Mayo Clinic Cancer Center

MC1572 Phase II study of pembrolizumab (MK-3475) in combination with standard therapy for newly diagnosed glioblastoma

Study Chair: [redacted]

Study Cochairs: [redacted]

Statistician: [redacted]

√Study contributor(s) not responsible for patient care

Drug Availability
Supplied Investigational Agents: MK-3475 (pembrolizumab) (IND# 131137)
Commercial Agents: Temozolomide
Drug Company Supplied: MK-3475 (pembrolizumab)

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Protocol Resources

Questions:	Contact Name:
Patient eligibility*, test schedule, treatment delays/interruptions/adjustments, dose modifications, adverse events, forms completion and submission	[redacted]
Forms completion and submission	[redacted]
Protocol document, consent form, regulatory issues	[redacted]
Paraffin-embedded tissue pathology	*TBD if sites other than Mayo Rochester*
Non-paraffin biospecimens	[redacted]
Serious Adverse Event Reporting	[redacted]

*No waivers of eligibility

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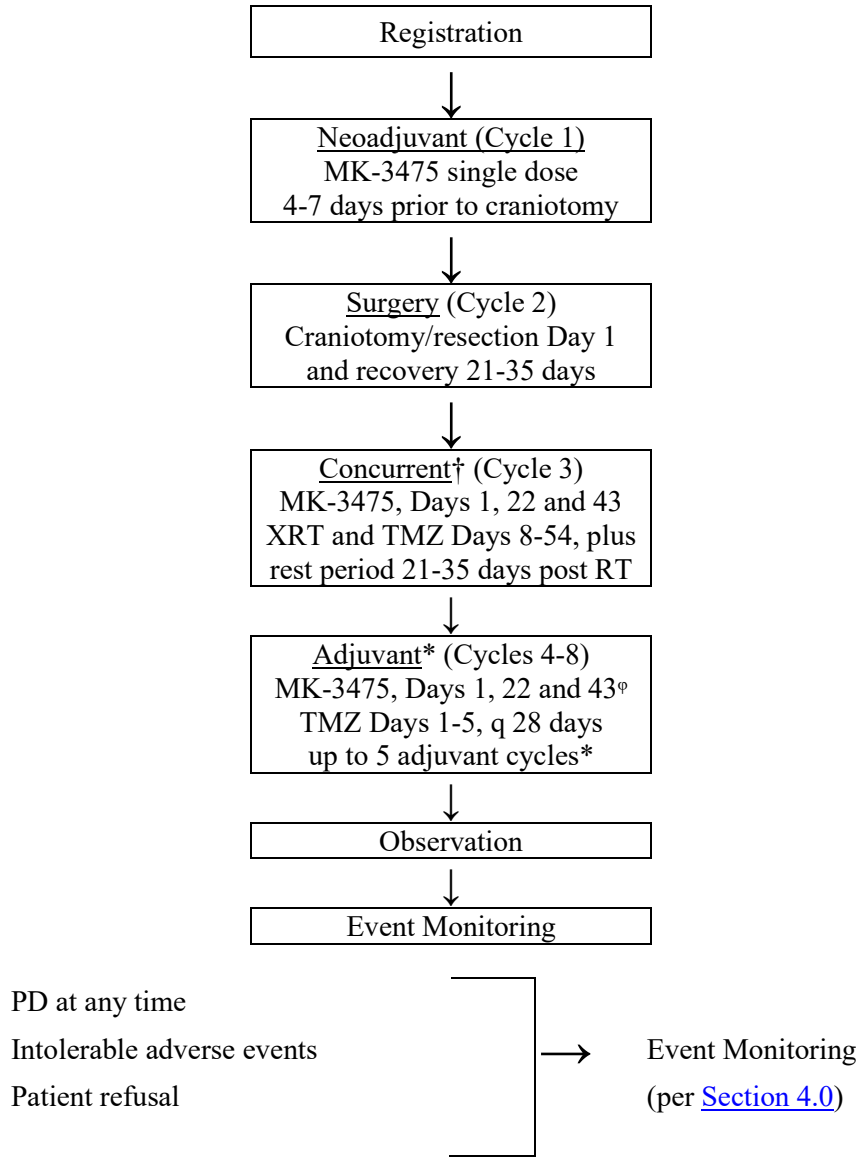
Schema – Neoadjuvant Patients (Group 1) – Rochester only

All Group 1 Patients: Prior to discussing protocol entry with the patient, call the MCCC Registration Office [redacted] to ensure that a place on the protocol is open to the patient



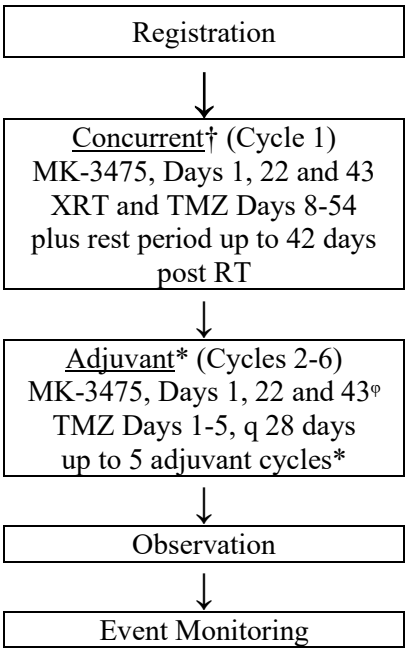
If a patient is deemed ineligible or a cancel, please refer to Section 13 for follow-up information.

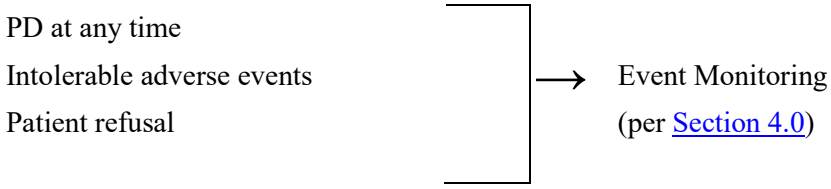
†Cycle length = 7 weeks only during Concurrent stage, plus 21-35 day rest period post-RT
*Cycle length = 63 days only during Adjuvant stage
φUp to maximum of 17 total doses of pembrolizumab

Generic names: pembrolizumab, MK-3475 Brand name(s): Keytruda® Mayo Abbreviation: MK-3475 Availability: Mayo Research Pharmacy	Generic name: temozolomide Brand name(s): Temodar® Mayo Abbreviation: TMZ Availability: commercial

Schema – Adjuvant Patients (Group 2)

Safety Run-In Only (first 6 patients in Group 2): Prior to discussing protocol entry with the patient, call the MCCC Registration Office [redacted] to ensure a place on the protocol is open to the patient





If a patient is deemed ineligible or a cancel, please refer to Section 13.0 for follow-up information.

†Cycle length = 7 weeks only during Concurrent stage, plus up to 42 day rest period post-RT
*Cycle length = 63 days only during Adjuvant stage
φUp to maximum of 17 total doses of pembrolizumab

Generic names: pembrolizumab, MK-3475 Brand name(s): Keytruda® Mayo Abbreviation: MK-3475 Availability: Mayo Clinic Research Pharmacy	Generic name: temozolomide Brand name(s): Temodar® Mayo Abbreviation: TMZ Availability: commercial

1.0 Background

1.1 Pharmaceutical and Therapeutic Background

The importance of intact immune surveillance in controlling outgrowth of neoplastic transformation has been known for decades *{Disis ML, 2010}*. 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 *{Dong , 2002; Sharpe, 2002; Brown 2003; Francisco, 2010; Thompson, 2007}*.

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)*{Talmadge 2007; Usubütün 1998}*. 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 *{Talmadge 2007; Deschoolmeester 2010; Diez 1998; Galon 2006}*. 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 *{Hiraoka 2010; Nobili 2008}*. 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 *{Hodi 2010; Kloor 2009}*. Expression has also been shown during thymic development on CD4-CD8- (double negative) T-cells as well as subsets of macrophages and dendritic cells *{Hillen 2008}*. 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 *{Lee 2008; Leffers 2009; Nishimura 2000; Hiraoka 2010}*. 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 *{Hiraoka 2010}*. 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) *{Liotta 2010}*. 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 been approved in the United Stated for the treatment of:

- Patients with unresectable or metastatic melanoma
- Patients with metastatic NSCLC whose tumors have high PD-L1 expression [(Tumor Proportion Score (TPS) ≥50%)] as determined by an FDA-approved test, with no EGFR or ALK genomic tumor aberrations, and no prior systemic chemotherapy treatment for metastatic NSCLC
- Patients with metastatic NSCLC whose tumors express PD-L1 (TPS ≥1%) as determined by an FDA-approved test, with disease progression on or after platinum-containing chemotherapy
- Patients with EGFR or ALK genomic tumor aberrations should have disease progression on FDA-approved therapy for these aberrations prior to receiving KEYTRUDA
- Patients with recurrent or metastatic HNSCC with disease progression on or after platinum-containing chemotherapy

1.2 Rationale for the Trial and Selected Subject Population

Glioblastoma multiforme (GBM), the most common primary brain tumor, is highly lethal despite aggressive therapy. Reported median survival is between 14 and 18 months. Immunotherapies such as tumor vaccines have shown promise in pre-clinical studies but more modest effects in clinical trials. This likely reflects tumor-mediated immunosuppression. Like many cancers, GBM's are markedly immunosuppressive both within the tumor microenvironment and systemically. This immunosuppression is mediated both by tumor cells themselves and by immunosuppressive leukocytes such as myeloid-derived suppressor cells (MDSC's) and regulatory T cells (T_{REG}'s) *{Parney 2000; Rodrigues 2010; Gustafson 2010}.*

PD-L1 (B7-H1, CD274) is a particularly potent cancer immune checkpoint inhibitor that was originally cloned by a member of our group (*Dong H et al, Nat Med 5: 1365-9*). It exerts its immunosuppressive effects by binding its receptor PD-1 on T cells. In GBM's, members of our group have shown that PD-L1 is expressed by both tumor cells *{Parsa 2006}* and circulating MDSC's *{Rodrigues 2010}* and is critical for inducing apoptosis in PD-1+ activated T cells that home to tumor and inducing MDSC expansion from naïve PD-1+ monocytes (Parney IF, unpublished). Cancer immunotherapy through PD-1/PDL1 checkpoint blockade is the subject of intense investigation. MK-3475 (pembrolizumab) is a humanized anti-PD-1 monoclonal antibody developed for this purpose. In a dose escalation study of 135 patients with advanced melanoma, largely low grade adverse events (e.g. fatigue, rash, pruritis, diarrhea) were observed. Response rates ranged from 35% (2 mg/kg every 3 weeks) to 56% (10 mg/kg every 2 weeks) *{Hamid 2013}*. Multiple other phase I, II, and III trials of MK-3475 alone or in combination with other agents are ongoing for a variety of advanced malignancies, including melanoma, non-small cell lung carcinoma, breast carcinoma, GI and urothelial cancers but not brain tumors. With that in mind, we plan a phase II of MK-3475 combined with standard therapy in newly diagnosed GBM patients. Standard therapy includes surgery, external beam radiotherapy (RT) with concurrent temozolomide (TMZ) chemotherapy, and adjuvant TMZ *{Stupp 2005}*. Administration of RT to cancer patients undergoing active treatment with immune check point inhibitors has been associated with beneficial "abscopal" (off-target) responses of other unirradiated tumors. This is thought to be immune-mediated and reflects the release of tumor antigens by irradiated cancer cells upon a primed immune

system. This has been reported for ipilimumab in melanoma *{Postow 2012}* and demonstrated with PD-1 blockade in a pre-clinical melanoma model by members of our group (*Park and Dong, unpublished*). These findings underscore the rationale for combining MK-3475 treatment with standard RT and TMZ for glioblastoma.

MK-3475's ability to cross the blood-brain barrier is not well defined. GBM vasculature is relatively leaky as demonstrated by contrast-enhancement on magnetic resonance imaging (MRI). However, this does not always translate to blood-brain barrier penetration for therapeutic agents. To address this, we propose a window of opportunity component to the study wherein patients with newly diagnosed brain lesions compatible with GBM on MRI scans who have undergone stereotactic biopsy with histopathology confirming GBM, will receive MK-3475 IV once then undergo definitive craniotomy and resection one week later. Comparison will be made between intra-tumoral PD-L1/PD-1 expression pre- and post-MK-3475. We will then re-initiate MK-3475 therapy one week prior to RT (~3 weeks post-op) to take advantage of potential abscopal RT effects on malignant cells beyond the radiation field. MK-3475 would then be continued with adjuvant TMZ.

It is probable that blood-brain barrier penetration is not necessary for MK-3475 to have efficacy against GBM's. GBM patients are systemically immunosuppressed and systemic immune modulation by MK-3475 may be therapeutic even if the agent itself does not reach the tumor directly. Monitoring systemic immunity will, therefore, be critical. Our research group has long-standing interests in monitoring systemic immune responses in GBM patients. We recently initiated a clinical trial of autologous dendritic cell / allogeneic tumor lysate vaccines for GBM patients (MC1272) that involves extensive immune monitoring including detailed immunophenotyping (flow cytometry analysis of >120 leukocyte surface markers on 5 mL of whole blood) and specific CD8 T cell response testing for a panel of 7 common GBM-associated antigens. We would propose a similar comprehensive immune monitoring in the present study.

1.3 Rationale for Dose Selection/Regimen/Modification

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

PK data analysis of MK-3475 administered Q2W and Q3W showed slow systemic clearance, limited volume of distribution, and a long half-life (*refer to Investigator Brochure*). 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. Based on data presented at the Society of Neuro-Oncology in November 2016, at least four patients have been treated with the combination of radiation therapy, temozolomide, and pembrolizumab followed by temozolomide and pembrolizumab without any Grade 3 or higher adverse events. *{Dixit K, 2016}*

When used as a single agent, Q3W dosing is supported by the data above. This will be the approximate timing between the neoadjuvant dose and the first dose given concurrent with radiation and low dose temozolomide in this study. It will also be the timing between doses during the concurrent treatment phase. However, during the adjuvant phase treatment will be combined with higher dose temozolomide given on days 1-5 every four weeks. Therefore, the cycle length will be 9 weeks (63 days) to harmonize the Q3W dosing and the clinical visits for typical MRI scans schedule at about every 8 weeks.

1.4 Standard Treatment for Glioblastoma

Standard treatment for patients with newly diagnosed glioblastoma has been defined for some time by the “Stupp regimen” {Stupp, 2005}. This includes maximal safe surgical resection, external beam radiation with concurrent temozolomide chemotherapy, and adjuvant temozolomide. Maximal safe resection is typically defined by the treating neurosurgeon. Practice patterns vary across the country regarding initial needle biopsy

followed by resection vs. proceeding directly with resection. At tertiary referral centers such as Mayo Clinic or MD Anderson, it is common to be referred patients who have undergone needle biopsy or subtotal resection elsewhere who subsequently undergo gross total resection at the tertiary center. In addition, a small set of patients have uncertain diagnosis based on imaging alone and confirming the diagnosis would potentially alter the need for resection (e.g. glioblastoma vs. metastasis, lymphoma, abscess, or inflammatory process). Radiation therapy is typically administered as approximately 59.4 Gy delivered in daily fractions of 1.8 Gy five days per week for thirty-three fractions. Temozolomide is administered orally at 75 mg/m^2 daily seven days per week from the first to last day of radiation. Patients typically have approximately 4 weeks of rest following radiation before initiating adjuvant temozolomide at 150 – 200 mg/m^2 daily for 5 days at the beginning of a 28 day cycle. Adjuvant temozolomide is frequently administered for up to twelve 28 day cycles.

1.5 Trial Design

This is a phase II trial of MK-3475 (pembrolizumab) in combination with standard therapy in the treatment of newly diagnosed adult patients with glioblastoma amenable to surgical resection. There will be an initial safety lead-in phase. Treatment will be administered in three stages: neoadjuvant, concurrent with radiation therapy, and adjuvant following radiation therapy. Following completion of accrual to the safety lead in, an expansion cohort with the same treatment schema will be opened if the safety profile was satisfactory. If not, we will consider a dose de-escalation cohort.

Update as of Amendment 3: Based on the Safety Run-In of 6 patients (1 patient replaced) in the Neoadjuvant design where 2 patients had dose limiting toxicities, we are altering the treatment schema. We will plan to enroll an additional 6 patients in the Neoadjuvant group (pilot phase/Safety Run-in/Group 1). In addition, because of uncertainty whether surgery is causing synergistic effects contributing to toxicities and because enrollment in the neoadjuvant protocol is limited by patient availability (need for biopsy or subtotal resection as part of their prior clinical care), we are adding an Adjuvant group (Group 2) to enroll patients who have already completed surgery and who could still benefit from the effects of pembrolizumab. We will have a Safety Run-In of 6 patients for this group (Group 2). This second group will enroll up to 33 patients.

1.51 Group 1 (Neoadjuvant) (Rochester Only)Neoadjuvant (Cycle 1):

- Patients with newly diagnosed enhancing brain lesions on MRI compatible with glioblastoma amenable to resection will first undergo stereotactic needle biopsy to establish histology. If this proves to be any diagnosis other than glioblastoma, they will not be eligible for the study. If histology confirms glioblastoma (a.k.a. Grade IV astrocytoma, gliosarcoma), they will be enrolled and receive a single 200 mg dose of MK-3475.
- Resection/Surgery (Cycle 2): Patients will then undergo definitive craniotomy and resection 4 – 7 days later. Post-operative MRI will be obtained within 72 hours of surgery to document extent of resection. Recovery period of 21-35 days is standard after surgical resection.
- Concurrent (Cycle 3): Treatment will be initiated between 3 to 7 weeks after craniotomy and resection. This treatment phase will consist of a single 7 week cycle. Patients will receive MK-3475 (200 mg) on Days 1, 22 and 43. Radiation will be administered in a standard 30 fraction regimen (5 days per week) beginning Day 8, one week after first receiving MK-3475 to take advantage of

potential abscopal effects of radiation following MK-3475 administration. Low dose TMZ will be administered daily throughout while radiation is being administered. Patients will be assessed clinically prior to each MK-3475 infusion, on Day 1 (±2d), and Day 22 (±2d). They will undergo imaging (MRI) for radiation planning purposes prior to initiating this cycle. Recovery period of 21-35 days is standard after radiation therapy.

- Adjuvant (Cycles 4-8): Treatment will be initiated between 4 to 6 weeks after completing concurrent therapy. Treatment will be in 63 day cycles. Patients will receive MK-3475 (200 mg) on Days 1, 22, and 43 up to a maximum of 17 doses. TMZ will be administered on 5 consecutive days every 28 days per current clinical standard of care. Patients will be assessed clinically prior to initiating each round of MK-3475. They will undergo imaging (MRI) prior to Cycle 4 and every cycle thereafter. Treatment will be continued for up to 5 adjuvant cycles or until tumor progression, unacceptable toxic effects develop, or consent is withdrawn.
- Safety Run-In: To ensure safety of treating patients with pembrolizumab in combination with standard therapy, an initial 6 patients will be enrolled and treated for adverse events assessment. Accrual of these patients will be in cohorts-of-3. Accrual will be temporarily suspended for evaluation of each cohort-of-3. If either of the two following criteria are met, accrual will be temporarily suspended and the study team will review toxicity data thoroughly and make decisions regarding changes to the protocol or permanently close the accrual to Group 1.
  - If more than 1 patient of the first 3 evaluable patients experienced at least one dose-limiting toxicity (DLT, see definitions in Section 7.0) during Cycles 1-3 (before surgery, during surgery, and concurrent with external beam radiation therapy)
  - If more than 1 patient of the first 6 evaluable patients experienced at least one dose-limiting toxicity (DLT, see definitions in Section 7.0) during Cycles 1-3 (before surgery, during surgery, and concurrent with external beam radiation therapy)

  Note: As of Amendment 3 the Group 1 Neoadjuvant study will reopen for at most an additional 6 DLT evaluable patients enrolled via the cohorts of 3+3 design as described above including the following DLT stopping rules.

  - The third cohort of 3 patients will receive pembrolizumab 200 mg intravenously (dose level 1). If less than 2 patients in this cohort experience a DLT (See Section 7.9a), the next cohort will be enrolled at the same pembrolizumab dose of 200 mg intravenously (dose level 1).
  - If DLTs are observed in two or more patients in this third cohort of 3, or more than 1/6 patients in both cohorts 3 and 4, then accrual to Group 1 will be temporarily suspended. The study team will conduct a comprehensive review of all the adverse event data, investigate the specifics of each DLT, and after consulting with the FDA and the drug supplier, will consider possible actions including at least the following: 1) permanently suspend accrual to Group 1.

1.52 Group 2 (Adjuvant)

- Concurrent (Cycle 1): Treatment will be initiated between 3 to 7 weeks after craniotomy and resection. This treatment phase will consist of a single 7 week cycle. Patients will receive MK-3475 (200 mg) on Days 1, 22, and 43. Radiation will be administered in a standard 30 fraction regimen (5 days per week) beginning Day 8, one week after first receiving MK-3475 to take advantage of potential abscopal effects of radiation following MK-3475 administration. Low dose TMZ will be administered daily throughout while radiation is being administered. Patients will be assessed clinically prior to each MK-3475 infusion, on Day 1 (±2d), and Day 22 (±2d). They will undergo imaging (MRI) for radiation planning purposes prior to initiating this cycle. Recovery period of 21-35 days is standard after radiation therapy.
- Adjuvant (Cycles 2-6): Treatment will be initiated between 4 to 6 weeks after completing concurrent therapy. Treatment will be in 63 day cycles. Patients will receive MK-3475 (200 mg) on Days 1, 22, and 43 up to a maximum of 17 doses. TMZ will be administered on 5 consecutive days every 28 days per current clinical standard of care. Patients will be assessed clinically prior to initiating each round of MK-3475. They will undergo imaging (MRI) prior to Cycle 2 and every cycle thereafter. Treatment will be continued for up to 5 adjuvant cycles or until tumor progression, unacceptable toxic effects develop, or consent is withdrawn.
- Safety Run-In: To ensure safety of treating patients with pembrolizumab in combination with standard adjuvant therapy, an initial 6 patients will be enrolled and treated for adverse events assessment. Enrollment to this group will be temporarily suspended for evaluating AEs in these 6 patients. If more than two patients of these first 6 evaluable patients experienced at least one dose-limiting toxicity (DLT, see definitions in Section 7.0) during Cycle 1 (concurrent with external beam radiation therapy) and attributable (possibly, probably, or definitely) to pembrolizumab, we will temporarily close the study and discuss options with the drug supplier and the FDA.

1.6 Rationale for Endpoints

1.61 Safety Endpoints

Dose limiting toxicities (DLTs) are defined in Section 7.0.

1.62 Efficacy Endpoints

The primary efficacy endpoint for this study will be 18 month overall survival. Stupp et al reported an 18 month overall survival rate (OS18) of 39% with standard surgery, radiation, and temozolomide *{Stupp 2005}*. This 39% is associated with a median overall survival of 14.6 months starting at the time of study registration, which for that study was within one week of starting concurrent RT+TMZ. Group 2 patients on this study will start treatment at the same time point; therefore this study will use this OS18 of 39% as the null hypothesis. A sample size of 33 evaluable Group 2 patients will provide a power of 85.3% to test the alternative hypothesis that the 18 month OS rate is at least 59% against the null hypothesis that the 18 months OS rate is at most 39%, at a one-sided significance level of 0.099. Progression-free survival will also be recorded.

