SPONSOR: Moffitt Cancer Center and Research Institute

TITLE: A Phase I Trial of Pembrolizumab and Vorinostat Combined with Temozolomide and Radiation Therapy for Newly Diagnosed Glioblastoma

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1.0 TRIAL SUMMARY

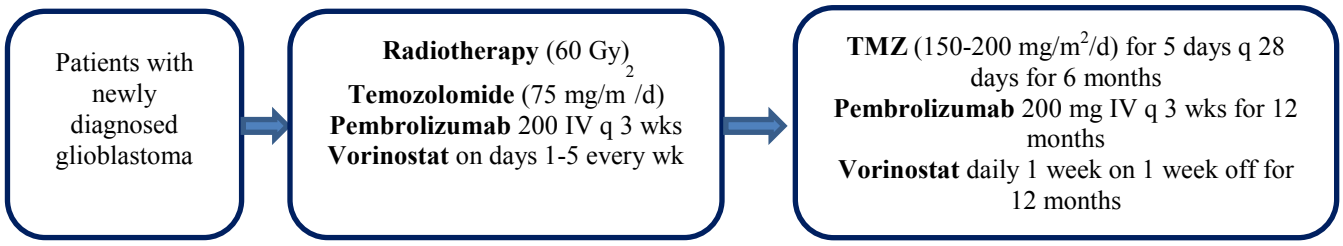
Abbreviated Title	**Phase I trial of pembrolizumab with vorinostat and temozolomide for newly diagnosed glioblastoma**
Trial Phase	Ib
Clinical Indication	Newly diagnosed glioblastoma
Trial Type	Open label
Type of control	Not applicable
Route of administration	Intravenous, Oral
Trial Blinding	Not applicable
Treatment Groups	1 Group
Number of trial subjects	32
Estimated enrollment period	24 months
Estimated duration of trial	36 months
Duration of Participation	24 months
Estimated average length of treatment per patient	15 months

2.0 TRIAL DESIGN

2.1 Trial Design

This is a standard 3+3 design and will include 2 cohorts: 1) dose escalation cohort, and 2) dose expansion cohort. Dose escalation will occur separately for concurrent radiotherapy part of treatment and maintenance part of treatment.

2.2 Trial Diagram



Dose Escalation Phase

Dose Escalation Schedule During Radiotherapy Phase		
Dose Level	**Dose**	
	Pembrolizumab	**Vorinostat**
Level -1	200 mg IV every 3 weeks	100 mg/day orally on days 1-5 every week during radiotherapy
Level 1	200 mg IV every 3 weeks	200 mg/day orally on days 1-5 every week during radiotherapy
Level 2	200 mg IV every 3 weeks	300 mg/day orally on days 1-5 every week during radiotherapy
Dose Escalation Schedule During Maintenance Phase		
Dose Level	**Dose**	
	Pembrolizumab	**Vorinostat**
Level -1	200 mg IV every 3 weeks	200 mg/day orally 1 week on 1 week off after radiotherapy
Level 1	200 mg IV every 3 weeks	300 mg/day orally 1 week on 1 week off after radiotherapy
Level 2	200 mg IV every 3 weeks	400 mg/day orally 1 week on 1 week off after radiotherapy

Dose Expansion Phase

Twenty patients will be treated with vorinostat at MTD (from dose escalation phase), pembrolizumab, temozolomide and radiation

3.0 OBJECTIVE(S) & HYPOTHESIS(ES)

3.1 Primary Objective(s) & Hypothesis(es)

(1) **Objective:** To evaluate the safety, tolerability, and to determine the maximum tolerated dose (MTD) of vorinostat given in combination with pembrolizumab, temozolomide, and radiotherapy in patients with newly diagnosed glioblastoma.

Hypothesis: Combination of pembrolizumab and vorinostat with radiotherapy and temozolomide will have acceptable safety and tolerability.

3.2 Secondary Objective(s) & Hypothesis(es)

(1) **Objective**: To evaluate the 12 months and 24 months survival rate in patients with newly diagnosed glioblastoma who are treated with pembrolizumab in combination with vorinostat and standard treatment with radiotherapy and temozolomide.

Hypothesis: Addition of pembrolizumab and vorinostat to standard treatment with radiotherapy and temozolomide will augment the survival.

3.3 Exploratory Objective

(1) **Objective:** To explore tissue biomarkers that may predict tumor response to pembrolizumab in combination with vorinostat and standard treatment with radiotherapy and temozolomide in patients with newly diagnosed glioblastoma.

4.0 BACKGROUND & RATIONALE

4.1 Background

Refer to the Investigator's Brochure (IB)/approved labeling for detailed background information on pembrolizumab and vorinostat.

4.1.1 Pharmaceutical and Therapeutic Background

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

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

regulate antigen receptor signaling upon engagement of its ligands (PD-L1 and/or PD-L2). The structure of murine PD-1 has been resolved. PD-1 and family members are type I transmembrane glycoproteins containing an Ig Variable-type (V-type) domain responsible for ligand binding and a cytoplasmic tail which is responsible for the binding of signaling molecules. The cytoplasmic tail of PD-1 contains 2 tyrosine-based signaling motifs, an immunoreceptor tyrosine-based inhibition motif (ITIM) and an immunoreceptor tyrosine-based switch motif (ITSM). Following T-cell stimulation, PD-1 recruits the tyrosine phosphatases SHP-1 and SHP-2 to the ITSM motif within its cytoplasmic tail, leading to the dephosphorylation of effector molecules such as CD3ζ, PKCθ and ZAP70 which are involved in the CD3 T-cell signaling cascade. The mechanism by which PD-1 down modulates T-cell responses is similar to, but distinct from that of CTLA-4 as both molecules regulate an overlapping set of signaling proteins. PD-1 was shown to be expressed on activated lymphocytes including peripheral CD4+ and CD8+ T-cells, B-cells, T regs and Natural Killer cells. Expression has also been shown during thymic development on CD4-CD8- (double negative) T-cells as well as subsets of macrophages and dendritic cells. The ligands for PD-1 (PD-L1 and PD-L2) are constitutively expressed or can be induced in a variety of cell types, including non-hematopoietic tissues as well as in various tumors . Both ligands are type I transmembrane receptors containing both IgV- and IgC-like domains in the extracellular region and contain short cytoplasmic regions with no known signaling motifs. Binding of either PD-1 ligand to PD-1 inhibits T-cell activation triggered through the T-cell receptor. PD-L1 is expressed at low levels on various non-hematopoietic tissues, most notably on vascular endothelium, whereas PD-L2 protein is only detectably expressed on antigen-presenting cells found in lymphoid tissue or chronic inflammatory environments. PD-L2 is thought to control immune T-cell activation in lymphoid organs, whereas PD-L1 serves to dampen unwarranted T-cell function in peripheral tissues. Although healthy organs express little (if any) PD-L1, a variety of cancers were demonstrated to express abundant levels of this T-cell inhibitor. PD-1 has been suggested to regulate tumor-specific T-cell expansion in subjects with melanoma (MEL). This suggests that the PD-1/PD-L1 pathway plays a critical role in tumor immune evasion and should be considered as an attractive target for therapeutic intervention.

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

Temozolomide is an oral alkylating agent. Continuous daily temozolomide (75 mg per square meter of body-surface area per day, 7 days per week from the first to the last day of radiotherapy) plus radiotherapy (fractionated focal irradiation in daily fractions of 2 Gy given 5 days per week for 6 weeks, for a total of 60 Gy), followed by six cycles of adjuvant temozolomide (150 to 200 mg per square meter for 5 days during each 28-day cycle) is the United States Federal Drug Administration (FDA) approved treatment for patients with newly diagnosed glioblastoma [22]. This treatment increased the median survival from 12.1 months with radiotherapy alone to 14.6 months [22]. The side effects of treatment included:

grade 3 or 4 neutropenia in 4%, and grade 3 or 4 thrombocytopenia in 3%. The most common nonhematologic adverse event was moderate-to-severe fatigue [22].

Vorinostat is a small-molecule inhibitor of histone deacetylases (HDAC) that binds directly to the enzyme's active site in the presence of a zinc ion and is approved by the FDA for use in patients with advanced cutaneous T-cell lymphoma. Vorinostat crosses blood-brain barrier and has shown activity against high-grade glioma in preclinical studies [23]. As per vorinostat Investigator Brochure, the most commonly reported adverse experiences are diarrhea, nausea, fatigue, thrombocytopenia, hyperglycaemia, vomiting, anorexia, anaemia, neutropenia, constipation, blood creatinine increased, leukopenia, dyspnea, weight decreased, decreased appetite, alopecia, aspartate aminotransferase increased and cough are the most common adverse events.

4.1.2 Preclinical and Clinical Trial Data

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

4.2 Rationale

4.2.1 Rationale for the Trial and Selected Subject Population

Glioblastoma (GBM) remains one of the most fatal tumors with a median survival of about 15 months, despite aggressive combination therapy with radiation and temozolomide (TMZ). Concurrent radiotherapy (60 Gy in 30 daily fractions) with TMZ (75 mg/m²/day) followed by 6 cycles of TMZ (150–200 mg/m²/day for 5 days every 28 days) and NovoTTF are the only treatments which have shown survival benefit in newly diagnosed GBM patients [22; 24]. Thus, GBM remains a largely unmet medical need requiring novel and effective treatment strategies.

<u>Rational for combining pembrolizumab with radiotherapy and TMZ</u>

Part of the challenge in treating GBM is the naturally immunoprivileged environment of the brain. Pre-clinical studies have shown a significant increase in expression of PD-1 on peripheral blood CD4+ and CD8+ T cells in patients with high grade gliomas. In a study by Wei et al., PD-1+CD4+ T cells were clearly increased in peripheral blood of patients with GBM (16.3±0.6 %) compared to healthy cohort (2.5 ± 0.2 %) [25]. Expression of PD-1 and PD-L1 is found in the microenvironment of most high grade gliomas [26; 27]. PD-1 is expressed on tumor-infiltrating lymphocytes whereas PD-L1 is expressed on tumor cells and microglia in GBM specimens [28].

