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Phase II Trial of Pembrolizumab and Reirradiation in Bevacizumab Naïve and Bevacizumab Resistant Recurrent Glioblastoma (DF/HCC #18-277)

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TITLE: Phase II Trial of Pembrolizumab and Reirradiation in Bevacizumab Naïve and Bevacizumab Resistant Recurrent Glioblastoma

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IND Sponsor: David A. Reardon, MD

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figure 1 STUDY SCHEMA

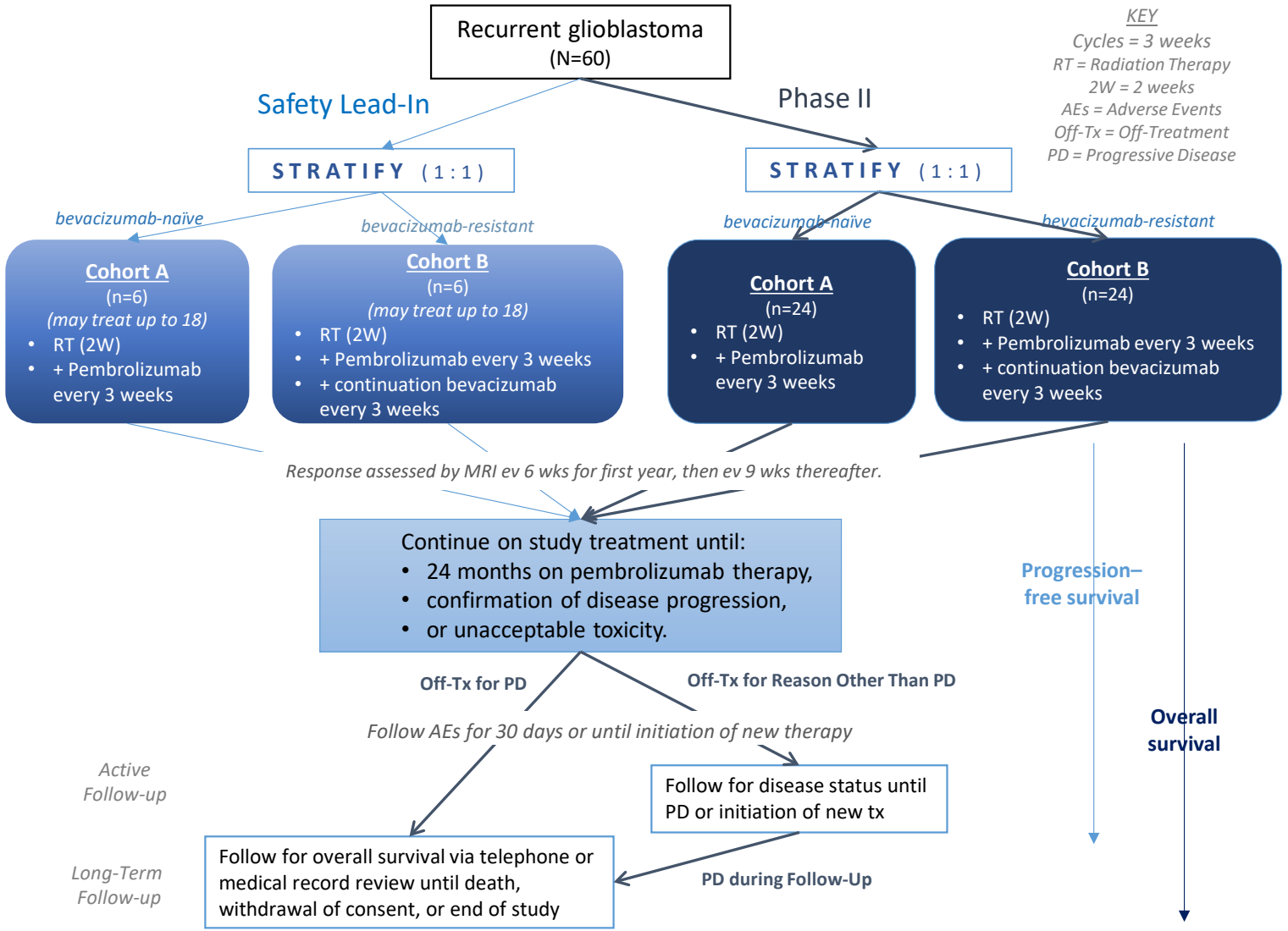


TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

1. TRIAL SUMMARY

Table 1. Trial Summary

Abbreviated Title	Pembrolizumab plus re-irradiation in recurrent GBM (Phase II)
Sponsor Product Identifiers	Pembrolizumab (MK-3475)
Trial Phase	Phase II
Clinical Indication	Treatment of patients with recurrent glioblastoma (GBM) who have received 1 or more previous standard treatment(s).
Trial Type	Interventional
Type of control	Historical controls
Route of administration	Intravenous and external beam radiotherapy
Trial Blinding	Unblinded Open-label
Treatment Groups	Cohort A: Pembrolizumab (MK-3475) 200 mg once every 3 weeks (Q3W) plus re-irradiation 35Gy/10fx Cohort B: Pembrolizumab (MK-3475) 200 mg Q3W plus re-irradiation 35Gy/10fx plus bevacizumab (or biosimilar) 15 mg/kg once every 3 weeks (Q3W)
Number of trial participants	Approximately 60 participants will be enrolled (up to 70 participants may be enrolled with the goal of treating 60 eligible participants).
Estimated duration of trial	The Sponsor estimates that the trial will require approximately 48 months from the time the first participant signs the informed consent until the last participant's last study-related phone call or visit.
Duration of Participation	Each participant will participate in the trial from the time the participant signs the informed consent form (ICF) through the final protocol-specified contact. After a screening phase of up to 28 days, eligible participants will be assigned to 1 of 2 cohorts based on history of prior bevacizumab treatment. Participants who are bevacizumab-naïve will be assigned to Cohort A, and participants who have previously been treated with bevacizumab will be assigned to Cohort B. A safety lead-in is included for each Cohort. All participants enrolled will receive pembrolizumab 200 mg on Day 1 of each 3-week (21 day) cycle until disease progression or study withdrawal. All participants enrolled will also receive 1 course of re-irradiation therapy (35 Gy/10fx) administered during Cycle 1. In addition to pembrolizumab and re-irradiation, participants in Cohort B will receive bevacizumab (or biosimilar) 15 mg/kg on Day 1 of each treatment cycle. Treatment in both cohorts will continue until disease progression is confirmed by the site per the Response Assessment in Neuro-Oncology (RANO) criteria, unacceptable adverse event(s) (AE), intercurrent illness that prevents further administration of treatment, investigator's decision to withdraw the participant, participant decides to withdraw from study, noncompliance with trial treatment or procedures requirements, administrative reasons requiring cessation of treatment, for a maximum of 24 months of treatment (up to 35 possible administrations) of pembrolizumab. After the end of treatment, each participant will be followed for 30 days for the occurrence of AEs and spontaneously reported pregnancy (described in Section 7.2). Participants with a Serious AE (SAE) will continue to be followed until death, SAE resolution, or SAE stabilization. Participants who discontinue for reasons other than disease progression will have post-treatment follow-up for disease status until disease progression is confirmed by the site, initiating a non-study cancer treatment, withdrawing consent, or becoming lost to follow-up. All participants will be followed by telephone or medical record review for overall survival until death, withdrawal of consent, or the end of the study.

2. OBJECTIVES

2.1 Study Design

This is a multicenter, open-label, phase II trial of pembrolizumab plus re-irradiation among recurrent glioblastoma patients enrolled to two parallel, non-comparative treatment arms including patients who are bevacizumab naïve (Arm A, n=30) and patients who are bevacizumab-resistant (Arm B, n=30). The toxicity of the study regimen for each cohort has not been formally evaluated among recurrent glioblastoma patients; thus a safety lead-in is included for each cohort (Section 6.1) and will define the maximum tolerated dose (MTD)/recommended phase II dose (RP2D) of pembrolizumab for each cohort independently.

Participants will be evaluated every 6 weeks with radiographic imaging to assess response to treatment in the first year and every 9 weeks thereafter. Modified Response Assessment in Neuro-Oncology (RANO) criteria[1] will be used as the primary efficacy endpoint of response rate. RANO will be adapted as described in Section 12.0 due to the tumor response patterns seen with pembrolizumab treatment (e.g., tumor flare); these criteria will be used for treatment decisions by the sites. Adverse events will be monitored throughout the trial and graded in severity according to the guidelines outlined in the NCI Common Terminology Criteria for Adverse Events (CTCAE) version 4.0. Treatment with study therapy will continue for a maximum of 24 months of treatment (up to 35 possible administrations) of pembrolizumab, or until documented disease progression, unacceptable adverse event(s), intercurrent illness that prevents further administration of treatment, investigator's decision to withdraw the participant, participant withdraws consent, pregnancy of the participant, noncompliance with trial treatment or procedure requirements, or administrative reasons. After the end of treatment, each participant will be followed for 30 days for adverse event monitoring. Participants who discontinue treatment for reasons other than disease progression will have post-treatment follow-up of disease status until disease progression, initiation of a new anti-cancer treatment, withdrawing consent, or becoming lost to follow -up. All participants will be followed by telephone contact or medical record review for overall survival until death, withdrawal of consent or the end of the study, whichever comes first.

The primary objective of the trial is to evaluate the anti-tumor activity of pembrolizumab when administered with re-irradiation versus the appropriate historical controls as measured by overall radiographic response (ORR) and overall survival at 12 months among participants with bevacizumab-naïve recurrent glioblastoma and at 6 months for those with bevacizumab-resistant, recurrent glioblastoma. Secondary objectives include safety and tolerability, progression-free survival (PFS), overall survival (OS), and ORR duration.

This study will be conducted in conformance with Good Clinical Practices.

Specific procedures to be performed during the trial, as well as their prescribed times and associated visit windows, are outlined in the Study Calendar Section 11.0.

2.2 Primary Objective

2.2.1 **Objective**: To evaluate the efficacy of the combination of pembrolizumab and re-RT in bevacizumab naïve patients (Cohort A) and bevacizumab resistant patients (Cohort B) as measured by ORR per Response Assessment in Neuro-Oncology (RANO, for both cohorts) and OS at 12 months (cohort A) and OS at 6 months (Cohort B).

Hypothesis: Administration of pembrolizumab with re-irradiation will result in a clinically meaningful benefit compared to the appropriate historical controls as measured by ORR or OS among participants with recurrent glioblastoma.

2.3 Secondary Objectives

2.3.1 **Objective:** To evaluate the safety and tolerability of the therapy used in each cohort.
2.3.2 **Objective:** To estimate duration of response in each cohort per RANO criteria.
2.3.3 **Objective:** To estimate median PFS and PFS at 6 months in each cohort.
2.3.4 **Objective**: To estimate median OS in each cohort.

Hypothesis: Intravenous administration of pembrolizumab with re-irradiation will result in a clinically meaningful benefit compared to historical controls as measured by PFS, OS and ORR duration among participants with bevacizumab-naïve and bevacizumab-refractory, recurrent glioblastoma.

2.4 Exploratory Objectives

2.4.1 **Objective**: To evaluate whether archival tumor expression of PD-L1, tumor infiltrating lymphocytes features, or T cell inflamed gene expression profile are associated with outcome.
2.4.2 **Objective**: To evaluate Neurologic Assessment in Neuro-Oncology (NANO) in each cohort
2.4.3 **Objective**: To evaluate the change of Patient Reported Outcome scores from baseline to post-baseline time-points using the EORTC QLQ-C30.
2.4.4 **Objective**: To estimate ORR per iRANO

3. BACKGROUND

3.1 Study Disease(s)

Glioblastoma (GBM), the most common primary brain neoplasm in adults, remains incurable. Approximately 13,000 new cases of GBM are diagnosed in the US each year with an estimated global incidence of 3.5/100,000 people.[2] Outcome following current standard of care therapy which includes surgery, radiation therapy and temozolomide remains poor with a median survival of 14.6 months and a five year survival rate of under 10%.[3] Following recurrence, no therapy has been established to prolong survival and such patients represent a dire unmet need in modern day oncology.[4] Although bevacizumab, a blocking antibody against vascular endothelial growth factor (VEGF), is FDA-approved for recurrent GBM, a recent phase 3 study demonstrated that it improves progression-free survival (PFS) but not overall survival (OS).[5] Furthermore, outcome following bevacizumab progression is dismal with a median OS of only 4 months.[6] Innovative treatment options are desperately needed.

3.2 Pembrolizumab

Refer to the pembrolizumab Investigator's Brochure for detailed information on pembrolizumab.

3.2.1 Background

Pembrolizumab is a potent humanized immunoglobulin G4 (IgG4) monoclonal antibody (mAb) with high specificity of binding to the programmed cell death 1 (PD-1) receptor, thus inhibiting its interaction with programmed cell death ligand 1 (PD-L1) and programmed cell death ligand 2 (PD-L2). Based on preclinical in vitro data, pembrolizumab has high affinity and potent receptor blocking activity for PD-1. Pembrolizumab has an acceptable preclinical safety profile and is in clinical development as an intravenous (IV) immunotherapy for advanced malignancies. Keytruda® (pembrolizumab) is indicated for the treatment of patients across a number of indications because of its mechanism of action to bind the PD-1 receptor on the T cell. For more details on specific indications refer to the Investigator brochure.

3.2.2 Pharmaceutical and Therapeutic Background

The importance of intact immune surveillance function in controlling outgrowth of neoplastic transformations has been known for decades.[7] Accumulating evidence shows a correlation between tumor-infiltrating lymphocytes in cancer tissue and favorable prognosis in various malignancies. In particular, the presence of CD8+ T-cells and the ratio of CD8+ effector T-cells/FoxP3+ regulatory T-cells (T-regs) correlates with improved prognosis and long-term survival in solid malignancies, such as ovarian, colorectal, and pancreatic cancer; hepatocellular carcinoma; malignant melanoma; and renal cell carcinoma. Tumor-infiltrating lymphocytes can be expanded ex vivo and reinfused, inducing durable objective tumor responses in cancers such as melanoma.[8,9]

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 immunoglobulin (Ig) superfamily member related to cluster of differentiation 28 (CD28) and cytotoxic T-lymphocyte-associated protein 4 (CTLA-4) that has been shown to negatively regulate antigen receptor signaling upon engagement of its ligands (PD-L1 and/or PD-L2).[10,11]

The structure of murine PD-1 has been resolved.[12] PD-1 and its family members are type I transmembrane glycoproteins containing an Ig-variable–type (IgV-type) domain responsible for ligand binding and a cytoplasmic tail 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, and an immunoreceptor tyrosine-based switch motif. Following T-cell stimulation, PD-1 recruits the tyrosine phosphatases, SHP-1 and SHP-2, to the immunoreceptor tyrosine-based switch motif within its cytoplasmic tail, leading to the dephosphorylation of effector molecules such as CD3 zeta (CD3ζ), protein kinase C-theta (PKCθ), and zeta-chain-associated protein kinase (ZAP70), which are involved in the CD3 T-cell signaling cascade.[11,13] The mechanism by which PD-1 down-modulates T-cell responses is similar to, but distinct from, that of CTLA-4, because both molecules regulate an overlapping set of signaling proteins.[14,15] PD-L1 has been shown to be upregulated by a number of aggressive cancers including glioblastoma[16,17] and its expression has been associated with a poorer outcome among glioblastoma patients.[17] As a consequence, the PD-1/PD-L1 pathway is an attractive target for therapeutic intervention in glioblastoma.

3.2.3 **Preclinical and Clinical Trial Data**

Refer to the pembrolizumab Investigator's Brochure for preclinical and clinical data.

3.3 Re-Irradiation

3.3.1 **Background**

A hypofractionated course of reirradiation has been shown to provide modest therapeutic benefit for recurrent GBM patients[18-21] including those who are bevacizumab-refractory[22,23] and the safety of re-irradiation with concurrent bevacizumab for recurrent GBM patients has been previously established.[24] Nonetheless, the primary goal of incorporating reirradiation in this study is to exploit the ability of radiation therapy to augment immune responses.[25] Radiation therapy can enhance anti-tumor immune responses by two primary mechanisms including: 1) increasing exposure of tumor antigens through immunogenic cell death and; 2) generating immuno-adjuvant effects through induction of a wide array of immuno-activating modulators. The dose and fractionation of radiotherapy can affect the degree and type of cell death in a tissue-specific manner[26] and immunogenic cell death from radiotherapy leads to enhanced efficiency of transfer of antigens from dendritic cells to T-cells, which in turn are capable of activating tumor-specific T cells resulting in increased therapeutic efficacy.[27] In addition, radiotherapy can act as an immunoadjuvant by enhancing expression of several proinflammatory molecules to enhance anti-tumor immune responses including cytokines such as CXCL9, CXCL10, CXCL16, IL-1β, TNFα, type I interferons,[28] as well as death receptors,[29] MHC class I molecules,[30] co-stimulatory molecules,[31] adhesion molecules[32] and stress-induced ligands.[33] Emerging clinical data supports the ability of radiotherapy to enhance anti-tumor activity both locally as well as systemically through induction of the abscopal effect.[34] Furthermore, preclinical studies utilizing an immunocompetent orthotopic GBM model demonstrate that an abbreviated course of radiotherapy can enhance the therapeutic efficacy of immune checkpoint blockade including the induction of long-term survivors.[35,36]

3.3.2 **Rationale for Dosing Schedule**

Fractionated radiotherapy will be administered according to established, standard-of-care guidelines utilizing intensity-modulated radiation therapy (IMRT), 3-dimensional conformal radiation therapy (3D-CRT) or proton beam radiation therapy at a dose of 3.5 Gy/fraction times 10 fractions (5 days a week for 2 weeks). Daily image-guided radiation therapy (IGRT) is required including non-volumetric (Orthogonal or near-orthogonal 2D imaging that is integrated with the radiation delivery device) and volumetric (diagnostic CT, cone beam CT with MV or kV x-ray beam, MRI-linac or Tomotherapy technology) systems. Although a variety of dosing schedules of re-irradiation have been utilized for recurrent glioblastoma patients, the largest series have utilized a targeted cumulative dose of 35-36 Gy administered over 10-18 fractions.[19,37,38] In general, these schedules have been well tolerated with adverse events typically limited to mild and manageable acute events, including fatigue, alopecia and nausea, as well as negligible rates of serious late events such as CNS toxicity or radiation necrosis. For example, among 147 patients with recurrent high-grade glioma reported by Fogh et al who received a median of 3.5 Gy/fraction times 10 fractions over 2 weeks, all patients were able to complete the prescribed radiation dose without interruption and no patients demonstrated clinically significant acute morbidity, while no patients required hospitalization or surgery for early acute or delayed toxicity. In this series, only one patient was reported to have developed a serious (grade 3) late CNS toxicity.[19]

Limited prospective data exist regarding the safety of immune checkpoint therapy when combined with radiotherapy. Although both immune checkpoint blockade and radiotherapy can increase inflammatory reactions and cerebral edema with published case reports of radiation necrosis,[39] studies to date in metastatic brain tumor patients demonstrate low rates of symptomatic radiation necrosis for combined modality therapy which do not appear to be significantly increased compared to radiation alone.[40-45] In this same patient population, one study to date reveals a modest increase in grade 3 seizures for patients treated with combined modality therapy compared to those treated with radiation therapy alone.[46]

3.4 Study Rationale

3.4.1 Rationale for Trial and Selected Population

Inhibitors of programmed death 1 (PD-1) signaling, such as pembrolizumab, have achieved dramatic benefit across a spectrum of cancers, although only a subset of patients respond.[47] Preliminary results of initial clinical trials evaluating pembrolizumab for recurrent GBM demonstrate similar findings. Among 26 patients treated with single agent pembrolizumab, there was one partial response (4%), while 44% of patients remained progression-free for at least six months and the median OS was 14 months.[48] Results of a recently reported randomized phase III study of nivolumab, another PD-1 blocking antibody, confirmed a low rate of therapeutic benefit among recurrent glioblastoma patients.[49] Specifically, the ORR for patients treated with nivolumab was only 8%, although the durability of radiographic response was encouraging at 11.4 months. One reason for the low rate of therapeutic benefit observed to date is that GBM is a "cold" tumor, characterized by a relatively low rate of mutational load and an overall low level of immune cell infiltrate.[50-54]

Tumors with a higher immune cell infiltrate exhibit a higher rate of therapeutic benefit with PD-1 blockade. Strategies to increase the number of infiltrating immune cells into the tumor microenvironment offer the potential to increase the rate of achieved therapeutic benefit associated with PD-1 blockade. In the current submission, we propose a phase 2 study to evaluate the impact of re-irradiation (re-RT), as a strategy to increase immune cell infiltration into the tumor microenvironment and thereby generate a "hot" tumor microenvironment, when combined with pembrolizumab for recurrent GBM patients.

The rationale for adding re-irradiation in the current proposal is based on several factors. First, preclinical data in several solid tumor types demonstrates enhanced activity when RT is combined with either PD-1 blockade or dual blockade of PD-1 and CTLA-4.[55] In addition, radiation therapy has been shown to enhance the therapeutic benefit of anti-PD-1 treatment in an orthotopic, immunocompetent GBM model,[35] while blocking PD-L1 can reverse radiation resistance.[56] Second, radiation therapy has been shown to induce immunogenic cell death[26] which can augment antigen-specific anti-PD-1 immune responses via cross presentation of tumor antigens.[57] Third, re-RT alone is considered a standard of care with modest benefit observed among a subset of recurrent GBM patients.[18,19,38] Fourth, local radiation therapy can generate abscopal responses at distant tumor sites among oncology patients[34,58] suggesting that such responses beyond the targeted radiation field could provide benefit for diffusely infiltrative tumors such as GBM.

In addition, a highly encouraging rate of durable radiographic response has been observed anecdotally among recurrent GBM patients treated with PD-1 blockade and re-RT. Specifically, a recent retrospective series at Columbia University included 20 consecutive patients with recurrent high-grade glioma (18 GBM) who were treated with re-RT and anti-PD-1 therapy.[59] Most patients were heavily pre-treated including a median number of 2 (range, 1-4) prior salvage treatments while 55% had progressed on prior bevacizumab. Eight patients received pembrolizumab (2 mg/Kg q3w) and 12 patients received nivolumab (3 mg/Kg or 240 mg q2w). The median re-RT dose was 35 Gy (12 Gy to 35 Gy). There were 7 confirmed partial responses (35% ORR), including 4/9 bevacizumab naïve (44%) and 3/11 bevacizumab failure patients (27%). The median duration of response was 5 months (2.2 to 10+ months), median PFS was 4 months and median OS was 10 months. There were neither obvious cases of cerebral edema related to treatment nor any new unexpected adverse events. Fifteen patients (75%) had stable or reduced dexamethasone dosing, while five patients (25%) required a mild increase of corticosteroid dosing (2-4 mg).

Our proposed study is therefore designed to prospectively evaluate the role of re-RT when added to pembrolizumab PD-1 blockade for recurrent GBM patients.

3.4.2 **Justification for Pembrolizumab Dose**

The planned dose of pembrolizumab for this study is 200 mg every 3 weeks (Q3W). Based on the totality of data generated in the Keytruda development program, 200 mg Q3W is the appropriate dose of pembrolizumab for adults across all indications and regardless of tumor type. As outlined below, this dose is justified by:

- Clinical data from 8 randomized studies demonstrating flat dose- and exposure-efficacy relationships from 2 mg/kg Q3W to 10 mg/kg every 2 weeks (Q2W),
- Clinical data showing meaningful improvement in benefit-risk including overall survival at 200 mg Q3W across multiple indications, and
- Pharmacology data showing full target saturation in both systemic circulation (inferred from pharmacokinetic [PK] data) and tumor (inferred from physiologically-based PK [PBPK] analysis) at 200 mg Q3W

Among the 8 randomized dose-comparison studies, a total of 2262 participants were enrolled with melanoma and non-small cell lung cancer (NSCLC), covering different disease settings (treatment naïve, previously treated, PD-L1 enriched, and all-comers) and different treatment settings (monotherapy and in combination with chemotherapy). Five studies compared 2 mg/kg Q3W versus 10 mg/kg Q2W (KN001 Cohort B2, KN001 Cohort D, KN002, KN010, and KN021), and 3 studies compared 10 mg/kg Q3W versus 10 mg/kg Q2W (KN001 Cohort B3, KN001 Cohort F2 and KN006). These studies demonstrated flat dose- and exposure-response relationships across the doses studied representing an approximate 5- to 7.5-fold difference in exposure. The 2 mg/kg (or 200 mg fixed-dose) Q3W provided similar responses to the highest doses studied. Subsequently, flat dose-exposure-response relationships were also observed in other tumor types including head and neck cancer, bladder cancer, gastric cancer and classical Hodgkin Lymphoma, confirming 200 mg Q3W as the appropriate dose independent of the tumor type. These findings are consistent with the mechanism of action of pembrolizumab, which acts by interaction with immune cells, and not via direct binding to cancer cells.

Additionally, pharmacology data clearly show target saturation at 200 mg Q3W. First, PK data in KN001 evaluating target-mediated drug disposition (TMDD) conclusively demonstrated saturation of PD-1 in systemic circulation at doses much lower than 200 mg Q3W. Second, a

PBPK analysis was conducted to predict tumor PD-1 saturation over a wide range of tumor penetration and PD-1 expression. This evaluation concluded that pembrolizumab at 200 mg Q3W achieves full PD-1 saturation in both blood and tumor.

Finally, population PK analysis of pembrolizumab, which characterized the influence of body weight and other participant covariates on exposure, has shown that the fixed-dosing provides similar control of PK variability as weight based dosing, with considerable overlap in the distribution of exposures from the 200 mg Q3W fixed dose and 2 mg/kg Q3W dose. Supported by these PK characteristics, and given that fixed-dose has advantages of reduced dosing complexity and reduced potential of dosing errors, the 200 mg Q3W fixed-dose was selected for evaluation across all pembrolizumab protocols.

3.4.3 **Rationale for Efficacy Endpoints**

The primary efficacy objective of this study is to evaluate the anti-tumor activity of pembrolizumab when administered with re-irradiation compared to historical controls among participants with bevacizumab-naïve (cohort A) and bevacizumab-refractory (cohort B) recurrent glioblastoma. Overall radiographic response (ORR) and overall survival at 12 months (cohort A) and overall survival at 6 months (cohort B) will be the primary endpoints, and ORR duration, as well as median OS and PFS (median and at 6 months) will be secondary efficacy endpoints.
Response per modified RANO criteria[1] as assessed by the investigator will be used for efficacy endpoints (Section 12). RANO will also be used by the local site to determine eligibility and make treatment decisions.

3.4.4 **Safety endpoints**

An important secondary objective of this study is to characterize the safety and tolerability of pembrolizumab when administered with re-irradiation among participants with recurrent glioblastoma. The safety analysis will be based on participants who experience toxicities as defined by CTCAE 4.0 criteria. Safety will be assessed by quantifying the toxicities and grades experienced by participants who have received pembrolizumab with re-irradiation, including serious adverse events (SAEs) and events of clinical interest (ECIs).

Safety will be assessed by reported adverse experiences using CTCAE, Version 4.0. The attribution to drug, time-of-onset, duration of the event, its resolution, and any concomitant medications administered will be recorded. AEs will be analyzed including but not limited to all AEs, SAEs, and fatal AEs. Furthermore, specific immune-related adverse events (irAEs) will be collected and designated as immune-related events of clinical interest (ECIs) as described in Section 8.4.4.2.

3.5 Correlative Studies Background

When available, archival tumor material will be evaluated for tumor infiltrating lymphocytes, PD-1 expressing lymphocytes, measurement of tumor cell PD-L1 expression and evaluation of an inflamed T cell gene expression profile.

4. PARTICIPANT SELECTION

Male/female participants of at least 18 years of age with recurrent glioblastoma will be enrolled in this trial.

Screening evaluations are detailed in Study Calendar (Section 11). All assessments are to occur within 14 days of start of study therapy except where otherwise noted. The participant must be thoroughly informed about all aspects of the study, including the study visit schedule and required evaluations and all regulatory requirements for informed consent. The written informed consent must be obtained from the participant prior to enrollment.

Following registration, any additional laboratory assessments obtained prior to start of treatment will not be used to re-confirm eligibility. Please refer to Section 7 Dosing Delays/Dose Modifications for toxicity management between registration and start of study treatment.