1.7 Biomarker Research

1.71 Tumor PD-1/PD-L1 Expression and Inflammatory Microenvironment

Tumor specimens will be available in all patients with histologically confirmed glioblastoma from stereotactic needle biopsy (pre-MK-3475) and definitive resection (post-MK-3475). PD-1 and PD-L1 expression will be determined by immunohistochemistry in pre- and post-treatment samples. Pre-treatment PD-L1 expression has been associated with subsequent response to anti-PD-1 blockade in other tumors *{Taube 2014}*. The response of intra-tumoral PD-1 and PD-L1 expression following anti-PD-1 blockade in GBM's is unknown. **We hypothesize that tumor PD-L1 expression will be unchanged but GBM-infiltrating leukocyte PD-1 expression will be decreased following MK-3475 administration,** reflecting MK-3475's effect on circulating leukocytes that subsequently infiltrate tumor but a relative inability to cross the blood-brain barrier itself. We will also perform immunohistochemical staining for CD3, CD4, CD8, and CD68 to assess inflammatory cell infiltrate in pre- and post-MK-3475 specimens. **We hypothesize that T lymphocyte (CD3+/CD4+, CD3+/CD8+) infiltrates will be increased but monocytic (CD68+) infiltrates will be decreased following MK-3475 administration**, reflecting reduced PD-L1-mediated apoptosis in tumor-infiltrating activated T cells and reduced PD-L1-mediated immunosuppressive monocyte (myeloid-derived suppressor cell) expansion from tumor-infiltrating monocytes following systemic anti-PD-1 blockade.

1.72 Immunomodulation

Blood draws for immune assays will be obtained prior to definitive craniotomy and resection, prior to initiating concurrent therapy, prior to initiating cycle 1 of adjuvant therapy, prior to initiating every second cycle thereafter, and at progression. Assays will include:

- Immunophenotyping: Our research group has developed methods for analyzing combinations of >120 leukocyte surface markers in small (5 mL) whole blood samples and pioneered interpretation of the resulting data with unbiased bioinformatics approaches. These methods allow for detailed immunophenotyping of leukocyte populations including normal T-cells, B-cells, NK-cells, monocytes, neutrophils, and eosinophils as well as immunosuppressive populations such as regulatory T cells (Treg) and myeloid-derived suppressor cells (MDSC). This provides a comprehensive picture of patients' systemic immune phenotype and has confirmed widespread systemic immunosuppression in GBM patients *{Gustafson 2010}*. In prior studies of a GBM vaccine, immunophenotype determined using an earlier version of this technique predicted clinical responsiveness to tumor vaccines *{Olin 2014}*. **We hypothesize that GBM patients with a systemically immunosuppressed phenotype at baseline will revert to a normal phenotype following MK-3475 treatment.**
- GBM-associated antigen-specific T cell responses: The frequency of CD8 (killer) T cells specific for individual antigens can be detected by flow cytometry using fluorescently labeled multimers of class I major histocompatibility complexes (MHC) bound to antigen peptides. Commercially available dextramers designed for this purpose are particularly sensitive and reliable. These reagents are restricted to specific MHC

haplotypes. Most commonly, they are restricted to HLA-A*0201 which is present in ~60% of Caucasian North Americans. Patients' peripheral blood will be screened for the HLA-A*0201^{+} haplotype by flow cytometry (anticipated to be >50% of our patient population), peripheral blood samples will be analyzed by flow cytometry for tumor-associated antigen (TAA)-specific T cell frequencies using dextramers specific for a panel of common GBM-associated antigens (Her2/Neu, MAGE A3, gp100, p53, EGFR, and IL13Rα2) and controls (non-specific negative control; influenza peptide m). These TAAs meet criteria identified by the National Cancer Institute for targeting in immunotherapy trials *{Cheever 2009}* and are commonly and widely expressed in GBM's. We have recently initiated testing with this panel in a pilot dendritic cell vaccine study in newly diagnosed GBM patients (MC1272; NCT01957956). Initial results suggest presence of TAA-specific CD8 T cells at baseline ranges from 0% - 0.98% depending on the specific antigen with an overall frequency TAA-specific CD8 T cells of ~1.5% *{Parney and Dietz unpublished}*. The presence of TAA-specific CD8 T cells in measurable frequencies at baseline highlights the potential for expanding these anti-tumor T cells in GBM patients if immunosuppression is disrupted through immune checkpoint blockade with MK-3475. **We hypothesize that GBM patients will undergo an increase in TAA-specific CD8 T cells following MK-3475 treatment.**

2.0 Goals

2.1 Primary

2.11 Neoadjuvant (Group 1)

To assess the safety and tolerability of pembrolizumab in combination with standard therapy (surgery, external beam radiation therapy and TMZ chemotherapy) in patients with newly diagnosed glioblastoma multiforme (GBM).

2.12 Adjuvant (Group 2)

To assess the 18 month overall survival rate of pembrolizumab in combination with standard therapy (surgery, external beam radiation therapy and TMZ chemotherapy) in patients with newly diagnosed glioblastoma multiforme (GBM).

2.2 Secondary

2.21 To assess adverse events (AE) and toxicity profile of pembrolizumab in combination with standard therapy in patients with newly diagnosed GBM.

2.22 To assess time to progression in patients treated with pembrolizumab in combination with standard therapy in patients with newly diagnosed GBM (Adjuvant only).

2.23 To assess progression-free survival in patients treated with pembrolizumab in combination with standard therapy in patients with newly diagnosed GBM (Adjuvant only).

2.24 To assess time to treatment failure in patients treated with pembrolizumab in combination with standard therapy in patients with newly diagnosed GBM (Adjuvant only).

2.3 Correlative Research

2.31 To assess the tumor PD-1/PD-L1 expression and inflammatory microenvironment profile by comparing PD-1/PD-L1 expression and T lymphocyte/monocytic infiltrates before and after administration of pembrolizumab treatment (Neoadjuvant only).

2.32 To assess the peripheral immunophenotype profile and GBM-associated antigen-specific T cell responses before and after receiving pembrolizumab treatment in combination with standard therapy.

3.0 Patient Eligibility

3.1 Registration – Inclusion Criteria

3.11 Age ≥18years.

3.12 Histological confirmation of supratentorial glioblastoma (also known as astrocytoma Grade IV, gliosarcoma)
NOTE: Grade IV IDH-mutant astrocytoma is also allowed.

3.13 Neoadjuvant patients only:
Have an enhancing mass on MRI amenable to >90% resection of contrast-enhancing tumor (as determined by the neurosurgeon pre-operatively) and histological diagnosis of glioblastoma or astrocytoma (as defined in Section 3.12 above) from a prior biopsy or surgery.
NOTE: Biopsy or subtotal resection must have been ≤43 days prior to registration.

3.14 Prior Treatment

3.141 Neoadjuvant patients only: Willing to undergo craniotomy and resection of their brain tumor at Mayo Clinic in Rochester, MN.

3.142 Adjuvant patients only: Must have undergone craniotomy and resection of their brain tumor ≤6 weeks prior to registration.

3.15 ECOG Performance Status (PS) of 0 or 1 (see Appendix I).

3.16 The following laboratory values obtained ≤28 days prior to registration.

- Absolute neutrophil count (ANC) ≥1500/mm^3
- Platelet count ≥100,000/mm^3
- Hemoglobin ≥9.0 g/dL without transfusion or EPO dependency (≤7 days prior to assessment)
- Prothrombin Time (PT) ≤1.5 x ULN unless patient is receiving anticoagulant therapy and PT or PTT is within therapeutic range of intended use of coagulants
- Activated Partial Thromboplastin Time (aPTT) ≤1.5 x ULN unless patient is receiving anticoagulant therapy and PT or PTT is within therapeutic range of intended use of coagulants
- Albumin ≥2.5 mg/dL
- Total bilirubin ≤1.5 x ULN OR Direct bilirubin ≤ULN for patients with total bilirubin levels >1.5 x ULN
- Aspartate transaminase (AST) AND alanine transaminase (ALT) ≤2.5 x ULN
- Creatinine ≤1.0 x ULN OR measured or calculated creatinine clearance (per institutional standard) must be ≥60 ml/min

3.17 Negative pregnancy test done ≤7 days prior to registration, for persons of childbearing potential only (POCBP).
NOTE: Serum or urine pregnancy test allowed. If urine test is positive or cannot be confirmed as negative, a serum pregnancy test will be required.

3.18 POCBP must be willing to use adequate contraception starting with first dose through 120 days after last dose. (See Section 9.9c)

3.19a Provide written informed consent.

3.19b Willing to return to enrolling institution for follow-up (during the Active Monitoring Phase of the study).

Note: During the **Active Monitoring** Phase of a study (i.e., active treatment and observation), participants must be willing to return to the consenting institution for follow-up.

3.19c Willing to provide tissue and blood samples for correlative research purposes (see Sections 6, 14 and 17).

3.2 Registration – Exclusion Criteria

3.21 Any of the following because this study involves an investigational agent whose genotoxic, mutagenic and teratogenic effects on the developing fetus and newborn are unknown:

- Pregnant persons
- Nursing persons
- Persons of childbearing potential who are unwilling to employ adequate contraception

3.22 Neoadjuvant patients only: Signs or symptoms of life-threatening raised intracranial pressure: as defined by the treating neurosurgeon, including severe headache, nausea, decreasing level of consciousness, precluding 4-7 day delay in scheduling neurosurgery.

3.23 Co-morbid systemic illnesses or other severe concurrent disease which, in the judgment of the investigator, would make the patient inappropriate for entry into this study or interfere significantly with the proper assessment of safety and toxicity of the prescribed regimens.

3.24 Immunocompromised patients and patients known to be HIV positive and currently receiving antiretroviral therapy.

3.25 Uncontrolled intercurrent illness including, but not limited to, ongoing or active infection, symptomatic congestive heart failure, unstable angina pectoris, cardiac arrhythmia, or psychiatric illness/social situations that would limit compliance with study requirements.

3.26 Receiving any other investigational agent which would be considered as a treatment for the primary neoplasm.

3.27 Other active malignancy ≤5 years prior to registration.
EXCEPTIONS: Non-melanotic skin cancer or carcinoma-in-situ of the cervix.
NOTE: If there is a history or prior malignancy, the patient must not be receiving other specific treatment for their cancer.

3.28 History of myocardial infarction ≤6 months prior to registration, or congestive heart failure requiring use of ongoing maintenance therapy for life-threatening ventricular arrhythmias.

3.29a 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).
NOTE: Replacement therapy (e.g., thyroxine, insulin, or physiologic corticosteroid replacement therapy for adrenal or pituitary insufficiency, etc.) is <u>not</u> considered a form of systemic treatment.

3.29b Known active Hepatitis B (e.g., HBsAg reactive) or Hepatitis C (e.g., HCV RNA [qualitative] is detected).

3.29c Known history of active TB (Bacillus Tuberculosis).

3.29d Received a live vaccine ≤30 days prior to registration.

3.29e History of (non-infectious) pneumonitis that required steroids or current pneumonitis.

3.29f Hypersensitivity to pembrolizumab or any of its excipients.

3.29g Received prior therapy with an anti-PD-1, anti-PD-L1, or anti-PD-L2 agent.

3.29h Received or planning to receive Optune® device.

4.0 Study Calendars

4.1 Test Schedule[1] for Neoadjuvant Patients (Group 1) - Rochester only

Trial Period	Screening	Active Treatment											Post-Treatment	
Tests and Procedures[2]	≤28 days prior to registration	Neoadjuvant (Cycle 1) D1	Neoadjuvant (Cycle 1) D6[7]	Surgery (C2)	Prior to RT (C2)[3]	Concurrent[4] with RT[5] (up to 54 days) (Cycle 3) plus up to 42 day rest post RT D1	Concurrent[4] with RT[5] (up to 54 days) (Cycle 3) plus up to 42 day rest post RT D22	Concurrent[4] with RT[5] (up to 54 days) (Cycle 3) plus up to 42 day rest post RT D43	Adjuvant (up to 5 cycles)[6] after RT (Cycles 4-8) D1	Adjuvant (up to 5 cycles)[6] after RT (Cycles 4-8) D22	Adjuvant (up to 5 cycles)[6] after RT (Cycles 4-8) D43	End of Tx (for any reason)	Observation: Safety follow up: 30 days post-discontinuation	At time of progression
Scheduling window (days)	-28 to -1	±3	±2		±3	±3	±3	±3	±3	±3	±3	±7	±7	
Clinical Procedures														
History and exam, weight, ECOG PS	X					X	X	X	X	X	X	X	X	X
Height	X													
Adverse event assessment	X		X		X	X	X	X	X	X	X	X	X	
Consultation with Radiation Oncologist (See Sect. 6.9d)	X													
Surgical consultations (See Sect. 6.9b)	X													
Medical Oncology consultation (See Sect. 6.9c)	X				X				X					
Hematology: CBC/diff[8]	X					X	X	X	X	X	X	X	X	
Chemistry Panel[9]	X					X	X	X	X	X	X	X	X	
Coagulation PT, PTT, aPTT	X					X			X					
Thyroid panel: T3, Free T4, TSH	X					X	X	X	X	X	X	X	X	

Cycle length = 63 days during Adjuvant treatment only

[1] All tests and procedures are clinically indicated and can be performed more often at the treating physician's discretion, unless noted with an R to indicate funding by research

[2] Each test or procedure should be obtained within ±3 business days of the designated date unless otherwise noted.

[3] Prior to RT items may overlap with Concurrent D1 items – in which case, separate assessments are not required

[4] Starting up to 42 days after surgery

[5] Recommendations for PJP/PCP prophylaxis are in Section 9.9f.

[6] Cycle length during adjuvant treatment = 63 days.

[7] Between Days 3-6, just prior to surgery

[8] Clinically indicated blood draws for monitoring temozolomide can be performed as needed by LMD and sent to Mayo Clinic.

[9] Complete metabolic panel (80053) or Hepatic function panel (80076) at treating physician discretion

Trial Period	Screening	Active Treatment											Post-Treatment	
Tests and Procedures[2]	≤28 days prior to registration	Neoadjuvant (Cycle 1) D1	Neoadjuvant (Cycle 1) D6[7]	Surgery (C2)	Prior to RT (C2)[3]	Concurrent[4] with RT[5] (up to 54 days) (Cycle 3) plus up to 42 day rest post RT D1	Concurrent[4] with RT[5] (up to 54 days) (Cycle 3) plus up to 42 day rest post RT D22	Concurrent[4] with RT[5] (up to 54 days) (Cycle 3) plus up to 42 day rest post RT D43	Adjuvant (up to 5 cycles)[6] after RT (Cycles 4-8) D1	Adjuvant (up to 5 cycles)[6] after RT (Cycles 4-8) D22	Adjuvant (up to 5 cycles)[6] after RT (Cycles 4-8) D43	End of Tx (for any reason)	Observation: Safety follow up: 30 days post-discon-tinuation	At time of progression
Urinalysis [10]	X					X			X			X	X	
Pregnancy test[11]	X	X												
MRI Brain [12]	X		X[13]		X[14]				X[15]					
Craniotomy and tumor resection				X										
Blood or Tissue- Analysis performed by Research Lab														
Blood for correlative studies (See Section 14.0) [R]		X[16]			X				X[17]				X	X
Mandatory tissue sample (see Section 17.0) [18R]	X			X										
Optional follow up tissue sample[19R]														X
MGMT and IDH testing[20]	X			X										

Cycle = 63 days during Adjuvant stage only; **R** = Research funded

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[10] Urinalysis for protein, glucose, blood, and specific gravity.

[11] For persons of childbearing potential only. Serum or urine. Must be done ≤7 days prior to registration and must be done again ≤72 hours prior to first dose if first test was >72 hours prior to first dose.

[12] Brain MRI as clinically indicated. MRI schedule may be adjusted at the discretion of the treating oncologist for clinical care at any time. Note: CT head is permissible instead of MRI Brain if patient is unable to undergo MRI (e.g. cardiac pacemaker).

[13] At the end of Cycle 1, just prior to surgery, typically this is the day prior to surgery or similar

[14] Post-surgery and prior to RT. This exam will be considered the starting baseline for measuring response and progression.

[15] Brain MRI as clinically indicated. Performed every cycle during adjuvant treatment unless indicated more frequently clinically at the treating oncologist's discretion.

[16] Must be collected prior to treatment.

[17] During adjuvant treatment, research blood samples are only collected prior to treatment on Cycle 4, Day 1 (Day 1 of the first adjuvant cycle)

[18] Submission of adequate tissue from the primary tumor is mandatory. See Section 17.0. Note: Can be submitted before or during active treatment.

[19] An optional newly-obtained core, or excisional biopsy is requested at the time of recurrence or progressive disease if clinical biopsy or resection is done.

[20] MGMT and IDH testing is only required once as part of clinical care. Either based on the original diagnosis biopsy or from the surgical resection.

4.2 Test Schedule[21] for Adjuvant Patients

Trial Period	Screening	Active Treatment							Post-Treatment	
		Concurrent[23] with RT[24] (up to 54 days) (Cycle 1) plus up to 42 day rest post RT			Adjuvant (up to 5 cycles) after RT (Cycles 2-6)			End of Tx (for any reason)	Observation Safety follow up: 30 days post-discontinuation	At time of progression
Tests and Procedures[22]	≤28 days prior to registration	D1[25]	D22	D43	D1	D22	D43			
Scheduling window (days)	-28 to -1	±3	±3	±3	±3	±3	±3	±7	±7	
Clinical Procedures										
History and exam, weight, ECOG PS	X	X	X	X	X	X	X	X	X	X
Height	X									
Adverse event assessment	X	X	X	X	X	X	X	X	X	
Consultation with Radiation Oncologist (See Sect. 6.9d)	X									
Medical Oncology consultation (See Sect. 6.9c)	X				X					
Hematology: CBC/diff[26]	X	X	X	X	X	X	X	X	X	
Chemistry Panel[27]	X	X	X	X	X	X	X	X	X	
Coagulation PT, PTT, aPTT	X	X			X					
Thyroid panel: T3, Free T4, TSH	X	X	X	X	X	X	X	X	X	
Urinalysis[28]	X	X			X			X	X	
Pregnancy test[29]	X									
MRI Brain[30]	X				X					

Cycle length = 63 days during Adjuvant treatment only

[21] All tests and procedures are clinically indicated and can be performed more often at the treating physician's discretion, unless noted with an R to indicate funding by research

[22] Each test or procedure should be obtained within ±3 business days of the designated date unless otherwise noted.

[23] Starting 21-35 days after surgery

[24] Recommendations for PJP/PCP prophylaxis are in Section 9.9f.

[25] May be waived if previous results ≤7 days prior to C1D1

[26] May be waived if previous results ≤7 days prior to C1D1

[27] Complete metabolic panel (80053) or Hepatic function panel (80076) at physician discretion

[28] Urinalysis for protein, glucose, blood, and specific gravity.

[29] For persons of childbearing potential only. Serum or urine. Must be done ≤7 days prior to registration and must be done again ≤72 hours prior to first dose, if previous test was >72 hours prior to first dose.

[30] Brain MRI as clinically indicated. MRI schedule may be adjusted at the discretion of the treating oncologist for clinical care at any time. Note: CT head is permissible instead of MRI Brain if patient is unable to undergo MRI (e.g. cardiac pacemaker).

Trial Period	Screening	Active Treatment							Post-Treatment	
		Concurrent[23] with RT[24] (up to 54 days) (Cycle 1) plus up to 42 day rest post RT			Adjuvant (up to 5 cycles) after RT (Cycles 2-6)				Observation	
Tests and Procedures[22]	≤28 days prior to registration	D1[25]	D22	D43	D1	D22	D43	End of Tx (for any reason)	Safety follow up: 30 days post-discontinuation	At time of progression
Blood or Tissue- Analysis performed by Research Lab										
Blood for correlative studies (See Section 14.0) [R]		X[31]			X[32]				X	X
Mandatory tissue sample (see Section 17.0) [33R]	X									
Optional follow up tissue sample[34R]										X
MGMT and IDH testing[35]	X									

Cycle = 63 days during Adjuvant treatment only; **R** = Research funded

[31] Baseline blood sample collected after registration and prior to treatment on Cycle 1, Day 1 (prior to radiation therapy)
[32] During adjuvant treatment, research blood samples are only collected prior to treatment on Cycle 2, Day 1 (Day 1 of the first adjuvant cycle)
[33] Submission of adequate tissue from the primary tumor (archived) is required if available. See Section 17.0. Note: Can be submitted before or during active treatment.
[34] An optional newly-obtained core, or excisional biopsy is requested at the time of recurrence or progressive disease if clinical biopsy or resection is done.
[35] MGMT and IDH testing is only required once as part of clinical care. Either based on the original diagnosis biopsy or from the surgical resection.

4.3 Event Monitoring/Survival Follow-up

	Event Monitoring Phase[1]				
	q. 3 months until PD	At PD	After PD q. 6 months	Death	New Primary
Event Monitoring	X	X	X	X	At each occurrence

1. Maximum follow-up time is 5 years after registration. No further follow-up is required after 5 years.

5.0 Grouping Factor

Group 1: Neoadjuvant vs. Group 2: Adjuvant

6.0 Registration Procedures

6.1 Registration Procedures

6.11 **Registration for Safety Run-in** for Neoadjuvant Patients (Group 1) (Rochester only) and first six Adjuvant Patients (Group 2) (All sites)

Prior to discussing protocol entry with the patient, call the Mayo Clinic Research Site Managment Office [redacted] to ensure that a place on the protocol is open to the patient

To register a patient, fax [redacted] a completed eligibility checklist to the Mayo Clinic Research Site Management Office between 8 a.m. and 4:30 p.m. Central Time Monday through Friday.

6.12 **Registration for Adjuvant Patients (Group 2) after first 6 patients have been enrolled**

To register a patient, access the Research Registration Application at [redacted] The Research Registration Application is available 24 hours a day, 7 days a week. Back up and/or system support contact information is available on the website. If unable to access the website, call the Research Site Management Office at [redacted] between the hours of 8 a.m. and 4:30 p.m. Central Time (Monday through Friday).

The instructions for the Research Registration Application are available on the Office of Clinical Trials web page [redacted] and detail the process for completing and confirming patient registration. Prior to initiation of protocol treatment, this process must be completed in its entirety and a subject ID number must be available as noted in the instructions. It is the responsibility of the individual and institution registering the patient to confirm the process has been successfully completed prior to release of the study agent. Patient registration via the registration/randomization application can be confirmed in any of the following ways:

- Contact Research Site Management [redacted] If the patient was fully registered, Research Site Management staff can access the information from the centralized database and confirm the registration.
- Refer to “Instructions for Remote Registration” in section “Finding/Displaying Information about A Registered Subject.”

6.2 Correlative research

6.21 Mandatory correlative research (Group 1 and Group 2)

A mandatory translational research component is part of this study; the patient will be automatically registered onto this component (Sections 3.0, 14.0, 17.0*)*.

6.22 Optional correlative research (Adjuvant Group 2 ONLY)

An optional correlative research component is part of this study. There will be an option to select whether the patient is to be registered onto this component (see Section 17.0).

- Patient has/has not given permission to give his/her tissue samples for research testing.

6.3 Verification

Prior to accepting the registration, registration/randomization application will verify the following:

- IRB approval at the registering institution
- Patient eligibility
- Existence of a signed consent form
- Existence of a signed authorization for use and disclosure of protected health information

6.4 Documentation

Documentation of IRB approval must be on file in the Research Site Management Office before an investigator may register any patients.

In addition to submitting initial IRB approval documents, ongoing IRB approval documentation must be on file (no less than annually) at the Research Site Management Office [redacted] If the necessary documentation is not submitted in advance of attempting patient registration, the registration will not be accepted and the patient may not be enrolled in the protocol until the situation is resolved.

When the study has been permanently closed to patient enrollment, submission of annual IRB approvals to the Research Site Management Office is no longer necessary.

6.5 Optional tissue banking permissions

At the time of registration, the following will be recorded:

- Patient has/has not given permission to store and use his/her sample(s) for future research on cancer at Mayo Clinic.
- Patient has/has not given permission to store and use his/her sample(s) for future research to learn, prevent, or treat other health problems.
- Patient has/has not given permission for MCCC to give his/her sample(s) to researchers at other institutions.

6.6 Treatment location

Treatment on this protocol must commence at Mayo Clinic under the supervision of a Mayo Clinic physician.

6.7 Treatment start

Treatment cannot begin prior to registration and must begin ≤7 days after registration.

6.8 Pretreatment tests/procedures

Pretreatment tests/procedures (see Section 4.0) must be completed within the guidelines specified in the test schedule.

6.9a Baseline symptoms

All required baseline symptoms (see Section 10.5) must be documented and graded.

