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**TITLE: A Phase II, open-label, single arm trial of Pembrolizumab for Refractory Atypical and Anaplastic Meningioma**

**IND NUMBER: MK-3475-415**

**EudraCT NUMBER (Studies in Europe only – delete if N/A):**  
**Protocol version 3.0 - 5 APRIL 2021**

## 1.0 TRIAL SUMMARY

Abbreviated Title	<b>Pembrolizumab for Refractory Atypical and Anaplastic Meningioma</b>
Trial Phase	<i>II</i>
Clinical Indication	Atypical Meningioma, Anaplastic Meningioma, hemangiopericytoma
Trial Type	Interventional
Type of control	No control
Route of administration	Intra-Venous (IV)
Trial Blinding	Unblinded open-label
Treatment Groups	IV Pembrolizumab 200mg, given every 3 weeks until disease progression or intolerable toxicity
Number of trial subjects	25
Estimated enrollment period	<i>2 years</i>
Estimated duration of trial	<i>4 years</i>
Duration of Participation	<i>2 years</i>
Estimated average length of treatment per patient	6 months

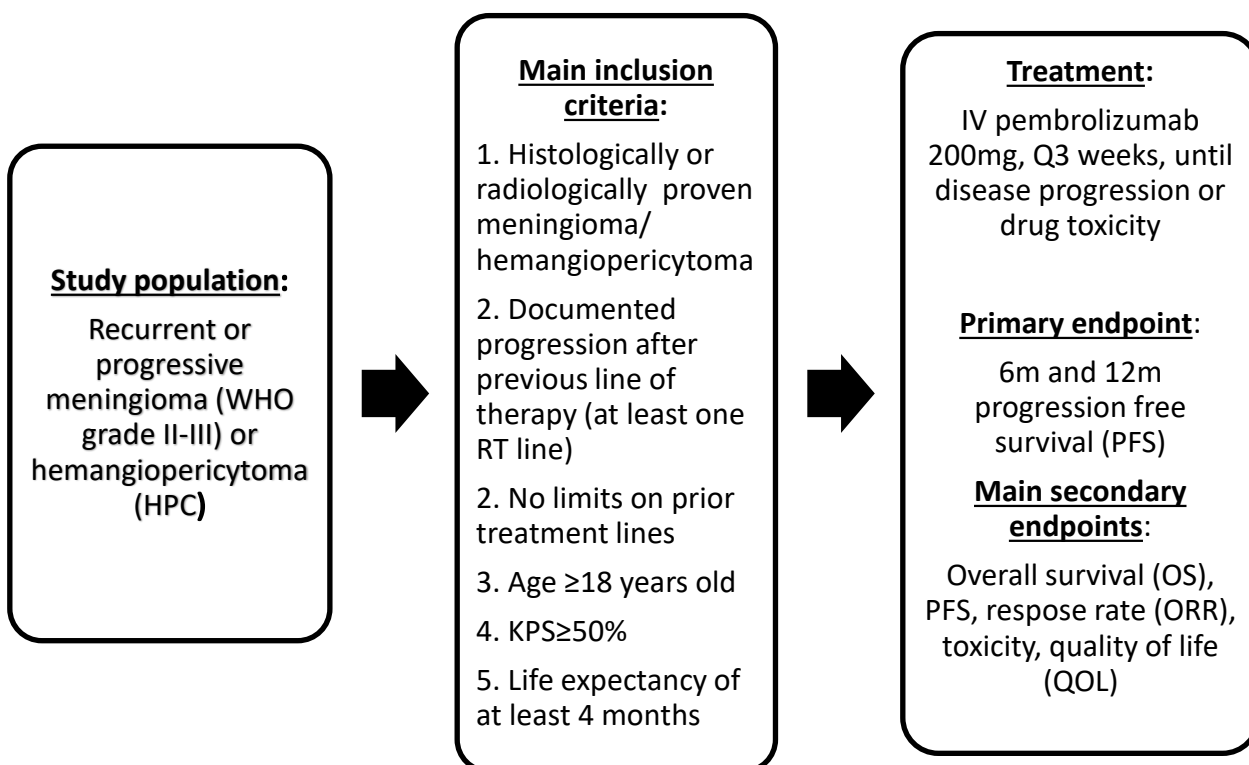
## 2.0 TRIAL DESIGN

### 2.1 Trial Design

This is a multicenter, prospective, single arm, open label, interventional study. The goal of this study, is to evaluate feasibility and efficacy of pembrolizumab for the treatment of recurrent or progressive meningioma (WHO grades II–III) or hemangiopericytoma (HPC). All patients will receive IV pembrolizumab, at a dose of 200mg, every 3 weeks. Patients will be treated until disease progression or intolerable toxicity. Treatment can be stopped after one year of treatment in case of stable disease or completer response, with re-initiation of treatment upon progression. Expression of PD1 and PD-L1 will be tested, on tumor cells, using IHC staining on biopsy material obtained from previous surgeries.

All patients will have a baseline neurologic and clinical exam, MRI scan, a baseline cognitive exam and QOL assessment with a dedicated questionnaire. Patients will have a clinical and neurological exam every treatment cycle. MRI scan will be repeated after 2 months from the beginning of the trial drug administration and then every 2-3 months. There are no designated and specific criteria for response assessment in the treatment of meningioma. Therefore, response evaluation will be made using the RECIST 1.1 criteria, as used for solid tumors. The trial will allow the continuation of pembrolizumab in case of stable or improved clinical response, when pseudo-progression is suspected in the MRI. In addition, response assessment will also be made according to the RANO criteria, as used for high grade glioma. This will be compared to the RECIST evaluation, but will not be used for treatment decision making.

QOL questionnaire will be repeated within 14 days of each radiographic response evaluation. Patients will be followed for treatment effect on QOL. Trial Diagram



### 3.0 OBJECTIVE(S) & HYPOTHESIS(ES)

#### 3.1 Primary Objective(s) & Hypothesis(es)

**Objective:** To determine the 6 and 12 months progression free survival (PFS) rate for patients with recurrent or progressive meningioma on pembrolizumab therapy, using the RECIST 1.1 criteria.

**Hypothesis (H1):** Pembrolizumab is estimated to produce a 6 and 12 months PFS rate which will be at least comparable to other drugs that were tested for recurrent or progressive meningioma.

#### 3.2 Secondary Objective(s) & Hypothesis(es)

(1) **Objective:** To determine OS of patients with recurrent or progressive meningioma treated with pembrolizumab.

**Hypothesis (H2):** Pembrolizumab is expected to have an influence on patients' OS.

- (2) **Objective:** To determine PFS of patients with recurrent or progressive meningioma treated with pembrolizumab.

**Hypothesis (H3):** Pembrolizumab is expected to have an influence on patients' PFS.

- (3) **Objective:** To determine the ORR according to pembrolizumab therapy in treating patients with recurrent or progressive meningioma using the RECIST 1.1 criteria.

**Hypothesis (H4):** Pembrolizumab effect on ORR is not entirely predictable due to expected immune response. This will be evaluated according to the RECIST 1.1 criteria.

- (4) **Objective:** To determine pembrolizumab toxicity and safety in treating patients with recurrent or progressive meningioma according to the Common Terminology Criteria for Adverse Events (CTCAE) v4.0.

**Hypothesis (H5):** Pembrolizumab is expected to have an acceptable toxicity and safety profile in this population of patients.

- (5) **Objective:** To determine the influence of pembrolizumab on quality of life (QOL) using the EORTC QLQ-C30, EORTC QLQ-BN20 and EuroQoLEQ-5D.

**Hypothesis (H6):** Pembrolizumab is expected to improve patients QOL.

**(6) Objective:** To determine the influence of pembrolizumab on neurocognitive changes.

**Hypothesis (H7):** Pembrolizumab is expected to preserve patients' neurocognitive status.

### 3.3 Exploratory Objective

- (1) **Objective:** To evaluate 6 and 12 PFS rate, OS, PFS and ORR according to PD-1 and PDL-1 expression status.
- (2) **Objective:** To estimate ORR to pembrolizumab therapy using MRI.
- (3) **Objective:** To estimate ORR to pembrolizumab therapy using different assessment methods – RECIST 1.1 criteria vs. RANO criteria.
- (4) **Objective:** To investigate the relationship between pembrolizumab treatment and biomarkers predicting response (e.g., PD-L1, genetic variation, serum soluble PD-L1) utilizing archival tumor tissue and blood sampling.

## 4.0 BACKGROUND & RATIONALE

### 4.1 Background

Refer to the Investigator's Brochure (IB)/approved labeling for detailed background information on MK-3475.

#### 4.1.1 Pharmaceutical and Therapeutic Background

The importance of intact immune surveillance in controlling outgrowth of neoplastic transformation has been known for decades [2]. Accumulating evidence shows a correlation between tumor-infiltrating lymphocytes (TILs) in cancer tissue and favorable prognosis in various malignancies [3-7]. In particular, the presence of CD8<sup>+</sup> T-cells and the ratio of CD8<sup>+</sup> effector T-cells / FoxP3<sup>+</sup> regulatory T-cells seems to correlate with improved prognosis and long-term survival in many solid tumors.

The PD-1 receptor-ligand interaction is a major pathway hijacked by tumors to suppress immune control. The normal function of PD-1, expressed on the cell surface of activated T-cells under healthy conditions, is to down-modulate unwanted or excessive immune responses, including autoimmune reactions. PD-1 (encoded by the gene *Pdcd1*) is an Ig superfamily member related to CD28 and CTLA-4 which has been shown to negatively regulate antigen receptor signaling upon engagement of its ligands (PD-L1 and/or PD-L2) [8; 9]. The structure of murine PD-1 has been resolved [10]. PD-1 and family members are type I transmembrane glycoproteins containing an Ig Variable-type (V-type) domain responsible for ligand binding and a cytoplasmic tail which is responsible for the binding of signaling molecules. The cytoplasmic tail of PD-1 contains 2 tyrosine-based signaling motifs, an immunoreceptor tyrosine-based inhibition motif (ITIM) and an immunoreceptor tyrosine-based switch motif (ITSM). Following T-cell stimulation, PD-1 recruits the tyrosine phosphatases SHP-1 and SHP-2 to the ITSM motif within its cytoplasmic tail, leading to the dephosphorylation of effector molecules such as CD3 $\zeta$ , PKC $\theta$  and ZAP70 which are involved in the CD3 T-cell signaling cascade [8; 11- 13]. The mechanism by which PD-1 down modulates T-cell responses is similar to, but distinct from that of CTLA-4 as both molecules regulate an overlapping set of signaling proteins [14; 15]. PD-1 was shown to be expressed on activated lymphocytes including peripheral CD4<sup>+</sup> and CD8<sup>+</sup> T-cells, B-cells, T regs and Natural Killer cells [16; 17]. Expression has also been shown during thymic development on CD4-CD8- (double negative) T-cells as well as subsets of macrophages and dendritic cells [18]. The ligands for PD-1 (PD-L1 and PD-L2) are constitutively expressed or can be induced in a variety of cell types, including non-hematopoietic tissues as well as in various tumors [19-21; 14]. Both ligands are type I transmembrane receptors containing both IgV- and IgC-like domains in the extracellular region and contain short cytoplasmic regions with no known signaling motifs. Binding of either PD-1 ligand to PD-1 inhibits T-cell activation triggered through the T-cell receptor. PD-L1 is expressed at low levels on various non-hematopoietic tissues, most notably on vascular endothelium, whereas PD-L2 protein is only detectably expressed on antigen-presenting cells found in lymphoid tissue or chronic inflammatory environments. PD-L2 is thought to control immune T-cell activation in lymphoid organs, whereas PD-L1 serves to dampen unwarranted T-cell function in peripheral tissues [14]. Although healthy organs express little (if any) PD-L1, a variety of cancers were demonstrated to express abundant levels of this T-cell inhibitor. PD-1 has been suggested to regulate tumor-specific T-cell expansion in subjects with melanoma (MEL). This suggests that the PD-1/PD-L1 pathway plays a critical role in tumor immune evasion and should be considered as an attractive target for therapeutic intervention.

