Confidential

TITLE: Pembrolizumab in Patients with Leptomeningeal Disease
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IND 131065 Sponsor, Julie Brahmer, MD.

Supplied Agent:
Pembrolizumab

Version: Protocol Version 2.0

Date: December 4, 2018

NCT03091478

1.0 TRIAL SUMMARY

Abbreviated Title	Pembrolizumab in Leptomeningeal Disease
Trial Phase	II
Clinical Indication	All solid tumors
Trial Type	Interventional
Type of control	No Treatment Control
Route of administration	Intravenous
Trial Blinding	Unblinded Open-label
Treatment Groups	Pembrolizumab (MK-3475) 200 mg every 3 weeks (Q3W)
Number of trial subjects	18 subjects
Estimated enrollment period	The sponsor estimates that the trial will require approximately 18 months from the time the first subject signs the informed consent until the last subject signs the informed consent.
Estimated duration of trial	The sponsor estimates that the trial will require approximately 24 months from the time the first subject signs the informed consent until the last subject's last visit.
Duration of Participation	6 months
Estimated average length of treatment per patient	3 months

2.0 TRIAL DESIGN

2.1 Trial Design

This is an open-label phase II study of pembrolizumab in patients with advanced solid tumors with leptomeningeal carcinomatosis (LMD). Patients may have received any number of prior therapies for their respective solid tumors, but must not have received prior anti-PD-1 therapy and developed progressive disease. Approximately 18 subjects in this study will receive pembrolizumab at a dose of 200mg intravenously (IV) every 3 weeks (Q3W) for 4 doses. In patients who derive clinical benefit from therapy, pembrolizumab may be continued until documented disease progression, unacceptable adverse event(s), intercurrent illness that prevents further administration of treatment, investigator's decision to withdraw the subject, subject withdrawal of consent, noncompliance with trial treatment or procedure requirements, or for administrative reasons.

This study aims to determine if pembrolizumab can cause a radiologic, cytologic or clinical response in the CNS in patients with advanced solid tumors with LMD. The primary endpoint is thus central nervous system (CNS) response, defined either as radiologic response (reduction in size of LMD on gadolinium-enhanced MRI imaging of the brain and total spine including T1- weighted, T2-weighted, fluid attenuated inversion recovery and post-gadolinium sequences)

and/or cytologic response (conversion of positive to negative CSF cytology on 2 consecutive samples) and/or clinical response (Table 8), as detailed in the section 4.1.5.1.1 and 6.1.2.7.

Secondary endpoints will include progression-free survival (PFS), overall survival (OS), and safety.

Patients will undergo routine screening investigations including CBC, CMP, urine, pregnancy test, standard radiologic imaging of the body (CT), cerebrospinal fluid (CSF) sampling for cytology, and a pre-treatment gadolinium-enhanced MRI scan of the brain and total-spine. During the trial, patients will be monitored with a clinical visit, adverse event assessment and routine laboratory tests at the time of each dose of pembrolizumab. Patients will have a CSF sample taken, blood draws, radiologic imaging of the body (CT), and a contrast-enhanced MRI scan of the brain and total-spine after 2 and 4 cycles of therapy for response assessment and correlative studies. In patients with a CSF sample that demonstrates negative cytology, an additional confirmatory CSF sample will be obtained 3 weeks after the first negative CSF cytology sample.

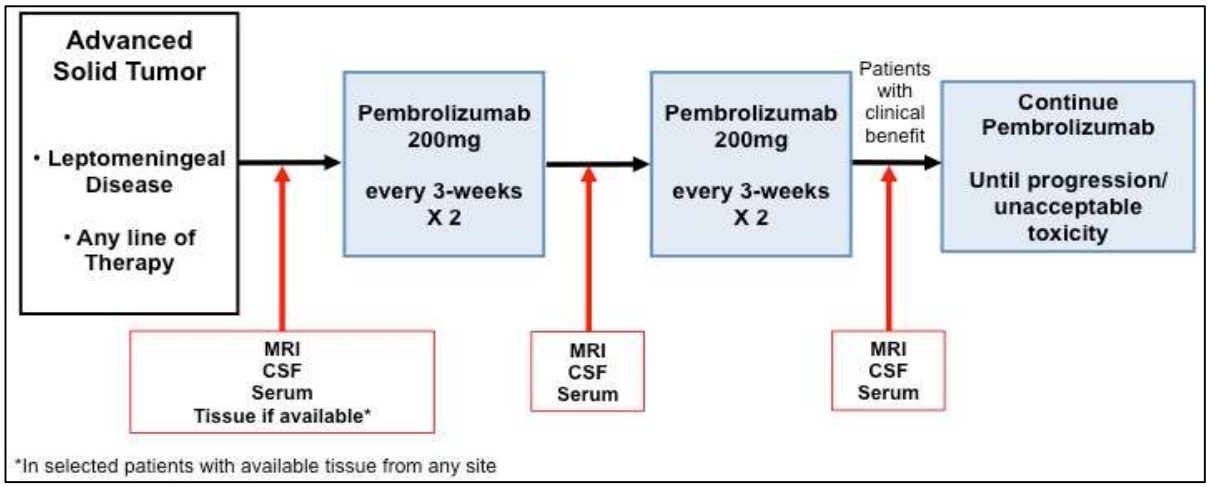
After completion of 4 cycles of therapy, subjects will be evaluated every 6-9 weeks with radiologic imaging of the body (CT) and CNS (MRI) to assess response to treatment both inside and outside of the CNS. Response assessments will be completed by a radiologist at the treating site, findings will be confirmed by an independent radiologist, and evaluated by RECIST 1.1 criteria and immune-related criteria (irRC) for systemic disease, and MRI criteria for CNS disease. Following the first radiologic assessment of the body that demonstrates radiologic progressive disease (PD), RECIST 1.1 will be adapted as described in section 6.1.2.7.5 (Table 9) to accommodate for the tumor response patterns seen with pembrolizumab treatment (e.g., tumor flare) using immune-related RECIST criteria. Contrast-enhanced MRI Brain scans will be used to assess for measurable disease in the CNS at the time of screening, and to determine CNS radiologic response during the study. CNS radiologic response by MRI will be defined as a reduction in size of a measurable lesion throughout the neuro-axis, where a measurable lesion will be defined as one that is greater than or equal to 3mm in size, as detailed in section 6.1.2.7. CNS cytologic response will be assessed by two serial CSF cytology samples, as detailed in the section 6.1.2.8.3. Clinical response will be evaluated by the treating investigator, detailed in section 6.1.2.7 (Table 8).

After completion of 4 cycles of therapy or the patient's last dose of therapy, each subject will be followed for 90 days after the end of treatment for adverse event monitoring, or 30 days after the end of treatment if the subject initiates new anti-cancer therapy. Subjects who discontinue treatment for reasons other than PD will have post-treatment follow-up for disease status until PD, initiation of a new cancer therapy, withdrawal of consent, or becoming lost to follow-up. All subjects will be followed by telephone contact for overall survival (OS) until death, withdrawal of consent or the Investigator is notified by the Sponsor to discontinue follow-up, whichever comes first.

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

Specific procedures to be performed during the trial, as well as their prescribed times and associated visit windows, are outlined in the Trial Flow Chart – Section 5.0 Details of each procedure are provided in Trial Procedures- Section 6.0.

2.2 Trial Diagram



3.0 OBJECTIVE(S) & HYPOTHESES

3.1 Primary Objective

(1) To determine whether pembrolizumab 200mg Q3W induces a radiologic, cytologic or clinical response in the CNS, in patients with LMD from solid tumors, as defined in section 4.1.5.1.

Hypothesis: Pembrolizumab may lead to a CNS response in patients with LMD from solid tumors.

3.2 Secondary Objectives

(1) To determine whether pembrolizumab administered in patients with LMD from solid tumors improves CNS progression-free survival (PFS) as defined in section 4.1.5.1

(2) To determine whether pembrolizumab administered in patients with LMD from solid tumors improves overall survival (OS), as defined in section 4.1.5.1

(3) To determine whether pembrolizumab administered in patients with LMD from solid tumors, is safe and tolerable, as defined in section 4.1.5.1.

Hypothesis: Pembrolizumab will improve CNS-PFS and OS in patients with solid tumors and LMD.

Hypothesis: Pembrolizumab will be safe and tolerable in patients with LMD from solid tumors.

3.3 Exploratory Objectives

(1) To determine whether genomic markers can be detected in the CSF of patients with LMD from solid tumors, as detailed in section 4.1.5.2.

(2) To investigate potential associations between genomic markers in the CSF and CNS/systemic tumor burden, clinical outcomes, and genomic markers in the serum, before and after pembrolizumab therapy, as detailed in section 4.1.5.2.

(3) To determine whether immune cells can be detected in the CSF of patients with LMD, before and after pembrolizumab, as detailed in section 4.1.5.2.

(4) To investigate potential associations between markers of immune activation on cells in the CSF, and clinical outcomes or response to pembrolizumab, as detailed in section 4.1.5.2.

Hypothesis: CSF t-DNA will be detectable in the CSF of patients with LMD. CSF t-DNA levels may correlate with tumor burden, clinical outcomes, or response to pembrolizumab therapy.

Hypothesis: Immune cells will be detectable in the CSF of patients with LMD, before and after pembrolizumab.

Hypothesis: Markers of immune activation on tumor or immune cells in the CSF will predict for improved clinical outcomes or response to pembrolizumab.

4.0 BACKGROUND & RATIONALE

4.1 Background

Refer to the Investigator's Brochure (IB)/approved labeling for detailed background information on pembrolizumab (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. Accumulating evidence shows a correlation between tumor-infiltrating lymphocytes (TILs) in cancer tissue and favorable prognosis in various malignancies. In particular, the presence of CD8+ T-cells and the ratio of CD8+ effector T-cells / FoxP3+ regulatory T-cells 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). The structure of murine PD-1 has been resolved. PD-1 and family members are type I transmembrane glycoproteins containing an Ig Variable-type (V-type) domain responsible for ligand binding and a cytoplasmic tail which is responsible for the binding of signaling molecules. The cytoplasmic tail of PD-1 contains 2 tyrosine-based signaling motifs, an immunoreceptor tyrosine-based inhibition motif (ITIM) and an immunoreceptor tyrosine-based switch motif

(ITSM). Following T-cell stimulation, PD-1 recruits the tyrosine phosphatases SHP-1 and SHP-2 to the ITSM motif within its cytoplasmic tail, leading to the dephosphorylation of effector molecules such as CD3ζ, PKCθ and ZAP70 which are involved in the CD3 T-cell signaling cascade. 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. PD-1 was shown to be expressed on activated lymphocytes including peripheral CD4+ and CD8+ T-cells, B-cells, T regs and Natural Killer cells. Expression has also been shown during thymic development on CD4-CD8- (double negative) T-cells as well as subsets of macrophages and dendritic cells. 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. 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. 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 Stated 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

Therapeutic studies in mouse models show that administration of antibodies blocking PD-1/PD-L1 interaction enhances infiltration of tumor-specific CD8+ T-cells and leads ultimately to tumor rejection, either as a monotherapy or in combination with other treatment modalities. Anti–mouse PD-1 and anti–mouse PD-L1 have demonstrated antitumor responses as a monotherapy in models of squamous cell carcinoma, pancreatic carcinoma, melanoma, and colorectal carcinoma. Blockade of the PD-1 pathway effectively promoted CD8+ T-cell infiltration into the tumor and the presence of IFN-γ, granzyme B, and perforin, indicating that the mechanism of action involved local infiltration and activation of effector T-cell function in vivo[1-5]. In addition, the combination of gemcitabine and anti–PD-L1 mAb demonstrated synergy in the rejection of pancreatic mouse tumors[1]. In-house experiments have confirmed the in vivo efficacy of PD-1 blockade as a monotherapy as well as in combination with chemotherapy in syngeneic mouse tumor models.

