Columbia University Irving Medical Center

Herbert Irving Comprehensive Cancer Center

Sponsor Investigator: Fabio Iwamoto, MD

Official Study Title: A Phase II, Open Label, Single Arm Study of Nivolumab for Recurrent or Progressive IDH Mutant Gliomas with Prior Exposure to Alkylating Agents

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Herbert Irving Comprehensive Cancer Center Protocol

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Columbia University Medical Center
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PROTOCOL SIGNATURE PAGE

I confirm that I have read this protocol, I understand it, and I will work according to this protocol and to the ethical principles stated in the latest version of the Declaration of Helsinki, the applicable ICH guidelines for good clinical practices, and the applicable federal, state, and local laws, rules, and regulations relating to the conduct of the protocol. I have read and understand the information in the Investigators' Brochure (or Manufacturer's Brochure) regarding the risks and potential benefits. I will promptly submit the protocol to the applicable IRB for review and approval. Once the protocol has been approved by the IRB, I understand that any modification made during the course of the study must first be approved by the IRB, prior to implementation except when such modification is made to remove an immediate hazard to the subject. I certify that I, and the study staff, have received the requisite training to conduct this research protocol. I agree to maintain adequate and accurate records in accordance with Columbia University and Herbert Irving Comprehensive Cancer Center policies, Federal, state and local laws and regulations. I agree to maintain the confidentiality of all information received or developed in connection with this protocol.

Instructions to Principal Investigator: Sign and Date this signature page and print your name. Return the original, completed and signed to the Clinical Protocol & Data Management Office. Retain a copy in the regulatory binder.

_____ _____
Signature of Principal Investigator Date

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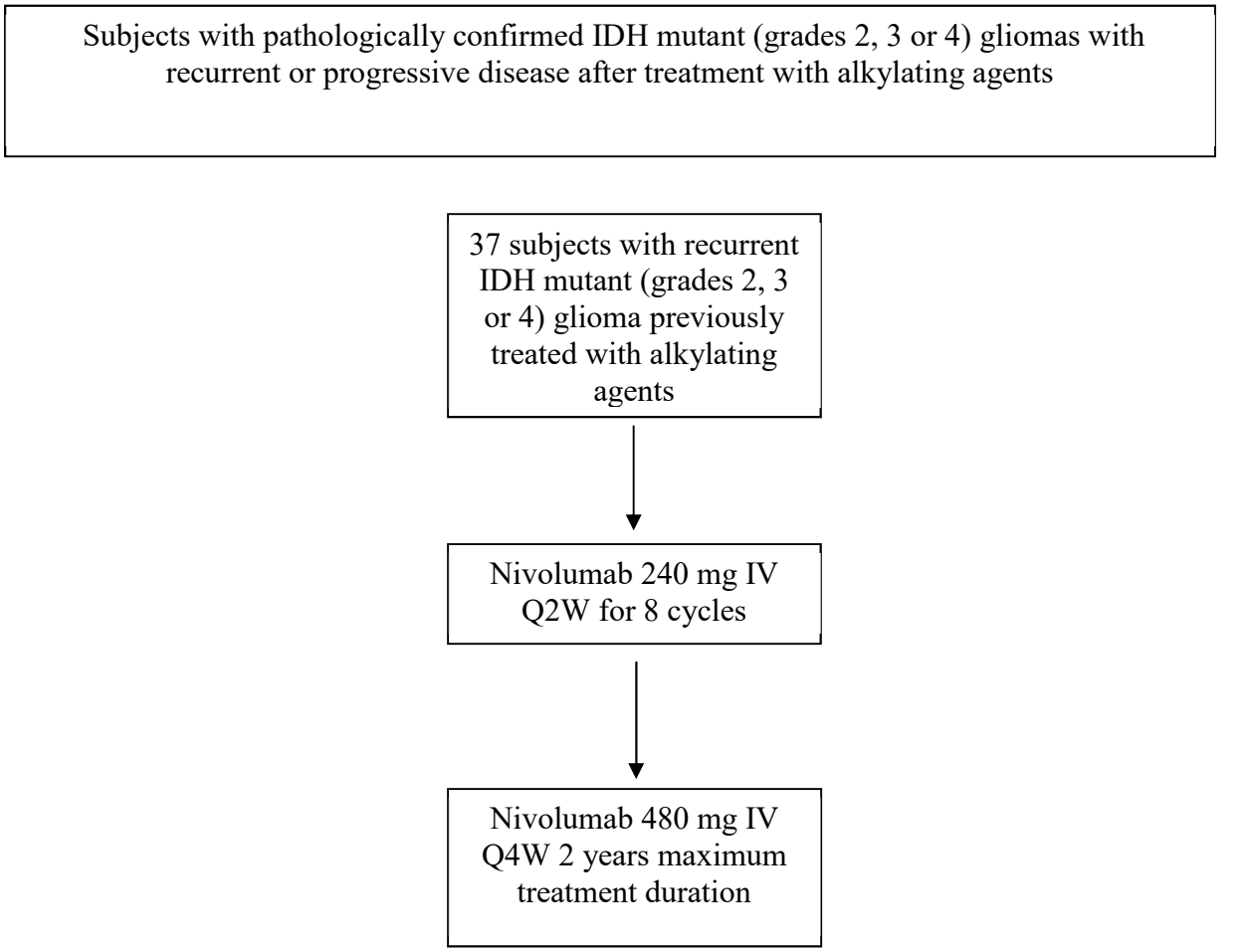
Principal Investigator Name (Print)

