A Phase I Trial of Hypofractionated Stereotactic Irradiation (HFSRT) with MK-3475 and Bevacizumab in Patients with Recurrent High Grade Gliomas

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TITLE: A Phase I Trial of Hypofractionated Stereotactic Irradiation (HFSRT) with Pembrolizumab and Bevacizumab in Patients with Recurrent High Grade Gliomas.

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1.0 TRIAL SUMMARY

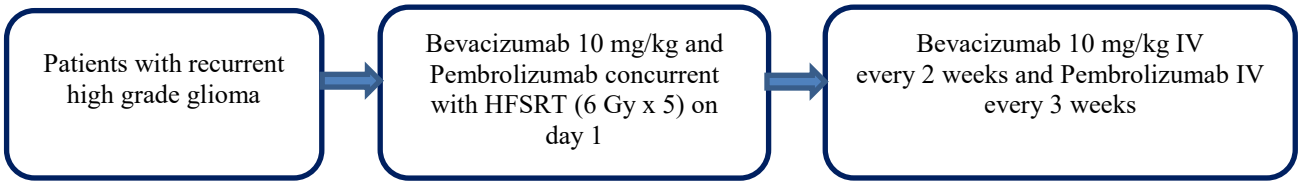
Abbreviated Title	**Phase I trial of HFSRT with pembrolizumab and bevacizumab for recurrent high grade gliomas**
Trial Phase	Ib
Clinical Indication	Recurrent high grade gliomas
Trial Type	Open label
Route of administration	Intravenous
Trial Blinding	Not applicable
Treatment Groups	1 Group
Number of trial subjects	32
Estimated duration of trial	36 months
Duration of Participation	24 months

2.0 TRIAL DESIGN

2.1 Trial Design

This is a standard 3+3 design and will include 2 cohorts: 1) dose escalation cohort, and 2) dose expansion cohort.

2.2 Trial Diagram



Dose Escalation Phase

Dose Escalation Schedule		
Dose Level	**Dose**	
	Pembrolizumab IV every 3 weeks	**Bevacizumab IV every 2 weeks**
Level 1	100 mg	10 mg/kg
Level 2	200 mg	10 mg/kg

Dose Expansion Phase

Two groups of patients (bevacizumab naïve and bevacizumab failure) will be treated with pembrolizumab at MTD (from dose escalation phase) and bevacizumab concurrent and after HFSRT

3.0 OBJECTIVE(S) & HYPOTHESIS(ES)

3.1 Primary Objective(s) & Hypothesis(es)

(1) **Objective:** To evaluate the safety, tolerability, and to determine the maximum tolerated dose (MTD) of pembrolizumab given in combination with bevacizumab and hypofractionated stereotactic re-irradiation of recurrent high grade gliomas.

Hypothesis: Intravenous administration of pembrolizumab in combination with bevacizumab and hypofractionated stereotactic re-irradiation will have acceptable safety and tolerability.

3.2 Secondary Objective(s) & Hypothesis(es)

(1) **Objective**: To evaluate the response rate of pembrolizumab given in combination with bevacizumab and hypofractionated stereotactic re-irradiation of recurrent high grade gliomas.

Hypothesis: Addition of pembrolizumab to bevacizumab and hypofractionated stereotactic re-irradiation will augment the response to treatment.

3.3 Exploratory Objective

(1) **Objective:** To explore tissue and blood biomarkers that may predict tumor response to pembrolizumab in combination with bevacizumab and hypofractionated stereotactic re-irradiation in patients with recurrent high grade gliomas.

4.0 BACKGROUND & RATIONALE

4.1 Background

4.1.1 Pharmaceutical and Therapeutic Background

The importance of intact immune surveillance in controlling outgrowth of neoplastic transformation has been known for decades [1]. Accumulating evidence shows a correlation between tumor-infiltrating lymphocytes (TILs) in cancer tissue and favorable prognosis in various malignancies [2; 3; 4; 5; 6]. In particular, the presence of CD8+ T-cells and the ratio of CD8+ effector T-cells / FoxP3+ regulatory T-cells seems to correlate with improved prognosis and long-term survival in many solid tumors.

The PD-1 receptor-ligand interaction is a major pathway hijacked by tumors to suppress immune control. The normal function of PD-1, expressed on the cell surface of activated T-cells under healthy conditions, is to down-modulate unwanted or excessive immune responses, including autoimmune reactions. PD-1 (encoded by the gene Pdcd1) is an Ig superfamily member related to CD28 and CTLA-4 which has been shown to negatively regulate antigen receptor signaling upon engagement of its ligands (PD-L1 and/or PD-L2) [7;

8]. The structure of murine PD-1 has been resolved [9]. PD-1 and family members are type I transmembrane glycoproteins containing an Ig Variable-type (V-type) domain responsible for ligand binding and a cytoplasmic tail which is responsible for the binding of signaling molecules. The cytoplasmic tail of PD-1 contains 2 tyrosine-based signaling motifs, an immunoreceptor tyrosine-based inhibition motif (ITIM) and an immunoreceptor tyrosine-based switch motif (ITSM). Following T-cell stimulation, PD-1 recruits the tyrosine phosphatases SHP-1 and SHP-2 to the ITSM motif within its cytoplasmic tail, leading to the dephosphorylation of effector molecules such as CD3ζ, PKCθ and ZAP70 which are involved in the CD3 T-cell signaling cascade [7; 10; 11; 12]. 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 [13; 14]. 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 [15; 16]. Expression has also been shown during thymic development on CD4-CD8- (double negative) T-cells as well as subsets of macrophages and dendritic cells [17]. The ligands for PD-1 (PD-L1 and PD-L2) are constitutively expressed or can be induced in a variety of cell types, including non-hematopoietic tissues as well as in various tumors [18; 19; 20; 13]. Both ligands are type I transmembrane receptors containing both IgV- and IgC-like domains in the extracellular region and contain short cytoplasmic regions with no known signaling motifs. Binding of either PD-1 ligand to PD-1 inhibits T-cell activation triggered through the T-cell receptor. PD-L1 is expressed at low levels on various non-hematopoietic tissues, most notably on vascular endothelium, whereas PD-L2 protein is only detectably expressed on antigen-presenting cells found in lymphoid tissue or chronic inflammatory environments. PD-L2 is thought to control immune T-cell activation in lymphoid organs, whereas PD-L1 serves to dampen unwarranted T-cell function in peripheral tissues [13]. Although healthy organs express little (if any) PD-L1, a variety of cancers were demonstrated to express abundant levels of this T-cell inhibitor. PD-1 has been suggested to regulate tumor-specific T-cell expansion in subjects with melanoma (MEL) [21]. This suggests that the PD-1/PD-L1 pathway plays a critical role in tumor immune evasion and should be considered as an attractive target for therapeutic intervention.

Pembrolizumab (previously known as SCH 900475) is a potent and highly selective humanized monoclonal antibody (mAb) of the IgG4/kappa isotype designed to directly block the interaction between PD-1 and its ligands, PD-L1 and PD-L2.

4.1.2 Preclinical and Clinical Trial Data

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

4.2 Rationale and Biomarker Research

4.2.1 Rationale for the Trial and Selected Subject Population

High grade gliomas remain one of the most fatal tumors with a median survival of about 15 months for glioblastoma (GBM), despite aggressive combination therapy.

Malignant gliomas are highly vascular and characterized by overexpression of VEGF-A which plays a key role in tumor-associated angiogenesis [22]. Bevacizumab, an anti-VEGF-A molecule, has shown clinical benefit in patients with recurrent GBM for which no effective treatment existed [23; 24]. However, the response to bevacizumab usually is short-lived and the overall survival for patients with recurrent GBM treated with bevacizumab monotherapy is about 9 months [23]. Thus, recurrent high grade gliomas remain a largely unmet medical need requiring novel and effective treatment strategies.

Pre-clinical studies have shown significant increase in expression of PD-1 on peripheral blood CD4+ and CD8+ T cells in patients with high grade gliomas. In a study by Wei et al., PD-1+CD4+ T cells were clearly increased in peripheral blood of patients with anaplastic astrocytoma (12.3±0.9 %) and GBM (16.3±0.6 %) [25].

Rational for combining bevacizumab with pembrolizumab

A growing body of evidence indicates that abnormal tumor vasculature, partly caused by proangiogenic factors such as VEGF, creates an immunosuppressive tumor microenvironment by increasing immunosuppressive cells (tumor associated macrophages and regulatory T cells) and decreasing antitumor lymphocytes [26; 27]. Furthermore, circulating VEGF exerts a systemic influence on the host immune system by affecting proliferation, differentiation, and function of immune cells [27]. Elevated levels of VEGF have been associated with inhibition of T-cell immune response by suppressing the maturation of Dendritic cell precursors and by enhancing the proliferation and peripheral blood proportion of regulatory T cells (Tregs) [28].

The benefit of combined anti-VEGF agents with immunotherapy has been studied in several cancer models including breast carcinoma, colon carcinoma, melanoma, and sarcoma [29; 30; 31; 32; 33]. In these models, combination therapy has resulted in increased tumoral infiltration of CD4+ and CD8+ T cells, decreased Tregs, significant decrease in negative co-stimulatory molecules PD-1 and CTLA4, and increased tumor growth delay.

Rational for combining re-irradiation therapy with bevacizumab and pembrolizumab

Concomitant administration of bevacizumab with hypofractionated stereotactic radiotherapy (HFSRT) in previously irradiated gliomas has shown promising anti-tumor activity in both preclinical and clinical studies [34]. VEGF has been shown to abrogate the killing of endothelial cells by radiation, whereas blockade of VEGF sensitizes the tumor endothelium to radiation and leads to a synergistic effect [35]. Safety and efficacy of this treatment strategy has been investigated in a prospective study carried out by Gutin et al. where 25 patients with recurrent high grade gliomas were treated with HFSRT (30 Gy; 6 Gy delivered in 5 fractions) combined with bevacizumab (10 mg/kg) every 2 weeks of 28-day cycles. The combination therapy was safe and well tolerated without any cases of radiation necrosis. The reported clinical outcome was more favorable than other trials using bevacizumab in recurrent high grade gliomas. For the GBM cohort, overall response rate was 50% with median survival of 12.5 months and 1 year survival of 54%. Five out of 25 patients enrolled

in this study achieved complete response. Partial response was observed in 8 out of 25 patients [34].

Moreover, there is emerging evidence that hypofractionated radiotherapy acts synergistically with immunotherapy to enhance the immune response against tumor cells. Several preclinical studies have shown that radiotherapy synergizes with CTLA-4 and anti-PD 1/PD-L1 blockade and produces tumor regression and long-term survival in a variety of cancer models [36; 37; 38; 39; 40]. In a study by Zeng et al., combination of anti-PD-1 antibody with stereotactic radiosurgery (10 Gy) in a mouse orthotopic GBM model generated robust and durable responses and doubled the survival when compared with either modality alone [40]. In this study, analysis of the brain and spinal cord of animals treated with combination therapy showed an increase in the cytotoxic to regulatory T cell ratio with increased tumor infiltration by cytotoxic T cells (CD8+/interferon-γ+/tumor necrosis factor-α+) [40].

The optimum human dose of radiation therapy in combination with immunotherapy is not known. However pre-clinical experiments have demonstrated the highest tumor-specific T cell response, lowest regulatory T cells and best tumor control with the use of a higher dose per fraction [41; 42]. For example, Schaue et al. investigated the optimal radiotherapy dose-fractionation that maximizes anti-tumor immunity in a murine melanoma model. They compared the following single fraction doses: 5 Gy; 7.5 Gy; 10 Gy; and 15 Gy. Radiotherapy-induced tumor growth delay after 7.5 Gy and 10 Gy were associated with an increase in tumor-specific T cell response and a decrease in the proportion of regulatory T cells (Tregs) in the spleen [42]. A single fraction of 5 Gy had little effect on tumor growth, whereas a single fraction of 15 Gy increased both the tumor-specific T cell response and Tregs. They also compared fractionated treatment: 3 Gy x 5; 5 Gy x 3; 7.5 Gy x 2 and 15 Gy x 1. Two fractions of 7.5 Gy resulted in the best tumor control, highest tumor-specific T cell response and lowest Tregs. Schaue et al. concluded that fractionated treatment with medium-size radiotherapy doses of 7.5 Gy per fraction gave the best tumor control and anti-tumor immunity [42]. Dewan et al. examined 3 dose-fractionation regimens for their ability to synergize with CTLA-4 blockade using poorly immunogenic murine mammary and colon carcinoma: 20 Gy x 1; 8Gy x 3; and 6 Gy x 5.10 Anti-CTLA-4 Ab by itself or in combination with a single fraction of 20 Gy was ineffective. Fractionated treatment with 8 Gy x 3 was more effective than 6 Gy x 5 at synergizing with anti-CTLA-4 Ab: 80% versus 60% of the tumors outside the radiation field regressed completely, respectively [41].