Immuno-modulatory agents recently showed promising efficacy in multiple cancer types. Two recent Phase III studies of IPI, an anti-CTL4 mAb, showed significant prolongation of

overall survival in subjects with melanoma[6,7]. Recent data with anti–PD-1 antibodies have validated PD-1 as an attractive target for clinical intervention[8,9]. Importantly, responses have been of long duration and pembrolizumab is generally well tolerated[9]. Based on these data and considerations, the anti–PD-1 antibody, pembrolizumab, appears to be an attractive candidate for continued clinical development in cancer.

4.1.3 Ongoing Clinical Trials

Ongoing clinical trials of pembrolizumab are being conducted in advanced melanoma, non-small cell lung cancer (NSCLC), a number of advanced solid tumor indications and hematologic malignancies. For study details please refer to the IB.

In addition, there are published and ongoing clinical studies of immune checkpoint blockade in patients with brain metastases, as detailed in section 4.1.4.2

Rationale

4.1.4 Rationale for the Trial and Selected Subject Population

4.1.4.1 Anti-PD-1 and Anti-PD-L1 Therapy in Solid Tumors

Immune checkpoint blockade with anti-PD-1 therapy is a promising treatment option for patients with multiple solid tumors. Anti-PD-1 agents nivolumab and pembrolizumab are FDA-approved for patients with metastatic melanoma[10,11] and second-line NSCLC[12,13,14], nivolumab monotherapy is approved for renal cell carcinoma[15] and Hodjkin's lymphoma[16], atezolizumab for bladder carcinoma[17], as well as the nivolumab/ipilimumab combination for metastatic melanoma[18]. There are ongoing studies of single agent anti-PD-1 therapy in a number of solid tumor indications that have demonstrated promising results[19-21], as well as the anti-PD-1/PD-L1 plus anti-CTLA-4 combination in NSCLC[22,23]. Ongoing clinical trials of pembrolizumab and other anti-PD-1/PD-L1 agents are being conducted in a number of advanced solid tumors and hematologic malignancies. For study details please refer to the IB.

Studies are needed to try to utilize these clinically effective agents in disease settings where they have not been previously tested, to advance progress in challenging patient populations with limited treatment options.

4.1.4.2 Rationale for Anti-PD-1 therapy in patients with CNS metastatic disease

CNS metastasis from solid tumors can occur as parenchymal brain metastasis (BM), or leptomeningeal metastasis (LMD) or both (BM)[24]. Parenchymal disease is more common and accounts for approximately 80% of CNS metastasis, while LMD is less commonly seen and carries a worse prognosis. Immunotherapeutic agents were previously thought to be ineffective in patients with CNS metastases, as they would not have the ability to penetrate the blood–brain barrier. However, published studies have demonstrated that activated T-cells have the ability to pass through the blood-brain barrier[25,26]. Therefore, immunotherapies that reinvigorate T-cell responses might be effective in achieving anti-tumor activity in patients with both parenchymal BM and LMD. While patients with stable or treated BM have been

included in many studies utilizing immune checkpoint antibodies to date, patients with LMD have been excluded from all of these studies thus far. Patients with LMD thus constitute a group of patients with a substantial unmet clinical need.

4.1.4.3 Clinical Studies of Anti-PD-1 therapy in patients with CNS metastatic disease

Immune checkpoint blockade has been investigated for therapeutic efficacy in patients with BM. The first immune checkpoint antibody to be clinically investigated in patients with BM was the anti-CTLA-4 monoclonal antibody (mAb) ipilimumab. This agent was administered at a dose of 3mg/kg Q3W for 4 doses in patients with stage III (unresectable) or IV metastatic melanoma with asymptomatic BM, in the context of an expanded access program (EAP). Of 855 patients participating in the EAP in Italy, 146 had asymptomatic BM. In these patients, the median PFS and OS with ipilimumab was 2.8 and 4.3 months, respectively, and nearly one-fifth of patients were alive 1 year after commencement of ipilimumab. Thus, ipilimumab demonstrated durable benefit in selected patients with advanced melanoma metastatic to the brain[27]. In addition, safety data from this study were similar to that of published clinical studies in patients with metastatic melanoma without BM. In a subsequent phase II study, the potential benefit of ipilimumab in patients with BM from melanoma who were both asymptomatic (n=51/72) and symptomatic (n=21/72), was investigated. Patients with asymptomatic BM had a 27% rate of CNS disease control (n=12/51) and those with symptomatic BM had a 10% rate of CNS disease control (n=2/21). In this study, patients with BM demonstrated similar anti-tumor activity, 2-year survival, and safety as patients treated with ipilimumab without BM in reported studies[28].

The potential clinical benefit of anti-PD-1 therapy with pembrolizumab 10mg/kg Q2W is currently being investigated in a phase II study of patients with BM from metastatic melanoma or NSCLC, with at least 1 asymptomatic 5-20mm BM not requiring immediate local therapy or systemic steroids, and at least 1 BM amenable to biopsy or resection. Seventeen melanoma patients have been treated thus far on this clinical study, of which 12 patients were evaluable for response, and 42% exhibited either a partial response (PR) or stable disease (SD) in the brain (n=5/12)[29]. Similarly, 15 patients with NSCLC and BM were treated in this study, and 10 were evaluable for response. Fifty percent of these patients (n=5/10) demonstrated a response in the brain with pembrolizumab (PR=4, CR=1)[30]. The duration of response in the brain was at least 12 weeks in 4 of the 5 responders in the NSCLC patients, and 7+, 6+ and 3+ months in the 3 melanoma responders. Taken together, these data indicate that immune checkpoint blockade with pembrolizumab may confer clinical benefit in patients with metastatic disease in the CNS.

While immune checkpoint blockade has demonstrated early reports of efficacy in patients with parenchymal BM, the potential efficacy of these agents in patients with CNS metastatic disease that takes the form of LMD, has not been studied. This group of patients have been excluded from therapeutic studies with these agents thus far, and are an underserved group of patients with limited or no treatment options.

4.1.4.4 Current Therapies for Leptomeningeal Disease

There are no standard therapies for patients with LMD from solid tumors. In patients with breast cancer and LMD, intrathecal (IT) chemotherapy with or without radiation to bulky disease [31,32] is supported by current NCCN guidelines (Figure 1) based on a small number of randomized studies that mainly include patients with breast cancer, and utilize a number of response assessment systems (Table 1). These approaches were limited by reduced efficacy in the setting of altered CSF flow dynamics (IT therapy), inability to target the entire neuro-axis (i.e. radiation therapy), and the need for additional treatment to manage systemic or parenchymal CNS disease, which is present in the majority of these patients [33,34]. In addition, IT therapy has been associated with both short and long-term neurotoxicity, and device-related complications from administration using Ommaya reservoirs. In patients with breast cancer, LMD may also be treated with high dose systemic chemotherapy with methotrexate (HD-MTX). This is based on two retrospective studies with substantial methodological limitations, one which included only one case of breast cancer[35], and the second that includes patients with both BM alone and BM with LMD[36].

There are no recommended treatment strategies for patients with lung cancer or patients with any other solid tumor and LMD. Retrospective studies have investigated the role of WBRT[37], and selected retrospective studies indicate that WBRT may confer a survival benefit in patients with LMD from NSCLC[38,39]. The use of IT chemotherapy with MTX and cytarabine has been investigated in patients with NSCLC, small cell lung carcinoma (SCLC) and LMD, and demonstrated no OS benefit, cytologic response and some neurologic stability/improvement was seen, but SCLC patients were excluded from the analysis[40,41]. A phase I study of high-dose gefinitib in patients with *EGFR*-mutant NSCLC and LMD accrued 7 patients, and did not identify an MTD. In this study, 4 patients had improvement in neurological symptoms, 1 patient cleared their CSF of NSCLC cells, and 2 patients demonstrated a decrease in CSF tumor cells[42]. There are reported case series and single cases of patients with both *EGFR*-mutant and *ALK*-rearranged NSCLC with LMD, who have sustained both clinical and radiologic responses to LMD with the use of targeted agents. In *EGFR*-mutant NSCLC, patients with LMD who received erlotinib demonstrated clearance of CSF cytology in 64% of cases (n=9/14) as opposed to those who received gefitinib (n=1/11, 9%)[43]. In addition, pulsatile high-dose erlotinib has been shown to achieve higher CSF concentrations in patients with CNS metastases, and resulted in responses in 2 patients of a 9 patient series of patients with LMD[44], and in 3 of a separate 10-patient series[45]. In *ALK*-rearranged NSCLC, strategies that have yielded CNS responses have included: crizotinib and IT-MTX methotrexate (MTX) in 2 crizotinib-naïve patients[46], treatment with second-generation ALK inhibitor ceritinib[47], and high dose second-generation inhibition with alectinib[48]. Other strategies that have been used to treat BM in patients with *ALK*-rearranged NSCLC, such as crizotinib and high-dose systemic chemotherapy[49], one daily dosing[50] or high-dose cirizotinib[51], have not been studied in patients with LMD. Similarly, case reports of melanoma patients detail prolonged survival in *BRAF*-mutant melanoma treated with either vemurafenib[52] or dabrafenib[53], respectively. This is despite reports that detail variable CSF concentrations of vemurafenib compared to systemic concentrations[54].

A limited number of prospective studies have been completed in patients with solid tumors and LMD. Most recently a phase II study of single agent temozolamide demonstrated a

response rate of 15.8% (n=3/19)[55], and single agent pemetrexed, 4% (n=1/21), in all solid tumors[56] (Table 1).

Patients with areas of bulky LMD that cause obstruction of CSF flow or are thought to be causing neurologic deficit, may be treated with local radiation therapy (RT) or WBRT for palliation (Figure 1). There are no prospective clinical studies evaluating the use of local RT or WBRT alone, however the Southwest Oncology Group (SWOG) investigated the combination of WBRT and IT-MTX in solid tumors in 1988[57] (Table 1).

Interpretation of clinical studies in patients with LMD are complicated by a lack of randomized data, and a variety of response assessments used in reported studies. In the studies detailed in Table 1 below, response may have been captured as clinical response, radiologic response, or cytologic response, or a combination of two or three of these response assessments, defined in different ways. Definitions for clinical response on these studies included: improvement or stability in neurologic symptoms[34,58], improvement in neurologic function and KPS at 1 month[35], or improvement in neurologic function with cessation of steroid use[55]. Definitions for radiologic response in these studies included: reduction in size of measurable lesions on brain MRI[36,55], CT brain or myelogram[31]; and definitions for cytologic response may have referred to clearance of previously positive CSF cytology at 1 month[35], or on 2 or more consecutive CSF samples[34]. In one study, response was defined by clinical, radiologic and cytologic parameters, such that a complete responder would demonstrate a normal neurologic examination, negative CSF cytology, normal CSF protein and glucose, and no measurable disease on CT or myelogram[31]. In a second study, response was defined by clinical and cytologic parameters, with the combination of a negative CSF cytology assessment and stable/improved neurologic function as response[32]. Additionally, selected studies included patients with both LMD and parenchymal brain metastases, which may confound the interpretation of some response data[36,56]. Therefore, historical data of response rates in patients with LMD are subject to wide variability and interpretation.

