_GI-087_ A Phase 2, Open-label Study of Pembrolizumab Monotherapy in Patients with Previously Treated Metastatic High Grade Neuroendocrine tumors

Supported by *(Merck)*

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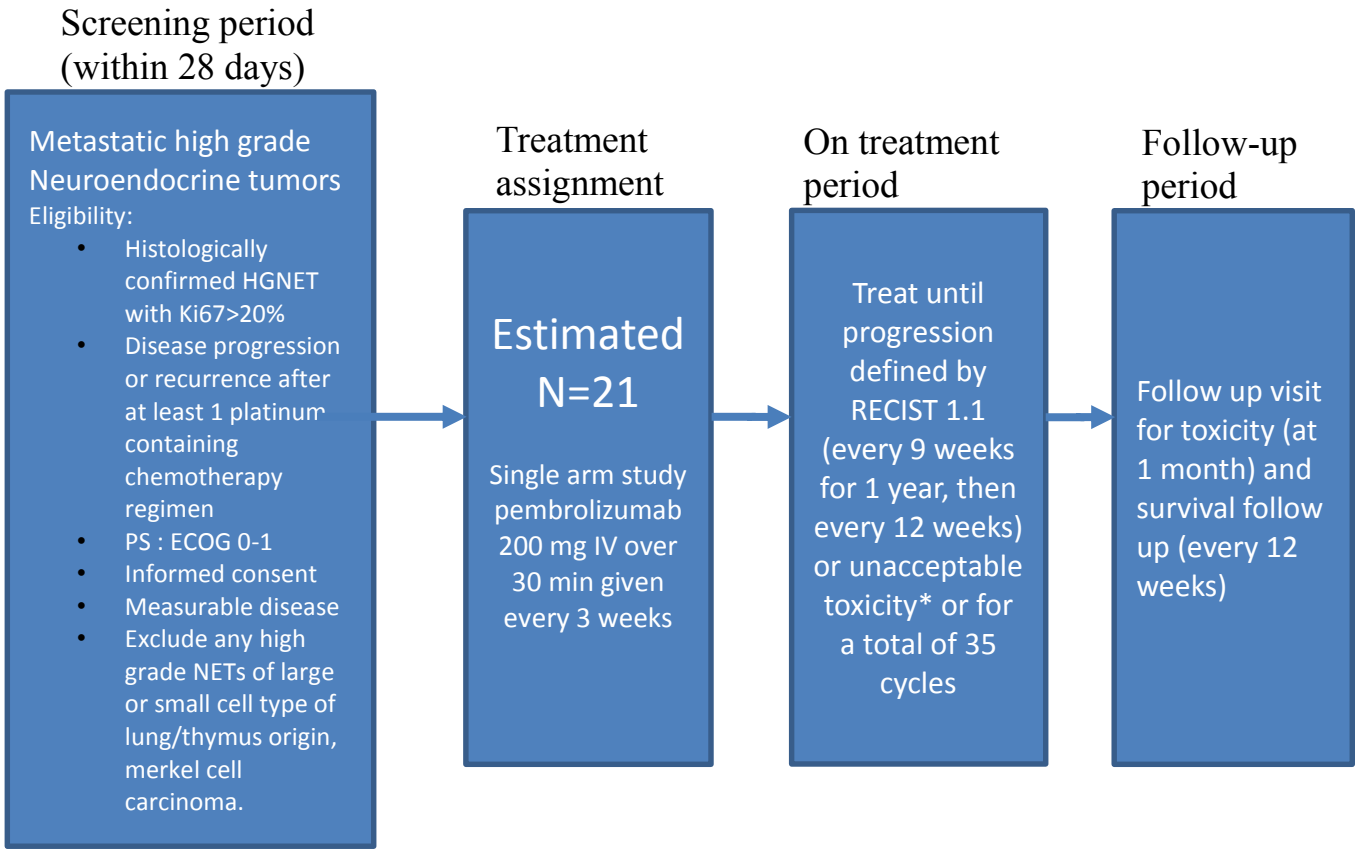
1.0 Trial Summary

Abbreviated Title	Pembrolizumab for previously treated high grade NETs
Trial Phase	*Phase 2*
Clinical Indication	Previously treated High Grade Neuroendocrine tumors
Trial Type	Open-label single arm
Type of control	None
Route of administration	Pembrolizumab given intravenously at a fixed dose of 200mg every 3 weeks
Trial Blinding	None
Treatment Groups	Single arm
Number of trial subjects	21
Estimated duration of trial	*3.5 years*
Duration of Participation	2 years

2.0 Trial Design

This is a single-arm, open label phase 2 study exploring monotherapy with the PD-1 antibody pembrolizumab (or MK-3475) given intravenously at a fixed dose of 200mg every 3 weeks for patients with high grade neuroendocrine tumors (except any high grade NETs of large or small cell type of lung/thymus origin and merkel cell carcinoma.), who have received at least 1 prior systemic therapy containing a platinum agent. The primary endpoint of the study is objective response rate. Secondary outcomes are progression free and overall survival and rate of toxicities. Patients will be assessed for response with CT scans every 9 weeks during the first year and every 12 weeks thereafter, using the RECIST 1.1 criteria. Correlative endpoints will be exploratory and assess PD-1 expression on peripheral blood mononuclear cells; peripheral blood NK-cell functional assays; PD-1 and PD-L1 expression on tumor tissue as well as mutational analysis of archived tumor tissue.

Treatment Schema



* Pts may be treated beyond first progression under protocol defined circumstances

3.0 Objectives

3.1. Primary Objective

To estimate objective response rate (ORR), using RECIST 1.1, in previously treated metastatic High Grade Neuroendocrine Tumors (HGNET) patients treated with pembrolizumab monotherapy

3.2. Secondary Objectives

- To evaluate progression free survival (PFS) (using RECIST 1.1) in metastatic HGNET patients treated with pembrolizumab monotherapy.
- To evaluate overall survival (OS) in metastatic HGNET patients treated with pembrolizumab monotherapy.
- Incidence of toxicity, graded according to National Cancer Institute Common Toxicity Criteria (NCI-CTC) version 4.0.

3.3. Exploratory objectives

- To correlate biomarkers related to PD-1 blockade in tumor samples (such as TILs, PD-1, PD-L1) with overall response rate, progression free survival, and overall survival
- To characterize molecular and biological profile of tumors that respond to pembrolizumab by performing genomic analysis of tumor samples and by evaluating the expression levels of PD-L1, PD-L2 on tumor cells; PD-L1, PD-1 on TILs and T-regulatory cells (T-regs) in the tumor microenvironment.To compare PD-1 expression and leukocyte activation markers on circulating T-regs pre-treatment, at week 6, and at time of disease progression
- To compare functional responses (degranulation) by NK cells pre-treatment, at week 6, and at end of treatment.

4.0 Introduction

4.1. Study Disease

Neuroendocrine tumors (NETs) consist of a spectrum of malignancies that can arise from neuroendocrine cells throughout the body. They are currently classified as well differentiated (low-grade to intermediate-grade) NETs and poorly differentiated or HGNET based on morphology and the proliferation rate.[1] NETs are rare tumors with an incidence of 3.5-5/100000 per year[2] and HGNETs account for about 10% to 20% of malignant digestive NETs.[3] HGNETs are defined as tumors with poorly differentiated morphology and a higher proliferation rate (Ki67 > 20%) than well differentiated NETs. They are characterized by a high proclivity for metastatic dissemination even among patients with clinically localized tumors.[4] Well and poorly differentiated NETs are grouped together in the general class of NET only because of generic neuroendocrine marker expression (ie, detection of synaptophysin and/or chromogranin by immunohistochemistry).[5]
Recent molecular discoveries have led to therapeutic advances in well differentiated NETs with the approval of targeted therapies like everolimus and sunitinib.[6] In contrast, much less is known about HGNETs, and no prospective studies have evaluated HGNETs originating outside of the lung. These are aggressive carcinomas that typically present at a late stage and have a dismal median overall survival of only 10 months.[2] To date, and even for the current standard of care regimen, no prospective trial has been conducted to guide treatment for this disease and current treatment recommendations are extrapolated from the small cell lung cancer literature.[7] These are generally managed with platinum-based chemotherapy with a modest PFS (4months) and OS (11 months) benefit.[7-11] After first-line treatment, no further standard therapy has been established for HGNETs. No prospective trials have been conducted and a few small, retrospective, studies with chemotherapy (temozolamide, oxaliplatin, taxanes etc.) have quoted a response rate between 0-20% in the second line setting and <5% in the third line setting[11-14]. The responses, however, are of short duration. Data pertaining to histologic classification and tumor biology are also extremely limited making the care of patients with this disease entity a significant challenge. Prospective studies evaluating potential treatment options with associated correlative studies to better understand the histologic and molecular features of these carcinomas are therefore desperately needed.

4.2. Agent under Investigation/intervention

The importance of intact immune surveillance in controlling outgrowth of neoplastic transformation has been known for decades[15]. Accumulating evidence shows a correlation between tumor-infiltrating lymphocytes (TILs) in cancer tissue and favorable prognosis in various malignancies[16-20]. In particular, the presence of CD8+ T-cells and the ratio of CD8+ effector T-cells / FoxP3+ regulatory T-cells seems to correlate with improved prognosis and long-term survival in many solid tumors.

The PD-1 receptor-ligand interaction is a major pathway hijacked by tumors to suppress immune control. The normal function of PD-1, expressed on the cell surface of activated Tcells 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) [21, 22]. The structure of murine PD-1 has been resolved [23]. 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[22, 24-26]. 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[27, 28]. 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[29, 30]. Expression has also been shown during thymic development on CD4-CD8- (double negative) T-cells as well as subsets of macrophages and dendritic cells[31]. 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[28, 32-34]. 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 Tcell 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[28]. Although healthy organs express little (if any) PD-L1, a variety of cancers were demonstrated to express abundant levels of this T-cell inhibitor. PD-1 has been suggested to regulate tumor-specific T-cell expansion in subjects with renal cell carcinoma[35]. 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 (MK-3475), previously known as 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.