Collectively, these studies suggest that **fractionated radiotherapy with medium-sized radiotherapy dose of 7.5 – 10 Gy per fraction is the optimal regimen for synergizing with immunotherapy.** Therefore, although the entire tumor will be treated with the 6 Gy x 5 hypofractionated regimen described above, a small volume within the tumor will be treated using a dose-painting technique to a dose of 8 Gy x 5 as a strategy to enhance immune response.

In summary, there is strong pre-clinical evidence that combining PD-1/PDL-1 blockade with antiangiogenic agents and hypofractionated radiotherapy independently enhance anti-tumor immune responses and tumor regression. In addition, HFSRT with bevacizumab represents a standard approach in the treatment of recurrent high grade gliomas. An additional benefit of

including bevacizumab in this regimen is its ability to decrease peritumoral edema, thereby obviating the need of steroids in this patient population, which would negatively influence the activity of pembrolizumab. Hence, it is of great interest to study the combination of all these three treatment modalities in high grade glioma patients with recurrent disease and with very limited treatment options.

4.2.2 Rationale for Dose Selection/Regimen/Modification

The dose regimen of 200 mg Q3W of pembrolizumab is planned for solid tumor trials including current study. Available PK results in subjects with melanoma, NSCLC, and other solid tumor types support a lack of meaningful difference in PK exposures obtained at a given dose among tumor types. An open-label Phase 1 trial (PN001) in melanoma subjects is being conducted to evaluate the safety and clinical activity of single agent pembrolizumab. The dose escalation portion of this trial evaluated three dose levels, 1 mg/kg, 3 mg/kg, and 10 mg/kg, administered every 2 weeks (Q2W) in subjects with advanced solid tumors. All three dose levels were well tolerated and no dose-limiting toxicities were observed. This first in human study of pembrolizumab showed evidence of target engagement and objective evidence of tumor size reduction at all dose levels (1 mg/kg, 3 mg/kg and 10 mg/kg Q2W). No maximum tolerated dose (MTD) has been identified.
In KEYNOTE-001, two randomized cohort evaluations of melanoma subjects receiving pembrolizumab at a dose of 2 mg/kg versus 10 mg/kg Q3W have been completed. The clinical efficacy and safety data demonstrate a lack of clinically important differences in efficacy response or safety profile at these doses. For example, in Cohort B2, advanced melanoma subjects who had received prior ipilimumab therapy were randomized to receive pembrolizumab at 2 mg/kg versus 10 mg/kg Q3W. The overall response rate (ORR) was 26% (21/81) in the 2mg/kg group and 26% (25/79) in the 10 mg/kg group (full analysis set (FAS)). The proportion of subjects with drug-related adverse events (AEs), grade 3-5 drug-related AEs, serious drug-related AEs, death or discontinuation due to an AE was comparable between groups or lower in the 10 mg/kg group.

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

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

data from 476 subjects from PN001. The distribution of exposures from the 200 mg fixed dose are predicted to considerably overlap those obtained with the 2 mg/kg dose, with some tendency for individual values to range slightly higher with the 200 mg fixed dose. The slight increase in PK variability predicted for the fixed dose relative to weight-based dosing is not expected to be clinically important given that the range of individual exposures is well contained within the range of exposures shown in the melanoma studies of 2 and 10 mg/kg to provide similar efficacy and safety. The population PK evaluation revealed that there was no significant impact of tumor burden on exposure. In addition, exposure was similar between the NSCLC and melanoma indications. Therefore, there are no anticipated changes in exposure between different tumor types and indication settings. However, due to lack of information on combination therapy with radiation and bevacizumab, starting dose of pembrolizumab for this study will be 100 mg Q3W.

4.2.3 Biomarker Research

- Archival tissue (mandatory for dose expansion cohort) will be assessed by immunohistochemistry (IHC) or immunofluorescence (IFC) staining for the following biomarkers for direct evaluation of the intratumoral immune compartment. If biopsy or surgical tumor specimens become available following stereotactic radiation therapy and pembrolizumab treatment, these tissues will be included in the analysis. First, PD-L1 expression by the tumor will be evaluated utilizing anti-PD-L1 antibody developed by Merck. Second, tumor infiltrating lymphocytes (TILs) will be identified and their PD1 expression level will be assessed by IFC. Third, intratumoral recruitment of the tolerogenic immune cells, Tregs and MDSCs, will be assessed.

- Phenotypic characterization of peripheral blood immune cell compartments including dendritic cells (DCs), myeloid derived suppressor cells (MDSCs), regulatory T lymphocytes (Tregs), CD4 and CD8 T lymphocytes will be also performed via flow cytometry prior to and after HFSRT + bevacizumab and pembrolizumab administration. The expression levels of CD86 expression on DCs or CD3z and PD1 expression on T lymphocytes will be analyzed to evaluate the overall immune activation/exhaustion status. These tests will be performed only in dose expansion cohort.

5.0 METHODOLOGY

5.1 Entry Criteria

5.1.1 Diagnosis/Condition for Entry into the Trial

Recurrent WHO Grade III (except anaplastic oligodendroglioma) or grade IV gliomas.

5.1.2 Subject Inclusion Criteria

In order to be eligible for participation in this trial, the below criteria must be met:

1. Histologically confirmed diagnosis of World Health Organization Grade III (except anaplastic oligodendroglioma) or IV malignant glioma.

2. Documented recurrence by diagnostic biopsy or contrast enhanced magnetic resonance imaging (MRI) performed within 28 days of entry in to the trial as per RANO criteria.

3. Patients with recurrent WHO Grade III gliomas should have received one prior treatment for recurrent high grade disease.

4. Maximum diameter of enhancing tumor (target lesion) should be ≤ 3.5 cm.

5. An interval of at least 6 months after the end of prior radiation therapy is required unless there is a new recurrence outside of the previous radiotherapy treatment field.

6. Previous first line treatment with at least standard dose of radiotherapy (total dose ≥ 54 Gy) and temozolomide

7. An interval of ≥ 4 weeks since surgical resection prior to entry in to the trial

8. An interval of ≥ 4 weeks after the last administration of any investigational agent or prior cytotoxic therapy (except bevacizumab). There should be 14 days interval between the last dose of bevacizumab and first day of treatment on study.

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

10. Karnofsky performance status of 70 or higher

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

Table 1 Adequate Organ Function Laboratory Values

System	Laboratory Value
Hematological	
Absolute neutrophil count (ANC)	≥1,500 /mcL
Platelets	≥100,000 / mcL
Hemoglobin	≥9 g/dL or ≥5.6 mmol/L
Renal	
Serum creatinine **OR** Measured or calculated[a] creatinine clearance (GFR can also be used in place of creatinine or CrCl)	≤1.5 X upper limit of normal (ULN) **OR** ≥60 mL/min for subject with creatinine levels > 1.5 X institutional ULN
Urine protein/ creatinine (UPC) ratio	< 1.0 within 14 days prior to registration

	If the UPC ratio is ≥ 1.0 then the patients should undergo a 24-hour urine collection and must demonstrate ≤ 1g of protein in 24 hours to be eligible).
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
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.	

12. Resting baseline O2 saturation by pulse oximetry of ≥ 92% at rest.

13. Patients must have recovered from the toxic effects of prior therapies.

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

15. Life expectancy ≥ 12 weeks

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

17. Female subjects of childbearing potential should be willing to use 2 methods of birth control or be surgically sterile, or abstain from heterosexual activity for the course of the study through 120 days after the last dose of study medication (Reference Section 5.7.2). Subjects of childbearing potential are those who have not been surgically sterilized or have not been free from menses for > 1 year.

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

5.1.3 Subject Exclusion Criteria

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

1. Has more than three recurrences of high grade glioma.

2. Has anaplastic oligodendroglioma.

3. Has received reradiation to recurrent disease (other than standard frontline adjuvant radiation therapy).

4. Recurrent tumors near the brainstem and optic chiasm must not have received prior radiation therapy.

5. Has infratentorial, or leptomeningeal evidence of recurrent disease.

6. Has recurrent or persistent tumor (enhancing area) greater than 3.5 cm in maximum diameter.

7. Has prior treatment with Gliadel unless it was administered as first line treatment and at least 3 months prior to study treatment.

8. Is unable (due to existent medical condition) or unwilling to have a contrast enhanced MRI of brain.

9. Is currently participating in or has participated in a study of an investigational agent or using an investigational device within 4 weeks of the first dose of treatment.

10. Has a diagnosis of immunodeficiency or is receiving systemic immunosuppressive therapy within 7 days prior to the first dose of trial treatment. Physiologic doses of steroid therapy (≤ 10 mg/day prednisone equivalents) is allowed.

11. Has had a prior chemotherapy, targeted small molecule therapy, or monoclonal antibody (except bevacizumab) within 4 weeks prior to study Day 1 or who has not recovered (i.e., ≤ Grade 1 or at baseline) from adverse events due to agents administered more than 4 weeks earlier. Wash out period for bevacizumab is 14 days.

12. Has a known additional malignancy that is progressing or requires active treatment. Exceptions include basal cell carcinoma of the skin, squamous cell carcinoma of the skin, or in situ cervical cancer that has undergone potentially curative therapy.

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

14. Has evidence of interstitial lung disease or active, non-infectious pneumonitis.

15. Has an active infection requiring systemic therapy.

16. Has prior allergic reaction to Bevacizumab.

17. Has prior history of uncontrolled hypertension, hypertensive crisis or hypertensive encephalopathy.

18. Has history of a non-healing wound, ulcer, or bone fracture within 90 days (3 months) prior to entry in to the trial.

19. Has history of gastrointestinal bleeding or any other hemorrhage/bleeding event ≥ grade 3 (CTCAE, v. 4) within 30 days prior to entry in to the trial.

20. Had major surgical procedure, open biopsy, or significant traumatic injury within 28 days prior to day 1 of treatment on study.

21. Requires escalating or chronic supraphysiologic doses of corticosteroids (> 10 mg/day prednisone equivalents).

22. 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.

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

24. Is pregnant or breastfeeding, or expecting to conceive or father children within the projected duration of the trial, starting with the pre-screening or screening visit through 120 days after the last dose of trial treatment.

25. Has received prior therapy with an anti-PD-1, anti-PD-L1, anti-PD-L2, anti-CD137, or anti-Cytotoxic T-lymphocyte-associated antigen-4 (CTLA-4) antibody (including ipilimumab or any other antibody or drug specifically targeting T-cell co-stimulation or checkpoint pathways).

26. Has a known history of Human Immunodeficiency Virus (HIV) (HIV 1/2 antibodies).

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

28. Has received a live vaccine within 30 days prior to the first dose of trial treatment.

5.2 Radiation therapy

5.2.1 Dose Specifications

Treatment will be performed using a dose-painting technique. The planning treatment volume (PTV), which is defined as the contrast enhancing lesion (or post-operative cavity if no residual disease is present) or gross tumor volume (GTV) + a 5 mm expansion, will be treated to a peripheral dose of 6 Gy/fraction x 5 fractions. If residual disease is present, a small volume within the GTV (≤0.5 cc), termed boost tumor volume (BTV), will be treated to 8 Gy/fraction x 5 fractions as a strategy to enhance immune response.

5.2.2 Critical Structures

Normal Structures to be contoured will include the brainstem, optic nerves, and chiasm. Normal tissue maximal dose limits are 25 Gy (0.03 cc).