Pembrolizumab is a potent and highly selective humanized monoclonal antibody (mAb) of the IgG4/kappa isotype designed to directly block the interaction between PD-1 and its ligands, PD-L1 and PD-L2. Keytruda™ (pembrolizumab) has recently been approved in the United States for the treatment of patients with unresectable or metastatic melanoma and disease progression following ipilimumab and, if BRAF V600 mutation positive, a BRAF inhibitor.

#### **4.1.2 Preclinical and Clinical Trial Data**

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

### **4.2 Rationale**

#### **4.2.1 Rationale for the Trial and Selected Subject Population**

Meningioma account for 36% of all primary brain tumors and 54% of non-malignant primary brain tumors (22). Meningioma incidence in Israel is higher due to the wide use of head irradiation about 50-60 years ago for the treatment of tinea capitis (23). Atypical meningioma (WHO grade II) and anaplastic meningioma (WHO grade III) incidence is not well reported but is estimated to account for less than 10% of all meningioma cases. Yet, these tumors are a major therapeutic problem, with mainstay treatment that includes surgery and radiotherapy. For refractory or recurrent disease, after previous surgery or radiotherapy, there is no proven or standard management. The 6-months progression free survival (PFS) rate for these patients is poor. A previous study in recurrent meningioma demonstrated a PFS at 6 months of 0% in the atypical and anaplastic cohort (24).

Previous trials with various systemic agents, like different chemotherapies (temozolomide, hydroxyurea, irinotecan, and triple therapy with cyclophosphamide + doxorubicin + vincristine), hormonal therapies (progesterone and estrogen modulators, somatostatin analogues), interferon alfa-2b, and molecularly targeted therapies, including inhibitors of platelet-derived growth factor receptors (PDGFRs; imatinib) and epidermal growth factor receptor (gefitinib and erlotinib), have all been disappointing (24-40). A recent study, examining the use of sunitinib, a multi tyrosine kinase inhibitor, showed more promising results than previous trials with a median PFS of 5.2 months, and a median overall survival (OS) of 24.6 months (41).

As mentioned before, pembrolizumab, an anti-programmed cell death (PD) 1 antibody, acts to block the PD-1 inhibition on T cells producing an enhanced immune response. It was shown to be active in other solid tumors with a positive correlation between PD-1 expression and response to treatment with pembrolizumab. The PD-1 ligand (PD-L1) was found to have an increased expression in anaplastic meningioma (42). Giving this high expression of PD-L1 in meningioma, and the good correlation between its presence and tumor response in other tumors, it stands as a reason to study the effect of pembrolizumab in refractory atypical/anaplastic meningiomas.

#### 4.2.2 Rationale for Dose Selection/Regimen/Modification

An open-label Phase I trial (Protocol 001) was conducted to evaluate the safety and clinical activity of single agent MK-3475. The dose escalation portion of this trial evaluated three dose levels, 1 mg/kg, 3 mg/kg, and 10 mg/kg, administered every 2 weeks (Q2W) in subjects with advanced solid tumors. All three dose levels were well tolerated and no dose-limiting toxicities were observed. This first in human study of MK-3475 showed evidence of target engagement and objective evidence of tumor size reduction at all dose levels (1 mg/kg, 3 mg/kg and 10 mg/kg Q2W). No MTD has been identified to date. Recent data from other clinical studies within the MK-3475 program has shown that a lower dose of MK-3475 and a less frequent schedule may be sufficient for target engagement and clinical activity.

PK data analysis of MK-3475 administered Q2W and Q3W showed slow systemic clearance, limited volume of distribution, and a long half-life (refer to IB). Pharmacodynamic data (IL-2 release assay) suggested that peripheral target engagement is durable (>21 days). This early PK and pharmacodynamic data provides scientific rationale for testing a Q2W and Q3W dosing schedule.

A population pharmacokinetic analysis has been performed using serum concentration time data from 476 patients. Within the resulting population PK model, clearance and volume parameters of MK-3475 were found to be dependent on body weight. The relationship between clearance and body weight, with an allometric exponent of 0.59, is within the range observed for other antibodies and would support both body weight normalized dosing or a fixed dose across all body weights. MK-3475 has been found to have a wide therapeutic range based on the melanoma indication. The differences in exposure for a 200 mg fixed dose regimen relative to a 2 mg/kg Q3W body weight based regimen are anticipated to remain well within the established exposure margins of 0.5 – 5.0 for MK-3475 in the melanoma indication. The exposure margins are based on the notion of similar efficacy and safety in melanoma at 10 mg/kg Q3W vs. the proposed dose regimen of 2 mg/kg Q3W (i.e. 5-fold higher dose and exposure). The population PK evaluation revealed that there was no significant impact of tumor burden on exposure. In addition, exposure was similar between the NSCLC and melanoma indications. Therefore, there are no anticipated changes in exposure between different indication settings.

The rationale for further exploration of 2 mg/kg and comparable doses of pembrolizumab in solid tumors is based on: 1) similar efficacy and safety of pembrolizumab when dosed at either 2 mg/kg or 10 mg/kg Q3W in melanoma patients, 2) the flat exposure-response relationships of pembrolizumab for both efficacy and safety in the dose ranges of 2 mg/kg Q3W to 10 mg/kg Q3W, 3) the lack of effect of tumor burden or indication on distribution behavior of pembrolizumab (as assessed by the population PK model) and 4) the assumption that the dynamics of pembrolizumab target engagement will not vary meaningfully with tumor type.

The choice of the 200 mg Q3W as an appropriate dose for the switch to fixed dosing is based on simulations performed using the population PK model of pembrolizumab showing that the fixed dose of 200 mg every 3 weeks will provide exposures that 1) are optimally consistent

with those obtained with the 2 mg/kg dose every 3 weeks, 2) will maintain individual patient exposures in the exposure range established in melanoma as associated with maximal efficacy response and 3) will maintain individual patients exposure in the exposure range established in melanoma that are well tolerated and safe.

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

### 4.2.3 Rationale for Endpoints

#### 4.2.3.1 Efficacy Endpoints

**Primary:** Progression free survival is an acceptable measure of clinical benefit for a non-randomized phase II trial. As mentioned above, most meningioma patients with recurrent or refractory disease show tumor progression earlier than 6 months (24). Setting the endpoint for 6 and 12 months PFS rate ensures a disease event in many of the patients. In addition, this endpoint was chosen for other relevant trials, such as the sunitinib trial, making it easier for estimate pembrolizumab effect in comparison to other drugs.

**Secondary:** Overall survival and overall PFS will be included as it is a standard assessment of clinical benefit in subjects with recurrent or progressive meningioma. ORR is considered as a marker for clinical benefit. Reporting response with immunotherapy is still controversial, so it will be estimated using MRI scans

**Patients Reported Outcomes:** EORTC QLQ-C30, EORTC QLQ-BN20 and Euro QoLEQ-5D questionnaire will be used for reporting QOL outcomes. Patient related outcomes endpoint is crucial in this population of patients with advanced, incurable disease, which usually already affects everyday function and QOL.

#### 4.2.3.2 Safety Endpoints

The primary safety objective of this trial is to characterize the safety and tolerability of pembrolizumab in subjects with recurrent or progressive meningioma. The primary safety analysis will be based on subjects who experienced toxicities as defined by CTCAE criteria. Safety will be assessed by quantifying the toxicities and grades experienced by subjects who have received pembrolizumab 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 event, its resolution, and any concomitant medications administered will be recorded. AEs will be analyzed including but not limited to all AEs, SAEs, fatal AEs, and laboratory changes. Furthermore, specific immune-related adverse events (irAEs) will be collected and designated as immune-related events of clinical interest (ECIs) as described in section 7.2.3.2. The mandatory Safety Follow-Up visit should be conducted approximately 30 days after the last dose of trial



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

#### **4.2.3.3 Biomarker Research**

Additional biomarker research to identify factors important for pembrolizumab therapy will be pursued. Tumor tissues will undergo RNA sequencing and proteomic, genomic and transcriptional analyses (both DNA and RNA analyses). This additional biomarker or genomic research may be conducted to identify factors important for pembrolizumab therapy and subject response to therapy (for example, to identify risk factors for adverse events or who might best respond to treatment).

## **5.0 METHODOLOGY**

### **5.1 Entry Criteria**

#### **5.1.1 Diagnosis/Condition for Entry into the Trial**

Male and female subjects with recurrent or progressive meningioma or HPC of at least 18 years of age will be enrolled in this trial.

#### **5.1.2 Subject Inclusion Criteria**

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

1. Be willing and able to provide written informed consent/assent for the trial.
2. Be  $\geq 18$  years of age on day of signing informed consent.
3. Have measurable disease based on RECIST 1.1.
4. Histologically, previously proven, grade II or III meningioma, HPC or classic radiographic features of a recurrent surgically inaccessible atypical or anaplastic meningioma and recurrent grade I meningioma with radiographic features of aggressive meningioma after failure of previous treatment with surgery and radiation when feasible.
5. All patients would have to have recurrence despite radiotherapy, unless radiotherapy is contraindicated.
6. No limit on the number of prior surgeries, radiation or radiosurgery treatments.

