Penn Medicine
University of Pennsylvania School of Medicine

CLINICAL RESEARCH PROTOCOL

Phase II Study of Pembrolizumab after Curative Intent Treatment for Oligometastatic Non-Small Cell Lung Cancer

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1.0 TRIAL SUMMARY

Abbreviated Title	Pembrolizumab in Oligometastatic NSCLC
Trial Phase	Phase II
Clinical Indication	The treatment of patients with oligometastatic non-small cell lung cancer (NSCLC), after treatment with definitive intent to all identifiable sites of disease.
Trial Type	Interventional
Type of control	Single arm – no control
Route of administration	Intravenous
Trial Blinding	Open-label
Treatment Groups	Pembrolizumab 200 mg every 3 weeks
Number of trial subjects	47 patients will be enrolled
Estimated duration of trial	The trial will require up to 60 months from the time the first subject signs informed consent until the last subject's last visit.
Duration of Participation	Each subject will participate in the trial from the time the subject signs the Informed Consent Form (ICF) through the final protocol-specified contact. Within 4-12 weeks of completing treatment with definitive intent, eligible subjects will receive assigned treatment on Day 1 of each 3-week (Q3W) dosing cycle. Treatment with Pembrolizumab will continue for up to 6 months or 8 cycles (24 weeks) in the absence of documented disease progression, unacceptable adverse event(s), intercurrent illness precluding further administration of treatment, investigator's decision to withdraw the subject, subject withdrawal of consent, pregnancy of the subject, noncompliance with trial treatment or procedure requirements, or administrative reasons. Patients with no evidence of disease progression at 6 months may receive an additional 6 months of therapy with Pembrolizumab, at the discretion of the treating oncologist. After the end of treatment, each subject will be followed for a minimum of 30 days for adverse event monitoring (serious adverse events will be collected for up to 90 days after the end of treatment). Subjects will have post-treatment follow-up for disease status for 5 years or until one of the following events: (1) disease progression; (2) initiation of non-study cancer treatment; (3) withdrawal of study consent; (4) loss to follow-up or (5) death. In addition, survival status beyond PD or subsequent therapies will be documented.

2.0 TRIAL DESIGN

2.1 Trial Design

This is a single-arm Phase II trial of intravenous (IV) Pembrolizumab (MK-3475) in subjects with oligometastatic non-small cell lung cancer (NSCLC) who have completed treatment with definitive intent to all identifiable sites of tumor. Forty-two subjects will be enrolled in this trial to examine the efficacy of adding Pembrolizumab to the treatment regimen for patients with oligometastatic NSCLC being treated with definitive intent. Within 4-12 weeks after completion of treatment with definitive intent, subjects will receive Pembrolizumab at a fixed dose of 200 mg every 3 weeks (q3W).

Subjects will be evaluated every 12 weeks (84 ± 7 days) with radiographic imaging to assess disease status. If new signs or symptoms of progression occur between scheduled scans, directed imaging will be obtained at the clinically appropriate time point to document disease status. Investigators will make all treatment-based decisions using RECIST 1.1. Adverse events will be monitored throughout the trial and graded in severity according to the NCI Common Terminology Criteria for Adverse Events (CTCAE) version 4.0.

Treatment with Pembrolizumab will continue for a minimum of six months in the absence of (1) documented disease progression, (2) unacceptable adverse event(s), (3) intercurrent illness that prevents further administration of treatment, (4) investigator's decision to withdraw the subject, (5) subject withdrawal of consent, (6) pregnancy of the subject, (7) noncompliance with trial treatment or procedure requirements, (8) institution of alternative systemic treatment, or (9) other administrative reasons. In the absence of disease progression, patients who have received 6 months of treatment may go on to receive an additional 6 months of therapy with Pembrolizumab, at the discretion of the treating oncologist.

After the end of treatment, each subject will be followed for a minimum of 30 days for adverse event monitoring (serious adverse events will be collected for up to 90 days after the end of treatment). Subjects will have post-treatment follow-up for disease status until one of the following events: (1) disease progression; (2) initiation of non-study cancer treatment; (3) withdrawal of study consent; (4) loss to follow-up or (5) death. In addition, survival status beyond the establishment of PD or initiation of subsequent therapies will be documented, as will all documented post-progression therapy. The primary objectives of the trial include determination of PFS per RECIST 1.1 and safety as assessed by a variety of parameters of adverse events (AEs), including incidence and time to first Grade 3-5 AE. Pre-specified adverse events of clinical interest include the following events: 1) Grade ≥ 3 diarrhea 2) Grade ≥ 2 colitis, 3) Grade ≥ 2 pneumonitis, 4) Grade ≥ 3 hypo- or hyperthyroidism, 5) Grade ≥ 2 hypophysitis, 6) Grade ≥ 2 uveitis, and 7) Grade ≥ 2 nephritis. Secondary objectives include Overall Survival and health-related quality-of-life.

Participation in this trial will require supplying tumor tissue from either a newly obtained formalin-fixed specimen (preferred) or an older formalin-fixed, paraffin-embedded specimen, from locations not radiated prior to biopsy. The specimen will be evaluated at a central laboratory facility for expression status of PD-L1 in a retrospective manner. Eligibility for the trial will not be dependent upon PD-L1 expression status, but the sponsor may amend the trial in the future if new data arise regarding the predictive value of PD-L1 expression. Any patient enrolled on the study prior to such an amendment, however, will remain on study.

3.0 OBJECTIVE(S) & HYPOTHESIS(ES)

3.1 Primary Objectives & Hypotheses

1) Objective: To evaluate the progression free survival of patients with oligometastatic NSCLC who are treated with Pembrolizumab after therapy with definitive intent

   Hypothesis 1: Patients treated with Pembrolizumab after definitive treatment for oligometastatic NSCLC will have an increased median progression free survival, as measured by RECIST 1.1.

   Exploratory Hypothesis: Patients treated with Pembrolizumab after definitive treatment for oligometastatic NSCLC will have an increased median progression free survival, as measured by immune related response criteria (irRC).

   Note: The inclusion of both RECIST and irRC measures in this objective indicates the equipoise in the research community regarding the most appropriate measure of PFS in patients receiving immunotherapy. Primary analysis is planned based upon RECIST criteria, but we will also monitor irRC closely.

2) Objective: To evaluate toxicities (CTCAE v4.0 scoring) of Pembrolizumab in patients with oligometastatic NSCLC after therapy with definitive intent

   Hypothesis: Pembrolizumab will be well tolerated in patients with oligometastatic NSCLC after therapy with definitive intent

3.2 Secondary Objective(s) & Hypothesis(es)

1) Objective: To assess the longitudinal effect of Pembrolizumab on quality of life when used after definitive treatment for oligometastatic NSCLC.

   Hypothesis: Patients treated with Pembrolizumab after definitive treatment for oligometastatic NSCLC will not have a significant decrement in quality of life compared to baseline, as measured by the FACT-L instrument.

2) Objective: To evaluate overall survival of patients with oligometastatic NSCLC who are treated with Pembrolizumab after therapy with definitive intent.

   Hypothesis: Overall survival will be determined from the time Pembrolizumab is first initiated, which will be pivotal in the design of future phase II and III trials.

3.3 Exploratory Objectives

Objective: To evaluate the PFS and OS as a function of PD-L1 expression, as well as other emerging indices of benefit.

4.0 BACKGROUND & RATIONALE

4.1 Background

4.1.1 Pharmaceutical and Therapeutic Background

The importance of intact immune surveillance in controlling outgrowth of neoplastic transformation has been known for decades [1]. Accumulating evidence shows a correlation between tumor-infiltrating lymphocytes (TILs) in cancer tissue and favorable prognosis in various malignancies [2-6]. 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 between tumor cells and the immune system 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) [7, 8]. The structure of murine PD-1 has been resolved.[9] 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 [10-13]. 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 [14, 15]. 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 [16, 17]. Expression has also been shown during thymic development on CD4-CD8- (double negative) T-cells as well as subsets of macrophages and dendritic cells [17]. 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 [14, 18-20]. 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.[14] Although healthy organs express little (if any) PD-L1, a variety of cancers have been 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).[21] This suggests that the PD-1/PD-L1 pathway plays a critical role in tumor immune evasion and should be considered as an attractive target for therapeutic intervention.

Pembrolizumab (previously known as MK-3475 and SCH 900475) 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.