4.3. Pre-clinical and Clinical Trials:

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

4.4. Study Rationale

Immune checkpoint blockade is a rapidly advancing therapeutic approach in the field of immuno-oncology and treatment with investigational agents targeting this mechanism has induced regressions in several types of cancer. These agents are tolerable and adverse effects (AEs) are generally manageable in patients. They have shown activity in wide range of

malignancies including melanoma, renal cell carcinoma and lung cancer, and more data is emerging by the day.[36-38] No published studies have evaluated PD-L1 expression in high grade NET. In SCLC, PD-L1 expression on tumor cells is reported to be low (0-27%) but 18.5% show PD-L1 expression in tumor-infiltrating macrophages and 48% harbor PD-1 positive lymphocytes.[39, 40] Immune checkpoint blockers have not been studied in NETs but are being actively investigated in SCLC and Merkel Cell Carcinoma with promising results. In a recently reported interim analysis of a study using Nivolumab+/- Ipilimumab in pretreated advanced small cell lung cancer, researchers reported a partial response in 15% and stable disease (SD) in 22.5% patients. In the combination arm, complete response was seen in 5%, partial response in 20% and stable disease in 30% patients.[41] In the KEYNOTE-028 study, rate of PD-L1 positivity in small cell lung cancer was found to be around 27%. In the cohort of 17 evaluable patients treated with pembrolizumab, there were no treatment-related deaths or discontinuations due to AEs. 25% patients had a partial response and 7% had stable disease, resulting in a disease control rate of 31%.[40] (**NCT02054806**) In the initial phase I study of Pembrolizumab, a patient with Merkel cell carcinoma experienced complete responses of 56+ weeks' duration[42]. This led to the phase II study in advanced merkel cell carcinoma where the objective response rate with pembrolizumab was 71%, which included a complete response in 2 of 14 patients[43]. The drug is currently being investigated as a first line therapy for patients with locally advanced/metastatic merkel cell carcinoma. (NCT02267603). Both these tumor types (small cell lung cancer and merkel cell carcinoma) are thought to be of neuroendocrine lineage and are treated similarly with frontline platinum/etoposide combinations, just like other high grade neuroendocrine carcinomas. The impressive activity of pembrolizumab in these tumors, presents a strong argument for investigating its role in HGNETs.

Snyder et.al.described the importance of tumor genetics in defining the basis of the clinical benefit from checkpoint blockade. In their study, mutational load correlated with improved overall survival and response to immunotherapy[44]. Preliminary data from our in-house IRB approved study, that utilized an NGS platform to detect somatic mutations in 50 cancer-related genes on archived tissue, found a staggering 77% (16/21) rate of mutations in the HGNETs with 44% of the tumors having more than one mutation (on the limited 50 gene panel). We enrolled 21 patients with HGNETs over 15 months in this study.[45] This provides another rationale for testing pembrolizumab in HGNETs.

As discussed in section 4.1, after first-line treatment, no further standard therapy has been established for HGNETs. Several small, retrospective, studies with chemotherapy (temozolamide, oxaliplatin, taxanes etc.) have quoted short lived responses after the first line setting.

In summary, the lack of second line treatment options for HGNETs highlights the unmet need for drug development in this rare tumor type. The higher mutational load exhibited by HGNETs and promising activity of checkpoint blockers in small cell lung cancer and merkel cell carcinoma provide strong rationale for studying pembrolizumab, a highly selective, humanized monoclonal antibody against PD-1, in HGNETs with respect to efficacy and toxicity. Therefore, we propose a phase II, open-label study of pembrolizumab monotherapy

in patients with metastatic HGNETs who have progressed on at least one platinum containing regimen.

We hypothesize that administration of pembrolizumab to patients with metastatic HGNETs will result in a clinically meaningful response rate and that it will have an acceptable safety profile when given as a single agent to patients with metastatic, HGNETs.

4.5. Rationale for Dose Selection/Regimen/Modification

Previously, an open-label Phase I trial (NCT01848834) was conducted to evaluate the safety and clinical activity of single agent Pembrolizumab (MK-3475). The dose escalation portion of the trial evaluated three dose levels, 1 mg/kg, 3 mg/kg, and 10 mg/kg, administered every 2 weeks (Q2W) in subjects with advanced solid tumors. All three dose levels were well tolerated and no dose-limiting toxicities were observed. This first in human study of pembrolizumab showed evidence of target engagement and objective evidence of tumor size reduction at all dose levels (1 mg/kg, 3 mg/kg and 10 mg/kg Q2W). No MTD has been identified to date. Recent data from other clinical studies within the pembrolizumab program has shown that a lower dose of pembrolizumab and a less frequent schedule may be sufficient for target engagement and clinical activity.

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

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

The rationale for further exploration of 2 mg/kg and comparable doses of Pembrolizumab in solid tumors was based on: 1) similar efficacy and safety of Pembrolizumab when dosed at either 2 mg/kg or 10 mg/kg Q3W in melanoma patients, 2) the flat exposure-response relationships of Pembrolizumab for both efficacy and safety in the dose ranges of 2 mg/kg Q3W to 10 mg/kg Q3W, 3) the lack of effect of tumor burden or indication on distribution

behavior of Pembrolizumab (as assessed by the population PK model) and 4) the assumption that the dynamics of Pembrolizumab target engagement will not vary meaningfully with tumor type.

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

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

4.6. Rationale for endpoints

4.6.1. Primary endpoint

The primary efficacy objective of this trial is to evaluate the anti-tumor activity of pembrolizumab (MK-3475) (200 mg Q3W) monotherapy in subjects with previously treated metastatic high grade neuroendocrine tumors. Objective response rate (ORR) based on RECIST 1.1 will be used as the primary efficacy endpoint. Secondary endpoints in this study is progression free survival (per RECIST 1.1), and overall survival.

4.6.2. Safety Endpoint

The safety endpoint in this study is to characterize the safety and tolerability of Pembrolizumab in patients with previously treated metastatic high grade neuroendocrine tumors. Adverse events and laboratory test values observed in this study are also safety endpoints. The primary safety analysis will be based on subjects who experienced toxicities requiring discontinuation of therapy as defined by the protocol (section 7.0). Safety will be assessed by quantifying the toxicities and grades experienced by subjects who have received pembrolizumab (MK-3475), including serious adverse events (SAEs) and events of clinical interest (ECIs). Safety will be assessed by reported adverse experiences using CTCAE, Version 4.0. The attribution to drug, time-of-onset, duration of the event, its resolution, and any concomitant medications administered will be recorded. AEs will be analyzed including but not limited to all AEs, SAEs, fatal AEs, and laboratory changes. Furthermore, specific immune-related adverse events (irAEs) will be collected and designated as immune-related events of clinical interest (ECIs) as described in Section 9.1.7.

4.7. Rationale for Correlative Testing

We will assess the expression level of PD-1, PD-L1 and PD-L2 and Tumor Infiltrating Lymphocytes (TIL) content in tumor samples and its correlation with response to investigational therapy. Initial studies suggest that baseline PD-L1 tumor cell expression

could serve as a key biomarker for response to PD-1 pathway inhibition. Tumor PD-L1 up-regulation has been the factor most strongly correlated with response to PD-1 blockade. Biopsy specimen analysis will endeavor to serve this question in HGNETs. We will utilize archived tumor tissue to perform the analysis and patients without available archived tissue; may undergo an optional fresh biopsy at enrollment. Tumor infiltrating lymphocytes (TILs) will be evaluated by H&E immunohistochemical staining. Guided by our preliminary work (section 4.4-study rationale)[45], mutational analysis of tumors using next gen sequencing platform will be conducted to identify predictive biomarkers and guide future therapy beyond checkpoint inhibitors.

Additionally, using peripheral blood samples, we will assess PD-1 expression and leukocyte activation markers on circulating lymphocytes as well as NK- and T-cell function pre-treatment, during treatment as well as at time of progression in order to assess potential associations with treatment response and outcome. Preliminary studies of immune cell biomarkers, including PD-1, on peripheral blood mononuclear cells in renal cell carcinoma by our group have indicated that PD-1 expression on fresh peripheral blood leukocytes may provide a useful marker for disease progression. Furthermore, the results suggest that measuring PD-1 levels in peripheral blood may assist in identifying patients likely to respond to PD-1 blocking antibodies.

5.0 Study Plan

5.1. Description of Study Design, Population and Duration of Study Therapy

This is a single arm phase II study of pembrolizumab in patients with metastatic high grade neuroendocrine carcinoma (except small cell and merkel cell carcinoma) who have failed therapy with a platinum agent. Objective response rate will be measured with disease imaging following every 3 cycles for the first year and then every 4 cycles. Patients will continue treatment until disease progression, unacceptable toxicity or for a total of 35 cycles. Overall survival will be assessed every 12 weeks during long term follow up.

Patient Selection Inclusion & Exclusion

5.2. Inclusion Criteria

5.2.1. Patients must have histologically or cytologically confirmed metastatic, high grade NET (Ki67 >20%), excluding any high grade NETs of large or small cell type of lung/thymus origin and merkel cell carcinoma

5.2.2. Patients must have measurable disease, defined as at least one lesion that can be accurately measured in at least one dimension in accordance with RECIST criteria v. 1.1 as described in detail in section 12.0

5.2.3. Has received prior therapy with at least 1 platinum-containing regimen

5.2.4. Age $\geq$ 18 years.

5.2.5. ECOG performance status *0 or 1*

5.2.6. Patients must have normal organ and marrow function as defined below in table 1

Table 1: Adequate Organ Function Laboratory Values

System	Laboratory Value
Hematological	
Absolute neutrophil count (ANC)	≥1,500 /mcL
Platelets	≥100,000 / mcL
Hemoglobin	≥8 g/dL or ≥5.6 mmol/L without transfusion or EPO dependency (within 7 days of assessment)
Renal	
Serum creatinine **OR** Measured or calculated[a] creatinine clearance (GFR can also be used in place of creatinine or CrCl)	≤1.5 X upper limit of normal (ULN) **OR** ≥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
Albumin	≥2.5 mg/dL
Coagulation	
International Normalized Ratio (INR) or Prothrombin Time (PT) Activated Partial Thromboplastin Time (aPTT)	≤1.5 X ULN unless subject is receiving anticoagulant therapy as long as PT or PTT is within therapeutic range of intended use of anticoagulants ≤1.5 X ULN unless subject is receiving anticoagulant therapy as long as PT or PTT is within therapeutic range of intended use of anticoagulants
[a]Creatinine clearance should be calculated per institutional standard.	

5.2.7. Female participants of childbearing potential must have a negative serum pregnancy within 72 hours prior to receiving the first dose of study medication). They should also be willing to use 2 methods of birth control or be surgically sterile, or abstain from heterosexual activity for the course of the study through 120 days after the last dose of study medication.

Note: Abstinence is acceptable if this is the usual lifestyle and preferred contraception for the subject.

5.2.8. Male participants must agree to use an adequate method of contraception starting with the first dose of study therapy through 120 days after the last dose of study therapy

Note: Abstinence is acceptable if this is the usual lifestyle and preferred contraception for the subject.

5.2.9. Ability to understand and willingness to sign a written informed consent and HIPAA consent document

5.3. Exclusion Criteria

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

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

5.3.3. Diagnosis of immunodeficiency or receiving systemic steroid therapy or any other form of immunosuppressive therapy within 7 days prior to the first dose of trial treatment.

5.3.4. Prior anti-cancer therapy with a monoclonal antibody (mAb) within 4 weeks prior to study Day 1 or not recovered from adverse events (improved to grade 1 or less) due to mAbs administered more than 4 weeks earlier.