5.2.3 Localization, Simulation, and Immobilization

MRI of ≤1.5mm slices will be obtained within 1 week of a treatment planning CT (≤3mm slices). MRI will be fused with the treatment planning CT. At the time of the treatment planning CT, a rigid immobilization device will be created. Image guided localization will be performed daily prior to treatment. Reduction in the PTV may be made at the discretion of the treating physician if the volume is adjacent to normal critical structures.

5.2.4 Radiation Therapy Adverse Events

5.2.4.1 Acute

Expected acute radiation-induced toxicities include hair loss, fatigue, and erythema or soreness of the scalp. Potential acute toxicities include nausea and vomiting as well as temporary aggravation of brain tumor symptoms such as headaches, seizures, and weakness. Reactions in the ear canals and on the ear should be observed and treated symptomatically; these reactions could result in short-term hearing impairment. Dry mouth or altered taste have been occasionally reported.

5.2.4.2 Early Delayed

Possible early delayed radiation effects include lethargy and transient worsening of existing neurological deficits occurring 1-3 months after radiotherapy treatment.

5.2.4.3 Late Delayed

Possible late delayed effects of radiotherapy include risk of radiation necrosis, and endocrine dysfunction. In addition, neurocognitive deficits, which could lead to mental slowing and behavioral change, are possible. Permanent hearing impairment and visual damage are rare. Cataracts can be encountered.

5.3 Trial Treatments

Treatment must begin within 14 days of registering to the trial. Each cycle will consist of 6 weeks.

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

Table 2 Trial Treatment

Drug	Dose/Potency	Dose Frequency	Route of Administration	Regimen/Treatment Period	Use
Pembrolizumab	100 mg or 200 mg based on dose level	Every 3 weeks	IV infusion	Until progression or up to 24 months, whichever occurs first	Experimental
Bevacizumab	10 mg/kg	Every 2 weeks	IV infusion	Until progression	Standard

Bevacizumab:

Bevacizumab will be administered intravenously at a dose of 10 mg/kg every 2 weeks. Doses will be adjusted if there is a > 10% change in weight.

Initial cycle of bevacizumab must start within 14 days of registering to the trial. It will be given concurrent with radiation therapy. Concurrent bevacizumab cycle may be given either on the day prior to start of radiation or on day 1 of radiation. Subsequent bevacizumab doses may be given every 14+/-3 days apart. In all patients, treatment with study drugs will continue until confirmed disease progression, patient refusal, patient lost to follow up, unacceptable toxicity, whichever occurs first, or the study is terminated by the Sponsor (Moffitt Cancer Center).

Pembrolizumab:

Pembrolizumab will be administered intravenously. Initial cycle of pembrolizumab must start within 14 days of entry in to the trial. It will be given concurrent with radiation therapy. Concurrent pembrolizumab may be given either on the day prior to start of radiation or on day 1 of radiation.

Dose Escalation Phase:

The dose of pembrolizumab will be escalated per schema in a 3+3 fashion. The starting dose (i.e., dose level 1) will be 100 mg. Provided that maximal tolerated dose (MTD) has not been reached, pembrolizumab dose will be increased to 200 mg as below:

Dose Escalation Schedule		
Dose Level	**Dose**	
	Pembrolizumab IV every 3 weeks	**Bevacizumab IV every 2 weeks**
Level 1	100 mg	10 mg/kg
Level 2	200 mg	10 mg/kg

Pembrolizumab will be given as 30-minute intravenous infusion every 3-week (+/-3 days). In all patients, treatment with study drugs will continue up to 24 months, until confirmed disease progression, patient refusal, patient lost to follow up, unacceptable toxicity, whichever occurs first, or the study is terminated by the Sponsor (Moffitt Cancer Center).

Dose Expansion Phase:

The pembrolizumab dose used in the dose expansion cohort will be MTD determined from the dose escalation phase.

Definition of Maximum Tolerated Dose:

The maximum tolerated dose (MTD) is the highest dose of pembrolizumab in combination with bevacizumab after radiation therapy that does not cause unacceptable toxicity in more than one of six patients at that dose level. The MTD is defined as one dose level below the highest toxic dose (i.e., the DLT dose).

5.3.1 Definition of Dose-Limiting Toxicity

Toxicities will be graded in severity according to the guidelines outlined in the NCI-CTCAE version 4.0. Dose limiting CNS and non-CNS toxicities will be defined differently and will be based on events that occur during the study period. In order to be declared as dose-limiting toxicity, an adverse event must be related to study treatment.

A dose-limiting toxicity (DLT) will be defined as any one of the following adverse events occurring within 6 weeks from last dose of radiation therapy:

CNS toxicities:

Acute CNS toxicities (occurring ≤ 30 days after completing radiation therapy):

- Any grade 3 or higher central nervous adverse events including but not limited to headache, dizziness, vertigo, new onset seizures, cerebral edema, cerebral hemorrhage, and new onset neurologic deficit.

Delayed onset CNS toxicities (occurring >30 days after completing radiation therapy):

- Any grade 3 or 4 adverse event arising within the irradiated volume including but not limited to radiation necrosis or focal neurological deficits.

Non-CNS toxicities:

- Any grade 3 or higher non-hematologic adverse event with the exception of alopecia, and fatigue.

- Grade ≥3 nausea, vomiting or diarrhea despite maximal medical therapy.

- Grade ≥ 3 hypertension despite maximal medical therapy.
- Grade ≥3 laboratory value if: 1) Medical intervention is required to treat the patient, or 2) The abnormality leads to hospitalization

Dose escalation will be determined based on the occurrence of DLTs. For the purposes of determining whether to advance the dose levels, DLTs will be counted by patient. In the event of the development of any grade 3 or 4 toxicity felt to be at least possibly related to study treatment, both drugs will be held until resolution to grade 1 or baseline assuming that occurs within 6 weeks window. Treatment with pembrolizumab can be resumed after resolution of DLT to grade 1 or baseline except for following adverse events: ≥ Grade 3 infusion reactions, ≥ Grade 3 pneumonitis, ≥ Grade 3 nephritis, ≥ Grade 3 colitis, increased alanine aminotransferase (ALT) or aspartate aminotransferase (AST) greater than 5 times upper limit of normal or total bilirubin greater than 3 times upper limit of normal.

Dose escalation will follow the standard 3+3 design. The enrollment to second dose level will be delayed for 6 weeks after the completion of radiation therapy by the last patient enrolled at the first dose level. This period of 6 weeks will allow monitoring potential delayed toxicities. Dose escalation will proceed according to the following scheme.

Number of Patients with DLT at a Given Dose Level	**Escalation Decision Rule**
0 out of 3	Enter 3 patients at the next dose level.
≥2	Dose escalation will be stopped. This dose level will be declared the maximally administered dose (highest dose administered). Three (3) additional patients will be entered at the next lowest dose level if only 3 patients were treated previously at that dose.
1 out of 3 or ≥ 2 grade 2 CNS toxicities	Enter at least 3 more patients at this dose level. • If 0 of these 3 patients experience DLT, proceed to the next dose level. • If 1 or more of this group suffer DLT, then dose escalation is stopped, and this dose is declared the maximally administered dose. Three (3) additional patients will be entered at the next lowest dose level if only 3 patients were treated previously at that dose.
≤1 out of 6 at highest dose level below the maximally administered dose	This is the dose to be used in the expanded cohort and will be considered recommended phase 2 dose. At least 6 patients must be entered at this dose.

5.3.2 Dose Selection/Modification

5.3.2.1 Dose Selection

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

Details on the dose calculation, preparation and administration are provided in the Pharmacy Manual.

5.3.2.2 Dose Modification

Pembrolizumab will be withheld for drug-related Grade 4 hematologic toxicities, Grade 2 pneumonitis, Grade 2 colitis, Grade 2 hypophysitis, Grade 2 nephritis, increased alanine aminotransferase (ALT) or aspartate aminotransferase (AST) greater than 3 times upper limit of normal and up to 5 times upper limit of normal or a total bilirubin greater than 1.5 and up to 3 times upper limit of normal, and other severe or life-threatening AEs as per Table 3 below.

Investigators should also refer to Section 5.6.1 and the "Pembrolizumab Event of Clinical Interest Guidance Document", available as an appendix, for additional instructions and information regarding the management of pembrolizumab toxicities.

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

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

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

In case toxicity does not resolve to Grade 0-1 within 12 weeks after last infusion, pembrolizumab should be discontinued after consultation with principal investigator. With investigator and Sponsor agreement, subjects with a laboratory adverse event still at Grade 2 after 12 weeks may continue treatment in the trial only if asymptomatic and controlled. For information on the management of adverse events, see Section 5.6.1.

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

Pembrolizumab should permanently discontinued for any of the following adverse events: ≥ Grade 3 infusion reactions, ≥ Grade 3 pneumonitis, ≥ Grade 3 nephritis, ≥ Grade 3 colitis, inability to reduce corticosteroid dose to 10 mg or less of prednisone or equivalent per day within 12 weeks, increased alanine aminotransferase (ALT) or aspartate aminotransferase (AST) greater than 5 times upper limit of normal or total bilirubin greater than 3 times upper limit of normal.

5.3.3 Timing of Dose Administration

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

All trial treatments will be administered on an outpatient basis.

Pembrolizumab will be administered every 3 weeks (+/- 3 days) starting on C1 Day 1. Bevacizumab will be administered every 2 weeks (+/- 3 days) starting on C1 D1.

Pembrolizumab will be administered as a 30 minute IV infusion. Every effort will be made to target infusion timing to be as close to 30 minutes as possible. However, given the variability of infusion pumps, a window of -5 minutes and +10 minutes is permitted (i.e., infusion time is 30 minutes: -5 min/+10 min).

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

Bevacizumab should be administered as a continuous intravenous infusion using a rate–regulating device. The initial dose will be administered over a minimum of 90 (-5 min/+10 min) minutes. If no adverse reactions occur, the second dose will be administered over a minimum of 60 (-5 min/+10 min) minutes. If no adverse reactions occur after the second dose, subsequent doses will be administered over a minimum of 30 (-5 min/+10 min) minutes. If infusion-related adverse reactions occur, all subsequent infusions should be administered over the shortest period that was well tolerated.

5.3.4 Trial Blinding/Masking

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

5.4 Treatment Allocation

Dose level allocation will be performed by the Sponsor after patients have given their written informed consent and have completed the necessary baseline assessments.

After review of patient's eligibility and concomitant medications, the Sponsor (Moffitt Cancer Center) will approve patient's enrollment, if appropriate, and assign a patient identification number, which will be used on all Case Report Form (CRF) pages and other trial-related documentation or correspondence referencing that patient.

5.5 Concomitant Medications/Vaccinations (allowed & prohibited)

Medications or vaccinations specifically prohibited in the exclusion criteria are not allowed during the ongoing trial. If there is a clinical indication for one of these or other medications or vaccinations specifically prohibited during the trial, discontinuation from trial therapy or

vaccination may be required. The investigator should discuss any questions regarding this with principal investigator of study. Prophylactic use of hematopoietic growth factors is not permitted. The final decision on any other supportive therapy or vaccination rests with the investigator and/or the subject's primary physician. However, the decision to continue the subject on trial therapy or vaccination schedule requires the mutual agreement of the Investigator, the Sponsor (Moffitt Cancer Center), and the subject.

5.5.1 Acceptable Concomitant Medications

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

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

5.5.2 Prohibited Concomitant Medications

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

- Anti-cancer systemic chemotherapy or biological therapy other than bevacizumab
- Immunotherapy other than pembrolizumab
- Investigational agents other than pembrolizumab
- Prophylactic hematopoietic growth factors
- Live vaccines within 30 days prior to the first dose of trial treatment and while participating in the trial. Examples of live vaccines include, but are not limited to, the following: measles, mumps, rubella, chicken pox, yellow fever, rabies, BCG, and typhoid (oral) vaccine. Seasonal influenza vaccines for injection are generally killed virus vaccines and are allowed; however intranasal influenza vaccines (e.g. Flu-Mist®) are live attenuated vaccines, and are not allowed.