7. No limit on prior systemic therapies – chemotherapy or biological agents.
8. Patients who received stereotactic radiosurgery (SRS) are eligible without histologic documentation of recurrence if at least 6 months have passed from previous SRS treatment..
9. KPS $\geq$ 50%
10. At least 4 weeks since any prior therapy.
11. Life expectancy of at least 4 months.
12. Dexamethasone use will be allowed up to a dose of 2mg per day. Steroids dose should be reduced or stopped 7 days prior to treatment with study drug.
13. Demonstrate adequate organ function as defined in Table 1, all screening labs should be performed within 10 days of treatment initiation.

Table 1 Adequate Organ Function Laboratory Values

System	Laboratory Value
<b>Hematological</b>	
Absolute neutrophil count (ANC)	$\geq$ 1,500 /mcL
Platelets	$\geq$ 100,000 / mcL
Hemoglobin	$\geq$ 9 g/dL or $\geq$ 5.6 mmol/L without transfusion or EPO dependency (within 7 days of assessment)
<b>Renal</b>	
Serum creatinine <b>OR</b> Measured or calculated creatinine clearance (GFR can also be used in place of creatinine or CrCl)	$\leq$ 1.5 X upper limit of normal (ULN) <b>OR</b>  $\geq$ 60 mL/min for subject with creatinine levels > 1.5 X institutional ULN
<b>Hepatic</b>	
Serum total bilirubin	$\leq$ 1.5 X ULN <b>OR</b> Direct bilirubin $\leq$ ULN for subjects with total bilirubin levels > 1.5 ULN
AST (SGOT) and ALT (SGPT)	$\leq$ 2.5 X ULN <b>OR</b> $\leq$ 5 X ULN for subjects with liver metastases
Albumin	$\geq$ 2.5 mg/dL
<b>Coagulation</b>	
International Normalized Ratio (INR) or Prothrombin Time (PT)	$\leq$ 1.5 X ULN unless subject is receiving anticoagulant therapy as long as PT or PTT is within therapeutic range of intended use of anticoagulants
Activated Partial Thromboplastin Time (aPTT)	$\leq$ 1.5 X ULN unless subject is receiving anticoagulant therapy as long as PT or PTT is within therapeutic range of intended use of anticoagulants
<sup>a</sup> Creatinine clearance should be calculated per institutional standard.	

14. Female subject of childbearing potential should have a negative urine or serum pregnancy within 72 hours prior to receiving the first dose of study medication. If the

urine test is positive or cannot be confirmed as negative, a serum pregnancy test will be required.

15. Female subjects of childbearing potential (Section 5.7.2) must be willing to use an adequate method of contraception as outlined in Section 5.7.2 – Contraception, for the course of the study through 120 days after the last dose of study medication.

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

16. Male subjects of childbearing potential (Section 5.7.1) must agree to use an adequate method of contraception as outlined in Section 5.7.1- Contraception, starting with the first dose of study therapy through 120 days after the last dose of study therapy.

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

### **5.1.3 Subject Exclusion Criteria**

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

1. Is currently participating and receiving study therapy or has participated in a study of an investigational agent and received study therapy or used an investigational device within 4 weeks of the first dose of treatment.
2. Has a diagnosis of immunodeficiency or is receiving other form of immunosuppressive therapy within 7 days prior to the first dose of trial treatment.
3. Patients who are steroid dependent and cannot reduce the dexamethasone dose to a maximal dose of 2mg per day.
4. Has a known history of active TB (Bacillus Tuberculosis)
5. Hypersensitivity to pembrolizumab or any of its excipients.
6. Has had a prior anti-cancer monoclonal antibody (mAb) within 4 weeks prior to study Day 1 or who has not recovered (i.e.,  $\leq$  Grade 1 or at baseline) from adverse events due to agents administered more than 4 weeks earlier.
7. Has had prior chemotherapy, targeted small molecule therapy, or radiation therapy within 2 weeks prior to study Day 1 or who has not recovered (i.e.,  $\leq$  Grade 1 or at baseline) from adverse events due to a previously administered agent.
  - Note: Subjects with  $\leq$  Grade 2 neuropathy are an exception to this criterion and may qualify for the study.

- Note: If subject received major surgery, they must have recovered adequately from the toxicity and/or complications from the intervention prior to starting therapy.
- 8. Has a known additional malignancy that is progressing or requires active treatment. Exceptions include basal cell carcinoma of the skin or squamous cell carcinoma of the skin that has undergone potentially curative therapy or in situ cervical cancer.
- 9. Has known active central nervous system (CNS) metastases and/or carcinomatous meningitis.
- 10. Has active autoimmune disease that has required systemic treatment in the past 2 years (i.e. with use of disease modifying agents, corticosteroids or immunosuppressive drugs). Replacement therapy (eg., thyroxine, insulin, or physiologic corticosteroid replacement therapy for adrenal or pituitary insufficiency, etc.) is not considered a form of systemic treatment.
- 11. Has known history of, or any evidence of active, non-infectious pneumonitis.
- 12. Has an active infection requiring systemic therapy.
- 13. Has a history or current evidence of any condition, therapy, or laboratory abnormality that might confound the results of the trial, interfere with the subject's participation for the full duration of the trial, or is not in the best interest of the subject to participate, in the opinion of the treating investigator.
- 14. Has known psychiatric or substance abuse disorders that would interfere with cooperation with the requirements of the trial.
- 15. Is pregnant or breastfeeding, or expecting to conceive or father children within the projected duration of the trial, starting with the pre-screening or screening visit through 120 days after the last dose of trial treatment.
- 16. Has received prior therapy with an anti-PD-1, anti-PD-L1, or anti-PD-L2 agent.
- 17. Has a known history of Human Immunodeficiency Virus (HIV) (HIV 1/2 antibodies).
- 18. Has known active Hepatitis B (e.g., HBsAg reactive) or Hepatitis C (e.g., HCV RNA [qualitative] is detected).
- 19. Has received a live vaccine within 30 days of planned start of study therapy.

*Note: Seasonal influenza vaccines for injection are generally inactivated flu vaccines and are allowed; however intranasal influenza vaccines (e.g., Flu-Mist®) are live attenuated vaccines, and are not allowed.*

## 5.2 Trial Treatments

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

Table 2 Trial Treatment

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

### 5.2.1 Dose Selection/Modification

#### 5.2.1.1 Dose Selection

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

Details on preparation and administration of pembrolizumab (MK-3475) are provided in the Pharmacy Manual.

#### 5.2.1.2 Dose Modification (Escalation/Titration/Other)

Adverse events (both non-serious and serious) associated with pembrolizumab exposure may represent an immunologic etiology. These adverse events may occur shortly after the first dose or several months after the last dose of treatment. Pembrolizumab must be withheld for drug-related toxicities and severe or life-threatening AEs as per Table 3 below. See Section 5.6.1 for supportive care guidelines, including use of corticosteroids.

Table 3 Dose Modification Guidelines for Drug-Related Adverse Events

Toxicity	Hold Treatment for Grade	Timing for Restarting Treatment	Treatment Discontinuation
Diarrhea/Colitis	2-3	Toxicity resolves to Grade 0-1	Toxicity does not resolve within 12 weeks of last dose or inability to reduce corticosteroid to 10 mg or less of prednisone or equivalent per day within 12 weeks
	4	Permanently discontinue	Permanently discontinue
AST, ALT, or Increased Bilirubin	2	Toxicity resolves to Grade 0-1	Toxicity does not resolve within 12 weeks of last dose
	3-4	Permanently discontinue	Permanently discontinue

Toxicity	Hold Treatment for Grade	Timing for Restarting Treatment	Treatment Discontinuation
Type 1 diabetes mellitus (if new onset) or Hyperglycemia	T1DM or 3-4	Hold pembrolizumab for new onset Type 1 diabetes mellitus or Grade 3-4 hyperglycemia associated with evidence of beta cell failure	Resume pembrolizumab when patients are clinically and metabolically stable
Hypophysitis	2-4	Toxicity resolves to Grade 0-1. Therapy with pembrolizumab can be continued while endocrine replacement therapy is instituted	Toxicity does not resolve within 12 weeks of last dose or inability to reduce corticosteroid to 10 mg or less of prednisone or equivalent per day within 12 weeks
Hyperthyroidism	3	Toxicity resolves to Grade 0-1	Toxicity does not resolve within 12 weeks of last dose or inability to reduce corticosteroid to 10 mg or less of prednisone or equivalent per day within 12 weeks
	4	Permanently discontinue	Permanently discontinue
Hypothyroidism		Therapy with pembrolizumab can be continued while thyroid replacement therapy is instituted	Therapy with pembrolizumab can be continued while thyroid replacement therapy is instituted
Infusion Reaction	2 <sup>a</sup>	Toxicity resolves to Grade 0-1	Permanently discontinue if toxicity develops despite adequate premedication
	3-4	Permanently discontinue	Permanently discontinue
Pneumonitis	2	Toxicity resolves to Grade 0-1	Toxicity does not resolve within 12 weeks of last dose or inability to reduce corticosteroid to 10 mg or less of prednisone or equivalent per day within 12 weeks
	3-4	Permanently discontinue	Permanently discontinue
Renal Failure or Nephritis	2	Toxicity resolves to Grade 0-1	Toxicity does not resolve within 12 weeks of last dose or inability to reduce corticosteroid to 10 mg or less of prednisone or equivalent per day within 12 weeks
	3-4	Permanently discontinue	Permanently discontinue
All Other Drug-Related Toxicity <sup>b</sup>	3 or Severe	Toxicity resolves to Grade 0-1	Toxicity does not resolve within 12 weeks of last dose or inability to reduce corticosteroid to 10 mg or less of prednisone or equivalent per day within 12 weeks
	4	Permanently discontinue	Permanently discontinue

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

<sup>a</sup> If symptoms resolve within one hour of stopping drug infusion, the infusion may be restarted at 50% of the original infusion rate (e.g., from 100 mL/hr to 50 mL/hr). Otherwise dosing will be held until symptoms resolve and the subject should be premedicated for the next scheduled dose; Refer to Table – Infusion Treatment Guidelines for further management details.

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

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

### 5.2.2 Timing of Dose Administration

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

All trial treatments will be administered on an outpatient basis.

Pembrolizumab 200 mg will be administered as a 30 minutes IV infusion every 3 weeks. Sites should make every effort to target infusion timing to be as close to 30 minutes as possible. However, given the variability of infusion pumps from site to site, a window of -5 minutes and +10 minutes is permitted (i.e., infusion time is 30 minutes: -5 min/+10 min).

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

### **5.2.3 Trial Blinding/Masking**

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

### **5.3 Randomization or Treatment Allocation**

This is an open-label, single-arm trial; therefore, there will be no treatment allocation. All subjects entering this trial will receive pembrolizumab monotherapy (200 mg Q3W)

### **5.4 Stratification**

This is an open-label, single-arm trial; therefore, there will be no stratification between treatment arms.