Moreover, there is emerging evidence that radiotherapy synergizes with CTLA-4 and anti-PD 1/PD-L1 blockade and produces tumor regression and long-term survival in a variety of cancer models [29; 30; 31; 32]. In a study by Zeng et al., combination of anti-PD-1 antibody with radiotherapy in a mouse orthotopic GBM model generated robust and durable responses and doubled the survival when compared with either modality alone [33]. In this study, analysis of the brain and spinal cord of animals treated with combination therapy showed an

increase in the cytotoxic to regulatory T cell ratio with increased tumor infiltration by cytotoxic T cells (CD8+/interferon-γ+/tumor necrosis factor-α+).

Our investigator initiated trial sponsored by Merck (NCT02313272) has shown promising results in patients with recurrent GBM who are treated with hypofractionated stereotactic radiotherapy combined with pembrolizumab and bevacizumab. We have treated 32 patients so far and combination is very well tolerated and several patients have achieved objective response (complete response+ partial response). Durable responses as long as 16 months have been observed.

This supports addition of pembrolizumab to standard concurrent chemoradiotherapy for newly diagnosed GBM.

Rational for combining vorinostat and pembrolizumab with radiotherapy and TMZ

Vorinostat, an orally bioavailable hydroxymate pan-histone deacetylase (HDAC) inhibitor, has shown anti-tumor activity against GBM cell lines in vitro and in vivo orthotopic xenografts models [33]. Combination of vorinostat with TMZ and radiotherapy has resulted on synergistic effect on growth inhibition of glioma cell lines. Moreover, vorinostat readily penetrates the blood-brain barrier and has radiosensitizing properties. Tumor samples of patients with GBM who have received vorinostat before surgery has shown that vorinostat can penetrate tumors and inhibit histone acetylation [34].

A growing body of evidence indicates that epigenetic silencing of genes involved in antigen processing and immune recognition results in immune escape and resistance to immunotherapy [35; 36]. Pre-clinical experiments have shown that use of HDAC inhibitors such as vorinostat can restore tumor immune recognition and synergize with anti-PD 1/PD-L1 antibodies [36]. Studies on several murine models have shown that combination therapy significantly enhances the response to PD-1 blockade immunotherapy by robustly inducing expression of multiple chemokines in tumor cells, tumor infiltrating macrophages and T cells. In addition, this combination has resulted in augmented T cell infiltration and T-cell dependent tumor regression [37]. These results suggest that combination of HDAC inhibitors with PD-1 blockade represents a potential therapeutic strategy to maximize the immune response to checkpoint inhibitors.

Furthermore, Galanis et al. have investigated the safety and efficacy of concurrent chemoradiotherapy with TMZ and vorinostat in patients with newly diagnosed GBM. The combination therapy was safe and well tolerated without any cases of radiation necrosis. Based on this study, maximum tolerated dose (MTD) for vorinostat in combination with TMZ and radiotherapy in patients with newly diagnosed GBM is 300 mg/day, days 1-5 weekly during concurrent therapy and 400 mg/day on days 1-7 and 15-21 during maintenance therapy with TMZ [34; 38].

Collectively, we haves strong pre-clinical evidence that combining PD-1/PDL-1 blockade with HDAC inhibitors such as vorinostat and radiotherapy plus TMZ independently enhance anti-tumor immune responses and tumor regression. Hence, it is of great interest to study the

combination of all these treatment modalities in newly diagnosed GBM patients with very limited treatment options.

4.2.2 Rationale for Dose Selection/Regimen/Modification of Pembrolizumab (MK-3475)

An open-label Phase I trial (Protocol 001) is being conducted to evaluate the safety and clinical activity of single agent pembrolizumab. The dose escalation portion of this trial evaluated three dose levels, 1 mg/kg, 3 mg/kg, and 10 mg/kg, administered every 2 weeks (Q2W) in subjects with advanced solid tumors. All three dose levels were well tolerated and no dose-limiting toxicities were observed. This first in human study of MK-3475 showed evidence of target engagement and objective evidence of tumor size reduction at all dose levels (1 mg/kg, 3 mg/kg and 10 mg/kg Q2W). No MTD has been identified to date. 10.0 mg/kg Q2W, the highest dose tested in PN001, will be the dose and schedule utilized in Cohorts A, B, C and D of this protocol to test for initial tumor activity. Recent data from other clinical studies within the MK-3475 program has shown that a lower dose of MK-3475 and a less frequent schedule may be sufficient for target engagement and clinical activity.

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

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

The rationale for further exploration of 2 mg/kg and comparable doses of pembrolizumab in solid tumors is based on: 1) similar efficacy and safety of pembrolizumab when dosed at either 2 mg/kg or 10 mg/kg Q3W in melanoma patients, 2) the flat exposure-response relationships of pembrolizumab for both efficacy and safety in the dose ranges of 2 mg/kg Q3W to 10 mg/kg Q3W, 3) the lack of effect of tumor burden or indication on distribution behavior of pembrolizumab (as assessed by the population PK model) and 4) the assumption

that the dynamics of pembrolizumab target engagement will not vary meaningfully with tumor type.

The choice of the 200 mg Q3W as an appropriate dose for the switch to fixed dosing is based on simulations performed using the population PK model of pembrolizumab showing that the fixed dose of 200 mg every 3 weeks will provide exposures that 1) are optimally consistent with those obtained with the 2 mg/kg dose every 3 weeks, 2) will maintain individual patient exposures in the exposure range established in melanoma as associated with maximal efficacy response and 3) will maintain individual patients exposure in the exposure range established in melanoma that are well tolerated and safe.

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

4.2.3 Biomarker Research

Archival tissue will be collected and assessed for direct evaluation of the intratumoral immune compartment. If biopsy or surgical tumor specimens become available following study treatment, these tissues will be included in the analysis.

5.0 METHODOLOGY

5.1 Entry Criteria

5.1.1 Diagnosis/Condition for Entry into the Trial

Newly diagnosed glioblastoma or gliosarcoma

5.1.2 Subject Inclusion Criteria

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

1. Histologically confirmed diagnosis of World Health Organization Grade IV malignant glioma.

2. An interval of ≥ 21 days since surgical resection prior to treatment on the trial

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

4. Karnofsky performance status of 70 or higher

5. Demonstrate adequate organ function as defined in Table 1, all screening labs should be performed within 21 days of treatment initiation.

Table 1 Adequate Organ Function Laboratory Values

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

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

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

8. Life expectancy ≥ 12 weeks

9. Willingness to discontinue medications known to be associated with risk of Torsades de Pointes such as quinidine, procainamide, disopyramide, amiodarone, erythromycin, clarithromycin, chlorpromazine and haloperidol.

10. Single lesion < 4 cm in longest diameter (diameter of enhancing lesion)

11. Patient shouldn't have received any anti-cancer therapy for glioblastoma in past.

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

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

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

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

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

15. Use of Optune device is allowed.

5.1.3 Subject Exclusion Criteria

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

1. Had prior treatment of GBM with radiation and temozolomide.
2. Has evidence of leptomeningeal disease.
3. Had prior treatment with Gliadel.
4. Is unable (due to existent medical condition) or unwilling to have a contrast enhanced MRI of brain.
5. Is currently participating and receiving study therapy or has participated in a study of an investigational agent and received study therapy or used an investigational device within 4 weeks of the first dose of treatment.
6. Has a diagnosis of immunodeficiency or is receiving systemic steroid therapy or any other form of immunosuppressive therapy within 7 days prior to the first dose of trial treatment. Physiologic doses of steroid therapy (≤ 2 mg/day dexamethasone equivalents) by the time of first dose of treatment are allowed.
7. Has a known history of active TB (Bacillus Tuberculosis)
8. Hypersensitivity to pembrolizumab or any of its excipients.
9. Has had a prior anti-cancer monoclonal antibody (mAb) within 4 weeks prior to study Day 1 or who has not recovered (i.e., ≤ Grade 1 or at baseline) from adverse events due to agents administered more than 4 weeks earlier.
10. Has had prior chemotherapy, targeted small molecule therapy, or radiation therapy within 2 weeks prior to study Day 1 or who has not recovered (i.e., ≤ Grade 1 or at baseline) from adverse events due to a previously administered agent.

- Note: Subjects with ≤ Grade 2 neuropathy are an exception to this criterion and may qualify for the study.

- Note: If subject received major surgery, they must have recovered adequately from the toxicity and/or complications from the intervention prior to starting therapy.

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

12. Has active autoimmune disease that has required systemic treatment in the past 2 years (i.e. with use of disease modifying agents, corticosteroids or immunosuppressive drugs). Replacement therapy (eg., thyroxine, insulin, or physiologic corticosteroid replacement therapy for adrenal or pituitary insufficiency, etc.) is not considered a form of systemic treatment. Subjects with vitiligo or resolved childhood asthma/atopy would be an exception to this rule. Subjects that require intermittent use of bronchodilators or local steroid injections would not be excluded from the study. Subjects with hypothyroidism stable on hormone replacement or Sjorgen's syndrome will not be excluded from the study.

13. Has known history of, or any evidence of active, interstitial lung disease or non-infectious pneumonitis requiring corticosteroid therapy.

14. Has an active serious infection requiring systemic therapy.

15. Had major surgical procedure, open biopsy, or significant traumatic injury within 21 days prior to day 1 of treatment on study.

16. Has a history or current evidence of any condition, therapy, or laboratory abnormality that might confound the results of the trial, interfere with the subject's participation for the full duration of the trial, or is not in the best interest of the subject to participate, in the opinion of the treating investigator.