6.9b Neurosurgery consult (Neoadjuvant Group 1 ONLY)

A neurosurgeon has seen the patient and confirms the patient is a suitable candidate for this trial.

6.9c Medical oncology consult

A medical oncologist has seen the patient and confirms the patient is a suitable candidate for this trial.

6.9d Radiation oncology consult

A radiation oncologist has seen the patient and confirms the patient is a suitable candidate for this trial.

6.9e Study drug

Study drug is available on site.

6.9f Kits

Blood draw kit availability checked (except Mayo Clinic in Rochester).

7.0 Protocol Treatment

7.1 Group 1 Neoadjuvant Trial Treatments

7.11 Neoadjuvant treatment will be divided into four stages:

1) **Neoadjuvant (Cycle 1)** prior to craniotomy
Single dose given 4-7 days prior to definitive craniotomy/resection

2) **Surgery (Cycle 2)** – Definitive craniotomy/resection and recovery.

3) **Concurrent (Cycle 3)** with radiation therapy and temozolomide starting 21-35 days after Surgery. Pembrolizumab initiated Day 1. Standard of care external beam RT and TMZ beginning Day 8 of Cycle 3 (See Appendix II for recommendations and Section 9.9f for PJP/PCP prophylaxis) plus 21-35 day rest period post RT

4) **Adjuvant (Cycles 4-8)** - Pembrolizumab with temozolomide following radiation therapy (63 day cycles, up to 5 adjuvant cycles)

7.12 Agents

Agent	**Dose**	**Route**	**Day**	**ReRx**
MK-3475 (pembrolizumab)*	200 mg	IV	Per stage	Per stage
Temozolomide**†	75mg/m^2 or 150mg/m^2 or 200mg/m^2	PO	Per stage	Per stage
* Pembrolizumab is given for 30 min -5 or +10 for a maximum total of 17 doses. **Tablets should be taken once daily, as directed, with a glass (8 ounces) of water one hour before or after food. †Because this agent is known to produce nausea and/or vomiting, an appropriate anti-emetic should be used 30-60 minutes before each dose.				

Table 7.13 **Neoadjuvant** Trial Treatment with Pembrolizumab (Cycle 1)

Drug/Therapy	Dose/Potency	Dose Frequency	Route of Administration	Regimen/ Treatment Period	Use
Pembrolizumab	200 mg	Once	IV infusion	Day 1	Experimental

Table 7.14 **Surgery** (Cycle 2) and recovery

Drug/Therapy	Dose/Potency	Dose Frequency	Route of Administration	Regimen/ Treatment Period	Use
Craniotomy/ Resection	N/A	Once	N/A	Day 4 - 7	Standard

Table 7.15 **Concurrent** Trial Treatment with Pembrolizumab, TMZ, and RT (Cycle 3)
Initiated 21-35 days post-op
Single 54 day cycle plus 21-35 day rest period post RT

Drug/Therapy	**Dose/Potency**	**Dose Frequency**	**Route of Administration**	**Regimen/ Treatment Period**	**Use**
Pembrolizumab	200 mg	Q3W	IV infusion	Days 1, 22, 43	Experimental
External Beam Radiation[a]	6000 cGy in 30 fractions	200 cGy/ fraction, 5 days per week	Standard or IMRT	Beginning Day 8	Standard
Temozolomide	75 mg/m^2	Daily	Oral	Day 8 – up through the end of radiation (Days 47-54)	Standard

a. Please see Appendix II for radiation therapy details

Table 7.16 **Adjuvant** Trial Treatment with Pembrolizumab and TMZ (Cycles 4-8)
Initiated 3 - 5 weeks after completing radiation
63 day cycle for up to 5 adjuvant cycles

Drug/Therapy	Dose/Potency	Dose Frequency	Route of Administration	Regimen/ Treatment Period	Use
Pembrolizumab	200 mg	Q3W	IV infusion	Days 1, 22, 43*	Experimental
Temozolomide**	150 mg/m^2 – 200 mg/m^2	Daily	Oral	Starting on Cycle 4 Day 1, Days 1 – 5, then 5 consecutive days every 28 days	Standard

*Pembrolizumab will stop when patient has received a total of 17 doses.
**Temozolomide must be stopped after completion of six (6) 5-day adjuvant "cycles"

7.2 Group 1: Neoadjuvant Treatment schedule (in order of occurrence)

7.21 Prior to study entry

- Histological diagnosis of glioblastoma (based on prior biopsy or subtotal resection performed for clinical indications)

7.22 Neoadjuvant - Prior to craniotomy (Cycle 1)

- Pembrolizumab single dose of 200 mg prior to definitive craniotomy/resection

7.23 Surgery (Cycle 2)

- Craniotomy and maximal safe tumor resection
- Recovery from surgery 21-35 days

7.24 Concurrent with standard of care RT and temozolomide (Cycle 3)

- Pembrolizumab 200 mg on Days 1, 22, and 43
- External beam RT beginning Day 8 (60.0 Gy in 30 equal fractions of 2.00 Gy administered 5 days per week)
- Temozolomide 75mg/m^2 daily during RT
- Rest period up to 42 days post RT

7.25 Adjuvant with standard of care temozolomide (63 day cycles up to 5 adjuvant cycles) (Cycles 4-8):

- Pembrolizumab 200 mg on Days 1, 22, and 43 up to a maximum of 17 total doses
- Temozolomide 150mg/m^2 starts Cycle 4, Days 1-5. If no treatment related toxicity higher than Grade 2 is observed after the first 5-day round, the dose of temozolomide can be increased to 200mg/m^2 for Cycle 4, Days 29-33, and subsequent 5-day rounds every 28 days.
  Note these rounds of TMZ will not be in sync with the Q3W frequency of pembrolizumab. **With no delays in the treatment schedule**, the following are the estimated start days of the 5-day rounds of TMZ within each cycle (see Table 7.251 below).
  NOTE: TMZ may be delayed for any number of reasons including TMZ treatment related AEs, time to mail the prescription, and others. There is no protocol violation for delays of TMZ dosing due to clinical need or for delays by less than or equal to 7 calendar days for administrative issues such as shipping.

Table 7.251 Approximate Timing of TMZ Doses during Adjuvant Treatment

Cycle	TMZ Round 1	TMZ Round 2	TMZ Round 3	Pembrolizumab
4	Days 1-5	Days 29-33	Days 57-61	Days 1, 22, 43
5	Days 22-26	Days 50-54	No 3rd round this cycle	Days 1, 22, 43
6	Days 15-19	Days 43-47**	No 3rd round this cycle	Days 1, 22, 43
7**	Days 8-12	Days 36-40	No 3rd round this cycle	Days 1, 22, 43
8**	Days 1-5	Days 29-33	Days 57-61	Day 1*

*Stop pembrolizumab when patient has received 17 total doses
**Temozolomide must be stopped after completion of six (6) 5-day adjuvant "cycles"

7.3 Group 2: Adjuvant Trial Treatments

7.31 Adjuvant treatment will be divided into two stages:

1) **Concurrent (Cycle 1)** with radiation therapy and temozolomide starting 21-35 days after Surgery. Pembrolizumab initiated Day 1. Standard of care external beam RT and TMZ beginning Day 8 of Cycle 1 (See Appendix II for recommendations and Section 9.9f for PJP/PCP prophylaxis) plus up to 42 day rest period post RT

2) **Adjuvant (Cycles 2-6)** - Pembrolizumab with temozolomide following radiation therapy (63 day cycles, up to 5 adjuvant cycles)

7.32 Agents

Agent	Dose	Route	Day	ReRx
MK-3475 (pembrolizumab)*	200 mg	IV	Per stage	Per stage
Temozolomide**†	75mg/m^2 or 150mg/m^2 or 200mg/m^2	PO	Per stage	Per stage
* Pembrolizumab is given for 30 min -5 or +10 for a maximum total of 17 doses. **Tablets should be taken once daily, as directed, with a glass (8 ounces) of water one hour before or after food. †Because this agent is known to produce nausea and/or vomiting, an appropriate anti-emetic should be used 30-60 minutes before each dose.				

7.33 **Concurrent** Trial Treatment with Pembrolizumab, TMZ, and RT (Cycle 1)

Initiated 21-35 days post-op
Single 54 day cycle plus up to 42 day rest period post RT

Drug/Therapy	Dose/Potency	Dose Frequency	Route of Administration	Regimen/ Treatment Period	Use
Pembrolizumab	200 mg	Q3W	IV infusion	Days 1, 22, 43	Experimental
External Beam Radiation[a]	6000 cGy in 30 fractions	200 cGy/ fraction, 5 days per week	Standard or IMRT	Beginning Day 8	Standard
Temozolomide	75 mg/m^2	Daily	Oral	Day 8 – up through the end of radiation (Days 47-54)	Standard

a. Please see Appendix II for radiation therapy details

7.34 **Adjuvant** Trial Treatment with Pembrolizumab and TMZ (Cycles 2-6)

Initiated 3 - 5 weeks after completing radiation
63 day cycle for up to 5 adjuvant cycles

Drug/Therapy	Dose/Potency	Dose Frequency	Route of Administration	Regimen/ Treatment Period	Use
Pembrolizumab	200 mg	Q3W	IV infusion	Days 1, 22, 43*	Experimental
Temozolomide**	150 mg/m^2 – 200 mg/m^2	Daily	Oral	Starting on Cycle 2 Day 1, Days 1 – 5, then 5 consecutive days every 28 days	Standard

*Pembrolizumab will be stopped when patient has received a maximum total of 17 doses.
**Temozolomide must be stopped after completion of six (6) 5-day adjuvant "cycles"

7.4 Adjuvant Treatment Schedule (in order of occurrence)

7.41 Prior to study entry

- Histological diagnosis of glioblastoma (based on prior biopsy or subtotal resection performed for clinical indications)
- Craniotomy and maximal safe tumor resection
- Recovery from surgery up to 42 days

7.42 Concurrent with standard of care RT and temozolomide (Cycle 1)

- Pembrolizumab 200 mg on Days 1, 22, and 43
- External beam RT beginning Day 8 (60.0 Gy in 30 equal fractions of 2.00 Gy administered 5 days per week)
- Temozolomide 75mg/m^2 daily during RT beginning on Day 8
- Rest period up to 42 days post RT

7.43 Adjuvant with standard of care temozolomide (63 day cycles up to 5 adjuvant cycles) (Cycles 2-6):

- Pembrolizumab 200 mg on Days 1, 22, and 43 up to a maximum of 17 total doses
- Temozolomide 150mg/m^2 starts Cycle 2, Days 1-5. If no treatment related toxicity higher than Grade 2 is observed after the first 5-day round, the dose of temozolomide can be increased to 200mg/m^2 for Cycle 2, Days 29-33, and subsequent 5-day rounds every 28 days.
  Note these rounds of TMZ will not be in sync with the Q3W frequency of pembrolizumab. **With no delays in the treatment schedule**, the following are the estimated start days of the 5-day rounds of TMZ within each cycle (see Table 7.431 below
  NOTE: TMZ may be delayed for any number of reasons including TMZ treatment related AEs, time to mail the prescription, and others. There is no protocol violation for delays of TMZ dosing by less than or equal to 7 calendar days.

Table 7.431 Approximate Timing of TMZ Doses during Adjuvant Treatment

Cycle	TMZ Round 1	TMZ Round 2	TMZ Round 3	Pembrolizumab
2	Days 1-5	Days 29-33	Days 57-61	Days 1, 22, 43
3	Days 22-26	Days 50-54	No 3rd round this cycle	Days 1, 22, 43
4	Days 15-19	Days 43-47**	No 3rd round this cycle	Days 1, 22, 43
5**	Days 8-12	Days 36-40	No 3rd round this cycle	Days 1, 22, 43
6**	Days 1-5	Days 29-33	Days 57-61	Days 1, 22*

*Pembrolizumab will be stopped when patient has received a maximum total of 17 doses.
**Temozolomide must be stopped after completion of six (6) 5-day adjuvant "cycles"

7.5 Radiotherapy - Radiotherapy will be the same for all patients

See Appendix II for Radiation Therapy Recommendations

Questions regarding the radiotherapy section of this protocol should be directed to:

[redacted]

[redacted]

7.6 Return to consenting institution

7.61 Neoadjuvant patients

For this protocol, the patient must have craniotomy / resection and radiation therapy at the consenting institution and return to the consenting institution for evaluation at least every 21 days during adjuvant treatment, 30 days after the end of treatment .

7.62 Adjuvant patients

For this protocol, the patient must have radiation therapy at the consenting institution and return to the consenting institution for evaluation at least every 21 days during adjuvant treatment, and 30 days after the end of treatment.

7.7 Local medical doctor

Treatment by a local medical doctor (LMD) is not allowed on this study, except for blood tests to monitor treatment with standard of care temozolomide.

7.8 IDH and MGMT testing of tumor

Patient tumors will be tested for IDH and MGMT as part of standard clinical practice. A portion of the tumor will be submitted to the Department of Laboratory Medicine and Pathology at Mayo Clinic to test for the presence of these two markers.

7.9a Dose-Limiting Toxicities for Safety Run-in (Group 1 and Group 2)

Dose-limiting toxicity (DLT) will be defined as an adverse event attributed (definitely, probably, or possibly) to pembrolizumab, from start of treatment through the end of concurrent treatment and the associated rest period, and meeting the following criteria:

Toxicity	**DLT Definition**
Cytopenias	≥Grade 4 per NCI Common Terminology Criteria for Adverse Events v4.0 excluding the following: • Grade 4 neutropenia lasting ≤7 days
Unspecified	≥Grade 3 per NCI Common Terminology Criteria for Adverse Events v4.0, excluding the following: • Any Grade 3 electrolyte alteration that resolves to Grade ≤1 within 72 hours after it occurs. • Grade 3 nausea, vomiting, or diarrhea (lasting ≤72 hours) which responds to maximal supportive treatment(s)
Neurologic toxicity	≥Grade 3 per NCI Common Terminology Criteria for Adverse Events v4.0
Others not covered above	See list below

Other scenarios that will be considered DLTs if they are attributed (definitely, probably, or possibly) to pembrolizumab:

- Toxicities leading to a delay of study treatment for ≥14 days.
- The inability to proceed to planned surgical resection within 10 days following pembrolizumab administration (Neoadjuvant Group 1 only)
- The inability to receive at least 75% of the cumulative radiation dose within 10 days of expected completion of radiation therapy.

Note: Any Grade 3 or greater adverse event common to treatment with standard of care RT and TMZ will be reviewed for relationship to pembrolizumab and will be defined as a DLT if it can be attributed (definitely, probably or possibly) to pembrolizumab as well.

7.9b Safety Run-in (Adjuvant Group 2)

The study will temporarily halt if 3 of the first 6 patients enrolled in the Adjuvant Group (Group 2) experience any of the following events attributed (definitely, probably, or possibly) to pembrolizumab:

- Adverse events leading to a delay of planned treatment with RT and/or TMZ for ≥14 days.
- The inability to receive at least 75% of the cumulative radiation dose within 10 days of expected completion of radiation therapy.

Note: Any Grade 3 or greater adverse event common to treatment with standard of care RT and TMZ will be reviewed for relationship to pembrolizumab and will result in temporary halt to the study if it can be attributed (definitely, probably or possibly) to pembrolizumab as well.

8.0 Dosage Modification Based on Adverse Events

These modifications should be regarded as guidelines to limit and/or reduce side effects.

Providers may hold, delay, or reduce (as allowed in Section 8.1) doses, even in the absence of a requirement to do so in the tables (Section 8.2-8.4) per clinical judgement to maximize patient safety. For example, if the patient's AE is Grade 2, and the tables do not indicate a change in action, if the provider determines that the patient's Grade 2 AE is severe enough to warrant a change in the patient's clinical care (i.e., for medically significant or intolerable Grade 2 AE despite appropriate (maximal) supportive care), then the provider may make that change, as long as the reason for the change is discussed with the PI, and documented in the medical record.

ALERT: ADR reporting may be required for some adverse events (See Section 10)

8.1 Dose Levels Based on Adverse Events in Tables 8.2 and 8.3

Dose Level	Pembrolizumab**	Temozolomide during Concurrent RT†	Temozolomide during Adjuvant Tx†
2	--		
1*	200 mg	75 mg/m^2	150-200 mg/m^2
-1	--		
-2	--		

*Dose level 1 refers to the starting dose.
**There are no dose modifications for pembrolizumab
†Dose modifications for temozolomide should follow institutional standard of care; suggested modifications are listed in Section 8.4

→ → ***Use the NCI Common Terminology Criteria for Adverse Events (CTCAE) version 4.0* unless otherwise specified*** ← ←

8.2 Treatment modifications for pembrolizumab

AEs associated with pembrolizumab exposure may represent an immunologic etiology. These immune-related AEs (irAEs) may occur shortly after the first dose or several months after the last dose of pembrolizumab treatment and may affect more than on body system simultaneously. Therefore, early recognition and initiation of treatment is critical to reduce complications. Based on existing clinical study data, most irAEs were reversible and could be managed with interruptions of pembrolizumab, administration of corticosteroids and/or other supportive care. For suspected irAEs, ensure adequate evaluation to confirm etiology or exclude other causes. Additional procedures or tests such as bronchoscopy, endoscopy, skin biopsy may be included as part of the evaluation. Based on the severity of irAEs, withhold or permanently discontinue pembrolizumab and administer corticosteroids. Dose modification and toxicity management guidelines for irAEs associated with pembrolizumab are provided in the following tables. See Section 9.0 for supportive care guidelines, including use of corticosteroids and management of symptoms.

8.21 Treatment Modification Guidelines for Drug-Related Adverse Events for Pembrolizumab during **Neoadjuvant** and **Concurrent** treatment.

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

CTCAE System/Organ/Class (SOC)	Adverse Event	Hold Treatment for Grade	Timing for Restarting Treatment	Treatment Discontinuation
Cardiac disorders	Myocarditis	Grade 1	AE resolves to Grade 0	Permanently discontinue if AE does not resolve within 12 weeks of last dose
		Grade 2, 3, or 4	Permanently discontinue	Permanently discontinue
Endocrine disorders	Endocrine disorders – Other, specify: Hypophysitis	Grade 2	AE resolves to Grade 0-1. Therapy with pembrolizumab can be continued while endocrine replacement therapy is instituted	Permanently discontinue if AE 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
		Grade 3 or4	Withhold or permanently discontinue at investigator's discretion	Withhold or permanently discontinue at investigator's discretion
Endocrine disorders	Hyperthyroidism	Grade 3 or 4	Withhold or permanently discontinue at investigator's discretion	Permanently discontinue at investigator's discretion
Endocrine disorders	Hypothyroidism	Grade 2-4	Therapy with pembrolizumab can be continued while thyroid replacement therapy is instituted	
Gastrointestinal disorders	Diarrhea or Colitis	Grade 2 or3	AE resolves to Grade 0-1	Permanently discontinue if AE 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
		Grade 4	Permanently discontinue	Permanently discontinue

CTCAE System/Organ/Class (SOC)	Adverse Event	Hold Treatment for Grade	Timing for Restarting Treatment	Treatment Discontinuation
General disorders and administration site conditions	Infusion related reaction	Grade 2	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 See Section 9.9b for more details.	Permanently discontinue if AE develops despite adequate premedication
		Grade 3 or 4	Permanently discontinue	Permanently discontinue
Investigations	Alanine aminotransferase increased (ALT), or Aspartate aminotransferase increased (AST), or Blood bilirubin increased	Grade 2	AE resolves to Grade 0-1	Permanently discontinue if AE does not resolve within 12 weeks of last dose
		Grade 3 or 4	Permanently discontinue	Permanently discontinue
Metabolism and nutrition disorders	Glucose intolerance (Type 1 diabetes mellitus [if new onset]) or Hyperglycemia	T1DM or Grade 3 or 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 subjects are clinically and metabolically stable	
Renal and urinary disorders	Acute kidney injury or Chronic kidney disease (e. g., Renal failure or Nephritis)	Grade 2	Withhold until AE resolves to Grade 0-1	Permanently discontinue if AE 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
		Grade 3 or 4	Permanently discontinue	Permanently discontinue

CTCAE System/Organ/Class (SOC)	Adverse Event	Hold Treatment for Grade	Timing for Restarting Treatment	Treatment Discontinuation
Respiratory, thoracic and mediastinal disorders	Pneumonitis	Grade 2	Withhold until AE resolves to Grade 0-1	Permanently discontinue if AE 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
		Grade 3 or 4, or recurrent Grade 2	Permanently discontinue	Permanently discontinue
	All Other Immune-Related Adverse Events	Intolerable or persistent Grade 2	Withhold at physician discretion until AE resolves to Grade 0-1	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
	All Other Immune-Related Adverse Events	Grade 3	Withhold or discontinue based on the type of event. Events that require discontinuation include and are not limited to: Guillain-Barre Syndrome, encephalitis	Permanently discontinue if AE 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.
		Grade 4 or recurrent Grade 3	Permanently discontinue	Permanently discontinue

8.22 Other instructions for pembrolizumab

If pembrolizumab-related adverse event does not resolve to Grade 0-1 within 12 weeks after last administration of study drug, study therapy discontinuation is recommended. With Investigator agreement, patients with a laboratory adverse event still at Grade 2 may continue in the study only if asymptomatic and controlled.

For patients who experience a recurrence of the same severe AEs listed above with rechallenge of pembrolizumab, a consultation with the Investigator will occur to determine whether the patient should continue in the study. A patient who

experiences the same SAE of the same NCI CTCAE grade or higher with rechallenge of pembrolizumab must discontinue pembrolizumab immediately.

Potential risks of adding pembrolizumab to TMZ and/or RT, include the possibility of increased radiation related toxicity, swelling in the brain and resulting neurological compromise that could lead to life threatening consequences and the risk of not being able to initiate or receive the full doses of RT and TMZ which have been shown to prolong survival in patients with newly diagnosed GBM. Although in an ongoing trial, this effect has not been seen as reported in Neuro-Oncology Nov 2016 (Abstract ATIM-10, Dixit et al.).