### **5.5 Concomitant Medications/Vaccinations (allowed & prohibited)**

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

#### **5.5.1 Acceptable Concomitant Medications**

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

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

### **5.5.2 Prohibited Concomitant Medications**

Subjects are prohibited from receiving the following therapies during the Screening and Treatment Phase (including retreatment for post-complete response relapse) of this trial:

- Antineoplastic systemic chemotherapy or biological therapy
- Immunotherapy not specified in this protocol
- Chemotherapy not specified in this protocol
- Investigational agents other than pembrolizumab
- Radiation therapy
  - Note: Radiation therapy to a symptomatic solitary lesion or to the brain may be allowed at the investigator's discretion.
- Live vaccines within 30 days prior to the first dose of trial treatment and while participating in the trial. Examples of live vaccines include, but are not limited to, the following: measles, mumps, rubella, varicella/zoster, yellow fever, rabies, BCG, and typhoid vaccine. Seasonal influenza vaccines for injection are generally killed virus vaccines and are allowed; however intranasal influenza vaccines (e.g. Flu-Mist®) are live attenuated vaccines, and are not allowed.
- Glucocorticoids not specified in this protocol or in doses that exceed the allowed specified dose.

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

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

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

## **5.6 Rescue Medications & Supportive Care**

### **5.6.1 Supportive Care Guidelines**

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



require additional supportive care. The treatment guidelines are intended to be applied when the investigator determines the events to be related to pembrolizumab.

Note: if after the evaluation the event is determined not to be related, the investigator does not need to follow the treatment guidance (as outlined below). Refer to Section 5.2.1 for dose modification.

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

- **Pneumonitis:**

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

- **Diarrhea/Colitis:**

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

- All subjects who experience diarrhea/colitis should be advised to drink liberal quantities of clear fluids. If sufficient oral fluid intake is not feasible, fluid and electrolytes should be 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.
- **Type 1 diabetes mellitus (if new onset, including diabetic ketoacidosis [DKA]) or  $\geq$  Grade 3 Hyperglycemia, if associated with ketosis (ketonuria) or metabolic acidosis (DKA)**
    - For **T1DM or Grade 3-4 Hyperglycemia**
      - Insulin replacement therapy is recommended for Type I diabetes mellitus and for Grade 3-4 hyperglycemia associated with metabolic acidosis or ketonuria.

- Evaluate patients with serum glucose and a metabolic panel, urine ketones, glycosylated hemoglobin, and C-peptide.
- **Hypophysitis:**
  - For **Grade 2** events, treat with corticosteroids. When symptoms improve to Grade 1 or less, steroid taper should be started and continued over no less than 4 weeks. Replacement of appropriate hormones may be required as the steroid dose is tapered.
  - For **Grade 3-4** events, treat with an initial dose of IV corticosteroids followed by oral corticosteroids. When symptoms improve to Grade 1 or less, steroid taper should be started and continued over no less than 4 weeks. Replacement of appropriate hormones may be required as the steroid dose is tapered.
- **Hyperthyroidism or Hypothyroidism:**

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

  - **Grade 2** hyperthyroidism events (and **Grade 2-4** hypothyroidism):
    - In hyperthyroidism, non-selective beta-blockers (e.g. propranolol) are suggested as initial therapy.
    - In hypothyroidism, thyroid hormone replacement therapy, with levothyroxine or 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.
- **Hepatic:**
  - For **Grade 2** events, monitor liver function tests more frequently until returned to baseline values (consider weekly).
    - Treat with IV or oral corticosteroids
  - For **Grade 3-4** events, treat with intravenous corticosteroids for 24 to 48 hours.
  - When symptoms improve to Grade 1 or less, a steroid taper should be started and continued over no less than 4 weeks.

- **Renal Failure or Nephritis:**
  - For **Grade 2** events, treat with corticosteroids.
  - For **Grade 3-4** events, treat with systemic corticosteroids.
  - When symptoms improve to Grade 1 or less, steroid taper should be started and continued over no less than 4 weeks.
- **Management of Infusion Reactions:** Signs and symptoms usually develop during or shortly after drug infusion and generally resolve completely within 24 hours of completion of infusion.

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

Table 4 Infusion Reaction Treatment Guidelines

NCI CTCAE Grade	Treatment	Premedication at subsequent dosing
<u>Grade 1</u> Mild reaction; infusion interruption not indicated; intervention not indicated	Increase monitoring of vital signs as medically indicated until the subject is deemed medically stable in the opinion of the investigator.	None
<u>Grade 2</u> Requires infusion interruption but responds promptly to symptomatic treatment (e.g., antihistamines, NSAIDS, narcotics, IV fluids); prophylactic medications indicated for < =24 hrs	<p><b>Stop Infusion and monitor symptoms.</b> Additional appropriate medical therapy may include but is not limited to:</p> <ul style="list-style-type: none"> <li>IV fluids</li> <li>Antihistamines</li> <li>NSAIDS</li> <li>Acetaminophen</li> <li>Narcotics</li> </ul> <p>Increase monitoring of vital signs as medically indicated until the subject is deemed medically stable in the opinion of the investigator. If symptoms resolve within one hour of stopping drug infusion, the infusion may be restarted at 50% of the original infusion rate (e.g., from 100 mL/hr to 50 mL/hr). Otherwise dosing will be held until symptoms resolve and the subject should be premedicated for the next scheduled dose.</p> <p><b>Subjects who develop Grade 2 toxicity despite adequate premedication should be permanently discontinued from further trial treatment administration.</b></p>	<p>Subject may be premedicated 1.5h (± 30 minutes) prior to infusion of pembrolizumab (MK-3475) with:</p> <p>Diphenhydramine 50 mg po (or equivalent dose of antihistamine).</p> <p>Acetaminophen 500-1000 mg po (or equivalent dose of antipyretic).</p>
<u>Grades 3 or 4</u>  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	<p><b>Stop Infusion.</b> Additional appropriate medical therapy may include but is not limited to:</p> <ul style="list-style-type: none"> <li>IV fluids</li> <li>Antihistamines</li> <li>NSAIDS</li> <li>Acetaminophen</li> <li>Narcotics</li> <li>Oxygen</li> <li>Pressors</li> <li>Corticosteroids</li> <li>Epinephrine</li> </ul> <p>Increase monitoring of vital signs as medically indicated until the subject is deemed medically stable in the opinion of the investigator. Hospitalization may be indicated. <b>Subject is permanently discontinued from</b></p>	No subsequent dosing

NCI CTCAE Grade	Treatment	Premedication at subsequent dosing
<b>further trial treatment administration.</b>		
Appropriate resuscitation equipment should be available in the room and a physician readily available during the period of drug administration.		

## 5.7 Diet/Activity/Other Considerations

### 5.7.1 Diet

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

### 5.7.2 Contraception

Pembrolizumab may have adverse effects on a fetus in utero. Furthermore, it is not known if pembrolizumab has transient adverse effects on the composition of sperm.

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

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

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

OR

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

OR

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

Female and male subjects of reproductive potential must agree to avoid becoming pregnant or impregnating a partner, respectively, while receiving study drug and for 120 days after the last dose of study drug by complying with one of the following:

(1) practice abstinence<sup>†</sup> from heterosexual activity;

OR

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

Acceptable methods of contraception are<sup>‡</sup>:

Single method (one of the following is acceptable):

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

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

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

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

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

Subjects should be informed that taking the study medication may involve unknown risks to the fetus (unborn baby) if pregnancy were to occur during the study. In order to participate in the study subjects of childbearing potential must adhere to the contraception requirement (described above) from the day of study medication initiation (or 14 days prior to the initiation of study medication for oral contraception) throughout the study period up to 120 days after the last dose of trial therapy. If there is any question that a subject of childbearing

potential will not reliably comply with the requirements for contraception, that subject should not be entered into the study.

### **5.7.3 Use in Pregnancy**

If a subject inadvertently becomes pregnant while on treatment with pembrolizumab, the subject will immediately be removed from the study. The site will contact the subject at least monthly and document the subject's status until the pregnancy has been completed or terminated. The outcome of the pregnancy will be reported to the Sponsor and to Merck without delay and within 24 hours to the Sponsor and within 2 working days to Merck if the outcome is a serious adverse experience (e.g., death, abortion, congenital anomaly, or other disabling or life-threatening complication to the mother or newborn).

The study investigator will make every effort to obtain permission to follow the outcome of the pregnancy and report the condition of the fetus or newborn to the Sponsor. If a male subject impregnates his female partner the study personnel at the site must be informed immediately and the pregnancy reported to the Sponsor and to Merck and followed as described above and in Section 7.2.2.

### **5.7.4 Use in Nursing Women**

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

## **5.8 Subject Withdrawal/Discontinuation Criteria**

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

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

- The subject or legal representative (such as a parent or legal guardian) withdraws consent.
- Confirmed radiographic disease progression

*Note:* For unconfirmed radiographic disease progression, please see Section 5.2.2

*Note:* A subject may be granted an exception to continue on treatment with confirmed radiographic progression if clinically stable or clinically improved, please see Section 7.1.2.7.1

- Unacceptable adverse experiences as described in Section 5.2.1.2

- Intercurrent illness that prevents further administration of treatment
- Investigator's decision to withdraw the subject
- The subject has a confirmed positive serum pregnancy test
- Noncompliance with trial treatment or procedure requirements
- The subject is lost to follow-up
- Completed 24 months of uninterrupted treatment with pembrolizumab or 35 administrations of study medication, whichever is later.

*Note: 24 months of study medication is calculated from the date of first dose. Subjects who stop pembrolizumab after 24 months may be eligible for up to one year of additional study treatment if they progress after stopping study treatment provided they meet the requirements detailed in Section 7.1.5.5*

- Administrative reasons

The End of Treatment and Follow-up visit procedures are listed in Section 6 (Protocol Flow Chart) and Section 7.1.5 (Visit Requirements). After the end of treatment, each subject will be followed for 30 days for adverse event monitoring (serious adverse events will be collected for 90 days after the end of treatment as described in Section 7.2.3.1). Subjects who discontinue for reasons other than progressive disease will have post-treatment follow-up for disease status until disease progression, initiating a non-study cancer treatment, withdrawing consent or becoming lost to follow-up. After documented disease progression each subject will be followed by telephone for overall survival until death, withdrawal of consent, or the end of the study, whichever occurs first.