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

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

19. Has received prior therapy with an anti-PD-1, anti-PD-L1, or anti-PD-L2 agent.

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

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

22. Has received a live vaccine within 30 days of planned start of study therapy.

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

5.2 Radiation therapy

5.2.1 Dose Specifications

Radiation therapy should begin after substantial recovery from surgical resection, not more than 42 (+/- 7) days after surgery. External-beam RT to a total dose of 60 Gy will be administered in daily doses of 2 Gy, typically on a 5 days on / 2 days off schedule as appropriate for scheduling, over 6-7 weeks. RT is administered to the pre-operative tumor volume plus a 2-3 cm margin, as directed by a radiation oncologist. Radiation therapy can be administered in a local facility.

5.2.2 Radiation Therapy Adverse Events

5.2.2.1 Acute

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

5.2.2.2 Early Delayed

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

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

5.2.2.3 Late Delayed

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

5.3 Trial Treatments

Treatment must begin within 21 days of registering to the trial. Treatment should also begin ≥ 3 weeks and ≤ 6 (+/1) weeks following surgery. Each cycle will consist of 12 weeks.

Dose Escalation Cohort:

Treatment will include two phases: 1) concurrent radiotherapy phase and 2) maintenance phase. Dose escalation will occur separately for concurrent radiotherapy part of treatment and maintenance part of treatment.

The dose of pembrolizumab will be 200 mg dose IV every 3 weeks. The starting dose (i.e., dose level 1) of vorinostat was 200 mg/day orally on days 1-5 every week during radiotherapy and 300 mg/day orally 1 week on 1 week off during maintenance phase, starting after completion of concurrent therapy with radiation (+/- 3 days). The dose of vorinostat during radiotherapy was reduced to 100 mg mg/day orally on days 1-5 every week due to DLT. This dose is well tolerated and is currently being expanded.

The starting dose of vorinostat during maintenance phase, beginning after completion of concurrent therapy with radiation (+/- 3 days) was 300 mg/day orally 1 week on 1 week off. The dose is escalated to 400 mg/day orally 1 week on 1 week off, as per schema in a 3+3 fashion.

Concurrent Radiotherapy Phase:

During concurrent radiotherapy phase of treatment, patients with newly diagnosed GBM will receive radiotherapy (60 Gy in 30 daily fractions) as mentioned above.

Temozolomide (75 mg/m^2/day orally) will be administered daily during the course of radiotherapy as per standard of care [22]. Temozolomide will be administered continuously from Day 1 of radiotherapy to the last day of radiation at a daily oral dose of 75 mg/m2. The dose will be determined using actual body surface area (BSA) as calculated in square meters at the beginning of the concomitant treatment. The BSA will be calculated from the height obtained at the screening visit and the weight obtained at the visit immediately before the first day of treatment. The dose of temozolomide does not have to be adjusted unless there has been at least a 10% change in body weight; recalculation of dose for < 10% weight changes is allowed at the discretion of the Investigator. The daily dose will be rounded to the nearest 5 mg.

Vorinostat will be administered orally at 100, 200 or 300 mg/day dose on days 1-5 every week (based on dose level); starting on first day of radiotherapy. Safety and tolerability of vorinostat 300 mg/day dose on days 1-5 every week in combination with temozolomide (75 mg/m^2/day orally) has been proven in a phase I/II trial (N0874-ABTC 0902, Alliance) by Galanis et al. 2014 [38].

Pembrolizumab will be administered as an IV intravenous infusion and will be evaluated at 200 mg. Pembrolizumab will be administered every 3 weeks (+/-3 days) starting on first day (+/- 3days) of radiotherapy.

Table 2 summarizes the doses for pembrolizumab and vorinostat during radiotherapy part of treatment.

Dose Escalation Schedule During Radiotherapy Phase		
Dose Level	**Dose**	
	Pembrolizumab	**Vorinostat**
Level -1	200 mg IV every 3 weeks	100 mg/day orally on days 1-5 every week during radiotherapy
Level 1	200 mg IV every 3 weeks	200 mg/day orally on days 1-5 every week during radiotherapy
Level 2	200 mg IV every 3 weeks	300 mg/day orally on days 1-5 every week during radiotherapy

Maintenance Phase:

During maintenance phase, temozolomide will start 4 weeks (+/- 7 days) after last dose of radiotherapy and will continue for 6 cycles post radiotherapy (150-200 mg/m^2/day, days 1-5 every 4 +/- 1 weeks) as per standard of care [22]. As per standard of care, the starting dose for the first cycle will be 150 mg/m2/day, with a single dose escalation to 200 mg/m2/day in subsequent cycles if no temozolomide-related adverse events > Grade 2 are noted. The dose will be determined using the BSA calculated at the beginning of each treatment cycle. The BSA will be calculated from the height obtained at the screening visit and from the weight obtained at the visit immediately before each cycle. The dose of temozolomide does not have to be adjusted unless there has been at least a 10% change in body weight; recalculation of dose for < 10% weight changes is allowed at the discretion of the Investigator. The dose will also not be capped for those that are overweight. The daily dose will be rounded to the nearest 5 mg (where dosage strengths are available to accommodate rounding to 5 mg).

Vorinostat will be administered orally at 200, 300 or 400 mg/day (based on dose level) on a 1 week on 1 week off schedule for **12 months**. Vorinostat will start the day after completion of radiotherapy (+ 3 days). Safety of vorinostat 400 mg/day on a 1 week on 1 week off schedule in combination with maintenance temozolomide has been shown in a phase 1 study by Lee et al. 2012 [34].

Pembrolizumab 200 mg IV will continue every 3 weeks (+/-3 days) for 12 months or 18 infusions whatever comes first.

Table 3 summarizes the doses for pembrolizumab and vorinostat during maintenance part of treatment.

Table 3 Dose Escalation Schedule for Pembrolizumab and Vorinostat maintenance part of treatment.

Dose Escalation Schedule During Maintenance Phase		
Dose Level	**Dose**	
	Pembrolizumab	**Vorinostat**
Level -1	200 mg IV every 3 weeks	200 mg/day orally 1 week on 1 week off after radiotherapy
Level 1	200 mg IV every 3 weeks	300 mg/day orally 1 week on 1 week off after radiotherapy
Level 2	200 mg IV every 3 weeks	400 mg/day orally 1 week on 1 week off after radiotherapy

In all patients, treatment with study drugs will continue until confirmed disease progression, patient refusal, patient lost to follow up, unacceptable toxicity, completion of scheduled dosing, whichever occurs first, or the study is terminated by the Sponsor (Moffitt Cancer Center).

Dose Expansion Phase:

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

Definition of Maximum Tolerated Dose:

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

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

5.3.1 5.3.1 Definition of Dose-Limiting Toxicity

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

A dose-limiting toxicity (DLT) will be defined as any one of the following adverse events occurring within 6 weeks from last dose of radiation therapy for radiotherapy phase and 4 weeks from the start day of maintenance dose of vorinostat [Cycle 1 Day 43 (+/-3)] for maintenance phase:

CNS toxicities:

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

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

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

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

Non-CNS toxicities:

- Any Grade 4 immune-related adverse event (irAE)
- Any ≥ Grade 3 colitis
- Any Grade 3 or 4 non-infectious pneumonitis irrespective of duration
- Any Grade 2 pneumonitis that does not resolve to ≤ Grade 1 within 3 days of the initiation of maximal supportive care
- Any Grade 3 irAE, excluding colitis or pneumonitis, that does not downgrade to Grade 2 within 3 days after onset of the event despite optimal medical management including systemic corticosteroids or does not downgrade to ≤ Grade 1 or baseline within 14 days
- Liver transaminase elevation > 8 × upper limit of normal (ULN) or total bilirubin > 5 × ULN
- Any ≥ Grade 3 non-irAE, except for the exclusions listed below

The definition excludes the following conditions:

- Grade 3 fatigue lasting ≤ 7 days
- Grade 3 endocrine disorder (thyroid, pituitary, and/or adrenal insufficiency) that is managed with or without systemic corticosteroid therapy and/or hormone replacement therapy and the subject is asymptomatic
- Grade 3 inflammatory reaction attributed to a local antitumor response (eg, inflammatory reaction)
- Concurrent vitiligo or alopecia of any AE grade

- Grade 3 infusion-related reaction (first occurrence and in the absence of steroid prophylaxis) that resolves within 6 hours with appropriate clinical management
- Grade 3 or 4 neutropenia that is not associated with fever or systemic infection that improves by at least 1 grade within 14 days. Grade 3 or Grade 4 febrile neutropenia will be a DLT regardless of duration or reversibility
- Grade 3 or 4 lymphopenia
- Grade 3 or 4 thrombocytopenia that is not associated with clinically significant bleeding that requires medical intervention, and improves by at least 1 grade within 14 days
- Isolated Grade 3 electrolyte abnormalities that are not associated with clinical signs or symptoms and are reversed with appropriate maximal medical intervention within 3 days
- Immune-related AEs are defined as AEs of an immune nature (ie, inflammatory) in the absence of a clear alternative etiology. In the absence of a clinically significant abnormality, repeat laboratory testing will be conducted to confirm significant laboratory findings prior to designation as a DLT. Laboratory abnormalities that are not deemed to be clinical significant will not be considered a DLT.

While the rules for adjudicating DLTs in the context of dose exploration are specified above, an AE not listed above may be defined as a DLT after a consultation with the sponsor and investigators, based on the emerging safety profile.

Dose escalation will be determined based on the occurrence of DLTs. For the purposes of determining whether to advance the dose levels, DLTs will be counted by patient. For all observed toxicities, subjects should be assessed for inter-current illness or other causes and treated as appropriate.