5.3.5. Prior chemotherapy, targeted small molecule therapy, or radiation therapy within 2 weeks (12 weeks for measurable sites of CNS disease) prior to study Day 1 or not recovered from adverse events (improved to grade 1 or less) due to a previously administered agent.

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

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

5.3.6. Known additional malignancy that is progressing or requires active treatment except superficial malignancies of the skin and in situ cervical cancer

5.3.7. Has an active autoimmune disease that has required systemic treatment in the past 2 years (i.e. with use of disease modifying agents, corticosteroids or immunosuppressive drugs). Replacement therapy (e.g., thyroxine, insulin, or physiologic corticosteroid replacement therapy for adrenal or pituitary insufficiency, etc.) is not considered a form of systemic treatment.

5.3.8. Has history of (non-infectious) pneumonitis that required steroids, evidence of interstitial lung disease or active non-infectious pneumonitis.

5.3.9. Active infection requiring systemic therapy at enrollment.

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

5.3.11. Hypersensitivity to pembrolizumab or any of its excipients

5.3.12. Has received a live virus vaccine within 30 days of planned start of trial treatment.

5.3.13. Pregnant, breastfeeding, or expecting to conceive or father children within the projected duration of the trial, starting with the screening period through 120 days after the last dose of trial treatment

5.3.14. Prior therapy with an anti-programmed cell death 1 (PD-1), anti-programmed cell death 1 ligand (PDL-1), anti-PD-L2, or with an agent directed to another co-inhibitory T-cell receptor (e.g. CTLA-4, OX-40, CD137)

5.3.15. Known history of human immunodeficiency virus (HIV)

5.3.16. Known active Hepatitis B (e.g., HBsAg reactive) or Hepatitis C (e.g., HCV RNA [qualitative]).

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

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

5.4. Inclusion of Women and Minorities

Men and women, regardless of race, ethnic group or sexual orientation are eligible for this study.

5.5. Patient Registration

Participants may be registered from 8:00 am to 4:00 pm EST excluding holidays by emailing the study monitor at: FCCC.MONITOR@fccc.edu. Eligible participants will be entered on study centrally once the following items have been received by email:

- Completed registration form
- Consent and HIPAA signature pages
- Eligibility checklist

Following registration, participants must begin protocol treatment within 7 days of registration. Issues that would cause treatment delays must be discussed with the Principal

Investigator. If a registered participant does not receive protocol therapy following registration, the participant will be recorded as withdrawn from study. The Study Monitor must be notified as soon as possible if a participant does not begin protocol treatment as scheduled. For additional registration questions, please email FCCC.MONITOR@fccc.edu or call (215) 728-5544.

The study monitor or their designee will notify the site by email once registration is confirmed and the sequence number has been assigned. Participants must be registered and have received a sequence number prior to the initiation of treatment.

Exceptions to the current registration policies will not be permitted.

6.0 Treatment Plan

No stratification based on age, sex or other characteristics will be used in this trial. Treatment will be administered on an outpatient basis. Treatment will be administered as described below. Dose delays and modifications should only be done following protocol guidelines described in section 7.0. If treatment delays are > 42 days study therapy will be discontinued.

6.1. Trial Treatments

Agent	Dose	Route	Schedule	Cycle Length	Use
Pembrolizumab	200 mg	IV infusion	Q 3 weeks	3 weeks (21 days)	Experimental

6.2. Dose Selection

The rationale for selection of doses to be used in this trial is provided in Section 4.5 – Rationale.
Details on preparation and administration of pembrolizumab (MK-3475) are provided in the Pharmacy Manual.

6.3. Dose Administration

Trial treatment should be administered on Day 1 of each cycle after all procedures/ assessments have been completed as detailed on the study calendar (Section 10.0). Trial treatment may be administered up to 3 days before or after the scheduled Day 1 of each cycle due to administrative reasons. All trial treatments will be administered on an outpatient basis. Pembrolizumab will be administered as a 30 minute IV infusion (treatment cycle intervals may be increased due to toxicity as described in Section 7.0). 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 -10 minutes and +10 minutes is permitted (i.e., infusion time is 30 minutes: -10 min/+10 min).

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

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

A sterile, non-pyrogenic, low-protein binding 0.2 to 5 µm in-line filter made of polyethersulfone (PES) must be used during administration to remove any adventitious particles. If the infusion set does not contain 0.2 to 5 µm in-line filter, it is recommended to use 0.2 to 5 µm add-on filter which may contain an extension line. Attach the infusion line to the pump and prime the line, either with normal saline (at least 25 mL) or with infusion solution as per local SOP, before starting the infusion. Infuse pembrolizumab (MK-3475) over approximately 30 minutes, with a window of -10 and +10 minutes, through a peripheral line or indwelling catheter. Ensure the entire contents of the bag are dosed and all remaining drug solution in the line is administered according to institutional guidelines for saline flushing. Document volume administered according to data entry guidelines. Vital signs will be monitored every 15 minutes during the infusion and at 60 minutes after completion of each infusion. In case of infusion reactions, infusion rate may differ; refer to protocol for specific instructions.

Whenever possible, the lowest infusion rate should be used that will allow completion of the infusion within the 30 minutes. Maximum rate of infusion should not exceed 6.7 mL/min. through a peripheral line or indwelling catheter. However, when it is necessary to infuse a larger volume (i.e. 250 mL), the flow rate may go as high as 10 mL/min (maximum) in order to keep the infusion within the window as defined above

6.4. Concomitant Medications, Supportive Care, Excluded Therapies and Restrictions

Medications or vaccinations specifically prohibited in the exclusion criteria are not allowed during the ongoing trial. If there is a clinical indication for any medication or vaccination specifically prohibited during the trial, discontinuation from trial therapy or vaccination may be required. The final decision on any supportive therapy or vaccination rests with the investigator and/or the subject's primary physician.

6.4.1. Acceptable Concomitant Medications

All treatments that the investigator considers necessary for a subject's welfare may be administered at the discretion of the investigator in keeping with the community standards of medical care. All concomitant medication received within 28 days before the first dose of trial treatment and 30 days after the last dose of trial treatment, 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. Patients may receive supportive blood products or antibiotics when appropriate. Patients requiring other supportive or adjunctive therapies, including but not limited to percutaneous drainage or biliary or genitourinary stent placement, may be considered on an individual patient basis to be permitted to hold investigational therapy for up to 42 days. Palliative radiation therapy is permitted for irradiating small areas of painful metastases (bony, or otherwise) or bleeding from a solitary site that cannot be managed adequately using systemic or local analgesics, as long as the treating clinician feels the patient is otherwise clinically benefitting and would more likely than not continue to garner benefit at the conclusion of this localized therapy.

Concomitant medications administered after 30 days after the last dose of trial treatment should be recorded for SAEs and ECIs as defined in Section 9.0.

6.4.2. Prohibited Concomitant Medications

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

- Antineoplastic systemic chemotherapy or biological therapy
- Immunotherapy not specified in this protocol
- Chemotherapy not specified in this protocol
- Investigational agents other than pembrolizumab
- Radiation therapy

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

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

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

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

6.4.3. Rescue Medications & Supportive Care

Subjects should receive appropriate supportive care measures as deemed necessary by the treating investigator. Suggested supportive care measures for the management of adverse events with potential immunologic etiology are outlined below and in greater detail in appendix (section 17.3). 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 may follow the AE reporting guidance but does not need to follow the treatment guidance (as outlined in appendix 17.3). Refer to section 7.0 for dose modification.

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

Pneumonitis:

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

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

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

Type 1 diabetes mellitus (if new onset, including diabetic ketoacidosis [DKA]) or ≥ Grade 3 Hyperglycemia, if associated with ketosis (ketonuria) or metabolic acidosis (DKA)

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

Hypophysitis:

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

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

- **Grade 2** hyperthyroidism events (and **Grade 3-4** hypothyroidism):
  - In hyperthyroidism, non-selective beta-blockers (e.g. propranolol) are suggested as initial therapy.
  - In hypothyroidism, thyroid hormone replacement therapy, with levothyroxine or liothyroinine, is indicated per standard of care.

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

Hepatic:

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

Renal Failure or Nephritis:

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

Management of Infusion Reactions: Signs and symptoms usually develop during or shortly after drug infusion and generally resolve completely within 24 hours of completion of infusion. Table 2 below shows treatment guidelines for subjects who experience an infusion reaction associated with administration of Pembrolizumab.

Table 2. Infusion Reaction Treatment Guidelines

NCI CTCAE Grade	Treatment	Premedication at subsequent dosing
Grade 1 Mild reaction; infusion interruption not indicated; intervention not indicated	Increase monitoring of vital signs as medically indicated until the subject is deemed medically stable in the opinion of the investigator.	None
Grade 2 Requires infusion interruption but responds promptly to symptomatic treatment (e.g., antihistamines, NSAIDS, narcotics, IV fluids); prophylactic medications indicated for < =24 hrs	**Stop Infusion and monitor symptoms.** Additional appropriate medical therapy may include but is not limited to: IV fluids Antihistamines NSAIDS Acetaminophen Narcotics Increase monitoring of vital signs as medically indicated until the subject is deemed medically stable in the opinion of the investigator. If symptoms resolve within one hour of stopping drug infusion, the infusion may be restarted at 50% of the original infusion rate (e.g., from 100 mL/hr to 50 mL/hr). Otherwise dosing will be held until symptoms resolve and the subject should be premedicated for the next scheduled dose. **Subjects who develop Grade 2 toxicity despite adequate premedication should be permanently discontinued from further trial treatment administration.**	Subject may be premedicated 1.5h (± 30 minutes) prior to infusion of Pembrolizumab with: Diphenhydramine 50 mg po (or equivalent dose of antihistamine). Acetaminophen 500-1000 mg po (or equivalent dose of antipyretic).
Grades 3 or 4 Grade 3: Prolonged (i.e., not rapidly responsive to symptomatic medication and/or brief interruption of infusion); recurrence of symptoms following initial improvement; hospitalization indicated for other clinical sequelae (e.g., renal impairment, pulmonary infiltrates) Grade 4: Life-threatening; pressor or ventilatory support indicated	**Stop Infusion.** Additional appropriate medical therapy may include but is not limited to: IV fluids Antihistamines NSAIDS Acetaminophen Narcotics Oxygen Pressors Corticosteroids Epinephrine Increase monitoring of vital signs as medically indicated until the subject is deemed medically stable in the opinion of the investigator. Hospitalization may be indicated. **Subject is permanently discontinued from further trial treatment administration.**	No subsequent dosing
Appropriate resuscitation equipment should be available in the room and a physician readily available during the period of drug administration.		

NCI CTCAE Grade	Treatment	Premedication at subsequent dosing

6.5. Diet/Activity/Other Considerations

6.5.1. Diet

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

6.5.2. 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.
For this trial, male subjects will be considered to be of non-reproductive potential if they have azoospermia (whether due to having had a vasectomy or due to an underlying medical condition).