### **5.8.1 Discontinuation of Study Therapy after CR**

Discontinuation of treatment may be considered for subjects who have attained a confirmed CR that have been treated for at least 24 weeks with pembrolizumab and had at least two treatments with pembrolizumab beyond the date when the initial CR was declared. Subjects who then experience radiographic disease progression may be eligible for up to one year of additional treatment with pembrolizumab via the Second Course Phase at the discretion of the investigator if no cancer treatment was administered since the last dose of pembrolizumab, the subject meets the safety parameters listed in the Inclusion/Exclusion criteria, and the trial is open. Subjects will resume therapy at the same dose and schedule at the time of initial discontinuation. Additional details are provided in Section 7.1.5.5.

### **5.9 Subject Replacement Strategy**

A subject who discontinues from the trial will not be replaced.

### **5.10 Clinical Criteria for Early Trial Termination**

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

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

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



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## 6.0 TRIAL FLOW CHART

### 6.1 Study Flow Chart

	Screening Phase		Treatment Cycles <sup>a</sup>								End of Treatment	Post-Treatment		
	Pre-screening (V1)	Main Study Screening (V2)	1	2	3	4	To be repeated beyond 8 cycles				Discon	Safety Follow-up	Follow Up Visits <sup>b</sup>	Survival Follow-Up
Days):						5	6	7	8	At time of Discon				
<b>Features</b>														
		X												
Criteria	X	X												
Medical		x												
		x												
		x	x	x	x	x	x	x	x	x				
therapy											x	x		
												x	x	x
<b>Assessments</b>														
		x	x	x	x	x	x	x	x	x	x			
on		x								x				
		x	x	x	x	x	x	x	x					
t	x				x				x	x				





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## **7.0 TRIAL PROCEDURES**

### **7.1 Trial Procedures**

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

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

#### **7.1.1 Administrative Procedures**

The Trial Flow Chart - Section 6.0 summarizes the trial procedures to be performed at each visit. Individual trial procedures are described in detail below. It may be necessary to perform these procedures at unscheduled time points if deemed clinically necessary by the investigator. Furthermore, additional evaluations/testing may be deemed necessary by the investigator and or the Sponsor for reasons related to subject safety.

##### **7.1.1.1 Informed Consent**

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

###### **7.1.1.1.1 General Informed Consent**

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

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

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

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

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

#### **7.1.1.2 Inclusion/Exclusion Criteria**

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

#### **7.1.1.3 Medical History**

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

#### **7.1.1.4 Prior and Concomitant Medications Review**

##### **7.1.1.4.1 Prior Medications**

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

##### **7.1.1.4.2 Concomitant Medications**

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

#### **7.1.1.5 Disease Details and Treatments**

##### **7.1.1.5.1 Disease Details**

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

##### **7.1.1.5.2 Prior Treatment Details**

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

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### **7.1.1.5.3 Subsequent Anti-Cancer Therapy Status**

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

### **7.1.1.6 Assignment of Screening Number**

All consented subjects will be given a unique screening number that will be used to identify the subject for all procedures that occur prior to allocation. Each subject will be assigned only one screening number. Screening numbers must not be re-used for different subjects. Any subject who is screened multiple times will retain the original screening number assigned at the initial screening visit. Specific details on the screening visit requirements (screening/rescreening) are provided in Section 7.1.5.1

### **7.1.1.7 Assignment of Randomization Number**

No randomization will be performed in this protocol.

### **7.1.1.8 Trial Compliance (Medication/Diet/Activity/Other)**

Interruptions from the protocol specified treatment plan for greater than 12 weeks between pembrolizumab doses require consultation between the investigator and the Sponsor and written documentation of the collaborative decision on subject management. Administration of trial medication will be witnessed by the investigator and/or trial staff. The total volume of pembrolizumab infused will be compared to the total volume prepared to determine compliance with each dose of pembrolizumab administered. The instructions for preparing and administering pembrolizumab are provided in the Pharmacy Manual.

## **7.1.2 Clinical Procedures/Assessments**

### **7.1.2.1 Adverse Event (AE) Monitoring**

The investigator or qualified designee will assess each subject to evaluate for potential new or worsening AEs as specified in the Trial Flow Chart and more frequently if clinically indicated. Adverse experiences will be graded and recorded throughout the study and during the follow-up period according to NCI CTCAE Version 4.0 (see Section 11.2). Toxicities will be characterized in terms regarding seriousness, causality, toxicity grading, and action taken with regard to trial treatment.

For subjects receiving treatment with pembrolizumab all AEs of unknown etiology associated with pembrolizumab exposure should be evaluated to determine if it is possibly an event of clinical interest (ECI) of a potentially immunologic etiology (termed immune-related adverse events, or irAEs); see the separate ECI guidance document in Appendix 4 regarding the identification, evaluation and management of potential irAEs.

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

#### **7.1.2.2 Full Physical Exam**

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

#### **7.1.2.3 Directed Physical Exam**

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

#### **7.1.2.4 Neurological assessment**

The investigator or qualified designee will perform a complete full neurological assessment during the screening period, will be repeated after 2 months from the beginning of the trial drug administration and then every 2-3 months, as clinically indicated (not earlier than 2 months and not later than 3 months) as specified in the Trial Flow Chart (Section 6.0). Clinically significant abnormal findings should be recorded as medical history.

#### **7.1.2.5 Vital Signs**

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

#### **7.1.2.6 ECG**

A standard 12-lead ECG will be performed using local standard procedures once at screening. Clinically significant abnormal findings should be recorded as medical history.

#### **7.1.2.7 Performance Score**

The investigator or qualified designee will assess Karnofsky Performance score (see Section 11.1) at screening, prior to the administration of each dose of trial treatment and discontinuation of trial treatment as specified in the Trial Flow Chart.

#### **7.1.2.8 Tumor Imaging and Assessment of Disease**

A baseline MRI scan will be performed. MRI scan will be repeated after 2 months from the beginning of the trial drug administration and then every 2-3 months, as clinically indicated (not earlier than 2 months and not later than 3 months) as specified in the Trial Flow Chart

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(Section 6.0).. Imaging schedule should be maintained until exclusion from trial, including follow-up periods without drug administration. Response evaluation will be made with every scan, using the RECIST 1.1 criteria, as used for solid tumors.

The trial will allow the continuation of pembrolizumab in case of stable or improved clinical response, when pseudo-progression is suspected in the MRI. Continuation of study drug under for suspected pseudo-progression requires consent from study PI (DL).

### **7.1.2.9 Patient Reported Outcomes (PROs)**

The EuroQol EQ-5D, EORTC QLQ-C30, and EORTC QLQ-BN20 questionnaires will be administered by trained site personnel and completed electronically by subjects prior to all other study procedures in the following order: EuroQol EQ-5D first, then EORTC QLQ-C30, and lastly the EORTC QLQ-BN20 at the time points specified in the Trial Flow Chart.

#### **7.1.2.10 Tumor Tissue Collection**

All subjects will submit an archival excisional biopsy to a central lab for characterization of PD-L1 status. Detailed instructions for tissue collection, processing and shipment are provided in the Procedures Manual.

### **7.1.3 Laboratory Procedures/Assessments**

Details regarding specific laboratory procedures/assessments to be performed in this trial are provided below. Laboratory Safety Evaluations (Hematology, Chemistry and Urinalysis)

Laboratory tests for hematology, chemistry, urinalysis, and others are specified in Table 7.



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Table 7 Laboratory Tests

Hematology	Chemistry	Urinalysis	Other
Hematocrit	Albumin	Blood	Serum $\beta$ -human chorionic gonadotropin†
Hemoglobin	Alkaline phosphatase	Glucose	( $\beta$ -hCG)†
Platelet count	Alanine aminotransferase (ALT)	Protein	PT (INR)
WBC (total and differential)	Aspartate aminotransferase (AST)	Specific gravity	aPTT
Red Blood Cell Count	Lactate dehydrogenase (LDH)	Microscopic exam ( <i>If abnormal</i> )	Total triiodothyronine (T3)
Absolute Neutrophil Count	Carbon Dioxide ‡	results are noted	Free tyroxine (T4)
Absolute Lymphocyte Count	( <i>CO<sub>2</sub> or bicarbonate</i> )	Urine pregnancy test †	Thyroid stimulating hormone (TSH)
	Uric Acid		
	Calcium		
	Chloride		Blood for correlative studies
	Glucose		
	Phosphorus		
	Potassium		
	Sodium		
	Magnesium		
	Total Bilirubin		
	Direct Bilirubin ( <i>If total bilirubin is elevated above the upper limit of normal</i> )		
	Total protein		
	Blood Urea Nitrogen		
† Perform on women of childbearing potential only. If urine pregnancy results cannot be confirmed as negative, a serum pregnancy test will be required. ‡ If considered standard of care in your region.			

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

#### **7.1.3.1 Withdrawal/Discontinuation**

When a subject discontinues/withdraws prior to trial completion, all applicable activities scheduled for the final trial visit should be performed at the time of discontinuation. Any adverse events which are present at the time of discontinuation/withdrawal should be followed in accordance with the safety requirements outlined in Section 7.2 - Assessing and Recording Adverse Events. Subjects who a) attain a CR or b) complete 24 months of treatment with pembrolizumab may discontinue treatment with the option of restarting treatment if they meet the criteria specified in Section 7.1.5.5. After discontinuing treatment following assessment of CR, these subjects should return to the site for a Safety Follow-up Visit (described in Section 7.1.5.3.1) and then proceed to the Follow-Up Period of the study (described in Section 7.1.5.4).

#### **7.1.3.2 Withdrawal from Future Biomedical Research**

Subjects may withdraw their consent for Future Biomedical Research and have their specimens and all derivatives destroyed. Subjects may withdraw consent at any time by contacting the principal investigator for the main trial. If medical records for the main trial are still available, the investigator will contact the Sponsor using the designated mailbox (clinical.specimen.management@merck.com), and a form will be provided by the Sponsor to obtain appropriate information to complete specimen withdrawal. Subsequently, the subject's specimens will be removed from the biorepository and be destroyed. A letter will be sent from the Sponsor to the investigator confirming the destruction. It is the responsibility of the investigator to inform the subject of completion of destruction. Any analyses in progress at the time of request for destruction or already performed prior to the request being received by the Sponsor will continue to be used as part of the overall research trial data and results. No new analyses would be generated after the request is received.

In the event that the medical records for the main trial are no longer available (e.g., if the investigator is no longer required by regulatory authorities to retain the main trial records) or the specimens have been completely anonymized, there will no longer be a link between the subject's personal information and their specimens. In this situation, the request for specimen destruction cannot be processed.

#### **7.1.3.3 Calibration of Critical Equipment**

The investigator or qualified designee has the responsibility to ensure that any critical device or instrument used for a clinical evaluation/test during a clinical trial that provides important information about inclusion/exclusion criteria and/or safety or efficacy parameters shall be suitably calibrated and maintained to ensure that the data obtained is reliable and/or

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reproducible. Documentation of equipment calibration must be retained as source documentation at the trial site.