In the event of the development of any grade 3 or 4 toxicity felt to be at least possibly related to pembrolizumab, pembrolizumab will be held until resolution to grade 1 or baseline assuming that occurs within 6 weeks window. Treatment with pembrolizumab can be resumed after resolution of DLT to grade 1 or baseline except for following adverse events: Grade 4 infusion reactions, ≥ Grade 3 pneumonitis, ≥ Grade 3 nephritis, ≥ Grade 3 colitis, increased alanine aminotransferase (ALT) or aspartate aminotransferase (AST) greater than 5 times upper limit of normal or total bilirubin greater than 3 times upper limit of normal.

Dose escalation for vorinostat will follow the standard 3+3 design. The enrollment to expansion cohort for radiotherapy phase will be delayed for 6 weeks after the completion of radiation therapy by the last patient enrolled at the MTD dose level for radiation therapy phase. The enrollment to expansion cohort for maintenance phase will be delayed for 4 weeks after the start day of maintenance dose of vorinostat [Cycle 1 Day 43 (+/-3)] by the

last patient enrolled at the MTD dose level for maintenance phase. This period will allow monitoring potential delayed toxicities. Dose escalation/de-escalation will proceed according to the following scheme.

Table 3 Dose Escalation Decision Rule

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

5.3.2 Dose Selection/Modification

5.3.2.1 Dose Selection

The rationale for selection of doses to be used in this trial is provided in Section 4.0 – Background and Rationale. Details on the dose calculation, preparation and administration are provided in the Pharmacy Manual.

5.3.2.2 Dose Modification/Delay

If the adverse event is related to only one drug, the dose modification/delay will be followed as per guidelines for that specific drug (outlined below) and other treatments will continue with no modification/delay. In cases that the AE can be related to more than one drug, all contributing drugs should be modified/delayed as per each drug's specific guideline.

5.3.2.2.1 Pembrolizumab

Adverse events (both non-serious and serious) associated with pembrolizumab exposure may represent an immunologic etiology. These adverse events may occur shortly after the first

dose or several months after the last dose of treatment. Pembrolizumab must be withheld for drug-related toxicities and severe or life-threatening AEs as per Table 4 below.

See Section 5.6.1 and Events of Clinical Interest Guidance Document for supportive care guidelines, including use of corticosteroids.

Table 4 Dose Modification Guidelines for Pembrolizumab-Related Adverse Events

Toxicity	Hold Pembrolizumab For Grade	Timing for Restarting Pembrolizumab	Discontinue Subject
Diarrhea/Colitis	2-3	Toxicity resolves to Grade 0-1.	Toxicity does not resolve within 12 weeks of last dose or inability to reduce corticosteroid to 10 mg or less of prednisone or equivalent per day within 12 weeks.
	4	Permanently discontinue	Permanently discontinue
AST, ALT, or Increased Bilirubin	2	Toxicity resolves to Grade 0-1	Toxicity does not resolve within 12 weeks of last dose.
	3-4	Permanently discontinue (see exception below)[1]	Permanently discontinue
Type 1 diabetes mellitus (if new onset) or Hyperglycemia	T1DM or 3-4	Hold pembrolizumab for new onset Type 1 diabetes mellitus or Grade 3-4 hyperglycemia associated with evidence of beta cell failure.	Resume pembrolizumab when patients are clinically and metabolically stable.
Hypophysitis	2-3	Toxicity resolves to Grade 0-1	Toxicity does not resolve within 12 weeks of last dose or inability to reduce corticosteroid to 10 mg or less of prednisone or equivalent per day within 12 weeks.
	4	Permanently discontinue	Permanently discontinue
Hyperthyroidism	3	Toxicity resolves to Grade 0-1	Toxicity does not resolve within 12 weeks of last dose or inability to reduce corticosteroid to 10 mg or less of prednisone or equivalent per day within 12 weeks.
	4	Permanently discontinue	Permanently discontinue
Hypothyroidism	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.
Infusion Reaction	3-4	Permanently discontinue	Permanently discontinue
Pneumonitis	2	Toxicity resolves to Grade 0-1 Permanently discontinue if recurrent pneumonitis.	Toxicity does not resolve within 12 weeks of last dose or inability to reduce corticosteroid to 10 mg or less of prednisone or equivalent per day within 12 weeks. Discontinue pembrolizumab permanently for recurrent Grade 2 pneumonitis.
	3-4	Permanently discontinue	Permanently discontinue
Renal Failure or Nephritis	2	Toxicity resolves to Grade 0-1	Toxicity does not resolve within 12 weeks of last dose or inability to reduce corticosteroid to 10 mg or less of prednisone or equivalent per day within 12 weeks.
	3-4	Permanently discontinue	Permanently discontinue
All Other Drug-Related Toxicity[2]	3 or Severe	Toxicity resolves to Grade 0-1	Toxicity does not resolve within 12 weeks of last dose or inability to reduce corticosteroid to 10 mg or less of prednisone or equivalent per day within 12 weeks.
	4	Permanently discontinue	Permanently discontinue

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

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

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

Toxicity	Hold Pembrolizumab For Grade	Timing for Restarting Pembrolizumab	Discontinue Subject
12 weeks of the last dose.			

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

5.3.2.2.2 Vorinostat

Dose interruption/hold/modification for vorinostat can occur at any time during treatment on study and are only performed if the event that caused the modification is possibly, probably or definitely related to vorinostat. Dosing interruptions are permitted in the case of medical / surgical events or logistical reasons not related to study therapy (e.g., elective surgery, unrelated medical events, patient vacation, and/or holidays).

Toxicity	Actions
Grade 1 hematological ANC ≥1500 Platelets < 100,000 but >75,000 **Grade 2 hematological** Platelets ≤ 75,000 but > 50,000 Neutrophils (ANC) < 1500 but > 1000 **Grade 3-4 hematological** Platelets and ANC Only Platelets < 50.0 x 10^9 /L Neutrophils (ANC) < 1.0 x 10^9/L **or Grade 3 non-hematological**	1. Continue with protocol therapy. 1. Hold vorinostat until toxicity recovered to ≤ grade 1 2. Check CBC prior to next planned vorinostat dose 3. If recovered resume treatment with no dose modification. If not recovered, continue to hold and re-check CBC at next planned vorinostat dose. 1. Interrupt vorinostat, instituting symptomatic therapy as appropriate, until recovery to grade ≤1 2. Reintroduce vorinostat as follows: reduce by one dose level. If vorinostat is already at the lowest dose level, discontinue further vorinostat. 3. If toxicity remains at grade ≤1 after 4 weeks of treatment at reduced dosage, **then at the discretion of the investigator** a return to the initial vorinostat dosage may be made
- If reappearance of above after actions 1 & 2	Discontinue treatment with vorinostat
- If reappearance of above after actions 1-3	Repeat 1 & 2 above but not 3.
Grade 3 non–hematological (only) - If failure to return to grade ≤ 1 after action 1	Consider action 2 **at the discretion of the investigator** only if toxicity is grade 2, manageable, and patient was benefiting from therapy
Grade 4 non- hematological toxicity	Discontinue vorinostat

5.3.2.2.3 Temozolomide

Temozolomide During Concomitant Radiation Therapy Phase

Prophylaxis against Pneumocystis *jirovecii* pneumonia (PCP) is required for all subjects

receiving concomitant temozolomide and radiotherapy.
No temozolomide dose reduction will be made, but delay or discontinuation of temozolomide administration will be decided weekly according to hematologic and non-hematologic adverse events (AEs), as specified below.
If the administration of temozolomide has to be interrupted, the radiotherapy, pembrolizumab and vorinostat will proceed normally as long as the adverse event is solely related to temozolomide as per investigator's assessment. Missed doses of temozolomide will not be made up at the end of radiotherapy.

If one or more of the following are observed:
- ANC ≥ 0.5 and $< 1.5 \times 10^9$/L
- Platelet count ≥ 10 and $< 100 \times 10^9$/L
- Grade 2 non-hematologic AE considered possibly related to temozolomide (except alopecia, nausea and vomiting while on maximal antiemetic therapy, and fatigue)

then treatment with concomitant temozolomide will be withheld until all of the following conditions are met:

- ANC $\geq 1.5 \times 10^9$/L
- Platelet count $\geq 100 \times 10^9$/L
- Grade ≤ 1 non-hematologic AE (except alopecia, nausea and vomiting, and fatigue)

In case of hematologic AE as defined above, a complete blood count (CBC) should be performed at least twice weekly. In case of non-hematologic AE, the subject should be assessed at least weekly with relevant laboratory test(s). As soon as all of the above conditions are met, the administration of temozolomide will resume at the same dose as used initially.

If one or more of the following are observed:
- ANC $< 0.5 \times 10^9$/L (Grade 4)
- Platelet count $< 10 \times 10^9$/L (Grade 4)
- Grade 3 or 4 non-hematologic AE considered possibly related to temozolomide (except alopecia, nausea and vomiting unless the subject has failed maximal antiemetic therapy, and fatigue)

then treatment with concomitant temozolomide should be stopped.

If the duration of radiotherapy exceeds 7 weeks, then concomitant treatment with temozolomide should be stopped after 42 days of temozolomide treatment.

Summary of Temozolomide Delay or Discontinuation During Concomitant Radiation Therapy

AE	Value	Grade	Action
ANC	≥ 0.5 and $< 1.5 \times 10^9$/L	2, 3	**Delay** temozolomide until: ---ANC $\geq 1.5 \times 10^9$/L ---Platelet $\geq 100 \times 10^9$/L ---Non-hem AE $\leq$ Grade 1
Platelet count	≥ 10 and $< 100 \times 10^9$/L	2, 3	
Non-hematologic (except alopecia, nausea/vomiting unless on maximal antiemetic therapy)	NA	2	
ANC	$< 0.5 \times 10^9$/L	4	**Stop** concomitant temozolomide
Platelet count	$< 10 \times 10^9$/L	4	
Non-hematologic (except alopecia, nausea/vomiting)	NA	3 or 4	

Post-Radiation (maintenance) Temozolomide

Continued dosing administration is based on adverse events (AEs) during the prior treatment cycle. If multiple AEs are seen, the dose administered should be based on the dose reduction required for the most severe grade of any single AE.