8.23 Treatment Modifications for Adverse Events during **Adjuvant** Treatment with pembrolizumab

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

CTCAE System/Organ/ Class (SOC)	Adverse Event	Hold Treatment for Grade	Timing for Restarting Treatment	Treatment Discontinuation
Cardiac disorders	Myocarditis	Grade 1	Withhold until AE resolves to Grade 0	Permanently discontinue if AE does not resolve within 12 weeks of last dose
		Grade 2, 3, or 4	Permanently discontinue	Permanently discontinue
Endocrine disorders	Endocrine disorders – Other, specify: Hypophysitis	Grade 2	Withhold	
		Grade 3 or 4	Withhold or permanently discontinue at investigator's discretion	Withhold or permanently discontinue at investigator's discretion
Endocrine disorders	Hyperthyroidism	Grade 3 or 4	Withhold or permanently discontinue at investigator's discretion	Withhold or permanently discontinue at investigator's discretion
Endocrine disorders	Hypothyroidism	Grade 2-4	Therapy with pembrolizumab can be continued while treatment for the thyroid disorder is instituted	Therapy with pembrolizumab can be continued while treatment for the thyroid disorder is instituted
Gastrointestinal disorders	Diarrhea or Colitis	Grade 2 or 3	Withhold until AE resolves to Grade 0-1	Permanently discontinue if AE 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

CTCAE System/Organ/ Class (SOC)	Adverse Event	Hold Treatment for Grade	Timing for Restarting Treatment	Treatment Discontinuation
		Grade 4	Permanently discontinue	Permanently discontinue
General disorders and administration site conditions	Infusion Reaction	Grade 2	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 See Section 9.9b for more details	Permanently discontinue if AE develops despite adequate premedication
		Grade 3 or 4	Permanently discontinue	Permanently discontinue
Investigations	Alanine aminotransferase (ALT) increased, or Aspartate aminotransferase (AST) increased or Blood bilirubin increased	Grade 2	Withhold until AE resolves to Grade 0-1	Permanently discontinue if AE does not resolve within 12 weeks of last dose
		Grade 3 or 4	Permanently discontinue	Permanently discontinue
Metabolism and nutrition disorders	Glucose intolerance (Type 1 diabetes mellitus [if new onset]) or Hyperglycemia	T1DM or Grade 3 or 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	
Renal and urinary disorders	Acute kidney injury or Chronic kidney disease (e.g. Renal Failure or Nephritis)	Grade 2	Withhold until AE resolves to Grade 0-1	Permanently discontinue if AE 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
		Grade 3 or 4	Permanently discontinue	Permanently discontinue

CTCAE System/Organ/ Class (SOC)	Adverse Event	Hold Treatment for Grade	Timing for Restarting Treatment	Treatment Discontinuation
Respiratory, thoracic and mediastinal disorders	Pneumonitis	Grade 2	Withhold until AE resolves to Grade 0-1	Permanently discontinue if AE 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
		Grade 3 or 4, or recurrent Grade 2	Permanently discontinue	Permanently discontinue
	All Other Immune-Related Adverse Events[C]	Intolerable/ persistent Grade 2	Withhold 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
		Grade 3	Withhold or discontinue based on the type of event Events that require discontinuation include and not limited to: Guillain-Barre Syndrome, encephalitis	Permanently discontinue if AE 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
		Grade 4 or recurrent Grade 3	Permanently discontinue	Permanently discontinue

8.3 Radiotherapy Dose Modifications

With the type and site of radiotherapy foreseen in this protocol, interruption due to acute radiation adverse events is unlikely. Individual reasons, such as major worsening of neurological or mental status or any other medical condition that would preclude the continuation of radiotherapy and conversely the decision to resume radiation therapy after interruption will be taken **on an individual basis** by the treating physician. For example, cranial irradiation can be withheld for CNS adverse events or toxicity ≥Grade 3 attributable to radiotherapy. The overall time of interruption and overall time of radiotherapy must be recorded. If radiotherapy is interrupted, actions regarding dosing on concomitant temozolomide are described below:

- If the administration of temozolomide is interrupted, the radiotherapy will proceed normally and no catch up days of temozolomide will be given after the end of radiotherapy.
- If the course of RT extends beyond 42 days because of delays, the course of temozolomide may be extended to a maximum of 49 days. If RT is still not completed, additional temozolomide beyond 49 days is not permitted.
- If radiotherapy definitely stopped for an adverse event felt clearly related to radiotherapy and not pembrolizumab/temozolomide, concomitant pembrolizumab/temozolomide should be continued per protocol unless PD occurs.

8.4 Suggested Temozolomide Dose Modifications

Once a dose has been reduced, it should not be subsequently increased.
NOTE: When switching from TMZ during RT to TMZ after RT, at that point (at the discretion of the treating physician) one can start with 150 or 200 mg/m^2/day if there was a dose reduction for TMZ during RT.

Patients with unresolved TMZ-related adverse event after 2 weeks should have TMZ dose reduction and/or discontinuation per Tables 8.41 and 8.42. If it is the treating physician's opinion that the patient may benefit from continued treatment the patient may continue on study (even if TMZ is discontinued and the treating physician believes it is safe and reasonable to continue on study with pembrolizumab and radiation). Patients may have a second dose reduction of TMZ for adverse event; however, patients requiring a third dose reduction should have TMZ permanently discontinued unless, in the opinion of the treating physician, there is reason to believe the patient may benefit from continued treatment. The decision to proceed with treatment should be made in consultation with the Principal Investigator, [redacted]

See Tables 8.41 and 8.42 for suggested temozolomide dose modifications during and after RT.

8.41 Suggested Temozolomide (TMZ) Dose Modifications during treatment with RT

CTCAE System/Organ/Category (SOC)	Adverse Event	Agent	Action
Gastrointestinal	Nausea or vomiting (while on optimal antiemetic treatment) Grade 3	TMZ	Reduce TMZ dose by 25% If not successful reduce dose by 50% Discontinue TMZ if still Grade 3 after second dose reduction

CTCAE System/Organ/Category (SOC)	Adverse Event	Agent	Action
Investigations	Aspartate aminotransferase increased or Alkaline phosphatase increased or Blood bilirubin increased Grade 3	TMZ	Reduce TMZ dose by 50%
	Grade 4		Discontinue TMZ
	Neutrophil count decreased Grade 2 ANC <1500 1000/mm^3 OR Platelet count decreased PLT <75,000-50,000/mm^3		Reduce TMZ dose by 25% and check CBC weekly
	Neutrophil count decreased Grade 3 ANC <1000 -500/mm^3 OR Platelet count decreased PLT <50,000-25,000/mm^3		Hold TMZ and check CBC weekly When ANC >1500 and PLTS >100,000, resume TMZ at 25% reduction from most recent dose If more than 2 dose reductions required, discontinue TMZ

8.42 Suggested Adjuvant Temozolomide (TMZ) Dose Modifications (after RT)

CTCAE System/Organ/Category (SOC)	Adverse Event	Agent	Action
Investigations	Interval: Neutrophil count decreased ANC <1000/mm^3 OR Platelet count decreased PLT <75,000/mm^3	TMZ	If ANC 500 to 1000 or PLT 50,000 to 75,000, reduce TMZ dose by 25% next cycle If ANC <500 or PLT <50,000, reduce TMZ dose by 50% next cycle
	At time of TMZ treatment Neutrophil count decreased ANC <1500/mm^3 OR Platelet count decreased PLT <75,000/mm^3	TMZ	Hold TMZ and check CBC weekly When ANC ≥1500 and PLT >100,000 begin TMZ based on interval results

9.0 Ancillary Treatment/Supportive Care

9.1 Full supportive care

Patients should receive full supportive care while on this study. This includes blood product support, antibiotic treatment, and treatment of other newly diagnosed or concurrent medical conditions. All blood products and concomitant medications such as antidiarrheals, analgesics, and/or antiemetics received from the first day of study treatment administration until 30 days after the final dose will be recorded in the medical records.

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 8.0 for dose modification.

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

9.2 Immunotherapy-related toxicities

9.21 General Instructions for immune-related adverse events (iRAEs) associated with pembrolizumab:

1. Corticosteroid taper should be initiated upon AE improving to Grade 1 or less and continue to taper over at least 4 weeks.
2. For situations where pembrolizumab has been withheld, pembrolizumab can be resumed after AE has been reduced to Grade 1 or 0 and corticosteroid has been tapered. Pembrolizumab should be permanently discontinued if AE does not resolve within 12 weeks of last dose or corticosteroids cannot be reduced to ≤10 mg prednisone or equivalent per day within 12 weeks.
3. For severe and life-threatening irAEs, IV corticosteroid should be initiated first followed by oral steroid. Other immunosuppressive treatment should be initiated if irAEs cannot be controlled by corticosteroids.

9.22 Patients should be monitored for signs and symptoms of immunotherapy-related toxicities, which include but are not limited to the following:

- **Pneumonitis**

  Monitor participants for signs and symptoms of pneumonitis
  - Evaluate participants with suspected pneumonitis with radiographic imaging and initiate corticosteroid treatment
  - Administer corticosteroids (initial dose of 1-2 mg/kg prednisone or equivalent) followed by taper
  - Add prophylactic antibiotics for opportunistic infections in the case of prolonged steroid administration.

- **Diarrhea/colitis**

  Patients 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 patients 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, 3 or 4 diarrhea/colitis, administer corticosteroids (initial dose of 1-2 mg/kg prednisone or equivalent) followed by taper.

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

  Monitor participants for hyperglycemia or other signs and symptoms of diabetes.

  For **T1DM** or **Grade 3-4** Hyperglycemia:
  - Initiate insulin replacement therapy for Type I diabetes mellitus
  - Administer anti-hyperglycemic in participants with hyperglycemia

- **Hypophysitis**
  Monitor for signs and symptoms of hypophysitis (including hypopituitarism and adrenal insufficiency)Administer corticosteroids and initate hormonal replacements as clinically indicated.

- **Hyperthyroidism or hypothyroidism**
  Monitor patients for signs and symptoms of thyroid disorders.
  - In hyperthyroidism, treat with non-selective beta-blockers (e.g., propranolol) or thionamides as appropriate.
  - In hypothyroidism, initiate thyroid replacement hormones (e.g., levothyroxine or liothyroinine) per standard of care.

- **Hepatic**
  Monitor with liver function tests (consider weekly or more frequently until liver enzyme value returned to baseline or is stable
  - For **Grade 2** events, administer corticosteroids (initial dose of 0.5- 1 mg/kg prednisone or equivalent) followed by taper
  - For **Grade 3-4** events, administer corticosteroids(initial dose of 1-2 mg/kg prednisone or equivalent) followed by taper .

- **Renal failure or nephritis**
  Monitor changes of renal function
  - Administer corticosteroids (prednisone 1-2 mg/kg or equivalent) followed by taper

- **Myocarditis**
  Ensure adequate evaluation to confirm etiology and/or exclude other causes
  - Based on severity of AE administer corticosteroids

9.3 Blood products and growth factors

Blood products and growth factors should be utilized as clinically warranted and following institutional policies and recommendations. The use of growth factors should follow published guidelines of the Journal of Clinical Oncology, Vol 33, No 28 (October 1), 2015: pp. 3199-3212 AND Journal of Clinical Oncology, Volume 28, No 33 (November 20), 2010: pp. 4955-5010 (darbepoetin/epoetin).

9.31 Neutropenia

Prophylactic use of colony-stimulating factors including Granulocyte Colony-Stimulating Factor (G-CSF), pegylated G-CSF or Granulocyte Macrophage Colony-Stimulating Factor GM-CSF is not allowed in this study. Therapeutic use of G-CSF is allowed in patients with Grade 3-4 febrile neutropenia.

9.32 Anemia

Transfusions and/or erythropoietin may be utilized as clinically indicated for the treatment of anemia, but should be clearly noted as concurrent medications.

9.33 Thrombocytopenia

Transfusion of platelets may be used if clinically indicated. ITP should be ruled out before initiation of platelet transfusion.

9.4 Anti-infectives

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

9.5 Cerebral Edema Management

Patients requiring chronic steroid administration (excluding inhaled steroids) for conditions other than their glioblastoma are excluded from the trial. Patients may continue on inhalation therapy. Corticosteroids are known immunosuppressive agents that can mitigate the effects of pembrolizumab. However, corticosteroids are required at times to treat symptomatic cerebral edema in glioblastoma patients. This requirement will be particularly true in the perioperative (neoadjuvant) period of this study. All patients in this study will undergo or have undergone craniotomy and resection of their tumor, which should result in decrease or elimination of corticosteroid requirements. Dexamethasone should be administered for symptomatic cerebral edema as clinically indicated, but should be tapered off or to the lowest possible dose that controls symptoms as soon as is practical. Otherwise, corticosteroids should be generally reserved to treat side effects of pembrolizumab. Steroids can be used as primary prevention of nausea per institutional guidelines, but steroid doses should be reduced in subsequent cycles if nausea/vomiting is absent or very mild (see Section 9.6).

Consider a short course of bevacizumab per standard treatment guidelines for cerebral edema if needed.

9.6 Antiemetics

Antiemetics may be used at the discretion of the attending physician. Nausea and vomiting should be treated aggressively, and consideration should be given to the administration of prophylactic antiemetic therapy according to standard institutional practice. Patients should be strongly encouraged to maintain liberal oral fluid intake. Volume depletion should be corrected before initiation of study drug.

9.7 Anti-diarrheals

Patients should be monitored for signs and symptoms of enterocolitis (such as diarrhea, abdominal pain, blood or mucus in stool, with or without fever) and of bowel perforation (such as peritoneal signs and ileus). In symptomatic patients, infectious etiologies should be ruled out, and if symptoms are persistent and/or severe, endoscopic evaluation should be considered. (See Section 9.7 for management of treatment-related enterocolitis)

All patients who experience diarrhea should be advised to drink liberal quantities of clear fluids. If sufficient oral fluid intake is not feasible, fluid and electrolytes should be substituted via IV infusion.

NOTE: Loperamide/diphenoxylate/atropines should NOT be used for diarrhea symptoms unless: (1) it is believed that pembrolizumab-related enterocolitis is unlikely to be present after detailed evaluation by gastroenterology, including endoscopy; PLUS (2) approval is documented by a gastroenterology specialist.

9.8 Management of treatment related enterocolitis

In patients with severe enterocolitis, MK-3475 will be held and treatment with systemic corticosteroids should be initiated at a dose of 1 to 2 mg/kg/day of prednisone or equivalent. When symptoms improve to Grade 1 or less, corticosteroid taper should be started and continued over at least 1 month.

In patients with moderate enterocolitis, MK-3475 should be withheld and antidiarrheal treatment should be started. If symptoms are persistent for more than one week, systemic corticosteroids should be initiated (e.g., 0.5 mg/kg/day of prednisone or equivalent). When symptoms improve to Grade 1 or less, corticosteroid taper should be started and continued over at least 1 month.

9.9a 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 any medication or vaccination specifically prohibited during the trial, discontinuation from trial therapy or vaccination may be required. The final decision on any supportive therapy or vaccination rests with the investigator and/or the patient's primary physician.

9.9a1 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 in the case report forms (CRF) including all prescription, over-the-counter (OTC), herbal supplements, and IV medications and fluids. If changes occur during the trial period, documentation of drug dosage, frequency, route, and date may also be included on the CRF.

All concomitant medications received within 28 days before the first dose of trial treatment and 30 days after the last dose of trial treatment should be recorded. Concomitant medications administered 30 days after the last dose of trial treatment should be recorded for SAEs and ECIs as defined in Section 10 and Appendix VI.

9.9a2 Prohibited Concomitant Medications

Participants are prohibited from receiving the following therapies during the screening and treatment phase (including retreatment for post-complete response relapse) of this trial:

- Anti-neoplastic systemic chemotherapy or biological therapy
  NOTE: With exception of short course of bevacizumab for management of cerebral edema for this protocol only
- Immunotherapy not specified in this protocol
- Chemotherapy not specified in this protocol
- Investigational agents other than pembrolizumab
- Live vaccines within 30 days prior to the first dose of trial treatment and while participating in the trial. Examples of live vaccines include, but are not limited to, the following: measles, mumps, rubella, varicella/zoster, yellow fever, rabies, BCG, and typhoid vaccine. Seasonal influenza vaccines for injection are generally killd virus vaccines and are allowed however intranasal influenza vaccines (e.g., FluMist®) are live attenuated vaccines and are not allowed.
- Systemic glucocorticoids for any purpose other than to reduce cerebral edema or 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 principal investigator.

Patients 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. All treatments that the investigator considers necessary for a participant's welfare may be administered at the discretion of the Investigator in keeping with the community standards of medical care..

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

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

9.9b Infusion Reaction

Table 9.9b Infusion Reaction Treatment Guidelines

NCI CTCAE Grade	Treatment	Premedication at subsequent dosing
Grade 1 Mild reaction; infusion interruption not indicated; intervention not indicated	Increase monitoring of vital signs as medically indicated until the participant is deemed medically stable in the opinion of the investigator.	None
Grade 2 Requires infusion interruption but responds promptly to symptomatic treatment (e.g., antihistamines, NSAIDS, narcotics, IV fluids); prophylactic medications indicated for ≤24 hrs	**Stop Infusion** Additional appropriate medical therapy may include but is not limited to: IV fluids Antihistamines NSAIDS Acetaminophen Narcotics Increase monitoring of vital signs as medically indicated until the participatn is deemed medically stable in the opinion of the investigator. If symptoms resolve within one hour of stopping treatment infusion, the infusion may be restarted at 50% of the original infusion rate (e.g., from 100 mL/hr to 50 mL/hr). Otherwise dosing will be held until symptoms resolve and the participant should be premedicated for the next scheduled dose. **Patients who develop Grade 2 toxicity despite adequate premedication should be permanently discontinued from further study drug treatment.**	Participant 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 analgesic).
Grades 3 or 4 Grade 3: Prolonged (i.e., not rapidly responsive to symptomatic medication and/or brief interruption of infusion); recurrence of symptoms following initial improvement; hospitalization indicated for other clinical sequelae (e.g., renal impairment, pulmonary infiltrates)	**Stop Infusion** Additional appropriate medical therapy may include but is not limited to: Epinephrine** IV fluids Antihistamines NSAIDS Acetaminophen Narcotics	No subsequent dosing

NCI CTCAE Grade	Treatment	Premedication at subsequent dosing
Grade 4: Life-threatening; pressor or ventilatory support indicated	Oxygen Pressors Corticosteroids Increase monitoring of vital signs as medically indicated until the participant is deemed medically stable in the opinion of the investigator. Hospitalization may be indicated. **In cases of anaphylaxis, epinephrine should be used immediately. **Participant is permanently discontinued from further study drug treatment**	

Appropriate resuscitation equipment should be available in the room and a physician readily available during the period of study treatment administration.

9.9c 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 patients 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 patients 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 female patients <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 female patients 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) have a congenital or acquired condition that prevents childbearing.

All patients of reproductive potential must agree to avoid becoming pregnant or impregnating a partner, as applicable, 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 participant'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 female participants only)
- contraceptive sponge (nulliparous female participants 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 patients participating at sites in this country/region.

Patients 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, patients 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 patient of childbearing potential will not reliably comply with the requirements for contraception, that patient should not be entered into the study.

9.9d Use in Pregnancy

If a patient inadvertently becomes pregnant while on treatment with pembrolizumab, the patient will immediately be removed from the study. The site will contact the patient at least monthly and document the patient's status until the pregnancy has been completed or terminated. The outcome of the pregnancy will be reported to Mayo Clinic and to Merck without delay and within 24 hours to Mayo Clinic 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. If a male subject impregnates his female partner the study personnel at the site must be informed immediately and the pregnancy reported to Mayo Clinic and to Merck and followed as described above.

9.9e Use in Nursing Patients

Since many drugs are excreted in human milk, and because of the potential for serious adverse reactions in the nursing infant, patients who are breast-feeding are not eligible for enrollment. Specific additional information follows for individual agents used in this trial.

9.9d1 Pembrolizumab

It is unknown whether pembrolizumab is excreted in human milk.

9.9d2 Temozolomide

It is unknown whether temozolomide is excreted in human milk.

9.9f Pneumocystis jirovecii pneumonia [PJP (PCP)] prophylaxis

Since low dose temozolomide is immunosuppressive and associated with an increased risk of PJP, all subjects must receive prophylaxis during RT with concomitant temozolomide and radiation therapy. Prophylaxis must be continued for at least two weeks after the completion of RT. The choice of prophylactic medications will be left to the discretion of the treating physician. Options include atovaquone and dapsone. Because, based on NABTC experience, trimethoprim-sulfamethoxazole appears to contribute to myelosuppression in patients on chemotherapy, this agent is not preferred. It may be used in patients who cannot tolerate other options listed above, although the final decision will be left to the discretion of the treating physician. The decision to continue PJP prophylaxis beyond the time points noted is left to the discretion of the treating physician. Subjects who continue to demonstrate lymphopenia after the continuous daily dosing of TMZ has been discontinued should be considered for ongoing prophylaxis.

10.0 Adverse Event (AE) Reporting and Monitoring

The site principal investigator is responsible for reporting any/all serious adverse events to the sponsor as described within the protocol, regardless of attribution to study agent or treatment procedure.

The sponsor/sponsor-investigator is responsible for notifying FDA and all participating investigators in a written safety report of any of the following:

- Any suspected adverse reaction that is both serious and unexpected.
- Any findings from laboratory animal or *in vitro* testing that suggest a significant risk for human subjects, including reports of mutagenicity, teratogenicity, or carcinogenicity.
- Any findings from epidemiological studies, pooled analysis of multiple studies, or clinical studies, whether or not conducted under an IND and whether or not conducted by the sponsor, that suggest a significant risk in humans exposed to the drug
- Any clinically important increase in the rate of a serious suspected adverse reaction over the rate stated in the protocol or Investigator's Brochure (IB).

Summary of SAE Reporting for this study
(please read entire section for specific instructions):

WHO:	WHAT form:	WHERE to send:
All sites	Pregnancy Reporting [redacted]	Mayo Sites – attach to MCCC Electronic SAE Reporting Form [redacted] Will automatically be sent to [redacted]
Mayo Clinic Sites	Mayo Clinic Cancer Center SAE Reporting Form: [redacted] AND attach MedWatch 3500A: [redacted]	Will automatically be sent to [redacted]

Definitions

Adverse Event
Any untoward medical occurrence associated with the use of a drug in humans, whether or not considered drug related.

Suspected Adverse Reaction
Any adverse event for which there is a reasonable possibility that the drug caused the adverse event.

Expedited Reporting
Events reported to sponsor within 24 hours, 5 days or 10 days of study team becoming aware of the event.

Routine Reporting
Events reported to sponsor via case report forms

Events of Interest
Events that would not typically be considered to meet the criteria for expedited reporting, but that for a specific protocol are being reported via expedited means in order to facilitate the review of safety data (may be requested by the FDA or the sponsor).

10.1 Adverse Event Characteristics

CTCAE term (AE description) and grade: The descriptions and grading scales found in the revised NCI Common Terminology Criteria for Adverse Events (CTCAE) version 4.0 will be utilized for AE reporting. All appropriate treatment areas should have access to a copy of the CTCAE version 4.0. A copy of the CTCAE version 4.0 can be downloaded from the CTEP web:

[redacted]

10.11 Adverse event monitoring and reporting is a routine part of every clinical trial. First, identify and grade the severity of the event using the CTCAE version 4.0. Next, determine whether the event is expected or unexpected (see Section 10.2) and if the adverse event is related to the medical treatment or procedure (see Section 10.3). With this information, determine whether the event must be reported as an expedited report (see Section 10.4). Expedited reports are to be completed within the timeframes and via the mechanisms specified in Sections 10.4. All AEs reported via expedited mechanisms must also be reported via the routine data reporting mechanisms defined by the protocol (see Sections 10.52 and 18.0).

10.12 Each CTCAE term in the current version is a unique representation of a specific event used for medical documentation and scientific analysis and is a single MedDRA Lowest Level Term (LLT).

NOTE: A severe AE, as defined by the above grading scale, is **NOT** the same as serious AE, which is defined in the table in Section 10.4.

10.2 Expected vs. Unexpected Events

Expected events - are those described within the Section 15.0 of the protocol, the study specific consent form, package insert (if applicable), and/or the investigator brochure, (if an investigator brochure is not required, otherwise described in the general investigational plan).

Unexpected adverse events or suspected adverse reactions are those not listed in Section 15.0 of the protocol, the study specific consent form, package insert (if applicable), or in the investigator brochure (or are not listed at the specificity or severity that has been observed); if an investigator brochure is not required or available, is not consistent with the risk information described in the general investigational plan.

Unexpected also refers to adverse events or suspected adverse reactions that are mentioned in the investigator brochure as occurring with a class of drugs but have not been observed with the drug under investigation.

An investigational agent/intervention might exacerbate the expected AEs associated with a commercial agent. Therefore, if an expected AE (for the commercial agent) occurs with a higher degree of severity or specificity, expedited reporting is required.

NOTE: *The consent form may contain study specific information at the discretion of the Principal Investigator; it is possible that this information may NOT be included in the protocol or the investigator brochure. Refer to protocol or IB for reporting needs.

10.3 Assessment of Attribution

When assessing whether an adverse event is related to a medical treatment or procedure, the following attribution categories are utilized:
Definite - The adverse event *is clearly related* to the agent(s).
Probable - The adverse event *is likely related* to the agent(s).
Possible - The adverse event *may be related* to the agent(s).
Unlikely - The adverse event *is doubtfully related* to the agent(s).
Unrelated - The adverse event *is clearly NOT related* to the agent(s).

Events determined to be possibly, probably or definitely attributed to a medical treatment suggest there is evidence to indicate a causal relationship between the drug and the adverse event.

10.31 AEs Experienced Utilizing Investigational Agents and Commercial Agent(s) on the SAME Arm

NOTE: The combination of an investigational agent with a commercial agent is considered investigational.

Routine Reporting

- Routine AE reporting for Phase 1 and Phase 2 clinical studies using an investigational agent /intervention in combination with a commercial agent is stated in the protocol. See Section 10.52.