Figure 1: NCCN Guideline for the Management of Leptomeningeal Metastasis

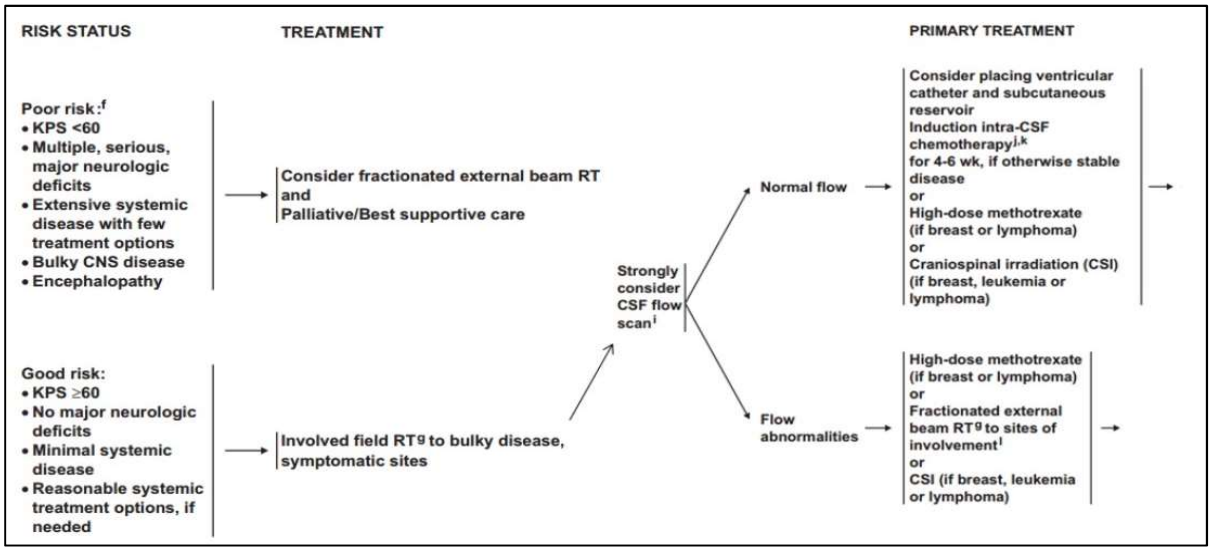


Table 1: Reported Responses for Standard Therapies for Leptomeningeal Disease

	Study Type	Treatment	No. Assessable Patients	Disease	Response Rate	Response Criteria	OS
Intrathecal chemotherapy							
Grossman et al JCO1993[31]	Prospective	IT-MTX vs. IT-thiotepa	52	Solid tumors[&]	0% (0/26) vs. 0% (0/26)	Clinical+ Radiologic + Cytologic response	15.9 vs. 14.1 weeks
Glantz et al Clin Can Res 1999[32]	Prospective	IT cytarabine vs. IT-MTX	61	Solid tumors[@]	26% (8/31, cyt) vs. 20% (6/30, MTX)	Clnical + Cytologic	11.1 weeks
Boogerd et al et al 2004[58]	Prospective	IT-MTX vs. No IT-MTX	35	Breast Cancer	41% (7/17) vs. 39% (7/18)	Clinical	1.8 vs. 30.3 weeks
High-dose chemotherapy							
Glantz et al JCO 1998[35]	Retrospective	8mg/m2 IV HD-MTX	16	Solid tumors*	12.5% (2/16)*	Clinical or Cytologic	55.2 weeks
Lassman et al J Neuro-Oncol 2006[36]	Retrospective	3.5 g/m2 IV HD-MTX	32	Solid tumors[#]	28% (9/32) [#]	Radiologic or Cytologic	12.6 weeks
Scott et al J Neuro-Oncol 2014	Retrospective	IT MTX + liposomal cytarabine	29	Solid tumors[$]	38% (11/29) [$]	Clnical + Cytologic	30.2 weeks
Standard Chemotherapy							
Segura et al J Neuro-oncol 2012[55]	Prospective	Temozolomide	19	Solid tumors[”]	10% (2/19)	Clinical+ Cytologic or Radiologic	6.1 weeks
Kumthekar et al J Neurooncol 2013[56]	Prospective	Pemetrexed	21	Solid tumors[**]	4% (1/21)	Clinical + Cytologic	7.3 months
Whole Brain Radiation							
Sause et al J Neuro-oncol 1988[57]	Prospective	WBRT + IT-MTX	26	Solid tumors[+]	31% (8/26)		3.1 months
Ozdemir et al J Neuro-Oncol 2016[37]	Retrospective	20-30 Gy in divided doses	51	NSCLC	7% (4/51)		3.9 months

*breast cancer (n=1), lymphoma (n=8), SCLC (n=1), NSCLC (n=1), malignant astrocytoma (n=4), anaplastic astrocytoma (n=1), clinical response reported here.
#breast cancer (n=29), cancer of unknown primary (n=1), head and neck carcinoma (n=1), NSCLC (n=1)
$breast cancer (n=15), GBM (n=6), NSCLC (n=5), Other (n=4)
&breast (n=25), NSCLC (n=12), lymphoma (n=10), Other/Unknown (n=5)

@ breast (n=22), SCLC (n=4), NDCLC (n=6), melanoma (n=14), primary brain (n=14), other (n=10)
+breast cancer (n=17), melanoma (n=3), lung cancer (n=4), bladder cancer (n=1), ovarian cancer (n=1)
^breast cancer (n=13), lung cancer (n=33), stomach cancer (n=5), other (n=4)
“breast cancer (n=10) NSCLC (n=7), melanoma (n=1), breast and NSCLC (n=1)
**breast (n=13), lung (n=4), colorectal (n=1), endometrial (n=1), esophageal (n=1) and pinealoblastoma (n=1).

4.1.4.5 Rationale for Anti-PD-1 Therapy in Patients with Leptomeningeal Disease

The most common solid tumors to metastasize to the leptomeninges include: NSCLC (25.8%), breast cancer (17.7%), small cell lung cancer (16.9%) and melanoma (8.9%) [59]. The incidence of LMD by disease-specific tumor type in the era of MRI scans, is estimated at: 3.8-5% of NSCLC patients[60,61], 5% of breast cancer patients[62], 2-3% of patients with metastatic melanoma[63], 2-10% of SCLC patients[64], and 0.03% of patients with genitourinary carcinomas[65]. The incidence of LMD is also projected to be higher in patients with oncogene-addicted cancers such as NSCLCs that harbor an activating mutation in the epidermal growth factor receptor (EGFR), or a chromosomal rearrangement such as EML4-ALK, or in patients with breast cancer that harbors a HER-2 mutation. These patients appear to have a longer clinical course than those without oncogenic driver mutations, and a subset of these patients tend to develop CNS progression with LMD. The median survival for patients with LMD is estimated at 3-6 months in recently published studies[33,39,66]. While this is relatively rare group of patients, there are no established treatment options for this group of patients. These patients thus constitute a critical mass with an empty therapeutic niche. This, coupled with compelling early signals of therapeutic efficacy for pembrolizumab in patients with BM as detailed above, and the fact that pembrolizumab is a generally well-tolerated therapy, makes the use of this agent in patients with LMD an exciting potential treatment option.

4.1.4.6 Rationale for Biomarker Discovery in Patients with Leptomeningeal Disease

Response to therapy in patients with LMD has been historically difficult to assess. In randomized trials, radiologic response has been assessed by contrast-enhanced MRI scans, and CSF response by clearance of initially positive CSF cytology[67]. However, novel genomic biomarkers of tumor burden have been identified in recent years include circulating tumor DNA (ctDNA) in the plasma[68-70] and in anatomically-relevant fluids such as sputum in lung cancer patients[71] and endocervical fluid in ovarian/cervix cancer patients[72]. Furthermore, Bettegowda, Vogelstein and colleagues at JHH were able to detect appreciable levels of tDNA in the CSF of patients with primary brain tumors, which was more sensitive for tumors that abutted a CSF reservoir, and in high-grade tumors[73,74]. In addition, it has been shown that the presence of an effector T-cell population in solid tumors[74,75], and the expression of immune checkpoint markers such as PD-L1 in infiltrating tumor and immune cells in the tumor microenvironment, correlates with prognosis and response to anti-PD-1 therapy in solid tumors including NSCLC[20] and other solid tumors[76]. The tumor microenvironment in patients with LMD is the CSF, and an assessment of the genomic and immunologic landscape of tumor cells/tDNA and immune cells present in the CSF has not been previously described. Since

LMD is in direct contact with CSF reservoirs, this may represent a population of patients in which to assess for the presence of CSF t-DNA, and if detectable, potentially expand its use to quantify tumor burden and measure response to therapy in these patients.

4.1.4.7 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. 10.0 mg/kg Q2W, the highest dose tested in PN001, will be the dose and schedule utilized in Cohorts A, B, C and D of this protocol to test for initial tumor activity. 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.

4.1.5 Rationale for Endpoints

Immune checkpoint blockade has demonstrated benefit in patients with parenchymal BM, but has not been studied in LMD. This study will provide an underserved group of patients with a treatment option that may benefit them. In addition, next-generation genomic and immunologic studies from CSF and serum may uncover new biomarkers in LMD.

4.1.5.1 Efficacy Endpoints

4.1.5.1.1 Primary Endpoint:

The primary efficacy endpoint is to evaluate CNS response with pembrolizumab in patients with LMD from solid tumors. CNS response will be defined either as radiologic response, cytologic response, or clinical response, whichever is easier to assess. Radiologic response will be defined as a reduction in size of a measurable lesion on a contrast-enhanced MRI scan of the brain. Cytologic response will be defined as a negative CSF cytology result in 2 consecutive samples, in patients who have initial positive cytology prior to treatment, or a clinical response, defined as an improvement in objective neurologic signs or symptoms attributable to LMD (Table 8). Response assessment is detailed in section 6.1.2.7. 8A

4.1.5.1.2 Secondary Endpoints:

1. CNS Progression-free Survival: A secondary endpoint of this study is to evaluate CNS-PFS, which will be defined as the time from study enrollment until CNS progression (radiologic, cytologic or clinical), or death, whichever occurs first. CNS progression will be classified as radiologic (determined by contrast-enhanced MRI scan), cytologic (determined by pathologic assessment of CSF cytology including cell count, differential, glucose) or clinical progression (defined as new objective neurologic signs or symptoms, attributable to LMD), as detailed in section 6.1.2.7.

2. **Overall Survival:** A secondary endpoint of this study is to evaluate OS, which will be defined as the time from study enrollment until death from any cause. Deaths from progressive disease will be stratified as related to CNS progression, related to systemic progression, or both.

3. **Safety:** Safety will be evaluated according to the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) version 4.0[27] safety will be determined by the number of treatment-related toxicities of > grade 3 severity by CTCAE Version 4.0.

4.1.5.2 Biomarker Research

Biomarker research will be aimed at identifying prognostic factors for patients with LMD, factors important for pembrolizumab therapy, and factors important for predicting response or resistance to pembrolizumab and other immunologic targets. Planned biomarker analyses are detailed in Table 2 below.

4.1.5.2.1. Genomic Correlates in CSF

CSF will be stored in 1 mL aliquots in cryovials, and flash frozen at -80C. Circulating tumor DNA will be assessed by Safe-SeqSwith primers and probes specific for tumor mutations as described above. CSF tumor cells will be isolated by microdissection. CSF will be collected as described in section 6.1.2.8.3.

Total circulating DNA is defined as the extracellular genome and mitochondrial DNA that is present in the CSF. It includes normal as well as mutant DNA and will be quantified by real-time PCR of a human LINE sequence. Additionally, size distribution of total circulating DNA will be determined by amplicons of varying lengths.

Due to low cellularity, a limited number of analyses can be done on CSF tumor cells. The presence of CSF-tDNA in patients with LMD has not been previously assessed at our institution. Depending on the number of tumor cells isolated and quantity of CSF-t-DNA available, we will assess: 1. Tumor cells and CSF-tDNA by next-generation sequencing, using described methods[73]. From here, candidate neoantigens may be identified using a bioinformatics platform.