Critical Equipment for this trial includes:

- Laboratory equipment – as required for inclusion labs and trial assessments
- Imaging equipment – as required for study objectives
- Drug administration equipment – as required for storing, preparing, and administering Study treatment

See protocol-specified guidance in the Administrative Binder, Procedures Manual and Site Imaging Manual.

#### **7.1.4 Visit Requirements**

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

##### **7.1.4.1 Screening**

###### **7.1.4.1.1 Screening Period**

Visit requirements are outlined in Section 6.0 – Trial Flow Chart.

Results of a test performed prior to the subject signing consent as part of routine clinical management are acceptable in lieu of a screening test if performed within the specified time frame. Screening procedures are to be completed within 28 days prior to the first dose of trial treatment except for the following:

- Laboratory tests and Karnofsky PS are to be performed within 10 days prior to the first dose of trial treatment.
- For women of reproductive potential, a serum pregnancy test will be performed within 72 hours prior to the first dose of trial treatment. A urine test maybe considered if serum test is not appropriate.
- Tumor sample collection is not required to be obtained within 28 days prior to the first dose of trial treatment.

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

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#### **7.1.4.2 Treatment Period**

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

##### **7.1.4.2.1 Re-treatment criteria**

Patient who completed a treatment period of 24 months may discontinue treatment in case of documented complete response. These patients will be allowed to restart treatment under the following conditions:

- a) Be willing and able to provide consent for the drug re-administration.
- b) Show a documented disease progression on MRI, based on RECIST 1.1 criteria.
- c) A period of at least 2 months has passed since drug discontinuation.
- d) No other treatment for meningioma was given during the discontinuation time (i.e. surgery, radiotherapy, systemic therapy, etc.).
- e) KPS $\geq$ 50%
- f) Demonstrate adequate organ function as defined in Table 1.
- g) Patient is not defendant on a steroids, allowing a dexamethasone dose of up to 2mg.

#### **7.1.4.3 End of Post-Treatment Visits**

##### **7.1.4.3.1 Discontinuation Visit**

The Discontinuation Visit should occur at the time study drug is discontinued for any reason. If the Discontinuation Visit occurs 30 days from the last dose of study treatment, at the time of the mandatory Safety Follow up Visit, procedures do not need to be repeated. Procedures at the time of discontinuation are detailed in Section 7.1.5.3.2 Mandatory Safety Follow up Visit.

##### **7.1.4.3.2 Mandatory Safety Follow up Visit**

##### **7.1.5.3.1 Safety Follow-Up Visit**

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

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treatment should also be followed and recorded. Subjects who are eligible for retreatment with pembrolizumab (as described in Section 7.1.5.5) may have up to two safety follow-up visits, one after the Treatment Period and one after the Second Course Phase.

#### **7.1.4.4 Follow-up Visits**

Subjects who discontinue trial treatment for a reason other than disease progression will move into the Follow-Up Phase and should be assessed every 8 weeks ( $56 \pm 7$  days) by radiologic imaging to monitor disease status. After 1 year, the imaging time point will occur every 9 weeks ( $\pm 7$  days). Every effort should be made to collect information regarding disease status until the start of new anti-neoplastic therapy, disease progression, death, end of the study or if the subject begins retreatment with pembrolizumab as detailed in Section 7.1.5.5. Information regarding post-study anti-neoplastic treatment will be collected if new treatment is initiated.

Subjects who are eligible to receive retreatment with pembrolizumab according to the criteria in Section 7.1.5.5 will move from the follow-up phase to the Second Course Phase when they experience disease progression. Details are provided in Section 6.2 – Trial Flow Chart for Retreatment.

##### **7.1.4.4.1 Survival Follow-up**

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

#### **7.1.4.5 Second Course Phase (Retreatment Period)**

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

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

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**OR**

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

**AND**

- Experienced an investigator-determined confirmed radiographic disease progression after stopping their initial treatment with pembrolizumab
- Did not receive any anti-cancer treatment since the last dose of pembrolizumab
- Has a KPS $\geq$ 50%
- Demonstrates adequate organ function as detailed in Section 5.1.2
- Female subject of childbearing potential should have a negative serum or urine pregnancy test within 72 hours prior to receiving retreatment with study medication.
- Female subject of childbearing potential should be willing to use 2 methods of birth control or be surgically sterile, or abstain from heterosexual activity for the course of the study through 120 days after the last dose of study medication (Reference Section 5.7.2). Subjects of child bearing potential are those who have not been surgically sterilized or have been free from menses for > 1 year.
- Male subject should agree to use an adequate method of contraception starting with the first dose of study therapy through 120 days after the last dose of study therapy.
- Does not have a history or current evidence of any condition, therapy, or laboratory abnormality that might interfere with the subject's participation for the full duration of the trial or is not in the best interest of the subject to participate, in the opinion of the treating investigator.

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

## **7.2 Assessing and Recording Adverse Events**

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

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frequency and/or intensity) of a preexisting condition that is temporally associated with the use of the Merck's product, is also an adverse event.

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

Merck product includes any pharmaceutical product, biological product, device, diagnostic agent or protocol-specified procedure, whether investigational (including placebo or active comparator medication) or marketed, manufactured by, licensed by, provided by or distributed by Merck for human use.

Adverse events may occur during the course of the use of Merck product in clinical trials, or as prescribed in clinical practice, from overdose (whether accidental or intentional), from abuse and from withdrawal.

Progression of the cancer under study is not considered an adverse event.

All adverse events that occur after the consent form is signed, but before treatment allocation, must be reported by the investigator if they cause the subject 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.

From the time of treatment allocation/randomization through 30 days following cessation of treatment, all adverse events must be reported by the investigator. Such events will be recorded at each examination on the Adverse Event case report forms/worksheets. The reporting timeframe for adverse events meeting any serious criteria is described in section 7.2.2. The investigator will make every attempt to follow all subjects with non-serious adverse events for outcome.

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

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

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

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

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

### **7.2.1 Reporting of Pregnancy and Lactation to the Sponsor and to Merck**

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

Pregnancies and lactations that occur after the consent form is signed but before treatment allocation/randomization must be reported by the investigator if they cause the subject 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 lactations 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 subject 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 must be reported within 24 hours to the Sponsor and within 2 working days to Merck Global Safety. (Attn: Worldwide Product Safety; FAX 215 993-1220)

### **7.2.2 Immediate Reporting of Adverse Events to the Sponsor and to Merck**

#### **7.2.2.1 Serious Adverse Events**

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

- Results in death;
  - Is life threatening;
  - Results in persistent or significant disability/incapacity;
  - Results in or prolongs an existing inpatient hospitalization;
  - Is a congenital anomaly/birth defect;
  - Is another important medical event
- 
- **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



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same timeframe as SAEs to meet certain local requirements. Therefore, these 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.

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

For the time period beginning when the consent form is signed until treatment allocation, any serious adverse event, or follow up to a serious adverse event, including death due to any cause other than progression of the cancer under study (reference Section 7.2.3.3 for additional details), that occurs to any subject must be reported within 24 hours to the Sponsor and within 2 working days to Merck Global Safety if it causes the subject 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 subject initiates new anticancer therapy, whichever is earlier, any serious adverse event, or follow up to a serious adverse event, including death due to any cause other than progression of the cancer under study (reference Section 7.2.3.3 for additional details), whether or not related to the Merck product, must be reported within 24 hours to the Sponsor and within 2 working days to Merck Global Safety.

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 the Sponsor and to Merck Global Safety.

All subjects 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: +1-215-993-1220**

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

#### **7.2.2.2 Events of Clinical Interest**

Selected non-serious and serious adverse events are also known as Events of Clinical Interest (ECI) and must be reported within 24 hours to the Sponsor and within 2 working days to Merck Global Safety. (Attn: Worldwide Product Safety; FAX 215 993-1220).

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For the time period beginning when the consent form is signed until treatment allocation any ECI, or follow up to an ECI, that occurs to any subject must be reported within 24 hours to the Sponsor and within 2 working days to Merck Global Safety if it causes the subject 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 subject 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 24 hours to the Sponsor and within 24 hours 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.

3. Additional adverse events: Any seizure in a patient with no history of previous seizures will be documented and reported. An increase in number of seizures in a patient with previous seizure history will have to be documented and reported, as well as a change in previously known pattern of seizures.

### **7.2.2.3 Protocol-Specific Exceptions to Serious Adverse Event Reporting**

Efficacy endpoints as outlined in this section will not be reported to Merck as described in Section 7.2.3.- Immediate Reporting of Adverse Events to the Sponsor and to Merck, unless there is evidence suggesting a causal relationship between the drug and the event. Any such event will be submitted to the Sponsor within 24 hours and to Merck Global Safety within 2 working days either by electronic or paper media.

Specifically, the suspected/actual events covered in this exception include any event that is disease progression of the cancer under study.

The Sponsor will monitor unblinded aggregated efficacy endpoint events and safety data to ensure the safety of the subjects in the trial. Any suspected endpoint which upon review is not progression of the cancer under study will be forwarded to Merck Global Safety as a SAE

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within 2 working days of determination that the event is not progression of the cancer under study

Hospitalization related to convenience (e.g. transportation issues etc.) will not be considered a SAE.