Female subjects will be considered of non-reproductive potential if they are either:

(1) postmenopausal (defined as at least 12 months with no menses without an alternative medical cause; in women < 45 years of age a high follicle stimulating hormone (FSH) level in the postmenopausal range may be used to confirm a post-menopausal state in women not using hormonal contraception or hormonal replacement therapy. In the absence of 12 months of amenorrhea, a single FSH measurement is insufficient.);

OR

(2) have had a hysterectomy and/or bilateral oophorectomy, bilateral salpingectomy or bilateral tubal ligation/occlusion, at least 6 weeks prior to screening;

OR

(3) has a congenital or acquired condition that prevents childbearing.

Female and male subjects of reproductive potential must agree to avoid becoming pregnant or impregnating a partner, respectively, while receiving study drug and for 120 days after the last dose of study drug by complying with one of the following:
(1) practice abstinence[†] from heterosexual activity;

OR

(2) use (or have their partner use) acceptable contraception during heterosexual activity.

Acceptable methods of contraception are[‡]:

Single method (one of the following is acceptable):

- intrauterine device (IUD)
- vasectomy of a female subject's male partner
- contraceptive rod implanted into the skin

Combination method (requires use of two of the following):

- diaphragm with spermicide (cannot be used in conjunction with cervical cap/spermicide)
- cervical cap with spermicide (nulliparous women only)
- contraceptive sponge (nulliparous women only)
- male condom or female condom (cannot be used together)
- hormonal contraceptive: oral contraceptive pill (estrogen/progestin pill or progestin-only pill), contraceptive skin patch, vaginal contraceptive ring, or subcutaneous contraceptive injection

†Abstinence (relative to heterosexual activity) can be used as the sole method of contraception if it is consistently employed as the subject's preferred and usual lifestyle and if considered acceptable by local regulatory agencies and ERCs/IRBs. Periodic abstinence (e.g., calendar, ovulation, sympto-thermal, post-ovulation methods, etc.) and withdrawal are not acceptable methods of contraception.

‡If a contraceptive method listed above is restricted by local regulations/guidelines, then it does not qualify as an acceptable method of contraception for subjects participating at sites in this country/region.

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 subjects of childbearing potential must adhere to the contraception requirement (described above) from the day of study medication initiation (or 14 days prior to the initiation of study medication for oral contraception) throughout the study period up to 120 days after the last dose of trial therapy. If there is any question that a subject of childbearing potential will not reliably comply with the requirements for contraception, that subject should not be entered into the study.

6.5.3. 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 Merck without delay and within 2 working days to Merck if the outcome is a serious adverse experience (e.g., death, abortion, congenital anomaly, or other disabling or life-threatening complication to the mother or newborn).
The study investigator will make every effort to obtain permission to follow the outcome of the pregnancy and report the condition of the fetus or newborn to Merck. If a male subject impregnates his female partner the study personnel at the site must be informed immediately and the pregnancy reported to Merck and followed as described above and in section 9.2.

6.5.4. 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.

6.6. Participant Withdrawal/Discontinuation Criteria

Participants 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 participant may be withdrawn by the investigator if enrollment into the trial is inappropriate, the trial plan is violated, or for administrative and/or other safety reasons. Specific details regarding discontinuation or withdrawal are provided in section 8.4 – Other Procedures.

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

- The subject or legal representative (such as a parent or legal guardian) withdraws consent.
- Disease progression (for definition see Section12)
- Unacceptable adverse experiences as described in Section 7.0
- Intercurrent illness that prevents further administration of treatment
- Investigator's decision to withdraw the subject
- The participant has a confirmed positive serum pregnancy test
- Noncompliance with trial treatment or procedure requirements
- The subject is lost to follow-up
- Completed 35 cycles of treatment with pembrolizumab

  Note: Subjects who stop pembrolizumab after 35 cycles may be eligible for up to 18 cycles of additional study treatment if they progress after stopping study treatment provided they meet the requirements detailed in Section8.5.4.
- Administrative reasons

The End of Treatment and Follow-up visit procedures are listed in Section 10 (Study calendar) and Section 8.5 (Visit Requirements). After the end of treatment, each subject will be followed for 120 days for adverse event monitoring (events of clinical interest will be collected for 120 days after the end of treatment). Subjects who discontinue for reasons other than progressive disease will have post-treatment follow-up for disease status until disease progression, initiating a non-study cancer treatment, withdrawing consent or becoming lost to follow-up. After documented disease progression each subject will be followed by telephone for overall survival until death, withdrawal of consent, or the end of the study, whichever occurs first.

6.7. Discontinuation of Study Therapy after CR

Discontinuation of treatment may be considered for subjects who have attained a confirmed CR that have been treated for at least 24 weeks with pembrolizumab and had at least two

treatments with pembrolizumab beyond the date when the initial CR was declared. Subjects who then experience radiographic disease progression may be eligible for up to 18 cycles of additional treatment with pembrolizumab via the Second Course Phase at the discretion of the investigator if no cancer treatment was administered since the last dose of pembrolizumab, the subject meets the safety parameters listed in the Inclusion/Exclusion criteria, and the trial is open. Subjects will resume therapy at the same dose and schedule at the time of initial discontinuation. Additional details are provided in Section 8.5.

6.8. Treatment beyond Disease Progression

Immunotherapeutic agents such as pembrolizumab (MK-3475) may produce antitumor effects by reactivating endogenous cancer-specific immune responses, which may be functionally exhausted. The response patterns seen with such therapies may extend beyond the typical time course of responses seen with cytotoxic agents, and can manifest a clinical response after an initial increase in tumor burden or even the appearance of new lesions. Standard RECIST criteria may not provide an accurate or complete response assessment of immunotherapeutic agents such as pembrolizumab (MK-3475). Data from previous trials has clearly demonstrated a phenomenon in which patients treated with PD-1 inhibitors may derive clinical benefit despite initial radiologic evidence of disease progression[46].Therefore, RECIST 1.1 will be used with the following adaptation:
If radiologic imaging by local/site assessment shows PD, tumor assessment may be repeated $\geq$ 4 weeks later in order to confirm PD with the option of continuing treatment per below while awaiting radiologic confirmation of progression. If repeat imaging shows SD, PR or CR, treatment may be continued as per treatment calendar. If repeat imaging still meets the threshold for PD ($\geq$ 20% increase in tumor burden compared to nadir) but shows a reduction in tumor burden compared to the previous time point, treatment may be continued as per treatment calendar after consultation with Sponsor Investigator. If repeat imaging confirms progressive disease without reduction in tumor burden compared to the previous time point, subjects will be discontinued from study therapy. In determining whether or not the tumor burden has increased or decreased, investigators should consider all target lesions as well as non-target lesions.

The decision to continue study treatment after the 1st evidence of disease progression is at the Investigator's discretion based on the clinical status of the subject as described in Section 8.5.5.

7.0 Dose Modifications

7.1. General Principles

Dose modifications will be made based only on the guidelines described in Section 7.0. Patients requiring treatment to be held > 42 days for recovery from toxicity must discontinue protocol treatment. Adverse events (both non-serious and serious) associated with Pembrolizumab exposure may represent an immunologic etiology. These adverse events may occur shortly after the first dose or several months after the last dose of treatment. Pembrolizumab must be withheld for drug-related toxicities and severe or life-threatening AEs as per Table 3 below. See Section 6.4 (Supportive Care Guidelines), Table 2 and

Appendix 17.3 for supportive care guidelines, including use of corticosteroids. For subjects whose dose interval was increased due to toxicity, subjects may resume Pembrolizumab upon resolution of toxicity to Grade 0-1 or baseline. This dose would be considered Day 1 of the next cycle and should be in alignment with the new schedule

Table 3. Dose Modification Guidelines for Pembrolizumab-Related Adverse Events

Toxicity	Hold Treatment For Grade	Timing for Restarting Treatment	Discontinue Subject if
Diarrhea/Colitis	2-3	Toxicity resolves to Grade 0-1.	Toxicity does not resolve to grade 0-1 within 6 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	2-3	Toxicity resolves to Grade 0-1	Toxicity does not resolve to grade 0-1 within 6 weeks of last dose.
	4	Permanently discontinue	Permanently discontinue
Type 1 diabetes mellitus (if new onset) or Hyperglycemia	T1DM or 3-4	Hold Pembrolizumab for new onset Type 1 diabetes mellitus or Grade 3-4 hyperglycemia associated with evidence of beta cell failure.	Resume Pembrolizumab when patients are clinically and metabolically stable.
Hypophysitis	2-3	Toxicity resolves to Grade 0-1	Toxicity does not resolve to grade 0-1 within 6 weeks of last dose or inability to reduce corticosteroid to 10 mg or less of prednisone or equivalent per day within 12 weeks.
	4	Permanently discontinue	Permanently discontinue
Hyperthyroidism	3	Toxicity resolves to Grade 0-1	Toxicity does not resolve to grade 0-1 within 6 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 treatment for the thyroid disorder is instituted	Therapy with Pembrolizumab can be continued while treatment for the thyroid disorder is instituted.
Infusion Reaction	3-4	Permanently discontinue	Permanently discontinue

Toxicity	Hold Treatment For Grade	Timing for Restarting Treatment	Discontinue Subject if
Pneumonitis	2	Toxicity resolves to Grade 0-1	Toxicity does not resolve to grade 0-1 within 6 weeks of last dose or inability to reduce corticosteroid to 10 mg or less of prednisone or equivalent per day within 12 weeks.
	3-4	Permanently discontinue	Permanently discontinue
Renal Failure or Nephritis	2	Toxicity resolves to Grade 0-1	Toxicity does not resolveto grade 0-1 within 6 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[1,2]	3 or Severe	Toxicity resolves to Grade 0-1	Toxicity does not resolve to grade 0-1 within 6 weeks of last dose or inability to reduce corticosteroid to 10 mg or less of prednisone or equivalent per day within 12 weeks.
	4	Permanently discontinue	Permanently discontinue

Note: Permanently discontinue for persistent grade 2 or 3 adverse reactions (excluding endocrinopathies controlled with hormone replacement therapy) that do not recover to Grade 0-1 within 6 weeks after last dose of Pembrolizumab

[1] Pembrolizumab-specific exclusions to grade 3 non-hematologic toxicity as DLT include:

1. Grade 3 rash in the absence of desquamation, no mucosal involvement, does not require steroids, and resolves to Grade 1 by the next scheduled dose of pembrolizumab.
2. Transient Grade 3 AST or ALT elevation, defined as no more than 3 days with or without steroid use

[2] Pembrolizumab-specific DLT: Episcleritis, uveitis, or iritis of Grade 2 or higher

Dosing interruptions are permitted in the case of medical / surgical events or logistical reasons not related to study therapy (e.g., elective surgery, unrelated medical events, patient vacation, and/or holidays). Subjects should be placed back on study therapy within 6 weeks of the scheduled interruption, unless otherwise discussed with the PI. The reason for interruption should be documented in the patient's study record.