4.1 Eligibility Criteria

In order to be eligible for participation in this trial, all participants must meet the following criteria on screening examination:

4.1.1 Have histologically confirmed World Health Organization (WHO) Grade IV glioblastoma. Participants will be eligible if the original histology was low-grade glioma and a subsequent histological diagnosis of glioblastoma is made. Other WHO grade IV glial neoplasms such as gliosarcoma are NOT eligible.

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

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

4.1.4 Have a Karnofsky performance status (KPS) ≥ 70 (Appendix A).

4.1.5 Participants must have shown unequivocal evidence for tumor progression by MRI scan.

4.1.6 MRI within 14 days prior to start of study therapy. MRIs should include vascular imaging when possible. Corticosteroid dose must be stable or decreasing for at least 5 days prior to the scan. If steroids are added or the steroid dose is increased between the date of the screening MRI scan and the start of treatment, a new baseline MRI or CT is required.

4.1.7 Measurable disease as per RANO criteria.

4.1.8 Be at first or second relapse (cohort A). For cohort B, participants must have progressed on no more than one prior bevacizumab-containing regimen (cohort B). Participants who were treated with prior bevacizumab but did not progress or experienced significant toxicity, are not eligible.

NOTE: Relapse is defined as progression following initial therapy (i.e., radiation ± chemotherapy).

- If the participant had a surgical resection for relapsed disease and no antitumor therapy was instituted for up to 12 weeks, this is considered one relapse.
- For participants who had prior therapy beyond surgery for a low-grade glioma that is considered standard of care for high-grade glioma (radiation therapy,

chemotherapy with temozolomide or nitrosoureas, etc), the surgical diagnosis of glioblastoma will be considered the first relapse.

- Patients in screening for Cohort B may have received any # of non-bevacizumab-containing regimens.

4.1.9 Previous first line therapy with at least radiotherapy utilizing standard dosing of CNS radiation - for either high-grade or low-grade glial neoplasm

4.1.10 From the projected start of scheduled study treatment, the following time periods must have elapsed:

1. At least 3 weeks from prior surgical resection
    a. Participants having undergone recent resection of recurrent or progressive tumor will be eligible as long as they have recovered from the effects of surgery and have measurable residual disease prior to starting study therapy.
2. At least 1 week from stereotactic biopsy
3. At least 6 months from completion of prior radiotherapy
    a. If patients have not passed an interval of at least 6 months, they may still be eligible if they meet the following criteria:
        i. New area of enhancement outside the 80% isodose line of the original radiation field as determined by the treating investigator.
4. At least 4 weeks *(or 5 half-lives, whichever is shorter)* from any investigational agent
5. At least 4 weeks from cytotoxic therapy
    a. Exceptions:
        i. At least 23 days for temozolomide
        ii. At least 6 weeks from nitrosoureas
    b. At least 4 weeks *(or 5 half-lives, whichever is shorter)* for daily administered chemotherapeutics
6. At least 6 weeks from antibodies
7. At least 4 weeks *(or 5 half-lives, whichever is shorter)* from other anti-tumor therapies (not including tumor treating fields or cancer vaccines); at least 1 week from NovoTTF (Optune) or other tumor treating fields and cancer vaccines
8. Cohort B patients only: Day 1 of bevacizumab (or biosimilar) on-study must be at least 3 weeks from last dose of prior course of Avastin/bevacizumab.

4.1.11 Participants must have recovered to grade 0 or 1 or pre-treatment baseline from clinically significant toxic effects of prior therapy (exceptions include alopecia, laboratory values listed per inclusion criteria, and lymphopenia, which is common after therapy with temozolomide).

4.1.12 Demonstrate adequate organ function as defined in Table 2, all screening labs should be performed within 14 days of treatment initiation.

Table 2. Adequate Organ Function Laboratory Values

Laboratory Values System	Laboratory Value
Hematologic	
Absolute neutrophil count (ANC)	≥1,500 /mcL
Platelets	≥100,000 / mcL
Hemoglobin	≥9 g/dL or ≥5.6 mmol/L[a]

Table 2. Adequate Organ Function Laboratory Values (cont.)

Laboratory Values System	Laboratory Value
Renal	
Serum creatinine **OR** Measured or calculated[b] creatinine clearance (GFR can also be used in place of creatinine or CrCl)	≤1.5 X institutional upper limit of normal (ULN) **OR** ≥60 mL/min for participant with creatinine levels > 1.5 X institutional ULN
Hepatic	
Serum total bilirubin	≤ 1.5 X institutional ULN **OR** Direct bilirubin ≤ institutional ULN for participants with total bilirubin levels > 1.5 X institutional ULN
AST (SGOT) and ALT (SGPT)	≤ 2.5 X institutional ULN OR ≤ 5 X institutional ULN for participants with Gilberts syndrome
Coagulation	
International Normalized Ratio (INR) or Prothrombin Time (PT) Activated Partial Thromboplastin Time (aPTT)	≤1.5 X institutional ULN unless participant is receiving anticoagulant therapy as long as PT or aPTT is within therapeutic range of intended use of anticoagulants
Pulmonary	
Resting baseline oxygen saturation by pulse oximetry	≥92% at rest

ALT (SGPT)=alanine aminotransferase (serum glutamic pyruvic transaminase); AST (SGOT)=aspartate aminotransferase (serum glutamic oxaloacetic transaminase); GFR=glomerular filtration rate; ULN=upper limit of normal.

[a] Criteria must be met without erythropoietin dependency and without packed red blood cell (pRBC) transfusion within last 2 weeks.

[b] Creatinine clearance (CrCl) should be calculated per institutional standard.

NOTE: This table includes eligibility-defining laboratory value requirements for treatment; laboratory value requirements should be adapted according to local regulations and guidelines for the administration of specific chemotherapies.

4.1.13 Women of child-bearing potential (WOCBP), defined as all women physiologically capable of becoming pregnant, must have a negative urine or serum pregnancy within 72 hours prior to registration. If the urine test is positive or cannot be confirmed as negative, a serum pregnancy test will be required.

- Women in the following categories are not considered WOCBP:
    - Premenarchal
    - Premenopausal female with 1 of the following:
        - Documented hysterectomy
        - Documented bilateral salpingectomy
        - Documented bilateral oophorectomy

      Note: Documentation can come from the site personnel's review of the participant's medical records, medical examination, or medical history interview.

- Postmenopausal female
  - A postmenopausal state is defined as no menses for 12 months without an alternative medical cause.
    - A high follicle stimulating hormone (FSH) level in the postmenopausal range may be used to confirm a postmenopausal state in women not using hormonal contraception or hormonal replacement therapy (HRT). However, in the absence of 12 months of amenorrhea, confirmation with two FSH measurements in the postmenopausal range is required.
  - Females on HRT and whose menopausal status is in doubt will be required to use one of the non-hormonal highly effective contraception methods if they wish to continue their HRT during the study. Otherwise, they must discontinue HRT to allow confirmation of postmenopausal status before study enrollment.

4.1.14 Women of child-bearing potential (WOCBP; see definition above), must agree to use a highly effective method of contraception consistently and correctly as described below during study treatment and for 120 days after study discontinuation.

1. **Highly Effective Contraceptive Methods That Are User Dependent** [a] *(Failure rate of < 1% per year when used consistently and correctly.)*
   a. Combined (estrogen- and progestogen- containing) hormonal contraception [b, c]
      i. Oral
      ii. Intravaginal
      iii. Transdermal
      iv. Injectable
   b. Progestogen-only hormonal contraception [b, c]
      i. Oral
      ii. Injectable
2. **Highly Effective Methods That Have Low User Dependency** *(Failure rate of <1% per year when used consistently and correctly)*
   a. Progestogen- only contraceptive implant [b, c]
   b. Intrauterine hormone-releasing system (IUS) [b]
   c. Intrauterine device (IUD)
   d. Bilateral tubal occlusion
   e. Vasectomized partner

      A vasectomized partner is a highly effective contraception method provided that the partner is the sole male sexual partner of the WOCBP and the absence of sperm has been confirmed. If not, an additional highly effective method of contraception should be used.
   f. Sexual abstinence

      Sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the study treatment. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the study and the preferred and usual lifestyle of the participant.

NOTES:

Use should be consistent with local regulations regarding the use of contraceptive methods for participants of clinical studies.

a. Typical use failure rates are lower than perfect-use failure rates (i.e. when used consistently and correctly).
b. If hormonal contraception efficacy is potentially decreased due to interaction with study treatment, condoms must be used in addition to the hormonal contraception during the treatment period and for at least during study treatment and for 120 days after study discontinuation after the last dose of study treatment.
c. If locally required, in accordance with Clinical Trial Facilitation Group (CTFG) guidelines, acceptable contraceptive implants are limited to those which inhibit ovulation.

4.1.15 Male participants must agree to use at least one of the following methods of contraception starting with the first dose of study therapy through 120 days after the last dose of therapy:

1. Be abstinent from penile-vaginal intercourse as their usual and preferred lifestyle (abstinent on a long term and persistent basis) and agree to remain abstinent
2. Use a male condom plus partner use of a contraceptive method with a failure rate of <1% per year as described in Eligibility criterion 4.1.14 when having penile-vaginal intercourse with a woman of childbearing potential who is not currently pregnant.
    a. Note: Men with a pregnant or breastfeeding partner must agree to remain abstinent from penile-vaginal intercourse or use a male condom during each episode of penile penetration.

4.2 Exclusion Criteria

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

4.2.1 Has recurrent tumor greater than 6 cm in maximum diameter

4.2.2 Is currently participating or plans to participate in another study of an investigational agent or using an investigational device.

Note: Participants who have entered the follow-up phase of an investigational study may participate as long as it has been at least 4 weeks *(or 5 half-lives, whichever is shorter)* from the last dose of the previous investigational agent to date of registration.

4.2.3 Has tumor primarily localized to the brainstem or spinal cord.

4.2.4 Has presence of multifocal tumor, diffuse leptomeningeal or extracranial disease.

NOTE: Not all instances of multifocal disease will exclude a potential patient; only patients with multifocal sites of *active disease* will be excluded. (e.g. A patient with a previously treated lesion that remains stable would not be excluded.)

Medical History/Conditions/Concomitant Medical Illnesses:

4.2.5 Has a diagnosis of immunodeficiency.

4.2.6 Has a history or current evidence of any condition, therapy, or laboratory abnormality that might confound the results of the trial, interfere with the participant's participation for the full duration of the trial, or is not in the best interest of the participant to participate, in the opinion of the treating investigator. Examples include - but are not limited to - unstable angina pectoris, cardiac arrhythmia or psychiatric illness/social situations that would limit compliance with study requirements.

4.2.7 Has history of known coagulopathy that increases risk of bleeding or a history of clinically significant hemorrhage within 12 months of start of study drug.

4.2.8 Has evidence of intratumoral or peritumoral hemorrhage on baseline MRI scan other than those that are grade ≤ 1 and either post-operative or stable on at least 2 consecutive MRI scans.

4.2.9 Has gastrointestinal bleeding or any other hemorrhage/bleeding event CTCAE Grade > 3 within 6 months of start of study drug.

4.2.10 Has a known additional malignancy that is progressing or requires active treatment within 1 year of start of study drug, except for those treated with surgical therapy only (e.g. basal cell carcinoma of the skin, squamous cell carcinoma of the skin, or in situ cervical cancer that has undergone potentially curative therapy).

4.2.11 Has active autoimmune disease requiring systemic treatment in the past 2 years (i.e. with use of disease modifying agents, corticosteroids or immunosuppressive drugs). Replacement therapy (eg thyroxine, insulin, or physiologic corticosteroid replacement for adrenal insufficiency or pituitary/hypothalamic dysfunction, etc.) is not considered a form of systemic treatment.

4.2.12 Has history of (non-infectious) pneumonitis that required steroids or has current pneumonitis.

4.2.13 Has an active infection requiring systemic therapy.

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

4.2.15 Has a known history of Human Immunodeficiency Virus (HIV) (HIV 1/2 antibodies) and is receiving antiretroviral therapy. Such patients are ineligible because of the potential for pharmacokinetic interactions with pembrolizumab and because these participants are at increased risk of lethal infections. Appropriate studies will be undertaken in participants receiving combination antiretroviral therapy when indicated.

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

4.2.17 Has a history of non-healing wounds or ulcers, or bone refractures within 3 months of fracture.

4.2.18 Has a history of arterial thromboembolism within 12 months of start of study drug.

4.2.19 Has had clinically significant cardiovascular disease within 12 months of start of study drug, including myocardial infarction, unstable angina, grade 2 or greater peripheral vascular disease, cerebrovascular accident, transient ischemic attack, congestive heart failure, or arrhythmias not controlled by outpatient medication, percutaneous transluminal coronary angioplasty/stent.

4.2.20 Has a known history of active TB (Bacillus Tuberculosis)

4.2.21 Has a known hypersensitivity to any of the study therapy products and/or any of their excipients.

4.2.22 Is pregnant or breastfeeding, or expecting to conceive within the projected duration of the trial, starting with the screening visit through 120 days after the last dose of trial treatment. Pregnant women are excluded because there is an unknown but potential risk for adverse events affecting a developing fetus and/or the mother secondary to treatment with pembrolizumab. There is also an unknown but potential risk for adverse events affecting nursing infants secondary to treatment of the mother with pembrolizumab, thus, breastfeeding must be discontinued if the mother is treated with pembrolizumab.

Prior Therapy:

4.2.23 Has received prior interstitial brachytherapy, implanted chemotherapy, stereotactic radiosurgery or therapeutics delivered by local injection or convection enhanced delivery (this exclusion applies to any locally administered therapy, including intratumoral vaccines).

4.2.24 Has received prior therapy with an anti-PD-1, anti-PD-L1, or anti-PD-L2 or with an agent directed to another stimulatory or co-stimulatory T-cell receptor (eg CTLA-4, OX-40, CD137)

4.2.25 Has received prior VEGF or VEGFR inhibitor therapy such as bevacizumab, cediranib, aflibercept, vandetanib, XL-184, sunitinib, etc. (Cohort A only)

Other Meds:

4.2.26 Is receiving any form of immunosuppressive therapy (e.g. chronic systemic steroid therapy exceeding dosage of 10 mg daily of prednisone equivalent) within 7 days prior to the first dose of study drug.

4.2.27 Has received systemic immunosuppressive treatments, aside from systemic corticosteroids as described in Section 4.2.28 (such as methotrexate, chloroquine, azathioprine, etc), within six months of start of study drug.

4.2.28 Requires treatment with high dose systemic corticosteroids defined as dexamethasone > 2 mg/day or bioequivalent for at least 3 consecutive days within 2 weeks of start of study drug.

- *Inhaled or topical steroids and adrenal replacement doses > 10 mg daily prednisone equivalents are permitted in the absence of active autoimmune disease.*
- *Participants are permitted to use topical, ocular, intra-articular, intranasal, and inhalational corticosteroids (with minimal systemic absorption).*
- *Physiologic replacement doses of systemic corticosteroids are permitted, even if > 10 mg/day prednisone equivalents.*
- *A brief course of corticosteroids for prophylaxis (eg, contrast dye allergy) or for treatment of non-autoimmune conditions (eg, delayed-type hypersensitivity reaction caused by contact allergen) is permitted.*

4.2.29 Requires therapeutic anticoagulation with warfarin at baseline; patients must be off warfarin or warfarin-derivative anti-coagulants for at least 7 days prior to starting study drug; however, therapeutic or prophylactic therapy with low-molecular weight heparin is allowed.

4.2.30 Has received a live vaccine within 30 days prior to the first dose of study drug.
Examples of live vaccines include - but are not limited to - the following: measles, mumps, rubella, varicella/zoster (chicken pox), yellow fever, rabies, Bacillus Calmette–Guérin (BCG), and typhoid vaccine. Seasonal influenza vaccines for injection are generally killed virus vaccines and are allowed; however, intranasal influenza vaccines (eg, FluMist®) are live attenuated vaccines and are not allowed.

4.3 Inclusion of Women and Minorities

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

5. REGISTRATION PROCEDURES

All sites should call the Study Coordinator at 617-582-7101 or email to NeuroOnc_Coor@dfci.harvard.edu to verify slot availability.

5.1 General Guidelines for DF/HCC Institutions

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

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

Following registration, participants may begin protocol therapy. Issues that would cause treatment delays should be discussed with the Overall Principal Investigator (PI). If a participant does not receive protocol therapy following registration, the participant must be taken off-study in the CTMS (OnCore) with an appropriate date and reason entered.

5.2 Registration Process for DF/HCC Institutions

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

5.3 General Guidelines for Other Investigative Sites

Eligible participants will be entered on study centrally at the Dana-Farber Cancer Institute by the DFCI Coordinating Center staff. All sites should contact the DFCI Coordinating Center to verify slot availabilities. A list of required forms can be found in Appendix E.

Following registration, participants should begin protocol therapy within 7 days. Issues that would cause treatment delays should be discussed with the Overall PI. If there is an issue with meeting this specified timeframe, please contact study's Overall PI for documented prospective approval. If a participant does not receive protocol therapy within 7 days following registration, and study's Overall PI has not approved the delay, the participant must be taken off-study in the CTMS (OnCore) with an appropriate date and reason entered. The DFCI Coordinating Center should be notified of potential delays and participants not proceeding to receive study treatment as scheduled as soon as possible.

5.4 Registration Process for Other Investigative Sites

Please refer to Appendix E (Section 3.7) for registration details.

6. TREATMENT PLAN

This is a multicenter, open-label, phase II trial of pembrolizumab with re-irradiation among recurrent glioblastoma patients enrolled to two parallel non-comparative treatment arms including patients who are bevacizumab naïve (Cohort A) and those who have progressed on one prior bevacizumab regimen (Cohort B). The combinatorial regimens assessed for each cohort have not been formally evaluated for toxicity, thus an initial safety lead-in will be performed to define the maximum tolerated dose (MTD)/recommended phase 2 dose (RP2D) of pembrolizumab when administered with re-irradiation (Cohort A) and when administered with re-irradiation and bevacizumab (Cohort B) as detailed below. Of note, the adverse event profiles of pembrolizumab, radiation therapy and bevacizumab are in general non-overlapping, thus the agents are expected to be well tolerated when co-administered. The dose of pembrolizumab administered during the safety lead-in will not exceed the established phase II dose of pembrolizumab when administered as monotherapy. The safety lead-in also incorporates a de-escalation of pembrolizumab dosing if unexpected dose-limiting toxicity is observed and follows standard 3+3 phase I guidelines. No investigational or commercial agents or therapies other than those described below may be administered with the intent to treat the participant's malignancy. Reported adverse events and potential risks are described in Section 8. Appropriate dose modifications are described in Section 7.

6.1 Safety Lead-In Treatment Regimen

The safety lead-in will utilize a standard 3+3 design to determine the RP2D/MTD of pembrolizumab for each cohort. Pembrolizumab will initially be administered at 200 mg (flat dosing) intravenously (IV) every 3 weeks, which is the RP2D established for monotherapy administration. The dose of pembrolizumab administered during the safety lead-in will not exceed 200 mg IV every 3 weeks. Bevacizumab will be administered at 15 mg/kg IV every 3 weeks for Cohort B. The first 6 patients for each cohort will be considered as safety lead-in and observed in groups of 3 for DLTs for an evaluation period of 42 days (see DLT definitions in Section 6.1.1) as follows for each cohort:

- If at Dose Level 0, ≤1 of the first 3 patients develop DLT, 3 more patients will be enrolled to Dose Level 0.
- If at Dose Level 0, >1 of the first 3 patients or >1 of the first 6 patients develop DLT, cohort enrollment will be stopped immediately, and re-started from the beginning with 3+3 patients enrolled at a pembrolizumab dosing interval of 4 weeks (Dose Level -1).
- If at Dose Level -1, >1 of the first 3 patients or >1 of 6 patients develop DLT, cohort enrollment will be stopped immediately, and re-started from the beginning with 3+3 patients enrolled at a pembrolizumab dosing interval of 6 weeks (Dose Level -2).
- If at Dose level -2, >1 of the first 6 patients develops DLT, the safety lead-in will be discontinued. In this case, the phase II portion of this study to the two independent cohorts will not be conducted.

NOTE: Patients will need to be assessed on or after their actual Day 42 on treatment for the DLT assessment to be considered comprehensive.

Dose-limiting toxicities (DLT) will be determined by toxicities related to pembrolizumab during or beginning over the first 42 days of treatment as defined below in Section 5.1.1.

Any necessary dose de-escalations will be made by extending the dosing interval of pembrolizumab as detailed below (Table 3):

Table 3 Dose levels and doses to be evaluated in Safety Lead-In

	Pembrolizumab (Cohorts A&B)		**Bevacizumab (Cohort B)**	
Dose Level	**Dose (mg)**	**Frequency**	**Dose (mg/kg)**	**Frequency**
Zero (0)	200	Every 3 weeks	15	Every 3 weeks
Minus one (-1)	200	Every 4 weeks	15	Every 3 weeks
Minus two (-2)	200	Every 6 weeks	15	Every 3 weeks

6.1.1 Definition of Dose-Limiting Toxicity (DLT)

A DLT is defined as any grade ≥ 3 adverse event that is at least possibly, probably or definitely related to pembrolizumab during the DLT period unless judged by the treating Investigator to be more likely related to underlying tumor, concurrent medication or co-morbid event. The DLT period is considered the first 42 days of study therapy; the DLT period does not necessarily need to include labs and other evaluations taken during cycle 3 restaging). Events that are considered unlikely related to pembrolizumab, but at least probably related to bevacizumab will not be considered a DLT.

The following exceptions will not be classified as DLT:

- Grade 3 Immune-related adverse events (irAEs – see definition below) that downgrade to Grade ≤ 2 within 5 days, or to Grade ≤ 1 or baseline within 14 days after onset of the event, whereby maximal supportive care, including systemic corticosteroids, is permitted.
- Grade 3 asymptomatic endocrinopathy, managed with or without systemic corticosteroid therapy and/or hormone replacement therapy.
- Grade 3 inflammatory reaction attributed to a local antitumor response (e.g., inflammatory reaction at sites of metastatic disease, lymph nodes, etc).
- Grade 2 pneumonitis, neurological event, or uveitis that downgrades to Grade ≤ 1 within 3 days, whereby maximal supportive care is permitted.
- Liver transaminase elevation ≤ 8 times institutional ULN.
- Total bilirubin ≤ 5 times institutional ULN.
- Any pre-existing lab abnormality that deteriorates to Grade 3/4, but where the increment of deterioration is considered not clinically significant by Investigator, overall study Principal Investigator and sponsor.

DLT will also include grade 2 immune-related adverse events that occur during the DLT period defined above that require interruption of pembrolizumab and do not improve to grade ≤ 1 with appropriate supportive care and symptomatic treatment with 14 days.

Immune-related adverse events (irAEs) are defined as AEs of immune nature (i.e., inflammatory) in the absence of a clear alternative etiology. In the absence of clinical abnormality, repeat laboratory testing will be conducted to confirm significant laboratory findings prior to designation as a DLT.

While rules for adjudicating DLTs are specified above, an AE of Grade < 3 (except if listed as exempt above), may also be defined as a DLT after a consultation with the Sponsor and the overall study Principal Investigator, based on the established safety profile of pembrolizumab.

Patients who experience DLT will be discontinued from study therapy and will enter the post-study follow-up phase of the study (see Section 6.9-6.12).

Adverse events that meet DLT criteria but occur outside the DLT window will be classified as unacceptable AEs and study treatment will be discontinued per Section 6.8

6.2 Phase II Treatment Regimen

The dose of pembrolizumab to be administered in this trial for all patients (cohort A and cohort B) is 200 mg (flat dosing) every three weeks intravenously because this is the FDA approved dosing schedule for melanoma, non-small cell lung cancer, head and neck squamous cell carcinoma, classical Hodgkin's lymphoma, urothelial carcinoma and microsatellite instability-high cancers (see pembrolizumab package insert). Re-irradiation will be administered to patients on cohort A and cohort B to achieve 35 Gy over ten fractions. Patients on Cohort B who have previously progressed on bevacizumab will continue bevacizumab – or biosimilar - at a dose of 15 mg/kg intravenously every three weeks.

Eligible, bevacizumab-naive patients will enroll to receive pembrolizumab plus re-irradiation (Cohort A; n=30). Eligible patients who have progressed on one prior bevacizumab regimen will enroll to receive pembrolizumab plus re-irradiation plus bevacizumab (or biosimilar) continuation (Cohort B; n=30). The outcome of each treatment arm will be assessed separately relative to appropriate historical controls.

Each treatment cycle for both cohorts will be 3 weeks (21 days).

The therapeutic agents to be used in this trial are outlined below in Table 3.

Table 3. Trial Treatment Overview

Treatment	Cohort	Dose/ Potency	Dose Frequency (& window)	Route of Administration	Treatment Period	Use
Pembrolizumab	A & B	200 mg	Q3W (+/- 3 days)	IV infusion	Day 1 of each cycle	Experimental
Re-irradiation	A & B	35 Gy	Daily	External beam	5 days/ week x 2 weeks	Standard of care
Bevacizumab (or biosimilar)	B	15 mg/kg	Q3W (+/- 3 days)	IV infusion	Day 1 of each cycle	Standard of care

Trial treatment should begin as close as possible to the date on which the participant is registered. See Section 5.3.

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 trial treatments in accordance with the protocol and any applicable laws and regulations.

6.3 Allocation of accrual to two parallel non-comparative treatment arms

Patients meeting eligibility criteria will be enrolled to the appropriate treatment cohort of the study at the time of registration in the Clinical Trials Management System (CTMS) OnCore directly by their Study Team (for DF/HCC patients) or by DFCI Coordinating Center Staff (for External Sites); see Section 5. The outcome for each treatment arm will be assessed separately relative to appropriate historical controls.

6.3.1 Trial Blinding/Masking

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

6.3.2 Stratification

Participants on this trial will be stratified to either Cohort A or Cohort B based on previous treatment with bevacizumab.

6.4 Patient Evaluability and Replacement

The analysis of the primary endpoint will be based on both the intent-to-treat (ITT) and the per-protocol (PP) populations. Patients who receive at least one dose of pembrolizumab and at least baseline and one post-baseline disease assessment will be included in the ITT population. Patients who receive at least 75% of the planned study re-irradiation therapy doses for each cohort and at least one dose of pembrolizumab, as well as respective disease assessments, without major protocol violations, are considered fully evaluable and will be included in the PP population.

6.5 Agent Administration

Trial treatment should be administered after all procedures/assessments have been completed as detailed on the Study Calendar (Section 11.0).

Order of Administration:

- For cohort B participants: On days when participants receive both pembrolizumab and bevacizumab (or biosimilar), pembrolizumab will be administered first (see section 6.4.1 for more information).
- For all participants: When radiation is received on the same day as another study agent, it does not matter whether radiation is given before or after the other study agent(s).

Trial treatment may be administered up to 3 days before or after the scheduled day of each cycle due to administrative reasons. All study treatments are anticipated to be administered on an outpatient basis; however, inpatient administration is permitted.

6.5.1 Pembrolizumab Administration

The rationale for selection of doses to be used in this trial is provided in Section 3.4.2 – Background and Rationale.

The dose amount required to prepare the pembrolizumab infusion solution will be 200 mg (flat dosing) for patients enrolled to both cohorts of this study. Pembrolizumab will start within 1 week of the start of re-irradiation and will then be administered at a dose frequency of every 3 weeks (+/-3 days), on Day 1 of each 21-day treatment cycle. Pembrolizumab will be

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

For cohort B participants receiving pembrolizumab and bevacizumab (or biosimilar), pembrolizumab will be administered first, and bevacizumab (or biosimilar) will begin no sooner than 1 hour after completion of pembrolizumab for the first cycle of therapy. Thereafter bevacizumab (or biosimilar) may begin upon completion of pembrolizumab.

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

Pembrolizumab will be provided to patients enrolled on this study by Merck Pharmaceuticals.

6.5.2 **Re-irradiation**

Fractionated radiotherapy will be administered according to established, standard-of-care guidelines utilizing intensity-modulated radiation therapy (IMRT), 3-dimensional conformal radiation therapy (3D-CRT) or proton beam radiation therapy at a dose of 3.5 Gy/fraction times 10 fractions (5 days a week for 2 weeks). Daily image-guided radiation therapy (IGRT) is required including non-volumetric (orthogonal or near-orthogonal 2D imaging that is integrated with the radiation delivery device) and volumetric (diagnostic CT, cone beam CT with MV or kV X-ray beam, MRI-linac or tomotherapy technology) systems. Please refer to Appendix H for Recommended Radiation Therapy Guidelines (to be provided to radiation oncologist).

