Ensure that each participating investigator and study team member receives adequate protocol training and/or a Site Initiation Visit prior to enrolling participants and throughout trial's conduct as needed.
- Ensure the protocol will be provided to each participating site in a language understandable to all applicable site personnel when English is not the primary language.
- Monitor progress and overall conduct of the study at all Participating Institutions.
- Ensure all DFCI Institutional Review Board (IRB), DF/HCC and other applicable reporting requirements are met.
- Review data and maintain timely submission of data for study analysis.
- Act as the single liaison with the FDA (investigator-held IND trials), as applicable.
- Ensure compliance with all requirements as set forth in the Code of Federal Regulations, applicable DF/HCC requirements, HIPAA requirements, and the approved protocol.
- Commit to the provision that the protocol will not be rewritten or modified by anyone other than the DF/HCC Sponsor.

- Identify and qualify Participating Institutions and obtain accrual commitments prior to extending the protocol to that site.
- Monitor accrual and address Participating Institutions that are not meeting their accrual requirements.

2.2 Coordinating Center

The general responsibilities of the Coordinating Center may include but are not limited to:

- Assist in protocol development.
- Maintain FDA correspondence, as applicable.
- Review registration materials for eligibility and register participants from Participating Institutions with DF/HCC ODQ.
- Distribute protocol and informed consent document updates to Participating Institutions as needed.
- Oversee the data collection process from Participating Institutions.
- Maintain documentation of Serious Adverse Event (SAE) reports and deviations/violation submitted by Participating Institutions and provide to the DF/HCC Sponsor for timely review.
- Distribute serious adverse events reported to the DF/HCC Sponsor that fall under the DFCI IRB Adverse Event Reporting Policy to all Participating Institutions.
- Provide Participating Institutions with information regarding DF/HCC requirements that they will be expected to comply with.
- Carry out plan to monitor Participating Institutions either by on-site or remote monitoring.
- Maintain Regulatory documents of all Participating Institutions which includes but is not limited to the following: local IRB approvals/notifications from all Participating Institutions, confirmation of Federalwide Assurances (FWAs) for all sites, all SAE submissions, Screening Logs for all sites, IRB approved consents for all sites
- Conduct regular communications with all Participating Institutions (conference calls, emails, etc) and maintain documentation all relevant communications.

2.3 Participating Institution

Each Participating Institution is expected to comply with all applicable federal regulations and DF/HCC requirements, the protocol and HIPAA requirements.

The general responsibilities for each Participating Institution may include but are not limited to:

- Document the delegation of research specific activities to study personnel.
- Commit to the accrual of participants to the protocol.
- Submit protocol and/or amendments to their local IRB.
- Maintain regulatory files as per sponsor requirements.
- Provide the Coordinating Center with regulatory documents or source documents as requested.

- Participate in protocol training prior to enrolling participants and throughout the trial as required (i.e. teleconferences).
- Update Coordinating Center with research staff changes on a timely basis.
- Register participants through the Coordinating Center prior to beginning research related activities.
- Submit Serious Adverse Event (SAE) reports to local IRB per local requirements and to the Coordinating Center, in accordance with DF/HCC requirements.
- Submit protocol deviations and violations to local IRB per local requirements and to the DF/HCC Sponsor in accordance with DF/HCC requirements.
- Order, store and dispense investigational agents and/or other protocol mandated drugs per federal guidelines and protocol requirements.
- Have office space, office equipment, and internet access that meet HIPAA standards.
- Participate in any quality assurance activities and meet with monitors or auditors at the conclusion of a visit to review findings.
- Promptly provide follow-up and/or corrective action plans for any monitoring queries or audit findings.

3. DF/HCC REQUIREMENTS FOR MULTI-CENTER PROTOCOLS

The following section will clarify DF/HCC Requirements and further detail the expectations for participating in a DF/HCC Multi-Center protocol.

3.1 Protocol Distribution

The Coordinating Center will distribute the final DFCI IRB approved protocol and any subsequent amended protocols to all Participating Institutions.

3.2 Protocol Revisions and Closures

The Participating Institutions will receive notification of protocol revisions and closures from the Coordinating Center. It is the individual Participating Institution's responsibility to notify its IRB of these revisions.