8.0 Trial Procedures

The study calendar - Section 10.0 summarizes the trial procedures to be performed at each visit. Individual trial procedures are described in detail below. It may be necessary to perform these procedures at unscheduled time points if deemed clinically necessary by the investigator.

Furthermore, additional evaluations/testing may be deemed necessary by the investigator for reasons related to subject safety.

8.1. Administrative Procedures

8.1.1. Informed Consent

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

8.1.2. Inclusion/Exclusion Criteria

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

8.1.3. 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.

8.1.4. Prior and Concomitant Medications Review

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.

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 9.2.

8.1.5. Disease Details and Treatments

Disease Details

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

8.1.6. Prior Treatment Details

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

Subsequent Anti-Cancer Therapy Status

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

8.2. Clinical Procedures/Assessments

8.2.1. 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.

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 6.4 regarding the identification, evaluation and management of AEs of a potential immunological etiology (also Appendix- section 17.3).

8.2.2. Physical Exam

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

8.2.3. Vital Signs

The investigator or qualified designee will take vital signs at screening, prior to the administration of each dose of trial treatment and at treatment discontinuation as specified in the study calendar (Section 10.0). Vital signs should include temperature, pulse, respiratory rate, weight and blood pressure. Height will be measured at screening only.

8.2.4. Eastern Cooperative Oncology Group (ECOG) Performance Scale

The investigator or qualified designee will assess ECOG status (see Appendix- section 17.1) at screening, prior to the administration of each dose of trial treatment and discontinuation of trial treatment as specified in the Trial Flow Chart.

8.2.5. Tumor Imaging and Assessment of Disease

Scans will be performed at baseline, and every 9 weeks (± 7 days) while on treatment for the first year and every 12 weeks (± 7 days) thereafter. Imaging during follow up is outlined in section 8.5.3.

8.2.6. Tumor Tissue Collection and Correlative Studies Blood Sampling

For details in regards to tumor tissue collection please see Section 8.3.1 Tumor tissue processing, and shipment instructions are provided in the Appendix – section 17.2 .

Peripheral blood samples will be collected immediately prior to the first dose of pembrolizumab (time 1), at cycle 3 (immediately prior to dose 3; time 2) and at time of progression (time 3) for correlative studies as outlined in Section 10.0 (study calendar).

Processing of blood samples will occur at FCCC as outlined in Appendix (section 17.2). Blood samples will be shipped to Protocol Support Laboratory (PSL) at Fo**x** Chase as outlined in Appendix. Samples will be distributed from the PSL at Fox Chase to Kerry Campbell's lab. Remaining cells will be stored in the PSL

8.3. Laboratory Procedures/Assessments

Details regarding specific laboratory procedures/assessments to be performed in this trial are provided below.

Laboratory tests for hematology, chemistry, urinalysis, and others are specified in Table 4.

Table 4. 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	Total Bilirubin	Microscopic exam *(If abnormal)*	Total thriiodothyronine (T3)
Absolute Neutrophil Count	Carbon Dioxide	results are noted	Free tyroxine (T4)
Absolute Lymphocyte Count	*(CO_2 or biocarbonate)*		Thyroid stimulating hormone (TSH)
	Blood Urea Nitrogen		Lipase
	Calcium		HIV antibody
	Chloride		Blood for correlative studies
	Glucose		HepBsAg
	Potassium		HCV RNA
	Sodium		
	Direct Bilirubin *(If total bilirubin is elevated above the upper limit of normal)*		
	Total protein		

† Perform on women of childbearing potential only.

Laboratory tests for screening will be performed within 10 days prior to the first dose of treatment. After Cycle 1, pre-dose laboratory procedures can be conducted up to 72 hours prior to dosing. Results must be reviewed by the investigator or qualified designee and found to be acceptable prior to each dose of trial treatment.

8.3.1. Biomarker Evaluations

Blood Collection for correlative studies/biomarkers
Sample collection, processing, storage, and shipment instructions for samples is provided in the Appendix (section 17.2).

Tumor tissue collection for correlative studies
Pathology samples from archived tumor biopsies (or optional fresh biopsy done before treatment initiation, if no archived tissue available) are to be submitted within 28 days of starting cycle 1. Representative FFPE tumor tissue blocks specimen are to be submitted to the Fox Chase Cancer Center PSL.

The following pathology material needs to be submitted:

- Paraffin embedded biopsy or cell block, and
- Any available pathology report related to that tumor sample

NOTE: If a block is unavailable for submission, slides are to be submitted. All slides must be adequately labeled, with slides numbered sequentially in the order cut. Alternative submission requirement:

- One (1) H&E slide, and
- Ten (10) 4 μm unstained air-dried on plus slides.

Shipment of pathology samples is outlined in the Appendix (section 17.2)

8.4. Other Procedures

8.4.1. 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 9.2 - Assessing and Recording Adverse Events. Subjects who a) attain a CR or b) complete 35 cycles of treatment with pembrolizumab may discontinue treatment with the option of restarting treatment if they meet the criteria specified in Section 8.5.4. After discontinuing treatment following assessment of CR, these subjects should return to the site for a Safety Follow-up Visit (described in Section 8.5.3) and then proceed to the Follow-Up Period of the study.

8.5. Visit Requirements

Visit requirements are outlined in Section 10.0 – study calendar. Specific procedure-related details are provided above in Section 8.0 - Trial Procedures.

8.5.1. Screening Period

Subjects will be screened within 28 prior to protocol treatment. Study procedures and information regarding the nature of the study will be reviewed with potential subjects and written informed consent will be obtained prior to any study related procedures. Screening procedures are described in Section 10.0 – study calendar.

8.5.2. Treatment Period

Subjects will be treated every 3 weeks of Pembrolizumab for up to 35 cycles. During the treatment phase patients will be evaluated clinically before each dose of Pembrolizumab for toxicities and radiologically every 9 weeks for disease progression as outlined in detail in Section 10.0 – study calendar.

8.5.3. Post-Treatment Visits

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 120 day 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 120 days of the end of treatment or before initiation of a new anti-cancer treatment should also be followed and recorded. Subjects who are eligible for retreatment with pembrolizumab (as described in Section 8.5.4) may have up to two safety follow-up visits, one after the Treatment Period and one after the Second Course Phase.

Follow-up Visits

Subjects who discontinue trial treatment for a reason other than disease progression will move into the Follow-Up Phase and should be assessed every 9 weeks (63 ± 7 days) by radiologic imaging to monitor disease status. After 1 year, the imaging time point will occur every 12 weeks (± 7 days). Every effort should be made to collect information regarding disease status until the start of new anti-neoplastic therapy, disease progression, death, end of the study or if the subject begins retreatment with pembrolizumab as detailed in Section 8.5.4. Information regarding post-study anti-neoplastic treatment will be collected if new treatment is initiated.

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.

8.5.4. Second Course Phase (Retreatment Period)

Subjects who stop pembrolizumab with SD or better may be eligible for up to 18 cycles of additional pembrolizumab therapy if they progress after stopping study treatment. This retreatment is termed the Second Course Phase of this study and is only available if the study remains open and the subject meets the following conditions:

Either

- Stopped initial treatment with pembrolizumab after attaining an investigator-determined confirmed CR according to RECIST 1.1, and
  - Was treated for at least 24 weeks with pembrolizumab before discontinuing therapy
  - Received at least two treatments with pembrolizumab beyond the date when the initial CR was declared

OR

- Had SD, PR or CR and stopped pembrolizumab treatment after 35 cycles of study therapy for reasons other than disease progression or intolerability

AND

- Experienced an investigator-determined confirmed radiographic disease progression after stopping their initial treatment with pembrolizumab
- Did not receive any anti-cancer treatment since the last dose of pembrolizumab
- Has a performance status of 0 or 1 on the ECOG Performance Scale
- Demonstrates adequate organ function as detailed in Section 6.1
- Female subject of childbearing potential should have a negative serum pregnancy test within 72 hours prior to receiving retreatment with study medication.
- Female subject of childbearing potential should be willing to use 2 methods of birth control or be surgically sterile, or abstain from heterosexual activity for the course of the study through 120 days after the last dose of study medication (Section 6.5.2). Subjects of child bearing potential are those who have not been surgically sterilized or have been free from menses for > 1 year.
- Male subject should agree to use an adequate method of contraception starting with the first dose of study therapy through 120 days after the last dose of study therapy.
- Does not have a history or current evidence of any condition, therapy, or laboratory abnormality that might interfere with the subject's participation for the full duration of the trial or is not in the best interest of the subject to participate, in the opinion of the treating investigator.

Subjects who restart treatment will be retreated at the same dose and dose interval as when they last received pembrolizumab. Treatment will be administered for up to 18 additional cycles.

Visit requirements are outlined in Section 10.0 – study calendar.

8.5.5. Treatment Beyond Disease Progression

See section 6.8 for further details**.** The decision to continue study treatment after the 1st evidence of disease progression is at the Investigator's discretion based on the clinical status of the subject as described in table 5. Confirmatory imaging maybe performed as early as 28 days later; alternatively, the scan performed at the next scheduled time point (every 42 days ± 7 days) may be used as confirmation. Subjects may receive study treatment while waiting for confirmation of PD if they are clinically stable as defined by the following criteria:

- Absence of signs and symptoms (including worsening of laboratory values) indicating
- disease progression
- No decline in ECOG performance status
- Absence of rapid progression of disease
- Absence of progressive tumor at critical anatomical sites (e.g., cord compression)
- Requiring urgent alternative medical intervention
- Subjects exhibiting toxicity from trial therapy requiring discontinuation of trial therapy as outlined in Section 6.4.and 7.0 may NOT continue to receive trial therapy.

Table 5

	Clinically stable		**Clinically unstable**	
	Imaging	**Treatment**	**Imaging**	**Treatment**
1st radiologic evidence of PD	Repeat imaging at > 4 weeks at site to confirm PD	May continue study treatment at the Investigator's discretion while awaiting confirmatory scan by site	Repeat imaging at > 4 weeks to confirm PD per physician discretion only	Discontinue treatment
Repeat scan confirms PD (no reduction in tumor burden from prior scan)	No additional imaging required	Discontinue treatment	No additional imaging required	**NA**
Repeat scan confirms PD (reduction in tumor burden from prior scan)	Continue regularly scheduled imaging assessments	Continue study treatment after consultation with Sponsor Investigator	Continue regularly scheduled imaging assessments	May restart study treatment if condition has improved and/or clinically stable per Investigator and Sponsor Investigators's discretion
Repeat scan shows SD, PR or CR	Continue regularly scheduled imaging assessments	Continue study treatment at the Investigator's discretion	Continue regularly scheduled imaging assessments	May restart study treatment if condition has improved and/or clinically stable per Investigator's discretion

NOTE: If a subject with confirmed radiographic progression (i.e. 2 scans at least 28 days apart demonstrating progressive disease) is clinically stable or clinically improved, and there is no further increase in the tumor dimensions at the confirmatory scan (as assessed by the investigator/site radiologist), an exception may be considered to continue treatment upon consultation with the Sponsor Investigator. All decisions to treat beyond progression

must be approved by the PI and the rationale must be clearly documented within the study records.
Upon radiographic or clinical evidence of second progression, defined as an additional 20% or greater increase in total sum of tumor burden, patients must discontinue study therapy

9.0 Adverse Events

9.1. Definitions:

9.1.1. 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 pembrolizumab is also an adverse event.