Participants are permitted to receive re-irradiation on study as described in this section (and Appendix H) at the following locations:

a. the Radiation Oncology Department of the participating institution;
b. an IRB-approved satellite site of the participating institution;
c. any NRG Oncology-approved site;
d. or at another location, with **prior documented approval from the study's Overall PI**.

Re-irradiation will ideally start on Day 1 of pembrolizumab/bevacizumab (or biosimilar) Cycle 1, but can start +/- 7 days from C1D1.

6.5.3 **Bevacizumab (or biosimilar)* Administration**

* DFCI recently released a guideline re: the use of commercial biosimilars in clinical trials, which states: "for standard of care treatment using biologic products in a clinical trial that are not paid for by sponsor and that are billed as standard of care to patient's insurance, the biosimilar products dictated by the patient's insurance would be used." Therefore, on this study, sponsor will allow the use of a bevacizumab biosimilar.

For cohort B participants receiving pembrolizumab and bevacizumab (or biosimilar), bevacizumab (or biosimilar) will be dosed at 15 mg/kg intravenously every 3 weeks (+/- 3 days), on Day 1 of each 21-day treatment cycle. Doses of bevacizumab (or biosimilar) must be at least 10 days apart. The baseline weight of the participant will be used to calculate the bevacizumab (or biosimilar) dose unless there is a $\geq$ 10% change during the course of the study. Alternatively, institutional standard practice for weight-based dose re-calculations can be utilized for bevacizumab (or biosimilar) dosing, provided site gets Overall PI's documented approval to do so prospectively. The rationale for the selection of bevacizumab (or biosimilar) dosing used in

this study is provided in the bevacizumab package insert. Bevacizumab (or biosimilar) will begin with the first pembrolizumab dose. The bevacizumab (or biosimilar) infusion will begin no sooner than 1 hour after completion of pembrolizumab for the first cycle of therapy. Thereafter bevacizumab (or biosimilar) may begin upon completion of pembrolizumab whenever both infusions fall on the same day. Bevacizumab (or biosimilar) should be stored, prepared and administered in accordance with each site's institutional standards.

6.6 Pre-Treatment Criteria

6.6.1 Initiation of Pembrolizumab and Re-irradiation (Cycle 1, day 1)

Initiation of pembrolizumab and re-irradiation (plus bevacizumab - or biosimilar - for Cohort B participants) will commence for patients meeting clinical and laboratory eligibility criteria defined in Section 4. Results of assessments performed during eligibility screening (within 14 days of initiation of study therapy) will be sufficient to start study therapy and will not need to be repeated prior to Cycle 1, day 1.

6.6.2 Subsequent Cycles

PEMBROLIZUMAB: Pembrolizumab dosing will continue every 3 weeks (+/- 3 days) unless criteria for dose interruption (Section 7.2) or study therapy discontinuation criteria (Section 6.7) are met. In the event of a dose delay, dosing will be resumed when criteria to resume treatment (Section 7.2) are met.

BEVACIZUMAB (OR BIOSIMILAR): For cohort B participants, bevacizumab (or biosimilar) will continue every 3 weeks (+/- 3 days) unless criteria for dose delay (Section 7.4) or study discontinuation criteria (Section 6.7) are met. In the event of a dose delay, dosing will be resumed when criteria to resume treatment (Section 7.4) are met.

IN THE EVENT OF A DOSE DELAY ON COHORT B:

In the event that both study drugs are held, dosing with either drug will resume when criteria to resume treatment with that drug are met (Section 7.2 for pembrolizumab and Section 7.4 for bevacizumab – or biosimilar).

NOTE: In the event that only one study drug is held, treatment with that drug will not be provided mid-cycle; that cycle's dose will be skipped and treatment with that drug will resume on Day 1 of the subsequent cycle, provided criteria to restart treatment is met at that time.

6.7 General Concomitant Medication and Supportive Care Guidelines

Medications or vaccinations specifically prohibited in the exclusion criteria (Sections 4.2 & 6.6.2) are not allowed during the ongoing trial except as outlined below. 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 treating investigator should discuss any questions regarding this with the sponsor and the overall study PI or his designee. The final decision on any supportive therapy or vaccination rests with the treating physician. However, the decision to continue the participant on trial therapy or vaccination schedule requires the mutual agreement of the Investigator, Sponsor & Overall study PI or his designee, and the participant.

6.7.1 **Acceptable Concomitant Medications**

All treatments that the investigator considers necessary for a participant'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 8.4.4.2.

6.7.2 **Prohibited Concomitant Medications**

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

- Anti-cancer systemic chemotherapy or biological therapy
- Immunotherapy not specified in this protocol
- Chemotherapy not specified in this protocol
- Investigational agents other than pembrolizumab
- Radiation therapy not specified in this protocol
- Live vaccines within 30 days prior to the first dose of study treatment and while participating in the study. Examples of live vaccines include, but are not limited to, the following: measles, mumps, rubella, varicella/zoster, yellow fever, rabies, BCG, and typhoid vaccine. Seasonal influenza vaccines for injection are generally killed virus vaccines and are allowed; however, intranasal influenza vaccines (eg, FluMist®) are live attenuated vaccines and are not allowed.
- Systemic glucocorticoids for any purpose other than to modulate symptoms from an event of clinical interest of suspected immunologic etiology or for the treatment of cerebral edema or supportive post-operative management. The use of physiologic replacement doses of corticosteroids for conditions such as adrenal insufficiency and pituitary/hypothalamic dysfunction are allowed.

Participants who, in the assessment by the investigator, require the use of any of the aforementioned treatments for clinical management should be removed from the study. All treatments that the Investigator considers necessary for a participant's welfare may be administered at the discretion of the Investigator in keeping with the community standards of medical care.

Medications or vaccinations specifically prohibited in the exclusion criteria are not allowed during the ongoing study. If there is a clinical indication for any medication or vaccination specifically prohibited during the study, discontinuation from study therapy or vaccination may be required. The final decision on any supportive therapy or vaccination rests with the investigator and/or the participant's primary physician. However, the decision to continue the participant on study treatment requires the mutual agreement of the investigator, the Sponsor and the participant.

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

6.7.3 General Supportive Care Guidelines

Participants should receive appropriate supportive care measures as deemed necessary by the treating investigator. Suggested supportive care measures for the management of AEs with potential immunologic etiology are outlined in Section 6.6.4 along with the pembrolizumab dose modification guidelines in Section 7.2. Where appropriate, these guidelines include the use of oral or IV treatment with corticosteroids, as well as additional anti-inflammatory agents if symptoms do not improve with administration of corticosteroids. Note that several courses of steroid tapering may be necessary as symptoms may worsen when the steroid dose is decreased. For each disorder, attempts should be made to rule out other causes such as metastatic disease or bacterial or viral infection, which might require additional supportive care. The treatment guidelines are intended to be applied when the Investigator determines the events to be related to pembrolizumab.

Participants should receive appropriate supportive care measures as deemed necessary by the treating investigator including but not limited to the items outlined below:

- 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. Participants should be strongly encouraged to maintain liberal oral fluid intake.
- Infection: Participants 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 6.6.4 below regarding diagnosis and management of adverse experiences of a potential immunologic etiology.

6.7.4 Supportive Care Guidelines

Participants should receive appropriate supportive care measures as deemed necessary by the treating Investigator. Suggested supportive care measures for the management of AEs with potential immunologic etiology are outlined below and in Section 7.2. Where appropriate, these guidelines include the use of oral or IV treatment with corticosteroids as well as additional anti-inflammatory agents if symptoms do not improve with administration of corticosteroids. Note that several courses of steroid tapering may be necessary as symptoms may worsen when the steroid dose is decreased. For each disorder, attempts should be made to rule out other causes such as metastatic disease or bacterial or viral infection, which might require additional supportive care. The treatment guidelines are intended to be applied when the Investigator determines the events to be related to pembrolizumab.

Note: If after the evaluation, the event is determined not to be related, the Investigator does not need to follow the treatment guidance (as outlined below and Section 7.2).

It may be necessary to perform conditional procedures such as bronchoscopy, endoscopy, or skin photography as part of evaluation of the event. Additional guidance for organ specific immune-related adverse events includes:

6.7.4.1 Pneumonitis:

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

- For **Grade 3-4 events**, immediately treat with intravenous steroids. Administer additional anti-inflammatory measures, as needed.
- Add prophylactic antibiotics for opportunistic infections in the case of prolonged steroid administration.

6.7.4.2 **Diarrhea/Colitis:**

Participants 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 participants, infectious etiologies should be ruled out, and if symptoms are persistent and/or severe, endoscopic evaluation should be considered.

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

6.7.4.3 **T1DM** or **Grade 3-4 hyperglycemia**

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

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

6.7.4.4 **Hypophysitis:**

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

6.7.4.5 **Hyperthyroidism or hypothyroidism:**

Thyroid disorders can occur at any time during treatment. Monitor participants 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 hyper**thyroidism events (and Grade 2-4 hypothyroidism):
  - In hyperthyroidism, non-selective beta-blockers (e.g. propranolol) are suggested as initial therapy.
  - In hypothyroidism, thyroid hormone replacement therapy, with levothyroxine or liothyronine, is indicated per standard of care.

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

6.7.4.6 **Hepatic:**

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

6.7.4.7 **Renal failure or nephritis:**

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

6.7.4.8 **Management of Infusion Reactions**:

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

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

Table 4. Pembrolizumab Infusion Reaction Treatment Guidelines

NCI CTCAE Grade	Treatment	Premedication at Subsequent Dosing
Grade 1 Mild reaction; infusion interruption not indicated; intervention not indicated	Increase monitoring of vital signs as medically indicated until the participant is deemed medically stable in the opinion of the investigator.	None
Grade 2	**Stop Infusion and monitor symptoms.**	Subject may be

NCI CTCAE Grade	Treatment	Premedication at Subsequent Dosing
Requires therapy or infusion interruption but responds promptly to symptomatic treatment (e.g., antihistamines, NSAIDs, narcotics, IV fluids); prophylactic medications indicated for ≤24 hrs	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 participant 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. **Participants who develop Grade 2 toxicity despite adequate premedication should be permanently discontinued from further administration of pembrolizumab on study.**	premedicated 1.5h (± 30 minutes) prior to infusion of pembrolizumab with: Diphenhydramine 50 mg po (or equivalent dose of antihistamine). Acetaminophen 500-1000 mg po (or equivalent dose of antipyretic).
Grades 3 or 4 Grade 3: Prolonged (i.e., not rapidly responsive to symptomatic medication and/or brief interruption of infusion); recurrence of symptoms following initial improvement; hospitalization indicated for other clinical sequelae (e.g., renal impairment, pulmonary infiltrates) Grade 4: Life-threatening; pressor or ventilatory support indicated	**Stop Infusion.** Additional appropriate medical therapy may include but is not limited to: Epinephrine** IV fluids Antihistamines NSAIDS Acetaminophen Narcotics Oxygen Pressors Corticosteroids Increase monitoring of vital signs as medically indicated until the participant is deemed medically stable in the opinion of the investigator. Hospitalization may be indicated. **In cases of anaphylaxis, epinephrine should be used immediately. **Participant is permanently discontinued from further administration of pembrolizumab on study.**	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		

6.7.4.1 Cerebral Edema

Due to the immunologic nature of anti-PD-1 therapy administration, cerebral edema could theoretically result as a consequence of anti-PD-1 therapy administration due to immune infiltration of the brain. In addition, re-irradiation is expected to elicit cerebral edema.[60] Symptoms related to cerebral edema may include headache or neurologic deficit that is either new or worsened. Participants with any signs or symptoms of cerebral edema in the investigator's judgement should be treated as clinically appropriate including initiation or increased systemic corticosteroid dosing, treatment with an osmotic diuretic or surgical decompression. Subsequent pembrolizumab dosing should be immediately interrupted if significant clinical symptoms attributable to cerebral edema in the investigator's judgement develop. Treatment with additional pembrolizumab doses may only be re-initiated if clinically significant symptoms attributable to cerebral edema have stabilized or significantly resolved in the investigator's judgement. Participants who develop gr 4 cerebral edema (CTCAE v.4) attributable to pembrolizumab administration in the investigator's judgement should not receive further pembrolizumab doses. Of note, gr 4 cerebral edema (CTCAE v.4) is defined as life-threatening or requiring urgent intervention. For this study, urgent intervention refers to interventions such as intensive care (ICU) admission, intubation for hyperventilation, administration of hypertonic or hyperosmotic agents and surgical decompression.

6.7.4.2 Other Central Nervous System (CNS) Toxicity

Anti-PD-1 therapy can rarely cause adverse events involving the peripheral and central nervous system including, but not limited to: neuropathy, myasthenia gravis, aseptic meningitis, paraneoplastic syndromes and encephalitis.[61] For suspected immune-mediated adverse reactions affecting the CNS, ensure adequate evaluation to confirm etiology or exclude other causes. Based on the severity of the CNS adverse reaction, withhold pembrolizumab and administer corticosteroids. Upon improvement to Grade 1 or less, initiate corticosteroid taper and consider continuing a gradual taper over at least 1 month. Based on limited data from clinical studies in patients whose CNS immune-related adverse reactions could not be controlled with corticosteroid use, administration of other systemic immunosuppressants can be considered. Resume pembrolizumab when the CNS immune-mediated adverse reaction remains at Grade 1 or less following corticosteroid taper. Permanently discontinue pembrolizumab for any Grade ≥ 3 CNS immune-mediated adverse reaction and for any life-threatening immune-mediated adverse reaction.

6.7.4.3 Hypertension

For grade ≥ 2, consider initiation of anti-hypertensive therapy per institutional guidelines.

6.7.5 Diet/Activity/Other Considerations

6.7.5.1 Diet

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

6.7.5.2 Contraception

Pembrolizumab and bevacizumab (or biosimilar) may have adverse effects on a fetus in utero. Refer to Section 4.1.14 for approved methods of contraception for female participants who are WOCP (defined in Section 4.1.13), and refer to Section 4.1.15 for approved methods of contraception for male participants.

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

6.7.5.3 Use in Pregnancy

If a participant inadvertently becomes pregnant while on treatment with pembrolizumab, the participant will be immediately discontinued from study treatment. The site will contact the participant at least monthly and document the participant's status until the pregnancy has been completed or terminated. The outcome of the pregnancy will be reported to Merck within 2 working days if the outcome is a serious adverse experience (eg, death, abortion, congenital anomaly, or other disabling or life-threatening complication to the mother or newborn). The study Investigator will make every effort to obtain permission to follow the outcome of the pregnancy and report the condition of the fetus or newborn to Merck. If a male participant impregnates his female partner, the study personnel at the site must be informed immediately.

6.7.5.4 Use in Nursing Women

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

6.8 Duration of Therapy and Criteria for Taking Participants Off Protocol Treatment

Duration of therapy will depend on individual response, evidence of disease progression and tolerance. In the absence of treatment delays due to adverse event(s), study treatment may continue up to completion of 35 pembrolizumab treatments (approximately 2 years), or until one of the following criteria applies:

- Disease progression (see modified RANO criteria and confirmation of disease progression criteria in Sections 12.2 and 12.5)
- Unacceptable adverse event(s)
- Recurrent Grade 2 pneumonitis
- Any clinical adverse event (AE), laboratory abnormality or intercurrent illness which, in the opinion of the investigator and/or sponsor, places the participant at unnecessary risk from continued administration of study treatment.
- General or specific changes in the participant's condition render the participant unacceptable for further treatment in the judgment of the treating investigator
- Any progression or recurrence of any malignancy, or any occurrence of another malignancy that requires active treatment
- The participant has a confirmed positive serum pregnancy test
- Noncompliance with trial treatment or procedure requirements
- Investigator's decision to withdraw the subject
- Participant decides to withdraw from the protocol therapy
- The subject or legal representative (such as a parent or legal guardian) withdraws consent.
- The participant is lost to follow-up
- Termination of the trial by the study's sponsor.

Participants will be removed from the protocol therapy when any of these criteria apply. The reason for removal from protocol therapy, and the date the participant was removed, must be documented in the case report form (CRF). Alternative care options will be discussed with the participant.

When a participant is removed from protocol therapy and/or is off of the study, the relevant Off-Treatment/Off-Study information will be updated in OnCore.

In the event of unusual or life-threatening complications, treating investigators must immediately notify the Overall PI, David A. Reardon, M.D. at 617-632-4750 or 617-632-3352, pager 43339.

6.9 Post-Therapy Adverse Events

After the end of treatment, all participants will be followed for 30 days for adverse event monitoring and 90 days for serious adverse event reporting (or until death, whichever occurs first).

Participants removed from protocol therapy for unacceptable adverse event(s) will be followed until resolution or stabilization of the adverse event.

6.10 End of Treatment Evaluation and 30-day Post Last Dose Follow-Up

Procedures to be conducted at both the 'End of Treatment' and '30-day Post Last Dose Follow-up' visits are listed in the Study Calendar (Section 11).

6.11 Active Follow-Up

Participants who discontinue for reasons other than progressive disease will have post-treatment follow-up for disease status until disease progression, initiating a non-study cancer treatment, withdrawing consent or becoming lost to follow-up. See Study Calendar (Section 11) for visit frequency (and acceptable windows).

6.12 Long-term Follow-Up

After documented disease progression, participants will be followed by telephone or medical record review for overall survival until they meet criteria for removal from study as detailed below. See Study Calendar (Section 11) for visit frequency (and acceptable windows).

6.13 Criteria for Taking a Participant Off Study

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

- Lost to follow-up
- Withdrawal of consent for data submission
- Death
- Sponsor decides to terminate the study

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

In addition, the study team will ensure Off Treatment/Off Study information is updated in OnCore in accordance with DF/HCC policy REGIST-101.

6.13.1 **Withdrawal of Informed Consent**

Participants who request to discontinue study treatment will remain in the study and must continue to be followed for protocol specified follow-up procedures. The only exception to this is when a participant specifically withdraws consent for any further contact with him/her or persons previously authorized by subject to provide this information. Participants should notify the investigator of the decision to withdraw consent from future follow-up in writing, whenever possible. The withdrawal of consent should be explained in detail in the medical records by the investigator, as to whether the withdrawal is from further treatment with study drug only or also from study procedures and/or post treatment study follow-up, and entered on the appropriate CRF page. In the event that vital status (whether the participant is alive or dead) is being measured, publicly available information should be used to determine vital status only as appropriately directed in accordance with local law.

6.13.2 **Lost to Follow-Up**

All reasonable efforts must be made to locate participants to determine and report their ongoing status. This includes follow-up with persons authorized by the participant as noted above. Lost to follow-up is defined by the inability to reach the participant after a minimum of three documented phone calls, faxes, or emails as well as lack of response by participant to one registered mail letter. All attempts should be documented in the participant's medical records. If it is determined that the participant has died, the site will use permissible local methods to obtain the date and cause of death.

The site staff and representative will consult publicly available sources, such as public health registries and databases, in order to obtain updated contact information. If after all attempts, the participant remains lost to follow-up, then the last known alive date as determined by the investigator should be reported and documented in the participant's medical records.

6.14 Participant Replacement Strategy

Additional participants may be enrolled in a given cohort to ensure that the required number of evaluable participants in each cohort is achieved. A participant that discontinues the trial for progressive disease or a drug-related AE will not be replaced and will be counted in the evaluable population of participants for the respective cohort.

6.15 Beginning and End of the Trial

The study begins when the first participant signs the informed consent form. The end of the study may be designated as the time point when all participants have discontinued the study or are a minimum of 6 months post initial study medication administration. If, by the end of the study, there remains at least 1 participant still on study treatment for at least 6 months, the participant(s) may enter additional treatment cycles.

The participant is considered on study until such time that s/he meets any of the discontinuation criteria and notification is given to the Sponsor.

6.16 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 participants
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 participant treatment can be made.

7. DOSING DELAYS/DOSE MODIFICATIONS

Dose delays and modifications will be made as indicated below. The descriptions and grading scales found in the revised NCI Common Terminology Criteria for Adverse Events (CTCAE) version 4.0 will be utilized for dose delays and dose modifications. A copy of the CTCAE version 4.0 can be downloaded from the CTEP website http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm.

7.1 Dose Selection/Modification: General Information

7.1.1 Baseline values are from screening assessments. Whenever treatment is held pending resolution of toxicity to grade 1 or return to baseline, this criterion may also be met if the toxicity resolves to within 1 grade of the baseline value for a pre-existing laboratory abnormality.

7.1.2 Participants who experience an adverse event that requires a treatment delay should be monitored with appropriate laboratory testing or other clinical evaluation at least weekly until resolution; if the adverse event does not resolve within 4 weeks, the interval for testing may be reduced after consultation and written approval by the Overall Principal Investigator (or his designee).

7.1.3 For Cohort A participants:

7.1.3.1 In the event of a treatment delay due to a toxicity, the cycle count should be interrupted until the criteria to resume treatment with pembrolizumab are met.

7.1.4 For Cohort B participants:

7.1.4.1 Study drugs are either held together or separately, depending on the reason for the hold.

7.1.4.2 If only one study drug is held, then the cycle count continues. If both study drugs are held, then cycle count should be interrupted until the criteria to resume treatment are met.

NOTE: In the event that only one study drug is held, treatment with that drug will not be provided mid-cycle; that cycle's dose will be skipped and treatment with that drug will resume on Day 1 of the subsequent cycle, provided criteria to restart treatment is met at that time.

7.1.5 If - in the best interest of the patient - the investigator wants to hold study agent(s) after an adverse event in a manner not outlined in Section 7, this is permissible following discussion and agreement with the overall Principal Investigator, Dr. David A. Reardon or designee.

7.1.6 For holds due to related toxicities, if the participant does not meet criteria to resume treatment within 12 weeks of the date of the toxicity (unless otherwise specified in the protocol), the participant must permanently discontinue the relevant study agent. However, if the participant is benefiting from the study, the investigator may contact the overall Principal Investigator, Dr. David A. Reardon or designee to determine if the participant can remain on study.

7.1.7 For all holds for reasons other than treatment-related toxicities

1. Ideally, participants will be placed back on study therapy within 3 weeks of the scheduled interruption (a 6 week hold);
2. However, the hold may be extended to 12 weeks, should the Treating Investigator deem it necessary to do so.
3. In the event that a participant is unable to resume treatment within 12 weeks of the event precipitating the hold, Investigator Team must receive approval from the overall Principal Investigator or designee if they intend to extend the hold and continue to treat the participant on study.

7.1.8 A participant in Cohort B is only considered to be off-treatment if s/he has discontinued both pembrolizumab and bevacizumab (or biosimilar). If the participant is discontinued from pembrolizumab but continues treatment with bevacizumab - or biosimilar (or if the participant is discontinued from treatment with bevacizumab (or biosimilar) but continues pembrolizumab), s/he will continue to be monitored per the regular study schedule.

7.1.9 For other unspecified events of any grade considered unlikely to be related or not related to study drug, participants should maintain treatment with pembrolizumab. Interruption of pembrolizumab is permitted if the investigator consults with the overall Principal Investigator or designee to determine that this is in the interest of the participant.

7.2 Pembrolizumab Dose Modifications

There are no reductions in the pembrolizumab dose. Guidelines for pembrolizumab dose management due to adverse events considered at least possibly related to pembrolizumab are summarized in Table 5 (immune-related events) and Table 6. If adverse events occur that require holding pembrolizumab, the dose will remain the same once treatment resumes. Patients who require pembrolizumab hold or discontinuation are permitted to continue to receive study treatment with bevacizumab (or biosimilar) alone.

Pembrolizumab will be withheld for drug-related Grade 4 hematologic toxicities, non-hematological toxicity ≥ Grade 3 including laboratory abnormalities despite appropriate replacement therapies when appropriate, and severe or life-threatening AEs as per Table 6 below.

NOTE: 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 treatment with Pembrolilzumab.

Immune-related AEs associated with pembrolizumab: AEs associated with pembrolizumab exposure may represent an immunologic etiology. These immune-related AEs (irAEs) may occur shortly after the first dose or several months after the last dose of pembrolizumab treatment and may affect more than on body system simultaneously. Therefore, early recognition and initiation of treatment is critical to reduce complications. Based on existing clinical study data, most irAEs were reversible and could be managed with interruptions of pembrolizumab, administration of corticosteroids and/or other supportive care. For suspected irAEs, ensure adequate evaluation to confirm etiology or exclude other causes. Additional procedures or tests such as bronchoscopy, endoscopy, skin biopsy may be included as part of the evaluation. Based on the severity of irAEs, withhold or permanently discontinue pembrolizumab and administer corticosteroids. Dose modification and toxicity management guidelines for irAEs associated with pembrolizumab are provided below in Table 5.

General irAE Instructions:

1. Severe and life-threatening irAEs should be treated with IV corticosteroids followed by oral steroids. Other immunosuppressive treatment should begin if the irAEs are not controlled by corticosteroids.
2. Study intervention must be permanently discontinued if the irAE does not resolve or the corticosteroid dose is not ≤10 mg/day within 12 weeks of the last study intervention treatment.
3. The corticosteroid taper should begin when the irAE is ≤ Grade 1 and continue at least 4 weeks.
4. If study intervention has been withheld, study intervention may resume after the irAE decreased to ≤ Grade 1 after corticosteroid taper.