- **Non life-threatening revisions:** Participating Institutions will receive written notification of protocol revisions regarding non life-threatening events from the Coordinating Center. Non-life-threatening protocol revisions must be IRB approved and implemented within 90 days from receipt of the notification.

- **Revisions for life-threatening causes:** Participating Institutions will receive immediate notification from the Coordinating Center concerning protocol revisions required to protect lives with follow-up by fax, mail, e-mail, etc. Life-threatening protocol revisions will be implemented immediately followed by IRB request for approval.

- **Protocol closures and temporary holds:** Participating Institutions will receive notification of protocol closures and temporary holds from the Coordinating

Center. Closures and holds will be effective immediately. In addition, the Coordinating Center, will update the Participating Institutions on an ongoing basis about protocol accrual data so that they will be aware of imminent protocol closures.

3.3 Informed Consent Requirements

The DF/HCC approved informed consent document will serve as a template for the informed consent for Participating Institutions. The Participating Institution consent form must follow the consent template as closely as possible and should adhere to specifications outlined in the DF/HCC Guidance Document on Model Consent Language for PI-Initiated Multi-Center Protocols. This document will be provided separately to each Participating Institution.

Participating Institutions are to send their version of the informed consent document and HIPAA authorization, if a separate document, to the Coordinating Center for review and approval prior to submission to their local IRB. The approved consent form must also be submitted to the Coordinating Center after approval by the local IRB for all consent versions.

The Principal Investigator (PI) at each Participating Institution will identify the physician members of the study team who will be obtaining consent and signing the consent form for therapeutic protocols. Participating institutions must follow the DF/HCC requirement that only attending physicians obtain informed consent and re-consent to interventional trials (i.e. drug and/or device trials).

3.4 IRB Documentation

The following must be on file with the Coordinating Center:

- Initial approval letter of the Participating Institution's IRB.
- Copy of the Informed Consent Form(s) approved by the Participating Institution’s IRB.
- Participating Institution’s IRB approval for all amendments.
- Annual approval letters by the Participating Institution's IRB.

3.5 IRB Re-Approval

Verification of IRB re-approval from the Participating Institutions is required in order to continue research activities. There is no grace period for continuing approvals.

The Coordinating Center will not register participants if a re-approval letter is not received from the Participating Institution on or before the anniversary of the previous approval date.

3.6 Participant Confidentiality and Authorization Statement

In 1996, congress passed the first federal law covering the privacy of health information known as the Health Insurance Portability and Accountability Act (HIPPA). Any information, related to the physical or mental health of an individual is called Protected Health Information (PHI). HIPAA outlines how and under what circumstances PHI can be used or disclosed.

In order for covered entities to use or disclose protected health information during the course of a study, the study participant must sign an authorization statement. This authorization statement may or may not be separate from the informed consent document. The Coordinating Center, with the approval from the DFCI IRB will provide a consent template, with information regarding authorization for the disclosure of protected health information.

The DF/HCC Sponsor will use all efforts to limit its use of protected health information in its trials. However, because of the nature of these trials, certain protected health information must be collected. DF/HCC has chosen to use authorizations, signed by the participant in the trial, rather than limited data sets with data use agreements.

3.6.1 DF/HCC Multi-Center Protocol Confidentiality

All documents, investigative reports, or information relating to the participant are strictly confidential. Whenever reasonably feasible, any participant specific reports (i.e. Pathology Reports, MRI Reports, Operative Reports, etc.) submitted to the Coordinating Center should be de-identified. It is recommended that the assigned DF/HCC ODQ case number (as described below) be used for all participant specific documents. Participant initials may be included or retained for cross verification of identification.

3.7 DF/HCC Multi-Center Protocol Registration Policy

Refer to protocol section 6.4 for registration procedures.

3.7.1 Initiation of Therapy

Participants must be registered with the DF/HCC ODQ before receiving treatment. Treatment may not be initiated until the Participating Institution receives confirmation of the participant's registration from the Coordinating Center. The DF/HCC Sponsor and DFCI IRB must be notified of any violations to this policy.

3.7.2 Eligibility Exceptions

The DF/HCC ODQ will make no exceptions to the eligibility requirements for a protocol without DFCI IRB approval. The DF/HCC ODQ requires each institution to fully comply with this requirement.