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

9.1.2. Serious Adverse Events

Serious Adverse Event (SAE) is an AE that is fatal or life threatening, requires inpatient hospitalization or prolongation of existing hospitalization (for > 24 hours), persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions, or is a congenital anomaly/ birth defect, or results in any important medical event that may not result in death, be life threatening, or require hospitalization may be considered an SAE when, based upon appropriate medical judgment, may jeopardize the subject and may require medical or surgical intervention to prevent any of the above outcomes. A "life-threatening" adverse event places the patient at immediate risk of death in the judgment of the investigator or sponsor.

Note: In addition to the above criteria, adverse events meeting either of the below criteria, although not serious per ICH definition, are considered serious for the purpose of this study and therefore must be reported in the same timeframe as SAEs.

- Is a new cancer (that is not a condition of the study);
- Is associated with an overdose.

9.1.3. Definition of Overdose for This Protocol

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

9.1.4. Severity Rating

The investigator will evaluate the severity of each adverse event. NCI Common Terminology Criteria for Adverse Events (CTCAE v.4.0) or study specific toxicity tables provided in the protocol define severity. If not included in CTCAE v.4.0, severity is expressed in numerical grade using the following definitions:

1. Grade 1: Mild-asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated.
2. Grade 2: Moderate-minimal, local or noninvasive intervention indicated; limiting age appropriate instrumental ADL.
3. Grade 3: Severe-severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self care ADL.
4. Grade 4: Life-threatening consequences; urgent intervention indicated.
5. Grade 5: Death related to AE

9.1.4.1. Attribution/Relationship to study drug

1. Definite – clearly related
2. Probable – likely related
3. Possible – may be related
4. Unlikely – doubtfully related
5. Unrelated – clearly not related

9.1.5. Expectedness

An Expected Adverse Event is one where the specificity or severity is consistent with the current information available from the resources.

An Unexpected Adverse Event is one where the nature, severity, or frequency of the event is related to participation in the research is not consistent with either:

1. The known or foreseeable risk of adverse events associated with the procedures involved in the research that are described in (a) the protocol-related documents, such as the IRB-approved research protocol, any applicable investigator brochure, and the current IRB-approved informed consent document, and (b) other relevant sources of information, such as product labeling and package inserts: or

2. The expected natural progression of any underlying disease, disorder, or condition of the subject (s) experiencing the adverse event and the subjects(s) predisposing risk factor profile for the adverse event.

(OHRP Guidance on reviewing unanticipated problems 2007)

9.1.6. Events of Clinical Interest

Selected non-serious and serious adverse events are also known as Events of Clinical Interest (ECI).

Events of clinical interest for this trial include:

1. An overdose of Merck product 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.

9.2. Assessing, Recording and Reporting Adverse Events

9.2.1. Investigative site recording responsibilities:

1. Upon identification of an AE or SAE, the site investigator will utilize the above definitions to properly classify the event. Each category listed above; in section 9.1; must be recorded for each event. Adverse events will be recorded from the time of treatment initiation through 120 days following cessation of treatment.

2. All AEs and SAEs will be recorded in the "AE case report forms" (CRF) and in progress reports with details about the grade and attribution of each episode, action taken with respect to the study drug, and the patient's outcome will be recorded in the CRF. All events will be recorded on case report forms for the duration of the study until they resolve.

3. All SAEs will be recorded on the FDA MedWatch form 3500a. After submitting the initial report it may be necessary to submit follow up reports to the Sponsor, Merck and the FDA should the event require further investigation.

9.2.2. Investigative site reporting responsibilities:

1. The investigator/ site is responsible to report all SAEs that occur on or after the first day of study treatment to the IST Regulatory Specialist within 24 hours of becoming aware

of the event.

Each investigator is responsible to report all SAEs to their local IRB following guidelines set by that IRB. The FCCC OCR reserves the right to request an event be reported to the IRB at their discretion. Copies of events reviewed by the IRB must be sent email to **SAE.FCCC@fccc.edu.**

2. If the investigator or IRB feels the event warrants a revision to the informed consent that was not already initiated by the OCR, draft revisions will be made in track changes and submitted to the OCR for consideration. Any consent revisions must receive OCR approval **prior** to submission to the IRB.

3. Any investigator who is in doubt of whether a particular AE needs to be reported is directed to call the Study Monitor for confirmation with the Sponsor Investigator.

4. If the results of an investigator or OCR investigation show an adverse event not initially determined to be reportable is so reportable, the investigator will report the event following the above guidelines based on the date the determination is made.

5. Copies of all related correspondence and reporting documents must be submitted to the ISRU and will be maintained in the trial master file.

Participating sites should report events to:

Investigator-Sponsored Research Unit
Office of Clinical Research
Fox Chase Cancer Center
SAE.FCCC@fccc.edu

9.2.3. Additional reporting guidelines for investigative sites:

Following events must be reported by investigative sites to IST Regulatory Specialist within 24 hours of being aware of the event:

- **Serious Adverse Events**

For the time period beginning at treatment initiation through 120 days following cessation of treatment, or 30 days following cessation of treatment if the subject initiates new anticancer therapy, whichever is earlier, any serious adverse event, or follow up to a serious adverse event, including death due to any cause other than progression of the cancer under study whether or not related to the pembrolizumab must be reported.

- **Overdose**

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

If a dose of pembrolizumab 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."

- **New cancer Incident**

If a new type of cancer is detected, which is not a condition of the study, it should be reported as a serious adverse event.

- **Pregnancies and Lactations**

Pregnancies and lactations that occur from the time of treatment initiation through 120 days following cessation of pembrolizumab, or 30 days following cessation of treatment if the subject initiates new anticancer therapy, whichever is earlier, must be reported .

All reported pregnancies 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.

- **Events of Clinical Interest (ECIs)**

For the time period beginning at treatment initiation through 120 days following cessation of treatment, or 30 days following cessation of treatment if the subject initiates new anticancer therapy, whichever is earlier, any ECI, or follow up to an ECI, whether or not related to pembrolizumab must be reported.

9.2.4. Sponsor Reporting Responsibilities:

1. Adverse events which meet all of the following criteria must be reported to all participating institutions for IRB submission within 2 weeks of notification of the event:
    i. Unexpected (in terms of nature, severity, or frequency) given (a) the research procedures that are described in the protocol-related documents, such as the IRB-approved research protocol and informed consent document; and (b) the characteristics of the subject population being studied;
    ii. Possibly related to participation in the research (possibly related means there is a reasonable possibility that the incident, experience, or outcome may have been caused by the procedures involved in the research); and

iii. Serious (refer to above definition) or otherwise one that suggests that the research places subjects or others at a greater risk of physical or psychological harm than was previously known or recognized.

2. Copies of all related correspondence and reporting documents will be maintained in a centralized regulatory file for this study at OCR.

3. SAEs that are related, unexpected, fatal, or life-threatening are reportable through the Food and Drug Administration (FDA) MedWatch program by telephone or fax no later than 7 calendar days after initial receipt of the information. Further information on the timing of submissions are as directed by FDA guidelines.(http://www.fda.gov/medwatch/index.html). Serious, unexpected events that suggest significant clinical risk will be submitted to within 15 calendar days after initial receipt of this information.

Food and Drug Administration:
Central Document Room
Center for Drug Evaluation and Research
Food and Drug Administration
5901-B Ammendale Road
Beltsville, MD 20705

(301) 827-3169 for any further questions regarding where to send drug mandatory reporting forms

9.2.5. Sponsor Reporting Responsibilities to Merck:

Sponsor must report the following to Merck Global Safety within 2 working days of notification by investigative sites:

- Serious Adverse Events
- All reports of overdose with and without an adverse event
- Pregnancy and Lactation
- Events of Clinical Interest (ECIs)

SAE reports and any other relevant safety information are to be forwarded to the Merck Global Safety (Attn: Worldwide Product Safety; FAX 215 993-1220)

A copy of all 15 Day Reports and Annual Progress Reports is submitted as required by FDA, 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.

10.0 Study Calendar

10.1. Initial Treatment Phase

Trial Period:	Screening Phase	Treatment Cycles[a]				End of Treatment[m]		Post-Treatment		
Treatment Cycle/Title:	Study Screening	1	2	3	Cycle 4 and beyond	35 cycles completed OR	Safety Follow-up	Safety Follow-up	Follow Up Visits[b]	Survival Follow-Up
Scheduling Window (Days):	-28 to -1		± 3	± 3	± 3	At time of Discon	30 days post discon	120 days post discon		Every 12 weeks
Administrative Procedures										
Informed Consent	x									
Inclusion/Exclusion Criteria	x									
Demographics and Medical History	X									
Prior and Concomitant Medication Review	X	x	x	x	x	x	X			
Pembrolizumab Administration		x	x	x	x					
Post-study anticancer therapy status									x	x
Survival Status										x
Review Adverse Events		x	x	x	x	x	x	x		
Full Physical Examination	x	X	X	x	X	x	x			
Vital Signs [i] and Weight	x	x	x	x	x	x	x			
Height	x									
ECOG Performance Status	x	x	x	x	x	x	x			
Laboratory Procedures/Assessments: analysis performed by LOCAL laboratory										
Pregnancy Test –Serum B-HCG	x [h]									
PT/INR and aPTT	x [g]									
CBC with Differential	x [g]	x	x	x	x	x	x			

Trial Period:	Screening Phase	Treatment Cycles[a]				End of Treatment[m]		Post-Treatment		
Treatment Cycle/Title:	Study Screening	1	2	3	Cycle 4 and beyond	35 cycles completed OR	Safety Follow-up	Safety Follow-up	Follow Up Visits[b]	Survival Follow-Up
Scheduling Window (Days):	-28 to -1		± 3	± 3	± 3	At time of Discon	30 days post discon	120 days post discon		Every 12 weeks
HIV antibody	x									
HepBsAg	x									
HCV RNA	x									
Comprehensive Serum Chemistry Panel [j]	x [g]	x	x	x	x	x	x			
Urinalysis	x [g]									
T3, FT4 and TSH	x [g]	x[c]				x	x			
Efficacy Measurements										
Tumor Imaging[d]	x	X[e]							X[l]	
Tumor Biopsies/Archival Tissue Collection/Correlative Studies Blood										
Archival Tissue requested[k]	x									
Correlative Studies Blood Collection [f]		x		x		x				
Optional blood collection for future studies[n]	x	x				x				

[a] Total of 35 treatment cycles. Treatment cycles are 3 weeks (21-days)

[b] Patients should be assessed every 9 weeks (63 ± 7 days) for the first 1 year (or until disease progression) for disease status. After 1 year, patients should be assessed every 12 weeks (± 7 days). Once a subject experiences confirmed disease progression or starts a new anti-cancer therapy they move into survival follow-up

[c] Check during treatment phase every 3 cycles (screening, cycle 3, 6, 9, 12, 15, 18, etc.)