On Day 1 of each cycle (within the prior 72 hours), ANC $\geq 1.5 \times 109$/L, platelet count $\geq 100 \times 109$/L and all treatment-related grade 3 or 4 non-hematologic AEs (except alopecia, nausea, and vomiting) must have resolved (to grade ≤ 1).
If temozolomide related AEs persist, treatment should be delayed by 2 weeks for up to 4 consecutive weeks. If, after 4 weeks of delay, all temozolomide related AEs have still not resolved, then any further adjuvant treatment with temozolomide should be stopped.

If, during the first cycle, all non-hematologic AEs observed were grade ≤ 2 (except alopecia, nausea and vomiting) and with platelets $\geq 100 \times 10^9$/L and ANC $\geq 1.5 \times 10^9$/L, then the temozolomide dose should be escalated to 200 mg/m^2/day and this dose should be used as the starting dose for subsequent cycles. If treatment after cycle 1 has to be delayed because of ongoing non-hematologic AEs of grade ≥ 2, then no escalation is possible. If the dose was not escalated at cycle 2, then the dose should not be escalated in further cycles (Cycles 3 – 6). Treatment beyond cycle 6 can be allowed after discussion with Sponsor. In such cases treatment with temozolomide should stop after total of 12 cycles.

If any non-hematologic AE observed was grade > 2 (except alopecia, nausea and vomiting) and/or if platelets $< 50 \times 10^9$/L and/or ANC $< 1 \times 10^9$/L, then the dose should be reduced to 150 mg/m^2/day if patient was receiving 200 mg/m^2/day or 100 mg/m2/day if patient was on 150 mg/m^2/day when the AE occurred.

For subjects who would require dose reductions to < 100 mg/m^2/day, temozolomide will be stopped. Also, if any of the same non-hematologic grade 3 AE recurs (except alopecia, nausea and vomiting) after reduction for that AE, then temozolomide will be stopped.
If any treatment-related non-hematologic AE observed was grade 4 (except alopecia, nausea and vomiting) then adjuvant temozolomide treatment should be stopped.

Important: If the dose was reduced or delayed for adverse events, there will be no dose escalation in future cycles.

5.3.3 Timing of Dose Administration

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

All trial treatments will be administered on an outpatient basis.

Pembrolizumab will be administered as a 30 minute IV infusion every 3 weeks (+/- 3 days). However, given the variability of infusion pumps, a window of -5 minutes and +10 minutes is permitted (i.e., infusion time is 30 minutes: -5 min/+10 min).

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

Vorinostat should be taken with food, at regular intervals regardless of pembrolizumab infusion time. On days the patient receives pembrolizumab, the vorinostat should be taken prior to the pembrolizumab infusion.

Temozolomide should be given on empty stomach, at regular intervals regardless of pembrolizumab infusions or vorinostat. On days the patient receives pembrolizumab, the temozolomide can be taken prior to or after the pembrolizumab infusion. In patients who do not experience nausea, temozolomide can be taken after a small meal.

5.3.4 Trial Blinding/Masking

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

5.4 Treatment Allocation

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

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

5.5 Concomitant Medications/Vaccinations (allowed & prohibited)

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

or vaccinations specifically prohibited during the trial, discontinuation from trial therapy or vaccination may be required. The investigator should discuss any questions regarding this with principal investigator of study. The final decision on any supportive therapy or vaccination rests with the investigator and/or the subject's primary physician. However, the decision to continue the subject on trial therapy or vaccination schedule requires the mutual agreement of the Investigator, the Sponsor (Moffitt Cancer Center), and the subject.

5.5.1 Acceptable Concomitant Medications

All treatments that the investigator considers necessary for a subject's welfare may be administered at the discretion of the investigator in keeping with the community standards of medical care. Only corticosteroids will be recorded on the case report form (CRF). If changes occur during the trial period, documentation of drug dosage, frequency, route, and date may also be included on the CRF.

Although single doses of Vorinostat of up to 800 mg did not result in QTc prolongation, Vorinostat should be administered with particular caution in patients taking anti-arrhythmic medicines or other medicinal products that lead to QT prolongation.

5.5.2 Prohibited Concomitant Medications

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

- Antineoplastic systemic chemotherapy or biological therapy other than temozolomide, pembrolizumab and vorinostat
- Immunotherapy not specified in this protocol
- Chemotherapy not specified in this protocol
- Investigational agents other than pembrolizumab and vorinostat
- Live vaccines within 30 days prior to the first dose of trial treatment and while participating in the trial. Examples of live vaccines include, but are not limited to, the following: measles, mumps, rubella, varicella/zoster, yellow fever, rabies, BCG, and typhoid vaccine.
- Systemic glucocorticoids for any purpose other than to modulate symptoms from an event of clinical interest of suspected immunologic etiology or required by patient's symptoms. The use of physiologic doses of corticosteroids may be approved after consultation with the Sponsor.
- Any drug which is associated with risk of Torsades de Pointes
- Vorinostat should not be administered concomitantly with other HDAC inhibitors (e.g., valproic acid) as class-specific adverse reactions may be additive.

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

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

The major pathway(s) for metabolism of vorinostat involves glucuronidation and hydrolysis followed by β-oxidation. Therefore, it is anticipated that vorinostat will not be subject to drug-drug interactions when co-administered with drugs that are known to be CYP enzyme inhibitors. Formal drug-drug interaction studies have not been performed with vorinostat.

- Prolongation of prothrombin time (PT) and International Normalized Ratio (INR) has been observed in patients receiving vorinostat concomitantly with coumarin- derivative anticoagulants. Physicians should carefully monitor PT and INR in patients concurrently administered vorinostat and coumarin derivatives.

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

5.6 Rescue Medications & Supportive Care

5.6.1 Supportive Care Guidelines

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

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

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

- **Pneumonitis**:

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

- **Diarrhea/Colitis**:

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

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

- **Type 1 diabetes mellitus (if new onset, including diabetic ketoacidosis [DKA]) or ≥ Grade 3 Hyperglycemia, if associated with ketosis (ketonuria) or metabolic acidosis (DKA)**
  - For **T1DM** or **Grade 3-4** Hyperglycemia
    - Insulin replacement therapy is recommended for Type I diabetes mellitus and for Grade 3-4 hyperglycemia associated with metabolic acidosis or ketonuria.
    - Evaluate patients with serum glucose and a metabolic panel, urine ketones, glycosylated hemoglobin, and C-peptide.

- **Hypophysitis**:

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

- **Hyperthyroidism or Hypothyroidism**:

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

  - **Grade 2** hyperthyroidism events (and **Grade 2-4** hypothyroidism):
    - In hyperthyroidism, non-selective beta-blockers (e.g. propranolol) are suggested as initial therapy.
    - In hypothyroidism, thyroid hormone replacement therapy, with levothyroxine or liothyroinine, is indicated per standard of care.
  - **Grade 3-4** hyperthyroidism
    - Treat with an initial dose of IV corticosteroid followed by oral corticosteroids. When symptoms improve to Grade 1 or less, steroid taper should be started and continued over no less than 4 weeks. Replacement of appropriate hormones may be required as the steroid dose is tapered.
- **Hepatic**:
  - For **Grade 2** events, monitor liver function tests more frequently until returned to baseline values (consider weekly).
    - Treat with IV or oral corticosteroids
  - For **Grade 3-4** events, treat with intravenous corticosteroids for 24 to 48 hours.
  - When symptoms improve to Grade 1 or less, a steroid taper should be started and continued over no less than 4 weeks.
- **Renal Failure or Nephritis**:
  - For **Grade 2** events, treat with corticosteroids.
  - For **Grade 3-4** events, treat with systemic corticosteroids.

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

- **Management of Infusion Reactions**: Signs and symptoms usually develop during or shortly after drug infusion and generally resolve completely within 24 hours of completion of infusion.

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

Table 5 Infusion Reaction (Pembrolizumab) Treatment Guidelines

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

- **Nausea and vomiting** should be treated aggressively, and strong consideration should be given to the administration of prophylactic antiemetic therapy according to standard institutional practice. In particular, the use of antiemetics including 5HT3 antagonists is encouraged. Patients should be strongly encouraged to maintain liberal oral fluid intake during therapy.

- **Hypokalemia or hypomagnesemia** should be corrected prior to administration of vorinostat, and consideration should be given to monitoring potassium and magnesium in symptomatic patients (e.g. patients with nausea, vomiting, diarrhea, or fluid imbalance.)

5.7 Diet/Activity/Other Considerations

5.7.1 Diet

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

5.7.2 Contraception

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

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

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

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

OR

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

OR

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

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

(1) practice abstinence† from heterosexual activity;

OR

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

Acceptable methods of contraception are‡:

Single method (one of the following is acceptable):

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

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

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

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

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

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

5.7.3 Use in Pregnancy

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

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

5.7.4 Use in Nursing Women

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

5.8 Subject Withdrawal/Discontinuation Criteria

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

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

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

- Unacceptable adverse experiences as described in Section 5.3.2
- Confirmed radiographic disease progression

  Note: For unconfirmed radiographic disease progression, please see Section 7.1.2.6

  Note: A subject may be granted an exception to continue on treatment with confirmed radiographic progression if clinically stable or clinically improved, please see Section 7.1.2.6

- Unacceptable adverse experiences as described in Section 5.3.2
- Intercurrent illness that prevents further administration of treatment
- Investigator's decision to withdraw the subject
- The subject has a confirmed positive serum pregnancy test
- Noncompliance with trial treatment or procedure requirements
- The subject is lost to follow-up
- Completed 15 months of uninterrupted treatment with pembrolizumab or 20 administrations of study medication, whichever is later.

  Note: 15 months of study medication is calculated from the date of first dose.