4.1.5.2.2 Genomic Correlates in Blood

Circulating tumor cells and cell-free DNA in serum obtained at pre-selected timepoints in this study, will be interrogated genomically. Circulating tumor cells and cfDNA will be obtained using methods described by Bettegowda and colleagues. Depending on the number of tumor cells isolated and quantity of cf-DNA available, we will assess: 1. Tumor cells and cf-DNA by whole-exome sequencing, using methods outlined by Bettegowda and colleagues[69], from here, candidate neoantigens may be identified using a bioinformatics platform.

Tumor-specific circulating DNA distinguishes from normal DNA by the occurrence of point mutations in tumor derived DNA. We will use Safe-SeqS, a next-generation sequencing assay that enables the detection of tumor specific DNA in a high background of normal DNA with high sensitivity and specify. In this study a panel of frequent point mutation or other genetic mutations specific for each tumor type is used to identify and monitor the fraction of tumor DNA. Tumor-specific circulating DNA as measured by the Safe-SeqS assay will be a continuous variable and shall be represented as a ratio between the mutant and wild-type allele evaluated. The development of techniques to analyze genetic alterations in blood of

patients is a rapidly changing field. The methods used to adequately detect mutated DNA and to differentiate it from wild type DNA will be adjusted and modified as appropriate on an ongoing basis. Total circulating DNA is defined as the extracellular genome and mitochondrial DNA that is present in the cell-free portion of the blood e.g. plasma or serum. It includes normal as well as mutant DNA and will be quantified by real-time PCR of a human LINE sequence. Additionally, size distribution of total circulating DNA will be determined by amplicons of varying lengths. We will also collect whole blood in 2x10 mL plasma preparation tubes with EDTA (PPT, BD Vacutainer, Franklin Lakes, NJ) and gently swirl tubes to mix blood with EDTA. Within two hours of collection, the sample will be processed using standard procedures for plasma separation. Plasma will be divided into 1 ml aliquots and stored at -80 degrees C. Pellets from this separation procedure will be washed in PBS and then divided into aliquots and also stored at -80C. These samples will be collected as detailed in section 6.1.2.8.2

4.1.5.2.3. Immunologic Correlates in CSF

Due to low cellularity, a limited number of analyses can be done on CSF immune cells. Depending on the number of cells available, analyses will include but may not be limited to: 1. Quantify the numbers of activated immune cells in the CSF by isolating immune cells with cytospin or flow cytometry, and then performing multi-color immunofluorescence with CD3 and additional immune markers such as PD-1, TIM-3, LAG-3. 2. We will assess immune activation markers present in the CSF and multiplex immune cytokine analyses.

4.1.5.2.4 Immunologic Correlates in Blood

PBMCs and serum will be banked first, and analyses will be prioritized depending on numbers of cells available for analysis and CSF findings. Planned analyses may include but may not be limited to: 1. T-cell phenotyping of peripheral blood lymphocytes (PBLs) evaluated by multi-color flow cytometry for selected immune markers 2. Immune ligand expression of PBLs explored using multi-color flow cytometry 3. Soluble immune factors using ELISA 4. Antigen-specific T-cells using MHC-multimer assays.

4.1.5.2.5 Tumor Tissue Analyses

Archival tissue, pre-treatment biopsy tissue or on-treatment biopsy tissue will be analyzed in patients where this tissue is available. From a genomic perspective, analyses from available tumor cells may include but may not be limited to: next generation sequencing of tumor and matched normal tissue, this will define the genomic landscape of these tumor cells. Candidate neoantigen determination using a bioinformatics platform. From an immunologic perspective, analyses from available tumor cells may include but may not be limited to by immunohistochemistry using monoclonal antibodies for immune checkpoint ligands and TIL populations, immune ligand expression of TILs using multi-color flow cytometry, assessment of soluble immune factors in the tumor microenvironment, and assessment for the presence of antigen-specific T-cells using MHC-multimer assays. Analyses will be prioritized depending on the amount of tissue available for analysis.

Table 2: Biomarker Analysis Table

	Pre-Tx	C1D1	C2D1	C3D1	C4D1	Post-4 cycles	Co-Investigators/ Site of Testing
Pembrolizumab		X	X	X	X		
Biospecimen collection for analysis							
CSF	X			X		X	
PBMCs/Serum	X			X		X	
Tumor tissue*	X*						
Tumor correlates (serum +/- tumor tissue* if available)							
Cell-free DNA	X			X		X	Bettegowda/ Vogelstein Lab
Immune activation*	X*						Venkatesan Lab
T-cell correlates (PBLs +/- tumor TILs* if available)							
Immune activation in PBLs	X			X		X	Venkatesan Lab
Immune activation in TILs*	X*						Venkatesan Lab
CSF analysis (tumor cells, CSF- tDNA, immune cells)							
CSF tumor cells	X			X		X	Bettegowda/ Vogelstein Lab
CSF- tDNA	X			X		X	Bettegowda/ Vogelstein Lab
CSF immune correlates	X			X		X	Venkatesan Lab

METHODOLOGY

4.2 Patient Sample

4.2.1 Sample Size: The accrual objective for this study is 18 eligible and evaluable patients

4.2.2 Accrual Rate: The expected accrual rate for this study is approximately 1 patient per month

4.2.3 Gender: Male and Female subjects

4.2.4 Race: Minorities will be actively recruited.

4.2.5 Diagnosis/Condition for Entry into the Trial: Patients with advanced solid tumors

4.2.6 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 for the trial.
2. Be ≥ 18 years of age on day of signing informed consent.
3. Patients with a histologically or cytologically confirmed solid tumor malignancy.
4. Cytologically-confirmed LMD or radiologically detectable LMD defined as either/or:

   A) A measurable lesion on contrast-enhanced MRI of either the Brain or Total-Spine >3mm that has not been radiated within the last 3 months prior to commencement of study therapy.

   B) Positive CSF cytology as defined in section 6.1.2.7.

5. Patients may be newly diagnosed or have received any number of lines of prior anti-cancer therapy. However, patients are required to have received available therapies for their primary disease, as deemed appropriate by the treating investigator.
6. Non-escalating steroid requirement at the time of consent and study drug initiation for the treatment of CNS symptoms.
7. Local radiation therapy (RT) is allowed as needed to manage symptoms appropriately, as long as there remains a measurable lesion in the CNS.
8. Whole-brain RT may be used, without a pre-defined washout period, prior to commencement of study therapy if the lesion that has been radiated is not the sole measurable lesion, or the patient is eligible based on positive CSF cytology.

9. Patients may continue therapy with a targeted agent if CNS disease developed while receiving the agent, and for defined regimens that have been deemed safe when combined with anti-PD-1 therapy.

10. Be willing to provide tissue from an archival tissue specimen in selected patients, where available.

11. Have a performance status of 0-1 on the ECOG Performance Scale.

12. Demonstrate adequate organ function as defined in Table 3, all screening labs should be performed within 10 days of treatment initiation.

Table 3. Adequate Organ Function Laboratory Values

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

13. 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.

14. Female subjects of childbearing potential (Section 4.8.2) must be willing to use an adequate method of contraception as outlined in Section 4.8.2 – 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.

15. Male subjects of childbearing potential (Section 4.8.2) must agree to use an adequate method of contraception as outlined in Section 4.8.2- 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.

4.2.7 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 or 5 half-lives of the first dose of treatment, whichever is shorter.

2. Has a diagnosis of immunodeficiency or is receiving systemic steroid therapy that exceeds a maximum amount of 10mg of prednisone/day or any other form of immunosuppressive therapy within 7 days prior to the first dose of trial treatment.

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

4. Hypersensitivity to pembrolizumab or any of its excipients.

5. Has had a prior anti-cancer monoclonal antibody (mAb) within 4 weeks prior to study Day 1 or who has not recovered (i.e., ≤ Grade 1 or at baseline) from adverse events due to agents administered more than 4 weeks earlier.

6. Has had prior chemotherapy, targeted small molecule therapy other than pre-specified allowed agents detailed in section 4.2.6, or who has not recovered (i.e., ≤ Grade 1 or at baseline) from adverse events due to a previously administered agent.

    - Note: Subjects with ≤ 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.

7. All major surgery including prior surgery to the brain within 3 weeks of commencement of study 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. Subjects with previously treated brain metastases may participate provided they are not using escalating steroids for brain metastases at the time of trial consent and study drug initiation, and there remains a measurable lesion in the CNS, as per section 4.2.6.

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 (e.g. thyroxine, insulin, or physiologic corticosteroid replacement therapy for adrenal or pituitary insufficiency, etc.) is not considered a form of systemic treatment.

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

12. Has an active infection requiring systemic therapy.

13. Prior disease progression on anti-PD-1 therapy

14. 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.

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

16. 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.

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.

20. Contraindication to MRI.

21. Patients with a condition related to their cancer or leptomeningeal disease requiring urgent intervention that has not been clinically managed or stabilized prior to the time of consent.

22. Brain metastases with risk of mass effect that would contraindicate lumbar puncture, as detailed in section 6.1.2.8.3.

23. Live vaccines within 30 days prior to the first dose of trial treatment. 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.

4.2.8 Eligibility Screening

Eligible patients will be reviewed at the weekly Johns Hopkins Neuro-Oncology Multidisciplinary Tumor Board for unbiased confirmation of diagnosis and treatment candidacy prior to enrollment.

4.2.9 Patient Registration Procedures

4.2.9.1. General Registration Guidelines

All patients entered on any Johns Hopkins trial, whether treatment, companion, or cancer control trial, must be registered with the Sidney Kimmel Comprehensive Cancer Center and complete Informed Consent. Patients will be registered through CRMS and must be registered prior to the initiation of treatment.

4.2.9.2 Recruitment

- Patients will be recruited through the Brain Cancer Program and the Upper Aerodigestive Division (UAD) at Johns Hopkins Medicine. Patients will be recruited from the Sidney Kimmel Comprehensive Cancer Center and 1-2 other participating sites if accrual is slow.

- Patient referrals will be accepted from other Johns Hopkins Medicine sites which include The Johns Hopkins Hospital, Johns Hopkins Bayview Medical Center, Howard County General Hospital, Sibley Memorial Hospital, and Suburban Hospital, and the other site.

- In addition, Johns Hopkins coordinates the Johns Hopkins Clinical Research Network (JHCRN) which was founded in 2009 as an integrated network of select academic and community-based medical institutions established within the Johns Hopkins Institute for Clinical and Translation Research. The JHCRN is comprised of the 6 hospitals within the Johns Hopkins Medicine, Anne Arundel Medical Center, Greater Baltimore Medical Center, INOVA Health Systems, Peninsula Regional Medical Center and Reading Hospital and Health System.

- Referrals from clinicians at these or other facilities will be accepted. In such a case, communication will be directed to the Principal Investigator of the study. This contact may be in the form of telephone, email, etc. The Principal Investigator may inquire as to patient age, diagnosis, prior treatment, timing of prior treatment, and extent of current disease to determine whether the patient would meet global criteria for the study. This information will not be collected, maintained or stored in any way. Patients referred in such a manner will be required to meet in person for review of eligibility, registration and informed consent. These patients will be referred to the study team members in the Brain Cancer Program and UAD Program at the Johns

Hopkins main campus to review eligibility.

- Additional potential participants will be identified during routine clinic visits to the UAD and Brain Cancer Program at Johns Hopkins. Individuals will be approached by the provider or study team to determine willingness to learn more about a study for which they may be eligible. Discussions regarding study participation will take place privately and individuals will be provided with the IRB approved consent form.

- In addition, potential participants may contact the study team directly. This contact may be in the form of telephone, email, etc. Initial discussions regarding study

4.3 Trial Treatments

The treatment to be used in this trial is outlined below in Table 4:

Table 4: Trial Treatment

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

Trial treatment should begin on the day of registration or as close as possible to the date on which treatment is allocated/assigned.

4.3.1 Dose Selection/Modification

4.3.1.1 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.