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.

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

5.6 Rescue Medications & Supportive Care

5.6.1 Supportive Care Guidelines for Pembrolizumab Toxicities

Investigator should consult Immune-Related Adverse Event Guidance (Appendix 12.2) for management of pembrolizumab toxicities. Subjects should receive appropriate supportive care measures as deemed necessary by the treating investigator including but not limited to the items outlined below:

- Diarrhea: 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). In symptomatic subjects, infectious etiologies should be ruled out, and if symptoms are persistent and/or severe, endoscopic evaluation should be considered.

    - In subjects with severe enterocolitis (Grade 3), pembrolizumab will be permanently discontinued and treatment with systemic corticosteroids should be initiated at a dose of 1 to 2 mg/kg/day of prednisone or equivalent. When symptoms improve to Grade 1 or less, corticosteroid taper should be started and continued over at least 1 month. Bevacizumab should be withheld until symptoms improve to grade 1 or less.

    - In subjects with moderate enterocolitis (Grade 2), pembrolizumab should be withheld and anti-diarrheal treatment should be started. If symptoms are persistent for more than one week, systemic corticosteroids should be initiated (e.g., 0.5 mg/kg/day of prednisone or equivalent). When symptoms improve to Grade 1 or less, corticosteroid taper should be started and continued over at least 1 month. Regarding guidelines for continuing treatment with pembrolizumab see Section 5.3.

    - All subjects who experience diarrhea 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.

- Nausea/vomiting: Nausea and vomiting should be treated aggressively, and consideration should be given in subsequent cycles to the administration of prophylactic antiemetic therapy according to standard institutional practice. Subjects should be strongly encouraged to maintain liberal oral fluid intake.

- Anti-infectives: Subjects with a documented infectious complication should receive oral or IV antibiotics or other anti-infective agents as considered appropriate by the treating investigator for a given infectious condition, according to standard institutional practice.

- Immune-related adverse events: Please see Section 5.6.1.1 below and the separate guidance document in the administrative binder regarding diagnosis and management of adverse experiences of a potential immunologic etiology.

- Management of Infusion Reactions: Acute infusion reactions (which can include cytokine release syndrome, angioedema, or anaphylaxis) are different from allergic/hypersensitive reactions, although some of the manifestations are common to both AEs. Signs and symptoms usually develop during or shortly after drug infusion and generally resolve completely within 24 hours of completion of infusion. Signs/symptoms may include: Allergic reaction/hypersensitivity (including drug fever); Arthralgia (joint pain); Bronchospasm; Cough; Dizziness; Dyspnea (shortness of breath); Fatigue (asthenia, lethargy, malaise); Headache; Hypertension; Hypotension; Myalgia (muscle pain); Nausea; Pruritis/itching; Rash/desquamation; Rigors/chills; Sweating (diaphoresis); Tachycardia; Tumor pain (onset or exacerbation of tumor pain due to treatment); Urticaria (hives, welts, wheals); Vomiting.

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

Table 4 Infusion Reaction (Pembrolizumab) 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).

NCI CTCAE Grade	Treatment	Premedication at subsequent dosing
Grades 3 or 4 Grade 3: Prolonged (i.e., not rapidly responsive to symptomatic medication and/or brief interruption of infusion); recurrence of symptoms following initial improvement; hospitalization indicated for other clinical sequelae (e.g., renal impairment, pulmonary infiltrates) Grade 4: Life-threatening; pressor or ventilatory support indicated	**Stop Infusion.** Additional appropriate medical therapy may include but is not limited to: IV fluids Antihistamines NSAIDS Acetaminophen Narcotics Oxygen Pressors Corticosteroids Epinephrine Increase monitoring of vital signs as medically indicated until the subject is deemed medically stable in the opinion of the investigator. Hospitalization may be indicated. **Subject is permanently discontinued from further trial treatment administration.**	No subsequent dosing
Appropriate resuscitation equipment should be available in the room and a physician readily available during the period of drug administration. For Further information, please refer to the Common Terminology Criteria for Adverse Events v4.0 (CTCAE) at http://ctep.cancer.gov		

5.6.1.1 Supportive Care Guidelines for Events of Clinical Interest and Immune-related Adverse Events (irAEs)

Events of clinical interest of a potential immunologic etiology (irECIs) may be defined as an adverse event of unknown etiology, associated with drug exposure and is consistent with an immune phenomenon. irAEs may be predicted based on the nature of the pembrolizumab compound, its mechanism of action, and reported experience with immunotherapies that have a similar mechanism of action. Special attention should be paid to AEs that may be suggestive of potential irAEs. An irAE can occur shortly after the first dose or several months after the last dose of treatment.

If an irAE is suspected, efforts should be made to rule out neoplastic, infectious, metabolic, toxin or other etiologic causes prior to labeling an adverse event as an irAE. Information on how to identify and evaluate irAEs has been developed and is included in the Event of Clinical Interest and Immune-Related Adverse Event Guidance Document (Appendix 12.2) located in the Administrative Binder. Subjects who develop a Grade 2 or higher irAE should be discussed immediately with principal investigator of the study.

Recommendations to managing irAEs not detailed elsewhere in the protocol are detailed in Table 5.

Table 5 General Approach to Handling irAEs

irAE	Withhold/Discontinue Pembrolizumab?	Supportive Care
Grade 1	No action	Provide symptomatic treatment
Grade 2	May withhold Pembrolizumab	Consider systemic corticosteroids in addition to appropriate symptomatic treatment
Grade 3 and Grade 4	Withhold Pembrolizumab Discontinue if unable to reduce corticosteroid dose to < 10 mg per day prednisone equivalent within 12 weeks of toxicity	Systemic corticosteroids are indicated in addition to appropriate symptomatic treatment. May utilize 1 to 2 mg/kg prednisone or equivalent per day. Steroid taper should be considered once symptoms improve to Grade 1 or less and tapered over at least 4 weeks.

5.6.1.2 Supportive Care Guidelines for Pneumonitis

Subjects with symptomatic pneumonitis should immediately stop receiving pembrolizumab and have an evaluation. The evaluation may include bronchoscopy and pulmonary function tests to rule out other causes such as infection. If the subject is determined to have study drug associated pneumonitis, the suggested treatment plan is detailed in Table 6 and Appendix 12.2.

Table 6 Recommended Approach to Handling Pneumonitis

Study drug associated pneumonitis	Withhold/Discontinue Pembrolizumab?	Supportive Care
Grade 1 (asymptomatic)	No action	Intervention not indicated
Grade 2	Withhold pembrolizumab, may return to treatment if improves to Grade 1 or resolves within 12 weeks	Systemic corticosteroids are indicated. Taper if necessary.
Grade 3 and Grade 4	Discontinue pembrolizumab	Systemic corticosteroids are indicated. The use of infliximab may be indicated as appropriate. Refer to the Event of Clinical Interest and Immune-related Adverse Event Guidance Document for additional recommendations.

For Grade 2 pneumonitis that improves to ≤ Grade 1 within 12 weeks, the following rules should apply:

- First episode of pneumonitis
    - May increase dosing interval by one week in subsequent cycles
- Second episode of pneumonitis – permanently discontinue pembrolizumab if upon rechallenge subject develops pneumonitis ≥ Grade 2

5.6.2 Supportive Care Guidelines for Bevacizumab Toxicities

Treatment should be interrupted or discontinued for certain adverse events, as described below. If bevacizumab is interrupted for > 8 weeks, the patient should discontinue bevacizumab therapy on protocol.

Event	NCI CTCAE Grade	Treatment	Premedication at subsequent dosing
Allergic reactions or Acute infusional reactions/ cytokine release syndrome	Grade 1-2	Increase monitoring of vital signs as medically indicated until the subject is deemed medically stable in the opinion of the investigator.	Subjects may be premedicated
	Grade 3	Stop Infusion and monitor symptoms. Do not restarted on the same day. Bevacizumab may be permanently discontinued or re-instituted with premedications. and administered no faster than 60 minutes. If bevacizumab is re-instituted, it should not been administered faster than 60 minutes and the patient should be closely monitored for a duration comparable to or longer than the duration of the previous reactions.	Subjects should be premedicated
	Grade 4	Discontinue bevacizumab permanently.	
Arterial Thrombosis - Cardiac ischemia/ infraction - CNS ischemia (TIA, CVA) - any peripheral or visceral arterial ischemia/thrombosis	Grade 2 (if new or worsened since bevacizumab therapy) Grade 3-4	Discontinue bevacizumab permanently. Discontinue bevacizumab permanently.	
Venous Thrombosis	Grade 3 OR asymptomatic Grade 4	Bevacizumab may be resumed during the period of full-dose anticoagulation IF all of the criteria below are met: - The subject must have an in-range INR (usually 2-3) on a stable dose of warfarin or be on a stable dose of heparin prior to restarting bevacizumab - The subject must not have pathological conditions that carry high risk of bleeding (eg, tumor involving major vessels or other conditions) - The subject must not have had hemorrhagic events while on study	

Event	NCI CTCAE Grade	Treatment	Premedication at subsequent dosing
		If thromboemboli worsen/recur upon resumption of study therapy, discontinue bevacizumab	
	Grade 4 (symptomatic)	Discontinue bevacizumab permanently.	
Congestive Heart Failure	≥ Grade 3	Discontinue bevacizumab permanently.	
Hypertension	Grade 1	Monitor BP frequently.	
	Grade 2 asymptomatic but diastolic BP < 100 mmHg	Begin anti-hypertensive therapy and continue bevacizumab.	
	Grade 2-3 Symptomatic OR Diastolic BP > 100 mmHg	Hold bevacizumab until symptoms resolve AND BP < 160/90mmHg.	
	Grade 4	Discontinue bevacizumab permanently.	
RPLS (reversible posterior leukoencephalopathy syndrome **or PRES** (posterior reversible encephalopathy syndrome)		Discontinue bevacizumab permanently.	
Proteinuria	Urine protein creatinine (UPC) < 3.5	Continue bevacizumab.	
	UPC ratio > 3.5	Hold bevacizumab until UPC recovers to < 3.5	
	Grade 4 or nephrotic syndrome	Discontinue bevacizumab permanently.	
Hemorrhage (CNS or pulmonary)	≥ Grade 2	Discontinue bevacizumab permanently.	
Hemorrhage (non-CNS; non-pulmonary)	Grade 3	If patient requires full-dose anticoagulation, discontinue bevacizumab permanently. If patient is not receiving full-dose anticoagulation, hold bevacizumab until ALL of the following criteria are met: - the bleeding has resolved and Hb is stable - there is no bleeding diathesis that would increase the risk of therapy - there is no anatomic or pathologic condition that could increase the risk of hemorrhage recurrence.	

Event	NCI CTCAE Grade	Treatment	Premedication at subsequent dosing
	Grade 4 or recurrence of Grade 3	Discontinue bevacizumab permanently.	
Gastrointestinal perforation, leak or fistula		Discontinue bevacizumab permanently.	
Bowel obstruction	Grade 2 requiring medical intervention ≥ Grade 3	Hold bevacizumab until complete resolution, with a minimum of 4 weeks after surgery. -Hold bevacizumab until complete resolution -If surgery is required, patient may restart bevacizumab after full recovery from surgery, and at investigator's discretion	
Wound dehiscence requiring medical or surgical intervention		Discontinue bevacizumab permanently.	

5.7 Diet/Activity/Other Considerations

5.7.1 Diet

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

5.7.2 Contraception

Pembrolizumab and bevacizumab may have adverse effects on a fetus in utero. Furthermore, it is not known if pembrolizumab or bevacizumab have transient adverse effects on the composition of sperm. Non-pregnant, non-breast-feeding women may be enrolled if they are willing to use 2 methods of birth control or are considered highly unlikely to conceive. Highly unlikely to conceive is defined as 1) surgically sterilized, or 2) postmenopausal (a woman who is ≥45 years of age and has not had menses for greater than 1 year will be considered postmenopausal), or 3) not heterosexually active for the duration of the study. The two birth control methods can be either two barrier methods or a barrier method plus a hormonal method to prevent pregnancy. Subjects should start using birth control from study Visit 1 throughout the study period up to 120 days after the last dose of study therapy.