Table 5. Pembrolizumab Dose Modification Guidelines for Pembro-related irAEs

Toxicity	Hold Treatment For Grade	Timing for Restarting Pembrolizumab	Discontinue Participant's Pembrolizumab	Corticosteroid and/or Other Therapies	Monitoring and Follow-up
Diarrhea/Colitis	2-3	Toxicity resolves to Grade 0-1	Toxicity does not resolve within 12 weeks of last dose or inability to reduce corticosteroid to 10 mg or less of prednisone or equivalent per day within 12 weeks	Administer corticosteroids (initial dose of 1 to 2 mg/kg prednisone or equivalent) followed by taper	• Monitor participants for signs and symptoms of enterocolitis (ie, diarrhea, abdominal pain, blood or mucus in stool with or without fever) and of bowel perforation (ie, peritoneal signs and ileus) • Participants with ≥Grade 2 diarrhea suspecting colitis should consider GI consultation and performing endoscopy to rule out colitis • Participants with diarrhea/colitis should be advised to drink liberal quantities of clear fluids. If sufficient oral fluid intake is not feasible, fluid and electrolytes should be substituted via IV infusion
	4, or recurrent G3	Permanently discontinue	Permanently discontinue		
AST/ALT elevation or Increased Bilirubin	2[a]	Toxicity resolves to Grade 0-1	Toxicity does not resolve within 12 weeks of last dose	Administer corticosteroids (initial dose of 0.5 to 1 mg/kg prednisone or equivalent) followed by taper	Monitor with liver function tests (consider weekly or more frequently until liver enzyme value returned to baseline or is stable)
	3[b] -4[c]	Permanently discontinue	Permanently discontinue	Administer corticosteroids (initial dose of 1 to 2 mg/kg prednisone or equivalent) followed by taper	
Type 1 diabetes mellitus (if new onset) or Hyperglycemia	T1DM or 3-4	Hold pembrolizumab for new onset Type 1 diabetes mellitus or Grade 3-4 hyperglycemia associated with evidence of beta cell failure[d]	Resume pembrolizumab when patients are clinically and metabolically stable	• Initiate insulin replacement therapy for participants with T1DM • Administer antihyperglycemic in participants with hyperglycemia	Monitor participants for hyperglycemia or other signs and symptoms of diabetes

Toxicity	Hold Treatment For Grade	Timing for Restarting Pembrolizumab	Discontinue Participant's Pembrolizumab	Corticosteroid and/or Other Therapies	Monitoring and Follow-up
Hypophysitis	2	Toxicity resolves to Grade 0-1. Therapy with pembrolizumab can be continued while endocrine replacement therapy is instituted	Toxicity does not resolve within 12 weeks of last dose or inability to reduce corticosteroid to 10 mg or less of prednisone or equivalent per day within 12 weeks	Administer corticosteroids and initiate hormonal replacements as clinically indicated	Monitor for signs and symptoms of hypophysitis (including hypopituitarism and adrenal insufficiency)
	3-4	Decision whether to withhold or permanently discontinue pembrolizumab is at the discretion of the Investigator / Treating MD. [d] Can restart when toxicity resolves to Grade 0-1. Therapy with pembrolizumab can be continued while endocrine replacement therapy is instituted	Permanently discontinue, or Toxicity does not resolve within 12 weeks of last dose or inability to reduce corticosteroid to 10 mg or less of prednisone or equivalent per day within 12 weeks		
Hyperthyroidism	2	Toxicity resolves to Grade 0-1	Toxicity does not resolve within 12 weeks of last dose or inability to reduce corticosteroid to 10 mg or less of prednisone or equivalent per day within 12 weeks	Treat with nonselective beta-blockers (eg, propranolol) or thionamides as appropriate	Monitor for signs and symptoms of thyroid disorders
	3-4	Decision whether to withhold or permanently discontinue pembrolizumab is at the discretion of the Investigator / Treating MD. [d]	Permanently discontinue, or Toxicity does not resolve within 12 weeks of last dose or inability to reduce corticosteroid to 10 mg or less of prednisone or equivalent per day within 12 weeks		
Hypothyroidism	2-4	Therapy with pembrolizumab can be continued while thyroid replacement therapy is instituted	Therapy with pembrolizumab can be continued while thyroid replacement therapy is instituted	Initiate thyroid replacement hormones (eg, levothyroxine or liothyronine) per standard of care	Monitor for signs and symptoms of thyroid disorders
Immune system disorders - Other: Guillain-Barre syndrome - Any Grade		Permanently discontinue	Permanently discontinue		
Myocarditis	1	Toxicity resolves to Grade 0	Toxicity does not resolve within 12 weeks of last dose	Based on severity of AE administer corticosteroids	Ensure adequate evaluation to confirm etiology and/or exclude other causes
	2-4	Permanently discontinue	Permanently discontinue		
Myositis	3	Toxicity resolves to Grade 0-1	Toxicity does not resolve within 12 weeks of last dose		
	4	Permanently discontinue	Permanently discontinue		

Toxicity	Hold Treatment For Grade	Timing for Restarting Pembrolizumab	Discontinue Participant's Pembrolizumab	Corticosteroid and/or Other Therapies	Monitoring and Follow-up
Neuropathy (peripheral motor or sensory)	3	Toxicity resolves to Grade 0-1	Toxicity does not resolve within 12 weeks of last dose		
	4	Permanently discontinue	Permanently discontinue		
Pancreatitis	3	Toxicity resolves to Grade 0-1	Toxicity does not resolve within 12 weeks of last dose		
	4	Permanently discontinue	Permanently discontinue		
Pneumonitis	2	Toxicity resolves to Grade 0-1	Toxicity does not resolve within 12 weeks of last dose or inability to reduce corticosteroid to 10 mg or less of prednisone or equivalent per day within 12 weeks	• Administer corticosteroids (initial dose of 1 to 2 mg/kg prednisone or equivalent) followed by taper • Add prophylactic antibiotics for opportunistic infections	• Monitor participants for signs and symptoms of pneumonitis • Evaluate participants with suspected pneumonitis with radiographic imaging and initiate corticosteroid treatment
	3-4, or recurrent G2	Permanently discontinue	Permanently discontinue		
Neurological Toxicities	2	Toxicity resolves to Grade 0-1	Toxicity does not resolve within 12 weeks of last dose	Based on severity of AE administer corticosteroids	Ensure adequate evaluation to confirm etiology and/or exclude other causes
	3- 4	Permanently discontinue	Permanently discontinue		
Nephritis (grading according to increased creatinine or acute kidney injury)	2	Toxicity resolves to Grade 0-1	Toxicity does not resolve within 12 weeks of last dose or inability to reduce corticosteroid to 10 mg or less of prednisone or equivalent per day within 12 weeks	Administer corticosteroids (prednisone 1 to 2 mg/kg or equivalent) followed by taper	Monitor changes of renal function
	3-4	Permanently discontinue	Permanently discontinue		
Exfoliative Dermatologic Conditions	Suspected SJS, TEN, or DRESS	Hold pembrolizumab until suspected conditions are ruled out	Permanently discontinue if suspected condition is confirmed	Based on severity of AE administer corticosteroids	Ensure adequate evaluation to confirm etiology or exclude other causes
	Confirmed SJS, TEN, or DRESS	Permanently discontinue	Permanently discontinue		
All Other irAEs[e]	Intolerable/ persistent Gr2	Toxicity resolves to Grade 0-1	Toxicity does not resolve within 12 weeks of last dose or inability to reduce corticosteroid to 10 mg or less of prednisone or equivalent per day within 12 weeks	Based on severity of AE administer corticosteroids	Ensure adequate evaluation to confirm etiology or exclude other causes
	3 (first occurrence)	Decision whether to withhold or permanently discontinue pembrolizumab depends on event.[f]	Permanently discontinue, or Toxicity does not resolve within 12 weeks of last dose or inability to reduce corticosteroid to 10 mg or less of prednisone or equivalent		

Toxicity	Hold Treatment For Grade	Timing for Restarting Pembrolizumab	Discontinue Participant's Pembrolizumab	Corticosteroid and/or Other Therapies	Monitoring and Follow-up
			per day within 12 weeks		
	4 (or recurrent Gr3)	Permanently discontinue	Permanently discontinue		

AE(s)=adverse event(s); ALT= alanine aminotransferase; AST=aspartate aminotransferase; CTCAE=Common Terminology Criteria for Adverse Events; DRESS=Drug Rash with Eosinophilia and Systemic Symptom; GI=gastrointestinal; IO=immuno-oncology; ir=immune related; IV=intravenous; SJS=Stevens-Johnson Syndrome; T1DM=type 1 diabetes mellitus; TEN=Toxic Epidermal Necrolysis; ULN=upper limit of normal.

Note: Permanently discontinue for any severe or Grade 3 (Grade 2 for pneumonitis) drug-related AE that recurs, or any life-threatening event.

Note: Non-irAE will be managed as appropriate, following clinical practice recommendations.

[a] AST/ALT: >3.0 to5.0 x ULN if baseline normal; >3.0 to 5.0 x baseline, if baseline abnormal;
bilirubin:>1.5 to 3.0 x ULN if baseline normal; >1.5 to 3.0 x baseline if baseline abnormal

[b] AST/ALT: >5.0 to 20.0 x ULN, if baseline normal; >5.0 to 20.0 x baseline, if baseline abnormal; bilirubin:>3.0 to 10.0 x ULN if baseline normal; >3.0 to 10.0 x baseline if baseline abnormal

[c] AST/ALT: >20.0 x ULN, if baseline normal; >20.0 x baseline, if baseline abnormal;
bilirubin: >10.0 x ULN if baseline normal; >10.0 x baseline if baseline abnormal

[d] The decision to withhold or permanently discontinue pembrolizumab is at the discretion of the investigator or treating physician. If control achieved or ≤ Grade 2, pembrolizumab may be resumed.

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

[f] Events that require discontinuation include - but are not limited to: encephalitis and other clinically important irAEs (eg, vasculitis and sclerosing cholangitis).

Table 6. Pembrolizumab Dose Modification Guidelines for Other Pembro-related AEs

Toxicity	Hold Treatment For Grade	Timing for Restarting Pembrolizumab	Discontinue Participant's Pembrolizumab
Infusion Reaction	2[a]	Toxicity resolves to Grade 0-1	Permanently discontinue if toxicity develops despite adequate premedication
	3-4	Permanently discontinue	Permanently discontinue
All Other Drug-Related Toxicity[b]	3 or Severe	Toxicity resolves to Grade 0-1	Toxicity does not resolve within 12 weeks of last dose or inability to reduce corticosteroid to 10 mg or less of prednisone or equivalent per day within 12 weeks
	4	Permanently discontinue	Permanently discontinue

Note: Permanently discontinue for any severe or Grade 3 (Grade 2 for pneumonitis) drug-related AE that recurs, or any life-threatening event.

[a] 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 participant should be premedicated for the next scheduled dose; Refer to Infusion Treatment Guidelines for further management details.

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

7.2.1 **Other allowed dose interruption for pembrolizumab**

Pembrolizumab may be interrupted for situations other than treatment-related AEs such as medical / surgical events or logistical reasons not related to study therapy. For all holds for reasons other than treatment-related toxicities:

1. Ideally, participants will be placed back on study therapy within 3 weeks of the scheduled interruption (a 6 week hold);
2. However, the hold may be extended to 12 weeks, should the Treating Investigator deem it necessary to do so.
3. In the event that a participant is unable to resume treatment within 12 weeks of the event precipitating the hold, Investigator Team must receive approval from the overall Principal Investigator or designee if they intend to extend the hold and continue to treat the participant on study.

The reason for interruption should be documented in the patient's study record

7.3 Re-Irradiation Dose Modification/Interruption/Discontinuation

There will be no dose modifications for re-irradiation dosing. Any toxicity associated or possibly associated with re-irradiation treatment should be managed according to standard medical practice. Participants who develop significant (grade ≥ 3) toxicity related to re-irradiation should be managed with maximal medical therapy and may be considered for dose interruption if inadequately responsive to maximal medical therapy. Every effort should be made to resume re-irradiation as soon as possible.

For any participant requiring interruption of re-irradiation for > 1 week: Sites must contact the Study PI to discuss whether it is in the patient's best interest to resume re-irradiation therapy or whether s/he should discontinue re-irradiation.

Re-irradiation will be discontinued for any participant who develops a grade 4 adverse event related to re-irradiation.

7.4 Bevacizumab (or Biosimilar) Dose Modification/ Interruption/ Discontinuation (Cohort B)

There are no reductions in the bevacizumab (or biosimilar) dose. Guidelines for bevacizumab (or biosimilar) dose management due to adverse events considered at least possibly related to bevacizumab (or biosimilar) are summarized in Table 7. If adverse events occur that require holding bevacizumab (or biosimilar), the dose will remain the same once treatment resumes. Patients who require bevacizumab (or biosimilar) hold or discontinuation are permitted to continue to receive study treatment with pembrolizumab alone.

Any toxicity associated or possibly associated with bevacizumab (or biosimilar) treatment should be managed according to standard medical practice. Bevacizumab (or biosimilar) has a terminal half-life of 2 to 3 weeks; therefore, its discontinuation results in slow elimination over several months. There is no available antidote for bevacizumab (or biosimilar).

Participants should be assessed clinically for toxicity prior to, during, and after each infusion. If unmanageable toxicity occurs because of bevacizumab (or biosimilar) at any time during the study, treatment with bevacizumab (or biosimilar) should be discontinued.

Adverse events requiring delays or permanent discontinuation of bevacizumab (or biosimilar) are listed in Table 7.

Table 7. Bevacizumab (or biosimilar) Dose Management Due to Adverse Events (Regardless of Attribution)

Event	CTCAE v. 4 Grade	Action to be Taken with Bevacizumab (or biosimilar) Dose
Arterial Thromboembolic event - Any grade (Angina, myocardial infarction, transient ischemic attack, cerebrovascular accident, and any other arterial thromboembolic event)		Discontinue bevacizumab (or biosimilar).
Bowel Obstruction	Grade 1	Continue patient on bevacizumab (or biosimilar) for partial obstruction NOT requiring medical intervention.
	Grade 2	Hold bevacizumab (or biosimilar) for partial obstruction requiring medical intervention. Patient may restart upon complete resolution.
	Grade 3/4	Hold bevacizumab (or biosimilar) for complete obstruction. If surgery is necessary, patient may restart bevacizumab (or biosimilar) after full recovery from surgery, and at investigator's discretion.
Congestive Heart Failure (Left ventricular systolic dysfunction)	Grade 1/2	No bevacizumab (or biosimilar) dose modifications
	Grade 3	Hold bevacizumab (or biosimilar) until resolution to Grade ≤ 1.
	Grade 4	Discontinue bevacizumab (or biosimilar).
GI Perforation	Any Grade	Discontinue bevacizumab (or biosimilar).
Hemorrhage	Grade 1 - non-CNS	No dose modifications
	Grade ≥ 1 New CNS hemorrhage	Discontinue bevacizumab (or biosimilar).
	Grade > 1 non-CNS hemorrhage	Discontinue bevacizumab (or biosimilar).
Hypertension	Grade 1/2	No bevacizumab (or biosimilar) dose modifications • For grade ≥ 2, consider initiation of anti-hypertensive therapy per institutional guidelines.
	Grade 3	If not controlled to ≤ 159/99 mmHg with medication, discontinue bevacizumab (or biosimilar).
	Grade 4, including RPLS (confirmed by MRI) or hypertensive encephalopathy	Discontinue bevacizumab (or biosimilar).
Infusion Related Reaction	Grade 1/2	Slow bevacizumab (or biosimilar) infusion to 50% or less or interrupt. When symptoms have completely resolved, the infusion may be continued at not more than 50% of the rate prior to the reaction and increased in 50% increments every 30 minutes if well tolerated. bevacizumab (or biosimilar) infusions may be restarted at the full rate during the next cycle.
	Grade 3/4	Discontinue bevacizumab (or biosimilar).
Proteinuria	Grade 1/2	No bevacizumab (or biosimilar) dose modifications
	Grade 3	Hold bevacizumab (or biosimilar) treatment until ≤ Grade 2, as determined by 24 hr collection ≤ 3.5 g
	Grade 4 (nephrotic syndrome)	Discontinue bevacizumab (or biosimilar)
Venous Thrombosis	Grade 1/2	No bevacizumab (or biosimilar) dose modifications

	Grade 3/ Asymptomatic Grade 4	Hold bevacizumab (or biosimilar). If the planned duration of full-dose anticoagulation is <2 weeks, bevacizumab (or biosimilar) should be held until the full-dose anticoagulation period is over. If the planned duration of full-dose anticoagulation is >2 weeks, bevacizumab (or biosimilar) may be resumed during the period of full-dose anticoagulation if the following criterion is met: • The participant must be therapeutically anti-coagulated with an approved anticoagulant agent according to standard prescribing guidelines.
	Symptomatic Grade 4	Discontinue bevacizumab (or biosimilar).
Wound dehiscence requiring medical or surgical therapy		Discontinue bevacizumab (or biosimilar)
Other Unspecified Bevacizumab (or biosimilar)-Related Adverse Events	Grade 3	Hold bevacizumab (or biosimilar) until recovery to ≤ Grade 1
	Grade 4	Discontinue bevacizumab (or biosimilar).

8. ADVERSE EVENTS: LIST AND REPORTING REQUIREMENTS

Adverse event (AE) monitoring and reporting is a routine part of every clinical trial. The following list of reported and/or potential AEs (Section 8.1) will determine whether the event requires expedited reporting **in addition** to routine reporting.

8.1 Anticipated Toxicities

A list of the adverse events and potential risks associated with the agents administered in this study appear below [reported by CTCAE v. 4 System Organ Class (SOC)],

In order for an event to be expected (known correlation to study drug) for the purposes of adverse event reporting on this study, the event must be included in this section (or be included in the informed consent document as a potential risk). This list will also be used to help determine whether dose delays and modifications will be made on study.

8.1.1 Adverse Events for Pembrolizumab

NOTE: The list below serves to provide study guidance and is not all-inclusive. Please refer to the current pembrolizumab Investigator Drug Brochure for a comprehensive list of adverse events and potential risks associated with pembrolizumab.

- BLOOD AND LYMPHATIC SYSTEM DISORDERS *: anemia
- CARDIAC DISORDERS: heart failure, myocarditis
- ENDOCRINE DISORDERS: adrenal insufficiency, hyperthyroidism, hypothyroidism,
- EYE DISORDERS *: uveitis
- GASTROINTESTINAL DISORDERS *: abdominal pain, colitis, constipation, diarrhea, nausea, pancreatitis, vomiting
- GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS: edema limbs, fatigue, fever, infusion related reaction
- HEPATOBILIARY DISORDERS: Hepatobiliary disorders - Other, specify: sclerosing cholangitis
- IMMUNE SYSTEM DISORDERS: allergic reaction, autoimmune disorder including but not limited to hypophysitis, thyroiditis, type 1 diabetes mellitus, iritis, hepatitis, myopathy, Guillain-Barre syndrome, myasthenia gravis (MG), Rejection of solid organ or tissue transplants (corneal, kidney, or liver), nephritis, pemphigus, vitiligo
- INFECTIONS AND INFESTATIONS: skin infection, urinary tract infection, upper respiratory infection, lung infection, hepatic infection, hepatitis viral
- INJURY, POISONING AND PROCEDURAL COMPLICATIONS *
- INVESTIGATIONS: activated partial thromboplastin time prolonged, alanine aminotransferase increased, alkaline phosphatase increased, aspartate aminotransferase increased, blood bilirubin increased, creatinine increased, GGT increased, INR increased, neutrophil count decreased, platelet count decreased, weight loss
- METABOLISM AND NUTRITION DISORDERS: anorexia, hypoalbuminemia, hyponatremia
- MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS: myalgia, arthralgia, arthritis, myositis
- NERVOUS SYSTEM DISORDERS *: dizziness, dysgeusia, edema cerebral**, headache, peripheral motor neuropathy, peripheral sensory neuropathy, seizures
    - Nervous system disorders – other, specify: Tumor inflammation**

- PSYCHIATRIC DISORDERS: confusion
- RENAL AND URINARY DISORDERS *: hematuria
- REPRODUCTIVE SYSTEM AND BREAST DISORDERS *
- RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS *: cough, dyspnea, pneumonitis
- SKIN AND SUBCUTANEOUS TISSUE DISORDERS: exfoliative dermatitis
    - All CTCAE v. 4 rashes are considered expected: bullous dermatitis, erythema multiforme, erythroderma, palmar-plantar erythrodysesthesia syndrome, pruritus, rash acneiform, rash maculo-papular, skin hyperpigmentation, skin hypopigmentation, skin induration, skin ulceration, Stevens-Johnson syndrome, toxic epidermal necrolysis (TEN)
- VASCULAR: vasculitis

* In addition, the following potential risk is considered expected within all applicable SOCs:
- bleeding/hemorrhage

**As CTCAE v. 4 recognizes 'Edema cerebral' only as a Gr4 event (no definition for Gr1, Gr2, Gr3, or Gr5), please record events of 'Edema cerebral' deemed by Investigator to be Gr1-Gr3 or Gr5 as 'Nervous system disorders, Other: Tumor inflammation' (as Gr1-Gr3 or Gr5, accordingly).

8.1.2 **Adverse Events for Re-Irradiation**

Acute:
- Expected:
    - Skin and subcutaneous tissue disorders: alopecia (radiation-induced)
    - General disorders and administration site conditions: fatigue
    - Injury, poisoning and procedural complications: dermatitis radiation
        - Injury, poisoning and procedural complications – other, specify:
            - soreness of the scalp
    - Nervous system disorders: edema cerebral**
        - Nervous system disorders – other, specify:
            - Tumor inflammation**
- Possible:
    - Ear and labyrinth disorders: Middle ear inflammation *(serous otitis media with short-term hearing impairment)*
    - Gastrointestinal disorders: dry mouth; nausea; vomiting
    - Nervous system disorders: dysgeusia; headache; seizure
        - Nervous system disorders – other, specify:
            - Weakness

Early Delayed:
- Possible:
    - Nervous system disorders: lethargy
    - Exacerbation of existing neurologic deficits (defined by CTCAE 4.0) occurring 1-3 months after radiotherapy

Late Delayed:
- Possible:
    - Endocrine disorders: Endocrine disorders – other, specify:
        - endocrine dysfunction

  - Eye disorders: cataracts
  - Nervous system disorders: cognitive disturbance; central nervous system necrosis
  - Psychiatric disorders: personality change
- Possible (in appropriate anatomic context):
  - Ear and labyrinth disorders: hearing impaired
  - Eye disorders: blurred vision

**As CTCAE v. 4 recognizes 'Edema cerebral' only as a Gr4 event (no definition for Gr1, Gr2, Gr3, or Gr5), please record events of 'Edema cerebral' deemed by Investigator to be Gr1-Gr3 or Gr5 as 'Nervous system disorders, Other: Tumor inflammation' (as Gr1-Gr3 or Gr5, accordingly).

8.1.3 Adverse Events for Bevacizumab (or biosimilar)

- BLOOD AND LYMPHATIC SYSTEM DISORDERS *: anemia, hemorrhage
- CARDIAC DISORDERS: acute coronary syndrome, ventricular arrhythmia, heart failure
- EYE DISORDERS *
- GASTROINTESTINAL DISORDERS *: abdominal pain, colonic perforation, constipation, nausea, esophageal fistula
- GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS: infusion related reaction
- HEPATOBILIARY DISORDERS *
- IMMUNE SYSTEM DISORDERS: allergic reaction
- INFECTIONS AND INFESTATIONS: skin infection
- INJURY, POISONING AND PROCEDURAL COMPLICATIONS*: wound complication, wound dehiscence
- INVESTIGATIONS: neutrophil count decreased, platelet count decreased
- NERVOUS SYSTEM DISORDERS *: headache, intracranial hemorrhage, leukoencephalopathy, seizures, stroke
- PSYCHIATRIC DISORDERS: confusion
- RENAL AND URINARY DISORDERS *: acute kidney injury, proteinuria
- REPRODUCTIVE SYSTEM AND BREAST DISORDERS *
- RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS *: dyspnea, hoarseness
- VASCULAR DISORDERS: hypertension, thromboembolic event

* In addition, the following potential risk is considered expected within all applicable SOCs:
- bleeding/hemorrhage

Please also refer to the current bevacizumab (or biosimilar) package insert for a comprehensive list of adverse events and potential risks associated with bevacizumab (or biosimilar).

8.2 Definitions

8.2.1 Adverse Event (AE)

An adverse event (AE) is any undesirable sign, symptom or medical condition or experience that

develops or worsens in severity after starting the first dose of study treatment or any procedure specified in the protocol, even if the event is not considered to be related to the study.

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

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

Abnormal laboratory values or diagnostic test results constitute adverse events only if they induce clinical signs or symptoms or require treatment or further diagnostic tests.

8.2.2 **Serious adverse event (SAE)**

A serious adverse event (SAE) is any adverse event, occurring at any dose and regardless of causality that:

- Results in death
- Is life-threatening. Life-threatening means that the person was at immediate risk of death from the reaction as it occurred, i.e., it does not include a reaction which hypothetically might have caused death had it occurred in a more severe form.
- Requires or prolongs inpatient hospitalization (i.e., the event required at least a 24-hour hospitalization or prolonged a hospitalization beyond the expected length of stay). Hospitalization admissions and/or surgical operations scheduled to occur during the study period, but planned prior to study entry are not considered SAEs if the illness or disease existed before the person was enrolled in the trial, provided that it did not deteriorate in an unexpected manner during the trial (e.g., surgery performed earlier than planned).
- Results in persistent or significant disability/incapacity. Disability is defined as a substantial disruption of a person's ability to conduct normal life functions.
- Is a congenital anomaly or birth defect; or
- Is an important medical event when, based upon appropriate medical judgment, it may jeopardize the participant and require medical or surgical intervention to prevent one of the outcomes listed above. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home; blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse.

Note: In addition to the above criteria, adverse events meeting either of the below criteria, although not serious per ICH definition, are reportable to the Merck in the same timeframe as SAEs to meet certain local requirements. Therefore, the following events are considered serious by Merck for collection purposes:

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

Events **not** considered to be serious adverse events in this trial are

- Lymphopenia (grades 2-4)
- Progression of the cancer under study
- A visit to the emergency room or another hospital department that does not result in a hospitalization of > 24 hours (unless considered an important medical or life-threatening event)
- And hospitalization for any of the following:
    - routine treatment or monitoring of the studied indication, not associated with any deterioration in condition, or for elective procedures
    - seizure, if felt related to patient's underlying disease
    - routine health assessment for baseline/trending of health status (eg, routine colonoscopy)
    - elective or pre-planned treatment for a pre-existing condition that did not worsen
    - scheduled debulking surgery
    - treatment of patient's underlying disease (e.g. admission after patient is removed from active study treatment for craniotomy)
    - emergency outpatient treatment for an event not fulfilling the serious criteria outlined above and not resulting in inpatient admission
    - respite care not associated with an adverse event attributed to the study drug
    - another life circumstance that carries no bearing on health status and requires no medical/surgical intervention (eg, lack of housing, economic inadequacy, caregiver respite, family circumstances, administrative reason).

8.3 Evaluating Adverse Events

All adverse events will be evaluated and assessed by a qualified Investigator (physician, when necessary per local institutional policy) for determinations of:

1. Grade[a], per 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.
2. Seriousness[a] as defined in Section 8.2.2, regardless of CTCAE grade
3. Attribution[a] to each of the aspects of study treatment: Pembrolizumab, Re-Irradiation (when applicable), and bevacizumab (or biosimilar, when applicable[b]. Attribution of AEs must be classified based on the following definitions:
    - Definite – The AE *is clearly related* to the study agent/treatment.
    - Probable – The AE *is likely related* to the study agent/treatment.
    - Possible – The AE *may be related* to the study agent/treatment.
    - Unlikely – The AE *is doubtfully related* to the study agent/treatment.
    - Unrelated – The AE *is clearly NOT related* to the study agent/treatment.
4. Expectedness[a] with each of the aspects of study treatment: Pembrolizumab, Re-Irradiation (when applicable), and bevacizumab (or biosimilar), when applicable. Adverse events can be 'Expected' or 'Unexpected.'

For the purposes of this study:

An adverse event is considered …	When it …	Or when it …
Expected	Appears in section 8.1 of the protocol (taken from the current Investigator's Brochure or package insert)	Is included in the informed consent document as a potential risk
Unexpected	Varies in nature, intensity, or frequency from information provided in the current protocol or IB / package insert	Is NOT included in the informed consent document as a potential risk

5. Duration[a] of event (start and stop dates)
6. Action Taken[a]:
   - Were any concomitant meds introduced as a result of the event?
   - Dechallenge[c]: Was any study drug/treatment discontinued, held, or dose/exposure/frequency reduced?

If yes, did the AE resolve or improve?	If yes …	Then this is a positive dechallenge
	If no …	Then this is a negative dechallenge

   - Rechallenge [d, e]: Was the subject re-exposed to the study drug/treatment?

If yes, did the AE recur or worsen?	If yes …	Then this is a positive rechallenge
	If no …	Then this is a negative rechallenge

7. Whether event meets definition of an Event of Clinical Interest (ECI); see section 8.4.4.2 of the protocol for definition.

NOTE: For events that are secondary to an event deemed expected with a study agent/modality (e.g. rectal pain as a result of diarrhea), please record as "possibly related to" and "expected with" the agent/modality.

Footnotes for Evaluating Adverse Events

a. These assessments should be recorded by the Investigator in real time if feasible, and maintained in either the patient's research chart or medical record for review by sponsor team upon trial monitoring.

b. For Cohort B (in which multiple agents are administered as part of a combination regimen), the investigator may attribute each adverse event causality to the combination regimen or to a single agent of the combination. In general, causality attribution should be assigned to the combination regimen (i.e., to all agents in the regimen). However, causality attribution may be assigned to a single agent if in the investigator's opinion, there is sufficient data to support full attribution of the adverse experience to the single agent.

c. This criterion is not applicable if: (1) the AE resulted in death or permanent disability; or (2) the AE resolved/improved despite continuation of study drugs

d. This criterion is not applicable if the initial AE resulted in death or permanent disability

e. If a rechallenge is planned for an AE which was serious and which may have been caused by study drug/treatment, or if reexposure to the drug/treatment poses additional potential significant risk to the subject, then the rechallenge MUST BE APPROVED IN ADVANCE by the Overall PI, as per dose modification guidelines in the protocol.