- Administrative reasons

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

5.9 Subject Replacement Strategy

In dose escalation phase, subject will be replaced if they are considered inevaluable. A subjects will be considered DLT-evaluable if they have incurred a DLT within a DLT evaluation period or meet all of the following criteria: a) have received at least 85% of the prescribed doses of vorinostat, b) have received at least 85% of the prescribed doses of pembrolizumab, and c) have received the full dose (60 Gy) of radiation.

5.10 Clinical Criteria for Early Trial Termination

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

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

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

6.0 TRIAL FLOW CHART

6.1 Study Flow Chart

Concurrent Radiotherapy Phase

Trial Period:	**Screening Phase**		**Treatment Cycles**											
Treatment Cycle/Title:	Pre-screening (Visit 1)	Main Study Screening (Visit 2) [a]	**Cycle 1 (Concurrent therapy with radiation, 12 weeks)**											
Scheduling Window (Days):		-21 to -1	D1 ± 3	D8 ± 3	D15 ± 3	D22 ± 3	D29 ± 3	D36 ± 3	D43 ± 3	D50 ± 3	D57 ± 3	D64 ± 3	D71 ± 7	D78 ± 3
Administrative Procedures														
Informed Consent	X													
Inclusion/Exclusion Criteria		X												
Demographics and Medical History	X	X	X			X			X			X		
Prior and Concomitant Medication Review	X	X	X			X			X			X		
Radiation therapy			X (Total dose of 60 Gy; Monday-Friday)											
Temozolomide			X Every day										X (5 day regimen every 28 days)	
Pembrolizumab			X			X			X			X		
Vorinostat			Days 1-5 of every week during radiation Daily one week on-one week off starting after radiation +/- 3 days											
Post-study anticancer therapy status														
Survival Status														
Clinical Procedures/Assessments														
Review Adverse Events [c]			X			X			X			X		
Full Physical Examination	X	X	X			X			X			X		

Trial Period:	Screening Phase		Treatment Cycles											
Treatment Cycle/Title:	Pre-screening (Visit 1)	Main Study Screening (Visit 2) [a]	Cycle 1 (Concurrent therapy with radiation, 12 weeks)											
Scheduling Window (Days):		-21 to -1	D1 ± 3	D8 ± 3	D15 ± 3	D22 ± 3	D29 ± 3	D36 ± 3	D43 ± 3	D50 ± 3	D57 ± 3	D64 ± 3	D71 ± 7	D78 ± 3
Vital Signs and Weight	X	X	X			X			X			X		
EORTC QLQ-C30 and BNS20 Questionnaire			X			X			X			X		
Karnofsky Performance Status	X	X	X			X			X			X		
Laboratory Procedures/Assessments: analysis performed by LOCAL laboratory														
Pregnancy Test – Urine or Serum β-HCG		X												
PT/INR and aPTT		X												
CBC with Differential	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Comprehensive Serum Chemistry Panel	X	X	X			X			X			X		
Urinalysis	X	X	X			X			X			X	X	
T3, FT4 and TSH	X	X	X			X			X			X		
Efficacy Measurements														
Brain MRI with/without contrast		X											X	
Tumor Biopsies/Archival Tissue Collection/Correlative Studies Blood														
Archival or Newly Obtained Tissue Collection		X												
Correlative Studies Blood Collection			X			X			X					

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

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

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

Maintenance Phase

Trial Period:	Treatment Cycles								
Treatment Cycle/Title:	Cycles 2 and 3 (12 weeks)								
Scheduling Window (Days):	D1± 3	D2-5± 3	D22± 3	D29 ± 3	D30-33 ± 3	D43± 3	D57± 3	D58-61± 3	D64 ± 3
Administrative Procedures									
Informed Consent									
Inclusion/Exclusion Criteria									
Demographics and Medical History	X		X			X			X
Prior and Concomitant Medication Review	X		X			X			X
Radiation therapy									
Temozolomide	X (5 consecutive days every 28 days for total of 6 months)								
Pembrolizumab	X		X			X			X
Vorinostat	Daily one week on-one week off +/- 3 days								
Post-study anticancer therapy status									
Survival Status									
Clinical Procedures/Assessments									
Review Adverse Events [c]	X		X			X			X
Full Physical Examination	X		X			X			X
Vital Signs and Weight	X		X			X			X
EORTC QLQ-C30 and BNS20 Questionnaire	X		X			X			X
Karnofsky Performance Status	X		X			X			X
Pregnancy Test – Urine or Serum β-HCG									
CBC with Differential	X		X	X		X	X		X
Comprehensive Serum Chemistry Panel	X		X			X			X

Trial Period:	**Treatment Cycles**								
Treatment Cycle/Title:	**Cycles 2 and 3 (12 weeks)**								
Scheduling Window (Days):	D1± 3	D2-5± 3	D22± 3	D29 ± 3	D30-33 ± 3	D43± 3	D57± 3	D58-61± 3	D64 ± 3
Urinalysis	X		X						X
T3, FT4 and TSH	X		X			X			X
Brain MRI with/without contrast	Every 6 +/- 4 weeks								
Archival or Newly Obtained Tissue Collection									
Correlative Studies Blood Collection	X		X			X			

Trial Period:	Treatment Cycles				End of Treatment	Post-Treatment		
Treatment Cycle/Title:	Cycles 4 and 5 (12 weeks)				Discon	Safety Follow-up	Follow Up Visits [b]	Survival Follow-Up
Scheduling Window (Days):	D1± 3	D22± 3	D43± 3	D64 ± 3	At time of Discon	30 (+7 days post discon	Every 8± 3 weeks post discon	Every 12 (+/- 4) weeks
Administrative Procedures								
Informed Consent								
Inclusion/Exclusion Criteria								
Demographics and Medical History	X	X	X	X				
Prior and Concomitant Medication Review	X	X	X	X	X	X		
Radiation therapy								
Temozolomide								
Pembrolizumab	X	X	X	X				
Vorinostat	Daily one week on-one week off ± 3 days							
Post-study anticancer therapy status						X	X	
Survival Status								X
Clinical Procedures/Assessments								
Review Adverse Events [c]	X	X	X	X	X	X	X	
Full Physical Examination	X	X	X	X	X	X	X	
Vital Signs and Weight	X	X	X	X	X	X	X	
EORTC QLQ-C30 and BNS20 Questionnaire	X		X	X	X		X	
Karnofsky Performance Status	X	X	X	X	X	X	X	
Pregnancy Test – Urine or Serum β-HCG								
CBC with Differential	X	X	X	X	X	X	X	
Comprehensive Serum Chemistry Panel	X	X	X	X	X	X	X	
Urinalysis	X		X		X	X	X	
T3, FT4 and TSH	X	X	X	X	X	X		

Trial Period:	Treatment Cycles				End of Treatment	Post-Treatment		
Treatment Cycle/Title:	Cycles 4 and 5 (12 weeks)				Discon	Safety Follow-up	Follow Up Visits [b]	Survival Follow-Up
Scheduling Window (Days):	D1± 3	D22± 3	D43± 3	D64 ± 3	At time of Discon	30 (+7 days post discon	Every 8± 3 weeks post discon	Every 12 (+/- 4) weeks
Brain MRI with/without contrast	Every 8 +/- 2 weeks				X		X	
Archival or Newly Obtained Tissue Collection								
Correlative Studies Blood Collection								

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

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

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

7.0 TRIAL PROCEDURES

7.1 Trial Procedures

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

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

7.1.1 Administrative Procedures

7.1.1.1 Informed Consent

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

7.1.1.1.1 General Informed Consent

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

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

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

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

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

7.1.1.2 Inclusion/Exclusion Criteria

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

7.1.1.3 Medical History

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

7.1.1.4 Prior and Concomitant Medications Review

7.1.1.4.1 Prior Medications

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

7.1.1.4.2 Concomitant Medications

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

7.1.1.5 Disease Details and Treatments

7.1.1.5.1 Disease Details

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

7.1.1.5.2 Prior Treatment Details

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

7.1.1.5.3 Subsequent Anti-Cancer Therapy Status

The investigator or qualified designee will review all new anti-neoplastic therapy initiated after the last dose of trial treatment. If a subject initiates a new anti-cancer therapy within 30 (+7) days after the last dose of trial treatment or discontinues active anti-tumor treatment (e.g. enrolling to hospice), the 30 day Safety Follow-up visit will not occur. Once new anti-cancer therapy has been initiated the subject will move into survival follow-up.

7.1.2 Clinical Procedures/Assessments

7.1.2.1 Adverse Event (AE) Monitoring

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

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

7.1.2.2 Full Physical Exam

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

7.1.2.3 Directed Physical Exam

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

7.1.2.4 Vital Signs

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

7.1.2.5 Karnofsky Performance Scale (KPS)

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

7.1.2.6 Tumor Imaging and Assessment of Disease

All subjects will receive efficacy assessments with brain MRI at time points specified in Trial Flow Chart. All MRIs (except the initial screening MRI) should occur at +/- 14 days per scheduled visits. Investigators may obtain more frequent follow-up MRI scans as medically indicated. Cases of suspected radiologic disease progression will be confirmed by an MRI performed approximately 8 weeks after the initial radiological assessment of progression.

Both Response Assessment Criteria for High-Grade Gliomas (RANO Criteria) and Immunotherapy Response Assessment in Neuro-Oncology (iRANO) will be used for assessing the response to study treatment.

7.1.2.7 Tumor Tissue Collection and Correlative Studies

Archival tumor tissue will be collected prior to therapy. If a biopsy or surgical resection is performed at the time of progression, tumor sample (block or slides) should be submitted for analysis.

7.1.3 Laboratory Procedures/Assessments

Laboratory tests for hematology, chemistry, urinalysis, and others are specified in Table 6. The total amount of blood to be drawn over the course of the trial (from pre-trial to post-trial visits), including approximate blood volumes drawn by visit and by sample type per subject can be found in the Procedures Manual.