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

estrogen and/or a progestational agent (including oral, subcutaneous, intrauterine, or intramuscular agents).

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

5.7.3 Use in Pregnancy

If a subject inadvertently becomes pregnant while on treatment with study treatments, the subject will immediately be removed from the study. The site will contact the subject at least monthly and document the subject's status until the pregnancy has been completed or terminated. The outcome of the pregnancy will be reported to the Sponsor (Moffitt Cancer Center) and to Merck without delay and within 24 hours if the outcome is a serious adverse experience (e.g., death, abortion, congenital anomaly, or other disabling or life-threatening complication to the mother or newborn). The study investigator will make every effort to obtain permission to follow the outcome of the pregnancy and report the condition of the fetus or newborn to the Sponsor. If a male subject impregnates his female partner the study personnel at the site must be informed immediately and the pregnancy reported to the Sponsor and to Merck and followed as described above and in Section 7.2.2.

5.7.4 Use in Nursing Women

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

5.8 Subject Withdrawal/Discontinuation Criteria

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

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

- The subject or legal representative (such as a parent or legal guardian) withdraws consent.
- Unacceptable adverse experiences as described in Section 5.3.2
- Intercurrent illness that prevents further administration of treatment
- Investigator's decision to withdraw the subject
- The subject has a confirmed positive serum pregnancy test
- Noncompliance with trial treatment or procedure requirements
- The subject is lost to follow-up
- Administrative reasons

The End of Treatment and Follow-up visit procedures are listed in Section 6 (Protocol Flow Chart) and Section 7.1.5 (Visit Requirements). After discontinuation of treatment, each subject will be followed for 30 days for adverse event monitoring (serious adverse events will be collected for 90 days after the end of treatment as described in Section 7.2.3.1). Subjects who discontinue treatment 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.

5.9 Subject Replacement Strategy

In dose escalation phase, subject will be replaced if they are considered inevaluable. A subjects will be considered DLT-evaluable if they have incurred a DLT within a DLT evaluation period or meet all of the following criteria: a) have received at least 85% of the prescribed doses of bevacizumab, b) have received at least 85% of the prescribed doses of pembrolizumab, and c) have received the full dose of HFSRT.

5.10 Clinical Criteria for Early Trial Termination

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

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

4. Plans to modify or discontinue the development of the study drug

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

5.11 STOPPING RULES

The reported rate for grade 3 CNS toxicity with HFSRT and bevacizumab is 4% [34]. A higher rate of treatment related grade 3 CNS toxicity (> 10%) in this study would imply that the combination of HFSRT with bevacizumab and pembrolizumab is excessively toxic and not suitable for further clinical development. In addition grade ≥ 3 delayed-onset toxicity in this study would imply that the combination of HFSRT with pembrolizumab and bevacizumab is excessively toxic. In such condition, the results will be discussed with Merck, Protocol Monitoring Committee and IRB to determine whether discontinuation of trial is subsequently warranted.

6.0 TRIAL FLOW CHART

6.1 Study Flow Chart

Trial Period:	**Screening Phase**		**Treatment Cycles**												**End of Treatment**	**Post-Treatment**		
Treatment Cycle/Title:	Pre-screening (Visit 1)	Main Study Screening (Visit 2) [a]	Cycle 1 (6 weeks)								Cycles 2 and beyond (6 weeks)				Discon	Safety Follow-up	Follow Up Visits [b]	Survival Follow-Up
Scheduling Window (Days):		-13 to -1	D1	D2	D3	D4	D5	D15 ± 3	D22 ± 3	D29 ± 3	D1 ± 3	D15 ± 3	D22 ± 3	D29 ± 3	At time of Discon	30 days post discon	Every 8 weeks post discon	Every 12 weeks
Administrative Procedures																		
Informed Consent	X																	
Inclusion/Exclusion Criteria		X																
Demographics and Medical History	X	X																
Prior and Concomitant Medication Review	X	X	X					X	X	X	X	X	X	X	X	X	X	
Radiation therapy			X	X	X	X	X											
Bevacizumab			X					X		X	X	X		X				
Pembrolizumab			X						X		X		X					
Post-study anticancer therapy status																X	X	
Survival Status																		X
Clinical Procedures/Assessments																		
Review Adverse Events [c]			X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Full Physical Examination	X	X	X					X	X	X	X	X	X	X	X	X	X	
Symptom Directed Physical Examination				X	X	X	X											
Vital Signs and Weight	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
EORTC QLQ-C30, BNS20, EQ-5D Questionnaire		X	X							X	X							
Karnofsky Performance Status	X	X	X					X	X	X	X	X	X	X	X	X	X	
Laboratory Procedures/Assessments: analysis performed by LOCAL laboratory																		

Trial Period:	**Screening Phase**		**Treatment Cycles**												**End of Treatment**	**Post-Treatment**		
Treatment Cycle/Title:	Pre-screening (Visit 1)	Main Study Screening (Visit 2) [a]	Cycle 1 (6 weeks)								Cycles 2 and beyond (6 weeks)				Discon	Safety Follow-up	Follow Up Visits [b]	Survival Follow-Up
Scheduling Window (Days):		-13 to -1	D1	D2	D3	D4	D5	D15 ± 3	D22 ± 3	D29 ± 3	D1 ± 3	D15 ± 3	D22 ± 3	D29 ± 3	At time of Discon	30 days post discon	Every 8 weeks post discon	Every 12 weeks
Pregnancy Test – Urine or Serum β-HCG		X																
PT/INR and aPTT		X	X							X	X			X	X	X	X	
CBC with Differential	X	X	X					X	X	X	X	X	X	X	X	X	X	
Comprehensive Serum Chemistry Panel	X	X	X					X	X	X	X	X	X	X	X	X	X	
Urinalysis	X	X	X							X	X			X	X	X	X	
T3, FT4 and TSH	X	X	X						X	X	X		X		X	X		
Efficacy Measurements																		
Brain MRI with/without contrast		X									Q6wk (C1-3),Q12wk then				X		X	
Tumor Biopsies/Archival Tissue Collection/Correlative Studies Blood																		
Archival or Newly Obtained Tissue Collection		X																
Correlative Studies Blood Collection			X					X	X	X								

[a] Visit 1 assessment (physical examination and laboratories) can be used for main study screening (visit 2) if visit 2 occurs within 3 days from visit 1.

[b] There will be two follow up visits which include full physical examination, laboratories, and brain MRI.

[c] After the end of treatment, each subject will be followed for 30 days for adverse event monitoring. Serious adverse events will be collected for 90 days after the treatment.

7.0 TRIAL PROCEDURES

7.1 Trial Procedures

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

Furthermore, additional evaluations/testing may be deemed necessary by the Sponsor for reasons related to subject safety. In some cases, such evaluation/testing may be potentially sensitive in nature (e.g., HIV, Hepatitis C, etc.), and thus local regulations may require that additional informed consent be obtained from the subject. In these cases, such evaluations/testing will be performed in accordance with those regulations.

7.1.1 Administrative Procedures

7.1.1.1 Informed Consent

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

7.1.1.1.1 General Informed Consent

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

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

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

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

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

7.1.1.2 Inclusion/Exclusion Criteria

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

7.1.1.3 Subject Identification Card

All subjects will be given a Subject Identification Card identifying them as participants in a research trial. The card will contain trial site contact information (including direct telephone numbers) to be utilized in the event of an emergency. The investigator or qualified designee will provide the subject with a Subject Identification Card after the subject provides written informed consent.

7.1.1.4 Medical History

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

7.1.1.5 Prior and Concomitant Medications Review

7.1.1.5.1 Prior Medications

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

7.1.1.5.2 Concomitant Medications

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

7.1.1.6 Disease Details and Treatments

7.1.1.6.1 Disease Details

The investigator or qualified designee will obtain prior and current details regarding status of brain cancer.

7.1.1.6.2 Prior Treatment Details

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

7.1.1.6.3 Subsequent Anti-Cancer Therapy Status

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

7.1.2 Clinical Procedures/Assessments

7.1.2.1 Adverse Event (AE) Monitoring

The investigator or qualified designee will assess each subject to evaluate for potential new or worsening AEs as specified in the Trial Flow Chart and more frequently if clinically indicated. Adverse experiences will be graded and recorded throughout the study and during the follow-up period according to NCI CTCAE Version 4.0 (see Section 12.2). Toxicities will be characterized in terms regarding seriousness, causality, toxicity grading, and action taken with regard to trial treatment.

All AEs of unknown etiology associated with study treatment should be evaluated to determine if it is possibly an event of clinical interest (ECI) of a potentially immunologic etiology (irAE). See Section 5.6.1.1 and the separate guidance document in the administrative binder regarding the identification, evaluation and management of AEs of a potential immunological etiology.

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

7.1.2.2 Full Physical Exam

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

7.1.2.3 Directed Physical Exam

For visits that do not require a full physical exam per the Trial Flow Chart, the investigator or qualified designee will perform a directed physical exam as clinically indicated.

7.1.2.4 Vital Signs

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

7.1.2.5 Karnofsky Performance Scale (KPS)

The investigator or qualified designee will assess KPS status at screening, prior to the administration of each dose of trial treatment and discontinuation of trial treatment as specified in the Trial Flow Chart.

7.1.2.6 Tumor Imaging and Assessment of Disease

All subjects will receive efficacy assessments with brain MRI at time points specified in Trial Flow Chart. All MRIs (except the initial screening MRI) should occur at +/- 7 days per scheduled visits. Investigators may obtain more frequent follow-up MRI scans as medically indicated. Cases of suspected radiologic disease progression will be confirmed by an MRI performed approximately 8 weeks after the initial radiological assessment of progression.

Response Assessment Criteria for High-Grade Gliomas (RANO Criteria) will be used for assessing the response to study treatment.

7.1.2.7 Tumor Tissue Collection and Correlative Studies Blood Sampling

Peripheral blood and archival tumor tissue will be collected prior to therapy. Peripheral blood samples will also be collected at selected time points specified in Trial Flow Chart. If a biopsy or surgical resection is performed at the time of progression, tumor sample (block or slides) should be submitted for analysis.

7.1.3 Laboratory Procedures/Assessments

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

7.1.3.1 Laboratory Safety Evaluations (Hematology, Chemistry and Urinalysis)

Laboratory tests for hematology, chemistry, urinalysis, and others are specified in Table 7. The total amount of blood to be drawn over the course of the trial (from pre-trial to post-trial visits), including approximate blood volumes drawn by visit and by sample type per subject can be found in the Procedures Manual.

Table 7 Laboratory Tests

Hematology	Chemistry	Urinalysis	Other
Hematocrit	Albumin	Blood	Serum β-human chorionic gonadotropin†
Hemoglobin	Alkaline phosphatase	Glucose	(β-hCG)†
Platelet count	Alanine aminotransferase (ALT)	Protein	PT (INR)
WBC (total and differential)	Aspartate aminotransferase (AST)	Specific gravity	aPTT
Red Blood Cell Count	Lactate dehydrogenase (LDH)	Microscopic exam *(If abnormal)*	Total thriiodothyronine (T3)
Absolute Neutrophil Count	Blood Urea Nitrogen	results are noted	Free tyroxine (T4)
	Uric Acid	Urine pregnancy test †	Thyroid stimulating hormone (TSH)
	Serum creatinine		
	Total protein		
	Calcium		
	Chloride		Blood for correlative studies
	Glucose		
	Phosphorus		
	Potassium		
	Sodium		
	Magnesium		
	Total Bilirubin		
	Direct Bilirubin *(If total bilirubin is elevated above the upper limit of normal)*		
† Perform on women of childbearing potential only. If urine pregnancy results cannot be confirmed as negative, a serum pregnancy test will be required.			

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

7.1.3.2 Pharmacodynamic Evaluations

7.1.3.2.1 Blood Collection for Correlative Studies

Sample collection, storage and shipment instructions for serum samples will be provided in the Procedures Manual.

The time points for blood sampling are described in Section 6 – Trial Flow Chart.