4.3.1.2 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 5 below. See Section 4.7 for supportive care guidelines, including use of corticosteroids.

Table 5. Dose Modification Guidelines for Drug-Related Adverse Events

Toxicity	Hold Treatment For Grade	Timing for Restarting Treatment	Treatment Discontinuation
Diarrhea/Colitis	2-3	Toxicity resolves to Grade 0-1	Toxicity does not resolve within 12 weeks of last dose or inability to reduce corticosteroid to 10 mg or less of prednisone or equivalent per day within 12 weeks
	4	Permanently discontinue	Permanently discontinue
AST, ALT, or Increased Bilirubin	2	Toxicity resolves to Grade 0-1	Toxicity does not resolve within 12 weeks of last dose
	3-4	Permanently discontinue (see exception below)[a]	Permanently discontinue
Type 1 diabetes mellitus (if new onset) or Hyperglycemia	T1DM or 3-4	Hold pembrolizumab for new onset Type 1 diabetes mellitus or Grade 3-4 hyperglycemia associated with evidence of beta cell failure	Resume pembrolizumab when patients are clinically and metabolically stable
Hypophysitis	2-4	Toxicity resolves to Grade 0-1. Therapy with pembrolizumab can be continued while endocrine replacement therapy is instituted	Toxicity does not resolve within 12 weeks of last dose or inability to reduce corticosteroid to 10 mg or less of prednisone or equivalent per day within 12 weeks
Hyperthyroidism	3	Toxicity resolves to Grade 0-1	Toxicity does not resolve within 12 weeks of last dose or inability to reduce corticosteroid to 10 mg or less of prednisone or equivalent per day within 12 weeks
	4	Permanently discontinue	Permanently discontinue
Hypothyroidism		Therapy with pembrolizumab can be continued while thyroid replacement therapy is instituted	Therapy with pembrolizumab can be continued while thyroid replacement therapy is instituted
Infusion Reaction	2[b]	Toxicity resolves to Grade 0-1	Permanently discontinue if toxicity develops despite adequate premedication
	3-4	Permanently discontinue	Permanently discontinue
Pneumonitis	2	Toxicity resolves to Grade 0-1	Toxicity does not resolve within 12 weeks of last dose or inability to reduce corticosteroid to 10 mg or less of prednisone or equivalent per day within 12 weeks
	3-4	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[c]	3 or Severe	Toxicity resolves to Grade 0-1	Toxicity does not resolve within 12 weeks of last dose or inability to reduce corticosteroid to 10 mg or less of prednisone or equivalent per day within 12 weeks
	4	Permanently discontinue	Permanently discontinue

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

[a] For patients with liver metastasis who begin treatment with Grade 2 AST or ALT, if AST or ALT increases by greater than or equal to 50% relative to baseline and lasts for at least 1 week then patients should be discontinued.

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

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

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.

4.3.2 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 5.0). 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 minute IV infusion every 3 weeks. Sites should make every effort to target infusion timing to be as close to 30 minutes as possible. However, given the variability of infusion pumps from site to site, a window of -5 minutes and +10 minutes is permitted (i.e., infusion time is 30 minutes: -5 min/+10 min).

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

4.3.3 Trial Blinding/Masking

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

4.4 Registration or Treatment Allocation

Assignment of the treatment/allocation number will be directed by the Lead Study Coordinator at Johns Hopkins. All enrolled subjects will be allocated to receive pembrolizumab 200mg Q3W as monotherapy in an unblinded fashion.

4.5 Stratification

No stratification based on age, sex or other characteristics will be used in this trial.

4.6 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.

4.6.1 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.

Palliative and supportive care is permitted during the course of this trial for underlying medical conditions and the management of symptoms. Major surgery for tumor control or symptom management is not permitted during the study or within 3 weeks of study commencement, as outlined in section 4.2.7. Palliative radiotherapy is permitted if considered medically necessary by the treating physician as long as the lesion is not the patient's sole measurable lesion on brain or spine MRI or a defined target lesion in the body by RECIST 1.1, as detailed in section 4.2.6. Trial therapy should be held during the course of palliative radiation, and should be resumed no early than the next schedules dose of trial therapy. The specifics of the radiation treatment given, including location, will be recorded. Additionally, patients who receive radiation therapy will be analyzed separately to assess the potential impact of radiation therapy on clinical outcomes.

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 6.2.

4.6.2 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 chemotherapy
- 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 lesion or to the brain may be allowed as per the inclusion criteria, detailed in section 4.6.1, or at the investigator's discretion.
- Live vaccines within 30 days prior to the first dose of trial treatment and while participating in the trial. Examples of live vaccines include, but are not limited to, the following: measles, mumps, rubella, varicella/zoster, yellow fever, rabies, BCG, and typhoid vaccine.
- Systemic glucocorticoids for any purpose other than to modulate symptoms from an event of clinical interest of suspected immunologic etiology. The use of physiologic doses of corticosteroids may be approved after consultation with the Sponsor.

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

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

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

4.7 Rescue Medications & Supportive Care

4.7.1 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 ≥ Grade 3 Hyperglycemia, if associated with ketosis (ketonuria) or metabolic acidosis (DKA)**
  - For **T1DM** or **Grade 3-4** Hyperglycemia
    - Insulin replacement therapy is recommended for Type I diabetes mellitus and for Grade 3-4 hyperglycemia associated with metabolic acidosis or ketonuria.
    - Evaluate patients with serum glucose and a metabolic panel, urine ketones, glycosylated hemoglobin, and C-peptide.
- **Hypophysitis**:
  - For **Grade 2** events, treat with corticosteroids. When symptoms improve to Grade 1 or less, steroid taper should be started and continued over no less than 4 weeks. Replacement of appropriate hormones may be required as the steroid dose is tapered.
  - For **Grade 3-4** events, treat with an initial dose of IV corticosteroids followed by oral corticosteroids. When symptoms improve to Grade 1 or less, steroid taper should be started and continued over no less than 4 weeks. Replacement of appropriate hormones may be required as the steroid dose is tapered.
- **Hyperthyroidism or Hypothyroidism**:

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

  - **Grade 2** hyperthyroidism events (and **Grade 2-4** hypothyroidism):
    - In hyperthyroidism, non-selective beta-blockers (e.g. propranolol) are suggested as initial therapy.
    - In hypothyroidism, thyroid hormone replacement therapy, with levothyroxine or liothyroinine, is indicated per standard of care.
  - **Grade 3-4** hyperthyroidism
    - Treat with an initial dose of IV corticosteroid followed by oral corticosteroids. When symptoms improve to Grade 1 or less, steroid taper should be started and continued over no less than 4 weeks. Replacement of appropriate hormones may be required as the steroid dose is tapered.
- **Hepatic**:

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

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

  Table 6 below shows treatment guidelines for subjects who experience an infusion reaction associated with administration of pembrolizumab (MK-3475).

Table 6. Infusion Reaction Treatment Guidelines

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

NCI CTCAE Grade	Treatment	Premedication at subsequent dosing
initial improvement; hospitalization indicated for other clinical sequelae (e.g., renal impairment, pulmonary infiltrates) Grade 4: Life-threatening; pressor or ventilatory support indicated	Oxygen Pressors Corticosteroids Epinephrine Increase monitoring of vital signs as medically indicated until the subject is deemed medically stable in the opinion of the investigator. Hospitalization may be indicated. **Subject is permanently discontinued from further trial treatment administration.**	
Appropriate resuscitation equipment should be available in the room and a physician readily available during the period of drug administration.		

4.8 Diet/Activity/Other Considerations

4.8.1 Diet

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

4.8.2 Contraception

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

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

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

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

OR

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

OR

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

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

(1) practice abstinence† from heterosexual activity;

OR

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

Acceptable methods of contraception are‡:

Single method (one of the following is acceptable):

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

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

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

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

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

Subjects should be informed that taking the study medication may involve unknown risks to the fetus (unborn baby) if pregnancy were to occur during the study. In order to participate in the study subjects of childbearing potential must adhere to the contraception requirement (described above) from the day of study medication initiation (or 14 days prior to the initiation of study medication for oral contraception) throughout the study period up to 120 days after the last dose of trial therapy. If there is any question that a subject of childbearing potential will not reliably comply with the requirements for contraception, that subject should not be entered into the study.

4.8.3 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 6.2.2.

4.8.4 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.

4.9 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.
- CNS progression (as detailed in Table 8)
- Unacceptable adverse experiences as described in Section 6.2.
- 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.

- Administrative reasons

The End of Treatment and Follow-up visit procedures are listed in Section 5.0 (Trial Flow Chart). 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 6.1.5.1). 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.

4.9.1 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.

4.9.2 Subject Replacement Strategy

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

4.10 Clinical Criteria for Early Trial Termination

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

1. Quality or quantity of data recording is inaccurate or incomplete

2. Poor adherence to protocol and regulatory requirements

3. Incidence or severity of adverse drug reaction in this or other studies indicates a potential health hazard to subjects

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

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

5.0 TRIAL FLOW CHART

Table 7: Study Flow Chart

Trial Period:	Screening Phase	Treatment Cycles[a]								End of Treatment		Post-Treatment	
						Cycles 5+ only in patients showing clinical benefit. May continue >8 cycles							
Treatment Cycle/Title:	Study Screening (Visit 1)	1	2	3	4	5	6	7	8	Discon[9]	Safety Follow-up	Follow Up Visits	Survival Follow-Up
Scheduling Window (Days):	-28 to -1	± 3[8]	± 3	± 3	± 3	± 3	± 3	± 3	± 3	At time of discon	30 days post discon	Every 6-9 weeks post discon	Every 12 weeks
Administrative Procedures													
Informed Consent	X												
Inclusion/Exclusion Criteria	X												
Demographics and Medical History	X												
Prior and Concomitant Medication Review	X	X	X	X	X	X	X	X	X	X	X	X	
Post-study anticancer therapy status	X									X	X	X	
Survival Status													X
Clinical Procedures/Assessments													
Review Adverse Events	X	X	X	X	X	X	X	X	X	X	X	X	
Full Physical Examination	X									X			
Directed Physical Examination		X	X	X	X	X	X	X	X				
Vital Signs, Weight	X	X	X	X	X	X	X	X	X	X			
Oxygen saturation	X	X	X	X	X	X	X	X	X	X			
ECOG Performance Status	X	X	X	X	X	X	X	X	X	X			
Pembrolizumab Administration		X	X	X	X	X	X	X	X				
Laboratory Procedures/Assessments: analysis performed by LOCAL laboratory													
Pregnancy Test – Urine or Serum β-HCG[1]	X	X	X	X	X	X	X	X	X	X	X		
PT/INR and aPTT	X												
CBC with Differential	X	X	X	X	X	X	X	X	X	X	X		

Trial Period:	Screening Phase	Treatment Cycles[a]								End of Treatment		Post-Treatment	
Treatment Cycle/Title:	Study Screening (Visit 1)	1	2	3	4	Cycles 5+ only in patients showing clinical benefit. May continue >8 cycles 5	6	7	8	Discon[9]	Safety Follow-up	Follow Up Visits	Survival Follow-Up
Scheduling Window (Days):	-28 to -1	± 3[8]	± 3	± 3	± 3	± 3	± 3	± 3	± 3	At time of discon	30 days post discon	Every 6-9 weeks post discon	Every 12 weeks
Comprehensive Serum Chemistry Panel	X	X	X	X	X	X	X	X	X	X	X		
Urinalysis	X												
TSH[2]	X		X		X		X		X	X			
Hepatitis B, C, HIV	X												
Efficacy Measurements													
MRI Brain and Full-spine with contrast	X			X[3]		X[3]				X[3]		X[4]	
CT chest/abdomen/pelvis with contrast	X			X[3]		X[3]				X[3]		X[4]	
Tumor Biopsies/Archival Tissue Collection/Correlative Studies Blood													
Archival Tissue Collection[5]	X												
Blood collection for Genomics	X			X		X				X			
Blood collection for Immune correlates	X			X		X				X			
CSF sample acquisition[6]	X			X		X[7]				X[7]			
CSF sample correlates	X			X		X[7]				X[7]			

[1] In women of childbearing potential only. If urine test is positive or not evaluable, serum test is required
[2] T3 and Free T4 will be done if TSH is abnormal
[3] Restaging with MRI Brain and CT scan should be completed anytime between cycle 2 and 3, and anytime between cycle 4 and 5. In patients who only received the planned 4 doses of therapy, this is replaced with the end of treatment MRI and CT, which should be done within +/-4 weeks of the last dose of therapy
[4] Re-imaging in follow-up will be completed every 9 weeks +/- 7 days or at the treating physician's discretion.
[5] In patients were tissue is available
[6] Via lumbar puncture or use of a CSF-device if available
[7] In patients who receive +4 treatments, a CSF sample will be taken prior to the 5th treatment. In patients who only received the planned 4 doses of therapy, the second CSF sample and blood collection for both genomic and immune correlates is an end-of-treatment sample and should be taken within 2 weeks of the last dose of therapy.
[8] Screening labs may be used for Cycle 1 Day 1 if they are done within 3 days of C1D1.
[9] the end of treatment visit will be considered to be performed at the date of the last dose of therapy, if the study participant goes on to receive a new anti-cancer agent within 30 days of last study therapy.