[d] Preferably a contrast-enhanced CT scan of chest/abdomen and pelvis (If cannot receive contrast, can substitute for CT chest without contrast and MRI abdomen/pelvis with contrast). Subsequent imaging should be of the same modality as the imaging at baseline. Imaging studies will be done every 9 weeks (± 7 days) after initiating treatment for the first year; subsequent imaging will be every 12 weeks (± 7days) thereafter during the treatment phase.

[e] Imaging studies will be done every 9 weeks (± 7 days) after initiating treatment for the first year; subsequent imaging will be every 12 weeks (± 7 days) thereafter during the treatment phase.

Trial Period:	Screening Phase	Treatment Cycles[a]				End of Treatment[m]		Post-Treatment		
Treatment Cycle/Title:	Study Screening	1	2	3	Cycle 4 and beyond	35 cycles completed OR	Safety Follow-up	Safety Follow-up	Follow Up Visits[b]	Survival Follow-Up
Scheduling Window (Days):	-28 to -1		± 3	± 3	± 3	At time of Discon	30 days post discon	120 days post discon		Every 12 weeks

[f] Peripheral blood samples will be collected immediately prior to cycle 1 , immediately prior to dose 1 (time 1), prior to dose 3, cycle 3 day 1 (time 2) and at time of progression (time 3). For sampling, handling, processing, and shipping, please see Appendix (Section 17.2)

[g] Within 10 days of treatment initiation

[h] Within 72 hours of treatment initiation if participant is a woman of child bearing potential

[i] Vital signs consist of temperature, pulse, respiration, and blood pressure and will be monitored every 15 minutes during the infusion and at 60 minutes after completion of each infusion.

[j] A direct bilirubin must be performed if the total bilirubin is above the upper limit of normal. This will also include Lipase testing.

[k] If archival tissue is not available, patient may undergo an optional fresh biopsy of tumor before day 1 of therapy. All archived tissues must be received within 28 days of starting cycle 1.

[l] In subjects who discontinue study therapy without documented disease progression, every effort should be made to continue monitoring their disease status by radiologic imaging every 9 weeks (63 ± 7days) in the first year and every 12 weeks (84 ± 7 days) after year 1 until (1) the start of new anti-cancer treatment, (2) disease progression as assessed by the investigator/site radiologist, (3) death, or (4)the end of the study, whichever occurs first.

[m] End of treatment procedures will be conducted at the time of treatment discontinuation or at the end of 35 cycles, whichever occurs sooner

[n] Optional blood collections in consenting patients for sera, plasma and red blood cells for future research. In consenting patients, blood will be drawn prior to cycle 1, every other assessment, and at the end of treatment for future research.

10.2. Retreatment Phase (Second Course of Treatment)

Trial Period:	Screening	Treatment Cycles[a]				End of Treatment	Post-Treatment			
Treatment Cycle/Title:	Pre-Re-Tx	1	2	3	Cycle 4 and beyond	Discon	Safety Follow-up	Safety Follow-up	Follow Up Visits[b]	Survival Follow-Up
Scheduling Window (Days):			± 3	± 3	± 3	At time of Discon	30 days post discon	120 days post discon		Every 12 weeks
Eligibility criteria	X									

Trial Period:	**Screening**	**Treatment Cycles[a]**				**End of Treatment**	**Post-Treatment**			
Treatment Cycle/Title:	Pre-Re-Tx	1	2	3	Cycle 4 and beyond	Discon	Safety Follow-up	Safety Follow-up	Follow Up Visits[b]	Survival Follow-Up
Scheduling Window (Days):			± 3	± 3	± 3	At time of Discon	30 days post discon	120 days post discon		Every 12 weeks
Prior and Concomitant Medication Review	X	X	X	X	X	X	X			
Pembrolizumab Administration		X	X	X	X					
Post-study anticancer therapy status									X	X
Survival Status										X
Review Adverse Events		X	X	X	X	X	X	X		
Full Physical Examination	X	X	X	X	X	X	X			
Vital Signs and Weight[i]	X	X	X	X	X	X	X			
ECOG Performance Status	X	X	X	X	X	X	X			
Pregnancy Test –Serum β-HCG	X[h]									
PT/INR and aPTT	X[g]									
CBC with Differential	X[g]	X	X	X	X	X	X			
Comprehensive Serum Chemistry Panel[j]	X[g]	X	X	X	X	X	X			
HIV antibody	x									
HepBsAg	x									
HCV RNA	x									
Urinalysis	X[g]									
T3, FT4 and TSH	X[g]	X[c]					X			
Tumor Imaging[d,]	X	X[e]				X[f]			X[k]	

a Treatment cycles are 3 weeks (21-days)

b Patients should be assessed every 9 weeks (63 ± 7 days) for the first 1 year (or until disease progression) for disease status. After 1 year, patients should be assessed every 12 weeks (± 7 days). Once a subject experiences confirmed disease progression or starts a new anti-cancer therapy they move into survival follow-up

c Check during treatment phase every 3 cycles (screening, cycle 3, 6, 9, 12, 15, 18, etc.)

d Preferably a contrast-enhanced CT scan of chest/abdomen and pelvis done within 28 days of restarting treatment(If cannot receive contrast, can substitute for CT chest without contrast and MRI abdomen/pelvis with contrast). Subsequent imaging should be of the same modality as the imaging at baseline.

Trial Period:	Screening	Treatment Cycles[a]				End of Treatment	Post-Treatment			
Treatment Cycle/Title:	Pre-Re-Tx	1	2	3	Cycle 4 and beyond	Discon	Safety Follow-up	Safety Follow-up	Follow Up Visits[b]	Survival Follow-Up
Scheduling Window (Days):			± 3	± 3	± 3	At time of Discon	30 days post discon	120 days post discon		Every 12 weeks

[e] Imaging studies will be done every 9 weeks (± 7 days) after initiating treatment for the first year; subsequent imaging will be every 12 weeks (± 7days) thereafter during the treatment phase.

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

[g] Within 10 days of treatment initiation

[h] Within 72 hours of treatment initiation if participant is a woman of child bearing potential

[i] Vital signs consist of temperature, pulse, respiration, and blood pressure and will be monitored every 15 minutes during the infusion and at 60 minutes after completion of each infusion.

[j] A direct bilirubin must be performed if the total bilirubin is above the upper limit of normal. This will also include Lipase testing. k In subjects who discontinue study therapy without documented disease progression, every effort should be made to continue monitoring their disease status by radiologic imaging every 9 weeks (63 ± 7days) in the first year and every 12 weeks (84 ± 7 days) after year 1 until (1) the start of new anti-cancer treatment, (2) disease progression as assessed by the investigator/site radiologist, (3) death, or (4)the end of the study, whichever occurs first

11.0 Labeling, Packaging, Storage and Return of Clinical Supplies

11.1. 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 6.

Table 6. Product Descriptions

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

11.2. Packaging and Labeling Information

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

11.3. Clinical Supplies Disclosure

This trial is open-label

11.4. Storage and Handling Requirements

Clinical supplies must be stored in a secure, limited-access location under the storage conditions specified on the label.
Receipt and dispensing of trial medication must be recorded by an authorized person at the trial site.
Clinical supplies may not be used for any purpose other than that stated in the protocol.

11.5. 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.

12.0 Measures of Effect

Response Evaluation Criteria in Solid Tumors (RECIST)

The Response Evaluation Criteria in Solid Tumors (RECIST 1.1) criteria will be used for objective tumor response assessment. Assessments will be performed after every 3 cycles for the first year and then every 4 cycles. Once protocol treatment has been completed subjects will be assessed every twelve weeks or sooner as indicated and judged by treating physicians.

12.1. Definitions

Evaluable for adverse events. All patients will be evaluable for adverse events from the time of their first treatment with pembrolizumab.

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

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

12.2. Disease Parameters

Measurable disease. Measurable lesions are defined as those that can be accurately measured in at least one dimension (longest diameter to be recorded) as $\geq$20 mm by chest x-ray, as $\geq$10 mm with CT scan or MRI, or $\geq$10 mm with calipers by clinical exam. All tumor measurements must be recorded in millimeters (or decimal fractions of centimeters).

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

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

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

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

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

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

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

12.3. Methods for Evaluation of Measurable Disease

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

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

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

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

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

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

12.4. Response Criteria

Evaluation of Target Lesions

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

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

Progressive Disease (PD): At least a 20% increase in the sum of the diameters of target lesions, taking as reference the smallest sum on study (this includes the baseline sum if that is the smallest on study). In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 5 mm. (Note: the appearance of one or more new lesions is also considered progressions).

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

Evaluation of Non-Target Lesions

Complete Response (CR): Disappearance of all non-target lesions and normalization of tumor marker level. All lymph nodes must be non-pathological in size (<10 mm short axis Note: If tumor markers are initially above the upper normal limit, they must normalize for a patient to be considered in complete clinical response.