7.1.4 Other Procedures

7.1.4.1 Withdrawal/Discontinuation

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

7.1.5 Visit Requirements

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

7.1.5.1 Screening

7.1.5.1.1 Screening Period

Screening period begins by establishing the subject's initial eligibility and signing of the informed consent form (ICF). Study treatment should be given within 14 days of signing ICF.

7.1.5.2 Treatment Period

Treatment period should start within 14 days of signing ICF. Treatment period will start with 5 days of radiation therapy (6 Gy x5) and one dose of bevacizumab 10 mg/kg IV and pembrolizumab IV on C1 D1.

Bevacizumab 10 mg/kg IV will be continued every two weeks. Pembrolizumab IV will start on C1 D1 and will be continued every three weeks.

All of the laboratories and vital signs will be collected prior to study drug dosing at the time points specified in Trial Flow Chart.

Adverse event assessments will be documented at each visit throughout the study.

Quality of Life assessments using EORTC QLQ-C30 and BNS20 and EQ-5D to be completed as described in Trial Flow Chart.

Correlative biomarker blood samples will be collected according to the schedule in Trial Flow Chart.

Response to treatment will be assessed by the investigator and according to the RANO criteria. Brain MRI will be performed every 6 weeks beginning at the end of Week 6 (± 1 week) for 3 cycles and then every 12 weeks (± 1 week) until disease progression or treatment discontinuation, whichever occurs later. Brain MRIs can be obtained in shorter intervals as per physician discretion.

7.1.5.3 Post-Treatment Visits

Post-Treatment period begins when the decision to discontinue a subject from study therapy is made (no further study treatment).

There will be two follow-up visits which include full physical examination, laboratories, and brain MRI.

Quality of Life questionnaires will be completed in post-treatment visits.

7.1.5.3.1 Safety Follow-Up Visit

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

7.1.5.4 Follow-up Visits

Subjects who discontinue trial treatment for a reason other than disease progression will move into the Follow-Up Phase and should be assessed every 8 weeks (± 1 week) by radiologic imaging to monitor disease status. All radiologically determined disease progression must be confirmed by an additional confirmatory MRI scan approximately 8 weeks following the initial assessment of radiological progression.

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

7.1.5.4.1 Survival Follow-up

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

7.2 Assessing and Recording Adverse Events

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

Adverse events may occur during the course of the use of study treatment in clinical trial or within the follow-up period, from overdose (whether accidental or intentional), and from withdrawal.

All adverse events will be recorded day 1 of study treatment (D1 C1) through 30 days following cessation of treatment and at each examination on the Adverse Event case report forms/worksheets. Relation of adverse event to study treatment will be defined as definitely, probably, possibly, unlikely, or unrelated. The reporting timeframe for adverse events meeting any serious criteria is described in section 7.2.3.1.

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

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

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

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

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

7.2.2 Reporting of Pregnancy and Lactation to Moffitt Cancer Center and to Merck

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

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

7.2.3 Immediate Reporting of Adverse Events to the Sponsor (Moffitt Cancer Center) and to Merck

7.2.3.1 Serious Adverse Events

A serious adverse event is any adverse event occurring during study treatment that:

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

Refer to Table 8 for additional details regarding each of the above criteria.

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

Any serious adverse event, or follow up to a serious adverse event, including death due to any cause other than progression of the cancer under study that occurs to any subject from the time of starting study treatment through 90 days following cessation of treatment, or the initiation of new anti-cancer therapy, whichever is earlier, whether or not related to study treatment, must be reported within 24 hours to the Sponsor (Moffitt Cancer Center) and within 2 working days to Merck Global Safety.

Non-serious Events of Clinical Interest will be forwarded to Moffitt Cancer Center and will be handled in the same manner as SAEs.

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

SAE reports and any other relevant safety information are to be forwarded to Moffitt Cancer Center.

A copy of all 15 Day Reports and Annual Progress Reports is submitted as required by FDA and other local regulators. Investigators will submit a copy of these reports to Merck & Co., Inc. (Attn: Worldwide Product Safety; FAX 215 993-1220) at the time of submission to FDA.

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

7.2.3.2 Events of Clinical Interest

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

Events of clinical interest for this trial include:

1. an overdose of pembrolizumab, as defined in Section 7.2.1 - Definition of an Overdose for This Protocol and Reporting of Overdose to the Sponsor (Moffitt Cancer Center), 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.*

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

3. In the event a subject develops any of the following AEs, a detailed narrative of the event should be reported as an ECI to the Sponsor (Moffitt Cancer Center) within 24 hours and to Merck Global Safety within 2 working days of the event:

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

A separate guidance document has been provided entitled "event of Clinical Interest and Immune-Related Adverse Event Guidance Document." This document provides guidance regarding identification, evaluation and management of ECIs and irAEs. Additional ECIs are identified in this guidance document and also need to be reported to the Sponsor (Moffitt Cancer Center) within 24 hours and to Merck Global Safety within 2 working days of the event.

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

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

7.2.4 Evaluating Adverse Events

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

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

Table 8 Evaluating Adverse Events

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

V4.0 CTCAE Grading	**Grade 1**	**Mild; asymptomatic or mid symptoms; clinical or diagnostic observations only; intervention not indicated.**
	Grade 2	**Moderate; minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental ADL.**
	Grade 3	**Severe or medically significant but not immediately life-threatening; hospitalization or prolongation or hospitalization indicated; disabling; limiting self-care ADL.**
	Grade 4	**Life threatening consequences; urgent intervention indicated.**
	Grade 5	**Death related to AE**
Seriousness	A serious adverse event is any adverse event occurring during study treatment that:	
	†**Results in death**; or	
	†**Is life threatening; or** places the subject, in the view of the investigator, at immediate risk of death from the event as it occurred (Note: This does not include an adverse event that, had it occurred in a more severe form, might have caused death.); or	
	†**Results in a persistent or significant disability/incapacity** (substantial disruption of one's ability to conduct normal life functions); or	
	†**Results in or prolongs an existing inpatient hospitalization** (hospitalization is defined as an inpatient admission, regardless of length of stay, even if the hospitalization is a precautionary measure for continued observation. (Note: Hospitalization [including hospitalization for an elective procedure] for a preexisting condition which has not worsened does not constitute a serious adverse event.); or	
	†**Is a congenital anomaly/birth defect** (in offspring of subject taking the product regardless of time to diagnosis);or	
	Is a new **cancer;** (that is not a condition of the study) **or**	
	Is an overdose (whether accidental or intentional). Any adverse event associated with an overdose is considered a serious adverse event. An overdose that is not associated with an adverse event is considered a non-serious event of clinical interest and must be reported within 24 hours.	
	Other important medical events that may not result in death, not be life threatening, or not require hospitalization may be considered a serious adverse event when, based upon appropriate medical judgment, the event may jeopardize the subject and may require medical or surgical intervention to prevent one of the outcomes listed previously (designated above by a †).	
Duration	Record the start and stop dates of the adverse event. If less than 1 day, indicate the appropriate length of time.	
Action taken	Did the adverse event cause the study treatment to be discontinued?	
Relationship to study treatment	Did the study treatment cause the adverse event? The determination of the likelihood that the study treatment caused the adverse event will be provided by an investigator who is a qualified physician. The investigator's signed/dated initials on the source document or worksheet that supports the causality noted on the AE form, ensures that a medically qualified assessment of causality was done. This initialed document must be retained for the required regulatory time frame. The criteria below are intended as reference guidelines to assist the investigator in assessing the likelihood of a relationship between the study treatment and the adverse event based upon the available information. **The following components are to be used to assess the relationship between the pembrolizumab and the AE**; the greater the correlation with the components and their respective elements (in number and/or intensity), the more likely the study treatment caused the adverse event (AE):	
	Exposure	Did the subject receive the study treatment?
	Time Course	Did the AE follow in a reasonable temporal sequence from administration of the study treatment? Is the time of onset of the AE compatible with a drug-induced effect?
	Likely Cause	Is the AE not reasonably explained by another etiology such as underlying disease, other drug(s)/vaccine(s), or other host or environmental factors

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

7.2.5 Sponsor Responsibility for Reporting Adverse Events

All Adverse Events except grade 1 and 2 toxicities which are unrelated to study treatment, will be reported to regulatory authorities, IRB/IECs and investigators in accordance with all applicable global laws and regulations.

8.0 STATISTICAL ANALYSIS PLAN

8.1 Statistical Analysis Plan Summary

The number of patients for the dose escalation cohort will depend on the number of dose levels reached. There are two dose escalation cohorts and therefore the maximum sample size for the dose escalation cohorts will be 12 patients. In the dose expansion cohort, a total of 20 (10 bevacizumab naïve and 10 bevacizumab failure) evaluable patients will be enrolled to confirm the safety at this dose and assess response to treatment. The sample size of 26 patients in the MTD dose (20 patients from dose expansion cohort and 6 patients from the dose escalation) will give a two-sided 95% confidence interval (95%CI) of 39% to 79% for a response rate of 60%. If the response rate increases to 80%, the corresponding 95%CI will be 60% to 93%. Therefore, the maximum sample size of the study is 32 patients.

8.2 Statistical Analysis Plan

Data will be summarized overall using descriptive statistics. Continuous data will be summarized with number of patients (n), mean, median, minimum, maximum, standard deviation, coefficient of variation, and geometric mean (where applicable). Categorical data will be summarized using frequency counts and percentages.

9.0 LABELING, PACKAGING, STORAGE AND RETURN OF CLINICAL SUPPLIES

9.1 Investigational Products

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 products in accordance with the protocol and any applicable laws and regulations.

Clinical Supplies will be provided by Merck as summarized in Table 9.

Table 9 Product Description

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

Bevacizumab should be stored, prepared, and administered in accordance to the package insert, summary of product characteristics (SmPC) or similar document.

9.2 Packaging and Labeling Information

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

9.3 Clinical Supplies Disclosure

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

9.4 Storage and Handling Requirements

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

Receipt and dispensing of trial medication must be recorded by an authorized person at Moffitt Cancer Center.

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

9.5 Returns and Reconciliation

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

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

10.0 ADMINISTRATIVE AND REGULATORY DETAILS

10.1 Confidentiality

The Investigator must ensure that the patient's confidentiality is maintained. Patient medical information obtained for the purposes of this study is confidential, and disclosure to third parties, other than those noted below, is prohibited. Patients should be identified only by their initials and protocol-assigned patient ID number. For those patients whose surgical specimen is processed and read by the central pathology laboratory, the patient's billing

information will be requested by this laboratory and will not be shared with the sponsor or any of its affiliates or representatives.

Study personnel should follow the requirements of the Health Insurance Portability and Accountability Act (HIPAA).

All clinical information is confidential, but data generated for this study must be available for inspection on request to representatives of the U.S. FDA, other national or local regulatory or health authorities, Endo Pharmaceuticals representatives, and the associated IRB.

All records must be kept in a secured area.

10.2 Compliance with Financial Disclosure Requirements

Documentation of each Investigator's proprietary or financial interest is required by the U.S. Code of Federal Regulations (21 CFR 54). A financial disclosure form provided by Moffitt Cancer Center must be completed, signed, and dated by the Principal Investigator and each Sub-investigator listed on the Form FDA 1572. This form must be executed prior to the personnel's participation in the study. The original form will be retained by Moffitt Cancer Center. Each Investigator must inform Moffitt Cancer Center of any change in his/her financial interest for up to one year after the end of the study.

10.3 Compliance with Law, Audit, Debarment and Quality Management System

The Investigator must conduct the study according to this protocol.

The study must be conducted by all Investigators in compliance with Good Clinical Practices (GCP) as defined as described in the U.S. FDA Code of Federal Regulations 21 CFR 312 (Investigational New Drug Application), 21 CFR 50 (Protection of Human Subjects), 21 CFR 54 (Financial Disclosure by Clinical Investigators), 21 CFR 56 (Institutional Review Boards) and ICH guidelines (Guideline to Good Clinical Practice).

The PI of this study is ultimately responsible for every aspect of the design, conduct and actions of all members of the research team. This includes the final analysis of the protocol.