8.3.1 Evaluating Adverse Events for Merck

See Table 8 below for Merck clarifications re: 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. Merck Clarifications re: Evaluating Adverse Events

A qualified investigator (physician, when necessary per local institutional policy), will evaluate all adverse events as to:

V4.0 CTCAE Grading	**Grade 1**	**Mild; asymptomatic or mid symptoms; clinical or diagnostic observations only; intervention not indicated.**
	Grade 2	**Moderate; minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental ADL.**
	Grade 3	**Severe or medically significant but not immediately life-threatening; hospitalization or prolongation or hospitalization indicated; disabling; limiting self-care ADL.**
	Grade 4	**Life threatening consequences; urgent intervention indicated.**
	Grade 5	**Death related to AE**
Seriousness	A serious adverse event is any adverse event occurring at any dose or during any use of Merck product that:	
	†**Results in death**; or	
	†**Is life threatening; or** places the subject, in the view of the investigator, at immediate risk of death from the event as it occurred (Note: This does not include an adverse event that, had it occurred in a more severe form, might have caused death.); or	
	†**Results in a persistent or significant disability/incapacity** (substantial disruption of one's ability to conduct normal life functions); or	
	†**Results in or prolongs an existing inpatient hospitalization** (hospitalization is defined as an inpatient admission, regardless of length of stay, even if the hospitalization is a precautionary measure for continued observation. (Note: Hospitalization for an elective procedure to treat a pre-existing condition that has not worsened is not a serious adverse event. A pre-existing condition is a clinical condition that is diagnosed prior to the use of a Merck product and is documented in the patient's medical history.); 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) **(**although not serious per ICH definition, is reportable to the Sponsor within 24 hours and to Merck within 2 working days to meet certain local requirements); **or**	
	Is an overdose (whether accidental or intentional). Any adverse event associated with an overdose is considered a serious adverse event for collection purposes. 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 to the Sponsor and to Merck within 2 working days..	
	Other important medical events that may not result in death, not be life threatening, or not require hospitalization may be considered a serious adverse event when, based upon appropriate medical judgment, the event may jeopardize the subject and may require medical or surgical intervention to prevent one of the outcomes listed previously (designated above by a †).	
Duration	Record the start and stop dates of the adverse event. If less than 1 day, indicate the appropriate length of time and units	
Action taken	Did the adverse event cause the Merck product to be discontinued?	
Relationship to Merck Product	Did the Merck product cause the adverse event? The determination of the likelihood that the Merck product caused the adverse event will be provided by an investigator who is a qualified physician. The investigator's signed/dated initials on the source document or worksheet that supports the causality noted on the AE form, ensures that a medically qualified assessment of causality was done. This initialed document must be retained for the required regulatory time frame. The criteria below are intended as reference guidelines to assist the investigator in assessing the likelihood of a relationship between the test drug and the adverse event based upon the available information. **The following components are to be used to assess the relationship between the Merck product and the AE**; the greater the correlation with the components and their respective elements (in number and/or intensity), the more likely the Merck product caused the adverse event (AE):	
	Exposure	Is there evidence that the subject was actually exposed to the Merck product such as: reliable history, acceptable compliance assessment (pill count, diary, etc.), expected pharmacologic effect, or measurement of drug/metabolite in bodily specimen?
	Time Course	Did the AE follow in a reasonable temporal sequence from administration of the Merck product? Is the time of onset of the AE compatible with a drug-induced effect (applies to trials with investigational medicinal product)?
	Likely Cause	Is the AE not reasonably explained by another etiology such as underlying disease, other drug(s)/vaccine(s), or other host or environmental factors

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

8.4 Procedures for AE and SAE Recording and Reporting

8.4.1 Assessing and Recording Adverse Events

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

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

All AEs, SAEs and other reportable safety events that occur after the consent form is signed but before treatment allocation/randomization must be reported by the investigator if the event causes the participant to be excluded from the study, or is the result of a protocol-specified intervention, including but not limited to washout or discontinuation of usual therapy, diet, or a procedure.

- All AEs from the time of treatment allocation/randomization through 30 days following cessation of study treatment must be reported by the investigator.
- All AEs meeting serious criteria, from the time of treatment allocation/randomization through 90 days following cessation of study treatment, or 30 days following cessation of study treatment if the participant initiates new anticancer therapy, whichever is earlier must be reported by the investigator.
- All pregnancies and exposure during breastfeeding, from the time of treatment allocation/randomization through 120 days following cessation of study treatment, or 30 days following cessation of study treatment if the participant initiates new anticancer therapy must be reported by the investigator.
- Additionally, any SAE brought to the attention of an investigator at any time outside of the time period specified above must be reported immediately by the investigator if the event is considered to be drug-related.

Investigators are not obligated to actively seek AE or SAE or other reportable safety events in former study participants. However, if the investigator learns of any SAE, including a death, at any time after a participant has been discharged from the study, and he/she considers the event to be reasonably related to the study treatment or study participation, the investigator must promptly notify Merck.

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

For purposes of this trial, an overdose of pembrolizumab will be defined as any dose of 1,000 mg or greater (≥5 times the indicated dose). No specific information is available on the treatment of overdose of pembrolizumab. In the event of overdose, pembrolizumab should be discontinued and the participant 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 pembrolizumab, the adverse event(s) is reported as a serious adverse event, even if no other seriousness criteria are met.

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

All reports of overdose with and without an adverse event must be reported by the investigator:

- Emailed within 24 hours to the Overall PI / Study Sponsor, Dr. David Reardon, and the DFCI Neuro Oncology Coordinating Center central SAE email at the following address: NeuroOnc_SAE@dfci.harvard.edu.
- and faxed within 2 working days to Merck Global Safety (Attn: Worldwide Product Safety); FAX 215-661-6229.

8.4.3 **Reporting of Pregnancy and Lactation to the Sponsor and to Merck**

Although pregnancy and infant exposure during breast feeding are not considered adverse events, it is the responsibility of investigators or their designees to report any pregnancy or lactation in a participant (spontaneously reported to them) that occurs during the study.

Pregnancies and infant exposures during breastfeeding that occur after the consent form is signed but before treatment allocation/randomization must be reported by the investigator if they cause the participant to be excluded from the trial, or are the result of a protocol-specified intervention, including but not limited to washout or discontinuation of usual therapy, diet, placebo treatment or a procedure.

Pregnancies and infant exposures during breastfeeding that occur from the time of treatment allocation/randomization through 120 days following cessation of Sponsor's product, or 30 days following cessation of treatment if the participant initiates new anticancer therapy, whichever is earlier, must be reported by the investigator. All reported pregnancies must be followed to the completion/termination of the pregnancy. Pregnancy outcomes of spontaneous abortion, missed abortion, benign hydatidiform mole, blighted ovum, fetal death, intrauterine death, miscarriage and stillbirth must be reported as serious events (Important Medical Events). If the pregnancy continues to term, the outcome (health of infant) must also be reported.

Such events (pregnancy and infant exposure during breast feeding) must be reported by the investigator:

- Emailed within 24 hours to the Overall PI / Study Sponsor, Dr. David Reardon, and the DFCI Neuro Oncology Coordinating Center central SAE email at the following address: NeuroOnc_SAE@dfci.harvard.edu.
- and faxed within 2 working days to Merck Global Safety (Attn: Worldwide Product Safety); FAX 215-661-6229.

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

8.4.4.1 Serious Adverse Events

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

For the time-period beginning at treatment allocation/randomization through 90 days following cessation of treatment, or 30 days following cessation of treatment if the participant initiates new anticancer therapy, whichever is earlier, any serious adverse event, or follow up to a serious adverse event, including death due to any cause whether or not related to the Merck product, must be reported within 24 hrs to the Sponsor & within 2 working days to Merck Global Safety.

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

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

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

SAE reports and any other relevant safety information are to be forwarded to the Merck Global Safety facsimile number: +1-215-661-6229

A copy of all 15 Day Reports and Annual Progress Reports is submitted as required by FDA, European Union (EU), Pharmaceutical and Medical Devices agency (PMDA) or other local regulators. Investigators will cross reference this submission according to local regulations to the Merck Investigational Compound Number (IND, CSA, etc.) at the time of submission. Additionally, investigators will submit a copy of these reports to Merck & Co., Inc. (Attn: Worldwide Product Safety; FAX 215-661-6229) at the time of submission to FDA.

8.4.4.2 Events of Clinical Interest (ECI)

Selected non-serious and serious adverse events are also known as Events of Clinical Interest (ECI) and must be reported within 2 working days to Merck Global Safety. (Attn: Worldwide Product Safety; FAX 215-661-6229).

For the time-period beginning when the consent form is signed until treatment allocation/randomization, any ECI, or follow up to an ECI, that occurs to any participant must be reported within 2 working days to Merck Global Safety if it causes the participant to be excluded

from the trial, or is the result of a protocol-specified intervention, including but not limited to washout or discontinuation of usual therapy, diet, placebo treatment or a procedure.

For the time-period beginning at treatment allocation/randomization through 90 days following cessation of treatment, or 30 days following cessation of treatment if the participant initiates new anticancer therapy, whichever is earlier, any ECI, or follow up to an ECI, whether or not related to Merck product, must be reported within 2 working days to Merck Global Safety.
Events of clinical interest for this trial include:

1. An overdose of Merck product, as defined in Section 7.2.1 - Definition of an Overdose for This Protocol and Reporting of Overdose to the Sponsor, that is not associated with clinical symptoms or abnormal laboratory results.
2. An elevated AST or ALT lab value that is greater than or equal to 3X the upper limit of normal and an elevated total bilirubin lab value that is greater than or equal to 2X the upper limit of normal and, at the same time, an alkaline phosphatase lab value that is less than 2X the upper limit of normal, as determined by way of protocol-specified laboratory testing or unscheduled laboratory testing.*

   *Note: These criteria are based upon available regulatory guidance documents. The purpose of the criteria is to specify a threshold of abnormal hepatic tests that may require an additional evaluation for an underlying etiology.

8.4.5 **Participant Deaths**

A death on study requires both routine and expedited reporting regardless of causality, unless as noted below. Attribution to treatment or other cause must be provided.

Death due to progressive disease should be reported as **Grade 5 "Neoplasms benign, malignant and unspecified (incl cysts and polyps) - Other (Progressive Disease)"** under the system organ class (SOC) of the same name. Evidence that the death was a manifestation of underlying disease (*e.g.*, radiological changes suggesting tumor growth or progression: clinical deterioration associated with a disease process) should be submitted.

If the participant is in long term follow up, report the death at the time of continuing review.

8.4.6 **Expedited Adverse Event Reporting Guidelines**

Adverse event reporting instructions for each site are detailed in Table 9 below.

8.4.6.1 **Expedited AE Reporting Requirements (By Site to Overall PI and Merck)**

The study must be conducted in compliance with local safety reporting requirements, and reporting requirements of the principal investigator.

Each adverse event will be assessed to determine if it meets the criteria for reporting. Adverse event reporting is to occur according to the site's specific IRB guidelines, and as outlined in this Section. Any serious adverse event occurring after the participant has initiated study treatment and until 90 days after the participant has stopped the study drug or the start of new anti-cancer treatment (whichever comes first) must be reported. Serious adverse events must be followed until resolution.

Investigators **must** report to the Overall PI and Merck any serious adverse event (SAE) that occurs after a subject's consent, during treatment, or within 90 days of the last dose of treatment (or until the start of new anti-cancer treatment, whichever comes first) via the appropriate applicable reporting form (MedWatch 3500A and/or local institutional IRB submission form).

Use the DF/HCC protocol number (18-277) and the protocol-specific participant ID assigned during trial registration on all reports.

It is the responsibility of each participating investigator to report adverse events to the Overall PI, Merck, DF/HCC IRB, and/or others as described below. Adverse event reporting by each site is detailed in Table 9. The Overall PI or representative Coordinating Center personnel will ensure the report is forwarded to the proper parties, as appropriate.

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

Submissions of Follow-Up Information:

Whenever feasible, the participating investigator should provide follow-up information on the serious adverse event within the following 24-48 hours. Follow-up information should describe whether the event has resolved or continues, if and how the event was treated, and whether the participant will continue or discontinue study participation.

For some SAEs, the study sponsor or designee may follow-up by telephone, fax, and/or monitoring visit to obtain additional case details deemed necessary to appropriately evaluate the SAE report (e.g., hospital discharge summary, consultant report, or autopsy report).

8.4.6.2 IRB Reporting

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

External participating sites will Submit Reportable AEs that occur (including up to within 90 days of the last administration of study therapy) to their respective IRB according to the local IRB's policies and procedures in reporting adverse events. A copy of the submitted institutional SAE form should be forwarded to the Overall PI within the timeframes detailed in Table 9. The Overall PI or representative will submit AE reports from external institutions to the DFCI OHRS according to DFCI IRB policies and procedures in reporting adverse events.

8.4.6.3 Expedited Reporting to Hospital Risk Management

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

Table 9. Reporting to Study's Overall PI & DFCI Coordinating Center, Merck, and IRB

Adverse Event Characteristics				Notification Requirement		
Serious-ness	**Toxicity Details**	**Known correlation**	**Attribution to study drug(s)**	**D. Reardon, MD** (Overall PI and IND-holder) **& DFCI Coordinating Center Via Email [b], with Safety Reporting Coversheet [c] & MedWatch 3500A [d]**	**Merck Global Safety Via Fax[c], with Safety Reporting Coversheet [c] and MedWatch 3500A [d]**	**IRB Submissions**
Serious	Any (incl any Grade 5)	Any (Expected or Unexpected)	Any	Within 2 working days from notification [a]		**All Local IRBs** (including IRB Submission for DF/HCC Sites) To be submitted to local IRB by Site Investigator Team if event meets local IRB submission requirements. To be submitted within IRB established reporting timelines. For DF/HCC sites, please ensure that Dr. Reardon (or representative) prospectively approves all submissions. **DF/HCC IRB** DFCI Coordinating Center will be responsible for submitting events from non-DF/HCC sites to DF/HCC IRB per DF/HCC reporting requirements.
Non-Serious	Events of Clinical Interest (ECIs)[e]					
Non-Serious	Grade 4	Unexpected	Any	Within 5 calendar days from notification[a]		
	Grade 2 or 3; moderate or severe		Possible, probable, definite			
Any	Overdose (as defined in Section 8.4.2)	N/A	N/A	Within 2 working days from notification [a]		
N/A	Pregnancy or Lactation (as defined in Section 8.4.3)					

a. In the event that the participating investigator does not become aware of the serious adverse event immediately (e.g., participant sought treatment elsewhere), the participating investigator is to report the event within 24 hrs (serious events) or 5 calendar days (non-serious events) after learning of it and document the time of his or her first awareness of the adverse event.

b. Email the Medwatch 3500A form, facsimile coversheet, and the IRB SAE report to the DFCI Coordinating Site with the subject title as "18-277: Pembro + Re-RT SAE" to NeuroOnc_SAE@dfci.harvard.edu. All SAE reports received at this account are forwarded immediately to Dr. David Reardon (the study's Overall Principal Investigator and sponsor/IND-holder), and to Coordinating Center personnel.

c. Safety Reporting Coversheet is found in Appendix B. Coversheet contains all applicable destinations: emails and FAX numbers.

d. Medwatch 3500A downloadable form at http://www.fda.gov/medwatch/getforms.htm

e. See Section 8.4.4.2 of the protocol for definition of Events of Clinical Interest (ECIs).

8.4.7 **Routine Adverse Event Reporting**

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

AEs reported through expedited processes (e.g., reported to the Sponsor, IRB, etc.) must also be reported in routine study data submissions (eDC).

8.4.8 **Adverse Event Reporting by Study's Sponsor and Overall PI**

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

Dr. Reardon (the study's Sponsor and Overall Principal Investigator) or a designee will:

- Submit to DF/HCC IRB any AE reports received from external institutions according to DFCI IRB policies and procedures in reporting adverse events.
- Circulate to all participating sites
    - All reportable adverse events received on study that are considered serious, unexpected, and at least possibly associated with study therapy. A cover letter will indicate the protocol title, the IND#, and whether the FDA and/or DF/HCC IRB were informed.
    - All IND safety reports received on study that have not occurred directly on this protocol. A letter will accompany the report indicating whether a consent form change or protocol change is required or other actions including a statement re: whether the report has been or will be submitted to DF/HCC IRB for review.
- NOTE: AEs will not be submitted to FDA for this study, as the trial was determined to be IND-exempt.
    - All communications with the FDA regarding this trial would be made by the Overall PI, as study sponsor (or an appropriate designee).

9. AGENT INFORMATION

9.1 Investigational Product: Pembrolizumab

Pembrolizumab is a potent humanized IgG4 mAb with high specificity of binding to the PD-1receptor, thus inhibiting its interaction with PD-L1 and PD-L2. Based on preclinical in vitro data, pembrolizumab has high affinity and potent receptor blocking activity for PD-1. Pembrolizumab has an acceptable preclinical safety profile and is being advanced for clinical development as an IV immunotherapy for advanced malignancies.

Additional detailed information on pembrolizumab is available in the Investigator's Brochure.

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

9.1.1 **Description**

Pembrolizumab is a humanized anti-PD-1 mAb of the IgG4/kappa isotype with a stabilizing S228P sequence alteration in the fragment crystallizable (Fc) region. Pembrolizumab binds to human PD-1 and blocks the interaction between PD-1 and its ligands. The theoretical molecular weight of the polypeptide is 146,288 Da and its theoretical pI is 7.5. Pembrolizumab exhibits linear pharmacokinetics at dose levels of clinical relevance (1-10 mg/kg). It exhibits low clearance and limited volume of distribution that is typical for therapeutic antibodies. Mean estimated t1/2 values are 14.1-21.6 days. Additional information on pembrolizumab nomenclature is detailed in the following table:

Table 10. Pembrolizumab Nomenclature Details

Code Name	Pembrolizumab (anti-PD-1)
Other Code Name	SCH 900475 (anti-PD-1)
Chemical Name	Humanized X PD-1 mAb (H409A11) IgG4
CAS Number	1374853-91-4
CAS Name	Anti-(human protein PDCD1 (programmed cell death 1)) immunoglobulin G4 (human-Mus musculus monoclonal heavy chain) disulfide with human-Mus musculus monoclonal light chain, dimer
Generic Name	Not available
Commercial Name	Pembrolizumab

9.1.2 **Form**

Pembrolizumab is supplied as a clear to opalescent solution that is essentially free of extraneous particles and may contain proteinaceous particulates. One dosage form of pembrolizumab will be provided by Merck in Type I glass vials intended for single use only as summarized in the Table 11 below.

The pembrolizumab to be supplied for this trial is commercial material which is manufactured in an FDA approved manufacturing facility and controlled in accordance with the KEYTRUDA BLA 125514.

Table 11. Pembrolizumab Study Supply Information

Product Name & Potency	Dosage Form	Source/Additional Information
Pembrolizumab 100 mg / 4 mL	Solution for Infusion	Provided centrally by Merck. • Liquid DP (manufactured using the fully formulated DS with L-histidine as a buffering agent, polysorbate 80 as a surfactant, and sucrose as a stabilizer/tonicity modifier) • Sterile, non-pyrogenic, aqueous, preservative-free solution. • Contains an excess fill of 6.25 mg (equivalent to 0.25 mL solution) to ensure the recovery of label claim of 100 mg pembrolizumab per vial (equivalent to 4.0 mL of solution).

9.1.3 **Packaging and Labeling Information**

Clinical supplies will be affixed with a clinical label in accordance with regulatory requirements. Vials will be provided in an open label fashion for subject dosing.

9.1.4 **Clinical Supplies Disclosure**

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

9.1.5 **Storage, Handling and Preparation Requirements**

Pembrolizumab is stored under refrigerated conditions (2° to 8°C), as specified in the Pharmacy Manual for pembrolizumab as provided by Merck.

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

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

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

9.1.6 **Administration**

Pembrolizumab will be administered as a 30 minute IV infusion using an infusion pump (treatment cycle intervals may be increased due to toxicity as described in Section 6.2). Sites should make every effort to target infusion timing to be as close to 30 minutes as possible. However, given the variability of infusion pumps from site to site, a window of -5 minutes and +10 minutes is permitted (i.e., infusion time is 30 minutes: -5 min/+10 min). Attach the infusion line to the pump and prime the line, either with normal saline (at least 25 mL) or with infusion solution as per local SOP, before starting the infusion. Maximum infusion rate should not exceed 6.7 ml/min through a peripheral or indwelling catheter. Use 30 mL normal saline to flush the infusion line at the end of the infusion if institutional guidelines allow.

Unused infusion solution should not be used for another infusion of the same participant or different participant.

DO NOT administer the product as an intravenous push or bolus.

DO NOT combine, dilute or administer it as an infusion with other medicinal products.

A central line is not required for Pembrolizumab administration, but may be used if available.

The following infusion set materials are compatible with Pembrolizumab

- PVC infusion set that is plasticized using Di-2-ethylhexyl Terephthalate DEHP
- PVC and tri-(2-ethylhexyl) trimellitate (TOTM) infusion set
- Polyehtylene lined PVC infusion set
- Polyrethane
- Plybutadiene

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

9.1.7 **Ordering**

Investigative sites will order and acquire Pembrolizumab directly from Merck per Section 4.0 of Appendix E (Data and Safety Monitoring Plan).

9.1.8 **Accountability**

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. The investigator, or a responsible party designated by the investigator, should maintain a careful record of the inventory and disposition of the agent using the NCI Drug Accountability Record Form (DARF) or another comparable drug accountability form. (See the NCI Investigator's Handbook for Procedures for Drug Accountability and Storage.)

9.1.9 **Destruction and Return**

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.

9.2 Bevacizumab*

* DFCI recently released a guideline re: the use of commercial biosimilars in clinical trials, which states: "for standard of care treatment using biologic products in a clinical trial that are not paid for by sponsor and that are billed as standard of care to patient's insurance, the biosimilar products dictated by the patient's insurance would be used." Therefore, on this study, sponsor will allow the use of a bevacizumab biosimilar.

Bevacizumab (NSC # 704865) is a humanized IgG1 monoclonal antibody (MAb) that binds all biologically active isoforms of human VEGF (or VEGF-A) with high affinity (kd = 1.1 nM). The antibody consists of a human IgG1 framework and the antigen-binding complementarity-determining regions from the murine anti-VEGF MAb A.4.6.1.16-18. Bevacizumab is commercially available and FDA approved for participants with recurrent glioblastoma. For further details and molecule characterization, see the bevacizumab FDA labeling information available at:
http://www.accessdata.fda.gov/scripts/cder/drugsatfda/index.cfm?fuseaction=Search.DrugDetails

The pharmacokinetic profile of bevacizumab was assessed using an assay that measures total serum bevacizumab concentrations (i.e., the assay did not distinguish between free bevacizumab and bevacizumab bound to VEGF ligand). Based on a population pharmacokinetic analysis of 491 participants who received 1 to 20 mg/kg of bevacizumab weekly, every 2 weeks, or every 3 weeks, the estimated half-life of bevacizumab was approximately 20 days (range 11−50 days). The predicted time to reach steady state was 100 days. The accumulation ratio following a dose of 10 mg/kg of bevacizumab every 2 weeks was 2.8.

The clearance of bevacizumab varied by body weight, gender, and tumor burden. After correcting for body weight, males had a higher bevacizumab clearance (0.262 L/day vs. 0.207 L/day) and a larger Vc (3.25 L vs. 2.66 L) than females. Participants with higher tumor burden (at or above median value of tumor surface area) had a higher bevacizumab clearance (0.249 L/day vs. 0.199 L/day) than participants with tumor burdens below the median.

9.2.1 Form

Bevacizumab is a clear to slightly opalescent, colorless to pale brown, sterile liquid concentrate for solution for intravenous (IV) infusion. Vials contain bevacizumab with phosphate, trehalose, polysorbate 20, and sterile water for injection (SWFI), USP. Vials contain no preservative and are suitable for single use only.

This agent is commercially obtained and is manufactured by Genentech.

9.2.2 Storage and Stability

According to guidelines specified in the package insert.

9.2.3 Preparation

According to guidelines specified in the package insert.

9.2.4 Administration

Bevacizumab is to be administered according to institutional standards and guidelines specified in the package insert.

The dose of bevacizumab is 15 mg/kg IV on Day 1 of each three-week cycle. A window of +/- 3 days for bevacizumab dosing is acceptable, but bevacizumab doses must always be at least 10 days apart.

There are no reductions in the bevacizumab dose. Guidelines for bevacizumab dose management due to adverse events considered at least possibly related to bevacizumab are summarized in Table 7. If adverse events occur that require holding bevacizumab, the dose will remain the same once treatment resumes. Patients who require bevacizumab hold or discontinuation are permitted to continue to receive study therapy with Pembrolizumab.

9.2.5 **Accountability**

The investigator or designated study personnel are responsible for maintaining accurate dispensing records of bevacizumab which are to include start time of infusion, stop time of infusion, total volume.

10. BIOMARKER STUDIES

The precise mechanism by which Pembrolizumab exerts anti-tumor activity is not clear but it is likely related to modulation of the immune system to generate anti-tumor immune responses that are capable of eliminating existing tumors and generating immune memory responses to prevent future relapse. The effect of PD-1 blockade on effector T cells and regulatory T cells is a critical component of anti-tumor activity. Archival tumor expression of PD-L1 will be evaluated. Archival tumor will be collected on all patients when available, and submission of archival tumor material will not be required prior to initiation of study therapy. In addition, if a biopsy or surgical resection is performed at the time of potential progression, a tumor sample (block or slides) should also be submitted if sufficient tumor material is available.

10.1 Archival Tumor PD-L1 Expression

If available, a minimum of 1 formalin-fixed paraffin-embedded (FFPE) archival tumor tissue block (preferred) or a minimum of 10 FFPE unstained sections from most recent pre-registration biopsy/surgery are to be submitted within 60 days of registration for tumor PD-L1 expression.

Guidelines for submission of archival tumor tissue:

- A memorandum indicating the study, the date of submission, name of study site submitting the tissue, and a list of contents. The DFCI Coordinating Center will supply a template memorandum to sites at the time of the SIV or upon request.
- A copy of the pathology and surgical report for the sample being submitted should be included in the shipment.
- Slides should be shipped in a plastic slide holder/slide box. Place a small wad of padding in top of the container in order to avoid slides breaking during shipping and handling process.
- An email is to be sent before or at the time of each shipment to the Coordinating Center (NeuroOnc_Coor@dfci.harvard.edu) indicating what is being shipped and when.
- Please note that the submitting institution is responsible for the costs of shipping and handling.

- Ship samples to:
  Dana-Farber Cancer Institute
  450 Brookline Ave, **LG-GC12D**
  Attn: DFCI Center for Neuro-Oncology Coordinating Center (Central Sub - study #18-277)
  Boston, MA 02215

  ph: 617-632-5394

Please find a sample requisition / shipment form for completion in Appendix C.

NOTE: Archival tumor samples will be shipped by Investigator Teams to the DFCI Coordinating Center, and subsequently batch shipped to a central lab determined by Merck for determination of PD-L1 expression at the end of the study.

10.2 Archival Tumor Immune Gene Expression Signature

If available, an additional formalin-fixed paraffin-embedded (FFPE) archival tumor tissue block - or 5-10 FFPE unstained sections from most recent pre-registration biopsy/surgery – will also be submitted within 60 days of registration for targeted gene expression profiling via a Nanostring assay.

Guidelines for submission of archival tumor tissue:

- A memorandum indicating the study, the date of submission, name of study site submitting the tissue, and a list of contents. The DFCI Coordinating Center will supply a template memorandum to sites at the time of the SIV or upon request.
- A copy of the pathology and surgical report for the sample being submitted should be included in the shipment.
- Slides should be shipped in a plastic slide holder/slide box. Place a small wad of padding in top of the container in order to avoid slides breaking during shipping and handling process.
- An email is to be sent before or at the time of each shipment to the Coordinating Center (NeuroOnc_Coor@dfci.harvard.edu) indicating what is being shipped and when.
- Please note that the submitting institution is responsible for the costs of shipping and handling.

Ship samples to:

Dana-Farber Cancer Institute
450 Brookline Ave, **LG-GC12D**
Attn: DFCI Center for Neuro-Oncology Coordinating Center (Central Sub - study #18-277)
Boston, MA 02215

ph: 617-632-5394

Please find a sample requisition / shipment form for completion in Appendix C.

NOTE: Archival tumor samples will be shipped by Investigator Teams to the DFCI Coordinating Center, and subsequently batch shipped to a central lab determined by Dr. Reardon for targeted gene expression profiling via a Nanostring assay at the end of the study.

11. STUDY CALENDAR (Protocol Table 12)

Baseline evaluations are to be conducted within 14 days of start of protocol therapy unless indicated otherwise. Pre-treatment baseline brain MRI must be done ≤ 14 days prior to the start of therapy. Cycles are 3 weeks (21 days). Study assessments must be performed and reviewed prior to administration of any study agent at any treatment visit. Study assessments and agents should be administered within +/-3 days of the protocol-specified date, unless otherwise noted.