4.1.2 Preclinical and Clinical Trial Data

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

4.2 Rationale

4.2.1 Rationale for the Trial and Selected Subject Population

NSCLC is the most common cause of cancer death in the United States. Almost half of patients present with metastatic disease at diagnosis, and are considered incurable with a historical median overall survival of 6 to 12 months.[22] Recent research, however, has revealed significant heterogeneity among patients with metastatic NSCLC. Patients with a targetable mutation detected by advanced molecular techniques can enjoy a much longer disease free interval compared to the overall population, if treated with appropriate therapy. In addition, approximately 7% of patients with NSCLC present with a solitary site of metastatic disease or later develop solitary sites of progression. In the past, such patents were generally considered incurable and treated with palliative chemotherapy and radiation therapy.[23] This conventional approach was based, in part, upon the Halstead theory of cancer progression, which holds that cancer spreads in an orderly fashion through the lymphatic system. Based upon this theory, which was first published in 1894, once a cancer metastasized, it became a systemic disease and cure was impossible.[24] Exposing patients with metastatic disease to the toxicities of definitive intent surgical and radiation treatments, with this rationale, could not be justified.

More recently, Hellman and Weichselbaum put forth a theory that the timing of cancer metastasis falls on a continuum. While some malignancies spread contiguously and others are systemic from diagnosis, most malignancies fall on a spectrum between these two extremes. This concept appears valid on the surface given our clinical observations in which we see some patients with a localized tumor fare poorly while others with disseminated metastases live for a prolonged time. Recent molecular analyses revealing heterogeneity between primary and metastatic lesions support this contemporary theory. One hypothesis that links this theory to our clinical observation is that a "second hit" must happen to the malignant cells to allow metastasis. An accumulation of additional "hits" can then allow a cancer cell to go from localized to oligometastatic to uncontrolled metastatic behavior. With this newer paradigm, the concept of treating some metastatic lesions aggressively is increasingly justified, as their mere presence no longer *de facto* rules out therapy with curative intent. The advent of minimally invasive surgery and stereotactic body radiotherapy (SBRT) has made such treatments feasible with less toxicity. This approach has already become standard of care for some patients with metastatic colorectal cancer with isolated or limited hepatic metastases, and has been extended to other malignancies such as breast cancer. Multiple retrospective studies now show that this approach in selected patients with lung cancer is associated with a significant improvement in overall and progression free survival when compared to historical controls.[23, 25, 26].

With limited formal data [27], this approach has been used for many years in NSCLC patients with isolated adrenal or CNS metastases, where long-term survival has been observed. Indeed, in some series the number of metastatic sites was more strongly prognostic than the presence of extrathoracic disease itself.[28] Based upon these and other data, patients with a small number of metastases are often treated definitively to their primary tumor and metastatic site, rendering them radiographically free of disease. This approach has recently been endorsed by the ESMO clinical practice guidelines.

It is unclear, however, whether these patients should receive systemic therapy after completion of definitive treatment to metastatic lesions. There are no data to guide the use of cytotoxic chemotherapy in this setting. In colorectal cancer, where the treatment of oligometastatic disease with curative intent is more established, there is no overall survival benefit for the use of perioperative chemotherapy in the oligometastatic setting.[29] The current standard of care for metastatic lung cancer involves the use of platinum doublet chemotherapy followed by consideration of maintenance chemotherapy. This approach has been validated for patients with clinically evaluable metastatic disease in whom cure is not possible, but has questionable validity in patients where all evident disease has been definitively removed or ablated. In retrospective analyses of patients with oligometastatic NSCLC treated with definitive intent, very few received subsequent chemotherapy and its use has never been documented to improve overall survival or progression free survival. Median overall survival in this group is approximately 20 months, with a progression free survival of approximately 6.6 months.[23]

NSCLC has historically been considered non-responsive to immunotherapy, but recent advances using monoclonal antibodies targeting the Programmed Death 1 (PD-1) pathway has yielded some impressive clinical responses using agents that are reasonably well tolerated. Single agent response rates in heavily pre-treated patients approach 20 to 25%, and those figures appear to be even higher in patients whose tumors express PDL1 or in patients without pretreatment. (Garon, et al, ASCO 2014 Abstracts 8007 and 8020). Many of the responses seen with targeting of the PD-1 pathway are quite durable. The use of such agents might be ideal in patients with oligometastatic disease, since the overall burden of disease is low, patients have recently completed a definitive treatment modality that may be associated with antigen release, and patients will generally be fit and able to tolerate therapy. This study aims to assess the feasibility of administering Pembrolizumab, a humanized monoclonal antibody binding PD-1, in patients with solitary and oligometastatic NSCLC who have undergone treatment with definitive intent and are technically cancer-free or at least free from “active disease.”

4.2.2 Rationale for Dose Selection/Regimen/Modification

An open-label Phase I trial (Protocol 001) evaluating Pembrolizumab at 1 mg/kg, 3 mg/kg, and 10 mg/kg, administered every 2 weeks (Q2W) revealed no dose-limiting toxicities and showed objective evidence of tumor size reduction at all dose levels. Recent data from other clinical studies in the Pembrolizumab program have shown that a lower dose of Pembrolizumab and a less frequent schedule may be sufficient for target engagement and clinical activity.

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.

4.2.3 Rationale for Endpoints

4.2.3.1 Efficacy Endpoints

4.2.3.1.1 Primary

Progression free survival (PFS), defined as the time from initiation of Pembrolizumab to documented disease progression, death due to any cause or last patient follow-up that documented lack of disease progression, is an acceptable scientific endpoint in the single-arm evaluation of novel treatment in a population that is expected to have a longer overall survival than would be expected from the general population of patients with metastatic NSCLC. In this case, patients with oligometastatic NSCLC are known to have significantly longer overall survival than patients with widely metastatic NSCLC. The choice of PFS is appropriate because a recurrence would indicate failure of the therapeutic approach to the patient.

4.2.3.1.2 Secondary

When adding systemic therapy in the definitive setting for oligometastatic disease, we are adding therapy with potential side effects to a time period often not associated with active therapy. As such, it is essential for us to monitor quality of life throughout the course of therapy. This will help determine if this treatment regimen is feasible when implemented widely. To do this, we will utilize prospective FACT-L scores. This extensively validated instrument incorporates the general FACT quality of life measure and also includes a subscale to identifying issues unique to patients with lung cancer.[30]

5.0 METHODOLOGY

5.1 Entry Criteria

5.1.1 Diagnosis/Condition for Entry into the Trial

Male/female patients with oligometastatic NSCLC (defined as ≤4 metastatic sites of disease), all treated with definitive intent using radiation, surgery, RFA, chemoradiation therapy, other definitive modalities or combinations of these.

5.1.2 Subject Inclusion Criteria

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

1. Provide written informed consent for the trial.
2. ≥ 18 years of age on day of signing informed consent.
3. Completion of definitive therapy 4-12 weeks prior to enrollment. There are no specific limitations on which treatment modalities can be used in the definitive setting (e.g. the use of adjuvant chemotherapy is acceptable), but all other treatments must be complete at least 4 weeks prior to enrollment.
4. Provision of tissue from an archival tissue sample or newly obtained core or excisional biopsy of a tumor lesion.
    a. Tumor tissue may be from a diagnostic biopsy or a portion of a surgical specimen, if surgery is a component of definitive intent therapy.

b. Formalin fixed paraffin embedded (FFPE) tissue samples are acceptable; a fine needle aspirate, frozen sample, plastic embedded sample, cell block, clot, bone, bone marrow or cytologic specimen will not be acceptable for IHC analysis.

c. It is recommended that FFPE blocks be sectioned fresh (within 7 days of sectioning and sending for PD-L1 analysis) onto positively charged slides.

d. Recommended fixation time for samples is 24 hours to 48 hours in 10% neutral buffered formalin.

5. Performance status of 0 or 1 on the ECOG Performance Scale.
6. Adequate organ function as defined in Table 1, all screening labs should be performed within 10 days of treatment initiation.

Table 1 Adequate Organ Function Laboratory Values

System	Laboratory Value
Hematological	
Absolute neutrophil count (ANC)	≥ 1,250 / mcL
Platelets	≥ 100,000 / mcL
Hemoglobin	≥ 9 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** ≥ 50 mL / min for subject with creatinine levels > 1.5 X institutional ULN
Hepatic	
Serum total bilirubin	≤ 1.5 X ULN **OR**
	Direct bilirubin ≤ ULN for subjects with total bilirubin levels > 1.5 ULN
AST (SGOT) and ALT (SGPT)	≤ 2.5 X ULN **OR** ≤ 5 X ULN for subjects with liver metastases
[a]Creatinine clearance should be calculated per institutional standard.	

7. Female subject of childbearing potential should have a negative urine or serum pregnancy within 72 hours prior to receiving the first dose of study medication. If the urine test is positive or cannot be confirmed as negative, a serum pregnancy test will be required.
8. Female subjects of childbearing potential should be willing to use 2 methods of birth control or be surgically sterile, or abstain from heterosexual activity for the duration of

the study through 120 days after the last dose of study medication. Subjects of childbearing potential are those who have not been surgically sterilized or have not been free from menses for > 1 year.