6.0 TRIAL PROCEDURES

6.1 Trial Procedures

The Trial Flow Chart – Section 5.0 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.

6.1.1 Administrative Procedures

6.1.1.1 Informed Consent

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

6.1.2.8 General Informed Consent

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

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

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

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

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

6.1.1.3 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.

6.1.1.4 Medical History

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

6.1.1.5 Prior and Concomitant Medications Review

6.1.1.5.1 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.

6.1.1.5.2 Concomitant Medications

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

6.1.1.6 Disease Details and Treatments

6.1.1.6.1 Disease Details

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

6.1.1.6.2 Prior Treatment Details

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

6.1.1.6.3 Subsequent Anti-Cancer Therapy Status

The investigator or qualified designee will review all new anti-neoplastic therapy initiated after the last dose of trial treatment. If a subject initiates a new anti-cancer therapy within 30 days after the last dose of trial treatment, the end-of treatment 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.

6.1.1.7 Assignment of Screening Number

All consented subjects will be given a unique screening number that will be used to identify the subject. Each subject will be assigned only one screening number. Screening numbers must not be re-used by 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 6.2.5.3.

6.1.1.8 Assignment of Treatment Number

All eligible subjects will be allocated by non-random assignment, and will receive a treatment allocation number. The allocation number identifies the subject for all procedures occurring after treatment allocation. Once an allocation number is assigned to a subject, it can never be re-assigned to another subject. A single subject cannot be assigned more than one allocation number.

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

Interruptions from the protocol-specified treatment for greater than 12 weeks between pembrolizumab doses due to non-drug-related or administrative reasons require consultation between the investigator and the Sponsor and written documentation of the collaborative decision on subject management.

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 the preparing and administering of pembrolizumab are provided in the Pharmacy Manual.

6.1.2 Clinical Procedures/Assessments

6.1.2.1 Adverse Event (AE) Monitoring

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

Please refer to section 6.2 for detailed information regarding the assessment and recording of Aes.

6.1.2.2 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,

6.1.2.3 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.

6.1.2.4 Vital Signs

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

6.1.2.5 Eastern Cooperative Oncology Group (ECOG) Performance Scale

The investigator or qualified designee will assess ECOG status (see Section 10.1) at screening, prior to the administration of each dose of trial treatment and discontinuation of trial treatment as specified in the Trial Flow Chart.

6.1.2.6 Post-study Anti-Cancer Therapy Status

The investigator or qualified designee will review all the new anti-cancer 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.

6.1.2.7 Tumor Imaging and Assessment of Response

Evaluation of response will include an evaluation of neurologic signs and symptoms (normal, improved, stable, deteriorated), CSF obtained from a previous positive site (lumbar or ventricular), and repeated radiologic evaluation of all ancillary studies (MRI Brain and Total spine with gadolinium contrast enhancement and CT scans of the body). Patients will be evaluated for CNS response based on a 4-point scale: complete response, improvement, stable disease and progression, as detailed in the Table below:

Table 8: Determination of Response to LMD

Clinical Assessment (Neurologic Function)	Size of LMD disease on MRI or CSF cytology	Overall Response Determination
No neurologic symptoms	None detectable	Complete response

Improved	Stable	Improved
Stable	Improved	Improved
Stable	Stable	Stable
Improved	Progression	Progression
Stable	Progression	Progression
Progression	Improved or Stable	Progression

We will define a positive CSF cytology result either detectable malignant cells in the CSF, or a pathology read that is reported as "suspicious for malignancy." We will define a negative CSF cytology result as either no detectable malignant cells in CSF, or a pathology read of "abnormal CSF cytology response," which will indicate conversion from positive/suspicious to negative/abnormal CSF cytology[31,32].

A complete responder will be defined as a patient with a normal neurologic examination, negative CSF cytology and no measurable leptomeningeal masses on radiologic imaging. Improved patients will be defined as those that have demonstrated improvement in neurologic signs or symptoms and/or a 50% decrease in CSF tumor cells or persistent positive CSF cytology as defined above, a 50% shrinkage in the bidirectional measurements of leptomeningeal disease. Patients with stable disease will be defined as less than 50% improvement in number of CSF tumor cells or abnormal CSF cytology response as defined above, or reduction in size of LMD on radiologic assessment, without evidence of progression. Progression will be defined as more than 25% increase in the number of tumor cells or persistent positive CSF cytology as defined above, an increase in size of LMD masses on radiologic assessment, or the development of new neurologic signs or symptoms after at least 2 cycles of pembrolizumab therapy.

Tumor imaging should be performed by computed tomography (CT) for body imaging (preferred) and for the CNS, gadolinium-enhanced MRI imaging of the brain and total spine including T1- weighted, T2-weighted, fluid attenuated inversion recovery and post-gadolinium sequences. The same imaging technique should be used throughout the trial. CT imaging should include the chest, abdomen and pelvis at baseline and all subsequent follow-up time-points, additional details are in the Site Imaging Manual (SIM).

6.1.2.7.1. Initial Tumor Imaging

Initial tumor imaging and screening should be performed within 28 days prior to the date of allocation. The site study team must review screening images to confirm the subject is assessable for response based on MRI, CSF cytology or clinical presentation, as detailed in Table 8.

Tumor imaging performed as part of routine clinical management are acceptable for use as initial tumor imaging if they are of diagnostic quality, include all anatomy as described in the SIM, and performed within 28 days of the date of allocation.

6.1.2.7.2. Tumor Imaging During the Trial

The first on study imaging assessment should be performed anytime between cycle 2 and 3 of planned therapy, and the second set of imaging should be performed anytime between cycle 4 and 5. In patients who only receive the planned 4 doses of therapy, this is replaced with the end of treatment MRI and CT, which should be done within 2 weeks of the last dose of therapy. Subsequent tumor imaging should be performed Q9W (±7 days) or more frequently if clinically indicated until PD. Imaging should not be delayed for delays in cycle starts or extension of pembrolizumab cycle intervals.

To assess radiologic response in the CNS, there are no standard radiologic response criteria for LMD on CT or MRI. The RANO group has proposed criteria for measuring BM[77], but not for LMD. From an extensive review of published literature of clinical trials and assessments of LMD in the modern MRI era[33,78], we propose using a radiologic cut-off of 3mm for measurable disease in the neuro-axis by gadolinium-enhanced MRI imaging of the brain and total spine including T1- weighted, T2-weighted, fluid attenuated inversion recovery and post-gadolinium sequences.

To assess for response outside of the CNS, per RECIST 1.1, partial or complete response should be confirmed by a repeat tumor imaging assessment not less than 4 weeks from the date the response was first documented. The tumor imaging for confirmation of response may be performed at the earliest 4 weeks after the first indication of response, or at the next scheduled tumor imaging (i.e. 9 weeks later), whichever is clinically indicated. Subjects will then return to regular scheduled imaging Q9W, starting with the next scheduled imaging time point. Subjects who obtain a confirmation imaging assessment do not need to undergo scheduled tumor imaging if it is < 4 weeks later and may wait until the next scheduled imaging time point.

Per irRECIST, if radiologic imaging identifies PD, tumor assessment should be repeated ≥ 4 weeks later in order to confirm PD with the option of continuing treatment while awaiting radiologic confirmation of progression. Subjects who obtain confirmation tumor imaging do not need to undergo scheduled tumor imaging if it is < 4 weeks later and may wait until the next scheduled imaging time point if clinically stable.

Imaging should continue to be performed until either CNS progression as per Table 8, withdrawal of consent, death, or notification by the Sponsor, whichever occurs first.

If the subject is clinically stable but has radiologic PD outside of the CNS, it is the discretion of the PI to continue to treat and image the subject at least 4 weeks after the first tumor imaging indicating PD by RECIST 1.1 by the site. irRECIST would then be followed by the study site to determine if the follow-up tumor imaging confirms PD (irPD). Subjects who have unconfirmed PD may continue on treatment and follow the regular imaging schedule intervals until subsequent PD (irPD) is confirmed by the site per irRECIST provided they

have met the conditions detailed in Section 6.1.2.7.5 (Table 8).

6.1.2.7.3. End of Treatment and Follow-up Tumor Imaging

In subjects who discontinue trial treatment, tumor imaging should be performed at the time of treatment discontinuation (± 4 week window). If a previous CT scan for body imaging and MRI for CNS imaging was obtained within 4 weeks prior to the date of discontinuation, then a scan at treatment discontinuation isn't mandatory.

6.1.2.7.4 RECIST 1.1 Assessment of Disease

RECIST 1.1 will be applied as an assessment of systemic tumor response outside the CNS.

During the follow-up period, imaging will be repeated every Q9W (±7 days) until PD. See the Trial Flow Chart for further information.

6.1.2.7.5 Immune-related RECIST

RECIST 1.1 will be adapted to account for the unique tumor response characteristics seen with treatment of pembrolizumab. Immunotherapeutic agents such as pembrolizumab may produce anti-tumor effects by potentiating endogenous cancer-specific immune responses. The response patterns seen with such an approach may extend beyond the typical time course of responses seen with cytotoxic agents, and cam manifest a clinical response after an initial increase in tumor burden or even the appearance of new lesions. RECIST may not provide an accurate response assessment of immunotherapeutic agents such as pembrolizumab. Immune-related RECIST (irRECIST) is RECIST 1.1 adapted as described below to account for the unique tumor response seen with immunotherapeutics. Following site identification of PD, irRECIST will be used by site investigators to assess tumor response and progression and make treatment decisions.

If radiologic imaging by the site identifies PD by RECIST 1.1, imaging should be repeated >4 weeks later in order to confirm PD with the option of continuing therapy per below while awaiting radiologic confirmation of progression.

If repeat imaging shows <20% tumor burden compared to nadir, stable or improved previous new lesion (if identified as cause for initial PD), and stable/improved non-target disease, if identified as cause of initial PD), PD is not confirmed. Treatment may continue and subsequently follow the regular imaging schedule.

If repeat imaging confirms PD (irPD) due to any of the scenarios listed below, this will be recorded. However, pembrolizumab may be continued in patients if they have not demonstrated CNS progression, as detailed in Table 8, at the discretion of the treating investigator.

If determining whether or not the tumor burden has increased or decreased, site study team should consider all target lesions as well as non-target lesions.