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

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

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

For Patients with Measurable Disease (i.e., Target Disease)

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

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

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

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

For Patients with Measurable Disease (i.e., Target Disease)

<table>
<tr><th>Target Lesions</th><th>Non-Target Lesions</th><th>New Lesions</th><th>Overall Response</th><th>Best Overall Response when Confirmation is Required*</th></tr>
<tr><td>CR</td><td>CR</td><td>No</td><td>CR</td><td>≥4 wks. Confirmation**</td></tr>
<tr><td>CR</td><td>Non-CR/Non-PD</td><td>No</td><td>PR</td><td rowspan="3">≥4 wks. Confirmation**</td></tr>
<tr><td>CR</td><td>Not evaluated</td><td>No</td><td>PR</td></tr>
<tr><td>PR</td><td>Non-CR/Non-PD /not evaluated</td><td>No</td><td>PR</td></tr>
<tr><td>SD</td><td>Non-CR/Non-PD /not evaluated</td><td>No</td><td>SD</td><td>documented at least once ≥4 wks. from baseline**</td></tr>
<tr><td>PD</td><td>Any</td><td>Yes or No</td><td>PD</td><td rowspan="3">no prior SD, PR or CR</td></tr>
<tr><td>Any</td><td>PD***</td><td>Yes or No</td><td>PD</td></tr>
<tr><td>Any</td><td>Any</td><td>Yes</td><td>PD</td></tr>
<tr><td colspan="5">* See RECIST 1.1 manuscript for further details on what is evidence of a new lesion.
** Only for non-randomized trials with response as primary endpoint.
*** In exceptional circumstances, unequivocal progression in non-target lesions may be accepted as disease progression.</td></tr>
</table>

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

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

Non-Target Lesions	New Lesions	Overall Response
CR	No	CR
Non-CR/non-PD	No	Non-CR/non-PD*
Not all evaluated	No	not evaluated
Unequivocal PD	Yes or No	PD
Any	Yes	PD
* 'Non-CR/non-PD' is preferred over 'stable disease' for non-target disease since SD is increasingly used as an endpoint for assessment of efficacy in some trials so to assign this category when no lesions can be measured is not advised		

12.5. Objective response rate (ORR)

Objective response rate (ORR) is defined as the proportion of subjects with metastatic high grade NETs who achieve a best response of complete response (CR) or partial response (PR) using the RECIST1.1 criteria. It will be determined by the investigator for each subject as either CR or PR and will be calculated as percentage CR + PR.

12.6. Duration of Response

Duration of overall response: The duration of overall response is measured from the time measurement criteria are met for CR or PR (whichever is first recorded) until the first date that recurrent or progressive disease is objectively documented (taking as reference for progressive disease the smallest measurements recorded since the treatment started).

The duration of overall CR is measured from the time measurement criteria are first met for CR until the first date that progressive disease is objectively documented.

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

Progression-Free Survival: Progression free survival is defined as the duration of time from start of treatment to time of progression or death, whichever occurs first.

13.0 Statistical Considerations

13.1. Study Design/Endpoints

The primary objective will be measured by the primary endpoint of Objective Response Rate (per RECIST 1.1) among all treated subjects. Secondary endpoints include PFS (per RECIST 1.1) and OS. As discussed in the background, no second line treatments have been studied prospectively for high grade neuroendocrine carcinomas and small retrospective studies have shown dismal results with chemotherapy[11-13]. Hence we decided to proceed with a single stage statistical design given minimal if any, harm associated with ineffective therapy to study participants.

A proportion of patients with favorable response less than 5.0% will be of no interest. The investigational agent would be of interest if the ORR is at least 20.0%. Estimates are based on historical controls from published data {Hentic, 2012 #70;Olsen, 2012 #71;{Sorbye, 2013 #36}. Only those patients who have measurable disease present at baseline, have received at least one cycle of therapy, and have had their disease re-evaluated will be considered evaluable for response. (Note: Patients who exhibit objective disease progression prior to the end of cycle 1 will also be considered evaluable.) Patients who are not evaluable for response will be replaced. However, all patients who received at least 1 dose of the study drug will be included in the safety analysis. Twenty-one patients would be needed to test the null hypothesis: $p <= 0.05$ against the alternative hypothesis: $p >= 0.20$ at the 8.5% level of significance and with 82.1% power. After 21 patients are evaluated if 3 or more patients with favorable response are observed then the null hypothesis is rejected.

Early stopping rules for safety/adverse events:

Adverse events will be assessed continuously throughout the study. If 6 of the first 12 patients have to discontinue study treatment due to treatment related adverse events the study will be interrupted for consideration of dose reduction or termination. If ever 8 of the 21 eligible patients have to discontinue study treatment due to treatment related adverse events the study will be suspended and early termination for excess toxicity will be considered after careful investigation of the causes of the higher than expected toxicities. Once the root of the higher than anticipated toxicities has been determined, the study team will confer with the FCCC DSMC and IRB to make a determination whether accrual can be resumed or the study will be terminated early. The chance of early termination with a true toxicity of 50% is 61%. The chance of early termination in error, when true toxicity is <20% is 1.9%. The overall chance of study termination under the null of 20% true toxicity is 2.7% and is 83% if true toxicity is 50%.

As discussed earlier, no second line therapies have been prospectively evaluated in high grade neuroendocrine carcinomas and small retrospective studies have shown dismal results with chemotherapy [11-13]. Hence we decided to proceed without a definite stopping rule for futility, given minimal if any, harm associated with ineffective therapy to study participants.]

Correlative studies: Due to this limited sample size, all exploratory analyses of associations of biomarkers with outcomes and changes in marker levels pre- and during treatment will be largely descriptive in nature.

13.2. Sample Size/Accrual Rate

We plan to accrue 21 eligible patients. The expected monthly accrual rate is 1-2 patients. Thus, accrual is anticipated to take approximately 2 years.

13.3. Stratification Factors

No stratification factors are pre-defined within the protocol

13.4. Reporting and Exclusions

13.4.1 Evaluation of toxicity**:** All patients will be evaluable for toxicity from the time of their first treatment with pembrolizumab

13.4.2 Evaluation of response: All patients included in the study must be assessed for response to treatment, even if there are major protocol treatment deviations or if they are ineligible. Each patient will be assigned one of the following categories: 1) complete response, 2) partial response, 3) stable disease, 4) progressive disease, 5) early death from malignant disease, 6) early death from toxicity, 7) early death because of other cause, or 9) unknown (not assessable, insufficient data). [Note: By arbitrary convention, category 9 usually designates the "unknown" status of any type of data in a clinical database.]

All of the patients who met the eligibility criteria (with the possible exception of those who received no study medication) should be included in the main analysis of the response rate. Patients in response categories 4-9 should be considered to have a treatment failure (disease progression). Thus, an incorrect treatment schedule or drug administration does not result in exclusion from the analysis of the response rate. Precise definitions for categories 4-9 will be protocol specific.

14.0 Data and Safety Monitoring Plan

14.1. Monitoring Plan

FCCC ISRU will monitor the medical and study records of each participant accrued throughout the course of the study. In addition, the ISRU will collect and report data to the study Sponsor Investigator who will review these data on a regular basis at a rate dependent on subject accrual. All serious adverse events (SAEs) will be reviewed on a real time basis first by the study site PI and subsequently by the ISRU and Sponsor Investigator as applicable.

14.2. Data Safety Monitoring Board

Interim analysis of toxicity, outcome and ongoing scientific investigations may be performed at least every 3 months by the Fox Chase Cancer Center Data Safety Monitoring Committee (FCCCDSMB). In this capacity the FCCCDSMB will serve as an advisory committee to the Sponsor Investigator. The FCCCDSMB will review those aspects of this trial that are outlined in the responsibilities section of the Data and Safety Monitoring Plan (DSMP). If the committee decides that changes should be made to this trial, it will make recommendations in writing to the Sponsor Investigator, the Associate Director of Clinical Research, and the Protocol Management Executive Committee, which, in turn, have the authority to approve or disapprove these recommendations. These changes will be discussed with the Sponsor Investigator before they are implemented. These changes may include early termination of accrual. Other changes might include altering the accrual goals or changing the eligibility criteria for the trial.

15.0 Administrative

This study will be conducted in accordance will local, state and Federal regulations and according to accepted good clinical practice guidelines.

15.1. Data Reporting

The FCCC Study Monitor will request eCRF to be completed within 2 weeks of the protocol visit. Participating sites are responsible to respond to queries prior to the next scheduled monitoring visit

The ISRU is responsible for compiling and submitting data to the Sponsor Investigator and statistician on an ongoing basis for monitoring as described in the data safety monitoring plan and reporting to the Data and Safety Monitoring Board.

All patient information will be stored in an EDC system accessible only to the study team members for the purpose of entering, reviewing and analyzing data. Any paper records, such as case report files, produced will be stored in a secure location.

The ISRU is responsible for distributing and tracking review of all IND Action Letters, Safety Reports, study specific Serious Adverse Events.

15.2. Retention of Records

In all cases the Study Monitor must be notified of any plans to move records to an offsite location prior to doing so.

15.3. Informed Consent

The IRB approved informed consent documents must be signed by the patient, or the patient's legally authorized representative, before his or her participation in the study. The case history for each patient shall document that informed consent was obtained prior to participation in the study. A copy of the informed consent documents must be provided to

the patient or the patient's legally authorized representative. If applicable, they will be provided in a certified translation of the local language.

Original signed consent forms must be filed in each patient's study file or medical record with a copy in the study file.

16.0 References

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17.0 Appendices

17.1. 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.

17.2. Collection, Shipment, and Processing of Blood Samples and Tissue for Correlative studies

Optional blood collection and storage of leftover tumor tissue sample for future exploratory research will be done only after obtaining informed consent from patients for future unspecified biomedical research. This consent will be a part of the informed consent process at the time of study entry.

Blood Sample Collection:

Three peripheral blood samples (up to 60 ml each) will be serially collected from each patient at the following time points:

1. Immediately prior to the first treatment, for a baseline assessment.
2. Immediately prior to the third treatment, which would occur at cycle 3.
3. When disease progression is observed, either during or post-treatment.

Instructions for Collection, Processing and Shipping Procedures for Blood and Tissue Specimens

Blood will be drawn by a physician, registered nurse or licensed phlebotomist prior to receiving the Pembrolizumab at the predefined time points. For correlative studies, blood will be drawn into **two (2) sodium heparin green top tubes** (about 20 ml) at the three time points. Also, one (1) red top tube and one (1) EDTA tube for cell free plasma (20 ml) will be drawn before cycle 1, every other assessment, and at the end of treatment for future research.

All blood samples for PBMC preparation will be processed in the Protocol Support Laboratory. Flow cytometry processing and analysis will be performed in the Campbell laboratory on an Aria II flow cytometer (BD). Compensation (parallel controls using cells singly stained for each color) and data analysis will be performed using FlowJo flow cytometry analysis software (TreeStar). The percentage and/or mean fluorescence intensity (MFI) of cells staining for individual markers will be determined, and CD107A+ degranulating NK cells in functional assays, will be compared to isotype controls to establish baseline values. Pembrolizumab will be used to stain for PD-1 expression on leukocytes in pre-treatment samples and a secondary anti-human IgG4 will be used to assess the remaining Pembrolizumab bound to PD-1 on treatment samples. Samples should be collected according to the institutional procedures for venipuncture.

Archival tissue or biopsy - Tissue will be used for immunohistochemistry and next gene sequencing. If archival tissue is not available an optional biopsy may be performed. *" Label slides with patient study #, pathology accession #. Slides will be prepared by PSL stored at 4°C, batched and transferred to Qualtek for immunohistochemistry analysis.*

PBMC preparation (green top tubes) –

Remaining PBMC will be frozen in 10%DMSO + 90% FBS at a conc. of 5-10 x 10^6 cells/vial and stored at –70°C and transferred to liquid nitrogen.

17.3. Management of immune related adverse events from Pembrolizumab.

PDF provided separately

17.4. 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)