9. Male subjects who are partnered with women of childbearing potential should be willing to use 2 methods of birth control, be surgically sterile or abstain from heterosexual activity for the duration of the study through 120 days after the last dose of study medication.

5.1.3 Subject Exclusion Criteria

The subject will be excluded from participating in the trial if any of the following criteria are met:

1. Currently participating in or has participated in a study of an investigational agent or using an investigational device within 4 weeks of the first dose of treatment.
2. Diagnosis of immunodeficiency or exposure to systemic steroid therapy or any other form of immunosuppressive therapy within 7 days prior to the first dose of trial treatment (Nasal or oral inhalers are permissible).
3. Prior monoclonal antibody within 4 weeks prior to study Day 1 or individuals who have not recovered (i.e., ≤ Grade 1 or at baseline) from adverse events due to agents administered more than 4 weeks earlier.
4. Prior chemotherapy, targeted small molecule therapy, or radiation therapy within 2 weeks prior to Day 1 drug administration on study or inability to recover (i.e., ≤ Grade 1 or at baseline) from adverse events due to a previously administered agent.
    - Note: Subjects with ≤ Grade 2 neuropathy or alopecia are exceptions to this criterion and may qualify for the study.
    - Note: If subject had major surgery, they must have recovered adequately from the toxicity and/or complications from the intervention prior to starting therapy.
5. Known additional malignancy that is progressing or requires active treatment. Exceptions include basal cell carcinoma of the skin, squamous cell carcinoma of the skin, non-invasive bladder tumors, or in situ cervical cancer
6. Known untreated central nervous system (CNS) metastases and/or carcinomatous meningitis.
7. Active autoimmune disease requiring systemic treatment within the past 3 months or a documented history of clinically severe autoimmune disease, or a syndrome that requires systemic steroids or immunosuppressive agents. Subjects with vitiligo or resolved childhood asthma/atopy are an exception to this rule. Subjects that require intermittent use of bronchodilators or local steroid injections are not excluded from the study. Subjects with hypothyroidism stable on hormone replacement or Sjorgen's syndrome are not excluded from the study.
8. Evidence of pre-existing interstitial lung disease, has a history of non-infectious pneumonitis which required steroids, or has current pneumonitis.
9. Active infection requiring systemic therapy with IV antibiotics
10. 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.

11. Known psychiatric or substance abuse disorders that would interfere with cooperation with the requirements of the trial.
12. 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.
13. Prior therapy with an anti-PD-1, anti-PD-L1, anti-PD-L2, anti-CD137, or anti-Cytotoxic T-lymphocyte-associated antigen-4 (CTLA-4) antibody (including ipilimumab or any other antibody or drug specifically targeting T-cell co-stimulation or checkpoint pathways).
14. Known history of Human Immunodeficiency Virus (HIV) (HIV 1/2 antibodies).
15. Known active Hepatitis B (e.g., HBsAg positive or HBV DNA detectable) or Hepatitis C (e.g., HCV RNA [qualitative] is detected).
16. Receipt of live vaccine within 30 days prior to the first dose of trial treatment.
17. Progressive disease or sites of new metastasis after definitive therapy for oligometastatic disease.
18. Completion of definitive therapy for oligometastatic disease greater than 12 weeks prior to enrollment.

5.2 Trial Treatments

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

Table 2 Trial Treatment

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

5.2.1 Dose Selection/Modification

5.2.1.1 Dose Selection

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

5.2.1.2 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. See Section 5.4.1 for supportive care guidelines, including use of corticosteroids.

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

Toxicity	Hold Treatment For Grade	Timing for Restarting Treatment	Treatment Discontinuation
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)[a]	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. Therapy with pembrolizumab can be continued while endocrine replacement therapy is instituted	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		Therapy with pembrolizumab can be continued while thyroid replacement therapy is instituted	Therapy with pembrolizumab can be continued while thyroid replacement therapy is instituted
Infusion Reaction	2[b]	Toxicity resolves to Grade 0-1	Permanently discontinue if toxicity develops despite adequate premedication
	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 or Recurrent Grade 2	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
Myocarditis	1-2	Toxicity resolves to Grade 0	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[c]	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

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

Toxicity	Hold Treatment For Grade	Timing for Restarting Treatment	Treatment Discontinuation
Note: Permanently discontinue for any severe or Grade 3 (Grade 2 for pneumonitis) drug-related AE that recurs or any life-threatening event.			
[a] 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.			
[b] 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; Refer to Table 4– Infusion Treatment Guidelines for further management details.			
[c] 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.			

With investigator and medical monitor agreement, subjects with a laboratory adverse event still at Grade 2 after 12 weeks may continue treatment in the trial only if asymptomatic.

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

5.2.2 Timing of Dose Administration

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

All trial treatments will be administered on an outpatient basis.

Pembrolizumab 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).

5.3 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 Sponsor. The final decision on any supportive therapy or vaccination rests with the investigator and/or the subject's primary physician. However, the decision to continue the subject on trial therapy or vaccination schedule requires the mutual agreement of the Investigator, the Sponsor, and the subject.

5.3.1 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 medications 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. Examples of acceptable concomitant medications include zoledronic acid, denosumab, megestrol acetate, and cannabinoids.

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

5.3.2 Prohibited Concomitant Medications

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

- Anti-cancer systemic chemotherapy or biological therapy
- Immunotherapy not specified in this protocol
- Investigational agents other than Pembrolizumab
- Radiation therapy
    - Note: Radiation therapy to a symptomatic solitary lesion or to the brain may be allowed after consultation with Sponsor, but would be regarded as a disease progression event for the primary outcome.
- Live vaccines within 30 days prior to the first dose of trial treatment and while participating in the trial. Examples of live vaccines include, but are not limited to, the following: measles, mumps, rubella, chicken pox, yellow fever, rabies, BCG, and typhoid (oral) vaccine. Seasonal influenza vaccines for injection are generally killed virus vaccines and are allowed; however intranasal influenza vaccines (e.g. Flu-Mist®) are live attenuated vaccines and are not allowed.
- Oral glucocorticoids for any purpose other than an abbreviated course to modulate symptoms from an event of clinical interest of suspected immunologic etiology. The use of physiologic replacement doses of corticosteroids may be approved after consultation with the Sponsor-Investigator and Medical Monitor. Inhaled and topical steroids are permitted.

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 or qualified designee deems to be medically necessary.

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

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

5.4 Rescue Medications & Supportive Care

5.4.1 Supportive Care Guidelines

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

Note: if after the evaluation the event is determined not to be related, the investigator does not need to follow the treatment guidance (as outlined below). Refer to Section 5.2.1.2 for dose modification.

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

- **Pneumonitis:**
    - For Grade 2 events, treat with systemic corticosteroids. When symptoms improve to Grade 1 or less, steroid taper should be started and continued over no less than 4 weeks.
    - For Grade 3-4 events, immediately treat with intravenous steroids. Administer additional anti-inflammatory measures, as needed.
    - Add prophylactic antibiotics for opportunistic infections in the case of prolonged steroid administration.
- Diarrhea/Colitis: Subjects should be carefully monitored for signs and symptoms of enterocolitis (such as diarrhea, abdominal pain, blood or mucus in stool, with or without fever) and of bowel perforation (such as peritoneal signs and ileus).
    - All subjects who experience diarrhea/colitis should be advised to drink liberal quantities of clear fluids. If sufficient oral fluid intake is not feasible, fluid and electrolytes should be replaced via IV infusion. For Grade 2 or higher diarrhea, consider GI consultation and endoscopy to confirm or rule out colitis.
    - For Grade 2 diarrhea/colitis, administer oral corticosteroids.
    - For Grade 3 or 4 diarrhea/colitis, treat with intravenous steroids followed by high dose oral steroids.
    - When symptoms improve to Grade 1 or less, steroid taper should be started and continued over no less than 4 weeks.
- **Type 1 diabetes mellitus (if new onset, including diabetic ketoacidosis [DKA]) or ≥ Grade 3 Hyperglycemia, if associated with ketosis (ketonuria) or metabolic acidosis (DKA)**

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

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

- **Hyperthyroidism or Hypothyroidism**:

  Thyroid disorders can occur at any time during treatment. Monitor patients for changes in thyroid function (at the start of treatment, periodically during treatment, and as indicated based on clinical evaluation) and for clinical signs and symptoms of thyroid disorders.
  - **Grade 2** hyperthyroidism events (and **Grade 2-4** hypothyroidism):
    - In hyperthyroidism, non-selective beta-blockers (e.g. propranolol) are suggested as initial therapy.
    - In hypothyroidism, thyroid hormone replacement therapy, with levothyroxine or liothyroinine, is indicated per standard of care.
  - **Grade 3-4** hyperthyroidism
    - Treat with an initial dose of IV corticosteroid followed by oral corticosteroids. When symptoms improve to Grade 1 or less, steroid taper should be started and continued over no less than 4 weeks. Replacement of appropriate hormones may be required as the steroid dose is tapered.