Table 6 Laboratory Tests

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

† Perform on women of childbearing potential only. If urine pregnancy results cannot be confirmed as negative, a serum pregnancy test will be required.

‡ If considered standard of care in your region.

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

7.1.3.1 Pharmacodynamic Evaluations

7.1.3.1.1 Blood Collection for Serum Correlative Studies

No serum correlative studies will be performed.

7.1.4 Other Procedures

7.1.4.1 Withdrawal/Discontinuation

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

7.1.5 Visit Requirements

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

7.1.5.1 Screening

7.1.5.1.1 Screening Period

Screening period begins by establishing the subject's initial eligibility and signing of the informed consent form (ICF). Study treatment should be given within 21 days of signing ICF.

7.1.5.2 Treatment Period

Treatment period should start within 21 days of signing ICF unless discussed by Sponsor. Treatment period will start with concurrent chemoradiotherapy with temozolomide, pembrolizumab and vorinostat on C1 D1 (Radiotherapy Phase).

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

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

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

Response to treatment will be assessed by the investigator and according to the RANO and iRANO criteria. Brain MRI will be performed according to the schedule in Trial Flow Chart until disease progression or treatment discontinuation, whichever occurs later. Brain MRIs can be obtained in shorter intervals as per physician discretion.

7.1.5.3 Post-Treatment Visits

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

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

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

7.1.5.3.1 Safety Follow-Up Visit

The mandatory Safety Follow-Up Visit should be conducted approximately 30 (+7) days after the last dose of trial treatment. If a subject initiates a new anti-cancer therapy within 30 days after the last dose of trial treatment or discontinues active anti-tumor treatment (e.g. enrolling to hospice), the 30 day Safety Follow-up visit will not occur. All AEs that occur prior to the Safety Follow-Up Visit should be recorded. Subjects with an AE of Grade > 1 will be followed until the resolution of the AE to Grade 0-1 or until the beginning of a new anti-neoplastic therapy, whichever occurs first. SAEs that occur within 90 days of the end of treatment or before initiation of a new anti-cancer treatment should also be followed and recorded.

7.1.5.4 Follow-up Visits

Subjects who discontinue trial treatment for a reason other than disease progression will move into the Follow-Up Phase and should be assessed every 8 weeks (± 3 week) by radiologic imaging to monitor disease status. All radiologically determined disease progression must be confirmed by an additional confirmatory MRI scan approximately 8+/- 3 weeks following the initial assessment of radiological progression.

Every effort should be made to collect information regarding disease status until the start of new anti-neoplastic therapy, disease progression, death or end of the study. Information regarding post-study anti-neoplastic treatment will be collected if new treatment is initiated. Subjects who are eligible to receive retreatment with pembrolizumab according to the criteria in Section 7.1.5.5 will move from the follow-up phase to the Second Course Phase when they experience disease progression. Details are provided in Section 6.2 – Trial Flow Chart for Retreatment.

7.1.5.4.1 Survival Follow-up

Once a subject experiences confirmed disease progression or starts a new anti-cancer therapy, the subject moves into the survival follow-up phase and should be contacted by telephone every 12 (+/- 4) weeks to assess for survival status until death, withdrawal of consent, or the end of the study, whichever occurs first.

7.2 Assessing and Recording Adverse Events

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

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

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

The investigator will make every attempt to follow all subjects with non-serious adverse events for outcome.

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

For purposes of this trial, an overdose of pembrolizumab will be defined as any dose of 1,000 mg or greater (≥5 times the indicated dose). No specific information is available on the

treatment of overdose of pembrolizumab. Appropriate supportive treatment should be provided if clinically indicated. In the event of overdose, the subject should be observed closely for signs of toxicity. Appropriate supportive treatment should be provided if clinically indicated.

For vorinostat, an overdose will be defined as any dose exceeding the prescribed dose by 20%.

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

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

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

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

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

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

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

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

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

7.2.3.1 Serious Adverse Events

A serious adverse event is any adverse event occurring at any dose or during any use of study treatment that:

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

- **Note:** In addition to the above criteria, adverse events meeting either of the below criteria, although not serious per ICH definition, are reportable to the Merck in the same timeframe as SAEs to meet certain local requirements. Therefore, these events are considered serious by Merck for collection purposes.
    - Is a new cancer (that is not a condition of the study);
    - Is associated with an overdose.

Refer to Table 7 for additional details regarding each of the above criteria.

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

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

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

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

SAE reports and any other relevant safety information are to be forwarded to the Merck Global Safety facsimile number: +1-215-993-1220

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

7.2.3.2 Events of Clinical Interest

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

For the time period beginning when the first dose of study treatment is administered, 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 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 first study treatment through 90 days following cessation of treatment, or 30 days following cessation of treatment if the subject initiates new anticancer therapy, whichever is earlier, any ECI, or follow up to an ECI, whether or not related to Merck product, must be reported within 24 hours to the Sponsor and within 24 hours to Merck Global Safety.

Events of clinical interest for this trial include:

1. an overdose of Merck product, as defined in Section 7.2.1 - Definition of an Overdose for This Protocol and Reporting of Overdose to the Sponsor, that is not associated with clinical symptoms or abnormal laboratory results.

2. an elevated AST or ALT lab value that is greater than or equal to 3X the upper limit of normal and an elevated total bilirubin lab value that is greater than or equal to 2X the upper limit of normal and, at the same time, an alkaline phosphatase lab value that is less than 2X the upper limit of normal, as determined by way of protocol-specified laboratory testing or unscheduled laboratory testing.*

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

7.2.4 Evaluating Adverse Events

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

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

Table 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 subject, in the view of the investigator, at immediate risk of death from the event as it occurred (Note: This does not include an adverse event that, had it occurred in a more severe form, might have caused death.); or	
	†**Results in a persistent or significant disability/incapacity** (substantial disruption of one's ability to conduct normal life functions); or	
	†**Results in or prolongs an existing inpatient hospitalization** (hospitalization is defined as an inpatient admission, regardless of length of stay, even if the hospitalization is a precautionary measure for continued observation. (Note: Hospitalization for an elective procedure to treat a pre-existing condition that has not worsened is not a serious adverse event. A pre-existing condition is a clinical condition that is diagnosed prior to the use of a Merck product and is documented in the patient's medical history.); or	
	†**Is a congenital anomaly/birth defect** (in offspring of subject taking the product regardless of time to diagnosis);or	
	Is a new **cancer** (that is not a condition of the study) **(**although not serious per ICH definition, is reportable to the Sponsor within 24 hours and to Merck within 2 working days to meet certain local requirements); **or**	
	Is an overdose (whether accidental or intentional). Any adverse event associated with an overdose is considered a serious adverse event for collection purposes. An overdose that is not associated with an adverse event is considered a non-serious event of clinical interest and must be reported within 24 hours to the Sponsor and to Merck within 2 working days..	

	Other important medical events that may not result in death, not be life threatening, or not require hospitalization may be considered a serious adverse event when, based upon appropriate medical judgment, the event may jeopardize the subject and may require medical or surgical intervention to prevent one of the outcomes listed previously (designated above by a †).	
Duration	Record the start and stop dates of the adverse event. If less than 1 day, indicate the appropriate length of time and units	
Action taken	Did the adverse event cause Merck product to be discontinued?	
Relationship to Merck Product	Did Merck product cause the adverse event? The determination of the likelihood that Merck product caused the adverse event will be provided by an investigator who is a qualified physician. The investigator's signed/dated initials on the source document or worksheet that supports the causality noted on the AE form, ensures that a medically qualified assessment of causality was done. This initialed document must be retained for the required regulatory time frame. The criteria below are intended as reference guidelines to assist the investigator in assessing the likelihood of a relationship between the test drug and the adverse event based upon the available information. **The following components are to be used to assess the relationship between Merck product and the AE**; the greater the correlation with the components and their respective elements (in number and/or intensity), the more likely Merck product caused the adverse event (AE):	
	Exposure	Is there evidence that the subject was actually exposed to Merck product such as: reliable history, acceptable compliance assessment (pill count, diary, etc.), expected pharmacologic effect, or measurement of drug/metabolite in bodily specimen?
	Time Course	Did the AE follow in a reasonable temporal sequence from administration of Merck product? Is the time of onset of the AE compatible with a drug-induced effect (applies to trials with investigational medicinal product)?
	Likely Cause	Is the AE not reasonably explained by another etiology such as underlying disease, other drug(s)/vaccine(s), or other host or environmental factors

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

relationship	AE.)

7.2.5 Sponsor Responsibility for Reporting Adverse Events

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

8.0 STATISTICAL ANALYSIS PLAN

8.1 Statistical Analysis Plan Summary

The number of patients for the dose escalation cohort will depend on the safety of dose level 1. There are two dose escalation levels and therefore the maximum sample size for the dose escalation cohorts will be 12 patients. In the dose expansion cohort, a total of 20 evaluable patients will be enrolled to confirm the safety at this dose and assess response to treatment. Therefore, the maximum sample size of the study is 32 patients. The sample size of 26 patients in treated at the MTD dose (20+3 patients from dose expansion cohort and 6+/-3 patients from the dose escalation) will give a two-sided 95% confidence interval (95%CI) of 39% to 79% for a 12-month overall survival rate of 60% when there is no censored data. If the 12-months overall survival rate increases to 80%, the corresponding 95%CI will be 60% to 93%. A two-sided 95% confidence interval for the median overall survival time is from 10 months to 23 months when the estimate of median overall survival time is 14.6 months and the percent censoring is anticipated to be 10%. These results assume Type-II Censoring and an exponential distribution of overall survival times with mean survival time of 21 months.

8.2 Statistical Analysis Plan

Data will be summarized overall using descriptive statistics. Continuous data will be summarized with number of patients (n), mean, median, minimum, maximum, standard deviation, coefficient of variation, and geometric mean (where applicable). Categorical data will be summarized using frequency counts and percentages. Time-to-event outcome data will be summarized using Kaplan-Meier survival curve and median survival time.