### **7.2.3 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.

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### Table 8 Evaluating Adverse Events

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

<b>V4.0 CTCAE Grading</b>	<b>Grade 1</b>	<b>Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated.</b>
	<b>Grade 2</b>	<b>Moderate; minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental ADL.</b>
	<b>Grade 3</b>	<b>Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care ADL.</b>
	<b>Grade 4</b>	<b>Life threatening consequences; urgent intervention indicated.</b>
	<b>Grade 5</b>	<b>Death related to AE</b>
<b>Seriousness</b>	A serious adverse event is any adverse event occurring at any dose or during any use of Merck product that:	
	† <b>Results in death</b> ; or	
	† <b>Is life threatening</b> ; 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	
	† <b>Results in a persistent or significant disability/incapacity</b> (substantial disruption of one's ability to conduct normal life functions); or	
	† <b>Results in or prolongs an existing inpatient hospitalization</b> (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	
	† <b>Is a congenital anomaly/birth defect</b> (in offspring of subject taking the product regardless of time to diagnosis); or	
	<b>Is a new cancer</b> (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	
	<b>Is an overdose</b> (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.	
<b>Other important medical events</b> 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		

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	listed previously (designated above by a †).
<b>Duration</b>	Record the start and stop dates of the adverse event. If less than 1 day, indicate the appropriate length of time and units
<b>Action taken</b>	Did the adverse event cause Merck product to be discontinued?
<b>Relationship to Merck Product</b>	<p>Did Merck product cause the adverse event? The determination of the likelihood that 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.</p> <p><b>The following components are to be used to assess the relationship between Merck product and the AE;</b> the greater the correlation with the components and their respective elements (in number and/or intensity), the more likely Merck product caused the adverse event (AE):</p>
<b>Exposure</b>	Is there evidence that the subject was actually exposed to Merck product such as: reliable history, acceptable compliance assessment (pill count, diary, etc.), expected pharmacologic effect, or measurement of drug/metabolite in bodily specimen?
<b>Time Course</b>	Did the AE follow in a reasonable temporal sequence from administration of Merck product? Is the time of onset of the AE compatible with a drug-induced effect (applies to trials with investigational medicinal product)?
<b>Likely Cause</b>	Is the AE not reasonably explained by another etiology such as underlying disease, other drug(s)/vaccine(s), or other host or environmental factors

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<b>Relationship to Merck Product (continued)</b>	<b>The following components are to be used to assess the relationship between the test drug and the AE: (continued)</b>	
	<b>Dechallenge</b>	Was 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 Sponsor's product; or (3) the trial is a single-dose drug trial; or (4) Sponsor's product(s) is/are only used one time.)
	<b>Rechallenge</b>	Was the subject re-exposed to 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) Sponsor's 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 MERCK PRODUCT, OR IF REEXPOSURE TO MERCK PRODUCT POSES ADDITIONAL POTENTIAL SIGNIFICANT RISK TO THE SUBJECT, THEN THE RECHALLENGE MUST BE APPROVED IN ADVANCE BY THE SPONSOR AS PER DOSE MODIFICATION GUIDELINES IN THE PROTOCOL.
	<b>Consistency with Trial Treatment Profile</b>	Is the clinical/pathological presentation of the AE consistent with previous knowledge regarding 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.		
<b>Record one of the following</b>	<b>Use the following scale of criteria as guidance (not all criteria must be present to be indicative of Merck product relationship).</b>	
<b>Yes, there is a reasonable possibility of Merck product relationship.</b>	There is evidence of exposure to Merck product. The temporal sequence of the AE onset relative to the administration of Merck product is reasonable. The AE is more likely explained by Merck product than by another cause.	
<b>No, there is not a reasonable possibility of Merck product relationship</b>	Subject did not receive the Merck product OR temporal sequence of the AE onset relative to administration of 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.)	

#### **7.2.4 Sponsor Responsibility for Reporting Adverse Events**

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

### **8.0 STATISTICAL ANALYSIS PLAN**

#### **8.1 Statistical Analysis Plan Summary**

##### **8.1.1 Efficacy Analyses**

The intention-to-treat (ITT) population that includes all allocated subjects will serve as the primary population for the analyses of efficacy data in this trial.

The primary efficacy endpoint is 6 and 12 months progression-free survival (PFS) rate (i.e., the proportion of subjects who did not experience progressive disease or died due to any cause at 6 and 12 months from randomization.) per RECIST 1.1 criteria, based on independent radiologists' review.

The secondary efficacy endpoints for this trial are overall survival (OS), progression-free survival (PFS) and overall response rate (ORR) per RECIST 1.1 criteria based on independent radiologists' review. The analysis plan for PROs will be provided in a separate document before the final PFS analysis.

##### **8.1.2 Safety Analysis**

The All Patients as Treated (APaT) population will be used for the primary analysis of safety data in this study. Investigators will report adverse experiences at every visit on this study (at least every three weeks during treatment) using Common Terminology Criteria for Adverse Events, Version 4.0. The attribution to drug, time -of-onset, duration of the event, its resolution, and any concomitant medications administered will be reported. AEs will be analyzed and reported, including but not limited to Events of Clinical Interest outlined in the separate ECI and irAE guidance document, all AEs, SAEs, fatal AEs, and laboratory changes.

##### **8.1.3 Power and Sample Size**

With a minimum sample size of 22 patients with atypical/malignant meningioma, we will have 80% power to detect an improvement in the 6mPFS rate from 5% to 25% with a significance level of 0.05. Together with a presumed 10% drop-out of patients, the number of patients we want to enroll is 25.

## **8.2 Statistical Analysis Plan**

### **8.2.1 Responsibility for Analyses**

The statistical analysis of the data obtained from this study will be the responsibility of the Clinical Biostatistics department of the Investigator.

### **8.2.2 Hypotheses/Estimation**

Objectives and hypotheses of the study are stated in Section 3. The study is considered to have met its primary objective if pembrolizumab if 6 or 12 months PFS which will be at least comparable to other drugs that were tested for recurrent or progressive meningioma, with a 6mo PFS of 40% and 12mo PFS of 15%.

### **8.2.3 Analysis Endpoints**

#### **8.2.3.1 Efficacy Endpoints**

##### **Primary**

##### **6 and 12 months Progression-free survival rate**

6 and 12 months progression-free survival (PFS) rate is defined as the proportion of subjects alive at 6 and 12 months without progression or death, whichever occurs first. The first documented disease progression will be assessed per RECIST 1.1 criteria, based on central radiologists' review. Death is considered as death due to any cause. The proportion is calculated from the intention-to-treat (ITT) population.

##### **Secondary**

##### **Overall Survival**

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

##### **Progression-free survival**

Progression-free-survival (PFS) is defined as the time from randomization to the first documented disease progression per RECIST 1.1 criteria based on central radiologists' review or death due to any cause, whichever occurs first.

##### **Overall Response Rate (ORR)**

Overall response rate is defined as the proportion of the subjects in the analysis population who have a complete response (CR) or partial response (PR). Responses are based upon central radiologists' review per RECIST 1.1 criteria.



### **8.2.3.2 Safety Endpoints**

Safety measurements are described in Section 7.

## **8.2.4 Analysis Population**

### **8.2.4.1 Efficacy Analysis Population**

The analysis of primary efficacy endpoints is based on the intention -to-treat (ITT) population.

Details on the approach to handling missing data are provided in Section 8.2.5 Statistical Methods.

### **8.2.4.2 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 randomized subjects who received at least one dose of study treatment. At least one laboratory or vital sign measurement obtained subsequent to at least one dose of trial treatment is required for inclusion in the analysis of each specific parameter. To assess change from baseline, a baseline measurement is also required.

Details on the approach to handling missing data for safety analyses are provided in Section 8.2.5 Statistical Methods.

## **8.2.5 Statistical Methods**

### **8.2.5.1 Statistical Methods for Efficacy Analyses**

#### **8.2.5.1.1 6 and 12 months Progression-Free Survival (PFS) rate**

6 and 12 months progression-free survival (PFS) rate is defined as the proportion of subjects alive at 6 and 12 months without progression or death, whichever occurs first. The rate will be compared with rates described for other investigational agents using non-parametric test. Since disease progression is assessed periodically, progressive disease (PD) can occur any time in the time interval between the last assessment where PD was not documented and the assessment when PD is documented. For the primary analysis, for the subjects who have PD, the true date of disease progression will be approximated by the date of the first assessment at which PD is objectively documented per RECIST 1.1 criteria, regardless of discontinuation of study drug. Death is always considered as a confirmed PD event. Sensitivity analyses will be performed for comparison of PFS based on investigator's assessment. In order to evaluate the robustness of the PFS endpoint, two sensitivity analyses will be performed with a different set of censoring rules. Sensitivity analysis 1 is the same as the primary analysis except that it censors at the last disease assessment without PD when PD or death is documented after more than one missed disease assessment. Sensitivity analysis 2 is the same as the primary analysis except that it considers discontinuation of treatment or initiation of new anticancer treatment, whichever occurs later, to be a PD event for subjects without documented PD or death.

### **8.2.5.1.2 Progression-Free Survival (PFS)**

The non-parametric Kaplan-Meier method will be used to estimate the PFS curve. Definition of PD and PFS evaluation is described in section 8.2.5.1.1.

### **8.2.5.1.3 Overall Survival (OS)**

The Kaplan-Meier method will be used to estimate the survival curves.

### **8.2.5.1.4 Overall Response Rate (ORR)**

Overall response rate is defined as the proportion of the subjects in the analysis population who have a complete response (CR) or partial response (PR). Responses are based upon central radiologists' review per RECIST 1.1 criteria.

### **8.2.5.1.5 Exploratory analyses**

If the number of responders permits, response duration will be summarized descriptively using Kaplan-Meier medians and quartiles. Only the combined subset of subjects who show a complete or partial response will be included in this analysis

To determine whether the treatment effect is consistent across various subgroups, the primary and secondary endpoints will be estimated within each category of the following classification variables:

- Age category ( $\leq 65$ ,  $>65$  years)
- Sex (female, male)
- Karnofsky performance status ( $\leq 80$ ,  $>80$ )
- PD-1 and PDL-1 expression status.
- Biomarkers

To determine whether the treatment effect is consistent across various assessment methods, the primary and secondary endpoints will be estimated within each category of the following classification variables:

- RECIST 1.1 vs RANO criteria

EORTC QLQ-C30, EORTC QLQ-BN20, EuroQoLEQ-5D, will be summarized as part of the exploratory analysis. Longitudinal and descriptive data analysis will be used to evaluate patient-reported outcomes (PRO). The detailed PRO analysis plan will be included in a separate document.

### **8.2.5.2 Statistical Methods for Safety Analyses**

Safety and tolerability will be assessed by clinical review of all relevant parameters including adverse experiences (AEs), laboratory tests, vital signs, and ECG measurements.

### **8.2.6 Extent of Exposure**

The extent of exposure will be summarized as duration of treatment in cycles. Dose intensity will also be summarized as appropriate.

## **9.0 LABELING, PACKAGING, STORAGE AND RETURN OF CLINICAL SUPPLIES**

### **9.1 Investigational Product**

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

Clinical Supplies will be provided by Merck as summarized in Table 7.

Table 7 Product Descriptions

<b>Product Name &amp; Potency</b>	<b>Dosage Form</b>
Pembrolizumab 50 mg	Lyophilized Powder for Injection
Pembrolizumab 100 mg/ 4mL	Solution for Injection

### **9.2 Packaging and Labeling Information**

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

### **9.3 Clinical Supplies Disclosure**

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

### **9.4 Storage and Handling Requirements**

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

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

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

## **9.5 Returns and Reconciliation**

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

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

## **10.0 ADMINISTRATIVE AND REGULATORY DETAILS**

### **10.1 Confidentiality**

### **10.2 Compliance with Financial Disclosure Requirements**

### **10.3 Compliance with Law, Audit and Debarment**

### **10.4 Compliance with Trial Registration and Results Posting Requirements**

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

### **10.5 Quality Management System**

### **10.6 Data Management**

## **11.0 LIST OF REFERENCES**

1. Lee JW, Kang KW, Park SH, et al. 18F-FDG PET in the assessment of tumor grade and prediction of tumor recurrence in intracranial meningioma. *Eur J Nucl Med Mol Imaging* 2009. 36:1574–1582.
2. Dong H, Strome SE, Salomao DR, Tamura H, Hirano F, Flies DB, et al. Tumor-associated B7-H1 promotes T-cell apoptosis: a potential mechanism of immune evasion. *Nat Med* 2002;8(8):793-800.
3. Sharpe AH, Freeman GJ. The B7-CD28 superfamily. *Nature* 2002; 2:116-26.