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

- **Renal Failure or Nephritis**:
  - For **Grade 2** events, treat with corticosteroids.

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

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

Table 4 below provides treatment guidelines for subjects who experience an infusion reaction associated with administration of Pembrolizumab.

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

Table 4 Infusion Reaction Treatment Guidelines		
NCI CTCAE Grade	**Treatment**	**Premedication at subsequent dosing**
Grade 2 Requires infusion interruption but responds promptly to symptomatic treatment (e.g., antihistamines, NSAIDS, 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 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 1.5 h (± 30 minutes) prior to infusion of Pembrolizumab with: Diphenhydramine 50 mg po (or equivalent dose of antihistamine). Acetaminophen 500-1000 mg po (or equivalent dose of antipyretic).

Table 4 Infusion Reaction Treatment Guidelines		
NCI CTCAE Grade	**Treatment**	**Premedication at subsequent dosing**
Grades 3 or 4 Grade 3: Prolonged (i.e., not rapidly responsive to symptomatic medication and/or brief interruption of infusion); recurrence of symptoms following initial improvement; hospitalization indicated for other clinical sequelae (e.g., renal impairment, pulmonary infiltrates) Grade 4: Life-threatening; pressor or ventilatory support indicated	**Stop Infusion.** Additional appropriate medical therapy may include but is not limited to: IV fluids Antihistamines NSAIDS Acetaminophen Oxygen Pressors Corticosteroids Epinephrine Increase monitoring of vital signs as medically indicated until the subject is deemed medically stable in the opinion of the investigator. Hospitalization may be indicated. **Subject is permanently discontinued from further trial treatment administration.**	No subsequent dosing
Appropriate resuscitation equipment should be available in the room and a physician readily available during the period of drug administration.		

5.5 Diet/Activity/Other Considerations

5.5.1 Diet

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

5.5.2 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. Male subjects of reproductive potential must agree to avoid impregnating a partner while receiving study drug and for 120 days after the last dose of study drug either by practicing total abstinence from heterosexual activity or with a female partner using 2 methods of birth control. 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, copper intrauterine device, sponge, or spermicide. Appropriate hormonal contraceptives will include any registered and marketed contraceptive agent that contains an estrogen and/or a progestational agent (including oral, subcutaneous, intrauterine, or intramuscular agents).

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

5.5.3 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 without delay and within 24 hours if the outcome is a serious adverse experience (e.g., death, abortion, congenital anomaly, or other disabling or life-threatening complication to the mother or newborn). The study investigator will make every effort to obtain permission to follow the outcome of the pregnancy and report the condition of the fetus or newborn to 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 followed as described above and in Section 7.2.2.

5.5.4 Use in Nursing Women

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

5.6 Subject Withdrawal/Discontinuation Criteria

Subjects may withdraw consent at any time for any reason or be dropped from the trial at the discretion of the investigator should any untoward effect occur. In addition, a subject may be withdrawn by the investigator or the Sponsor if enrollment into the trial is inappropriate, the trial plan is violated, or for administrative and/or other safety reasons. Specific details regarding discontinuation or withdrawal are provided in Section 7.1.4 – Other Procedures.

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

- Withdrawal of consent.
- Confirmed radiographic disease progression

  Note: A subject may be granted an exception to continue on treatment with confirmed radiographic progression if clinically stable or clinically improved, as consistent with irRC.

- Unacceptable adverse experiences or toxicities
- Intercurrent illness that prevents further administration of treatment
- Investigator's decision to withdraw the subject
- Confirmed positive serum pregnancy test and unwillingness to abort pregnancy
- Noncompliance with trial treatment or procedure requirements
- Loss to follow-up
- Completion of 12 months of treatment with Pembrolizumab

  Note: 12 months of study medication is calculated from the date of first dose.
- Other Administrative reasons

The End of Treatment and Follow-up visit procedures are listed in Section 6 (Protocol Flow Chart) and Section 7.1.5 (Visit Requirements). After the end of treatment, each subject will be followed for 30 days for adverse event monitoring (serious adverse events will be collected for 90 days after the end of treatment as described in Section 7.1.5.3.1). Subjects who discontinue for reasons other than progressive disease will have post-treatment follow-up for disease status until disease progression, initiation of non-study cancer treatment, withdrawal of consent or loss to follow-up. After documented disease progression each, subject will be followed by telephone or chart review for overall survival until death, withdrawal of consent, or the end of the study, whichever occurs first. All subsequent therapies will be recorded, if feasible.

5.7 Subject Replacement Strategy

Subjects who receive at least 1 dose of Pembrolizumab will be considered evaluable and will not be replaced.

5.8 Clinical Criteria for Early Trial Termination

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

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

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

6.0 TRIAL FLOW CHART

6.1 Study Flow Chart

Trial Period:	**Screening Phase**		**Treatment Cycles**								**End of Treatment**	**Post-Treatment**		
Treatment Cycle/Title:	Pre-screening (Visit 1)	Main Study Screening (Visit 2)	1	2	3	4	To be repeated beyond 8 cycles 5	6	7	8	Discon	Safety Follow-up	Follow Up Visits	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 8-12 weeks post discon*	Every 12 weeks [a]
Administrative Procedures														
Pre-screening Consent	X													
Informed Consent		X												
Inclusion/Exclusion Criteria		X												
Subject Identification Card		X												
Demographics and Medical History		X												
Prior and Concomitant Medication Review		X	X	X	X	X	X	X	X	X				
Trial Treatment Administration			X	X	X	X	X	X	X	X				
Post-study anticancer therapy status											X	X	X	X
Survival Status			X	X	X	X	X	X	X	X	X	X	X	X

6.1 Study Flow Chart														
Trial Period:	**Screening Phase**		**Treatment Cycles**								**End of Treatment**	**Post-Treatment**		
Treatment Cycle/Title:	Pre-screening (Visit 1)	Main Study Screening (Visit 2)	1	2	3	4	To be repeated beyond 8 cycles 5	6	7	8	Discon	Safety Follow-up	Follow Up Visits	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 8-12 weeks post discon*	Every 12 weeks [a]
Clinical Procedures/Assessments														
Review Adverse Events				X	X	X	X	X	X	X	X	X	X[c]	
Full Physical Examination		X				X				X	X	X	X	
Directed Physical Examination			X	X	X		X	X	X					
Vital Signs and Weight		X	X	X	X	X	X	X	X	X	X	X	X	
ECOG Performance Status	X	X	X	X	X	X	X	X	X	X	X	X	X	
Laboratory Procedures/Assessments: analysis performed by LOCAL laboratory														
Pregnancy Test – Urine or Serum β-HCG	X													
PT/INR and aPTT	X													
CBC with Differential		X		X	X	X	X	X	X	X	X	X	X	
Comprehensive Serum Chemistry Panel		X		X	X	X	X	X	X	X	X	X		
Urinalysis		X				X				X		X		

6.1 Study Flow Chart														
Trial Period:	**Screening Phase**		**Treatment Cycles**								**End of Treatment**	**Post-Treatment**		
Treatment Cycle/Title:	Pre-screening (Visit 1)	Main Study Screening (Visit 2)	1	2	3	4	To be repeated beyond 8 cycles 5	6	7	8	Discon	Safety Follow-up	Follow Up Visits	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 8-12 weeks post discon*	Every 12 weeks [a]
TSH		X		X			X				X	X	X (First 6 months of follow-up; then per physician discretion)	
T3 and FT4		X		X			X				X	X		
Basic Metabolic Panel													X	
Efficacy Measurements														
Tumor Imaging		X[b]				X				X	X		X	
Tumor Biopsies/Archival Tissue Collection/Correlative Studies Blood														
Archival or Newly Obtained Tissue Collection	X													
Patient Reported Outcomes														
FACT-L		X		X	X	X	X	X	X	X	X	X	X[d]	

* Follow-up scans for the first year can be 8-12 weeks. Follow-up beyond the first year should be every 12 weeks (3 months) until 3 years, at which time scan frequency can be at the oncologists' discretion.

[a] Patients in survival follow up (who are no longer on treatment and have moved on to further therapies) require only 6 month follow up of survival status and subsequent cancer therapy treatment only

[b] Tumor imaging may be up to 30 days prior to the start of treatment per section 7.1.5.1

[c] After the end of treatment, each subject will be followed for 30 days for adverse event monitoring (serious adverse events will be collected for 90 days after the end of treatment as described in Section 7.1.5.3.1).