All protocols include a Data Safety Monitoring Plan (DSMP) and procedures for its implementation commensurate with the risk and complexity of the study. The DSMP must include a structured adverse event determination, monitoring and reporting system, including standardized forms and procedures for referring and/or treating subjects experiencing adverse events. The plan must include data and safety-monitoring procedures for subjects enrolled who may be receiving a part of their protocol-required treatment at community sites.

The PI of this study will have primary responsibility for ensuring that the protocol is conducted as approved by the SRC and IRB. The PI will ensure that the monitoring plan is followed, that all data required for oversight of monitoring are accurately reported to a DSMP and/or to the Protocol Monitoring Committee (PMC) and IRB as required, that all

adverse events are reported according to protocol guidelines, and that any adverse actions reflecting patient safety concerns are appropriately reported.

Data will be captured in Oncore, Moffitt's Clinical Trials Database. Regulatory documents and case report forms will be monitored internally according to Moffitt Cancer Center Monitoring Policies. Monitoring will be performed regularly to verify data is accurate, complete, and verifiable from source documents; and the conduct of the trial is in compliance with the currently approved protocol/amendments, Good Clinical Practice (GCP), and applicable regulatory requirements.

The PMC monitors its assigned ongoing research protocols monthly for: adverse event reporting, data and safety monitoring, and internal audit findings. The PMC upon review of any agenda item may approve the study for continuation, require revisions, suspend or close a protocol.

Investigators of studies which are designed to be reviewed by the PMC for data and safety monitoring, shall provide a statistical report of the study's progress and summary of adverse events and deviations based on the phase of the study and the associated risk of the study or more often if applicable. The external DSMP (if applicable) shall forward its report for high-risk studies designated for external review at least annually or more often if applicable.

10.4 Compliance with Trial Registration and Results Posting Requirements

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

10.5 Data Management

Data will be maintained by the Moffitt Cancer Center.

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12.0 APPENDICES

12.1 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)

12.2 Immune-Related Adverse Event Guidance

PEMBROLIZUMAB PROGRAM
(MK-3475)

EVENT OF CLINICAL INTEREST

GUIDANCE DOCUMENT

Version 5.0

REVISION HISTORY LOG

Version	Effective Date*	Revision Author	Action
1	08-Aug-2012	Kevin Gergich	Initial Release of guidance document for MK-3475
2	07-June-2013	Marty Huber, Kevin Gergich, Holly Brown	Revised title, formerly was "MK-3475 Immune-Related Adverse Event Identification, Evaluation and Management Guidance Document for Investigators" Revised the format of irAE Guidance document, including layout, font, sectioning, etc. for consistency with Sponsor Events of Clinical Interest guidance documents. Modified Categories for irAEs: – Replaced GI with Colitis category. – Removed Neurologic category. – Added Renal category. Removed detail in the irAE Guidance document that can be located in the Investigator's Brochure for MK-3475. Removed details regarding non-MK-3475 compounds. Added ECI reporting guidelines. Included a Table Events of Clinical Interest: Immune-Related Adverse Events that includes the key terms. – Also placed a pull-out quick-review sheet in the Appendix. Updated background, diagnosis and course of treatment details for irAEs.
3	10-Sep-2014	Marty Huber, Kevin Gergich, Holly Brown	Renamed the document: "Pembrolizumab Program (MK-3475) - Events of Clinical Interest Guidance Document". Introduced generic name: pembrolizumab (MK-3475) and inserted throughout the document. Updated Overview – Section 1 - Clarified the scope of the document and the reporting window for ECIs - Updated Table 1 with medDRA Preferred Terms for adverse events to correspond with reporting of terms to clinical database, rearranged the order, and updated the reporting criteria. - Updated the dose modification/discontinuation section to clarify discontinuation and hold terminology. Updated Section 2 – ECI Reporting Guidelines

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

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

4	04-Dec-2014	Scot Ebbinghaus, Oswaldo Bracco, Holly Brown, Kevin Gergich	- Table 1
			  - Updated Endocrine (reported as ECI if ≥ Grade 3 or ≥ Grade 2 and resulting in dose modification or use of systemic steroids to treat the AE) Section to include:
			  - Hyperglycemia, if ≥Grade 3 and associated with ketosis or metabolic acidosis (DKA)
			  - Created new section in Table 1 – Endocrine (reported as ECI) and added:
			  - Type 1 diabetes mellitus (if new onset)
			  - Hepatic: Clarified Transaminase elevations as:
			  - Transaminase elevations (ALT and/or AST)
			- Section 3.2 Colitis
			  - Updated the duration of diarrhea requirments under the Course of Action for Grade 2 and Grade 3
			- Section 3.3 Endocrine
			  - Clarified Course of Action for hyperthyroidism and hypothyroidism
			  - Added Course of Action section for Type 1 diabetes mellitus (if new onset) and ≥ Grade 3 hyperglycemia
			- Section 5
			  - Updated Reference Table in Appendix 1

5	18-Dec-2014	Holly Brown
		Kevin Gergich
			- Section 3.3 Endocrine
			  - Updated the Course of Action for Hypophysitis
			  - Merged Grades 2-4 into one course of action

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

TABLE OF CONTENTS

1. OVERVIEW

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

Based on the literature review [1-11], and consideration of mechanism of action of pembrolizumab, potential immune-related adverse events (irAEs) are the primary Event of Clinical Interest (ECI). Immune-related AEs are adverse events associated with the treatment of patients with immunotherapy treatments that appear to be associated with the immune therapy's mechanism of action. Based on these potential irAEs, the sponsor has defined a list of specific adverse event terms (ECIs) that are selected adverse experiences that **must be reported to Merck within 24 hours** from the time the Investigator/physician is aware of such an occurrence, regardless of whether or not the investigator/physician considers the event to be related to study drug(s). In addition, these ECIs require additional detailed information to be collected and entered in the study database. ECIs may be identified through spontaneous patient report and / or upon review of subject data. **Table 1** provides the list of terms and reporting requirements for AEs that must be reported as ECIs for MK-3475 protocols. Of note, the requirement for reporting of ECIs applies to all arms, including comparators, of MK-3475 clinical trials

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

Table 1: Events of Clinical Interest

Pneumonitis (reported as ECI if ≥ Grade 2)		
Acute interstitial pneumonitis	Interstitial lung disease	Pneumonitis
Colitis (reported as ECI if ≥ Grade 2 or any grade resulting in dose modification or use of systemic steroids to treat the AE)		
Intestinal Obstruction	Colitis	Colitis microscopic
Enterocolitis	Enterocolitis hemorrhagic	Gastrointestinal perforation
Necrotizing colitis	Diarrhea	
Endocrine (reported as ECI if ≥ Grade 3 or ≥ Grade 2 and resulting in dose modification or use of systemic steroids to treat the AE)		
Adrenal Insufficiency	Hyperthyroidism	Hypophysitis
Hypopituitarism	Hypothyroidism	Thyroid disorder
Thyroiditis	Hyperglycemia, if ≥Grade 3 and associated with ketosis or metabolic acidosis (DKA)	
Endocrine (reported as ECI)		
Type 1 diabetes mellitus (if new onset)		
Hematologic (reported as ECI if ≥ Grade 3 or any grade resulting in dose modification or use of systemic steroids to treat the AE)		
Autoimmune hemolytic anemia	Aplastic anemia	Thrombotic Thrombocytopenic Purpura (TTP)
Idiopathic (or immune) Thrombocytopenia Purpura (ITP)	Disseminated Intravascular Coagulation (DIC)	Haemolytic Uraemic Syndrome (HUS)
Any Grade 4 anemia regardless of underlying mechanism		
Hepatic (reported as ECI if ≥ Grade 2, or any grade resulting in dose modification or use of systemic steroids to treat the AE**)**		
Hepatitis	Autoimmune hepatitis	Transaminase elevations (ALT and/or AST)
Infusion Reactions (reported as ECI for any grade)		
Allergic reaction	Anaphylaxis	Cytokine release syndrome
Serum sickness	Infusion reactions	Infusion-like reactions
Neurologic (reported as ECI for any grade)		
Autoimmune neuropathy	Guillain-Barre syndrome	Demyelinating polyneuropathy
Myasthenic syndrome		
Ocular (report as ECI if ≥ Grade 2 or any grade resulting in dose modification or use of systemic steroids to treat the AE)		
Uveitis	Iritis	
Renal (reported as ECI if ≥ Grade 2)		
Nephritis	Nephritis autoimmune	Renal Failure
Renal failure acute	Creatinine elevations (report as ECI if ≥Grade 3 or any grade resulting in dose modification or use of systemic steroids to treat the AE)	
Skin (reported as ECI for any grade)		
Dermatitis exfoliative	Erythema multiforme	Stevens-Johnson syndrome
Toxic epidermal necrolysis		
Skin (reported as ECI if ≥ Grade 3)		
Pruritus	Rash	Rash generalized
Rash maculo-papular		
Any rash considered clinically significant in the physician's judgment		
Other (reported as ECI for any grade)		
Myocarditis	Pancreatitis	Pericarditis
Any other Grade 3 event which is considered immune-related by the physician		

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

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

Dose Modification/Discontinuation

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

2. ECI REPORTING GUIDELINES

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

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

3. ECI CATEGORIES AND TERMS

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

3.1 Pneumonitis

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

- Pneumonitis
- Interstitial lung disease
- Acute interstitial pneumonitis

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

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

Course of Action

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

Grade 3 and 4 events:
- Report as ECI
- Discontinue pembrolizumab.
- Hospitalize patient
- Bronchoscopy with biopsy and/or BAL is recommended.
- Immediately treat with intravenous steroids (methylprednisolone 125 mg IV). When symptoms improve to Grade 1 or less, a high dose oral steroid (prednisone 1 to 2 mg/kg once per day or dexamethasone 4 mg every 4 hours) taper should be started and continued over no less than 4 weeks.
- If IV steroids followed by high dose oral steroids does not reduce initial symptoms within 48 to 72 hours, treat with additional anti-inflammatory measures. Discontinue additional anti-inflammatory measures upon symptom relief and initiate a prolonged steroid taper over 45 to 60 days. If symptoms worsen during steroid reduction, initiate a retapering of steroids starting at a higher dose of 80 or 100 mg followed by a more prolonged taper and administer additional anti-inflammatory measures, as needed
- Add prophylactic antibiotics for opportunistic infections.

3.2 Colitis

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

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

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

Course of Action

Grade 2 Diarrhea/Colitis (4-6 stools/day over baseline, dehydration requiring IV fluids < 24 hours, abdominal pain, mucus or blood in stool):

- Report as ECI
- Hold pembrolizumab.
- Symptomatic Treatment
- For Grade 2 diarrhea that persists for greater than 3 days, and for diarrhea with blood and/or mucus,
  - Consider GI consultation and endoscopy to confirm or rule out colitis
  - Administer oral corticosteroids (prednisone 1-2 mg/kg QD or equivalent)
- When symptoms improve to Grade 1 or less, steroid taper should be started and continued over no less than 4 weeks.
- Permanently discontinue for inability to reduce corticosteroid dose to 10 mg or less of prednisone or equivalent per day within 12 weeks.
- If symptoms worsen or persist > 3 days treat as Grade 3

Grade 3 Diarrhea/Colitis (or Grade 2 diarrhea that persists for > 1 week):

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

Grade 4 events:

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

3.3 Endocrine

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

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

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

Hypophysitis or other symptomatic endocrinopathy other than hypo- or hyperthyroidism

Grade 2-4 events:

- Report as ECI if appropriate
- Hold pembrolizumab
- Rule out infection and sepsis with appropriate cultures and imaging.
- Monitor thyroid function or other hormonal level tests and serum chemistries more frequently until returned to baseline values.
- Pituitary gland imaging should be considered (MRIs with gadolinium and selective cuts of the pituitary can show enlargement or heterogeneity and confirm the diagnosis).
- Treat with prednisone 40 mg p.o. or equivalent per day. When symptoms improve to Grade 1 or less, steroid taper should be started and continued over no less than 4 weeks. Replacement of appropriate hormones may be required as the steroid dose is tapered.
- Permanently discontinue for inability to reduce corticosteroid dose to 10 mg or less of prednisone or equivalent per day within 12 weeks.
- Hypophysitis with clinically significant adrenal insufficiency and hypotension, dehydration, and electrolyte abnormalities (such as hyponatremia and hyperkalemia) constitutes adrenal crisis.
- Consultation with an endocrinologist may be considered.