Assessments	Screening [a]	Pembro/Bev Treatment Cycles		End of Tx [c, gg]	30-Day Post Last Dose [d, gg]	Follow-Up	
		Cycle 1 D1[b]	D1[b] of Subsequent Cycles			Active [e]	Long Term [f]
Informed consent [g]	X						
Background information/history [h]	X						
Inclusion/exclusion criteria [i]	X						
Vital signs [j, gg]	X	X	X	X			
Resting O_2 sat by pulse oximetry	X						
Physical Exam [k]	X	X[k]	X	X			
Neurologic Exam [l]	X	X	X	X			
Karnofsky Performance Status [m]	X	X	X	X	X		
Concomitant medications [n]	X	X[n]					
Adverse event assessment [o]		X[o]					
Pregnancy Test – Urine or Serum β-HCG [p]	X	X	X	X			
Coagulation [q]	X						
Hematology [r]	X	X	X	X			
Serum Chemistry [s, gg]	X	X	X	X			
Urinalysis [t, gg]	X	X	X				
T3, FT4, TSH [u]	X	X	X	X			
EORTC QLQ-C30 [v]		X	X	X			
Imaging – CT or MRI [w]	X	X	X	X		X	
Response Assessment [x]		X	X	X		X	
NANO Scale [y]	X	X	X	X		X	
Pembrolizumab [z]		X	X				
Re-Irradiation [aa]		X [aa]					
Bevacizumab (or biosimilar)		X	X				
Submission of archival tissue [cc]		X	X				
Submission of tumor sample at the time of progression or suspected progression [dd]							
Post-end-of-treatment oncology therapies [ee]					X	X	X
Survival [ff]					X	X	X

Footnotes:

a. All screening procedures to be performed within 14 days of start of study treatment, except informed consent may occur up to 28 days prior to registration.
b. Day 1 Assessments:
    a. For C1D1 - and Day 1 of Re-Irradiation - Assessments ONLY: Screening assessments may serve as day 1 assessments *(exceptions below)*:
        i. Pregnancy Test: In the event that 72 hours have elapsed between the screening pregnancy test and the first dose of study treatment, another pregnancy test - urine or serum - must be performed and confirmed negative before subject may receive Day 1 dose
        ii. In the event that there are any indications that the participant's condition is deteriorating, laboratory evaluations should be repeated within 48 hours prior to initiation.
    b. For all subsequent Day 1 assessments: Required assessments will be performed and reviewed prior to study agent administration (+/-3 days of scheduled cycle day 1).
        i. Pembrolizumab and bevacizumab (or biosimilar) to be administered +/-3 days from Day 1 of each cycle.
c. End of Tx: End of treatment assessments to be performed within 7 days after last day drug administration or within 7 days after decision to end treatment. Assessments may continue for ongoing reportable adverse events.
d. 30-Day Post Drug: A contact/visit is to be performed at 30 days (+7 days) after the last study drug is given. This may be performed via documented phone conversation with a study nurse or clinician or a clinic visit. All participants will be followed until resolution or stabilization of any serious or reportable adverse events occurring during treatment or starting within 30 days of last study drug.
e. Active Follow Up: For participants who discontinue study treatment for reasons other than disease progression, every effort should be made to continue monitoring their disease status by radiologic imaging at a schedule developed by the treating investigator until: (1) documented disease progression, (2) death or (3) the end of the study, whichever occurs first.
f. Long Term Follow Up: Participants will be followed every 3 months (+/- 1 month) via contact or medical record review until death for post-treatment therapies, reason for stopping those therapies, and survival.
g. Informed Consent: Must be obtained by MD attending. No study specific screening procedures may occur until after the informed consent process is complete. Informed Consent may be obtained within 28 days of registration.
h. Background information/history: To include review of treatment history for GBM, any ongoing medical conditions and medical history pertaining to eligibility on study and involvement during study.
i. Inclusion/exclusion criteria: Source documentation providing investigator's confirmation that the participant had met all eligibility criteria must be available prior to registration.
j. Vital signs: Weight, heart rate, blood pressure, & respiration rate. Vital signs must be performed prior to administration of treatment on treatment days. Temperature is required at screening and should be obtained as clinically indicated thereafter. Height required only at screening and may be obtained within 1 year of registration.
k. Physical Exams: Complete Physical Exam will be completed by the investigator or qualified designee at screening, C1D1, weekly while receiving RT (during Cycle 1), and at the start of all subsequent cycles.
l. Neurologic Exam: To be completed by the investigator or qualified designee at screening, C1D1 and start of all subsequent cycles.
m. Performance Status: See Appendix A for KPS scale.
n. Concomitant medications: Concomitant medications and reason for administration should be documented in the case history from within 28 days before starting study treatment up to the 30-Day Post Drug Visit. Concomitant medications administered after 30 days after the last dose of trial treatment should be recorded for SAEs and ECIs.
o. Adverse event assessment: Adverse events experienced by participants will be collected and recorded registration to the 30-Day Post Last Dose Visit (+ 7 days depending on when 30-Day Post Last Dose visit/contact occurs) and all SAEs (related and unrelated to trial treatment) / ECIs up to 90 days after the last dose of trial treatment or the start of new anti-cancer treatment, whichever comes first. Afterwards, report only SAEs and ECIs that are considered related to trial treatment.
    a. NOTE: Adverse events may also occur in screened subjects during pre-dose period as a result of a protocol-specific intervention, including washout or discontinuation of usual therapy, diet, placebo treatment or a procedure.
p. Pregnancy Test: For women of child bearing potential, a pregnancy test must be performed. If urine pregnancy results cannot be confirmed as negative, a serum pregnancy test will be required.
q. Coagulation: PT, PT/INR, aPTT required at screening only and then as clinically indicated.
r. Hematology: erythrocytes (RBC), hemoglobin, hematocrit, platelets, total WBC plus differential (neutrophils,

lymphocytes, monocytes, eosinophils, basophils).

s. Serum Chemistry: albumin, alkaline phosphatase (ALP), bicarbonate/HCO3 or CO2 *(if considered standard of care in your region)*, BUN, calcium, chloride, creatinine, glucose, lactate dehydrogenase (LDH), magnesium, phosphorus, potassium, SGOT (AST), SGPT (ALT), sodium, total protein, total bilirubin (direct bilirubin, if total bilirubin is elevated above the upper limit of normal), uric acid.

t. Urinalysis: blood, glucose, protein, specific gravity. Microscopic exam if abnormal results are noted. If dipstick protein is ≥ 2+, then a urine protein creatinine ratio should be obtained.

u. T3, FT4, & TSH: total triiodothyronine (T3), free tyroxine (T4), and thyroid stimulating hormone (TSH). T3, FT4, & TSH must be drawn prior to pembrolizumab administration; if results are not available for review prior to pembrolizumab administration, study treatment may proceed. Results should be reviewed when they become available.

v. In most cases, EORTC QLQ-C30 Assessments to be self-administered by patients; when necessary, they may be administered by a qualified Study Team member; see Appendix G for copies of the QOLs. NOTES:
    a. Scores do NOT need to be documented and reviewed prior to patient receiving study therapy.
    b. If the QLQ is administered as an interview, the patient's responses will be recorded verbatim and the interviewer should not influence the patient's answers.

w. Imaging: gadolinium-enhanced contrast and non-contrast MRI. CT alternative, if MRI contraindicated. Initial imaging should be performed within 14 days prior to start of study therapy. On-study imaging should be performed every 6 weeks, on Day 1 of Cycle 3 and every odd cycle for the first year, and then every 9 weeks (Day 1 of every 3rd cycle) thereafter. Scans should be performed within 7 days prior to the cycle start (and *ideally* within 3 days prior). Adjustments to this -7 day window are allowable per the treating physician's discretion; however, restaging scans MUST BE performed and reviewed before the subsequent cycle's dose may be initiated.
    a. NOTE: The same imaging technique should be used for a participant throughout the trial, whenever feasible. Local reading (investigator assessment) will be used to determine eligibility and for participant management.
    b. NOTE: In the event that a study patient has a treatment-delay, the imaging interval will be maintained at every 6 weeks (every 9 weeks after 1 year on treatment) rather than adjusted to align with updated timing of odd cycle restaging.

x. Response Assessment – Per modified RANO criteria (section 11);

y. NANO scale (Section 12.6) will be completed by delegated study physician or mid-level prior to Cycle 1 Day 1 dose, and then with each MRI (but must be completed before MRI scan results are reviewed with the subject) using the scorecard provided in Appendix D.

z. See Sections 6.5.1 & 9.1 for pembrolizumab details. Pembrolizumab to be administered +/-3 days from Day 1 of each cycle *(aside from C1D1)*.

aa. Re-irradiation will ideally start on Day 1 of pembrolizumab/bevacizumab (or biosimilar) Cycle 1, but can start +/- 7 days from C1D1. See Section 6.5.2 for re-irradiation details.

bb. See Section 6.5.3 & 9.2 for bevacizumab (or biosimilar) details. Bevacizumab (or biosimilar) to be administered +/-3 days from Day 1of each cycle *(aside from C1D1)*, and bevacizumab (or biosimilar) doses must always be at least 10 days apart

cc. Submission of archival tissue: Available tissue from most recent pre-registration biopsy/surgery to be submitted within 60 days of registration, if feasible. Please see section 10 for details.

dd. Submission of tumor sample at the time of progression or suspected progression: submission of available tissue from tumor sample at the time of progression or suspected progression (per section 10) within 60 days of resection, biopsy, if feasible. This is an optional submission.

ee. Post-end-of-treatment oncology therapies: Start/stop dates, names of treatment regimens and reason for stopping should be collected.

ff. Survival: Date of death and reason should be collected for overall survival purposes, when applicable.

gg. Although an explanation must be documented and filed in patient's research chart, the following scenarios will not be considered protocol violations if the circumstances are beyond the study team's ability to control:
- Patient is unable to be weighed by standard methods in clinic, and weight is not needed at that visit for bev dose calculation.
- Missed EOT or 30-day-follow-up labs or assessments if decision to come off active study treatment is made when patient is not on site
- Urinalysis is not performed at a given timepoint because patient is PHYSICALLY UNABLE to provide a sample
- Blood sample is collected but hemolyzes prior to analysis

12. MEASUREMENT OF EFFECT

Tumor response will be assessed by MRI (or CT, if MRI contraindicated) every 6 weeks, on Day 1 of Cycle 3 and every odd cycle for the first year, and then every 9 weeks (Day 1 of every 3rd cycle) thereafter. Scans should be performed within 7 days prior to the cycle start (and ideally within 3 days prior). Adjustments to this -7 day window are allowable per the treating physician's discretion; however, restaging scans MUST BE performed and reviewed before the subsequent cycle's dose may be initiated. Modified RANO criteria[1] will be utilized as outlined below. Clinicians may repeat response assessment more frequently as clinically indicated.

> NOTE: In the event that a study patient has a treatment-delay, the imaging interval will be maintained at every 6 weeks (every 9 weeks after 1 year on treatment) rather than adjusted to align with updated timing of odd cycle restaging.

Local radiologic assessment of tumor measurements will be used during the study for clinical management and investigator-assessed disease progression. Cases of suspected radiologic disease progression will be confirmed by an MRI (or CT, as applicable) performed approximately 12 weeks after the initial radiological assessment of progression, as described below.

12.1 Anti-Tumor Effect Definitions

12.1.1 **Evaluable for toxicity:** All participants who receive at least one dose of study treatment will be evaluable for toxicity from the time of their first treatment.

12.1.2 **Evaluable for objective response:** Only those participants who have measurable disease present at baseline (obtained within 14 days of cycle 1, day 1) scan and have received at least one dose of therapy will be considered evaluable for response. These participants will have their response classified according to the definitions stated below. (Note: Participants who exhibit objective disease progression or die prior to the end of cycle 1 will also be considered evaluable.)

12.1.3 **Measurable disease:** Bi-dimensionally, contrast-enhancing, measurable lesions with clearly defined margins by CT or MRI scan, with a minimal diameter of 1 cm, and visible on 2 axial slices which are at least 5 mm apart with 0 mm skip. Measurement of tumor around a cyst or surgical cavity, if necessary, requires a minimum thickness of 3 mm. If there are too many measurable lesions to measure at each evaluation, the investigator must choose the largest two to be followed before a participant is entered on study. The remaining lesions will be considered non-measurable for the purpose of objective response determination. Unless progression is observed, objective response can only be determined when all measurable and non-measurable lesions are assessed.

12.1.4 **Non-measurable evaluable disease:** Unidimensionally measurable lesions, masses with margins not clearly defined, lesions with maximal diameter < 1cm.

12.2 Response/Progression Categories

Investigator-assessed tumor response will be based upon RANO/iRANO criteria. Radiologic response will be assessed by comparing the pretreatment baseline and on-treatment MRI scans. Radiologic progression will be determined by using the smallest tumor measurement at either the pretreatment baseline or after initiation of study medication. Table 13 describes the radiologic and clinical criteria that will be used for determining tumor response.

Table 13 Criteria for Response Assessment Incorporating MRI and Clinical Factors	
Response	**Criteria**

Complete Response	Requires all of the following:
	• Complete disappearance of all enhancing measurable and non-measurable disease sustained for at least 4 weeks;
	  o *In the absence of a confirming scan 4 weeks later, this scan will be considered only stable disease.*
	• No new lesions;
	• Stable or improved non-enhancing (T2/FLAIR) lesions;
	• Patients must be off corticosteroids (or on physiologic replacement doses only);
	• And stable or improved clinically.
	  o *Any clinical signs/symptoms must have been present at baseline and noted as disease-related*
	Notes:
	- *All measurable and non-measurable lesions must be assessed using the same techniques as baseline.*
	- *Patients with non-measurable disease only cannot have a complete response; the best response possible is stable disease.*

Partial Response	Requires all of the following:
	• ≥ 50% decrease compared with baseline in the sum of products of perpendicular diameters of all measurable enhancing lesions sustained for at least 4 weeks;
	  o *In the absence of a confirming scan 4 weeks later, this scan will be considered only stable disease.*
	• No progression of non-measurable disease;
	• No new lesions;
	• Stable or improved non-enhancing (T2/FLAIR) lesions on same or lower dose of corticosteroids compared with baseline scan;
	• The corticosteroid dose at the time of the scan evaluation should be no greater than the dose at time of baseline scan;
	• And stable or improved clinically.
	  o *Any clinical signs/symptoms must have been present at baseline and noted as disease-related*
	Notes:
	- *All measurable and non-measurable lesions must be assessed using the same techniques as baseline.*
	- *Patients with non-measurable disease only cannot have a complete response; the best response possible is stable disease.*

Progressive Disease	Defined by any of the following: • ≥ 25% increase in sum of the products of perpendicular diameters of enhancing lesions compared with the smallest tumor measurement [obtained either at baseline (if no decrease) or best response], on stable or increasing doses of corticosteroids*; • Any new enhancing measurable lesion; • Clear clinical deterioration not attributable to other causes apart from the tumor (eg, seizures, medication adverse effects, complications of therapy, cerebrovascular events, infection, and so on) or changes in corticosteroid dose; o *The definition of clinical deterioration is left to the discretion of the*

	investigator, but it is recommended that a decline in the Karnofsky Performance Score (KPS) from 100 or 90 to 70 or less, a decline in KPS of at least 20 from 80 or less, or a decline in KPS from any baseline to 50 or less, for at least 7 days, be considered neurologic deterioration, unless attributable to co-morbid events or changes in corticosteroid dose. • Cohort B: Significant increase in T2/FLAIR non-enhancing lesions on stable or increasing doses of corticosteroids compared with baseline scan or best response after initiation of therapy* not felt to be caused by co-morbid events (eg, radiation therapy, tumor flare from inflammation due to immunotherapy, demyelination, ischemic injury, infection, seizures, postoperative changes, or other treatment effects); • Clear progression of non-measurable disease; • Or failure to return for evaluation as a result of death or deteriorating condition. <u>Notes</u>*:* - *Confirmation of radiographic progression should be performed on follow-up imaging for participants who are not developing significant neurologic decline felt to be attributable to underlying tumor growth as detailed in Section 12.4.*
<u>Stable Disease</u>	Requires all of the following: • Does not qualify for complete response, partial response, or progression; • Stable non-enhancing (T2/FLAIR) lesions on same or lower dose of corticosteroids compared with baseline scan. • And stable clinically. <u>Notes</u>*:* - *All measurable and non-measurable lesions must be assessed using the same techniques as baseline.* -
<u>Unknown response status</u>	Progressive disease has not been documented and one or more measurable or non-measurable lesions have not been assessed.
* Stable doses of corticosteroids include subjects not on corticosteroids Abbreviations: MRI, magnetic resonance imaging; FLAIR, fluid-attenuated inversion recovery	

For purposes of this study, the minimum time from baseline for determination of SD will be 4 weeks.

The modified RANO Response Criteria to be used in this study are summarized in Table 14:

Table 14. Summary of the RANO Response Criteria

	CR	PR	SD	PD#
T1-Gd +	None	≥50% decrease	<50% decrease-<25% increase	≥25% increase*
T2/FLAIR	Stable or decrease	Stable or decrease	NA	NA
New Lesion	None	None	None	Present*
Corticosteroids	None	Stable or decrease	Stable or decrease	Stable or increasing
Clinical Status	Stable or increase	Stable or increase	Stable or increase	Decrease*
Requirement for Response	All	All	All	Any*

CR=complete response; PR=partial response; SD=stable disease; PD=progressive disease; NA= not applicable

#: Progression occurs when any of the criteria with * is present

Increase in corticosteroids alone will not be taken into account in determining progression in the absence of persistent clinical deterioration

Of note, patients who require increased corticosteroids within two weeks of MRI assessment (relative to the dose taken at the time of the prior assessment) cannot be classified as CR, PR or SD and should be classified as non-evaluable at that time point. Conversely, patients who decrease corticosteroids within two weeks of MRI assessment (relative to the dose taken at the time of the prior assessment) cannot be classified as PD and should be classified as non-evaluable.

12.3 Methods for Evaluation of Measurable Disease

All measurements should be taken and recorded in metric notation, using a ruler, calipers, or digital measurement tool. All baseline evaluations should be performed as closely as possible to the beginning of treatment and never more than 14 days before the beginning of the treatment.

The same method of assessment and the same technique should be used to characterize each identified and reported lesion at baseline and during follow-up.

12.4 Evaluation of Best Response

The best overall response is the best response recorded from the start of the treatment until disease progression (taking as reference for progressive disease the smallest measurements recorded since the treatment started). If a response recorded at one scheduled MRI does not persist at the next regular scheduled MRI, the response will still be recorded based on the prior scan, but will be designated as a non-sustained response. If the response is sustained, i.e. still present on the subsequent MRI at least four weeks later, it will be recorded as a sustained response, lasting until the time of tumor progression. Participants without measurable disease may only achieve SD or PD as their best "response."

12.5 Study Continuation Beyond Initial Progressive Disease

Immunotherapeutic agents such as pembrolizumab may produce antitumor effects by potentiating endogenous cancer-specific immune responses which may manifest as initial worsening of enhancement and edema on MRI or CT scans (i.e. pseudoprogression). In addition, the response patterns seen with immunotherapeutics may extend beyond the typical time course of responses seen with cytotoxic agents, and can manifest a clinical response after an initial increase in tumor burden or even the appearance of new lesions. For these reasons, the immune-related response criteria (irRC) have endorsed continuation of study therapy beyond initial radiographic evidence of progression for clinically stable patients undergoing immune based therapies.[62]

A major advance of the RANO criteria[1] to assess response in neuro-oncology over the previously used Macdonald criteria[63] includes recognition of the prevalence of pseudoprogression during the first three months following completion of radiation and daily temozolomide.[64,65] Specifically, RANO permits patients with such progressive MRI findings to continue temozolomide therapy for up to three months in order to avoid inaccurately classifying such patients as progressive. Furthermore, RANO permits patients with progressive radiographic findings at any time to continue current therapy pending follow-up imaging if the etiology of progressive imaging findings is unclear. Standard RANO may not provide an accurate response assessment of immunotherapeutic agents such as pembrolizumab.

Therefore, the following adaptations of the RANO criteria, as reflected in the Immunologic Response Assessment in Neuro-Oncology (iRANO) criteria[66] will be used to assess response for patients treated on this study (Table 15):

- Potential Pseudoprogression: If radiologic imaging shows initial PD, participants who are not experiencing significant clinical decline, may be allowed to continue study treatment for up to three months. Patients who have radiographic evidence of further progression after up to three months, or who decline significantly at any time, will be classified as progressive with the date of disease progression back-dated to the first date that the participant met criteria for progression and such participants will be discontinued from study therapy. Although the kinetics of pseudoprogression due to immune checkpoint blockade among glioblastoma patients is currently unknown, three months is a reasonable estimate based on: 1) the peak time for XRT/daily temozolomide-related pseudoprogression is usually within three months of completion for glioblastoma patients[64,65] and; 2) three months is also the most common timeframe for pseudoprogression observed among patients with advanced melanoma or other solid tumors treated with PD-1/PD-L1immune checkpoint blockade to date.[67-69]

  Among patients on this study with initial radiographic PD, tumor assessment should be repeated regularly in order to confirm PD with the option of continuing treatment as described below while awaiting radiologic confirmation of progression. If repeat imaging shows a stabilization or reduction in the tumor burden compared to the initial scan demonstrating PD, treatment may be continued / resumed. If repeat imaging after up to three months confirms progressive disease, then the date of disease progression will be the first date the participant met criteria for progression and participants will be discontinued from study therapy. Participants who have confirmed disease progression will discontinue study medication and enter the follow up/survival phase of the study. In determining whether or not the tumor burden has increased or decreased, investigators should consider all target lesions as well as non-target lesions.

In participants who have initial evidence of radiographic PD, it is at the discretion of the treating physician whether to continue a participant on study treatment for up to three months pending confirmation of PD on follow-up imaging. This clinical judgment decision should be based on the participant's overall clinical condition, including performance status, clinical symptoms, and laboratory data. Participants may receive study treatment while waiting for confirmation of PD if they are not experiencing significant clinical decline and if:

- The participant is believed to demonstrate clinical benefit from the study regimen as determined by the treating physician;
- The participant is adequately tolerating study therapy.

When feasible, study therapy should not be discontinued until radiographic progression is confirmed. This allowance to continue treatment despite initial radiologic progression takes into account the observation that some participants can have a transient tumor flare in the first few months after the start of immunotherapy, but with subsequent disease response.[62] Participants that are exhibiting significant neurologic decline are not required to have repeat imaging for confirmation of progressive disease.

Table 15. Imaging and Treatment After 1st Radiologic Evidence of Progression

1st radiologic evidence of PD

	Imaging	Treatment
No Significant Neurologic Decline	Repeat imaging for up to 3 months to confirm PD	May continue study treatment at the Investigator's discretion for up to 3 months while awaiting confirmatory scans
Significant Neurologic Decline	Repeat imaging >6 weeks later to confirm PD if possible	Discontinue treatment

Repeat scan after 3 months

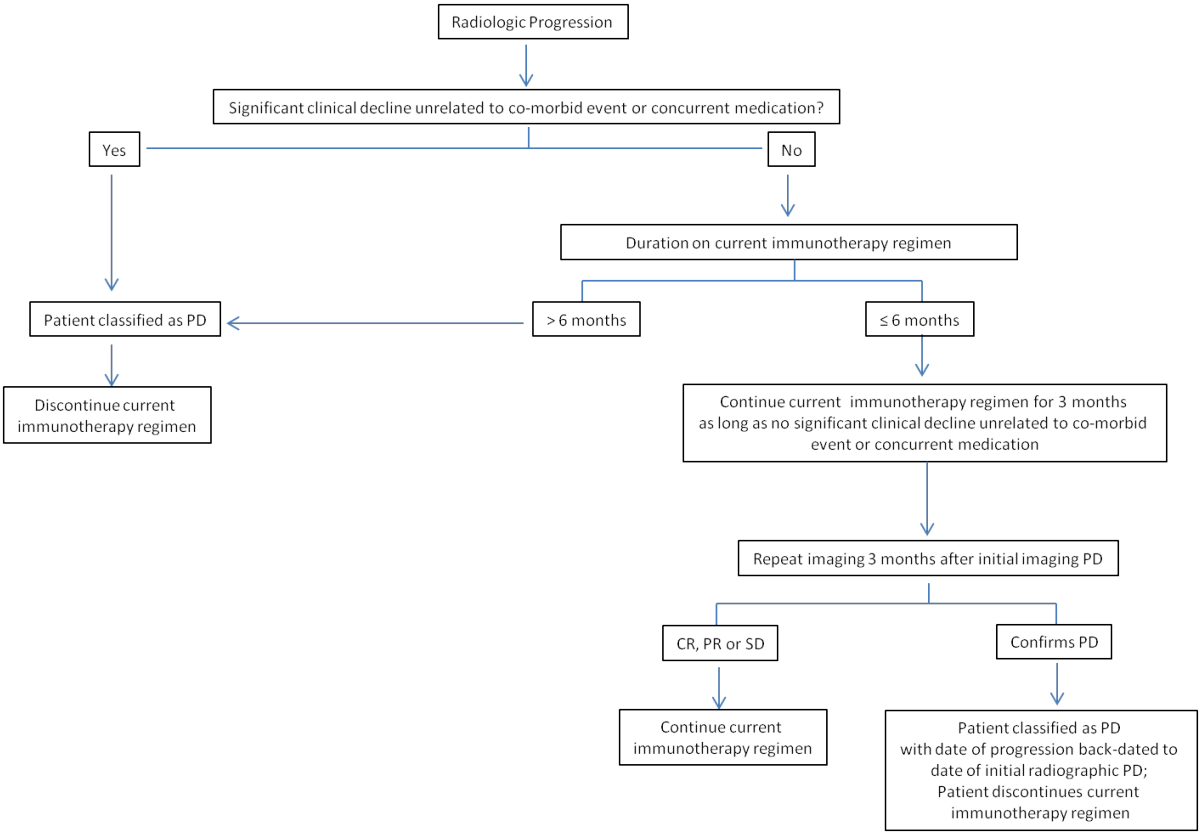
Repeat scan confirms PD

	Imaging	Treatment
No Significant Neurologic Decline	No additional imaging required; date of tumor progression back-dated to date of initial radiographic PD	Discontinue treatment
Significant Neurologic Decline	No additional imaging required; date of tumor progression back-dated to date of initial radiographic PD	Discontinue treatment

Repeat scan shows SD, PR or CR

	Imaging	Treatment
No Significant Neurologic Decline	Continue regularly scheduled imaging assessments every 6 weeks	Continue study treatment at the Investigator's discretion
Significant Neurologic Decline	Continue regularly scheduled imaging assessments every 6 weeks	May restart study treatment if condition has improved and/or clinically stable per Investigator's discretion

Figure 2 iRANO Algorithm for Treatment Decision Making for Radiographic Progression



Participants with progressive radiographic findings are encouraged to undergo surgical intervention in order to delineate pseudoprogression due to inflammation associated with PD-1 blockade from true tumor progression. Participants with histopathologic findings of significant immune infiltrate and evolving gliosis will be allowed to continue study therapy. In contrast, those with clear evidence of progressive tumor by histopathologic evaluation will be defined as progressive and discontinued from study therapy. For such patients, the date of tumor progression will be the first date the participant met radiographic criteria for PD.

12.6 Central Radiology Review

For this trial where the objective response rate is the primary co-endpoint, all responses determined by the investigator assessment will be reviewed by an expert(s) independent of the study at its completion. This independent review of neuroimaging (MRI or CT) - to include simultaneous review of the participants' files including corticosteroids usage and neurological status - will be performed centrally by an objective Investigator to be determined by Overall PI.

All films of all views from pre-registration and subsequent scans must be submitted for central review when requested from the DFCI Coordinating Center on behalf of the Overall PI. CDs are preferred.

A copy of the local treating investigator's tumor measurements and response assessment must be submitted with the films. A copy of all scan reports must be attached for inclusion in the submission.

NOTE: Information re: participants' steroids usage and neurological status will be gathered from the study's database, but the review itself may result in queries / requests for confirmatory source from the site.

Once the Central Review is complete the Reviewing Physician will document the review results. Once the Central Review is complete, the central review results can be made available to the local PI.