[d] The FACT L is only required to be completed for the first 3 months post treatment (in patients who have not progressed and entered into survival only follow up)

7.0 TRIAL PROCEDURES

7.1 Trial Procedures

The Trial Flow Chart - Section 6.0 summarizes the trial procedures to be performed at each visit. Individual trial procedures are described in detail below. It may be necessary to perform these procedures at unscheduled time points if deemed clinically necessary by the investigator.

Furthermore, additional evaluations/testing may be deemed necessary by the Sponsor for reasons related to subject safety. In these cases, such evaluations/testing will be performed in accordance with those regulations.

7.1.1 Administrative Procedures

7.1.1.1 Informed Consent

The Investigator or qualified designee must obtain documented consent from each potential subject prior to participating in a clinical trial. Copies of the informed consent form must be placed in the electronic medical record as well as study folder.

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

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

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

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

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

7.1.1.2 Inclusion/Exclusion Criteria

All inclusion and exclusion criteria will be reviewed by the investigator or qualified designee to ensure that the subject qualifies for the trial. Waivers will not be granted without the explicit approval of the study monitor

7.1.1.3 Medical History

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

7.1.1.4 Prior and Concomitant Medications Review

7.1.1.4.1 Prior Medications

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

7.1.1.4.2 Concomitant Medications

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

7.1.1.5 Disease Details and Treatments

7.1.1.5.1 Disease Details

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

7.1.1.5.2 Prior Treatment Details

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

7.1.1.5.3 Subsequent Anti-Cancer Therapy Status

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

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

Interruptions from the protocol specified treatment plan for greater than 12 weeks between Pembrolizumab doses due to toxicity will require consultation between the investigator and the medical monitor and written documentation of the collaborative decision on subject management.

7.1.2 Clinical Procedures/Assessments

7.1.2.1 Adverse Event (AE) Monitoring

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

All AEs of unknown etiology associated with Pembrolizumab exposure should be evaluated to determine if it is possibly an event of clinical interest (ECI) of a potentially immunologic etiology (irAE). See Section 7.5.3.2 regarding the identification, evaluation and management of AEs of a potential immunological etiology.

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

7.1.2.2 Full Physical Exam

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

7.1.2.3 Directed Physical Exam

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

7.1.2.4 Vital Signs

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

7.1.2.5 Eastern Cooperative Oncology Group (ECOG) Performance Scale

The investigator or qualified designee will assess ECOG status (see Section 11.0) at screening, prior to the administration of each dose of trial treatment and discontinuation of trial treatment as specified in the Trial Flow Chart. After Cycle 8 assessment of ECOG status will be performed every other cycle in conjunction with the directed or full physical exam.

7.1.2.6 Tumor Imaging and Assessment of Disease

The initial tumor imaging will be performed within 30 days prior to the first dose of trial treatment. Scans performed as part of routine clinical management are acceptable for use as the screening scan if they are of diagnostic quality and performed within 30 days prior to the first dose of trial treatment. On-study imaging will be performed every 12 weeks (84 ± 7

days) after the first dose of trial treatment or more frequently if clinically indicated. Tumor imaging timing should follow calendar days and should not be adjusted for delays in cycle starts or extension of Pembrolizumab cycle frequencies.

After the first documentation of progression (if the subject is clinically stable) confirmatory scans may be performed as early as 28 days later; alternately, the scan performed at the next scheduled timepoint (e.g. every 63 ±7 days) may be used as confirmation.

After the first documentation of progression, it is at the discretion of the investigator either to verify true PD, to keep a clinically stable subject on trial treatment or to stop trial treatment until repeat imaging performed at least 28 days later confirms progression. Clinical Stability is defined as:

1) Absence of symptoms and signs indicating clinical significant progression of disease (including worsening of laboratory values) indicating disease progression.

2) No decline in ECOG performance status.

3) Absence of rapid progression of disease or progressive tumor at critical anatomical sites (e.g., cord compression) requiring urgent alternative medical intervention.

Subjects who are deemed clinically unstable are not required to have repeat imaging for

confirmation. If progression is confirmed, then the subject will be discontinued from trial treatment. If progression is not confirmed, then the subjects should resume/continue trial treatment and have their next scan after two more cycles of treatment which would be approximately 6 weeks from the date of the scan that first showed progression. When feasible, subjects should not be discontinued until progression is confirmed.

Imaging during the follow-up period is to be repeated a **minimum** of every 12 weeks (84 ± 7 days) for subjects who discontinue trial treatment for reasons other than disease progression until the subject experiences confirmed disease progression or starts a new antineoplastic therapy.

The same imaging techniques should be used in a subject throughout the trial. For patients with brain metastases, MRI brain should be included in the imaging follow up prior to treatment and at any time when a patient develops new neurologic symptoms. Ideally, CT scans should be used in lieu of PET imaging as the means of determining tumor status. But PET imaging may be used to confirm PD, if suspected, but not yet clear.

7.1.3 Laboratory Procedures/Assessments

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

7.1.3.1 Laboratory Safety Evaluations (Hematology, Chemistry and Urinalysis)

Laboratory tests for hematology, chemistry, urinalysis, and others are specified in Table 9. The total amount of blood/tissue to be drawn/collected over the course of the trial (from pre-trial to post-trial visits), including approximate blood/tissue volumes drawn/collected by visit

and by sample type per subject may vary depending upon clinical course of the subject and length of time on trial.

Table 9 Laboratory Tests

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

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

After Cycle 1, pre-dose laboratory procedures can be conducted up to 72 hours prior to dosing. Results must be reviewed by the investigator or qualified designee and found to be acceptable prior to each dose of trial treatment.

7.1.4 Other Procedures

7.1.4.1 Withdrawal/Discontinuation

When a subject discontinues/withdraws prior to trial completion, all applicable activities scheduled for the final trial visit should be performed at the time of discontinuation. Any adverse events which are present at the time of discontinuation/withdrawal should be followed in accordance with the safety requirements outlined in Section 7.2 - Assessing and Recording Adverse Events. After discontinuing treatment, these subjects should return to the site for a Safety Follow-up Visit (described in Section 7.1.5.3.1) and then proceed to the Follow-Up Period of the study (described in Section 7.1.5.4).

7.1.4.2 Blinding/Unblinding

Study treatment is open label for this study.

7.1.5 Visit Requirements

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

7.1.5.1 Screening

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

Approximately 28 days prior to treatment initiation, potential subjects will be evaluated to determine that they fulfill the entry requirements as set forth in Section 5.1. Screening procedures may be repeated.

Written informed consent must be obtained prior to performing any protocol specific procedure.

Results of a test performed prior to the subject signing consent as part of routine clinical management are acceptable in lieu of a screening test if performed within the specified time frame. Screening procedures are to be completed within 42 days prior to the first dose of trial treatment except for the following:

- Laboratory tests are to be performed within 10 days prior to the first dose of trial treatment.
- For women of reproductive potential, a urine pregnancy test will be performed within 72 hours prior to first dose of trial treatment. If urine pregnancy results cannot be confirmed as negative, a serum pregnancy test, performed by the local study site laboratory, will be required.
- Tumor imaging must be performed within 30 days prior to the first dose of trial treatment.

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

7.1.5.2 Treatment Period

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

7.1.5.3 Post-Treatment Visits

Visit requirements are outlined in Section 6.0 - Trial Flow Chart. Specific procedure-related details are provided above in Section 7.1 - Trial Procedures. Patients will be followed for up to 5 years for both PFS and OS status. If the subject experiences tolerable toxicity in the absence of progression while on Pembrolizumab after 6 months of therapy, he/she will be eligible to receive up to 6 additional months of therapy with Pembrolizumab. After the completion of all therapy, subjects should be followed for up to 5 years, with no option for retreatment with Pembrolizumab on study.

7.1.5.3.1 Safety Follow-Up Visit

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

7.1.5.4 Follow-up Visits

Subjects who discontinue trial treatment for a reason other than disease progression will move into the Follow-Up Phase and should be assessed every 8-12 weeks (56-84 ± 7 days) by radiologic imaging to monitor disease status. After a year of follow up without progression, the patient can be assessed every 12 weeks (3 months) at the discretion of the treating physician. A patient who has not experienced disease progression 3 years after enrollment may have his/her follow up visits and scans spaced out to every 6 months (24 weeks), at the discretion of the treating oncologist.

Every effort should be made to collect information regarding disease status until the start of new anti-neoplastic therapy, disease progression, death, or end of the study. Information regarding post-study anti-neoplastic treatment will be collected if new treatment is initiated.

7.1.5.5 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.

7.2 Assessing and Recording Adverse Events

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

Non-clinically significant labs as deemed by the investigator will not be captured as adverse events.

Merck product includes any pharmaceutical product, biological product, device, diagnostic agent or protocol-specified procedure, whether investigational (including placebo or active comparator

medication) or marketed, manufactured by, licensed by, provided by or distributed by Merck for human use.