NOTE: When a commercial agent(s) is (are) used on the same treatment arm as the investigational agent/intervention (also, investigational drug, biologic, cellular product, or other investigational therapy under an IND), the entire combination (arm) is then considered an investigational intervention for reporting.

Expedited Reporting

- An AE that occurs on a combination study must be assessed in accordance with the guidelines for CTEP investigational agents/interventions in Section 10.4, and where indicated, an expedited report must be submitted.
- An AE that occurs prior to administration of the investigational agent/intervention must be assessed as specified in the protocol. In general, only Grade 4 and 5 AEs that are unexpected with at least possible attribution to the commercial agent require an expedited report. Refer to Section 10.4 for specific AE reporting requirements or exceptions.
- Commercial agent expedited reports must be submitted to the FDA via MedWatch.
- An investigational agent/intervention might exacerbate the expected AEs associated with a commercial agent. Therefore, if an expected AE (for the commercial agent) occurs with a higher degree of severity, expedited reporting is required. The clinical investigator must determine severity.

10.32 Special Situations for Expedited Reporting and Submission of Notification Forms

Exceptions to Expedited Reporting and Submission of Notification Forms: EXPECTED Serious Adverse Events[1]

For this protocol only, the following Adverse Events/Grades are expected to occur within this population and do not require Expedited Reporting. These events must still be reported via Routine Reporting (see Section 10.6).*
*Report any clinically important increase in the rate of a serious suspected adverse reaction (at your study site) over that which is listed in the protocol or investigator brochure as an expedited event.
*Report an expected event that is greater in severity or specificity than expected as an expedited event.
*Specific protocol exceptions to expedited reporting should be reported expeditiously by investigators **ONLY** if they exceed the expected grade of the event.

System Organ Class (SOC)	Adverse event/ Symptoms	CTCAE Grade at which the event will not be expeditedly reported[1]
General disorders and administrations site conditions	Fatigue	Grade 3
Gastrointestinal	Vomiting	Grade 3
	Nausea	Grade 3
	Diarrhea	Grade 3
Investigations	Neutrophil count decreased	Grade 3 or 4
	White blood cell count decreased	Grade 3 or 4
	Lymphocyte count decreased	Grade 3 or 4
	Platelet count decreased	Grade 3 or 4
Blood and lymphatic system disorders	Anemia	Grade 3 or 4

[1]These exceptions only apply if the adverse event does not result in hospitalization. If the adverse event results in hospitalization, then the standard expedited adverse events reporting requirements must be followed.
NOTE: Hospitalization related to convenience (e.g. transportation issues etc.) will *not* be considered an SAE for purposes of reporting to Merck.

NOTE: The consent form may contain study specific information at the discretion of the Principal Investigator; it is possible that this information may NOT be included in the protocol or the investigator brochure.

Efficacy endpoints as outlined in this section will not be reported 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 (Mayo Clinic) 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.

The following hospitalizations are not considered to be SAEs because there is no "adverse event" (*i.e.*, there is no untoward medical occurrence) associated with the hospitalization:

- Hospitalizations for respite care
- Planned hospitalizations required by the protocol
- Hospitalization planned before informed consent (where the condition requiring the hospitalization has not changed post study drug administration)
- Hospitalization for elective procedures unrelated to the current disease and/or treatment on this trial
- Hospitalization for administration of study drug or insertion of access for administration of study drug
- Hospitalization for routine maintenance of a device (*e.g.*, battery replacement) that was in place before study entry
- Hospitalization, or other serious outcomes for signs and symptoms of progression of the cancer.

10.321 Persistent or Significant Disabilities/Incapacities

Any AE that results in persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions (formerly referred to as disabilities), congenital abnormities or birth defects, must be reported immediately if they occur at any time following treatment with an agent under an IND/IDE since they are considered to be a serious AE and must be reported to the sponsor as specified in 21 CFR 312.64(b).

10.322 Death

- Any death occurring within 30 days of the last dose, regardless of attribution to an agent/intervention under an IND/IDE requires expedited reporting within 24-hours.
- Any death occurring greater than 30 days with an attribution of possible, probable, or definite to an agent/intervention under an IND/IDE requires expedited reporting within 24-hours.

Reportable categories of Death

- Death attributable to a CTCAE term.
- Death Neonatal: A disorder characterized by cessation of life during the first 28 days of life.
- Death NOS: A cessation of life that cannot be attributed to a CTCAE term associated with Grade 5.
- Sudden death NOS: A sudden (defined as instant or within one hour of the onset of symptoms) or an unobserved cessation of life that cannot be attributed to a CTCAE term associated with Grade 5.
- Death due to progressive disease should be reported as **Grade 5 "Neoplasms benign, malignant and unspecified (including cysts and polyps) – Other (Progressive Disease)"** under the system organ class (SOC) of the same name. Evidence that the death was a manifestation of underlying disease (e.g.,

radiological changes suggesting tumor growth or progression: clinical deterioration associated with a disease process) should be submitted.

- Any death occurring **within 30 days** of the last dose, regardless of attribution to the investigational agent/intervention requires expedited reporting within 24 hours.
- Any death occurring **greater than 30 days** after the last dose of the investigational agent/intervention requires expedited reporting within 24 hours **only if** it is possibly, probably, or definitely related to the investigational agent/intervention.

10.323 Secondary Malignancy

- A ***secondary malignancy*** is a cancer caused by treatment for a previous malignancy (e.g., treatment with investigational agent/intervention, radiation or chemotherapy). A secondary malignancy is not considered a metastasis of the initial neoplasm.
- All secondary malignancies that occur following treatment with an agent under an IND/IDE must be reported. Three options are available to describe the event:
  - Leukemia secondary to oncology chemotherapy (e.g., Acute Myeloctyic Leukemia [AML])
  - Myelodysplastic syndrome (MDS)
  - Treatment-related secondary malignancy
- Any malignancy possibly related to cancer treatment (including AML/MDS) should also be reported via the routine reporting mechanisms outlined in each protocol.

10.324 Second Malignancy

A second malignancy is one unrelated to the treatment of a prior malignancy (and is NOT a metastasis from the initial malignancy). Second malignancies require ONLY routine reporting.

10.4 Expedited Reporting Requirements for IND/IDE Agents

10.41 Phase 1 and Early Phase 2 Studies: Expedited Reporting Requirements for Adverse Events that Occur on Studies under an IND/IDE within 30 Days of the Last Administration of the Investigational Agent/Intervention[1, 2]

FDA REPORTING REQUIREMENTS FOR SERIOUS ADVERSE EVENTS (21 CFR Part 312)
NOTE: Investigators **MUST** immediately report to the sponsor **ANY** Serious Adverse Events, whether or not they are considered related to the investigational agent(s)/intervention (21 CFR 312.64)
An adverse event is considered serious if it results in **ANY** of the following outcomes:

1) Death
2) A life-threatening adverse event
3) An adverse event that results in inpatient hospitalization or prolongation of existing hospitalization for ≥24 hours
4) A persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions
5) A congenital anomaly/birth defect.
6) Important Medical Events (IME) that may not result in death, be life threatening, or require hospitalization may be considered serious when, based upon medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. (FDA, 21 CFR 312.32; ICH E2A and ICH E6).

ALL SERIOUS adverse events that meet the above criteria **MUST** be immediately reported within the timeframes detailed in the table below.

Hospitalization	Grade 1 Timeframes	Grade 2 Timeframes	Grade 3 Timeframes	Grade 4 & 5 Timeframes
Resulting in Hospitalization ≥24 hrs	7 Calendar Days			24-Hour 3 Calendar Days
Not resulting in Hospitalization ≥24 hrs	Not required		7 Calendar Days	

Expedited AE reporting timelines are defined as:

- "24-Hour; 3 Calendar Days" - The AE must initially be reported within 24 hours of learning of the AE, followed by a complete expedited report within 3 calendar days of the initial 24-hour report.
- "7 Calendar Days" - A complete expedited report on the AE must be submitted within 7 calendar days of learning of the AE.

[1]Serious adverse events that occur more than 30 days after the last administration of investigational agent/intervention and have an attribution of possible, probable, or definite require reporting as follows:

Expedited 24-hour notification followed by complete report within 3 calendar days for:

- All Grade 4, and Grade 5 AEs

Expedited 7 calendar day reports for:

- Grade 2 adverse events resulting in hospitalization or prolongation of hospitalization
- Grade 3 adverse events

[2] For studies using PET or SPECT IND agents, the AE reporting period is limited to 10 radioactive half-lives, rounded UP to the nearest whole day, after the agent/intervention was last administered. Footnote "1" above applies after this reporting period.

Effective Date: May 5, 2011

NOTE: Protocol specific exceptions to expedited reporting of serious adverse events are found in Section 10.32 of the protocol.

NOTE: Hospitalization related to convenience (e.g.transportation issues etc.) will not be considered an SAE for purposes of reporting to Merck.

10.42 Additional instructions:

Mayo Clinic Cancer Center (MCCC) Institutions:
Complete online form at
[redacted]

AND attach MedWatch 3500A:
[redacted]

System will automatically email MCCC Regulatory Affairs Unit (RAU) Risk Information Specialist [redacted] who will determine and complete IRB reporting. The RAU will submit to the MCCC SAE Coordinator and the MCCC IND Coordinator to determine if FDA submission is needed.

10.5 Other Required Reporting

10.51 Adverse events to be graded at each evaluation and pretreatment symptoms/conditions to be evaluated at baseline

(Per CTCAE v4.0 grading unless otherwise stated in the table below):

CTCAE SYSTEM/ORGAN/CLASS	Adverse event/Symptoms	Baseline	Each evaluation
Investigations	Creatinine increased	X	X
	Neutrophil count decreased	X	X
	Platelet count decreased	X	X
General disorders and administration site conditions	Fatigue	X	X
Gastrointestinal Disorders	Nausea	X	X
	Vomiting	X	X
	# of Stools	X	
	Diarrhea		X
	Constipation		X
Infections and infestations	Sepsis	X	X
Blood and lymphatic system disorders	Febrile neutropenia	X	X
Skin and subcutaneous tissue disorders	Rash, maculo-papular	X	X
Nervous system disorders	Ataxia	X	X
	Cognitive disturbance	X	X
	Dysarthria	X	X
	Dysphasia	X	X
	Edema, cerebral	X	X
	Facial muscle weakness	X	X
	Headache	X	X
	Pyramidal tract syndrome	X	X
	Seizure	X	X
Nervous system disorders	Central nervous system disorders – Other, specify: Hemisensory loss and/or Visual field cut	X	X

10.52 Additional Considerations for this study

10.521 Neoadjuvant Only

Surgical outcomes will be recorded in the CRFs to ensure that there is no increase in incidence due to neoadjuvant pembrolizumab.

The following items will be collected:

- Neurological Outcome
    - Improved
    - Stable
    - Worse
        - Temporary
        - Permanent (> 6 weeks)
        - New neurological symptoms
            - Seizures
            - Visual field cut
            - Facial droop
            - Hemiparesis
            - Hemisensory loss
            - Ataxia
            - Dysphasia
            - Dysarthria

- Cognitive impairment
- Other

- Regional Complications
  - Pseudomeningocele
  - CSF leak
  - Wound dehiscence
  - Superficial wound infection
  - Deep wound infection
  - Epidural hematoma
  - Subdural hematoma
  - Intraparenchymal hematoma
  - Other
- Systemic complications
  - Deep venous thrombosis
  - Pulmonary embolism
  - Urinary tract infection
  - Pneumonia
  - Myocardial infarction
  - Other

10.53 Submit via appropriate MCCC Case Report Forms (i.e., paper or electronic, as applicable) the following AEs experienced by a patient and not specified in Section 10.51:

10.531 Grade 2 AEs deemed *possibly, probably, or definitely* related to the study treatment or procedure.

10.532 Grade 3 and 4 AEs regardless of attribution to the study treatment or procedure.

10.533 Grade 5 AEs (Deaths)

10.5331 Any death within 30 days of the patient's last study treatment or procedure regardless of attribution to the study treatment or procedure.

10.5332 Any death more than 30 days after the patient's last study treatment or procedure that is felt to be at least possibly treatment related must also be submitted as a Grade 5 AE, with a CTCAE type and attribution assigned.

10.54 Pregnancy, Fetal Death, and Death Neonatal

If a female subject (or female partner of a male subject) taking investigational product becomes pregnant, the subject taking should notify the Investigator, and the pregnant female should be advised to call her healthcare provider immediately. The patient should have appropriate follow-up as deemed necessary by her physician. If the baby is born with a birth defect or anomaly, a second expedited report is required.

Prior to obtaining private information about a pregnant woman and her infant, the investigator must obtain consent from the pregnant woman and the newborn infant's parent or legal guardian before any data collection can occur. A consent form will need to be submitted to the IRB for these subjects if a pregnancy occurs. If informed consent is not obtained, no information may be collected.

In cases of fetal death, miscarriage or abortion, the mother is the patient. In cases where the child/fetus experiences a serious adverse event other than fetal death, the child/fetus is the patient.

NOTE: When submitting Mayo Expedited Adverse Event Report reports for "Pregnancy", "Pregnancy loss", or "Neonatal loss", the potential risk of exposure of the fetus to the investigational agent(s) or chemotherapy agent(s) should be documented in the "Description of Event" section. Include any available medical documentation. Include this form:

[redacted]

10.541 Pregnancy

Pregnancy should be reported in an expedited manner as **Grade 3 "Pregnancy, puerperium and perinatal conditions - Other (pregnancy)"** under the Pregnancy, puerperium and perinatal conditions SOC. Pregnancy should be followed until the outcome is known.

10.542 Fetal Death

Fetal death is defined in CTCAE as "A disorder characterized by death in utero; failure of the product of conception to show evidence of respiration, heartbeat, or definite movement of a voluntary muscle after expulsion from the uterus, without possibility of resuscitation."

Any fetal death should be reported expeditiously, as **Grade 4 "Pregnancy, puerperium and perinatal conditions - Other (pregnancy loss)"** under the Pregnancy, puerperium and perinatal conditions SOC.

10.543 Death Neonatal

Neonatal death, defined in CTCAE as "A disorder characterized by cessation of life occurring during the first 28 days of life" that is felt by the investigator to be at least possibly due to the investigational agent/intervention, should be reported expeditiously.

A neonatal death should be reported expeditiously as **Grade 4 "General disorders and administration - Other (neonatal loss)"** under the General disorders and administration SOC.

10.55 Events of Clinical Interest (ECIs)

ECIs are selected non-serious and serious adverse experiences that must be reported (as described in Section 10.42) within 24 hours to Mayo Clinic via email [redacted] and within 2 working days to Merck Global Safety [redacted]

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

For the time period beginning at treatment allocation/randomization through 90 days following cessation of treatment, or 30 days following cessation of

treatment if the subject initiates new anticancer therapy, whichever is earlier, any ECI, or follow up to an ECI, whether or not related to Merck product, must be reported within 24 hours to the Sponsor and within 24 hours to Merck Global Safety.

Events of clinical interest for this trial include:

1. A new cancer (that is not a condition of the study)

2. An overdose of Merck product, as defined in Section 10.61, that is not associated with clinical symptoms or abnormal laboratory results.

3. 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.

10.56 Late occurring AEs

Refer to the instructions in the Forms Packet (or electronic data entry screens, as applicable) regarding the submission of late occurring AEs following completion of the Active Monitoring Phase (i.e., compliance with Test Schedule in Section 4.0).

10.57 Procedures for Reporting Drug Exposure during Pregnancy and Birth Events

If a woman becomes pregnant or suspects that she is pregnant while participating in this study, she must inform the investigator immediately and permanently discontinue study drug. The sponsor-investigator must fax a completed Pregnancy Form to Regulatory Affairs Unit per instructions below. The pregnancy must be followed for the final pregnancy outcome.

If a female partner of a male patient becomes pregnant during the male patient's participation in this study, the sponsor-investigator must also immediately fax a completed Pregnancy Form to the Regulatory Affairs Unit per instructions below. Every effort should be made to follow the pregnancy for the final pregnancy outcome.

Suggested Pregnancy Reporting Form:

Use form available from the CTEP protocol development page:

[redacted]

Mayo Clinic Cancer Center (MCCC) Institutions: Provide copies using Mayo Cancer Center automated system

[redacted] which will automatically be routed to the MCCC Regulatory Affairs Unit (RAU) Risk Information Specialist who will determine and complete IRB reporting. The RAU will submit to the MCCC SAE Coordinator and the MCCC IND Coordinator to determine if FDA submission is needed.

10.6 Additional Instructions for AE Reporting to Merck

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

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

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.

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

- All AEs from the time of treatment allocation/randomization through 30 days following cessation of study treatment must be reported by the investigator.

- All AEs meeting serious criteria, from the time of treatment allocation/randomization through 90 days following cessation of study treatment, or 30 days following cessation of study treatment if the participant initiates new anticancer therapy, whichever is earlier must be reported by the investigator.

- All pregnancies and exposure during breastfeeding, from the time of treatment allocation/randomization through 120 days following cessation of study treatment, or 30 days following cessation of study treatment if the participant initiates new anticancer therapy must be reported by the investigator.

- Additionally, any SAE brought to the attention of an investigator at any time outside of the time period specified above must be reported immediately by the investigator if the event is considered to be drug-related.

Investigators are not obligated to actively seek AE or SAE or other reportable safety events in former study participants. However, if the investigator learns of any SAE, including a death, at any time after a participant has been discharged from the study, and

he/she considers the event to be reasonably related to the study treatment or study participation, the investigator must promptly notify Merck.

10.61 Definition of an Overdose for this Protocol and Reporting of Overdose to the Sponsor and to Merck

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

If an adverse event(s) is associated with ("results from") the overdose of a Merck product (pembrolizumab), 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 (as described in Section 10.42) within 24 hours to Mayo Clinic ([redacted] and within 2 working days hours to Merck Global Safety. ([redacted]

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

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

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

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

Such events must be reported within 24 hours to the Sponsor and within 2 working days to Merck Global Safety. [redacted]

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

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 an other 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 7 for additional details regarding each of the above criteria.

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

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

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

SAE reports and any other relevant safety information are to be forwarded to the Merck Global Safety facsimile number: [redacted]
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. [redacted]

[redacted] at the time of submission to FDA.

10.64 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 2 working days to Merck Global Safety. [redacted]
For the time period beginning when the consent form is signed until treatment allocation/randomization, any ECI, or follow up to an ECI, that occurs to any participant must be reported within 2 working days to Merck Global Safety if it causes the participant to be excluded from the trial, or is the result of a protocol-specified intervention, including but not limited to washout or discontinuation of usual therapy, diet, placebo treatment or a procedure.

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

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

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

10.65 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.

10.66 Table 7 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 participant, 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 participant 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 participant 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 participant 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
	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 participant 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 PARTICIPANT, 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	Participant 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 participant with overdose without an associated AE.)

11.0 Treatment Evaluation Using iRANO Guideline

Tumor response and regrowth can frequently be difficult to measure directly. Serial MRI/CT scans along with neurological exams will provide a guide for the effectiveness of therapy and the time-course of the disease.

Time interval to progression will be measured from beginning of study therapy until deterioration is documented by the individual investigator using the guidelines in Section 11.4. The patient should use the same diagnostic imaging modality (MRI or CT) throughout the study. Ideally, patients should also be evaluated on the same physical imaging device throughout the length of the study to ensure the most accurate assessments of tumor response. (Note: The CT evaluation option should ONLY be used for patients unable to undergo MR imaging because of non-compatible devices).

Overall survival will be measured from beginning of study therapy to death. Progression-free survival will be measured from beginning of study therapy until the first occurrence of progression or death. The quality of survival will be measured by performance status.

The primary measure of response will be by serial measures of the product of the two largest cross-sectional diameters (bidirectional product) using the RANO (Wen, et al 2010) and iRANO criteria (Okada, et al 2015).

11.1 Schedule of Evaluations:

11.11 Baseline

For the purposes of this study (for both treatment groups) the initial baseline measurement will be based on the post-surgery measurements obtained prior to RT.

11.12 Follow-up Evaluations

For the purposes of this study, patients should be reevaluated every 9 weeks while on therapy and then every 2 months until confirmed progression.

11.2 Definitions of Measurable and Non-Measurable Disease

11.21 Measurable Disease

We will define Measurable and Non-Measurable disease according to the updated RANO criteria. In short, measurable disease requires bidimensional contrast enhancing lesions with clearly defined margins on MRI (or CT scan) with two perpendicular diameters of at least 10mm, visible on two or more axial slices that are at most 5 mm in thickness (0-mm skip).

11.22 Non-Measurable Disease

We will define non-measurable disease as either unidimensionally measurable lesions, masses with indistinct margins, or lesions with maximal perpendicular diameters less than 10mm.

11.3 Guidelines for Evaluation of Measurable Disease

11.31 Measurement Methods:

- All measurements should be recorded in metric notation (i.e., decimal fractions of centimeters) using a ruler or calipers. We will measure all lesions in millimeters using standard ruler tools in the PACS system.

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

11.32 Acceptable Modalities for Measurable Disease:

- **Conventional MRI and CT:** CT scan imaging is only acceptable if patients are medically unable to undergo MR evaluation. This guideline has defined measurability of lesions on MRI scan based on the assumption that MRI slice thickness is 5 mm or less. If MRI scans have slice thickness greater than 5 mm, the minimum size for a measurable lesion should be twice the slice thickness.

  As with MRI, if a CT scan is performed, the technical specifications of the scanning sequences used should be optimized for the evaluation of the brain tumors. Ideally, the same type of scanner should be used and the image acquisition protocol should be followed as closely as possible to prior scans.

11.4 Measurement of Treatment/Intervention Effect

11.41 Target Lesions

- Measurable lesions (as defined in Section 11.21) up to a maximum of 5 lesions should be identified as "Target Lesions" and recorded and measured at baseline.

Note: If fewer than 5 target lesions are identified (as there often will be), there is no reason to perform additional studies beyond those specified in the protocol to discover new lesions.

- Target lesions should be selected on the basis of their size, be representative of all involved sites of disease, and should lend themselves to reproducible and repeated measurements.
- **Baseline Sum of Largest Bi-Dimensional Measurement (Baseline BDM):** The sum of product of the largest bi-dimensional measurements for all target lesions will be calculated and reported as the baseline sum of bi-dimensional measurement. The baseline sum of the largest bi-dimensional measurement will be used as reference to further characterize any objective tumor response in the measurable dimension of the disease.
- **Post-Baseline Sum of Bi-Dimensional Measurement (Post-Baseline BDM):** The sum of product of the largest bi-dimensional measurements for all target lesions will be calculated and reported as the post-baseline sum of bi-dimensional measurements (Post-Baseline BDM). If the radiologist is able to provide an actual measure on the target lesion, that should be recorded. If the target lesion is believed to be present and is faintly seen but too small to measure, a default value of 0.5 cm^2 should be assigned. If it is the opinion of the radiologist that the target lesion has likely disappeared, the measurement should be recorded as 0 cm^2.
- The minimum sum of the largest bi-directional measurements (Minimum BDM) is the minimum of the BDM of the baseline and post-baseline BDMs.

11.42 Non-Target Lesions

Non-measurable sites of disease (Section 11.22) are classified as non- target lesions and should also be recorded at baseline.

11.43 Response Criteria

11.431 Radiographic Response

Radiographic response should be determined in comparison to the tumor measurements obtained at baseline for determination of response. Radiographic progression is to be determined using one of the following as the reference when comparing the current measurements: 1) the smallest sum of tumor measurements at either baseline or following initiation of therapy, or 2) the initial radiographic enhancement increased (IREI) new reference scan if treatment was continued under the iRANO criteria.

Because the current treatment is likely to result in a higher than normal incidence of treatment-related contrast enhancement ("pseudoprogression"), patients should continue therapy with close observation (e.g. 4 to 8 week intervals) if there is a suspicion of pseudoprogression. If subsequent imaging studies and/or clinical observations demonstrate that progression in fact has occurred, the date of confirmed progression should be noted as the scan at which the potential progression was first identified. We will define complete response, partial response, progressive disease, and stable disease based on updated RANO criteria and in addition the iRANO criteria will apply if the patient has had less than or equal to 6 months of immunotherapy.