When requested from the DFCI Coordinating Center, please send a copy of all scans (and any corresponding paperwork) to:

David A. Reardon, MD
c/o Christine McCluskey
Center for Neuro-Oncology
Dana-Farber Cancer Institute
450 Brookline Ave, LG1B12F
Boston, MA 02215
ph: 617-632-5394
fax: 617-394-2683
NeuroOnc_Coord@dfci.harvard.edu

A memo must be submitted to the DFCI Coordinating Center each time submissions are made including DFCI study number, participant identifiers and details of what is being submitted.

The submitting institution is responsible for the costs of shipping and handling.

12.7 Neurologic Assessment in Neuro-Oncology (NANO) Scale

The Neurologic Assessment in Neuro-Oncology (NANO) scale (Appendix D) was developed by an international, multidisciplinary committee of neuro-oncology experts to objectively assess neurologic function of neuro-oncology patients.[70] In this trial, the NANO scale will be assessed by the investigator or designated study physician or mid-level at baseline (prior to ignition of study treatment) as well as at each clinic visit that includes an MRI evaluation as a method to characterize relevant changes in neurologic function. Of note, the NANO scale will not be used in this study to define clinical progression because the scale has not been adequately validated to date.

13. DATA REPORTING / REGULATORY REQUIREMENTS

13.1 Data Reporting

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

13.1.1 Responsibility for Data Submission

All investigative sites are responsible for submitting data and/or data forms to the ODQ according to the schedule set by the ODQ as noted in Table 16 below.

Table 16. Study Data Submission Table

Form	**Submission Timeline**
Eligibility Checklist	Complete prior to study registration
On Study Form	Within 30 days of registration
Baseline Assessment Form	Within 30 days of registration
Treatment Form	Within 30 days of treatment administration
Adverse Event Report Form	Within 30 days of AE assessment/notification
Response Assessment Form	Within 30 days of the response assessment
Off Treatment/Off Study Form	Within 30 days of completing treatment or being taken off study for any reason
Follow up/Survival Form	Within 30 days of the protocol defined follow up visit date or call

13.1.2 **Data Safety Monitoring**

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

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

13.1.3 **Multicenter Guidelines**

This protocol will adhere to the policies and requirements of the DF/HCC Multi-Center Data and Safety Monitoring Plan (Appendix E), which includes the specific responsibilities of the Overall PI, Coordinating Center, and Participating Institutions and the procedures for auditing.

- The Overall PI/Coordinating Center is responsible for distributing all IND Action Letters or Safety Reports to all participating institutions for submission to their individual IRBs for action as required.
- Mechanisms will be in place to ensure quality assurance, protocol compliance, and adverse event reporting at each site.
- Except in very unusual circumstances, each participating institution will order the study agent(s) directly from supplier. A participating site may order the agent(s) only after the initial IRB approval for the site has been forwarded to the Coordinating Center.

14. STATISTICAL ANALYSIS PLAN

This section outlines the statistical analysis strategy and procedures for the study. If, after the study has begun, changes are made to primary and/or key secondary hypotheses, or the statistical methods related to those hypotheses, then the protocol will be amended (consistent with ICH Guideline E-9). Changes to exploratory or other non-confirmatory analyses made after the protocol has been finalized, along with an explanation as to when and why they occurred, will be listed in the Clinical Study Report (CSR) for the study. Post hoc exploratory analyses will be clearly identified in the CSR. No separate Statistical Analysis Plan (SAP) for the primary, secondary and exploratory endpoints will be issued for this study.

14.1 Statistical Analysis Plan Summary

This section contains a summary of the statistical analyses for this trial. This trial includes allocation of accrual to two experimental treatment arms including patients who are bevacizumab naïve (Cohort A) and those who have progressed on one prior bevacizumab regimen (Cohort B). The outcome of each treatment arm will be assessed separately relative to appropriate historical controls. Enrollment will continue until target accrual for each arm is achieved. The two experimental arms will not be compared to each other and are independently designed as phase II studies for preliminary assessment of efficacy in comparison to historical control rates. Both arms have independent decision rules. Full detail is in the Statistical Analysis Plan (SAP) (Section 14.2).

14.1.1 **Efficacy Analysis**

The primary and key secondary endpoints, primary analysis population, and statistical methods that will be employed for the efficacy analyses are discussed in detail in the following sections**.**

The primary hypothesis of efficacy will be evaluated independently in each cohort.

14.1.2 **Safety Analyses**

Adverse events will be graded according to Common Terminology Criteria for Adverse Events (CTCAE) version 4.0. All patients who receive any amount of Pembrolizumab will be evaluable for toxicity. The All-Patients-as-Treated population will be employed for safety analyses. Immune related adverse experiences are prespecified as Events of Clinical Interest (Section 8.4.4.2).

14.2 Statistical Analysis Plan

14.2.1 **Responsibility for Analyses/In-House Blinding**

The statistical analysis of the data obtained from this study will be the responsibility of the biostatistics department of the Dana-Farber/Harvard Comprehensive Cancer Center.

This trial is being conducted as an open-label study, i.e., participants, investigators, and sponsor personnel will be aware of participant treatment assignments after each participant is enrolled and treatment is assigned.

14.2.2 **Hypotheses/Estimation**

Objectives and hypotheses of the study are stated in Section 2 (2.2 – 2.4).

14.2.3 **Power and Sample Size**

Participants will enroll to one of two treatment arms in order to estimate the anti-tumor activity as well as safety of pembrolizumab plus re-irradiation among bevacizumab-naive (Cohort A) as well as bevacizumab-refractory (Cohort B) patients. Up to 35 participants will accrue to each cohort, with the goal of treating 30 eligible patients. Statistical success will be evaluated separately for each cohort relative to historical controls as described below.

The primary objective of cohort A is to evaluate the efficacy of pembrolizumab plus re-RT in bevacizumab naïve patients through the frequency of participants with objective tumor responses and the frequency of participants who survive for at least 12 months (OS12). The null hypothesis relating to uninteresting levels of activity was determined from historical data. Fogh et al. reported on 147 patients treated with re-RT for recurrent high-grade astrocytoma and found an objective response rate (ORR) of < 10% and median survival of 11 months.[19] The null hypothesis is specified for each endpoint independently. the null probability of a participant experiencing a tumor response – ORR – is set at ≤ 10% and the null probability of a patient being alive at 12 months – OS12 is set at ≤ 45%. Clinically significant differences constitute an increase in ORR to 30% and/or an increase in OS12 to 70%. For the ORR endpoint, enrollment of 30 participants will provide 84% power at 0.026 significance level to reject the null in favor of the alternative. For the OS12 endpoint, 30 patients will provide 84% power at 0.03 significance level to reject the null in favor of the alternative. If ≥7 Cohort A participants have responses and/or ≥19 Cohort A participants are alive at 12 months, this regimen will be deemed worthy of further study.

The primary objective of cohort B is to evaluate the efficacy of continuation of bevacizumab and addition of pembrolizumab plus re-RT in bevacizumab resistant participants through the frequency of participants with objective tumor responses and the frequency of participants who survived for at least 6 months (OS6). The null hypothesis relating to uninteresting levels of activity was determined from historical data. Reardon et al. reported on 33 GBM patients treated with continuation of bevacizumab and addition of metronomic chemotherapy post bevacizumab progression and found no objective responses and median survival of 4 months.[6] The CABARET study which compared continuing bevacizumab to cessation of therapy following disease progression on bevacizumab also showed no objective responses and median survival of 3.4 months.

The null hypothesis is specified for each endpoint independently. The null probability of a participant experiencing a tumor response – ORR – is set at ≤ 4% and the null probability of a participant being alive at 6 months – OS6 – is set at ≤ 25%. Clinically significant differences constitute an increase in ORR to 20% and/or an increase in OS6 to 50%. For the ORR endpoint, enrollment of 30 participants will provide 87% power at 0.03 significance level to reject the null in favor of the alternative. For the OS6 endpoint, 30 patients will provide 89% power at 0.0507 significance level to reject the null in favor of the alternative. If ≥4 Cohort B participants have a response and/or ≥12 Cohort B participants are alive at 6 months, this regimen will be deemed worthy of further study.

14.2.4 **Analysis Endpoints**

Efficacy and safety endpoints that will be evaluated for within- and/or between-treatment differences are listed below, followed by the descriptions of the derivations of selected endpoints.

14.2.4.1 **Efficacy Endpoints**

Efficacy endpoints that will be evaluated for are listed below, followed by the descriptions of the derivations of selected endpoints.

Objective response rate, defined as the proportion of participants in the analysis population who achieve a complete response (CR) or partial response (PR) using RANO criteria[1] is a primary endpoint for each cohort. Overall survival at 12 months, defined as the proportion of participants in the analysis population who are alive for at least 12 months following initiation of study therapy is also a primary efficacy endpoint for cohort A. Overall survival at 6 months, defined as the proportion of participants in the analysis population who are alive for at least 6 months following initiation of study therapy is also a primary efficacy endpoint for cohort B. Response for the primary analysis will be determined by the investigator assessment, and a confirmation assessment is required per RANO.[1] All patients in Cohort A will be followed for a minimum of 12 months and all patients in Cohort B will be followed for a minimum of 6 months.

For this trial where the objective response rate is the primary co-endpoint, all responses determined by the investigator assessment will be reviewed by an expert(s) independent of the study at its completion. Simultaneous review of the participants' files including corticosteroids usage and neurological status in conjunction with radiological images is the best approach.

Secondary efficacy endpoints include: (1) PFS-6 defined as the proportion of participants in the analysis population who remain progression-free for at least six months following initiation of study therapy.; (2) progression-free survival (PFS), defined as the time from allocation to the first documented disease progression according to RANO or death due to any cause, whichever occurs first; (3) overall survival (OS), and (4) duration of response.

Additional supportive analyses duration of response will be conducted using RANO criteria, in which a confirmation assessment of disease response must be obtained at least 4 weeks after the initial disease assessment response.

14.2.4.2 **Safety Endpoints**

Safety & Tolerability of the therapy used in each cohort = a secondary objective of this study. The primary safety endpoints are AEs graded using CTCAE (Version 4.0) criteria. Safety will be assessed by quantifying the toxicities and grades experienced by participants who have received Pembrolizumab, including serious adverse events (SAEs), other Reportable Adverse Events, and events of clinical interest (ECIs – Section 8.4.4.2). Immune related adverse experiences (irAEs, as defined in Section 7.2) are prespecified as events of interest. Other safety endpoints include laboratory safety assessments, KPS status, vital signs and physical examinations.

14.2.4.3 **Exploratory Endpoints**

- **Objective**: To evaluate whether archival tumor expression of PD-L1, tumor infiltrating lymphocytes features, or T cell inflamed gene expression profile are associated with outcome.
- **Objective**: To evaluate Neurologic Assessment in Neuro-Oncology (NANO) in each cohort
- **Objective**: To evaluate the change of Patient Reported Outcome scores from baseline to post-baseline time-points using the EORTC QLQ-C30.
- **Objective**: To estimate ORR per iRANO

14.2.5 **Analysis Population**

14.2.5.1 **Efficacy Analysis Populations**

The Full Analysis Set (FAS) population will serve as the primary population for the analysis of efficacy data in this study. The FAS population consists of all participants within each cohort who have received at least one dose of study pembrolizumab treatment and have completed at least 75% of the planned re-irradiation therapy.

Two supportive analyses of the primary and selected secondary efficacy endpoints will be conducted. The first supportive analysis will be conducted in the FAS-2 population, defined as all participants who meet the FAS population definition and have a post baseline scan OR discontinue the trial due to progressive disease/drug related AE. The second analysis will be conducted using the intention to treat (ITT) population, defined as all registered participants.

Participants will be included in the cohort to which they are allocated for the analysis of efficacy data.

14.2.5.2 **Safety Analysis Populations**

The All Patients as Treated (APaT) population will be used for the analysis of safety data in this study. The APaT population consists of all allocated participants who received at least one dose of study pembrolizumab treatment.

At least one laboratory or vital sign measurement obtained after at least one dose of study pembrolizumab treatment is required for inclusion in the analysis of each specific parameter. To assess change from baseline, a baseline measurement is also required.

Details on the approach to handling missing data for safety analyses are provided in Section 14.2.6 Statistical Methods.

14.2.6 **Statistical Methods**

Nominal p –values may be computed for efficacy analyses as a measure of strength of association between the endpoint and the treatment effect rather than formal tests of hypotheses. Unless otherwise stated, all statistical tests will be conducted at the α=0.05 (2-sided) level. All estimated rates will be reported with corresponding 95% CI.

14.2.6.1 **Statistical Methods for Efficacy Analyses**

Efficacy will be evaluated separately in each cohort. Primarily, rates comparison will be conducted using exact methods. In addition, OS andPFS endpoints will be calculated using the Kaplan-Meier (KM) method and curves and median estimates with corresponding 95% CI will be provided as appropriate. Participants without efficacy evaluation data or without survival data will be censored at Day 1. The final efficacy analysis will be conducted whenever all patients achieved the required follow-up time in their respective cohort. This analysis is expected to take place at study closure: around 2 years after first patient has been consented.

14.2.6.2 **Statistical Methods for Safety Analyses**

Safety and tolerability will be assessed by clinical review of all relevant parameters including adverse experiences (AEs), laboratory tests, and vital signs. Safety summaries will be reported for both cohorts.

Immune related adverse experiences (irAEs, as defined in Section 7.2) are prespecified as events of interest. These events will be summarized in separate tables from other AEs by toxicity grade and will include the counts, percentage, and 95% CI. Any AE of unknown etiology associated with pembrolizumab exposure will be evaluated to determine if it is possibly an event of clinical interest (ECI) of a potentially immunologic etiology (irECI). Other ECIs listed in Section 8.4.4.2 will also be summarized in the same manner as irAEs.

Adverse experiences (specific terms as well as system organ class terms) and predefined limits of change in laboratory, and vital sign parameters that are not pre-specified as events of interest will be summarized with descriptive statistics (counts, percentage, mean, standard deviation, etc.).

Continuous measures such as changes from baseline in laboratory, and vital signs parameters that are not pre-specified as events of interest will be summarized using descriptive statistics (mean, standard deviation, etc.) for baseline, on-treatment, and change from baseline values.

14.2.7 Summary of Baseline Characteristics, Demographics, and Immunocorrelative Analyses

14.2.7.1 Demographic and Baseline Characteristics

Baseline characteristics will be assessed using tables and/or graphs for each cohort separately. No statistical hypothesis tests will be performed on these characteristics. The number and percentage of participants screened, allocated to treatment arm, the primary reasons for screening failure, and the primary reason for discontinuation will be displayed. Demographic variables (e.g., age, gender), baseline characteristics, primary and secondary diagnoses, and prior and concomitant therapies will be summarized by treatment either by descriptive statistics or categorical tables.

14.2.8 Interim Analyses

14.2.8.1 Monitoring of Efficacy (Stopping Rule for Unexpected Efficacy)

Given that re-irradiation is considered standard treatment for patients with glioblastoma, and all participants will be treated with re-irradiation, there is no planned interim analysis for unexpected efficacy.

14.2.8.2 Monitoring of Toxicity (Stopping Rule for Unexpected Toxicity)

The primary focus of toxicity monitoring will be the toxicity profile of participants treated with pembrolizumab. For study purposes, the occurrence of toxicity attributable to pembrolizumab that requires discontinuation of pembrolizumab therapy as defined in Section 7.2 is defined as unacceptable. Unacceptable toxicity rates of 20% or less are considered desirable. Sequential boundaries will be used to monitor the unacceptable toxicity rate for each cohort. Accrual to that cohort will be halted if excessive numbers of unacceptable toxicities are seen at any time during the course of study therapy for a given participant; that is, if the number of toxicities is equal to or exceeds bn out of n patients with full follow-up (see below table). This is a Pocock-type stopping boundary that yields the probability of crossing the boundary at most 0.05 when the rate of unacceptable toxicity is equal to 0.2.

Table 17. Stopping Rule for Unacceptable Toxicity

Participants, n	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17
Boundary, bn	-	-	3	4	4	4	5	5	6	6	6	7	7	7	8	8	8
Participants, n	18	19	20	21	22	23	24	25	26	27	28	29	30				
Boundary, bn	8	9	9	9	10	10	10	11	11	11	11	12	12				

14.2.9 **Compliance (Medication Adherence)**

A day within the study will be considered an 'On-Therapy' day if the participant receives the study medication infusion. The 'Number of Days Should be on Therapy' is the total number of days from the first day of study medication to the date of the last dose of study medication. For each participant, compliance rate will then be calculated using the following formula:

Compliance Rate = (Actual number of therapy days/planned number of therapy days) x 100

Summary statistics will be provided on percent compliance by treatment group for the FAS population.

14.2.10 **Extent of Exposure**

Extent of Exposure for a participant is defined as number of cycles in which the participant receives the study medication infusion. Summary statistics will be provided on Extent of Exposure for APaT population.

14.2.11 **Accrual Targets**

Table 18. Accrual Targets by Gender, ethnic category and racial category.

Accrual Targets					
Ethnic Category	**Sex/Gender**				
	Females		**Males**		**Total**
Hispanic or Latino	2	+	3	=	5
Not Hispanic or Latino	23	+	32	=	55
Ethnic Category: Total of all participants	25	+	35	=	60
Racial Category					
American Indian or Alaskan Native	0	+	0	=	0
Asian	1	+	1	=	2
Black or African American	1	+	2	=	3
Native Hawaiian or other Pacific Islander	0	+	0	=	0
White	23	+	32	=	55
Racial Category: Total of all participants	25	+	35	=	60

15. PUBLICATION PLAN

This trial is intended for publication, even if terminated prematurely. Publication may include any or all of the following: posting of a synopsis online, abstract and/or presentation at a scientific conference, or publication of a full manuscript. The Sponsor will work with the authors to submit a manuscript describing trial results within 12 months after the last data become available, which may take up to several months after the last participant visit in some cases. Sponsor will post a synopsis of trial results for approved products on www.clinicaltrials.gov by 12 months after the last participant's last visit for the primary outcome, 12 months after the decision to discontinue development, or product marketing (dispensed, administered, delivered or promoted), whichever is later.

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

For multicenter trials, subsequent to the multicenter publication (or after public disclosure of the results online at www.clinicaltrials.gov if a multicenter manuscript is not planned), an investigator and his/her colleagues may publish their data independently. In most cases, publication of individual trial site data does not add value to complete multicenter results, due to statistical concerns. In rare cases, publication of single trial site data prior to the main paper may be of value. Limitations of single trial site observations in a multicenter trial should always be described in such a manuscript.

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

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

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APPENDIX A PERFORMANCE STATUS CRITERIA

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

APPENDIX B: STUDY SAFETY REPORTING COVERSHEET

Study Safety Reporting Coversheet – All Cohorts

DF/HCC Protocol No. 18-277 Merck & Co., Inc. Protocol No. 3475-787

Date:_____ Number of pages including cover sheet:_____

To *(check off recipient of this submission)*:

☐ David Reardon, MD, MD (Overall PI) @ Dana Farber Cancer Institute:
NeuroOnc_SAE@dfci.harvard.edu
Please e-mail coversheet and MedWatch with the words "18-277: Pembrolizumab + re-RT SAE" in the subject line

☐ Merck Global Safety, Attention: Worldwide Product Safety; Fax #: 215-661-6229

From:	Phone No:
Study Site:	Fax No.:
Participant # and Initials:	Participant Cohort:
Type of Report: ☐ Initial ☐ Follow-up	Was Patient Hospitalized? ☐ Yes ☐ No
Date Event 1st Met Reporting Criteria *(as defined in protocol)*:	Date Investigator Team Made Aware of Event:

(Please use another sheet if more than 2 events being reported at this time)

Event #1 Description *(CTCAE v. 4 term)*:	Event #2 *(if applicable)* Description *(CTCAE v. 4 term)*:
Meets Protocol Definition of Serious AE? ☐ Serious ☐ Non-serious	Meets Protocol Definition of Serious AE? ☐ Serious ☐ Non-serious
Toxicity Grade: ☐ G1/mild ☐ G2/moderate ☐ G3/severe ☐ G4/life threatening ☐ G5	Toxicity Grade: ☐ G1/mild ☐ G2/moderate ☐ G3/severe ☐ G4/life threatening ☐ G5
Historical/Known Correlation to **Pembrolizumab**: ☐Expected ☐Unexpected ☐N/A *(only if unrelated)*	Historical/Known Correlation to **Pembrolizumab**: ☐Expected ☐Unexpected ☐N/A *(only if unrelated)*
Attribution to **Pembrolizumab**: ☐ Unrelated ☐ Unlikely ☐ Possible ☐ Probable ☐ Definite	Attribution to **Pembrolizumab**: ☐ Unrelated ☐ Unlikely ☐ Possible ☐ Probable ☐ Definite
Historical/Known Correlation to **bevacizumab (or biosimilar)**: ☐Expected ☐Unexpected ☐N/A *(only if unrelated or pt is NOT on Coh B)*	Historical/Known Correlation to **bevacizumab (or biosimilar)**: ☐Expected ☐Unexpected ☐N/A *(only if unrelated or pt is NOT on Coh B)*
Attribution to **bevacizumab (or biosimilar)**: ☐ Unrelated ☐ Unlikely ☐ Possible ☐ Probable ☐ Definite ☐N/A *(pt is NOT on Coh B)*	Attribution to **bevacizumab (or biosimilar)**: ☐ Unrelated ☐ Unlikely ☐ Possible ☐ Probable ☐ Definite ☐N/A *(pt is NOT on Coh B)*
Historical/Known Correlation to **RT**: ☐Expected ☐Unexpected ☐N/A *(only if unrelated)*	Historical/Known Correlation to **RT**: ☐Expected ☐Unexpected ☐N/A *(only if unrelated)*
Attribution to **RT**: ☐ Unrelated ☐ Unlikely ☐ Possible ☐ Probable ☐ Definite ☐N/A	Attribution to **RT**: ☐ Unrelated ☐ Unlikely ☐ Possible ☐ Probable ☐ Definite ☐N/A
Reporting Investigator:	

Signature of Investigator:_____Date:_____

APPENDIX C: PEMBRO + RE-RT TISSUE REQUISITION/SUBMISSION FORM

DF/HCC #18-277 (*Pembrolizumab + Re-RT for Recurrent GBM*) Tissue Requisition / Submission Form:

For shipment to: David A. Reardon (c/o Christine McCluskey) at DFCI's Center for Neuro-Oncology

Participant ID # *e.g. "00001"*	**Participant Initials** *e.g. "ABC" or "D-F"*	**Study Cohort** A *(= no bev)* or B (= *bev)*	**Site** DFCI, MGH, DUKE, or Columbia	**Tissue Type** Unstained Slides, Blocks, FFPE Scrolls, etc.	**Submission Type** Archival tumor from most recent pre-reg biopsy/surgery Or Tissue from time of progression or suspected progression	**Date of Procedure** *e.g. "01/02/2017"*	**Accession #**	**Block or Section #** ***(if known)***	**# of specimens (slides, etc.) included in this shipment**	**Copy of corresponding surgical and/or path report included with this submission?**

Printed Name, Signature, and phone # of person responsible for this shipment of tissue:

Name: _____ Signature: _____ Date: _____ Phone #: _____

-

For DFCI NOC Coordinating Center Completion:

The above materials were received by _____ *(print name)* **on** _____ *(date)* **at** _____ *(time)*

Please confirm whether above inventory = accurate, and make note of any discrepancies, issues with samples, etc.:

_____

_____

_____ *(signature)*

APPENDIX D NEUROLOGIC ASSESSMENT IN NEURO-ONCOLOGY (NANO) SCALE

Scoring assessment is based on direct observation and testing performed during clinical evaluation and is not based on historical information or reported symptoms. Please check 1 answer per domain. Please check "Not assessed" if testing for that domain is not done. Please check "Not evaluable" if a given domain cannot be scored accurately due to pre-existing conditions, co-morbid events and/or concurrent medications.

Participant ID #, Initials, and Study Site: _____

Date Assessment Performed (day/month/year): _____

Study time point (i.e. cycle 1, day 1, etc): _____

Assessment performed by (please print name): _____

Domains	**Key Considerations**
Gait 0 ☐ Normal 1 ☐ Abnormal but walks without assistance 2 ☐ Abnormal and requires assistance (companion, cane, walker, etc.) 3 ☐ Unable to walk ☐ Not assessed ☐ Not evaluable	• Walking is ideally assessed by at least 10 steps
Strength 0 ☐ Normal 1 ☐ Movement present but decreased against resistance 2 ☐ Movement present but none against resistance 3 ☐ No movement ☐ Not assessed ☐ Not evaluable	• Test each limb separately • Recommend assess proximal (above knee or elbow) and distal (below knee or elbow) major muscle groups • Score should reflect worst performing area • Patients with baseline level 3 function in one major muscle group/limb can be scored based on assessment of other major muscle groups/limb
Ataxia (upper extremity) 0 ☐ Able to finger to nose touch without difficulty 1 ☐ Able to finger to nose touch but difficult 2 ☐ Unable to finger to nose touch ☐ Not assessed ☐ Not evaluable	• Non-evaluable if strength is compromised • Trunk/lower extremities assessed by gait domain • Particularly important for patients with brainstem and cerebellar tumors • Score based on best response of at least 3 attempts
Sensation 0 ☐ Normal 1 ☐ Decreased but aware of sensory modality 2 ☐ Unaware of sensory modality ☐ Not assessed ☐ Not evaluable	• Recommend evaluating major body areas separately (face, limbs and trunk) • Score should reflect worst performing area • Sensory modality includes but not limited to light touch, pinprick, temperature and proprioception • Patients with baseline level 2 function in one major body area can be scored based on assessment of other major body areas

NANO SCALE (pg 2 of 2)

Participant ID #, Initials, and Study Site: _____

Date Assessment Performed (day/month/year): _____

Visual Fields

- 0 ☐ Normal
- 1 ☐ Inconsistent or equivocal partial hemianopsia (≥quadrantanopsia)
- 2 ☐ Consistent or unequivocal partial hemianopsia (≥quadrantanopsia)
- 3 ☐ Complete hemianopsia
- ☐ Not assessed
- ☐ Not evaluable

- Patients who require corrective lenses should be evaluated while wearing corrective lenses
- Each eye should be evaluated and score should reflect the worst performing eye

Facial Strength

- 0 ☐ Normal
- 1 ☐ Mild/moderate weakness
- 2 ☐ Severe facial weakness
- ☐ Not assessed
- ☐ Not evaluable

- Particularly important for brainstem tumors
- Weakness includes nasolabial fold flattening, asymmetric smile and difficulty elevating eyebrows

Language

- 0 ☐ Normal
- 1 ☐ Abnormal but easily conveys meaning to examiner
- 2 ☐ Abnormal and difficulty conveying meaning to examiner
- 3 ☐ Abnormal. If verbal, unable to convey meaning to examiner. OR non-verbal (mute/global aphasia)
- ☐ Not assessed
- ☐ Not evaluable

- Assess based on spoken speech. Non-verbal cues or writing should not be included.
- Level 1: Includes word finding difficulty; few paraphasic errors/neologisms/word substitutions; but able to form sentences (full/broken)
- Level 2: Includes inability to form sentences (<4 words per phrase/sentence); limited word output; fluent but "empty" speech.

Level of Consciousness

- 0 ☐ Normal
- 1 ☐ Drowsy (easily arousable)
- 2 ☐ Somnolent (difficult to arouse)
- 3 ☐ Unarousable/coma
- ☐ Not assessed
- ☐ Not evaluable

- *None*

Behavior

- 0 ☐ Normal
- 1 ☐ Mild/moderate alteration
- 2 ☐ Severe alteration
- ☐ Not assessed
- ☐ Not evaluable

- Particularly important for frontal lobe tumors
- Alteration includes but is not limited to apathy, disinhibition and confusion
- Consider subclinical seizures for significant alteration

APPENDIX E DANA-FARBER/HARVARD CANCER CENTER MULTI-CENTER DATA AND SAFETY MONITORING PLAN

DFCI IRB Protocol #: 18-277

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

TABLE OF CONTENTS

1.0 INTRODUCTION

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

1.1 Purpose

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

1.2 Multi-Center Data and Safety Monitoring Plan Definitions

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

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

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

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

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

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

DF/HCC Clinical Trials Research Informatics Office (CTRIO): A group within DF/HCC responsible for providing a comprehensive data management platform for managing clinical trial data.