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

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

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

Adverse events will not be collected for subjects during the pre-screening period (for determination of archival tissue status) as long as that subject has not undergone any protocol-specified procedure or intervention. If the subject requires a blood draw, fresh tumor biopsy etc., the subject is first required to provide consent to the main study and AEs will be captured according to guidelines for standard AE reporting.

Applicable reporting to Abramson Cancer Center Data and Safety Monitoring Committee (DSMC) will occur as follows:

On-Site subjects (this includes any subjects enrolled at other sites on an in-house study)

Every effort should be made to report an event as a diagnosis, not as a list of symptoms. Symptoms that led to the diagnosis should be included in the event description, but should not be the actual event.

1. Unless covered by exclusions below all Grade 3 or higher events must be reported within 10 days of knowledge.

2. All unexpected deaths within one business day of knowledge.

3. All other deaths within 30 days of knowledge. Deaths of subjects off-study for greater than 30 days from the last study treatment/intervention are not reportable unless a longer time frame is specified in the protocol.

EXCEPTIONS to AE/SAE Reporting:

a. Grade 3 or 4 events that are judged by a study investigator to be clearly unrelated to protocol therapy. The reason for determining that the event is unrelated must be clearly documented in the EMR.

b. Grade 3 or 4 events that are probably or definitely related to progression of disease as judged by a study investigator. The fact that this event is related to disease progression must be clearly documented in the EMR.

c. Grade 3 or 4 events that are probably or definitely related to an FDA approved agent. The fact that this event is related to the FDA approved agent must be clearly documented in the EMR.

7.3 Exceptions

A **one time**, **intentional** action (planned prospectively) or process that departs from the IRB and CTSRMC approved study protocol, intended for **one** occurrence. Advance documented IRB and DSMC approval is required.

For in-house studies with a Medical Monitor or Safety Monitoring Committee (not DSMB), approval must be obtained from the Medical Monitor or Safety Monitoring Committee prior to submitting the exception request to the DSMC. The following information must be contained in your exception request:

- When it is needed and why it is needed in that timeframe
- Has the Medical Monitor or Sponsor approved and provide the documentation of approval
- Is this an exception from eligibility, treatment, disease progression, study calendar windows, etc.
- Why the exception is needed (cite the section(s) of the protocol) along with the full clinical details of the subject. This must be determined by the sub-Investigator or PI.
- The reason why the protocol currently doesn't allow the situation for which an exception is being requested. This must be determined by the sub-Investigator or PI.
- If there are plans to amend the protocol and if not, why not.
- If additional follow-up or interventions will be required in order to protect the subject as a result of this exception.

Study Exceptions the DSMC may Reject:

Exceptions to eligibility, treatment/dosing, contraindicated treatment/therapies/interventions or safety tests for the following types of studies may be rejected by the DSMC:

1. Any investigator-initiated treatment study.
2. Any treatment study involving on-campus manufacturing of any component, regardless of sponsor.

To seek approval, you must provide the DSMC with strong and compelling scientific and clinical information to support your request. You should also include a statement explaining whether or not the protocol will be amended. If the protocol will not be amended your reasoning must be provided. If this situation is likely to happen again, the DSMC will require a protocol amendment.

7.4 Deviation

Any **unintentional** action or process that departs from the IRB and DSMC approval and is **identified retrospectively**. The deviation is reportable to the DSMC and the IRB within 10 days from the time the event becomes known to the study team only when: one or more participants were placed at increased risk of harm, or, the event has the potential to occur again, or the event has the potential to qualify as serious or continuing noncompliance.

If the PI determines that a deviation has any potential to impact participant safety (harm and/or risk), or the integrity of data produced from the participant, or some other overall impact on the study, the PI must report the deviation to the IRB and DSMC as described above. The IRB will make the final assessment of the impact. The DSMC will assess for additional safety and scientific integrity concerns.

The following information must be contained in your deviation report:

- When it happened? When the study team (any member) became aware
- The full description of the deviation including important dates, test results, actions taken towards the subject, etc. Also, why it happened and how it was identified.
- Was the Medical Monitor or Sponsor notified. If so, their response?
- The PIs assessment of the impact on risk, safety and/or outcome. If no impact, why. If impact, what and what will happen next.
- The corrective actions that have been implemented to date and the impact of those corrective action plans.
- Future corrective action plans (if applicable) and the impact of those plans.
- If there are plans to amend the protocol (if applicable to prevent future deviations) and if not, why not.

If the PI determines that the event had no potential to impact participant safety (harm and/or risk) or the integrity of data produced from the participant, the PI must fully document his/her rationale for each category (risk, harm, and participant data).

7.5 Events Requiring Prompt Reporting to the IRB including Unanticipated Problem Involving Risks to Subjects or Others Reporting Requirements

Federal Regulation 21CFR §56.108(b)(1) and 45 CFR 46.103(b)(5) require the IRB to "follow written procedures for ensuring prompt reporting to the IRB…any unanticipated problems involving risk to human subjects or others."

In alignment with 21 CFR 312, investigators are required to promptly report to the IRB:

(1) Unanticipated problems including suspected adverse reactions and adverse reactions.

- An event is considered a “suspected adverse reaction” when there is *reasonable possibility* that the drug/investigational product caused the adverse event. For these reporting purposes, *reasonable possibility* means there is evidence to suggest a causal relationship between the drug/investigational product and the event.

- **For University of Pennsylvania IRB reporting, this means an event should be considered *probably or definitely related to the research procedures.***

- An event is “unexpected” if it is not listed in the investigator’s brochure/package insert, or, is not listed at the specificity or severity that has previously been observed with the specific drug/investigational product; if an investigator’s brochure/package insert is not available, is not consistent with the risk information described in the general investigational plan.)

- "Unexpected" also refers to events that are mentioned in the investigator's brochure/package insert as occurring with a class of drugs or as anticipated, but, are not mentioned as to have been occurring (have been seen) with the particular drug/investigational product under study.

(2) Unanticipated adverse device reaction. Any serious adverse effect on health or safety or any life-threatening problem or death caused by, or associated with, a device, if that effect, problem, or death was not previously identified in nature, severity, or degree of incidence in the investigational plan or application (including a supplementary plan or application, or any other unanticipated serious problem associated with a device that relates to the rights, safety, or welfare of subjects.

- For drug/investigational product and device events, "serious" is defined as any death, life-threatening adverse event, inpatient hospitalization or prolongation of existing hospitalization, a persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions, or a congenital anomaly/birth defect. Other events that may be considered "serious" but not meet the prior criteria include: those events that may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes noted above.

(3) In addition to unanticipated problems, the IRB also requires prompt reporting of the following events:

- Complaint of a participant when the complaint indicates unexpected risks or the complaint cannot be resolved by the research team.
- Violation or deviation (meaning an accidental or unintentional change to the IRB approved protocol) only when: one or more participants were placed at increased risk of harm, or, the event has the potential to occur again, the event represents serious or continuing noncompliance.

(4) Breach of confidentiality.

(5) Incarceration of a participant when the research was not previously approved under Subpart C and the investigator believes it is in the best interest of the subject to remain on the study.

This study will be monitored in accordance with the DSMC monitoring plan. Dr. Dan Vogl will serve as medical monitor and will consult on decisions made as a part of this trial as noted above.

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

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

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

If a dose of Merck's product meeting the protocol definition of overdose is taken without any associated clinical symptoms or abnormal laboratory results, the overdose is reported as a non-serious

Event of Clinical Interest (ECI), using the terminology “accidental or intentional overdose without adverse effect.”

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

7.5.2 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. 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)

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

7.5.3.1 Serious Adverse Events

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

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

SAE reports and any other relevant safety information are to be forwarded to the Merck Global Safety facsimile number: +1-215-993-1220 within two (2) business days of learning of the information.

A copy of all 15 Day Reports and Annual Progress Reports is submitted as required by FDA, European Union (EU), Pharmaceutical and Medical Devices agency (PMDA) or other local regulators. Investigators will cross reference this submission according to local regulations to the Merck Investigational Compound Number (IND, CSA, etc.) at the time of submission. Additionally

investigators will submit a copy of these reports to Merck & Co., Inc. (Attn: Worldwide Product Safety; FAX 215 993-1220) at the time of submission to FDA.

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

7.5.3.2 Events of Clinical Interest

Selected non-serious and serious adverse events are also known as Events of Clinical Interest (ECI) and must be recorded as such on the Adverse Event case report forms/worksheets and reported within 24 hours to the 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 7.5.1 - Definition of an Overdose for This Protocol and Reporting of Overdose to the Sponsor, and to Merck 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).