Hyperthyroidism and Hypothyroidism

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

Grade 2 hyperthyroidism, Grade 2-4 hypothyroidism events:

- Report as ECI if appropriate (see Table 1)
- Monitor thyroid function or other hormonal level tests and serum chemistries more frequently until returned to baseline values.
- Thyroid hormone and/or steroid replacement therapy to manage adrenal insufficiency.
- Therapy with pembrolizumab can be continued while treatment for the thyroid disorder is instituted.
- In hyperthyroidism, non-selective beta-blockers (e.g. propranolol) are suggested as initial therapy.
- In hypothyroidism, thyroid hormone replacement therapy, with levothyroxine or liothyroinine, is indicated per standard of care.
- Consultation with an endocrinologist may be considered.

Grade 3 hyperthyroidism events:

- Report as ECI
- Hold pembrolizumab.
- Rule out infection and sepsis with appropriate cultures and imaging.
- Treat with an initial dose of methylprednisolone 1 to 2 mg/kg intravenously followed by oral prednisone 1 to 2 mg/kg per day. When symptoms improve to Grade 1 or less, steroid taper should be started and continued over no less than 4 weeks. Replacement of appropriate hormones may be required as the steroid dose is tapered.
- Permanently discontinue for inability to reduce corticosteroid dose to 10 mg or less of prednisone or equivalent per day within 12 weeks.

Grade 4 hyperthyroidism events:

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

Type 1 diabetes mellitus (if new onset) and ≥ Grade 3 Hyperglycemia

The following AE terms are considered ECIs and should be reported to the Sponsor within 24 hours of the event:

- Type I diabetes mellitus (T1DM), if new onset, including diabetic ketoacidosis (DKA)
- Grade 3 or higher hyperglycemia, if associated with ketosis (ketonuria) or metabolic acidosis (DKA).

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

Course of Action

T1DM should be immediately treated with insulin.

T1DM or Grade 3-4 Hyperglycemia events:

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

3.4 Hematologic

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

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

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

Course of Action

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

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

Grade 4 events:
- Report as ECI
- Hematology consultation
- Discontinue pembrolizumab for all solid tumor indications; refer to protocol for hematologic malignancies.
- Treat with methylprednisolone 125 mg iv or prednisone 1-2 mg/kg p.o. (or equivalent) as appropriate

3.5 Hepatic

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

- Autoimmune hepatitis
- Hepatitis
- Transaminase elevations

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

Drug Induced Liver Injury (DILI)

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

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

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

Course of Action

Grade 2 events:

- Report as ECI
- Hold pembrolizumab when AST or ALT >3.0 to 5.0 times ULN and/or total bilirubin >1.5 to 3.0 times ULN.
- Monitor liver function tests more frequently until returned to baseline values (consider weekly).
    - Treat with 0.5-1 mg/kg/day methylprednisolone or oral equivalent and when LFT returns to grade 1 or baseline, taper steroids over at least 1 month, consider prophylactic antibiotics for opportunistic infections, and resume pembrolizumab per protocol
- Permanently discontinue for inability to reduce corticosteroid dose to 10 mg or less of prednisone or equivalent per day within 12 weeks.
- Permanently discontinue pembrolizumab for patients with liver metastasis who begin treatment with Grade 2 elevation of AST or ALT, and AST or ALT increases ≥50% relative to baseline and lasts ≥1 week.

Grade 3 events:

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

- Several courses of steroid tapering may be necessary as symptoms may worsen when the steroid dose is decreased.
- Permanently discontinue for inability to reduce corticosteroid dose to 10 mg or less of prednisone or equivalent per day within 12 weeks.

Grade 4 events:

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

3.6 Neurologic

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

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

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

Course of Action

Grade 2 events:

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

Grade 3 and 4 events:

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

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

3.7 Ocular

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

- Uveitis
- Iritis

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

Course of Action

Grade 2 events:
- Evaluation by an ophthalmologist is strongly recommended.
- Treat with topical steroids such as 1% prednisolone acetate suspension and iridocyclitics.
- Discontinue pembrolizumab as per protocol if symptoms persist despite treatment with topical immunosuppressive therapy.

Grade 3 events:
- Evaluation by an ophthalmologist is strongly recommended
- Hold pembrolizumab and consider permanent discontinuation as per specific protocol guidance.
- Treat with systemic corticosteroids such as prednisone at a dose of 1 to 2 mg/kg per day. When symptoms improve to Grade 1 or less, steroid taper should be started and continued over no less than 4 weeks.
- Permanently discontinue for inability to reduce corticosteroid dose to 10 mg or less of prednisone or equivalent per day within 12 weeks.

Grade 4 events:
- Evaluation by an ophthalmologist is strongly recommended
- Permanently discontinue pembrolizumab.
- Treat with corticosteroids as per Grade 3 above

3.8 Renal

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

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

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

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

Course of Action

Grade 2 events:

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

Grade 3-4 events:

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

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

3.9 Skin

Rash and Pruritus

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

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

Other Skin ECIs

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

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

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

Course of Action

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

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

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

3.9.1. Immediate Evaluation for Potential Skin ECIs

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

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

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

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

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

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

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

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

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

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

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

3.10 Other

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

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

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

Course of Action

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

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

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

3.11 Infusion Reactions

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

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

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

Course of Action

Refer to infusion reaction table in the protocol and below.

Infusion Reactions

NCI CTCAE Grade	Treatment	Premedication at subsequent dosing
Grade 1 Mild reaction; infusion interruption not indicated; intervention not indicated	Increase monitoring of vital signs as medically indicated until the subject is deemed medically stable in the opinion of the investigator.	None
Grade 2 Requires infusion interruption but responds promptly to symptomatic treatment (e.g., antihistamines, NSAIDS, narcotics, IV fluids); prophylactic medications indicated for < =24 hrs	**Stop Infusion.** Additional appropriate medical therapy may include but is not limited to: IV fluids Antihistamines NSAIDS Acetaminophen Narcotics Increase monitoring of vital signs as medically indicated until the subject is deemed medically stable in the opinion of the investigator. If symptoms resolve within one hour of stopping drug infusion, the infusion may be restarted at 50% of the original infusion rate (e.g. from 100 mL/hr to 50 mL/hr). Otherwise dosing will be held until symptoms resolve and the subject should be premedicated for the next scheduled dose. **Subjects who develop Grade 2 toxicity despite adequate premedication should be permanently discontinued from further trial treatment administration.**	Subject may be premedicated 1.5h (± 30 minutes) prior to infusion of pembrolizumab with: Diphenhydramine 50 mg p.o. (or equivalent dose of antihistamine). Acetaminophen 500-1000 mg p.o. (or equivalent dose of antipyretic).
Grades 3 or 4 Grade 3: Prolonged (i.e., not rapidly responsive to symptomatic medication and/or brief interruption of infusion); recurrence of symptoms following initial improvement; hospitalization indicated for other clinical sequelae (e.g., renal impairment, pulmonary infiltrates) Grade 4: Life-threatening; pressor or ventilatory support indicated	**Stop Infusion.** Additional appropriate medical therapy may include but is not limited to: IV fluids Antihistamines NSAIDS Acetaminophen Narcotics Oxygen Pressors Corticosteroids Epinephrine Increase monitoring of vital signs as medically indicated until the subject is deemed medically stable in the opinion of the investigator. Hospitalization may be indicated. **Subject is permanently discontinued from further trial treatment administration.**	No subsequent dosing
Appropriate resuscitation equipment should be available in the room and a physician readily available during the period of drug administration. For Further information, please refer to the Common Terminology Criteria for Adverse Events v4.0 (CTCAE) at http://ctep.cancer.gov		

3.12 Follow-up to Resolution

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

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

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

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

Pneumonitis (reported as ECI if ≥ Grade 2)		
Acute interstitial pneumonitis	Interstitial lung disease	Pneumonitis
Colitis (reported as ECI if ≥ Grade 2 or any grade resulting in dose modification or use of systemic steroids to treat the AE)		
Intestinal Obstruction	Colitis	Colitis microscopic
Enterocolitis	Enterocolitis hemorrhagic	Gastrointestinal perforation
Necrotizing colitis	Diarrhea	
Endocrine (reported as ECI if ≥ Grade 3 or ≥ Grade 2 and resulting in dose modification or use of systemic steroids to treat the AE)		
Adrenal Insufficiency	Hyperthyroidism	Hypophysitis
Hypopituitarism	Hypothyroidism	Thyroid disorder
Thyroiditis	Hyperglycemia, if ≥Grade 3 and associated with ketosis or metabolic acidosis (DKA)	
Endocrine (reported as ECI)		
Type 1 diabetes mellitus (if new onset)		
Hematologic (reported as ECI if ≥ Grade 3 or any grade resulting in dose modification or use of systemic steroids to treat the AE)		
Autoimmune hemolytic anemia	Aplastic anemia	Thrombotic Thrombocytopenic Purpura (TTP)
Idiopathic (or immune) Thrombocytopenia Purpura (ITP)	Disseminated Intravascular Coagulation (DIC)	Haemolytic Uraemic Syndrome (HUS)
Any Grade 4 anemia regardless of underlying mechanism		
Hepatic (reported as ECI if ≥ Grade 2, or any grade resulting in dose modification or use of systemic steroids to treat the AE**)**		
Hepatitis	Autoimmune hepatitis	Transaminase elevations (ALT and/or AST)
Infusion Reactions (reported as ECI for any grade)		
Allergic reaction	Anaphylaxis	Cytokine release syndrome
Serum sickness	Infusion reactions	Infusion-like reactions
Neurologic (reported as ECI for any grade)		
Autoimmune neuropathy	Guillain-Barre syndrome	Demyelinating polyneuropathy
Myasthenic syndrome		
Ocular (report as ECI if ≥ Grade 2 or any grade resulting in dose modification or use of systemic steroids to treat the AE)		
Uveitis	Iritis	
Renal (reported as ECI if ≥ Grade 2)		
Nephritis	Nephritis autoimmune	Renal Failure
Renal failure acute	Creatinine elevations (report as ECI if ≥Grade 3 or any grade resulting in dose modification or use of systemic steroids to treat the AE)	
Skin (reported as ECI for any grade)		
Dermatitis exfoliative	Erythema multiforme	Stevens-Johnson syndrome
Toxic epidermal necrolysis		
Skin (reported as ECI if ≥ Grade 3)		
Pruritus	Rash	Rash generalized
Rash maculo-papular		
Any rash considered clinically significant in the physician's judgment		
Other (reported as ECI for any grade)		
Myocarditis	Pancreatitis	Pericarditis
Any other Grade 3 event which is considered immune-related by the physician		

6. APPENDIX 2 – Past Medical History Related to Dermatologic Event

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

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

If yes, please obtain the following information:

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

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

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

Describe the agent and type of allergic response: _____
_____

c. Any allergy to food? □ Yes □ No

Describe the food and type of allergic response: _____
_____

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

Describe the allergen and type of allergic response: _____
_____

e. Any other allergy? □ Yes □ No

Describe the allergen and type of allergic response: _____
_____

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

If so what kind? _____

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

If so what kind? _____

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

7. APPENDIX 3 – Presentation of the Dermatologic Event

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

1. What is the onset time of the skin reaction, skin eruption, or rash relative to dose of study drug?
_____

2. Has the subject contacted any known allergens? □ Yes □ No

If so what kind? _____

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

If so what kind? _____

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

If so what kind? _____

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

If so what kind? _____

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

If so what kind? _____

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

If so who and what? _____

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

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

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

If so what kind? _____

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

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

If so what kind? _____

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

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

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

8. APPENDIX 4 – Focused Skin Examination

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

Primary Skin Lesions Description
Color: _____

General description:
_____
_____

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

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

Any associated signs on physical examination?
_____