Scenarios where PD is confirmed at repeat imaging:

- Tumor burden remains >20% and at least 5mm absolute increase compared to nadir
- Non-target disease resulting in initial PD is worse (qualitative)
- New lesion resulting in initial PD is worse (qualitative)
- Additional new lesion(s) since last evaluation
- Additional new non-target progression since last evaluation

In subjects who have initial evidence of radiologic PD by the site, it is at the discretion of the site investigator whether to continue the subject of study treatment, until repeat imaging is obtained. This clinical judgment decision should be based in the subject's overall clinical condition, including performance status, clinical symptoms, and laboratory data. Subjects may receive study treatment while waiting for confirmation of PD if they are clinically stable, as defined by the following criteria:

- Absence of symptoms and signs indicating clinically significant progression of disease including worsening laboratory values
- No decline in ECOG performance status
- Absence of rapid progression of disease
- Absence of progressive tumor at critical anatomical sites (e.g. spinal cord compression) requiring urgent alternative medical intervention

When feasible subjects, radiologic progression should be confirmed. This takes into account the observation that some subjects can have transient tumor flare in the first few months after the start of immunotherapy, but with subsequent disease response. Subjects that are deemed clinically unstable are not required to have repeat imaging for confirmation of PD.

Pembrolizumab may be continued in patients with radiologic PD in the body if a subject is clinically stable and has not demonstrated CNS progression, as detailed in Table 8 and Table 9, at the discretion of the treating investigator.

These details are summarized in Table 9, below.

Table 9: Imaging and Treatment after First Radiologic Evidence of PD

	Clinically Stable		Clinically Unstable	
	Tumor imaging	Treatment	Tumor imaging	Treatment
1st radiologic evidence PD	Repeat tumor imaging at > 4 weeks at site to	May continue study treatment at the local site	Repeat tumor imaging at > 4 weeks to	Discontinue treatment

	confirm PD	investigator's discretion while awaiting confirmatory tumor imaging by site	confirm PD per physician discretion only	
Repeat imaging confirms PD	No additional tumor imaging required	May continue treatment, at discretion of treating investigator	No additional tumor imaging required	Discontinue treatment
Repeating imaging show SD, PR, CR	Continue regularly scheduled tumor imaging assessments	Continue study treatment at the local site investigator's discretion	Continue regularly scheduled tumor imaging assessments	May restart study treatment if condition has improved and/or clinically stable per local site investigator's discretion

- In determining whether or not the tumor burden has increased or decreased, local study site investigators should consider all target lesions as well as non-target lesions as per irRECIST. Subjects that are deemed clinically unstable are not required to have repeat tumor imaging for confirmation. [L SEP]

- For a clinically stable subject with first radiologic evidence of PD (i.e., unconfirmed progression of disease), it is at the discretion of the site investigator to continue treating the subject with the assigned treatment per protocol until progression of disease is confirmed at least 28 days from the date of the tumor imaging first suggesting PD. Pembrolizumab may be continued in patients if they have not demonstrated CNS progression, as detailed in Table 8, at the discretion of the treating investigator.

irRECIST data will be collected in the clinical database.

6.1.2.8 Tumor Tissue Collection and Correlative Studies: Blood and CSF Sampling

6.1.2.8.2 Tumor Tissue Collection

Submission of archival tumor tissue is optional in this study. If tumor tissue is available, exploratory analyses may be undertaken as detailed in section 4.1.5.2. If there is any leftover blood, the tissue will be stored for future research purposes if he/she consents to any separate tissue banking protocol. If not, the remaining tissue will be destroyed.

6.1.2.8.2. Blood collection for Correlative Studies

Additional biomarker research to identify factors important for pembrolizumab therapy as detailed in section 4.1.5.2, may be pursued. If there is any leftover blood, the blood will be stored for future research purposes if he/she consents to any separate tissue banking protocol. If not, the remaining blood will be destroyed.

6.1.2.8.3. CSF Sample collection

Patients will undergo a lumbar puncture using routine clinical care procedures to collect up to 10-15cc of CSF for research purposes, after routine clinical CSF is obtained. In patients with a CSF-access device such as an Ommaya reservoir or shunt reservoir, the study team may use this device to obtain CSF as an alternative to lumbar puncture. A CSF sample will be obtained during screening to obtain a "baseline" sample, and assess for eligibility based on CSF cytology. In patients who proceed with the study, repeat CSF samples will be obtained prior to administration of cycle 3 of therapy and 2-3 weeks after administration of cycle 4 (if last treatment, as end-of-treatment sample) or prior to cycle 5, if the patient is planned to receive cycle 5. The maximum number of lumbar punctures from an individual patient is four. In order to safely complete an LP for the acquisition of a CSF sample, patients must:

a) Have an ECOG performance status < 2

b) Have normal laboratory criteria as defined below:

-Platelets >100,000/mcL

-PTT above institutional limits

-INR above institutional limits

c) No clinical or radiographic evidence of elevated intracranial pressure (such as papilledema, obstructive hydrocephalus, or signs of herniation).

d) Not be taking blood-thinning products such as clopidogrel, low-molecular weight heparin, or coumadin.

5) For patients undergoing an LP, no history of LP complication such as hematoma, infection, herniation, or blood patch, and a complicated LP procedure in the past.

6.1.3 Laboratory Procedures/Assessments

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

6.1.3.1 Local Laboratory Assessments

Laboratory tests for screening should be performed within 10 days prior to the first dose of trial treatment. After cycle 1, pre-dose laboratory tests can be conducted up to 72 hours prior to dosing.

Laboratory test results must be reviewed by the investigator or qualified designee and found to be acceptable prior to administration of each dose of trial treatment. Unresolved abnormal laboratory tests that are drug-related AEs should be followed until resolution. Laboratory tests do not need to be repeated after the end of the treatment if laboratory values are within normal range.

6.1.3.2. Serum and Urine Pregnancy Tests

All women who are being considered for participation in the trial who are not surgically sterilized or postmenopausal, must be tested for pregnancy within 72 hours of each cycle of treatment and 30 days post the last dose of study treatment. If a urine test is positive or not evaluable a serum test will be required. Subjects must be excluded/discontinued from the study in the event of a positive or borderline-positive test result.

Table 10. Laboratory Tests

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

6.1.3.3. Pharmacokinetic/Pharmacodynamic Evaluations

6.1.3.3.1 Blood Collection for Serum Pembrolizumab

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

6.1.4 Other Procedures

6.1.4.1 Withdrawal/Discontinuation

When a subject discontinues/withdraws prior to trial completion, all applicable activities scheduled for the final trial visit should be performed at the time of discontinuation. Any adverse events which are present at the time of discontinuation/withdrawal should be followed in accordance with the safety requirements outlined in Section 6.2. - Assessing and Recording Adverse Events. Subjects who a) attain a CR or b) complete 24 months of treatment with pembrolizumab may discontinue treatment. After discontinuing treatment, these subjects should return to the site for a Safety Follow-up Visit and then proceed to the Follow-Up Period of the study as per the Trial Flow Sheet, unless they begin a new anti-cancer agent within 30 days of the last study treatment, in which case the end of treatment visit will be the day of the last dose of study therapy (section 5.0).

6.1.4.2 Blinding/Unblinding

This is an open label trial; there is no blinding for this trial.

6.1.5 Visit Requirements

Visit requirements are outlined in the Trial Flow Chart- Section 5.0. Specific procedure-related details are provided in section 6.0.

6.1.5.1 Screening

6.1.5.1.1 Screening Period

Approximately 28 days prior to treatment allocation, potential subjects will be evaluated to determine that they fulfill the entry requirements as set forth in Section 5.0. Screening procedures may be repeated.

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 ECOG 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 may be considered if serum test is not appropriate. Subjects may be rescreened after initially failing to meet the inclusion/exclusion criteria. Results from assessments performed during the initial screening period are acceptable in lieu of repeat screening test if performed within the specified time frame and the inclusion/exclusion criteria is met. Subjects who are rescreened will retain their original screening number.

6.1.5.2 Treatment Period

Visit requirements are outlined in the Trial Flow Chart (Section 5.0). Specific procedure-related details are provided above in the Trial Procedures (Section 6.0).

6.1.5.3 Post-Treatment Visits

6.1.5.3.1. Safety Follow-Up Visit

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

6.1.5.3.2. Follow-up Visits

Subjects who discontinue trial treatment for a reason other than CNS progression will move into the Follow-Up Phase and should be assessed every 6-9 weeks by radiologic imaging to monitor disease status. After 1 year, the imaging time point will occur every 9 weeks (± 7 days). Every effort should be made to collect information regarding disease status until the start of new anti-neoplastic therapy, disease progression, death, end of the study. Information regarding post-study anti-neoplastic treatment will be collected if new treatment is initiated.

6.1.5.3.3. Survival Follow-up

Once a subject experiences confirmed CNS 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.

6.2. Assessing and Recording Adverse Events

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

specified procedure. Any worsening (i.e., any clinically significant adverse change in frequency and/or intensity) of a preexisting condition that is temporally associated with the use of the Merck's product, is also an adverse event.

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/registration 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 through 30 days following cessation of treatment, the investigator must report all adverse events. 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 7.2.3.1. The investigator will make every attempt to follow all subjects with non-serious adverse events for outcome.

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

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

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

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

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

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

6.2.2 Reporting of Pregnancy and Lactation to the Sponsor and to Merck

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

Pregnancies and lactations that occur after the consent form is signed but before treatment allocation/registration 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/registration 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)

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

6.2.3.1 Serious Adverse Events

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

- Results in death;
- Is life threatening;
- Results in persistent or significant disability/incapacity;
- Results in or prolongs an existing inpatient hospitalization;
- Is a congenital anomaly/birth defect;
- Is 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 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 11 for additional details regarding each of the above criteria.

For the time period beginning when the consent form is signed until treatment allocation/registration, any serious adverse event, or follow up to a serious adverse event, including death due to any cause other than progression of the cancer under study that occurs to any subject 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/registration 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 Table 11 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.

6.2.4 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).

For the time period beginning when the consent form is signed until treatment allocation/registration, 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 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 6.2.1 - 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.

6.2.5 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 6.2.3- 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

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.

6.2.6 Evaluating Adverse Events

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

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

Table 11. Evaluating Adverse Events

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

V4.0 CTCAE Grading	**Grade 1**	**Mild; asymptomatic or mid symptoms; clinical or diagnostic observations only; intervention not indicated.**
	Grade 2	**Moderate; minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental ADL.**
	Grade 3	**Severe or medically significant but not immediately life-threatening; hospitalization or prolongation or hospitalization indicated; disabling; limiting self-care ADL.**
	Grade 4	**Life threatening consequences; urgent intervention indicated.**
	Grade 5	**Death related to AE**
Seriousness	A serious adverse event is any adverse event occurring at any dose or during any use of Merck product that:	
	†**Results in death**; or	
	†**Is life threatening; or** places the subject, in the view of the investigator, at immediate risk of death from the event as it occurred (Note: This does not include an adverse event that, had it occurred in a more severe form, might have caused death.); or	
	†**Results in a persistent or significant disability/incapacity** (substantial disruption of one's ability to conduct normal life functions); or	
	†**Results in or prolongs an existing inpatient hospitalization** (hospitalization is defined as an inpatient admission, regardless of length of stay, even if the hospitalization is a precautionary measure for continued observation. (Note: Hospitalization for an elective procedure to treat a pre-existing condition that has not worsened is not a serious adverse event. A pre-existing condition is a clinical condition that is diagnosed prior to the use of a Merck product and is documented in the patient's medical history.); or	
	†**Is a congenital anomaly/birth defect** (in offspring of subject taking the product regardless of time to diagnosis);or	
	Is a new **cancer** (that is not a condition of the study) **(**although not serious per ICH definition, is reportable to the Sponsor within 24 hours and to Merck within 2 working days to meet certain local requirements); **or**	
	Is an overdose (whether accidental or intentional). Any adverse event associated with an overdose is considered a serious adverse event for collection purposes. An overdose that is not associated with an adverse event is considered a non-serious event of clinical interest and must be reported within 24 hours to the Sponsor and to Merck within 2 working days.	
	Other important medical events that may not result in death, not be life threatening, or not require hospitalization may be considered a serious adverse event when, based upon appropriate medical judgment, the event may jeopardize the subject and may require medical or surgical intervention to prevent one of the outcomes listed previously (designated above by a †).	