4. Brown JA, Dorfman DM, Ma F-R, Sullivan EL, Munoz O, Wood CR, et al. Blockade of programmed death-1 ligands on dendritic cells enhances T cell activation and cytokine production. *J Immunol* 2003; 170:1257-66.
5. Francisco LM, Sage PT, Sharpe AH. The PD-1 pathway in tolerance and autoimmunity. *Immunol Rev* 2010; 236:219-42.
6. Thompson RH, Dong H, Lohse CM, Leibovich BC, Blute ML, Cheville JC, et al. PD-1 expressed by tumor-infiltrating immune cells and is associated with poor outcome for patients with renal cell carcinoma. *Clin Cancer Res* 2007;13(6):1757-61.
7. Talmadge JE, Donkor M, Scholar E. Inflammatory cell infiltration of tumors: Jekyll or Hyde. *Cancer Metastasis Rev* 2007;26:373-400.
8. Usubütün A, Ayhan A, Uygur MC, zen H, klu C, acan S. Prognostic factors in renal cell carcinoma. *J Exp Clin Cancer Res* 1998;17(1):77-81.
9. Al-Shibli KI, Donnem T, Al-Saad S, Persson M, Bremnes RM, Busund L-T. Prognostic effect of epithelial and stromal lymphocyte infiltration in non-small cell lung cancer. *Clin Cancer Res* 2008;14(16):5220-7.
10. Deschoolmeester V, Baay M, Van Marck E, Weyler J, Vermeulen p, Lardon F, et al. Tumor infiltrating lymphocytes: an intriguing player in the survival of colorectal cancer patients. *BMC Immunol* 2010; 11:19.
11. Diez M, Pollán M, Enriquez JM, Dominguez P, Santana A, Tobaruela E, et al. Histopathologic prognostic score in colorectal adenocarcinomas. *Anticancer Res* 1998; 18:689-94.
12. Galon J, Costes A, Sanchez-Cabo F, Kirilovsky A, Mlecnik B, Lagorce-Pagès C, et al. Type, density, and location of immune cells within human colorectal tumors predict clinical outcome. *Science* 2006; 313:1960-4.
13. Hiraoka N. Tumor-infiltrating lymphocytes and hepatocellular carcinoma: molecular biology. *Int J Clin Oncol* 2010; 15:544-51.
14. Nobili C, Degrate L, Caprotti R, Franciosi C, Leone BE, Trezzi R, et al. Prolonged survival of a patient affected by pancreatic adenocarcinoma with massive lymphocyte and dendritic cell infiltration after interleukin-2 immunotherapy. Report of a case. *Tumori* 2008; 94:426-30.
15. Hodi FS, Dranoff G. The biologic importance of tumor-infiltrating lymphocytes. *J Cutan Pathol* 2010;37(Suppl 1):48-53.
16. Kloor M. Lymphocyte infiltration and prognosis in colorectal cancer. *Lancet* 2009;10(840):841.

17. Hillen F, Baeten CIM, van de Winkel A, Creytens D, van der Schaft DWJ, Winnepenninckx V, et al. Leukocyte infiltration and tumor cell plasticity are parameters of aggressiveness in primary cutaneous melanoma. *Cancer Immunol Immunother* 2008;57:97-106.
18. Lee HE, Chae SW, Lee YJ, Kim MA, Lee HS, Lee BL, et al. Prognostic implications of type and density of tumour-infiltrating lymphocytes in gastric cancer. *Br J Cancer* 2008;99(10):1704-11.
19. Leffers N, Gooden MJM, de Jong RA, Hoogeboom B-N, ten Hoor KA, Hollema H, et al. Prognostic significance of tumor-infiltrating T-lymphocytes in primary and metastatic lesions of advanced stage ovarian cancer. *Cancer Immunol Immunother* 2009; 58:449-59.
20. Nishimura H, Honjo T, Minato N. Facilitation of  $\beta$  selection and modification of positive selection in the thymus of PD-1-deficient mice. *J Exp Med* 2000;191(5):891-7.
21. Liotta F, Gacci M, Frosali F, Querci V, Vittori G, Lapini A, et al. Frequency of regulatory T cells in peripheral blood and in tumour-infiltrating lymphocytes correlates with poor prognosis in renal cell carcinoma. *BJU Intern* 2010; 107:1500-6.
22. Ostrom QT, Gittleman H, Liao P, et al. CBTRUS Statistical Report: Primary Brain and Central Nervous System Tumors Diagnosed in the United States in 2007–2011. *Neuro-oncol.* 2014; 16: iv1-iv63.
23. Sadetzki S, Modan B, Chetrit A, et al. Iatrogenic Epidemic of Benign Meningioma. *Am J Epidemiol* 2000; 151: 266-272.
24. Wen PY, Yung WK, Lamborn KR, et al. Phase II study of imatinib mesylate for recurrent meningiomas (North American Brain Tumor Consortium study 01–08). *NeuroOncol.* 2009; 11(6):853–860.
25. Chamberlain MC. Hydroxyurea for recurrent surgery and radiation refractory high-grade meningioma. *J Neurooncol.* 2012; 107(2): 315–321.
26. Chamberlain MC, Tsao-Wei DD, Groshen S. Temozolomide for treatment-resistant recurrent meningioma. *Neurology.* 2004; 62(7):1210–1212.
27. Chamberlain MC, Tsao-Wei DD, Groshen S. Salvage chemotherapy with CPT-11 for recurrent meningioma. *J Neurooncol.* 2006; 78(3): 271–276.
28. Swinnen LJ, Rankin C, Rushing EJ, et al. South west Oncology Group S9811: a phase II study of hydroxyurea for unresectable meningioma (abstract #2063). *J Clin Oncol.* 2009; 27:15s.
29. Grunberg SM, Rankin C, Townsend J, et al. Phase III double-blind randomized placebo-controlled study of mifepristone (RU) for the treatment of unresectable meningioma. *Proc Am Soc Clinical Oncol.* 2001; 20:56a. (Abstract 222).
30. Goodwin JW, Crowley J, Eyre HJ, et al. A phase II evaluation of tamoxifen in unresectable or refractory meningiomas: a South west Oncology Group study. *J Neurooncol.* 1993; 15(1):75–77.
31. Grunberg SM, Weiss MH, Spitz IM, et al. Treatment of unresectable meningiomas with the antiprogestone agent mifepristone. *J Neurosurg.* 1991; 74(6):861–866.

32. Johnson DR, Kimmel DW, Burch PA, et al. Phase II study of subcutaneous octreotide in adults with recurrent or progressive meningioma and meningeal hemangiopericytoma. *Neuro Oncol.* 2011; 13(5):530–535.
33. Kaba SE, DeMonte F, Bruner JM, et al. The treatment of recurrent unresectable and malignant meningiomas with interferon alpha-2B. *Neurosurgery.* 1997; 40(2):271–275.
34. Lou E, Sumrall AL, Turner S, et al. Bevacizumab therapy for adults with recurrent/progressive meningioma: a retrospective series. *J Neurooncol.* 2012; 109(1):63–70.
35. Markwalder TM, Seiler RW, Zava DT. Antiestrogenic therapy of meningiomas—a pilot study. *Surg Neurol.* 1985; 24(3):245–249.
36. Nayak L, Iwamoto FM, Rudnick JD, et al. Atypical and anaplastic meningiomas treated with bevacizumab. *J Neurooncol.* 2012; 109(1):187–193.
37. Norden AD, Drappatz J, Wen PY. Advances in meningioma therapy. *Curr Neurol Neurosci Rep.* 2009; 9(3):231–240.
38. Norden AD, Raizer JJ, Abrey LE, et al. Phase II trials of erlotinib or gefitinib in patients with recurrent meningioma. *J Neurooncol.* 2010; 96(2):211–217.
39. Raizer JJ, Abrey LE, Lassman AB, et al. A phase I trial of erlotinib in patients with nonprogressive glioblastoma multiforme postradiation therapy, and recurrent malignant gliomas and meningiomas. *Neuro Oncol.* 2010; 12(1):87–94.
40. Reardon DA, Norden AD, Desjardins A, et al. Phase II study of Gleevec(R) plus hydroxyurea (HU) in adults with progressive or recurrent meningioma. *J Neurooncol.* 2012; 106(2): 409–415.
41. Kaley TJ, Wen P, Schiff D, et al. Phase II trial of sunitinib for recurrent and progressive atypical and anaplastic meningioma. *NeuroOncol.* 2015; 17(1), 116–121.
42. Ziming Du1, Malak Abedalthagafi1, Ayal A. Aizer. Increased expression of the immune modulatory molecule PD-L1 (CD274) in anaplastic meningioma. *Oncotarget.* 2015; 6(7): 4704-4716.

## 12.0 APPENDICES

### 12.1 Karnofsky Performance scale

Grade	Description
100	Normal; no complaints; no evidence of disease.
90	Able to carry on normal activity; minor signs or symptoms of disease.
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.
60	Requires occasional assistance, but is able to care for most of their personal needs.
50	Requires considerable assistance and frequent medical care.
40	Disabled; requires special care and assistance.
30	Severely disabled; hospital admission is indicated although death not imminent.
20	Very sick; hospital admission necessary; active supportive treatment necessary.
10	Moribund; fatal processes progressing rapidly.
0	Dead
* As published in Karnofsky DA Burchenal JH. (1949). "The Clinical Evaluation of Chemotherapeutic Agents in Cancer." In: MacLeod CM (Ed), Evaluation of Chemotherapeutic Agents. Columbia Univ Press. Page 196.	

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

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



### **12.3 Response Evaluation Criteria in Solid Tumors (RECIST) 1.1 Criteria for Evaluating Response in Solid Tumors**

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

\* As published in the European Journal of Cancer:

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

### **12.4 Revised Assessment in Neuro-Oncology (RANO) criteria for Evaluating Response**

The Revised Assessment in Neuro-Oncology (RANO) criteria\* was published in 2010, as an update to the existing MacDonald criteria as published in the *Journal of Clinical Oncology*: “Updated Response Assessment Criteria for High-Grade Gliomas: Response Assessment in Neuro-Oncology Working Group.” *Journal of Clinical Oncology*. 2010 Apr 10; 28(11):1963-72. In addition, volumetric analysis will be explored by central review for response assessment.