11.432 RANO Evaluation of Target Lesions

Note: For patients with less than or equal to 6 months of immunotherapy these criteria apply along with the iRANO evaluation criteria listed in Section 11.433.

- **Pseudoprogression (PsP):** All of the following must be true:
  a. Progression of contrast enhancing lesions and or T2/FLAIR is restricted to the initial radiation therapy volume.
  b. There are no new enhancing lesions outside of the initial radiation therapy volume.
  c. Patients are stable or improved clinically.

  Note: PsP may be diagnosed at any time during therapy (beyond the typical 12 week post-chemoradiotherapy window defined by RANO).
- **Complete Response (CR):** All of the following must be true:
  a. Disappearance of all enhancing measurable and non-measurable disease (sustained for at least 4 weeks).
  b. No new enhancing lesions.
  c. Stable or improved non-enhancing (T2/FLAIR) lesions
  d. Patients must be off corticosteroids (or on physiologic replacement doses only).
  e. Stable or improved clinically

NOTE: Patients with non-measurable disease only cannot have CR; the best response possible is stable disease.

- **Partial Response (PR):** Requires all of the following:
  a. ≥50% decrease in sum of products of perpendicular diameters of all measurable enhancing lesions (sustained for at least 4 weeks) compared with baseline.
  b. No progression of non-measurable disease
  c. No new lesions
  d. Stable or improved non-enhancing (T2/FLAIR) lesions on same or lower dose of corticosteroids compared with baseline scan
  e. Steroid dose should be same or lower compared with baseline scan.
  f. Stable or improved clinically

NOTE: Patients with non-measurable disease only cannot have PR; the best response possible is stable disease.

- **Progressive Disease (PD):** Defined by any of the following:
  a. ≥25% increase in sum of products of perpendicular diameters of enhancing lesions, compared with the smallest tumor measurement obtained either at baseline (if no decrease) or best response (on stable or increasing steroid dose).
  b. Significant increase in T2/FLAIR non-enhancing lesion on stable or increasing doses of corticosteroids compared with baseline scan or best response after therapy initiation (stable doses of steroids include patient not on steroids) not caused by comorbid events (e.g., radiation therapy, demyelination, ischemic injury, infection, seizures, post-operative change).
  c. Any new lesion
  d. Clear clinical deterioration not attributable to other causes apart from tumor (e.g., seizures, medication adverse effect, therapy complication, stroke, infection) or change in corticosteroid dose
  e. Failure to return for evaluation as a result of death or deteriorating condition
  f. Clear progression of non-measurable disease

- **Stable Disease (SD):** Requires all of the following:
  a. Does not qualify for complete response, partial response, or progression.
  b. Stable non-enhancing (T2/FLAIR) lesions on same or lower dose of corticosteroids compared with baseline scan.
  c. In the event that corticosteroid dose was increased (for new symptoms/signs) without confirmation of disease progression on neuroimaging, and subsequent follow-up imaging shows that the steroid increase was required because of disease progression, the last scan considered to show stable disease will be the scan obtained when the corticosteroid dose was equivalent to the baseline dose.

11.433 iRANO Evaluation of Target Lesions for patients with less than or equal to 6 months of immunotherapy.

- **CR, PR, and SD:** All are the same as defined by the above RANO criteria
- **Progressive Disease (PD):** All of the following must be true:
  a. Progessive Disease or PsP defined by RANO criteria.
  b. Less than or equal to 6 months from the start of immunotherapy.
  c. Significant clinical decline unrelated to comorbid events or concurrent medication; or, new or substantially worsened neurological deficits which are not due to comorbid events of concurrent medication.
- **Initial Radiographic Enhancement Increased (IREI):** All of the following must be true:
  a. Progressive Disease or PsP defined by RANO criteria including new lesions.
  b. Less than or equal to 6 months from the start of immunotherapy.
  c. No new or substantially worsened neurological deficits which are not due to comorbid events of concurrent medication.
  d. No substantial clinical decline.

NOTE: Patients with IREI that continue therapy will now use the IREI measurements as the "new reference scan" for evaluation of measurable disease for subsequent evaluations.

- **Confirmed Progressive Disease (PD):** All of the following must be true:
  a. Previously considered IREI.
  b. Repeat imaging not less than 3 months after initial imaging shows progression from the IREI new reference scan.

NOTE: Patients with confirmed progressive disease via iRANO criteria will have their date of progressive disease back-dated to the IREI date. The date of progressive disease is to be noted on the Event Monitoring Form.

11.44 Overall Objective Status

The overall objective status for an evaluation is determined by combining the patient's status on target lesions, non-target lesions, new sites of disease, and symptomatic or neurologic deterioration as defined in the following table:

NOTES:

1) Patients with possible PsP should initially be given the Objective Status of Preliminary Progressive Disease.

- If Progressive Disease is subsequently confirmed, the Objective Status is to be recorded for the current cycle as PD (confirmed) and the back-dated date of the progressive disease (from the cycle with the initial Preliminary PD) is to be used as the date of progressive disease which is documented via the Event Monitoring Form.
- If progressive disease is not confirmed the Objective Status for the current cycle can be documented as SD, PR, or CR as appropriate using the baseline scan measurement as the baseline for comparison with the

current measurements. The Objective Status for the cycle initially documented as Preliminary PD can be changed to PsP.

2) Patients with IREI should be initially given the Objective Status of IREI.

- If progressive disease is subsequently confirmed, the Objective Status is to be recorded for the current cycle as PD (confirmed) and the back-dated date of progressive disease (from the cycle with the initial IREI) is to be used as the date of progressive disease which is documented via the Event Monitoring Form.
- If progressive disease is not confirmed, the Objective Status for the current cycle can be documented as SD, PR, or CR as appropriate using the IREI new reference scan as the baseline for comparison with the current measurements.

11.441 Summary for Patients with Measurable and Non-measureable Disease

Target Lesions and/or Non-Target Lesions via RANO Response Criteria	**New Sites of Disease**	**Symptomatic or Neurologic Deterioration**	**Pts with Treatment ≤6 mos iRANO[1] Overall Objective Status**	**Pts with Treatment >6 mos RANO Overall Objective Status**
CR	No	No	CR	CR
PR	No	No	PR	PR
SD	No	No	SD	SD
Not all Evaluated	No	No	UNKN	UNKN
PD[1]	Yes[1] or No	No	IREI[1]	PD (confirmed)
CR/PR/SD/PD/Not all Evaluated	Yes[1]	No	IREI[1]	PD (confirmed)
Possible PsP	No	No	IREI[1]	Preliminary PD
PsP	No	No	IREI[1]	PsP
Any status	Any status	Yes	PD (confirmed)	PD (confirmed)

1) iRANO criteria to be used for initial radiographic enhancement increased (IREI) when patient has received ≤6 months of immunotherapy.

11.45 Symptomatic Deterioration: Patients with global deterioration of health status or new or substantially worsened neurological deficits which are not due to comorbid events of concurrent medication, requiring discontinuation of treatment without objective evidence of disease progression at that time, and not either related to study treatment or other medical conditions, should be reported as PD due to "symptomatic deterioration." Every effort should be made to document the objective progression even after discontinuation of treatment due to symptomatic deterioration.

11.5 Definitions of analysis variables

Formal definitions of variables used in analyses can be found in the Statistical Considerations section of the protocol.

12.0 Descriptive Factors

12.1 Corticosteroid therapy at study entry: Yes vs. no
12.2 Extent of resection: Subtotal resection vs. gross total resection
12.3 MGMT promoter methylation: Yes vs. no vs unknown vs indeterminate
12.4 IDH mutation: Yes vs. no vs. unknown
12.7 Family history of brain tumor: Yes vs. no
If yes, check all that apply:
_____ Father
_____ Mother
_____ Brother/Sister
_____ Child
_____ Other (list: _____)

13.0 Treatment/Follow–up Decision at Evaluation of Patient

13.1 Continuation of treatment

Patients who are CR, PR, SD, PsP or IREI will continue treatment per protocol.

13.2 PD during therapy

Patients who develop PD while receiving therapy will go to the event-monitoring phase.

13.3 Follow-up

After treatment completion patients will have one safety-observation visit at 30 days post-treatment and then be followed every 3-4 months for progression and survival per Section 4.0.

13.4 Off treatment for reasons other than PD

Patients who go off protocol treatment for reasons other than PD (for example: pregnancy, unacceptable toxicity (See Section 8), start of new therapy, etc.) will be followed per observation schedule per Section 4.0.

13.5 Failure to complete treatment

Inevaluable for either Safety Run-In (Group 1 or Group 2) Cohorts:
If a patient fails to complete either of the following treatment steps for reasons other than toxicity considered at least possibly related to pembrolizumab, the patient will be regarded as inevaluable for a Safety Run-In Cohort and will be replaced

- Neoadjuvant: fails to go on to craniotomy
- Concurrent: fails to complete at least 75% of the chemoradiation treatment.

13.6 Ineligible

A patient is deemed *ineligible* if after registration, it is determined that at the time of registration, the patient did not satisfy each and every eligibility criteria for study entry. The patient may continue treatment at the discretion of the physician as long as there are no safety concerns, and the patient was properly registered.
If treatment is stopped, the patient will go directly to the event-monitoring phase of the study (or off study, if applicable).

- If the patient received treatment, all data up until the point of confirmation of ineligibility must be submitted. Event monitoring will be required per Section 4.0 of the protocol.
- If the patient never received treatment, on-study material must be submitted. Event

monitoring will be required per Section 4.0 of the protocol.

13.7 Major violation

A patient is deemed a *major violation*, if protocol requirements regarding treatment in Cycles 1, 2, 3, or 4 of the therapy are severely violated that evaluability for primary end point is questionable. All data up until the point of confirmation of a major violation must be submitted. The patient will go directly to the event-monitoring phase of the study. The patient may continue treatment at the discretion of the physician as long as there are no safety concerns, and the patient was properly registered. Event monitoring will be required per Section 4.0 of the protocol.

13.8 Cancel

A patient is deemed a *cancel* if he/she is removed from the study for any reason before any study treatment is given. On-study material and the End of Active Treatment/Cancel Notification Form must be submitted. No further data submission is necessary.

13.9 Off treatment for withdrawal of consent

Patients who go off protocol treatment for withdrawal of all consent will be encouraged to have one final safety-observation visit at 30 days post-treatment. No further data submission is necessary.

14.0 Body Fluid Biospecimens

14.1 Summary Tables of Research Blood and Body Fluid Specimens to be Collected for this Protocol

14.11 Summary Table for Neoadjuvant Patients

Correlative Study (Section for more information)	Mandatory or Optional	Blood or Body Fluid being Collected	Type of Collection Tube (color of tube top)	Volume to collect per tube (# of tubes to be collected)	Prior to Cycle 1	Prior to RT	Prior to Tx (Adj) Cycle 4 Day 1	30 day Safety follow up[1]	At Time of PD[1]	Process at site? (Yes or No)	Temper-ature Conditions for Storage /Shipping
Tumor-associated antigen specific T cell frequency	Mandatory	Whole Blood	EDTA (purple)	10 mL (x 1)	X	X	X	X	X	Yes	Ambient
Treatment-induced T cell responses	Mandatory	Whole Blood	ACD (yellow)	6 mL (x 2)	X	X	X	X	X	Yes	Ambient
Immunophenotyping	Mandatory	Whole Blood	EDTA (purple)	10 mL (x 1)	X	X	X	X	X	Yes	Ambient

[1]Samples at time of safety follow-up and/or time of PD are requested, and if patient refuses, there is no protocol deviation.

14.12 Summary Table for Adjuvant Patients

Correlative Study (Section for more information)	Mandatory or Optional	Blood or Body Fluid being Collected	Type of Collection Tube (color of tube top)	Volume to collect per tube (# of tubes to be collected)	Prior to RT	Prior to Tx Cycle 2 Day 1 after RT	30 day Safety follow up[1]	At Time of PD[1]	Process at site? (Yes or No)	Temper-ature Conditions for Storage /Shipping
Tumor-associated antigen specific T cell frequency	Mandatory	Whole Blood	EDTA (purple)	10 mL (x 1)	X	X	X	X	Yes	Ambient
Treatment-induced T cell responses	Mandatory	Whole Blood	ACD (yellow)	6 mL (x 2)	X	X	X	X	Yes	Ambient
Immunophenotyping	Mandatory	Whole Blood	EDTA (purple)	10 mL (x 1)	X	X	X	X	Yes	Ambient

[1]Samples at time of safety follow-up and/or time of PD are requested, and if patient refuses, there is no protocol deviation.

14.2 Collection and Processing

All samples collected for ancillary studies will be collected on site at Mayo Clinic Rochester. All ancillary samples are derived from blood and will be collected by nurses or approved phlebotomists and delivered to Biospecimens Accessioning and Processing (BAP) Shared Resource.

14.3 Shipping and Handling

No specimens will be shipped outside of Mayo Clinic Rochester Campus. Internal transport of specimens will be at room temperature and delivered to the Human Cell Therapy Lab within 24 hours of collection. After collection call [redacted] for pick up.

14.31 **Kits will be used for this study** (only for sites outside of Mayo Clinic in Rochester, MN)

14.311 Kits will be supplied by the Biospecimen Accessioning and Processing Shared Resource (BAP).

14.312 The kit contains supplies and instructions for collecting, processing and shipping specimens.

14.313 Participating institutions may obtain kits by faxing the Supply Order Form to the number listed on the form. Because we are charged for all outgoing kits, a small, but sufficient, supply of the specimen collection kits should be ordered prior to patient entry. **Supply Order Forms must be filled in completely and legibly for quick processing.**

14.314 Kits will be sent via FedEx® Ground at no additional cost to the participating institutions. **Allow at least two weeks to receive the kits.**

14.315 Kits will not be sent via rush delivery service unless the participating institution provides their own Fed Ex® account number or alternate billing number for express mail. **Cost for rush delivery of kits will not be covered by the study.**

14.316 **All specimens must be collected and shipped Monday – Thursday ONLY.**

14.32 Shipping Specimens

Specimens will be shipped by FedEx overnight to:

[redacted]

14.33 Handling Specimens

Specimens will be stored at 4°C after acquisition until packaged for shipping. They will be shipped the same day as they are acquired. For packaging, blood collection tubes will be placed in a plastic bag, then packed in a Styrofoam box containing dry ice.

14.4 Background and Methodology

14.41 Measuring changes in treatment-induced frequency of tumor-associated antigen specific T cells

Glioblastomas express and/or amplify multiple tumor-associated or tumor-specific antigens, including EGVFviii, WT1, Her2/Neu, non-mutant p53, mutant p53, IL13Rα2, MAGE A3, MART-1, hTERT, gp100, tenascin, and others. Expression of these antigens varies between tumors and across different glioblastoma subtypes. The National Cancer Institute recently published a ranking of 75 tumor associated antigens appropriate for vaccine development based upon pre-determined criteria (therapeutic function, immunogenicity, specificity, oncogenicity, expression level, stem cell expression, percent of patients with antigen-positive tumors, number of epitopes, cellular location of expression). Two previously reported glioblastoma-associated antigens were ranked in the top five (WT1, EGFRviii), another three in the top ten (Her2/Neu, MAGE A3, non-mutant p53), and three further antigens in the top twenty (MART1, gp100, mutant p53). Of these, we found EGFRviii, ErbB2. gp100, MAGE A3, and p53 were commonly expressed in our Good Manufacturing Practices-grade human GBM cell lines. We additionally found common high levels of expression of EGFR and IL13Rα2. We therefore chose to focus our analysis of antigen-specific responses on these tumor-associated antigens.

Antigen-specific responses can be measured in peripheral blood using commercially-available Dextramer technology (Immundex, Fairfax, VA). Fluorescently-labeled multimers of class I MHC molecules from common haplotypes (e.g. HLA-A*0201) bound to specific nonapeptide antigens will bind to HLA-matched CD8+ T cells with T cell receptors (TCR) that specifically recognize these antigens. Increased frequency of tetramer-positive CD8+ T cells in peripheral blood as determined by flow cytometry after therapy is an indication of positive changes in immune response. The source and specificity of HLA-A*0201 multimers to be used in this study are shown below. Antigen-specific dextramer staining will only be performed in patients that are HLA-A*0201 positive.

Tumor-Associated Antigen	***MHC***	***Peptide***	***Source***
Her-2/Neu (Erb-B2)	HLA-A*0201	KIFGSLAFL	Immudex (Fairfax, VA)
MAGE A3	HLA-A*0201	FLWGPRALV	Immudex (Fairfax, VA)
gp100	HLA-A*0201	IMDQVPFSV	Immudex (Fairfax, VA)
p53 (wild type)	HLA-A*0201	LLGRNSFEV	Immudex (Fairfax, VA)
EGFR	HLA-A*0201	KLFGTSGQKT	Immudex (Fairfax, VA)
IL13Rα2	HLA-A*0201	ALPFGFILV	Immudex (Fairfax, VA)
Negative control	HLA-A*0201	ALIAPVHAV	Immudex (Fairfax, VA)

Dextramer sStaining will be performed with whole blood samples according to standard protocols. Samples will be analyzed using FlowJo software (Treestar).

14.42 Measuring treatment-induced T cell responses to vaccine

We will measure vaccine-induced changes in the immune response by measuring using the following (or similar) assays prior to and after treatment. We will

measure changes in cytotoxic T lymphocyte (CTL) frequency after co-culturing autologous CD8+ or CD4+ T cells and autologous tumor lysate-pulsed autologous DC for 48 hours. Practical limitations in cell numbers will not allow us to test each individual TAA peptide listed in Section 14.41 but DC pulsed with EGFRviii nonapeptide (LEEKKGNYV) will be used as EGFRviii dextramers are not available and the reliability of EGFRviii tetramers (standard antigen-specific T cell detection reagents) has been questioned. In all cases, antigen specificity of the response (either to tumor lysate or EGFRviii peptide) will be determined by comparison to control T cell co-cultures with naïve DC. CTL frequency will be estimated by IFNγ ELISPOT assays. Naïve DC and pre-treatment T cells alone will be used as negative controls. DC pulsed with EGFRviii peptide and co-cultured with autologous T cells pre-incubated with EGFRviii peptide-pulsed DC (5 days) will be used as positive controls. If for any reason this method of measuring induced T cell responses cannot be used, a similar method (e.g. ^{51}Cr-release or other cytotoxic T cell assays) using the same starting samples and measuring the same response will be used.

14.43 Immunophenotyping.

Glioblastoma patients have well-defined defects in circulating immune cells and are characterized by global reductions n T cell numbers and responsiveness combined with increases in circulating myeloid-derived suppressor cells and regulatory T cells. This has significant implications for response to immunotherapy.

We have extensive experience in immunophenotyping whole blood samples from glioblastoma patients using flow cytometry. We routinely perform 24 panels of four-color FACS staining on 5 mL blood samples. This generates a detailed picture of patients' peripheral blood immunophenotype, including lymphocyte, monocyte, and granulocyte subsets, regulatory T cells, and myeloid-derived suppressor cells. If for any reason this method of measuring immunophenotyping cannot be used a similar method using the same starting samples and measuring the same response will be used.

14.44 Additional ancillary studies

We will collect plasma at each blood collection point that may be used to measure changes in immune related cytokines and growth factors. We may also collect and store immune cell subtypes (such as T cells and monocytes) for transcriptome analysis or other global measures of the change in immune status. Finally, we may perform other molecular tests (including DNA sequencing) to identify changes in the behavior of the immune response during the course of therapy.

15.0 Drug Information

15.1 Pembrolizumab (MK-3475, SCH 900475, Keytruda®)

15.11 **Background**
Pembrolizumab is a potent humanized IgG4 monoclonal antibody with high specificity of binding to the PD-1 receptor, thus inhibiting its interaction with PD-L1 and PD-L2. Based on preclinical *in vitro* data, pembrolizumab has high affinity and potent receptor blocking activity for PD-1.

15.12 **Formulation**
Pembrolizumab is available as a liquid 25 mg/mL, 100 mg/vial.

15.13 **Preparation and storage**
Vials should be stored in the refrigerator at temperatures between 2-8°C.

Drug concentrate is further diluted with normal saline (or 5% dextrose in the concentration range of 1 to 10 mg/mL) in IV containers made of polyvinyl chloride (PVC) or non-PVC material. The infusion solution in the IV bag should be immediately administered. Diluted pembrolizumab solutions may be stored at room temperature for a cumulative period of up to 4 hours. This includes room temperature storage of admixture solutions in the IV bags and the duration of infusion. In addition, IV bags may be stored at 2-8°C for up to a cumulative time of 20 hours. This 24-hour total hold time from dilution may include up to 6 hours at room temperature

15.14 **Administration**
Pembrolizumab is administered by intravenous infusion over 30 minutes via a 0.22 micron in-line filter. The final infusion volume must be between 1 and 10 mg/mL. Maximum rate of infusion should not exceed 6.7 mL/minute through a peripheral or indwelling catheter. Flush the line with 0.9% NaCL following the completion of the infusion.

15.15 **Pharmacokinetic information**

a) Absorption – Because pembrolizumab is administered intravenously, it is immediately and completely bioavailable. Steady-state concentrations of pembrolizumab are reached by16 weeks of repeated dosing with a Q3W regimen, and the systemic accumulation is 2.1-fold. The peak concentration, trough concentration, and area under the plasma concentration versus time curve at steady state of pembrolizumab increased dose proportionally in the dose range of 2 to 10 mg/kg Q3W.
b) Distribution – Pembrolizumab has a limited volume of distribution.
c) Excretion – CL is approximately 23% lower after achieving maximal change at steady state compared with the first dose. The terminal elimination half-life (t½) is estimated to be 22 days at steady state.
d) Metabolism - Pembrolizumab is catabolized through non-specific pathways; metabolism does not contribute to its CL.

15.16 **Potential Drug Interactions**: There are no known significant drug interactions.

15.17 **Known potential adverse events**:
Very common known potential adverse events, ≥10%:
Skin and subcutaneous tissue disorders: Pruritus, skin rash
Gastrointestinal disorders: Diarrhea, nausea, abdominal pain
General disorders and administration site conditions: fatigue

Common known potential adverse events, >10%:
Blood and lymphatic system disorders: anemia
Immune system disorders: infusion related reaction
Endocrine disorders: hyperthyroidism, hypothyroidism
Metabolism and nutrition disorders: decreased appetite
Nervous system disorders: headache, dizziness, dysgeusia
Respiratory, thoracic, and mediastinal disorders: pneumonitis, dyspnea, cough
Gastrointestinal disorders: colitis, vomiting, constipation, dry mouth
Skin and subcutaneous tissue disorders: severe skin reactions, vitiligo, dry skin, erythema
Musculoskeletal and connective tissue disorders: arthralgia, myositis, musculoskeletal pain, arthritis, pain in extremity
General disorders and administration site conditions: asthenia, edema, pyrexia, influenza like illness, chills
Investigations: alanine aminotransferase increased, aspartate aminotransferase increased, blood alkaline phosphatase increased, blood creatinine increased

Uncommon known potential adverse events, 1% - 10%:
Infusion related reactions
Blood and lymphatic system disorders: neutropenia, thrombocytopenia, leukopenia, lymphopenia, eosinophilia
Endocrine disorders: hypophysitis, adrenal insufficiency, thyroiditis, hypopituitarism
Metabolism and nutrition disorders: type I diabetes mellitus, hyponatremia, hypokalemia, hypocalcemia
Psychiatric disorders: insomnia, confusional state
Nervous system disorders: epilepsy, lethargy, peripheral neuropathy
Eye disorders: uveitis, dry eye
Cardiac disorders: myocarditis, atrial fibrillation
Vascular disorders: hypertension
Gastrointestinal disorders: pancreatitis
Hepatobiliary disorders: hepatitis
Skin and subcutaneous tissue disorders: lichenoid keratosis, psoriasis, alopecia, dermatitis, dermatitis acneiform, eczema, hair color changes, papule
Musculoskeletal and connective tissue disorders: tenosynovitis
Renal and urinary disorders: nephritis, acute kidney injury
Investigations: blood bilirubin increased, amylase increased, hypercalcemia

Rare known potential adverse events, <1% (Limited to important or life-threatening):
Blood and lymphatic system disorders: immune thrombocytopenic purpura, hemolytic anemia
Immune system disorders: sarcoidosis
Nervous system disorders: Guillain-Barre syndrome, myasthenic syndrome
Gastrointestinal disorders: small intestinal perforation
Skin and subcutaneous tissue disorders: toxic epidermal necrolysis, Stevens-Johnson syndrome, erythema nodosum

The risk profile for pembrolizumab also includes two important potential risks: a) myasthenic syndrome, and b) an increased risk of severe complications (such as early severe graft versus host disease and veno-occlusive disease) of allogeneic transplant in patients with hematologic malignancies who have previously been treated with PD-1 inhibitors.