Duration	Record the start and stop dates of the adverse event. If less than 1 day, indicate the appropriate length of time and units	
Action taken	Did the adverse event cause Merck product to be discontinued?	
Relationship to Merck Product	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. **The following components are to be used to assess the relationship between Merck product and the AE**; 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):	
	Exposure	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?
	Time Course	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)?
	Likely Cause	Is the AE not reasonably explained by another etiology such as underlying disease, other drug(s)/vaccine(s), or other host or environmental factors

Relationship to Merck Product (continued)	**The following components are to be used to assess the relationship between the test drug and the AE: (continued)**	
	Dechallenge	Was 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.)
	Rechallenge	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.
	Consistency with Trial Treatment Profile	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.		
Record one of the following	**Use the following scale of criteria as guidance (not all criteria must be present to be indicative of Merck product relationship).**	
Yes, there is a reasonable possibility of Merck product relationship.	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.	
No, there is not a reasonable possibility of Merck product relationship	Subject did not receive the Merck product OR temporal sequence of the AE onset relative to administration of 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.)	

6.2.7 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.

7. STATISTICAL ANALYSIS PLAN

7.1. Statistical Analysis Plan Summary

Key elements of the statistical plan are summarized in Table 12 below. A comprehensive plan is detailed in section 7.2

Table 12: Statistical Overview

Study Design Overview	Open-label, single arm phase II study of pembrolizumab in patients with advanced solid tumors with leptomeningeal carcinomatosis (LMD)
Treatment Assignment	pembrolizumab 200mg Q3W
Analysis Population	Eligible patients who receive at least one dose of pembrolizumab
Primary Endpoint	CNS response at 12 weeks based on either radiologic, cytologic or clinical evidence
Statistical Methods for Key Efficacy Analyses	The proportion of CNS response and associated 95% exact confidence interval will be provided
Statistical Methods for Key Safety Analyses	Descriptive analysis based on Clopper-Pearson's exact binomial confidence interval method.
Multiplicity	N.A.
Sample Size and Power	No formal statistical inference will be provided. The proposed sample size will provide appropriate estimation precision for the primary efficacy endpoint.

7.2. Statistical Analysis Plan

7.2.1 Statistical Plan

This is an open-label phase II study aimed at establishing the efficacy of single agent pembrolizumab, at the FDA-approved dose of 200mg every 3 weeks, in patients with solid

tumors and LMD. The primary endpoint will be CNS response at 12 weeks/after 4 cycles of therapy. The sample size is calculated with Clopper-Pearson's exact binomial confidence interval method. With 16 analyzable patients, defined as eligible patients who receive at least one dose of pembrolizumab, we determine that we will have an appropriate level of estimation accuracy for the first study of this experimental regimen. The following table summarizes the two-sided 90% exact confidence interval for different observed CNS response rate. Guarding against a 10% rate of patients either being ineligible or dropping out, the final sample size is 18 patients. If a higher rate of ineligible and drop-out rate is observed during the study conduct, the protocol may be amended to ensure at least 16 analyzable cases.

No. of patients with CNS response (%)	90% Confidence Interval for Observed CNS Response Rate (N=16)	
	Lower (%)	Upper (%)
1 (6.3%)	0.3	26.4
2 (12.5%)	2.3	34.4
3 (18.8%)	5.3	41.7
4 (25%)	9.0	48.4
5 (31.3%)	13.2	54.8
6 (37.5%)	17.8	60.1

Secondary endpoints will include CNS-PFS, OS and safety. Kaplan-Meier curves will be used to assess CNS-PFS and OS. Cause of death will be recorded. Safety will be assessed as detailed above, and monitored as per JHH SKCCC Data Safety and Monitoring Plan. Exploratory endpoints will include genomic testing of tumor cells and cell-free DNA in CSF and serum, and immunologic studies of immune cells in CSF and serum at pre-defined time-points. These data will be presented descriptively. Genomic and immunologic correlates from available tissue in selected patients, will be presented descriptively. Means and standard deviations of all markers will be computed and 95% confidence intervals will be constructed. For serum markers, linear regression model (with proper transformation of the data) will be used to compare slopes in repeated measures between pre-defined time-points. Our institution sees 250 new patients per year with advanced lung cancer, 5% of which will have LMD (n=18 in 18 months), 200 new patients with breast cancer, 5% of which will have LMD (n=15 patients in 18 months), and selected patients with other solid tumors per year with LMD (n=10 per year), not including patients in follow-up. Taking into account that this may be a less fit patient population, we conservatively estimate that we will accrue 1 patient per month at our institution and 1 additional site that have agreed to participate in the study. Study duration will be approximately 24 months, allowing 18 months for accrual and 6 months for follow-up and data analysis.

7.2.2 Responsibility for Analyses

The statistical analysis of the data obtained from this study will be the responsibility of the institution, which is the study sponsor of this trial.

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

The Clinical Biostatistics department of the sponsor will generate the allocation schedule.

7.2.3 Hypotheses/Estimation

Objectives and hypotheses of the study are stated in Section 3.0.

7.2.4 Primary Efficacy Endpoint

CNS response

CNS response rate is defined as the proportion of the subjects in the analysis population who have a radiologic reduction in size of measurable CNS tumor lesions on an MRI brain scan, develop clearance of positive CSF cytology on 2 consecutive CSF specimens after an initial positive specimen has been obtained, or an improvement in neurologic function, as detailed in Table 8. In patients with more than one available response criterion, the most easily assessable criterion will be used.

7.2.5. Secondary Efficacy Endpoints

1. CNS Progression-Free Survival (PFS)

PFS is defined as the time from first day of study treatment until date of progression. Progression will be stratified into CNS progression (radiologic or cytology or clinical). CNS radiologic progression will be assessed by MRI criteria, CNS cytologic progression will be determined pathologically, and neurologic progression will be determined as per section 6.1.2.7 and Table 8 respectively. PFS will be calculated using the Kaplan-Meier method.

2. Overall Survival

Overall survival will be defined as the date of study entry until date of death from any cause. Cause of death will be recorded.

3. Safety

The primary safety objective of this trial is to characterize the safety and tolerability of pembrolizumab in subjects with LMD. The primary safety analysis will be based on subjects who experienced toxicities as defined by CTCAE, Version 4.0 criteria (Appendix 2). The attribution to drug, time-of-onset, duration of the event, its resolution, and any concomitant

medications administered will be recorded. AEs will be analyzed including but not limited to all AEs, SAEs, fatal AEs, and laboratory changes. Furthermore, specific immune-related adverse events (irAEs) will be collected and designated as immune-related events of clinical interest (ECIs) as described in Section 6.2.3.2

8. LABELING, PACKAGING, STORAGE AND RETURN OF CLINICAL SUPPLIES

8.1. 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 13.

Table 13. Product Descriptions

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

8.2. Packaging and Labeling Information

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

8.3. 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.

8.4. 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.

8.5. 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.

9. ADMINISTRATIVE AND REGULATORY DETAILS

9.1. Confidentiality

9.1.1 Confidentiality of Data

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

9.1.2. Confidentiality of Subject Records

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

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

9.1.3 Confidentiality of Investigator Information

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

. name, address, telephone number and e-mail address;

. hospital or clinic address and telephone number;

. curriculum vitae or other summary of qualifications and credentials; and

. other professional documentation.

Consistent with the purposes described above, this information may be transmitted to the Sponsor, and subsidiaries, affiliates and agents of the Sponsor, in your country and other countries, including countries that do not have laws protecting such information. Additionally, the investigator's name and business contact information may be included when reporting certain serious adverse events to regulatory authorities or to other investigators. By signing this protocol, the investigator expressly consents to these uses and disclosures.

If this is a multicenter trial, in order to facilitate contact between investigators, the Sponsor may share an investigator's name and contact information with other participating investigators upon request.

9.1.4 Confidentiality of IRB/IEC Information

The Sponsor is required to record the name and address of each IRB/IEC member that reviews and approves this trial. The Sponsor is also required to document that each IRB/IEC meets regulatory and ICH GCP requirements by requesting and maintaining records of the names and qualifications of the IRB/IEC members and to make these records available for regulatory agency review upon request by those agencies.

9.2. Compliance with Financial Disclosure Requirements

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

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

9.3. Compliance with Law, Audit and Debarment

By signing this protocol, the investigator agrees to conduct the trial in an efficient and diligent manner and in conformance with this protocol; generally accepted standards of Good

Clinical Practice (e.g., International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use Good Clinical Practice: Consolidated Guideline and other generally accepted standards of good clinical practice); and all applicable federal, state and local laws, rules and regulations relating to the conduct of the clinical trial.

The Code of Conduct, a collection of goals and considerations that govern the ethical and scientific conduct of clinical investigations sponsored by Merck, is provided in Section 12.1-Merck Code of Conduct for Clinical Trials.

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

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

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

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

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

period and upon request, will provide guidance to the investigator when documents no longer need to be retained. The sponsor also recognizes that documents may need to be retained for a longer period if required by local regulatory requirements. All trial documents shall be made available if required by relevant regulatory authorities. The investigator must consult with and obtain written approval by the Sponsor prior to destroying trial and/or subject files.

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

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

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

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

A Sponsor must designate an overall coordinating investigator for a multi-center trial (including multinational). For a single-center trial, the Protocol CI is the principal investigator. In addition, the Sponsor must designate a principal or coordinating investigator to review the trial report that summarizes the trial results and confirm that, to the best of his/her knowledge, the report accurately describes the conduct and results of the trial [Clinical Study Report (CSR) CI]. The Sponsor may consider one or more factors in the selection of the individual to serve as the Protocol CI and or CSR CI (e.g., availability of the CI during the anticipated review process, thorough understanding of clinical trial methods, appropriate enrollment of subject cohort, timely achievement of trial milestones). The Protocol CI must be a participating trial investigator.

This is a DSMP Level II study under the SKCCC Data Safety Monitoring Plan (12/06/2012). Data monitoring of this protocol will occur on a regular basis with the frequency dependent on the rate of subject accrual and the progress of the study. The protocol will be monitored internally at SKCCC by the Principal Investigator and externally by the SKCCC CRO in accordance with SKCCC guidelines. Trial monitoring and reporting will be done through the Safety Monitoring Committee (SMC) at SKCCC.

9.4. 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.

9.5. Quality Management System

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

9.6. Data Management

The investigator or qualified designee is responsible for recording and verifying the accuracy of subject data. The investigator acknowledges that his/her electronic signature is the legally binding equivalent of a written signature. By entering his/her electronic signature, the investigator confirms that all recorded data have been verified as accurate. Detailed information regarding Data Management procedures for this protocol will be provided separately.

The study case report forms (CRFs) are the primary data collection instrument for the study. All data requested on the CRF will be recorded for each subject. If a procedure was not done or a question was not asked, this will be recorded as “N/D”. If the item is not applicable to the individual case, this will be recorded as “N/A”. CRFs will be built electronically in CRMS. All data will be entered electronically onto the electronic CRF through CRMS by the Study Coordinator and/ or Data Manager from each site.

10. APPENDICES

10.1. ECOG Performance Status

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

10.2. 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)

10.3. 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.

In addition, volumetric analysis will be explored by central review for response assessment.

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