3.8 DF/HCC Protocol Case Number

At the time of registration, ODQ requires the following identifiers for all subjects: initials, date of birth, gender, race and ethnicity. Once eligibility has been established and the participant successfully registered, the participant is assigned a unique protocol case number. Participating Institutions should submit all de-identified subsequent communication and documents to the Coordinating Center, using this case number to identify the subject.

3.9 Protocol Deviations, Exceptions and Violations

Federal Regulations require an IRB to review proposed changes in a research activity to ensure that researchers do not initiate changes in approved research without IRB review and approval, except when necessary to eliminate apparent immediate hazards to the participant. DF/HCC requires all departures from the defined procedures set forth in the IRB approved protocol to be reported to the DF/HCC Sponsor, who in turn is responsible for reporting to the DFCI IRB.

For reporting purposes, DF/HCC uses the terms "violation", "deviation" and "exception" to describe departures from a protocol. All Participating Institutions must adhere to these requirements for reporting to the DF/HCC Sponsor and will follow their institutional policy for reporting to their local IRB.

3.9.1 Definitions

Protocol Deviation: Any departure from the defined procedures set forth in the IRB-approved protocol which is *prospectively approved* prior to its implementation.

Protocol Exception: Any protocol deviation that relates to the eligibility criteria, e.g. enrollment of a participant who does not meet all inclusion/exclusion criteria.

Protocol Violation: Any protocol deviation that was not *prospectively approved* by the IRB prior to its initiation or implementation.

3.9.2 Reporting Procedures

DF/HCC Sponsor: is responsible for ensuring that clear documentation is available in the medical record and/or regulatory documents to describe all protocol exceptions, deviations and violations. The DF/HCC Sponsor will also be responsible for ensuring that all protocol violations/deviations are promptly reported per DFCI IRB guidelines.

Participating Institutions: Protocol deviations require prospective approval from the DFCI IRB. The Participating Institution must submit the deviation request to the Coordinating Center who will then submit the deviation request to the DFCI IRB. Upon DFCI IRB approval the deviation is submitted to the Participating Institution IRB, per institutional policy. A copy of the Participating Institution's IRB report and determination will be

forwarded to the Coordinating Center within 10 business days after the original submission.

All protocol violations must be sent to the Coordinating Center in a timely manner.

Coordinating Center: Upon receipt of the violation/deviation report from the Participating Institution, the Coordinating Center will submit the report to the DF/HCC Sponsor for review. Subsequently, the Participating Institution's IRB violation/deviation report will be submitted to the DFCI IRB for review per DFCI IRB reporting guidelines.

3.10 Safety Assessments and Toxicity Monitoring

The study teams at all participating institutions are responsible for protecting the safety, rights and well-being of study participants. Recording and reporting of adverse events that occur during the course of a study help ensure the continuing safety of study participants.

All participants receiving investigational agents will be evaluated for safety. The safety parameters include all laboratory tests and hematological abnormalities, physical examination findings, and spontaneous reports of adverse events reported by participants. All toxicities encountered during the study will be evaluated according to the NCI criteria specified in the protocol. Life-threatening toxicities must be reported immediately to the DF/HCC Sponsor via the Coordinating Center.

Additional safety assessments and toxicity monitoring will be outlined in the protocol.

3.10.1 Guidelines for Reporting Serious Adverse Events

Guidelines for reporting Adverse Events (AEs) and Serious Adverse Events (SAEs) are detailed in protocol section 9.

Participating Institutions must report the SAEs to the DF/HCC Sponsor and the Coordinating Center following the DFCI IRB Adverse Event Reporting Policy.

The Coordinating Center will maintain documentation of all Participating Institution Adverse Event reports and be responsible for communicating to all participating investigators, any observations reportable under the DFCI IRB Reporting Requirements. Participating Institutions will review and submit to their IRB according to their institutional policies and procedures

3.10.2 Guidelines for Processing IND Safety Reports

The DF/HCC Sponsor will review all IND Safety Reports and ensure that all IND Safety Reports are distributed to the Participating Institutions. Participating Institutions will review and submit to their IRB according to their institutional policies and procedures.