2.0 GENERAL ROLES AND RESPONSIBILITIES

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

2.1 DF/HCC Sponsor

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

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

- Commit to the provision that the protocol will not be rewritten or modified by anyone other than the DF/HCC Sponsor.
- Identify and qualify Participating Institutions and obtain accrual commitments prior to extending the protocol to that site.
- Monitor accrual and address Participating Institutions that are not meeting their accrual requirements.

2.2 Coordinating Center

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

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

2.3 Participating Institution

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

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

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

3.0 DF/HCC REQUIREMENTS FOR MULTI-CENTER PROTOCOLS

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

3.1 Protocol Distribution

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

3.2 Protocol Revisions and Closures

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

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

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

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

3.3 Informed Consent Requirements

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

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

The Principal Investigator (PI) at each Participating Institution will identify the physician members of the study team who will be obtaining consent and signing the consent form for therapeutic protocols. Participating institutions must follow the DF/HCC requirement that for all interventional drug, biologic, or device research, only attending physicians obtain initial informed consent and any re-consent that requires a full revised consent form.

3.4 IRB Documentation

The following must be on file with the Coordinating Center:
- Initial approval letter of the Participating Institution's IRB
- Copy of the Informed Consent Form(s) approved by the Participating Institution’s IRB
- Participating Institution’s IRB approval for all amendments
- Annual approval letters by the Participating Institution’s IRB

3.5 IRB Re-Approval

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

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

3.6 Participant Confidentiality and Authorization Statement

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

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

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

3.6.1 DF/HCC Multi-Center Protocol Confidentiality

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

3.7 DF/HCC Multi-Center Protocol Registration Policy

Eligible participants will be entered on study centrally at the DFCI Coordinating Center (by a Coordinating Center specialist, if participant is at a non-DF/HCC site). Registration must occur prior to the initiation of therapy. Any participant not registered to the protocol before treatment begins will be considered ineligible and registration will be denied.

A qualified member of the study team will confirm eligibility criteria and complete the protocol-specific eligibility checklist.

Issues that would cause treatment delays should be discussed with the Principal Investigator. If a participant does not receive protocol therapy following registration, the participant's protocol status must be changed. A Coordinating Center specialist should be notified of cancellations - or any status changes - as soon as possible.

In order to register a participant onto study, the following must be done:

- Obtain written informed consent from the participant prior to the performance of any study related procedures or assessments.
- Complete the protocol-specific eligibility checklist using the eligibility assessment documented in the participant's medical/research record.
    - **To be eligible for registration to the study, the participant must meet each inclusion and exclusion criteria listed on the eligibility checklist.**

Reminder: Confirm eligibility for ancillary studies at the same time as eligibility for the treatment study. Registration to both treatment and ancillary studies will not be completed if eligibility requirements are not met for all studies.

3.7.1 Participant Registration and Randomization at a non-DF/HCC Site

To register a participant at any non-DF/HCC site, the subsequent procedure is to be followed:

1. The participating site's data manager/coordinator/research nurse should contact a DFCI Neuro-Oncology Coordinating Center team member via telephone or email to:
    - Notify regarding the pending registration
    - Confirm the methods of sending documents and communication for registration
    - Communicate desired timeline of the registration (i.e. the next day, etc.).

    Multi-Center DFCI Neuro-Oncology Designee contact information:
    E-mail: NeuroOnc_Coor@dfci.harvard.edu
    Phone: 617-582-7101

2. The data manager/coordinator/research nurse should then send the following documents to the Coordinating Center specialist:
    - Completed DF/HCC study specific Eligibility Screening Worksheet
    - Copy of protocol required test results (e.g. coagulation studies, hematology panel, serum pregnancy test, serum chemistry panel, urinalysis -- all as applicable per protocol)
    - Copy of the pathology and surgical reports
    - List of current concomitant medications (obtained within the protocol-specified screening window) including sign/date by RN/other clinician and documentation of when reviewed/confirmed with patient
    - Copy of signed informed consent form
    - Copy of signed HIPAA authorization form (if separate from the informed consent document)
    - Copy of clinic note(s) and other medical records that document consenting process, screening and eligibility, if available***

    Documents will be transmitted via one of the following methods:
    - *Scanned and emailed to: NeuroOnc_Coor@dfci.harvard.edu or direct email of Coordinating Center specialist*
    - *Faxed to: 617-394-2683*

**** The Coordinating Center Specialists would like to review and monitor participant eligibility, informed consent, screening and baseline assessments on all participants. Providing a complete set of source documents prior to registration may delay registration. Participating Institutions will work with the Coordinating Center Specialists to determine what documents may feasibly be available for review prior to enrollment, and these documents are to be provided for pre-enrollment review. A complete set of documents will be provided to the Coordinating Center after registration; the timeline will be determined by the Coordinating Center Specialist based on the study team's experience with the trial and prior monitoring findings. If there are persistent issues with eligibility at a site or with a study overall, the Coordinating Center may require that all source documentation relevant to participant eligibility be provided prior to proceeding with participant registration.*

3. After having received all transferred documentation, the Designee (Coordinating Center specialist) will review the documents to verify eligibility, and notify the participating site of the result.
4. To complete the registration process, the Designee (Multi-Center Coordinating Center specialist) will follow DF/HCC Standard Operating Procedure for Human Participant Research Titled *Participant Protocol Registration* (SOP #: REGIST-101) and register the participant centrally on the protocol, and subsequently inform the participating site of the successful registration via Fax or email, to include:
    - Participant case number
    - Applicable Dose Treatment level and treatment arm assignment
5. The Designee (Multi-Center Coordinating Center specialist) will follow-up to confirm registration.

Treatment may not begin without confirmation from the Coordinating Center that the participant has been registered.

3.7.2 Initiation of Therapy

Participants must be centrally registered with the Multi-Center Coordinating Center and the DF/HCC CTMS before the initiation of treatment or other protocol-specific interventions. Treatment and other protocol-specific interventions may not be initiated until the Participating Institution receives confirmation of the participant's registration from the Coordinating Center. Therapy must be initiated per protocol guidelines. The DF/HCC Sponsor and DFCI IRB must be notified of any violations to this policy.

3.7.3 Eligibility Exceptions

No exceptions to the eligibility requirements for a protocol without DFCI IRB approval will be permitted. All Participating Institutions are required to fully comply with this requirement. The process for requesting an eligibility exception is defined below.

3.8 DF/HCC Protocol Case Number

At the time of registration, DFCI Multi-Center Coordinating Center requires the following identifiers for all participants: initials, date of birth, gender, race and ethnicity. Once eligibility has been established and the participant successfully registered, the participant is assigned a unique protocol case number. Participating Institutions should submit all de-

identified subsequent communication and documents to the Coordinating Center, using this case number to identify the participant.

3.9 Protocol Deviations, Exceptions and Violations

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

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

3.9.1 Definitions

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

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

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

3.9.2 Reporting Procedures

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

Participating Institutions: Protocol deviations require prospective approval from the DFCI IRB. The Participating Institution must submit the deviation request to the Coordinating Center who will then submit the deviation request to the DFCI IRB. Upon DFCI IRB approval the deviation is submitted to the Participating Institution IRB, per institutional policy. A copy of the Participating Institution's IRB report and determination will be forwarded to the Coordinating Center within 10 business days after the original submission. The deviation may not be implemented without all required approvals.

All protocol violations must be sent to the Coordinating Center in a timely manner. The Coordinating Center will provide training for the requirements for the reporting of violations.

Protocol violations occurring at a Participating Institution will be submitted to that site's own IRB per the IRB's reporting policy. Whether or not a violation needs to be reported to the local IRB, notification to the Coordinating Center of any violation should occur in a timely manner. If a report is made to the Participating Institution's IRB, the report and determination should also be forwarded to the Coordinating Center in a timely manner.

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

3.10 Safety Assessments and Toxicity Monitoring

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

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

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

3.10.1 Guidelines for Reporting Serious Adverse Events

Guidelines for reporting Adverse Events (AEs) and Serious Adverse Events (SAEs) are detailed in protocol section 7.

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

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

3.10.2 Guidelines for Processing IND Safety Reports

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

3.11 Data Management

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

3.11.1 Data Forms Review

Data submissions are monitored for timeliness and completeness of submission. If study forms are received with missing or questionable data, the submitting institution will receive a written or electronic query from the DF/HCC Office of Data Quality, Coordinating Center, or designee.

Responses to all queries should be completed and submitted within 14 calendar days.

Responses may be returned on the written query or on an amended paper case report form, or in the case of electronic queries, within the electronic data capture (eDC) system. In the case of a written query for data submitted on a paper case report form, the query must be attached to the specific data being re-submitted in response.

If study forms are not submitted on schedule, the Participating Institution will periodically receive a Missing Form Report from the Coordinating Center noting the missing forms.

4.0 REQUISITIONING INVESTIGATIONAL DRUG

The ordering of Pembrolizumab for this trial is described below:

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

5.0 MONITORING: QUALITY CONTROL

Monitoring and oversight of a clinical trial are federally mandated for all IND held trials. This quality control process for a clinical trial requires verification of protocol compliance and data accuracy and the protection of the rights and welfare of participants. The Coordinating Center, with the aid of the ODQ, provides quality control oversight for the protocol.

5.1 Ongoing Monitoring of Protocol Compliance

The Participating Institutions may be required to submit participant source documents to the Coordinating Center for monitoring. Participating Institutions may also be subject to on-site monitoring conducted by the Coordinating Center.

The Coordinating Center will implement ongoing monitoring activities to ensure that Participating Institutions are complying with regulatory and protocol requirements, data quality, and participant safety. Monitoring will occur before the clinical phase of the

protocol begins, continue during protocol performance and through study completion. Additional monitoring practices may include but are not limited to; source verification, review and analysis of the following: eligibility requirements of all participants , informed consent procedures, adverse events and all associated documentation, study drug administration/treatment, regulatory files, protocol departures, pharmacy records, response assessments, and data management.

Remote monitoring of participant eligibility, the initial informed consent process, and screening evaluation completion will occur via a two-stage process.

- Prior to registering each participant, a Coordinating Center Specialist will review the source documentation provided in the enrollment packet to confirm, (a) that based on all objective measurements (lab tests; pathology report) that the prospective participant is eligible, (b) that the objective measurements were performed per protocol within the appropriate protocol-defined windows, (c) that the prospective participant does not have concomitant medication that precludes eligibility, and, if documentation is provided, (d) that the consenting process was adequate/adequately documented, (e) that the participant met criteria for eligibility. Furthermore, using the Eligibility Screening Worksheet, the Specialist will verify that the investigator has indicated that s/he has reviewed and confirmed as "eligible" the prospective participant
- A Coordinating Center Specialist will review the second set of participant-specific source documents provided by study teams to confirm that (a) all screening and baseline assessments were completed per protocol, including AE assessment, and documented appropriately, (b) that all eligibility criteria were met and appropriately documented, and, if not previously reviewed, (c) that the consenting process was adequate/adequately documented. The timeline for this review will be based on the experience with the study team, and the study team's experience with the protocol.

Interim monitoring visits will occur on the following schedule:

- Once a site has registered a participant, up until all participants (and planned participants) have discontinued taking study agent (may be in follow-up), interim monitoring visits will occur at least twice per year (either on-site or virtula). The first interim monitoring visit will occur approximately two months after the registration of the site's first participant.
- Once a site is closed to accrual and all participants have discontinued study agent, interim monitoring visits will occur virtually, and on-site as needed.

On-Site Monitoring: On-site monitoring will occur on a regular basis. Participating Institutions will be required to provide access to participants' complete medical record and source documents for source documentation verification during the on-site visit. In addition, upon request from a monitor or auditor, Participating Institutions should provide access to regulatory documents, pharmacy records, local policies related to the conduct of research, and any other trial-related documentation maintained by the participating site. If there are concerns for protocol compliance, issues that impact participant safety or the integrity of the study are found, or trends identified based on areas of need, additional monitoring visits may be scheduled.

Virtual Monitoring: The Coordinating Center will reasonably request source documentation from participating Institutions as needed to complete monitoring activities. Participating Institutions will be asked to forward copies of participants' medical record and source documents to the Coordinating Center to aid in source documentation verification.

Regular all-sites teleconferences will be hosted on a monthly basis by the Coordinating Center (unless otherwise specified by the Overall PI). During the teleconferences, sites should convey the following information:

- Updates on participants: holds, dose reductions, significant events, how participant is doing, date of progression and date of death when available and if not already communicated to the Coordinating Center
- Protocol status: which version is being used, and the status of any amendments
- Any Reportable Adverse Events or Deviations/violations that have yet to be communicated to the Coordinating Center (informing the sponsor should not wait for the call, and the call does not supplant communicating the events via the regular email methods of communication).
- Review of prospective participants

If sites are not able to have a representative participant, they should email this information to the Coordinating Center.

During the teleconferences, the Coordinating Center may discuss any or all of the following information:

- Accrual/enrollment updates
- Pending amendments
- Safety reports circulated or to be circulated
- ODQ-generated numbers and percentage of missing of missing forms, number of open queries with date of oldest open query, and, for participants on treatment, the date of their last study agent form
- Review of new deviations, violations
- Review of recently received expedited adverse events

5.2 Monitoring Reports

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

5.3 Accrual Monitoring

Prior to extending a protocol to an external site, the DF/HCC Sponsor will establish accrual requirements for each participating institution. Accrual will be monitored for each participating institution by the DF/HCC Sponsor or designee. Sites that are not meeting their accrual expectations may be subject to termination.

Accrual expectations for Participating Institutions: As this is a Phase II trial, Study Sponsor is requesting that each participating site accrue at least 3 patients annually.

6.0 AUDITING: QUALITY ASSURANCE

Auditing is a method of Quality Assurance and involves the systematic and independent examination of all trial related activities and documents. Audits determine if evaluated activities were appropriately conducted and whether data was generated, recorded and analyzed, and accurately reported per the protocol, applicable Policies, and the Code of Federal Regulations (CFR).

6.1 DF/HCC Internal Audits

All Participating Institutions are subject to audit by the DF/HCC Office of Data Quality (ODQ). Typically, approximately 3-4 participants would be audited at the site over a 2 day period. If violations which impact participant safety or the integrity of the study are found, more participant records may be audited.

6.2 Audit Notification

It is the Participating Institution's responsibility to notify the Coordinating Center of all external audits or inspections (e.g., FDA, EMA, NCI) that involve this protocol. All institutions will forward a copy of final audit and/or re-audit reports and corrective action plans (if applicable) to the Coordinating Center, within 12 weeks after the audit date.

6.3 Audit Reports

The DF/HCC Sponsor will review all final audit reports and corrective action plans, if applicable. The Coordinating Center, must forward any reports to the DF/HCC ODQ per DF/HCC policy for review by the DF/HCC Audit Committee. For unacceptable audits, the DF/HCC Audit Committee would forward the final audit report and corrective action plan to the DFCI IRB as applicable.

6.4 Participating Institution Performance

The DF/HCC Sponsor and the IRB of record are charged with considering the totality of an institution's performance in considering institutional participation in the DF/HCC Multi-Center protocol.

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

APPENDIX F **MERCK DRUG SUPPLY REQUEST FORM: PEMBROLIZUMAB**

(DF/HCC #18-277; Merck #3475-787)

351 N. Sumneytown Pike
UG-2C-56
North Wales, PA 19454

Supply Request

Date:

To: Tammy Moll and Deb Perlow
E-mail: tammy.moll@merck.com ;
debbie.perlow@merck.com

From:
Phone:
Fax:

Investigator Name:	Merck Protocol # 3475-787	Institution Study #:	Initial Shipment: / Resupply Shipment:

Protocol Title: Phase II Trial of Pembrolizumab and Reirradiation in Bevacizumab Naïve and Bevacizumab Resistant Recurrent Glioblastoma

Institution Name:	Site Phone #:	Site Fax #:

Product	Description	Units
KEYTRUDA	Solution for Infusion 100mg/vial	

Shipping Name:	Shipping Address *(w/ instructions)*: *(34 character limit)* *(34 character limit)* *(40 char limit - Street Address ONLY)* *(City/State/Zip ONLY)* Important note: Character limits are absolute. Please include a study identifier *(i.e., Merck protocol number, MISP number, name for shipment, etc.)* within the shipping address; otherwise, this information will not be present on the packing slip.
Shipping Phone #: Shipping Fax #:	
Shipping E-Mail Address:	License information *(can be PI or Pharmacy)*: License #: State of License issue #: Name on License: Expiration date:

Special Instructions:

APPENDIX G Quality of Life (QoL) Assessment: EORTC QLQ-C30

EORTC QLQ-C30 (version 3)

We are interested in some things about you and your health. Please answer all of the questions yourself by circling the number that best applies to you. There are no "right" or "wrong" answers. The information that you provide will remain strictly confidential.

* NOTE: Sometimes, these questions may be read to you by someone from your Study Treatment Team.

Pt ID #, Initials, and Study Site: _____

Date Assessment Performed (day/month/year): _____/_____/_____

Study timepoint (i.e. cycle 1, day 1, etc): _____

	Not at All	A Little	Quite a Bit	Very Much
1. Do you have any trouble doing strenuous activities, like carrying a heavy shopping bag or a suitcase?	1	2	3	4
2. Do you have any trouble taking a long walk?	1	2	3	4
3. Do you have any trouble taking a short walk outside of the house?	1	2	3	4
4. Do you need to stay in bed or a chair during the day?	1	2	3	4
5. Do you need help with eating, dressing, washing yourself or using the toilet?	1	2	3	4

During the past week:	Not at All	A Little	Quite a Bit	Very Much
6. Were you limited in doing either your work or other daily activities?	1	2	3	4
7. Were you limited in pursuing your hobbies or other leisure time activities?	1	2	3	4
8. Were you short of breath?	1	2	3	4
9. Have you had pain?	1	2	3	4
10. Did you need to rest?	1	2	3	4
11. Have you had trouble sleeping?	1	2	3	4
12. Have you felt weak?	1	2	3	4
13. Have you lacked appetite?	1	2	3	4
14. Have you felt nauseated?	1	2	3	4
15. Have you vomited?	1	2	3	4
16. Have you been constipated?	1	2	3	4

Please go on to the next page

EORTC QLQ-C30 (pg 2 of 2)

Pt ID #, Initials, and Study Site: _____

Date Assessment Performed (day/month/year): _____/_____/_____

Study timepoint (i.e. cycle 1, day 1, etc): _____

During the past week:	**Not at All**	**A Little**	**Quite a Bit**	**Very Much**
17. Have you had diarrhea?	1	2	3	4
18. Were you tired?	1	2	3	4
19. Did pain interfere with your daily activities?	1	2	3	4
20. Have you had difficulty in concentrating on things, like reading a newspaper or watching television?	1	2	3	4
21. Did you feel tense?	1	2	3	4
22. Did you worry?	1	2	3	4
23. Did you feel irritable?	1	2	3	4
24. Did you feel depressed?	1	2	3	4
25. Have you had difficulty remembering things?	1	2	3	4
26. Has your physical condition or medical treatment interfered with your family life?	1	2	3	4
27. Has your physical condition or medical treatment interfered with your social activities?	1	2	3	4
28. Has your physical condition or medical treatment caused you financial difficulties?	1	2	3	4

For the following questions please circle the number between 1 and 7 that best applies to you

29. How would you rate your overall health during the past week?

1	2	3	4	5	6	7
Very poor						Excellent

30. How would you rate your overall quality of life during the past week?

1	2	3	4	5	6	7
Very poor						Excellent

- **Please initial _____ & date _____/____/_____ when assessment is complete**
- **Who completed this form?** ☐ Self ☐ Other, specify: _____

APPENDIX H **Radiation Therapy Guidelines (To be provided to Radiation Oncologist)**

You are receiving the below guidelines because you will be treating _____, a patient enrolled on a clinical trial. Please ensure they are followed as closely as possible. If there are any significant deviations from the below guidelines, please contact the patient's protocol treatment team as soon as possible (prospectively, whenever possible).

Should you have any concerns or questions, please contact: _____
at _____ (email) or _____ (phone).

Thank you so much for being such a significant part of our patient's quality care.

Patient will be administered fractionated radiotherapy according to established, standard-of-care guidelines utilizing intensity-modulated radiation therapy (IMRT), 3-dimensional conformal radiation therapy (3D-CRT) or proton beam radiation therapy at a dose of 3.5 Gy/fraction times 10 fractions (5 days a week for 2 weeks). Daily image-guided radiation therapy (IGRT) is required including non-volumetric (orthogonal or near-orthogonal 2D imaging that is integrated with the radiation delivery device) and volumetric (diagnostic CT, cone beam CT with MV or kV X-ray beam, MRI-linac or tomotherapy technology) systems.

1.0 Dose Specifications

Photons: Treatment shall consist of 35 Gy delivered in 10 fractions. Target coverage and homogeneity limits and deviations are listed in Table I-1 based on guidance from the ongoing randomized, national, phase II RTOG 1205 (NCT01730950).

Protons – Absorbed dose: Doses are expressed in units of RBE-weighted absorbed dose, DRBE. For protons, the RBE is taken to be 1.1. DRBE = 1.1 x D, where D represents the absorbed dose in Gy. Treatment shall consist of 35 Gy(RBE) delivered in 10 fractions. Target coverage and homogeneity limits and deviations are listed in Table I-1.

Table I-1. Radiation Therapy Target Coverage and Dose Limits

Dose Metric	**Per Protocol**	**Variation Acceptable**	**Deviation Unacceptable**
Volume of PTV covered by the prescription dose photons 35 Gy – protons 35 Gy(RBE)	Greater than or equal to 95% of the PTV should receive greater than or equal to photons 35 Gy – protons 35 Gy(RBE)	Greater than or equal to 90% of the PTV receiving greater than or equal to photons 35 Gy – protons 35 Gy(RBE)	Less than 90% of the PTV receiving greater than or equal to photons 35 Gy – protons 35 Gy(RBE)
Minimum dose to the PTV (0.03 cc)	Greater than or equal to 29.75 Gy (85% of the prescription dose) – protons 29.75 Gy(RBE)	prescription dose) – protons 28 Gy(RBE); Minimum doses of less than 28 Gy are acceptable if they occur due to OAR/PTV overlap greater than or equal to 28 Gy (80% of the	Less than 28 Gy (80% of the prescription dose) –protons 28 Gy(RBE); Minimum doses of less than 28 Gy are unacceptable unless they occur in regions of OAR/PTV overlap
Maximum dose to the PTV (0.03 cc)	Less than or equal to 42 Gy (120% Rx Dose) – protons 42 Gy(RBE)	Less than or equal to 45.50 Gy (130% Rx Dose) – protons 45.50 Gy(RBE)	Greater than 45.50 Gy (130% Rx Dose) – protons 45.50 Gy(RBE)

2.0 Technical Factors [Equipment, energies]

The 10 treatment fractions of 3.5 Gy each will be delivered on consecutive treatment days (typically 5 fractions per week). Any FDA cleared external beam radiation delivery system may be used (including conventional linear accelerators, Cyberknife systems, tomotherapy, proton therapy, etc.). Imaging for treatment planning will be obtained with the patient in the same position and immobilization device as for treatment. All patients will be positioned via a combination of rigid immobilization and daily image guidance to ensure positioning accuracy of 3 mm or better, and of a magnitude that justifies the PTV margin applied (the participating institutions must document the immobilization and localization methods applied).

3.0 Localization, Simulation, and Immobilization

An MRI and/or CT scanning obtained with the patient immobilized in the treatment position is required for treatment planning with slice thickness no greater than 3mm. Immobilization must be rigid (e.g. thermoplastic masks). For daily treatment, localization will include the steps of a) immobilization with the same device used for simulation, and b) daily image guidance (IGRT) using at a minimum non-volumetric (i.e. orthogonal pairs of radiographs aligned to DRRs as a computer-assisted process) or volumetric (i.e. cone beam CT with MV or kV x-ray beams or MRI Linac systems.

4.0 Treatment Planning/Target Volumes

A GTV will be defined as the residual, enhancing tumor (and non-enhancing tumor for Cohort B participants) with or without the most recent post-operative cavity on the most recent MRI images. The post-operative resection cavity will be outlined if no residual enhancing tumor is noted. A CTV expansion of no more than 5 mm is optional for lesions measuring less than 3.5 cm in maximum diameter or if this is a new lesion, but must be reported when used. Otherwise,

no additional CTV expansion will be added. A PTV expansion that is justified based on image guidance and immobilization will be applied. Regardless of immobilization and localization methods, the PTV expansion should be no smaller than 3 mm. If protons are used, an adjustment must be made within the treatment planning process to take into account of range uncertainties along the beam direction, following the established practice at the specific proton facility, which should be based on the recommendations contained in ICRU 78, paragraph 5.1.4.4.

Treatment planning using multiple, non-coplanar beams or arc-based therapy is advised. IMRT based planning is allowed. In any case, the objective of treatment planning is to ensure sufficient dose conformity that the normal tissue constraints are met.

5.0 Critical Structures

Normal tissues to be contoured will include the brain, brainstem, optic nerves and chiasm. Planning risk volume (PRV) expansions (minimum of 3 mm) should be utilized for optic nerves and chiasm. Special consideration should be given to avoid doses greater than the prescription dose within the scalp as well as limiting the exit dose through the oral cavity and mucosa. The treatment parameters should be modified to optimize the conformity of the prescription isodose volume to the target volume while minimizing dose to critical structures. There are two scenarios for normal tissues limits: (1) previous radiation to the local area including critical organs at risk and (2) no previous radiation to the local area or organs at risk. The limits for both scenarios are given in Table I-2, based on guidance from the ongoing randomized, national, phase II RTOG 1205 (NCT01730950).

Table I-2. Normal Tissue Dose Limits

Dose Metric	Per Protocol	Variation Acceptable	Deviation Unacceptable
Scenario (1): Previous radiation to the local area including critical organs at risk			
Maximum Dose to PRV for Optic Nerves and Chiasm (0.03 cc)	Less than or equal to 20 Gy photons – 20 Gy (RBE) protons	Greater than 20 Gy but less than or equal to 25 Gy photons – 25 Gy (RBE) protons	Greater than 25 Gy photons – 25 Gy (RBE) protons
Maximum Dose to Brainstem (0.03 cc)	Less than or equal to 24 Gy photons – 24 Gy (RBE) protons	Greater than 24 Gy but less than or equal to 30 Gy photons – 30 Gy (RBE) protons	Greater than 30 Gy photons – 30 Gy (RBE) protons
Scenario (2): No previous radiation to the local area or critical organs at risk			
Maximum Dose to PRV for Optic Nerves and Chiasm (0.03 cc)	Less than or equal to 35 Gy (the prescription dose) photons – 35 Gy (RBE) protons	Greater than 35 Gy but less than or equal to 36.75 Gy (105 % of the prescription dose) photons – 36.75 Gy (RBE) protons	Greater than 36.75 Gy (105% of the prescription dose) photons – 36.75 Gy (RBE) protons
Maximum Dose to Brainstem (0.03 cc)	Less than or equal to 35 Gy (the prescription dose) photons – 35 Gy (RBE) protons	Greater than 35 Gy but less than or equal to 36.75 Gy (105 % of the prescription dose) photons – 36.75 Gy (RBE) protons	Greater than 36.75 Gy (105% of the prescription dose) photons – 36.75 Gy (RBE) protons

6.0 Standard Structure Names

Standard structure names and dose references are summarized in Table I-3.

Table I-3. Standard structure names and reference doses.

Standard Name	Description	Reference Dose (Gy)	Validation Profile
GTV_3500	Residual enhancing tumor or post-operative resection cavity	35	Required
CTV_3500	An Optional CTV expansion of no more than 5 mm.	35	Required
PTV_3500	planning target volume; an additional margin of 3 to 5 mm	35	Required
Brain	Outline of the brain		Required
OpticChiasm	Optic Chiasm		Required
OpticChiasm_PRV	Optic Chiasm planning risk volume		Required
BrainStem	Brain stem		Required
BrainStem_PRV	Brain stem planning risk volume		Required
OpticNerve_L	Left optic nerve		Required
OptNrv_L_PRV	Left optic nerve planning risk volume		Required
OpticNerve_R	Right optic nerve		Required
OptNrv_R_PRV	Right optic nerve planning risk volume		Required