9.0 LABELING, PACKAGING, STORAGE AND RETURN OF CLINICAL SUPPLIES

9.1 Investigational Product

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

Clinical Supplies will be provided by Merck as summarized in Table 8.

Table 8 Product Descriptions

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

9.2 Packaging and Labeling Information

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

9.3 Clinical Supplies Disclosure

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

9.4 Storage and Handling Requirements

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

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

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

9.5 Returns and Reconciliation

The investigator is responsible for keeping accurate records of the clinical supplies received from Merck or designee, the amount dispensed to and returned by the subjects and the amount remaining at the conclusion of the trial. Upon completion or termination of the study, all unused and/or partially used investigational product will be destroyed at the site per institutional policy. It is the Investigator's responsibility to arrange for disposal of all empty containers, provided that procedures for proper disposal have been established according to applicable federal, state, local and institutional guidelines and procedures, and provided that appropriate records of disposal are kept.

10.0 ADMINISTRATIVE AND REGULATORY DETAILS

10.1 Confidentiality

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

specimen is processed and read by the central pathology laboratory, the patient's billing information will be requested by this laboratory and will not be shared with the sponsor or any of its affiliates or representatives.

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

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

All records must be kept in a secured area.

10.2 Compliance with Financial Disclosure Requirements

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

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

The Investigator must conduct the study according to this protocol.

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

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

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

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

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

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

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

The PMC meets monthly and reviews accrual, patterns and frequencies of all adverse events, protocol violations and when applicable, internal audit results.

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

10.4 Compliance with Trial Registration and Results Posting Requirements

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

10.5 Data Management

Data will be maintained by the Moffitt Cancer Center.

11.0 APPENDICES

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

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

11.2 Immune-Related Adverse Event Guidance

RISK LANGUAGE (RL) FOR Pembrolizumab (MK-3475)

Implementation of Changes
An implementation plan has been determined for the updated RL including notification of the subject group(s), the investigator and Institutional Review Board/Institutional Ethics Committee (IRB/IEC) as indicated below.
Relevant Subject Groups to be Notified of Updated RL
☒ New subjects to be enrolled in a new trial
☒ New subjects to be enrolled in ongoing trial(s)
☒ Subjects in an ongoing trial still receiving treatment
☒ Subjects in an ongoing trial who have been off of study treatment but are still within the SAE Follow Up Period (≤90 days)
☐ Subjects who completed participation in an ongoing trial
Additional Comments: **Note:** The IRB/ERC, with input from the investigator (as needed), will make the final decision about the need to update consents and/or re-consent patients regardless of the Sponsor recommendations.

What is known about this study drug?

Pembrolizumab, which is approved in the USA and some other countries, is available by prescription to treat several different cancers, but may not be approved to treat your type of cancer.

Pembrolizumab works by helping your immune system to fight your cancer.

However, pembrolizumab can also cause your immune system to attack normal organs and tissues in your body and can affect the way they work, which can result in side effects that may become serious or life-threatening, and in some cases, may lead to death.

What side effects could the study drug(s) cause?

VERY COMMON, SOME MAY BE SERIOUS (i.e. causing hospitalization, life-threatening or where noted, may cause death)

Out of 100 people who receive pembrolizumab, 20 or more people may have the following:

- Itching of the skin
- Loose or watery stools
- Cough

COMMON, SOME MAY BE SERIOUS (i.e. causing hospitalization, life-threatening, or where noted, may cause death)

Out of 100 people who receive pembrolizumab, at least 5 but less than 20 people may have the following:

- Joint pain
- Rash
- Fever
- Back pain
- Pain in your belly
- Loss of skin color
- Not enough thyroid hormone so you may feel tired, gain weight, feel cold, have infrequent or hard stools
- Low levels of salt in the blood that may cause you to feel tired, confused, have a headache, muscle cramps and/or feel sick to your stomach

UNCOMMON, SOME MAY BE SERIOUS (i.e.causing hospitalization, life- threatening, or where noted, may cause death)

Out of 100 people who receive pembrolizumab, at least 1 but less than 5 people may have the following:

- Inflammation of the lungs so you may feel short of breath and cough. Sometimes this might lead to death
- Too much thyroid hormone so you may feel anxious, angry, have trouble sleeping, feel weak, tremble, sweat, feel tired, have loose and watery stools
- Infusion reaction, where you may feel dizzy or faint, flushed, get a rash, have a fever, feel short of breath at the time of receiving your infusion (IV) or just after, or pain at the site of infusion
- Inflammation of the bowels/gut, which may cause severe pain in your belly with loose or watery stools, and black, tarry, sticky stools or stools with blood or mucus
- Inflammation of the skin so you may have peeling of the skin, itchiness, and/or skin redness. The skin inflammation (i.e. peeling, itching and redness) could also be widespread throughout your body. More severe skin reactions may involve the inside of your mouth, the surface of your eye and genital areas, and/or may cause the top layer of your skin to peel from all over your body which can cause severe infection. These severe conditions can sometimes lead to death.

RARE, SOME MAY BE SERIOUS (i.e. causing hospitalization, life-threatening, or where noted, may cause death)

Out of 100 people who receive pembrolizumab, less than 1 person may have the following:

- Inflammation of the nerves that may cause pain, weakness or tingling in your hands and feet, and may spread to your legs, arms and upper body leading to severe muscle weakness and possible temporary paralysis
- Inflammation of the muscles so you may feel weak or have pain in your muscles
- Inflammation of the pancreas (a gland in your abdomen that controls sugar levels) so you may have severe pain in the top part of your belly that may move to your back, feel sick to your stomach, and vomiting that gets worse when you eat
- Inflammation of the eye so you may have eye redness, blurred vision, sensitivity to light, eye pain, see floaters or have headaches

- Inflammation of the liver that may make you feel sick to your stomach and vomit, feel like not eating,, feel tired, have a mild fever, have a pain in the right side of your belly, yellow eyes and skin, and dark urine
- Inflammation of the pituitary gland (a gland in the head), which may cause

  you to feel sick to your stomach or have headaches, changes in your behavior, double vision, few to no menstrual cycles, weakness, vomiting and dizziness or fainting

- Adrenal glands (glands on top of the kidneys) that may not make enough hormone, which could cause tiredness, weight loss, muscle weakness, feeling faint, joint, muscle and belly aches, nausea, vomiting, loose or watery stools, fever, salt craving, and sometimes darkening of the skin like a suntan

- Type 1 Diabetes, a condition that can cause too much sugar in your blood, feeling thirstier than usual, frequent urination and weight loss. You are likely to need regular insulin shots.

- Inflammation of the kidney so you may pass less urine or have cloudy or bloody urine, swelling and low back pain

- Inflammation of the middle layer of your heart wall that may cause your heart to have difficulty pumping blood throughout your body, which can cause chest pain, shortness of breath and swelling of the legs. You may experience a fast or irregular heartbeat that may cause dizziness or fainting. Sometimes this condition can lead to death

- Inflammation of the thyroid gland, an organ that makes and stores thyroid hormones. This condition may lead to change in your heart rate, blood pressure, body temperature, and the rate at which food is converted into energy.

- A condition that may make you feel weak and tired and might have drooping of the eyelids, blurred or double vision, difficulty swallowing, slurred speech, weakness in your arms and legs, or difficulty breathing

- The formation of small clusters of immune cells (called granulomas) in parts of your body such as your lymph nodes, eyes, skin, or lungs

- Inflammation of the brain with confusion and fever. This may also include: disorientation, memory problems, seizures (fits), changes in personality and behavior, difficulty speaking, weakness or loss of movement in some parts of your body, and loss of consciousness

<< NOTE: Only add the following language to all informed consents for hematologic malignancies trials. >>

Patients treated with pembrolizumab who then go on to allogeneic stem cell transplant (a procedure in which a person receives blood-forming stem cells from a donor), should inform their transplant physicians that they have received pembrolizumab in the past.

In patients with any hematologic malignancy (cancers of the blood like Hodgkin lymphoma, multiple myeloma): there is a potential for an increased risk of severe complications following allogeneic stem cell transplant in patients who previously received pembrolizumab.

Reports clotting of blood within the liver and severe graft versus host disease (which can include skin, liver and gastrointestinal symptoms), including death, have been received for patients who received allogeneic stem cell transplant after pembrolizumab therapy.

High Level Summary of Most Recent Changes

1. General
    a. Wording of Rarely this condition can lead to death has been changed to Sometimes this condition can lead to death
    b. Changed the wording of some terms to align better with the other terms with regards to grammar and/or addition of symptoms upon Medical Director review
    c. Removed KEYTRUDA® from document
2. Relevant Subject Groups to be Notified of Updated Risk Language
    a. Clarified the choice regarding subjects who are no longer receiving treatment
    b. Deleted Additional Comment
3. What side effects could the study drug(s) cause? section
    a. Section streamlined to remove specific reference to the approved indications by name as well as specific clinical trial exposure numbers, etc. as information changes continually.
    b. Added pembrolizumab information from patient medication guides (USPI medication guide and/or SmPC patient leaflet) to explain how pembrolizumab works and how it may cause side effects.
    c. Used the format of 4 categories (Very Common, Common, Uncommon, and Rare) which simplifies and eliminates need for repetition of terms by overall and serious frequencies, etc. vs percentages.
        i. Removed duplicate terms, ie, that were in the previous version's Common and Serious side effect percentage categories
    d. Removed reference to "immune-mediated" serious events <1%, as not helpful or informative for patient and has created numerous site/IRB/EC and Health Authority questions.
    e. Added simplified language for 4 new terms: thyroiditis, myasthenic syndrome, sarcoidosis, and encephalitis.
4. Hematologic Malignancy trials language
    a. Changed paragraph order and text for readability

Events of Clinical Interest (ECI) – Reference Table

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

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