3.11 Data Management

The DF/HCC ODQ develops case report forms (CRF/eCRFs), for use with the protocol. These forms are designed to collect data for each study. The DF/HCC ODQ provides a web based training for eCRF users.

3.11.1 Data Forms Review

Data submissions are monitored for timeliness and completeness of submission. Participating Institutions are notified of their data submission delinquencies in accordance with the following:

Incomplete or Questionable Data
If study forms are received with missing or questionable data, the submitting institution will receive a written or electronic query from the DF/HCC ODQ Data Analyst, Coordinating Center or designee. Responses to all queries should be completed and submitted within 14 calendar days. Responses may be returned on the written query or on an amended paper case report form, or in the case of electronic queries, within the electronic data capture (eDC) system. In the case of a written query for data submitted on a paper case report form, the query must be attached to the specific data being re-submitted in response.

Missing Forms
If study forms are not submitted on schedule, the Participating Institution will receive a Missing Form Report from the Coordinating Center noting the missing forms. These reports are compiled by the DF/HCC ODQ and distributed on a monthly basis.

4. REQUISITIONING INVESTIGATIONAL DRUG

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 local 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.

5. MONITORING: QUALITY CONTROL

The quality control process for a clinical trial requires verification of protocol compliance and data accuracy. The Coordinating Center, with the aid of the ODQ provides quality control oversight for the protocol.

5.1 Ongoing Monitoring of Protocol Compliance

The Participating Institutions will be required to submit participant source documents to the Coordinating Center for monitoring. Participating Institution will also be subject to at least one on-site monitoring conducted by the Coordinating Center's Clinical Trial Specialist.

The Coordinating Center will implement ongoing monitoring activities to ensure that Participating Institutions are complying with regulatory and protocol requirements, data quality, and participant safety. Monitoring will occur before the clinical phase of the protocol begins, continue during protocol performance and through study completion. Additional monitoring practices may include but are not limited to; source verification, review and analysis of the following: eligibility requirements of all participants , informed consent procedures, adverse events and all associated documentation, study drug administration/treatment, regulatory files, protocol deviations, pharmacy records, response assessments, and data management.

The DF/HCC Lead Institution will maintain regular and ongoing communication to Participating Institutions about study related information.

On-Site Monitoring will occur at least once per non DF/HCC site. Initial site visit to occur after first participant is enrolled or after study has been activated for 9 months, whichever comes first. Additional on-site monitoring may occur at the request of the DF/HCC Sponsor. Participating Institutions will be required to provide access to participants' complete medical record and source documents for source documentation verification and Site Regulatory Binder.

Virtual Monitoring will take place for verification of informed consent and eligibility, study visit source documents and CRF, investigational product accountability, CRF review for missing data and query resolution, AEs, SAEs, and protocol endpoints unless on-site monitoring is requested by the DF/HCC Sponsor. Participating Institutions will be required to forward de-identified copies of participants' medical record and source documents to the Coordinating Center.

All data submitted to the DF/HCC ODQ will be monitored for timeliness of submission, completeness, and adherence to protocol requirements. The Coordinating Center and if applicable, ODQ Data Analysts assigned to the protocol, will perform the ongoing protocol data compliance monitoring.

5.2 Monitoring Reports

The DF/HCC Sponsor will review all monitoring reports for on-site and remote monitoring of Participating Institutions to ensure protocol compliance. The DF/HCC Sponsor may increase the monitoring activities at Participating Institutions that are unable to comply with the protocol, DF/HCC Sponsor requirements or federal and local

regulations. Participating Institutions may also be subject to an audit as determined by the DF/HCC Sponsor.

6. AUDITING: QUALITY ASSURANCE

Auditing is a method of Quality Assurance. Its main focus is to measure whether standards and procedures were followed. Auditing is the systematic and independent examination of all trial related activities and documents. Audits determine if evaluated activities were appropriately conducted and whether data was generated, recorded and analyzed, and accurately reported per the protocol, Standard Operating Procedures (SOPs), and the Code of Federal Regulations (CFR).

6.1 Audit Plan: DF/HCC Sponsored Trials

Auditing of this protocol will take place as determined by DFCI ODQ. One on-site audit will be scheduled by the ODQ, assuming at least three participants have been treated on protocol at the site. Approximately 3-4 participants would be audited at the site over a 2 day period. If violations which impact participant safety or the integrity of the study are found, more participant records may be audited.