15.18 **Drug procurement**

Pembrolizumab will be provided free of charge to study participants by Merck.

15.19 **Nursing Guidelines**

15.191 Pembrolizumab side effects vary greatly from those of traditional chemotherapy and can vary in severity from mild to life threatening. Instruct patients to report any side effects to the study team immediately. Side effects may be immediate or delayed up to months after discontinuation of therapy. Most side effects are reversible with prompt intervention of corticosteroids.

15.192 Diarrhea can be seen, however is less common than that seen with anti-CTLA-4 agents. However it can be severe, leading to colonic perforation. Instruct patients to report ANY increase in the number of stools and/or change in baseline, blood in the stool, abdominal pain to the study team immediately.

15.193 Rash/pruritis/dermatitis is seen. Patients should report any rash to the study team. Treat per section 9.0 and monitor for effectiveness.

15.194 Monitor LFTs closely as elevations in these levels could indicate early onset autoimmune hepatitis. Patients should also be instructed to report any jaundice, or right upper quadrant pain to the study team immediately.

15.195 Pneumonitis can be seen and may be mild (only seen on imaging) to severe. Patients should be instructed to report any SOB, dyspnea, cough, chest pain, etc. to the study team immediately. Patients reporting these symptoms should have a pulse ox checked and consider immediate imaging per the treating MD.

15.196 Endocrinopathies (including hypopituitarism, hypothyroidism, hypophysitis, and adrenal insufficiency) are seen with this agent. Patients may present only with the vague sense of fatigue and “not feeling well.” Additional symptoms may be that of nausea, sweating and decreased activity tolerance. Instruct patients to report these signs or symptoms immediately and obtain appropriate labs as ordered by MD.

15.197 Patients who are started on steroid therapy for any side effects of pembrolizumab toxicity should be instructed to take the steroids as ordered, and not to discontinue abruptly as symptoms may return and be severe. Patients may be on steroid therapy for weeks. Instruct patients to report any increase or change in side effects with any dosage decrease as patients may need a slower taper.

15.198 Fatigue is common and may or may not be associated with immune related side effects. Assess patient’s fatigue level prior to each cycle of therapy and report any changes to the study team.

15.199a Patients should avoid receiving live vaccines within 30 days of study drug administration or per other study guidelines.

15.199b Patients who have undergone an allogenic bone marrow transplant, have an increased risk of severe complications including early GVHD, and veno-occlusive disease, if they have previously been treated with pembrolizumab

15.199c Myocarditis has been reported and associated with pembrolizumab. Instruct patients to report chest pain, SOB, or dyspnea to study team immediately and/or seek emergency medical attention.

15.199d Autoimmune hematologic disorders including ITP and hemolytic anemia have been reported. Monitor blood counts closely and report any abnormalities to the study team.

15.199e Rare neurologic disorders including Guillain-Barre syndrome and myasthenia gravis have been reported. Instruct patients to report any neurologic symptoms including weakness, paresthesias or numbness, tingling to the study team immediately.

15.2 Temozolomide for Oral Administration (Temodar®, TMZ)

15.21 **Background**: Like dacarbazine, temozolomide is converted to the active alkylating metabolite MTIC [(methyl-triazene-1-yl)-imidazole-4-carboxamide]. Unlike dacarbazine, however, this conversion is spontaneous, nonenzymatic, and occurs under physiologic conditions in all tissues to which the drug distributes.

15.22 **Formulation**: Commercially available for oral administration as:
Capsules: 5 mg, 20 mg, 100 mg, 140 mg, 180 mg, 250 mg

15.23 **Preparation, storage, and stability**: Refer to package insert for complete dispensing instructions. Store capsules at room temperature of 15ºC to 30ºC.

15.24 **Administration:** Refer to the treatment section for specific administration instructions. Capsules should not be opened or chewed but swallowed whole with a glass of water. Temozolomide may be administered on an empty stomach to reduce nausea and vomiting. Bedtime administration may be advised. Do not repeat if vomiting occurs after dose is administered; wait until the next scheduled dose.

15.25 **Pharmacokinetic information**:
Absorption: Rapid and complete
Distribution: V_d: Parent drug: 0.4 L/kg; penetrates blood brain barrier; CSF levels are ~35% to 39% of plasma levels
Protein binding: 15%
Bioavailability: 100%
Time to peak, serum: Empty stomach: 1 hour; with food (high-fat meal): 2.25 hours
Metabolism: Prodrug, hydrolyzed to the active form, MTIC; MTIC is eventually eliminated as CO_2 and 5-aminoimidazole-4-carboxamide (AID), a natural constituent of urine
Half-life elimination: Mean: Parent drug: 1.8 hours
Excretion: Urine (~38%; parent drug 6%); feces <1%

15.26 **Potential Drug Interactions**:
Ethanol/Nutrition/Herb Interactions: Food reduces rate and extent of absorption.

15.27 **Known potential adverse events:** Consult the package insert for the most current and complete information. With CNS malignancies, it is difficult to distinguish between CNS adverse events caused by temozolomide versus the effects of progressive disease.

Common known potential toxicities, >10%:
Cardiovascular: Peripheral edema (11%)
Central nervous system: Fatigue (34% to 61%), headache (23% to 41%), seizure (6% to 23%), hemiparesis (18%), fever (13%), dizziness (5% to 12%), coordination abnormality (11%)
Dermatologic: Alopecia (55%), rash (8% to 13%)
Gastrointestinal: Nausea (49% to 53%; grades 3/4: 1% to 10%), vomiting (29% to 42%; grades 3/4: 2% to 6%), constipation (22% to 33%), anorexia (9% to 27%), diarrhea (10% to 16%)

Hematologic: Lymphopenia (grades 3/4: 55%), thrombocytopenia (grades 3/4: adults: 4% to 19%), neutropenia (grades 3/4: adults: 8% to 14%), leukopenia (grades 3/4: 11%)
Miscellaneous: Viral infection (11%)

Less common known potential toxicities, 1% - 10%:
Central nervous system: Amnesia (10%), insomnia (4% to 10%), somnolence (9%), ataxia (8%), paresis (8%), anxiety (7%), memory impairment (7%), depression (6%), confusion (5%)
Dermatologic: Pruritus (5% to 8%), dry skin (5%), radiation injury (2% maintenance phase after radiotherapy), erythema (1%)
Endocrine & metabolic: Hypercorticism (8%), breast pain (females 6%)
Gastrointestinal: Stomatitis (9%), abdominal pain (5% to 9%), dysphagia (7%), taste perversion (5%), weight gain (5%)
Genitourinary: Incontinence 98%), urinary tract infection (8%), urinary frequency (6%)
Hematologic: Anemia (grades 3/4: 4%)
Neuromuscular & skeletal: Paresthesia (9%), back pain (8%), abnormal gait (6%), arthralgia (6%), myalgia (5%)
Ocular: Blurred vision (5% to 8%), diplopia (5%), vision abnormality (visual deficit/vision changes 5%)
Respiratory: Pharyngitis (8%), upper respiratory tract infection (8%), cough (5% to 8%), sinusitis (6%), dyspnea (5%)
Miscellaneous: Allergic reaction (up to 3%)

Rare toxicities <1%:
Alkaline phosphatase increased, alveolitis, anaphylaxis, aplastic anemia, emotional lability, erythema multiforme, febrile neutropenia, flu-like syndrome, hallucination, hematoma, hemorrhage, herpes simplex, herpes zoster, hyperglycemia, hypokalemia, interstitial pneumonia/pneumonitis, myelodysplastic syndrome, opportunistic infection (e.g., PCP), oral candidiasis, pancytopenia, peripheral neuropathy, petechiae, pneumonitis, pulmonary fibrosis, secondary malignancies (including myeloid leukemia), Stevens-Johnson syndrome, toxic epidermal necrolysis

15.28 **Drug procurement:** Commercial supplies. Pharmacies or clinics shall obtain supplies from normal commercial supply chain or wholesaler.

15.29 **Nursing Guidelines**

15.291 Myelosuppression has been found to be the dose-limiting toxicity. Gr 3 thrombocytopenia occurred in 6% of patients and Gr 4 in 1%. Gr 3 and Gr 4 lymphopenia occurred in 55% of patients. Leukopenia, lymphopenia, thrombocytopenia and anemia usually occur 2-8 weeks after initiation of treatment. Monitor CBC carefully and report any significant changes to MD. Instruct patient to report signs/symptoms of infection, unusual bruising and bleeding to health care team.

15.292 In previous studies, patients have developed *pneumocystis carinii* pneumonia (PCP) when taking concomitant temozolomide and steroids. Instruct patient to report any fever, cough, chest pain, of other

signs of infection to the health care team. Counsel patients on the importance of taking PCP prophylaxis as prescribed if ordered.

15.293 Advise patient that a mild-moderate rash may be experienced.

15.294 Fatigue may be experienced. Work with patient in energy conserving lifestyle.

15.295 Remind patient that drug needs to be taken on an empty stomach with a full glass of water. Drug should not be crushed, chewed, opened, or dissolved.

15.296 Nausea and vomiting are common. Teach patient to self-medicate with anti-emetics one hour prior to dose. Assess for effectiveness. If vomiting occurs, do not repeat dose. Wait until next scheduled dose.

15.297 Temozolomide may interact with valproic acid by reducing the clearance of temozolomide by 5%. Assess concomitant medication use.

15.298 Constipation is common. Encourage patient to increase fluid intake. Administer stool softeners or laxatives as ordered and monitor for their effectiveness.

15.299a Monitor for cytopenia (i.e. CBC w/differential). Instruct patient to report any fever, signs or symptoms of infection, or any unusual bruising or bleeding to the study team.

15.299b Headache may be seen. Assess for more serious condition (i.e. cerebral bleed, disease progression) first and then treat symptomatically and monitor for effectiveness.

16.0 Statistical Considerations and Methodology

16.1 Study design

This study is comprised of two separate treatment groups; Group 1 Neoadjuvant and Group 2 Adjuvant. Group 1 Neoadjuvant is a pilot study where patients begin treatment prior to surgery. These patients enter treatment at a different point in their treatment process and will be evaluated separately from the Group 2 patients. Group 2 Adjuvant is a single arm, one stage phase II study designed to evaluate the 18 month overall survival rate of pembrolizumab in combination with standard therapy after surgery (external beam radiation therapy plus concomitant TMZ and then adjuvant TMZ chemotherapy) in patients newly diagnosed glioblastoma. Group 1 has a safety run-in phase to conduct a thorough review of adverse event data within the initial 6 patients. Other endpoints are adverse event profile, time to progression, progression free survival, and time to treatment failure.

16.11 Group 1 Neoadjuvant Safety Run-In Cohort: Early adverse event assessment (run-in phase)

To ensure safety of treating patients with pembrolizumab in combination with standard therapy, an initial 6 patients will be enrolled and treated for adverse events assessment. These patients will be enrolled in cohorts of 3+3 design.

The first cohort of 3 patients will receive pembrolizumab 200 mg intravenously (dose level 1). If less than 2 patients in this first cohort experience a DLT (See Section 7.9), the next cohort will be enrolled at a pembrolizumab dose of 200 mg intravenously (dose level 1).

> If DLTs are observed in two or more patients in the initial cohort of 3, or more than 1/6 patients in both cohorts, then accrual will be temporarily suspended. The study team will conduct a comprehensive review of all the adverse event data, investigate the specifics of each DLT, and after consulting with the FDA and the drug supplier, will consider possible actions including at least the following: permanently suspend accrual,

Patients who have signed consent form, are deemed eligible, and have either completed the first 3 cycles (neoadjuvant, surgery, concurrent) of protocol treatment; or, are off protocol treatment due to toxicities, or other treatment related complications are evaluable for decision-making regarding early adverse event evaluation. If the pembrolizumab is deemed safe for the Group 1 study population, then these patients will be included in exploratory and hypothesis generating analysis of similar endpoints as listed for the Group 2 primary and secondary analysis.

As of Amendment 3 the Group 1 Neoadjuvant study will reopen for at most an additional 6 DLT evaluable patients enrolled via the cohorts of 3+3 design as described above including the following DLT stopping rules.

The third cohort of 3 patients will receive pembrolizumab 200 mg intravenously (dose level 1). If less than 2 patients in this cohort experience a DLT (See Section 7.9), the next cohort will be enrolled.

If DLTs are observed in two or more patients in this third cohort of 3, or more than 1/6 patients in both cohorts 3 and 4, then accrual to Group 1 will be temporarily suspended. The study team will conduct a comprehensive review of all the adverse event data, investigate the specifics of each DLT, and after

consulting with the FDA and the drug supplier, will consider possible actions including at least the following: permanently suspend accrual.

16.12 Group 2 Adjuvant: Single arm, one-stage phase II design

16.121 Primary endpoint

The primary endpoint of this study is the number of 18 month overall survival (OS18) successes. OS18 is defined as the number of patients who are alive at least 18 months after beginning study therapy divided by the total evaluable patients. All patients who have signed a consent form, are eligible, and have begun treatment in Cycle 3 (concurrent RT+TMZ+MK-3475) will be considered evaluable for the primary endpoint. The patients enrolled for early adverse events evaluation who meet this evaluable status will be included in the primary efficacy decision-making procedures and the analysis of the primary endpoint.

Definition of Success: An evaluable patient will be classified as a "success" for the primary endpoint if the patient is alive at least 18 months after beginning study therapy.

16.122 Decision Rule and Power Considerations

Stupp et al. reported an 18 month OS rate (OS18) of 39.4% for newly diagnosed GBM received radiotherapy plus TMZ. This 39.4% is associated with a median overall survival of 14.6 months starting at the time of study registration, which for that study was within one week of starting concurrent RT+TMZ. This study starts at the same timepoint. A sample size of 33 evaluable patients will provide a power of 85.3% to test the alternative hypothesis that the 18 month OS rate is at least 59.0% against the null hypothesis that the 18 months OS rate is at most 39.0%, at a one-sided significance level of 0.099.

At the conclusion of the trial, the regimen will be concluded that the combination of MK-3475 and standard therapy warrants the further investigation, if at least 17 patients are alive at least 18 months after beginning of study therapy. Otherwise, we will conclude that the proposed regimen does not warrant the further investigation.

16.123 Safety Run-In Cohort: Early adverse event assessment (run-in phase)

To ensure safety of treating patients with pembrolizumab in combination with standard therapy, an initial cohort of 6 patients will be enrolled and treated for adverse events assessment. Enrollment will be temporarily suspended for the Safety Run-In AE assessment of these patients.

If DLTs are observed in three or more patients in the initial cohort of 6 DLT-evaluable patients, then accrual will be temporarily suspended. The study team will conduct a comprehensive review of all the adverse event data, investigate the specifics of each DLT, and after consulting with the FDA and the drug supplier, will consider possible actions including at least the following: permanently suspend accrual.

Patients who have signed consent form, are deemed eligible, and have either completed the first cycle (concurrent) of protocol treatment; or, are off protocol treatment due to toxicities, or other treatment related

complications are evaluable for decision-making regarding early adverse event evaluation.

16.13 Sample Size

A total of 33 evaluable Group 2 patients are required for primary endpoint assessment per study design stated in Section 16.12. We anticipate accruing an additional 3 patients in Group 1 and 4 patients to Group 2 to account for ineligibilities, cancelations, major violations, and other reasons. Thus, the maximum accrual is 52 patients in total (15 patients in Group 1 and 37 in Group 2. To account for patients that are consented and do not meet full eligibility criteria, we anticipate having to consent and screen 90 patients to achieve the maximum accrual of 52 patients.

16.14 Accrual and Study Duration

Given previous data from Mayo Clinic Cancer Center Phase I and Phase II clinical trials, it is expected that the accrual rate will be about 2 patients every month to this trial. Taking into account the minimal follow-up of 18 months after beginning of study therapy for the last enrolled patients, the overall study duration will be approximately 40 months.

16.15 Primary Endpoint Completion Date for [redacted] Reporting

For purposes of [redacted] reporting, the Primary Endpoint Completion Date for this study is the latest date all Group 2 patients have died or have been followed for at least 18 months whichever comes first. An initial Anticipated Primary Completion Data for this study is 40 months after the Group 2 study opens to accrual.

16.2 Analysis plans

16.21 Primary Endpoints

16.211 Group 1: Dose-Limiting Toxicity Rate: The rate of DLTs within each dose-level cohort will be reported along with confidence intervals. All DLT evaluable patients will be included and DLT will be evaluated during all cycles of treatment.

16.212 Group 2: Overall Survival 18 month successes. OS18 successes will be measured as the number of evaluable patients classified as a “success” for the primary endpoint based on if the patient is alive at least 18 months after beginning study therapy. The OS18 percentage will also be calculated in an exploratory manner as measured by the percentage of Group 2 evaluable patients alive at 18 months after beginning study treatment. The OS18 percentage and 95% confidence intervals will be calculated via the Kaplan-Meier method.

16.22 Secondary Analysis

16.221 Adverse Events Profile (Group1 and Group 2)

The number and severity of all adverse events will be tabulated and summarized in this patient population. Specifically, the overall toxicity percentages for Grade 3 or higher adverse events considered at least possibly related to treatment will also calculated and reported. All other adverse event analysis will be exploratory and hypothesis generating. This may include and not be limited to: a summary of non-hematologic (unspecified) adverse events will be evaluated via the

ordinal CTCAE grading, measures of thrombocytopenia, neutropenia, and leukopenia will be assessed using continuous variables as the outcome measures (primarily nadir) as well as categorization via CTCAE grading, overall adverse event incidence as well as profiles by dose level and by tumor type will be explored and summarized, time until any treatment related adverse event, time until treatment related Grade 3+ adverse event, time until hematologic nadirs (WBC, ANC, platelets), and frequency distributions, graphical techniques and other descriptive measures will form the basis of these analyses.

16.222 Time to progression (Group 2 only)

Time to Progression is defined as the length of time from start of study treatment to progression via the iRANO criteria listed in Section 11. The median and 95% confidence intervals will be calculated via the Kaplan-Meier method.

16.223 Progression Free Survival time (Group 2 only)

Progression free survival (PFS) is defined as the time from the date of starting study treatment to the date of disease progression or death resulting from any cause, whichever comes first. Progression is defined according to iRANO criteria found in Section 11. The median and 95% confidence intervals will be estimated using the Kaplan-Meier estimator.

16.224 Time to Treatment Failure (TTF) (Group 2 only) TTFTime to treatment failure is defined as the time from beginning study therapy to documentation of progression, unacceptable adverse event(s), or refusal to continue participation by the patient. The median and 95% confidence intervals will be estimated using the Kaplan-Meier estimator.

16.23 Translational Endpoints

The biomarkers listed in Sections 14.0 and 17.0 will analyzed in an exploratory and hypothesis generating manner which may include and not be limited to: being examined at all defined time points and will be explored descriptively to detect patterns and substantial changes. In addition, differences between post-baseline and baseline apoptotic scores will be analyzed using a paired-sample t-test or the nonparametric equivalent.

16.3 Data & Safety Monitoring:

16.31 The principal investigator(s) and the study statistician(s) will review the study at least twice a year to identify accrual, adverse event, and any endpoint problems that might be developing. The Mayo Clinic Cancer Center (MCCC) Data Safety Monitoring Board (DSMB) is responsible for reviewing accrual and safety data for this trial at least twice a year, based on reports provided by the MCCC Statistical Office.

16.32 Adverse Event Stopping Rules:

The stopping rules below will be assessed independently for Group 1 and Group 2. The stopping rules specified below are based on the knowledge available at study development. We note that the Adverse Event Stopping Rule may be adjusted in the event of either (1) the study re-opening to accrual or (2) at any time during the conduct of the trial and in consideration of newly acquired

information regarding the adverse event profile of the treatment(s) under investigation. The study team may choose to suspend accrual to either Group 1 or Group 2 independently because of unexpected adverse event profiles that have not crossed the specified rule below.

Accrual will be temporarily suspended to Group 1 and/or Group 2 if at any time we observe events considered at least possibly related to study treatment (i.e. an adverse event with attribution to pembrolizumab specified as "possible", "probable", or "definite") that satisfy either of the following:

- In addition to the stopping rules associated with the safety run-in cohort (see Section 16.11), if at any time >1/3rd of patients experience a DLT as specified in Section 7.0.
- If there is one patient death that is considered related to pembrolizumab any time during the study

Any group closed to accrual will not be re-opened without proper protocol modification. If no modifications are possible then accrual to the group will close i.e. accrual to the appropriate group will be permanently stopped. We note that we will review Grade 4 and 5 adverse events deemed "unrelated" or "unlikely to be related", to verify their attribution and to monitor the emergence of a previously unrecognized treatment-related adverse event.

16.4 Inclusion of Minorities

16.41 Availability

This study will be available to all eligible patients, regardless of race or ethnic origin.

16.42 Power for Subset Analyses

Although the planned analysis will, as always, look for differences in treatment effect based on racial groupings the sample size is not increased in order to provide additional power for subset analyses.

16.43 Population

Based on prior studies involving similar disease sites conducted at Mayo Clinic in Rochester, MN, we expect about 7% of patients will be classified as minorities by race/ethnicity and about 40% of patients will be women. Expected sizes of racial subsets are shown in the following table:

Accrual Targets			
	Sex/Gender		
Ethnic Category	**Females**	**Males**	**Total**
Hispanic or Latino	1	1	2
Not Hispanic or Latino	20	30	50
Ethnic Category: Total of all subjects	21	31	52
Racial Category			
American Indian or Alaskan Native	1	1	2
Asian	1	0	1
Black or African American	1	2	3
Native Hawaiian or other Pacific Islander	0	1	1
White	18	27	45
Racial Category: Total of all subjects	21	31	52

Ethnic Categories:	**Hispanic or Latino –** a person of Cuban, Mexican, Puerto Rican, South or Central American, or other Spanish culture or origin, regardless of race. The term "Spanish origin" can also be used in addition to "Hispanic or Latino."
	Not Hispanic or Latino
Racial Categories:	**American Indian or Alaskan Native –** a person having origins in any of the original peoples of North, Central, or South America, and who maintains tribal affiliations or community attachment.
	Asian – a person having origins in any of the original peoples of the Far East, Southeast Asia, or the Indian subcontinent including, for example, Cambodia, China, India, Japan, Korea, Malaysia, Pakistan, the Philippine Islands, Thailand, and Vietnam. (Note: Individuals from the Philippine Islands have been recorded as Pacific Islanders in previous data collection strategies.)
	Black or African American – a person having origins in any of the black racial groups of Africa.
	Native Hawaiian or other Pacific Islander – a person having origins in any of the original peoples of Hawaii, Guam, Samoa, or other Pacific Islands.
	White – a person having origins in any of the original peoples of Europe, the Middle East, or North Africa.