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

ECIs that occur in any subject from the date of first dose through 90 days following cessation of treatment, or the initiation of a new anticancer therapy, whichever is earlier, whether or not related to the Merck's product, must be reported within 24 hours to the Sponsor and to Merck Global Safety within 2 working days.

7.5.4 Evaluating Adverse Events

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

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

Table 10 Evaluating Adverse Events		
An investigator who is a physician or qualified designee, 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.	

Table 10 Evaluating Adverse Events		
	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 Merck product	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

Table 10 Evaluating Adverse Events		
Relationship to Merck product	**The following components are to be used to assess the relationship between the test drug and the AE:**	
	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?

Table 10 Evaluating Adverse Events	
The assessment of relationship will be reported on the case report forms /worksheets by an investigator who is a qualified physician according to his/her best clinical judgment, including consideration of the above elements.	
Record one of the following	**Use the following scale of criteria as guidance (not all criteria must be present to be indicative of a Merck product relationship).**
Yes, there is a reasonable possibility of Merck product relationship.	There is evidence of exposure to the Merck product. The temporal sequence of the AE onset relative to the administration of the Merck product is reasonable. The AE is more likely explained by the Merck product than by another cause.
No, there is not a reasonable possibility Merck product relationship	Subject did not receive the Merck product OR temporal sequence of the AE onset relative to administration of the Merck product is not reasonable OR there is another obvious cause of the AE. (Also entered for a subject with overdose without an associated AE.)

7.5.5 Sponsor Responsibility for Reporting Adverse Events

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

8.0 STATISTICAL ANALYSIS PLAN

8.1 Statistical Analysis Plan Summary

The statistical analysis of the data obtained from this study will be the responsibility of the Biostatistics Core Facility of the Abramson Cancer Center.

8.2 Statistical Analysis Plan

8.2.1 Hypothesis/Evaluation

Objectives and hypotheses of the study are stated in Section 3. The primary intent-to-treat analysis will estimate PFS from start of Pembrolizumab. A secondary proof of principle analysis will evaluate the benefit of adding Pembrolizumab after definitive therapy, determined by testing whether PFS is improved as compared an historical control population who received definitive therapy only. For this analysis, PFS is defined from the start of definitive therapy, which precedes enrollment on this trial. Since all patients signed informed consent agreeing that treatment history may be collected and analyzed, as part of this study, PFS from initiation of definitive therapy may be analyzed in a secondary analysis. For this proof of principle analysis, the null hypothesis is that the median PFS from start of definitive therapy is 6.6 months as compared to the alternative hypothesis that the median PFS is increased to 10 months. The study is considered to have met this objective if we reject the null hypothesis.

8.2.2 Analysis Endpoints

Primary

There are two primary endpoints of this study: progression free survival (PFS) and tolerability of therapy.

Progression Free Survival (PFS) from initiation of Pembrolizumab per RECIST 1.1

For the primary analysis, Progression Free Survival is defined as the time from initiation of Pembrolizumab to the first documented disease progression per RECIST 1.1 based on radiologists' review or death due to any cause, whichever occurs first or last patient follow-up that documented lack of disease progression. Since by definition all patients will have NED at time of enrollment, all instances of progressive disease will refer to new sites of disease. Patients who have not had disease progression or who have died, will be censored on most recent clinical evaluation date that documented that they were progression-free.

Tolerability of Therapy

Tolerability of therapy will be determined on the basis of CTCAE adverse event reporting.

Secondary

Progression Free Survival (PFS) from start of definitive therapy

For the secondary analysis, Progression Free Survival is defined as the time from initiation of definitive therapy to the first documented disease progression, whichever occurs first or last patient follow-up that documented lack of disease progression. Patients who have not had disease progression or who have died, will be censored on most recent clinical evaluation date that documented that they were progression-free.

Overall Survival

Overall Survival (OS) is defined as the time from initiation of Pembrolizumab to death due to any cause or last patient contact alive. Subjects without documented death at the time of the final analysis will be censored at the date of the last follow-up.

Progression Free Survival (PFS) per irRC

Progression free survival is defined as the time from initiation of Pembrolizumab to the first documented disease progression per irRC based on investigators' review or death due to any cause, whichever occurs first or last patient follow-up that documented lack of disease progression.

Patient Reported Quality of Life

FACT-L will be assessed in an exploratory analysis. FACT-L is not a pure efficacy or safety endpoint, because it is affected by both disease progression and treatment tolerability.

8.2.3 Analysis Populations

8.2.3.1 Efficacy Analysis Populations

The analysis of primary efficacy endpoints is based on the intention -to-treat (ITT) population. A supportive analysis will be conducted in the full analysis set (FAS) that excludes those who did not meet the eligibility criteria or discontinued before receiving any dose of assigned treatment.

8.2.3.2 Safety Analysis Populations

The All Patients as Treated (APaT) population will be used for the analysis of safety data in this study. The APaT population consists of all enrolled subjects who received at least one dose of study treatment. At least one laboratory or vital sign measurement obtained subsequent to at least one dose of trial treatment is required for inclusion in the analysis of each specific parameter. To assess change from baseline, a baseline measurement is also required.

8.2.4 Statistical Methods

Primary Objectives

1. The primary intent-to-treat analysis will estimate progression free survival from initiation of study therapy (Pembrolizumab) by the Kaplan-Meier method. Median PFS and 95% CI will be determined.

2. A secondary proof of principle analysis will determine the clinical benefit of adding consolidation Pembrolizumab after definitive therapy. In this proof of principle analysis, we will compare progression free survival from initiation of definitive therapy to that of a historical control population who only received definitive therapy. This is the optimal comparator for our study population. We assume the median PFS for the historical control population treated with definitive therapy only is 6.6 months and the median PFS for the patients treated with definitive therapy and consolidation Pembrolizumab is 10 months. Assuming 47 patients are enrolled over 2 years and followed for an additional 12 months, the final analysis will have 80% power to detect an improvement in median PFS assuming exponential survival and 1-sided 5% significance level. This trial design was deliberately structured to be slightly underpowered, given concerns that the patient population would be difficult to identify and accrual would be difficult. In the case of robust accrual, however, we will plan to accrue up to 5 additional patients for a maximum sample size of 47 patients.

3. Toxicities will be graded, categorized and tabled.

Secondary Objectives

1. Trends over time in QOL scores will first be visualized with boxplots and then will be analyzed with descriptive statistics (i.e., mean$\pm$SE). An exploratory analysis will compare baseline and end of treatment (at 6 months) QOL scores within patients using the Student's t test for paired data (or by the nonparametric Wilcoxon signed ranks test, if necessary). Longitudinal methods, such as linear mixed effects models, will be used to examine trends over time in QOL scores.

2. Overall survival will be estimated by the Kaplan-Meier method. Median OS and 95% CI will be determined.

9.0 LABELING, PACKAGING, STORAGE AND RETURN OF CLINICAL SUPPLIES

9.1 Investigational Product

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

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

Table 11 Product Descriptions

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

9.2 Packaging and Labeling Information

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

9.3 Clinical Supplies Disclosure

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

9.4 Storage and Handling Requirements

Clinical supplies must be stored in a secure, limited-access location under the storage conditions specified on the label. They will be stored in the Investigational Drug Pharmacy as part of the Abramson Cancer Center.

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

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

9.5 Returns and Reconciliation

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

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

10.0 ADMINISTRATIVE AND REGULATORY DETAILS

10.1 Confidentiality

10.1.1 Confidentiality of Data

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

10.1.2 Confidentiality of Subject Records

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

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

10.1.3 Confidentiality of Investigator Information

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

1. Name, address, telephone number and e-mail address;
2. Hospital or clinic address and telephone number;
3. Curriculum vitae or other summary of qualifications and credentials; and
4. Other professional documentation.

Consistent with the purposes described above, this information may be transmitted to the Sponsor, and subsidiaries, affiliates and agents of the Sponsor, in this and other countries, including countries that do not have laws protecting such information.

Additionally, the investigator’s name and business contact information may be included when reporting certain serious adverse events to regulatory authorities or to other investigators. By signing this protocol, the investigator expressly consents to these uses and disclosures.

10.2 Compliance with Financial Disclosure Requirements

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

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

10.3 Compliance with Law, Audit and Debarment

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

The investigator also agrees to allow monitoring, audits, IRB/ERC review and regulatory authority inspection of trial-related documents and procedures and provide for direct access to all trial-related source data and documents.

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

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

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

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

retention period and notify the investigator when documents may be destroyed. The sponsor also recognizes that documents may need to be retained for a longer period if required by local regulatory requirements. All trial documents shall be made available if required by relevant regulatory authorities. The investigator must consult with and obtain written approval by the Sponsor prior to discarding trial and/or subject files.

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

The investigator will promptly inform the Sponsor of any regulatory authority inspection conducted for this trial.