6.2 Audit Notification

It is the Participating Institution's responsibility to notify the Coordinating Center of all scheduled audit dates (internal or NCI) and re-audit dates (if applicable), which involve this protocol. All institutions will forward a copy of final audit and/or re-audit reports and corrective action plans (if applicable) to the Coordinating Center, within 12 weeks after the audit date.

6.3 Audit Reports

The DF/HCC Sponsor will review all final audit reports and corrective action plans if applicable. The Coordinating Center, must forward these reports to the DF/HCC ODQ per DF/HCC policy for review by the DF/HCC Audit Committee. Based upon the audit assessments the DF/HCC Audit Committee could accept or conditionally accept the audit rating and final report. Conditional approval could require the DF/HCC Sponsor to implement recommendations or require further follow-up. For unacceptable audits, the DF/HCC Audit Committee would forward the final audit report and corrective action plan to the DFCI IRB as applicable.

6.4 Participating Institution Performance

The DF/HCC Sponsor, DFCI IRB is charged with considering the totality of an institution's performance in considering institutional participation in the protocol.

6.4.1 Corrective Actions

Participating Institutions that fail to meet the performance goals of accrual, submission of timely and accurate data, adherence to protocol requirements, and compliance with state and federal regulations, may be recommended for a six-month probation period. Such institutions must respond with a corrective action plan and must demonstrate during the probation period that deficiencies have been corrected, as evidenced by the improved performance measures. Participating Institutions that fail to demonstrate significant improvement will be considered by the DF/HCC Sponsor for revocation of participation. A DF/HCC Sponsor and/or the DFCI IRB may terminate a site's participation if it is determined that a site is not fulfilling its responsibilities as described above.

DANA-FARBER CANCER INSTITUTE
Nursing Protocol Education Sheet

Protocol Number:	16-301
Protocol Name:	A Multicenter Phase 2 Clinical Trial of Pembrolizumab in Refractory Metastatic Anal Cancer
DFCI Site PI:	James Cleary, MD
DFCI Research Nurse:	Christopher Graham, RN, BSN ; Laura Casadonte, RN

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. • The Study Design is in Section 2 • The Study Rationale is in Section 4.3 • A cycle is defined as 21 days– Section 7.1
Dose Calc.	• *Pembrolizumab* is dosed in mg and is a fixed dose (Table 2)
Study Drug Administration	Agent *Administration* Guidelines are found in Section 7 • *Pembrolizumab* is given intravenously every 3 weeks(Section 7.1.1 • *Pembrolizumab* is administered over 30 minutes. A window of -5 minutes to +10 minutes is acceptable (Section 7.1.1) • Criteria to treat in section 8.1
Dose Mods & Toxicity	*Dose Modifications/Dosing Delay for Toxicity* are outlined in Section 8.1 • This protocol uses NCI CTCAE criteria, version 4.0 (Section 9.8.2)
Con Meds	*Concomitant Therapy* Guidelines are in Section 7.3 • Permitted concomitant medications are in section 7.3.1 • Prohibited concomitant medications are in section 7.3.2
Required Data	*Study Calendar and Assessment Required data* are outlined in Section 12 • The study calendar is in Section 12 • **Vital signs:** The time points are in Section 12. ○ Specific vital sign guidelines for infusion reactions are listed in Section 8, Table 4 • **PKs**: The time points are in Section 12 • **Biomarkers**: The time points are in Section 12
Charting Tips	**All study drugs require documentation of exact administration time.** Please be sure to DOCUMENT study medication **actual** UP/DOWN times in medical record (e.g. LMR, eMAR, nursing notes). **Edit eMAR as needed to match the exact time given**. • If there is a discrepancy in the infusion time, delay in administration, or the infusion takes longer than is permitted by the guidelines of the protocol, please **document the reason for the discrepancy in the medical record.** Please be sure to also DOCUMENT any required observation periods, any additional vital signs, routes of administration, injection sites, and exact time of PK collections.

PHARMACY MANUAL

PEMBROLIZUMAB (MK-3475)

KEYNOTE 289

MSD
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

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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.