17.0 Pathology Considerations / Tissue Specimen Submission

17.1 Summary Table of Research Tissue Specimens to be Collected for this Protocol

Correlative Study (Section for more information)	Mandatory or Optional	Type of Tissue to Collect	Block, Slides, Core, etc. (# of each to submit)	Tissue from Pre-treatment Biopsy (Group 1) or Surgery (Group 2)	Craniotomy/ tumor resection at Mayo Clinic (Group 1)	At Time of Progressive Disease (Group 1 and 2)	Process at site? (Yes or No)	Temperature Conditions for Storage /Shipping
Antigen	Mandatory*	Formalin fixed and paraffin embedded (FFPE)	1 block or 5 slides at 5 microns +1 H&E	X			Yes	Ambient
Antigen	Mandatory	FFPE	1 block or 5 slides at 5 microns +1 H&E		X**		Yes	Ambient
Antigen	Mandatory*	FFPE	1 block or 5 slides at 5 microns +1 H&E			X	Yes	Ambient

*Only if available

** Neoadjuvant patients (Group 1) only

17.2 Diagnostic Slides from Original and /or Recurrent Tissue

Along with original diagnostic slides, include the surgical pathology report. Send slides to the [redacted]

17.3 Correlative Tissue Collection

17.31 Tissue kits will not be provided for this protocol.

17.32 Paraffin Embedded Tissue

17.321 Provision of a single block of tumor tissue each from the biopsy prior to enrollment and the subsequent craniotomy and resection is mandatory. If available, provision a single block of tumor tissue obtained at time of progression is optional. NOTE: For biopsy prior to enrollment, if block is not available, then submit 5 unstained slides at 5 microns plus one H&E slide.

17.322 Label slides with the study number, the patient study ID number, patient initials, and the date of the operative procedure.

17.323 Samples are to be sent to the [redacted]

17.324 Samples can be stored at room temperature.

17.4 Background and Methodology

17.41 Immunohistochemistry

Immunohistochemical techniques have been validated on paraffin-embedded tissues and appropriate specific antibodies are available for CD4, CD8, CD68, PD-1, and PD-L1. Accordingly, we will be obtaining immunohistochemical stains for these antigens on glioblastoma tissue from initial diagnostic biopsy and subsequent craniotomy and resection as well as at recurrence when such tissue slides are availability. This may be limited if the initial diagnosis was based on needle biopsy (not resection) or if further resection is not clinically indicated at time of recurrence. Tissue availability for these ancillary studies will not be an entrance criteria and this testing, while highly desirable, will be considered optional.

18.0 Records and Data Collection Procedures

18.1 Submission Timetable

18.11 Initial Material(s)

CRF	Active-Monitoring Phase (Compliance with Test Schedule Section 4.0)
On-Study	≤2 weeks after registration
Adverse Event - Baseline	
Measurement – On Study	
Baseline Research Blood Submission (see Section 14.0)	
Concurrent Steroids and Anticonvulsants	
OP and Path Reports (see Section 17.0)	
End of Active Treatment/Cancel Notification	Submit ≤2 weeks after registration if withdrawal/refusal occurs prior to beginning protocol therapy

18.12 Pathology and Research Tissue Material(s)

CRF	Active-Monitoring Phase (Compliance with Test Schedule Section 4.0)
Baseline Research Tissue Submission (See Section 17.0)	Can be submitted before or during active treatment. (see Section 17.0)
Pathology Materials	
Pathology Reporting Brain Tumor GBM Trials	

18.13 Test Schedule Material(s)

CRF	Active-Monitoring Phase (Compliance with Test Schedule Section 4.0)		
	At each evaluation during treatment	At end of treatment	Observation
Evaluation/Treatment	X[1]	X	
Evaluation/Observation			X
Adverse Event	X	X	X
Measurement[3]	X	X	
Research Blood Submission	X (see Section 14.0)		X
Research Tissue Submission	X (see Section 17.0)		
Concurrent Steroids and Anticonvulsants	X	X	X
Surgery	X[2]		
Radiation Therapy Reporting Brain	X[4]		
Pathology Reporting Brain Tumor GBM Trials	X[2]		
End of Active Treatment/Cancel Notification		X	
ADR/AER	At each occurrence (see Section 10.0)		
Dose Limiting Toxicity	At each occurrence		

1. Complete at each evaluation during Active Treatment (see Section 4.0).
2. Complete following Craniotomy/tumor resection.
3. Cycle 1 form is at the end of Cycle 1 and just Prior to Surgery, and Cycle 2 form is Post Surgery, pre-RT.
4. Submit following completion of radiation therapy

18.14 Follow-up Material(s)

CRF	Event Monitoring Phase[1]				
	q. 2 months until PD[2]	At PD[2]	After PD q. 6 mos.	Death	New Primary
Event Monitoring	X[3]	X[3]	X	X	At each occurrence

1. If a patient is still alive 3 years after registration, no further follow-up is required.
2. If PD is determined at site outside of Mayo Clinic that does not use Epic Clinical Systems: Submit relevant radiographic images as a digital image with a viewing tool free of marks that may obscure the lesions or bias the evaluation of the independent reviewer(s) of tumor response at baseline and tumor response and/or progression to address in note below.
3. Submit copy of documentation of response or progression to the [redacted]

18.2 CRF completion

This study will use Medidata Rave® for remote data capture (rdc) of all study data. Data collection for this study will be done exclusively through the Medidata Rave® clinical data management system. Access to the trial in Rave is granted through the iMedidata application to all persons with the appropriate roles assigned in Regulatory Support System (RSS). To access Rave via iMedidata, the site user must have an active account and the appropriate Rave role (Rave CRA, Read-Only, Site Investigator) on the organization roster at the enrolling site.

18.3 Site responsibilities

Each site will be responsible for insuring that all materials contain the patient's initials, MCCC registration number, and MCCC protocol number. Patient's name must be removed.

18.5 Supporting Documentation

This study requires supporting documentation for evidence of response to study therapy and progression after study therapy. Pathology and operative reports for pre-treatment biopsy and surgery are also required.

18.6 Incomplete materials

Any data entered into a form will result in that form being marked as "received." However, missing data will be flagged by edit checks in the database.

18.7 Overdue lists

A list of overdue materials and forms for study patients will be generated monthly. The listings will be sorted by location and will include the patient study registration number. The appropriate site will be responsible to obtain the overdue material.

19.0 Budget

19.1 Costs charged to patient: routine clinical care

19.2 Tests to be research funded: Correlative studies and research analyses of blood and tissue samples

19.3 Other budget concerns: Pembrolizumab will be provided by Merck.

20.0 References

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Appendix I ECOG Performance Status

ECOG PERFORMANCE STATUS*	
Grade	**ECOG**
0	Fully active, able to carry on all pre-disease performance without restriction
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light house work, office work
2	Ambulatory and capable of all selfcare but unable to carry out any work activities. Up and about more than 50% of waking hours
3	Capable of only limited selfcare, confined to bed or chair more than 50% of waking hours.
4	Completely disabled. Cannot carry on any selfcare. 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 ECOG Performance Status is in the public domain therefore available for public use. To duplicate the scale, please cite the reference above and credit the Eastern Cooperative Oncology Group, Robert Comis M.D., Group Chair.

[redacted]

Appendix II Radiation Therapy Recommendations

II.1 Certification:

Standard conformal techniques will be allowed in this study along with IMRT.

II.2 Radiation Energy:

Minimum photon energy of 4MV with multiple ports designed and verified by simulation. If IMRT is utilized, 6 MV is preferred. Minimum SSD or SAD of 80 cm.

II.3 Treatment Volumes

II.3.1 Gross Tumor Volume 1 (GTV1):

A postoperative MRI must be used for tumor localization, with the exception of 1) patient in whom MRI is contraindicated (e.g., pacemaker, claustrophobia, etc.) in which case a CT scan can be used, and 2) patients who underwent biopsy only; in which case the preoperative MRI scan can be used. For purposes of the protocol, the GTV1 will be the so-called “edema volume” which is best visualized on the FLAIR or T2-weighted MR images. The GTV1 should also include the surgical resection cavity and any FLAIR or T2 abnormalities beyond the edges of the cavity. The GTV1 should also encompass all of GTV2, which is defined by regions of contrast enhancement. In the case of a gross total resection without any residual FLAIR/T2 abnormalities, then the surgical cavity will be considered the GTV1. In cases where a partial or complete lobectomy has been performed, the region distal to the edge of the resection (i.e., where no brain tissue is present) does not need to be included in the GTV1 (or the CTV1). For example, if a patient has an anterior temporal lobectomy, the anterior middle cranial fossa does not need to be included in the tumor volume. In this situation, the GTV1 should encompass the resection margin and any FLAIR to T2-weighted abnormalities and areas of tumor enhancement.

II.3.2 Clinical Target Volume 1 (CTV1):

The CTV1 is the GTV1 plus a margin of 1.0 cm in all directions. However, the CTV1 must not extend outside the brain. The CTV1 may also be modified to meet critical dose constraints (e.g., optic nerves) but should never be less than the GTV1. In cases where a partial or complete lobectomy has been performed, the region distal to the edge of the resection (i.e., where no brain tissue is present) does not need to be included in the CTV1. For example, if a patient has an anterior temporal lobectomy, the anterior middle cranial fossa does not need to be included in the tumor volume. In this situation, the CTV1 should be an expansion of the GTV1 in all directions, but not into the resection cavity.

II.3.3 Planning Target Volume 1 (PTV1):

The PTV expansion is institution dependent to account for set-up uncertainty. Typically, the PTV1 expansion is 3 to 5 mm in all directions to account for daily setup variation and patient movement, but not beam penumbra or buildup. Generally another 5-7 mm is added to block edge in 3D planning to account for penumbra.

II.3.4 GTV2

The region of contrast enhancement on T1 imaging should be contoured to define GTV2. In the case of a resection, the resection margin should be included in the GTV2 even if there is no residual contrast enhancement.

II.3.5 CTV2

CTV2 is defined by a 1 cm expansion of GTV2.

11.3.6 PTV2

The PTV expansion is institution dependent to account for set-up uncertainty. Typically, the PTV2 expansion is 3 to 5 mm in all directions to account for daily setup variation and patient movement, but not beam penumbra or buildup.

II.3.6 Internal Margin (IM), Set-Up Margin (SM):

There will be no IM or SM.

II.4 Prescription Isodose:

The prescription isodose (i.e. the isodose that is 100% of the prescription dose) should be the isodose surface (i.e. curve) that encompasses 95% of the PTV. In addition, the goal of the treatment plan is to encompass the entire PTV within the 95% isodose surface. The dose uniformity guidelines below should be met for both the PTV1 and the PTV2. If IMRT is used, the PTV and the PTV boost should be treated concomitantly.

II.5 Tissue Heterogeneity:

Calculations are required for IMRT and strongly recommended for 3D treatment planning to take into account the effect of tissue heterogeneities whenever CT-based planning is used.

II.6 Total Dose:

II.6.1 3D Total Dose:

The dose to the prescription isodose for the PTV1 (derived from the GTV1 – see above) will be 5000 cGy in 25 daily fractions of 200 cGy each. The dose will be delivered to the treatment volumes as previously described. The dose to the prescription isodose for the PTV2 (derived from the GTV2 – see above) will be 1000 cGy in 5 daily fractions of 200 cGy each. The dose will be delivered to the treatment volumes as previously described. Therefore, the total dose will be 6000 cGy in 30 daily fractions of 200 cGy each.

II.6.2 IMRT Total Dose:

The dose to the prescription isodose for the PTV1 (derived from the GTV1 – see above) will be 5400 cGy in 30 daily fractions of 180 cGy each. The dose to the prescription isodose for the PTV2 (derived from the GTV2 – see above) will be 6000 cGy in 30 daily fractions of 200 cGy each. The dose should be delivered concurrently to the treatment volumes as previously described. Alternatively, use of 2 sequential IMRT plans to deliver 5000 cGy in 25 fractions to PTV1 followed by an additional 1000 cGy to PTV2 is acceptable

II.7 Dose Uniformity:

The entire PTV should be encompassed within the 95% isodose surface as evaluated by dose volume histogram. Please note it is preferable that 95% or more of the PTV receives the prescribed dose. The uniformity guidelines should be met for both the PTV 1 and the PTV boost. In addition, none of the PTV boost should receive more than 110% of the prescription dose.

II.8 Time Considerations:

Patients will receive one treatment per day, five days per week (Monday through Friday with the exception of holidays). All fields will be treated each day. At least two fractions must be given during the first week of treatment.

II.8.1 Interruptions:

No special considerations need to be made for treatment delays of 1 week or less. Treatment may be given on weekends to make up for treatment interruptions. If treatment is delayed more than 1 week, notify the Study Chair.

II.9 Simulation:

Simulation will be performed using either a conventional CT or MRI simulator.

II.9.1 Patient Position and Immobilization:

The patient shall be treated in the supine or other appropriate position, depending on the location of the lesion. A head-holding device that is transparent to x-rays (thermoplast masks, bit-block, etc) must be used to ensure adequate immobilization during therapy of reproducible treatment setups.

II.10 Organs at Risk (OAR):

When possible, without shielding GTV/CTV/PTV, no more than 1% of the volume or 1 cc of each of the following OAR should receive more than the following doses: brainstem 5500 cGy, optic nerves and optic chiasm 5400 cGy, retina 4500 cGy, cervical spinal cord 5000 cGy, and lens 1000 cGy. These constraints may have a higher priority than the target volumes at the treating physician's discretion. If possible, no more than 1% or 1 cc of the contralateral uninvolved brain should receive more than 3000 cGy. Also, no more than 1% or 1 cc of unspecified tissue outside of the PTV to receive >110% of the prescribed dose. Planning organ at risk volumes (PRVs) are recommended such that the spinal cord should have 3-dimensional expansion by 5 mm while the optic nerves, optic chiasm, and brainstem should have a 3 dimensional expansion by at least 1 mm. The dose constraints to the PRVs will be the same as for their respective OARs as outlined above. Lower priority (lower priority than PTV coverage) include: Parotids (entire volume) ≤10 Gy, oral cavity/lips/nasal cavity mean dose 20 Gy and <1% >40 Gy; inner/middle ear mean dose 30 Gy and <1% >50 Gy; lens as low as reasonable possible. Typically 100% of the parotids should receive <10 Gy, but tumor coverage is of higher priority in cases where this dose will exceed 10 Gy.

II.11 Dose Calculation and Reporting:

Not applicable for this study

II.12 Dose Volume Histograms:

Dose volume histograms must include GTVs, CTVs, PTVs, and OARs as noted above. A DVH in absolute dose must also be submitted for so called "unspecified tissue," i.e., tissue contained within the skin, but not included with the GTV, CTV, PTV, or OAR.

II.13 IMRT Plan Verification:

If IMRT is used, the monitor units generated by the IMRT planning system must be independently checked prior to the patient's first treatment. Measurements in a QA phantom can suffice for a check as long as the plan's fluence distribution can be re-computed for a phantom geometry.

II.14 Quality Control and Definitions of Deviations:

This will be done according to standard guidelines. All plans and associated materials as per Mayo Clinic standard will be reviewed by 2 radiation oncologists.

II.15 Verification of treatment set-up:

Port films of each field will be obtained and compared with initial simulation films at least weekly. Alternatively, after initial ports are taken of all fields (excluding vertex), an orthogonal pair of reference ports may be taken on a weekly basis. For IMRT, orthogonal pair of reference films is sufficient for the initial and subsequent ports.

Questions regarding the radiotherapy section of this protocol should be directed to:

Appendix III Pembrolizumab ECI Drug-Induced Liver Injury (DILI)

Hepatotoxicity is injury or damage to the liver that may be associated with impaired liver function (Navarro and Senior 2006). Drug-induced hepatotoxicity is one of the most common causes of termination of drug development, a major reason for refusal of market authorization and for restricted use, and the single most important cause of the withdrawal of market authorization for products (Björnsson 2006). Thus, drug-induced hepatotoxicity is a major concern during the discovery, development to postauthorization phases of the product life cycle (excerpted from Draft Guidance Document, Hepatotoxicity of Health Products, Ministry of Public Health, Canada, December 2010).

As stated in the United States Food and Drug Administration (FDA) Guidance for Industry - Drug-Induced Liver Injury: Premarketing Clinical Evaluation; hepatocellular injury (usually detected by serum aminotransferase elevations [AT]) can be caused by drugs that rarely, if ever, cause severe DILI (e.g. aspirin, tacrine, statins, and heparin) as well as by drugs that do cause such injury. The frequency of serum AT elevations also is not a good indicator of a potential for severe DILI, because drugs such as tacrine (not a cause of severe DILI) can cause AT elevations in as many as 50 percent of patients. Very high levels of observed ATs may be a somewhat better indicator of potential for severe DILI, but the most specific indicator is evidence of altered liver function accompanying or promptly following evidence of hepatocellular injury.

The single clearest (most specific) predictor found to date of a drug's potential for severe hepatotoxicity, is the occurrence of hepatocellular injury (AT elevation) accompanied by increased serum total bilirubin (TBL), not explained by any other cause, such as viral hepatitis or exposure to other hepatotoxins, and without evidence of cholestasis, together with an increased incidence of AT elevations in the overall trial population compared to control. Increased plasma prothrombin time, or its international normalized ratio (INR), a consequence of reduced hepatic production of Vitamin K dependent clotting factors, is another potentially useful measure of liver function that might suggest the potential for severe liver injury.

Recognition of the importance of altered liver function, in addition to liver injury, began with Hyman Zimmerman's observation that drug-induced hepatocellular injury (i.e. AT elevation) accompanied by jaundice (i.e. TBL elevation) had a poor prognosis, with a 10 to 50 percent mortality from acute liver failure (in pretransplantation days) (Zimmerman 1978, 1999). This became known as "Hy's Law". This document describes the recommended process for monitoring and evaluation of subjects meeting the laboratory criteria for potential DILI defined as:

- an elevated alanine transaminase (ALT) or aspartate transaminase (AST) lab value that is greater than or equal to three times (3X) the upper limit of normal (ULN)
  and
- an elevated total bilirubin (TBL) lab value that is greater than or equal to two times (2X) ULN
  and
- at the same time, an alkaline phosphatase (ALP) lab value that is less than 2X ULN,

as a result of within-protocol-specific testing or unscheduled testing.

The protocol identifies these laboratory criteria for potential DILI as ECIs. ECIs are selected adverse experiences that must be reported within 24 hours.

Initiate **close observation** as defined below and continue follow-up until resolution.

- Repeat liver enzyme and serum bilirubin tests two (2) or three (3) times weekly. Frequency of retesting can decrease to once a week or less if abnormalities stabilize or study drug has been discontinued and the subject is asymptomatic.
- Obtain a more detailed history of symptoms and prior or concurrent diseases.
- Obtain a history of concomitant medication use (including prescription and nonprescription medications, herbal and other dietary supplements), alcohol use, recreational drug use and special diets. (See Section 5 for details.)
- Obtain a history of exposure to chemical agents or other environmental toxins.
- Obtain additional history and complete Stage 1 workup to attempt to rule out other potential causes of the transaminase elevation, including but not limited to the following: acute viral hepatitis types A, B, C, D, and E; autoimmune or alcoholic hepatitis; non-alcoholic steatohepatitis (NASH); hypoxic/ischemic hepatopathy; and biliary tract disease
- Consider gastroenterology or hepatology consultation

Appendix IV Presentation of Dermatologic Event

Collect information on clinical presentation and potential contributing factors. Key information should be summarized and entered on the Adverse Experience CRF. Any treatments administered should be entered on the Concomitant Medication CRF. ***Scan and forward this form to Principal Investigator***.

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

   _____

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

   If so what kind? _____

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

   If so what kind? _____

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

   If so what kind? _____

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

   If so what kind? _____

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

   If so what kind? _____

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

   If so what kind? _____

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

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

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

    If so what kind? _____

    i. Anaphylaxis? ☐ Yes ☐ No

    ii. Signs of hypotension? ☐ Yes ☐ No

    iii. Signs of dyspnea? ☐ Yes ☐ No

iv. Fever, night sweats, chills? ☐ Yes ☐ No

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

If so what kind? _____

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

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

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

Focused Skin Examination

Focused Skin Examination:

Key information should be summarized and entered on the Adverse Experience CRF.

Primary Skin Lesions Description

Color: _____

General description:

_____

_____

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

_____

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

_____

Any associated signs on physical examination?

_____

Scan this form and forward by email to the Principal Investigator listed on the cover page of the protocol.

Appendix V Patient Medication Diary MC1572

MC1572 Patient Medication Diary during Concurrent Radiation Therapy (RT)

Please record the time you take your temozolomide (Temodar®) medication and number of pills taken. Return this diary at your next clinic visit and make sure you get another diary.
If steroids are taken on any day, please record the time and number of pills.
If an area is shaded gray, that means you are NOT scheduled to take that drug on that day.

{Pembrolizumab given in clinic}		Temozolomide Taken daily during RT		Steroid dose (if applicable)	
Day	Date (mm/dd/yy)	Time taken (please circle am or pm):	Number of tablets:	Time taken (please circle am or pm):	Number of capsules:
1		am/pm		am/pm	
2		am/pm		am/pm	
3		am/pm		am/pm	
4		am/pm		am/pm	
5		am/pm		am/pm	
6		am/pm		am/pm	
7		am/pm		am/pm	
8		am/pm		am/pm	
9		am/pm		am/pm	
10		am/pm		am/pm	
11		am/pm		am/pm	
12		am/pm		am/pm	
13		am/pm		am/pm	
14		am/pm		am/pm	
15		am/pm		am/pm	
16		am/pm		am/pm	
17		am/pm		am/pm	
18		am/pm		am/pm	
19		am/pm		am/pm	
20		am/pm		am/pm	
21		am/pm		am/pm	
22		am/pm		am/pm	
23		am/pm		am/pm	
24		am/pm		am/pm	
25		am/pm		am/pm	
26		am/pm		am/pm	
27		am/pm		am/pm	
28		am/pm		am/pm	
29		am/pm		am/pm	
30		am/pm		am/pm	
31		am/pm		am/pm	
32		am/pm		am/pm	
33		am/pm		am/pm	

{Pembrolizumab given in clinic}		Temozolomide Taken daily during RT		Steroid dose (if applicable)	
Day	Date (mm/dd/yy)	Time taken (please circle am or pm):	Number of tablets:	Time taken (please circle am or pm):	Number of capsules:
34		am/pm		am/pm	
35		am/pm		am/pm	
36		am/pm		am/pm	
37		am/pm		am/pm	
38		am/pm		am/pm	
39		am/pm		am/pm	
40		am/pm		am/pm	
41		am/pm		am/pm	
42		am/pm		am/pm	
43		am/pm		am/pm	
44		am/pm		am/pm	
45		am/pm		am/pm	
46		am/pm		am/pm	
47		am/pm		am/pm	
48		am/pm		am/pm	
49		am/pm		am/pm	
50		am/pm		am/pm	
51		am/pm		am/pm	
52		am/pm		am/pm	
53		am/pm		am/pm	
54		am/pm		am/pm	
55		am/pm		am/pm	
56		am/pm		am/pm	
57		am/pm		am/pm	

_____ _____
Participant Signature Date

_____ _____
Medical Personnel Signature Date

My next scheduled visit is: _____

If you have any questions, please call: _____
Bring *all* bottles and any unused study medication along with this diary when you return for your next appointment.

Study Coordinator Use Only
Number of pills returned _____ Number of vials returned: _____
Discrepancy Yes____/No____ Verified by _____ Date_____

MC1572 Patient Medication Diary during Adjuvant Treatment

Please record the time and date that you take your study medications. Return this diary, the medication bottles (even if empty or unopened), and any unused tablets or capsules at your next clinic visit and make sure you get another diary. If an area is shaded gray, that means you are **not** scheduled to take that particular drug on that day.

Day	Temozolomide		# of tablets
	Date taken (mm/dd/yy)	Time taken (circle a.m. or p.m.)	
1		a.m./ p.m.	
2		a.m./ p.m.	
3		a.m./ p.m.	
4		a.m./ p.m.	
5		a.m./ p.m.	
6	No temozolomide taken		
7			
8			
9			
10			
11			
12			
13			
14			
15			
16			
17			
18			
19			
20			
21			
22			
23			
24			
25			
26			
27			
28			

_____ _____
Participant Signature Date

_____ _____
Medical Personnel Signature Date

My next scheduled visit is: _____
If you have any questions, please call: _____
Bring *all* bottles and any unused study medication along with this diary when you return for your next appointment.

Study Coordinator Use Only
Number of pills returned _____ Number of vials returned: _____
Discrepancy Yes____/No____ Verified by _____ Date_____