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

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

10.4 Compliance with Trial Registration and Results Posting Requirements

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

10.5 Quality Management System

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

10.6 Data Management

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

Detailed information regarding Data Management procedures for this protocol will be provided by the Sponsor.

10.7 Publications

This trial is intended for publication, even if terminated prematurely. Publication may include any or all of the following: posting of a synopsis online, abstract and/or presentation at a scientific conference, or

publication of a full manuscript. The Sponsor will work with the authors to submit a manuscript describing trial results within 12 months after the last data become available, which may take up to several months after the last subject visit in some cases such as vaccine trials. However, manuscript submission timelines may be extended on OTC trials.

These timelines may be extended for products that are not yet marketed, if additional time is needed for analysis, to protect intellectual property, or to comply with confidentiality agreements with other parties. Authors of the primary results manuscript will be provided the complete results from the Clinical Study Report, subject to the confidentiality agreement. When a manuscript is submitted to a biomedical journal, the Sponsor's policy is to also include the protocol and statistical analysis plan to facilitate the peer and editorial review of the manuscript. If the manuscript is subsequently accepted for publication, the Sponsor will allow the journal, if it so desires, to post on its website the key sections of the protocol that are relevant to evaluating the trial, specifically those sections describing the trial objectives and hypotheses, the subject inclusion and exclusion criteria, the trial design and procedures, the efficacy and safety measures, the statistical analysis plan, and any amendments relating to those sections. The Sponsor reserves the right to redact proprietary information.

Authorship credit should be based on 1) substantial contributions to conception and design, or acquisition of data, or analysis and interpretation of data; 2) drafting the article or revising it critically for important intellectual content; and 3) final approval of the version to be published. Authors must meet conditions 1, 2 and 3. Significant contributions to trial execution may also be taken into account to determine authorship, provided that contributions have also been made to all three of the preceding authorship criteria. Although publication planning may begin before conducting the trial, final decisions on authorship and the order of authors' names will be made based on participation and actual contributions to the trial and writing, as discussed above. The first author is responsible for defending the integrity of the data, method(s) of data analysis and the scientific content of the manuscript.

The Sponsor must have the opportunity to review all proposed abstracts, manuscripts or presentations regarding this trial 45 days prior to submission for publication/presentation. Any information identified by the Sponsor as confidential must be deleted prior to submission; this confidentiality does not include efficacy and safety results. Sponsor review can be expedited to meet publication timelines.

11.0 APPENDICES

11.1 ECOG Performance Status

Grade	Description
0	Normal activity. Fully active, able to carry on all pre-disease performance without restriction.
1	Symptoms, but ambulatory. Restricted in physically strenuous activity, but ambulatory and able to carry out work of a light or sedentary nature (e.g., light housework, office work).
2	In bed <50% of the time. Ambulatory and capable of all self-care, but unable to carry out any work activities. Up and about more than 50% of waking hours.
3	In bed >50% of the time. Capable of only limited self-care, confined to bed or chair more than 50% of waking hours.
4	100% bedridden. Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair.
5	Dead.
* As published in Am. J. Clin. Oncol.: *Oken, M.M., Creech, R.H., Tormey, D.C., Horton, J., Davis, T.E., McFadden, E.T., Carbone, P.P.: Toxicity And Response Criteria Of The Eastern Cooperative Oncology Group. Am J Clin Oncol 5:649-655, 1982.* The Eastern Cooperative Oncology Group, Robert Comis M.D., Group Chair.	

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

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

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

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

* As published in the European Journal of Cancer:

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

11.4 References

1. Disis ML. Immune regulation of cancer. J Clin Oncol 2010;28(29):4531-8.

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

3. Sharpe AH, Freeman GJ. The B7-CD28 superfamily. Nat Rev Immunol 2002;2(2):116-26.

4. Brown JA, Dorfman DM, Ma FR*, et al.* Blockade of programmed death-1 ligands on dendritic cells enhances T cell activation and cytokine production. J Immunol 2003;170(3):1257-66.

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

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

7. Hino R, Kabashima K, Kato Y*, et al.* Tumor cell expression of programmed cell death-1 ligand 1 is a prognostic factor for malignant melanoma. Cancer 2010;116(7):1757-66.

8. Nomi T, Sho M, Akahori T*, et al.* Clinical significance and therapeutic potential of the programmed death-1 ligand/programmed death-1 pathway in human pancreatic cancer. Clin Cancer Res 2007;13(7):2151-7.

9. Al-Shibli KI, Donnem T, Al-Saad S*, et al.* Prognostic effect of epithelial and stromal lymphocyte infiltration in non-small cell lung cancer. Clin Cancer Res 2008;14(16):5220-7.

10. Talmadge JE, Donkor M, Scholar E. Inflammatory cell infiltration of tumors: Jekyll or Hyde. Cancer Metastasis Rev 2007;26(3-4):373-400.

11. Deschoolmeester V, Baay M, Van Marck E*, et al.* Tumor infiltrating lymphocytes: an intriguing player in the survival of colorectal cancer patients. BMC Immunol 2010;11:19.

12. Diez M, Pollan M, Enriquez JM*, et al.* Histopathologic prognostic score in colorectal adenocarcinomas. Anticancer Res 1998;18(1B):689-94.

13. Galon J, Costes A, Sanchez-Cabo F*, et al.* Type, density, and location of immune cells within human colorectal tumors predict clinical outcome. Science 2006;313(5795):1960-4.

14. Hiraoka N. Tumor-infiltrating lymphocytes and hepatocellular carcinoma: molecular biology. Int J Clin Oncol 2010;15(6):544-51.

15. Nobili C, Degrate L, Caprotti R*, et al.* Prolonged survival of a patient affected by pancreatic adenocarcinoma with massive lymphocyte and dendritic cell infiltration after interleukin-2 immunotherapy. Report of a case. Tumori 2008;94(3):426-30.

16. Hodi FS, Dranoff G. The biologic importance of tumor-infiltrating lymphocytes. J Cutan Pathol 2010;37 Suppl 1:48-53.

17. Kloor M. Lymphocyte infiltration and prognosis in colorectal cancer. Lancet Oncol 2009;10(9):840-1.

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

19. Leffers N, Gooden MJ, de Jong RA*, et al.* Prognostic significance of tumor-infiltrating T-lymphocytes in primary and metastatic lesions of advanced stage ovarian cancer. Cancer Immunol Immunother 2009;58(3):449-59.

20. Nishimura H, Honjo T, Minato N. Facilitation of beta selection and modification of positive selection in the thymus of PD-1-deficient mice. J Exp Med 2000;191(5):891-8.

21. Liotta F, Gacci M, Frosali F*, et al.* Frequency of regulatory T cells in peripheral blood and in tumour-infiltrating lymphocytes correlates with poor prognosis in renal cell carcinoma. BJU Int 2011;107(9):1500-6.

22. Siegel R, Naishadham D, Jemal A. Cancer statistics, 2013. CA Cancer J Clin 2013;63(1):11-30.

23. Griffioen GHMJ, Toguri D, Dahele M*, et al.* Radical treatment of synchronous oligometastatic non-small cell lung carcinoma (NSCLC): patient outcomes and prognostic factors. Lung cancer (Amsterdam, Netherlands) 2013;82(1):95-102.

24. Villaruz LC, Kubicek GJ, Socinski MA. Management of non-small cell lung cancer with oligometastasis. Current oncology reports 2012;14(4):333-341.

25. Collaud S, Stahel R, Inci I*, et al.* Survival of patients treated surgically for synchronous single-organ metastatic NSCLC and advanced pathologic TN stage. Lung cancer (Amsterdam, Netherlands) 2012;78(3):234-238.

26. Tanvetyanon T, Padhya T, McCaffrey J*, et al.* Prognostic Factors for Survival After Salvage Reirradiation of Head and Neck Cancer. Journal of Clinical Oncology 2009;27(12):1983-1991.

27. Patchell RA, Tibbs PA, Walsh JW*, et al.* A randomized trial of surgery in the treatment of single metastases to the brain. N Engl J Med 1990;322(8):494-500.

28. Ashworth AB, Senan S, Palma DA*, et al.* An Individual Patient Data Metaanalysis of Outcomes and Prognostic Factors After Treatment of Oligometastatic Non-Small-Cell Lung Cancer. Clin Lung Cancer 2014; 10.1016/j.cllc.2014.04.003.

29. Wieser M, Sauerland S, Arnold D*, et al.* Peri-operative chemotherapy for the treatment of resectable liver metastases from colorectal cancer: A systematic review and meta-analysis of randomized trials. BMC Cancer 2010;10:309.

30. Cella DF, Bonomi AE, Lloyd SR*, et al.* Reliability and validity of the Functional Assessment of Cancer Therapy-Lung (FACT-L) quality of life instrument. Lung Cancer 1995;12(3):199-220.