_____
Name of Institution

Protocol Synopsis

Title	A Phase II, Open Label, Single Arm Study of Nivolumab for Recurrent or Progressive IDH Mutant Gliomas with Prior Exposure to Alkylating Agents
Short Title	Nivolumab for IDH mutant gliomas
Protocol Number	AAAR6354
Phase	Phase 2
Methodology	Open label, single arm
Study Duration	36 months
Study Center(s)	Multi-center, 3 sites
Objectives	Objective response rate (partial and complete responses) to nivolumab of recurrent or progressive IDH mutant (grades 2, 3 or 4) gliomas with prior exposure to alkylating agents.
Number of Subjects	37 subjects
Diagnosis and Main Inclusion Criteria	Recurrent or progressive IDH mutant (grades 2, 3 or 4) gliomas in subjects 18 years of age or older with prior exposure to alkylating agents.
Study Product, Dose, Route, Regimen	Nivolumab (Opdivo®) 240mg IV every 2 weeks for 8 cycles. Starting with cycle 9, nivolumab 480mg IV every 4 weeks until completion of study.
Duration of administration	Up to 2 years
Reference therapy	Not applicable
Statistical Methodology	Objective response rates (partial and complete responses) will be calculated. The null hypothesis is set at an overall response rate of 10% based on historical data in subjects with recurrent high-grade gliomas with the alternative hypothesis being an overall response rate of 30%.

Protocol Schema:



Contents

1 INTRODUCTION

This document is a protocol for a human research study. This study is to be conducted according to US and international standards of Good Clinical Practice (FDA Title 21 part 312 and International Conference on Harmonization guidelines), applicable government regulations and Columbia University Medical Center institutional research policies and procedures.

2 STUDY OBJECTIVES

2.1 Primary Objective

- To evaluate the objective response rate (partial and complete responses) to nivolumab of recurrent or progressive IDH mutant (grades 2, 3 or 4) gliomas with prior exposure to alkylating agents.

2.2 Secondary Objectives

- To determine progression-free and overall survival
- To determine duration of response (DOR)

2.3 Exploratory Objectives

- To correlate response rate to nivolumab with mutational load analyses and specific tumor mutations
- To study clonal evolution of the tumor cell populations in IDH mutated gliomas undergoing therapy whenever tumor tissue is available
- To evaluate the longitudinal changes in the IDH mutant metabolite product 2-hydroxyglutarate (2HG) using magnetic resonance spectroscopy
- To evaluate spatial profiling of PD-1/PD-L1 interaction in IDH mutated gliomas and response to nivolumab

3 BACKGROUND

Gliomas are the most common malignant primary brain tumor in adults. Their clinical presentation is heterogeneous and prognosis is dependent on both the grade of the tumor and the molecular subtype. Somatic mutations in *Isocitrate dehydrogenase 1* (*IDH1*) or, less commonly, *IDH2* genes have emerged as an important prognostic factor in gliomas and are associated with longer survival.[1] Regardless of initial grade, recurrence and transformation into higher grade tumors is almost universal. There is high unmet medical need in treating recurrent gliomas as there is currently no established standard of care therapy.[2] Recent trials of IDH inhibitors in IDH mutant gliomas and PD-1 and PD-L1 inhibitors in recurrent gliomas have been disappointing.[3,4] Multiple studies in other cancers have demonstrated that hypermutated tumors are associated with response to immunotherapeutic agents,[5] including anti-CTLA4 agents in melanoma,[6] anti-PD1 therapy in bladder cancer,[7] and anti-PD-1 therapy in lung[8] and colorectal cancer.[9] There is evidence to suggest that gliomas with somatic IDH mutations are more prone to develop

hypermutation after exposure to alkylating agents than IDH wildtype tumors,[10,11] providing strong scientific rationale for establishing nivolumab as a treatment option in this subgroup of patients.

Gliomas represent approximately 25% of newly diagnosed primary brain tumors but account for 75% of all malignant primary brain tumors diagnosed yearly in the United States.[12] Annually, between 4500-5000 people in the U.S. are diagnosed with a grade II or III oligodendroglioma or astrocytoma and an additional 12,000 are diagnosed with glioblastoma (grade IV astrocytoma).[13,14] Malignant gliomas are slightly more common in men and incidence of high grade gliomas increases with increasing age. Low grade (Grade II) and anaplastic (Grade III) gliomas tend to present with seizures without focal neurologic deficits.[14] Glioblastoma (Grade IV) is more likely to present with focal neurologic deficits and clinical presentation varies depending on the tumor size and location but symptoms can include focal weakness, numbness, cognitive changes or changes in personality.[13] Survival in high grade gliomas (grade III and IV) is poor with less than 10% of patients surviving longer than 5 years.[12]

Historically, gliomas were categorized based on tumor morphology into oligodendrogliomas, astrocytomas, or oligoastrocytomas. The 2016 edition of the WHO Classification system has shifted to a molecular based classification system based on IDH mutation status and the presence or absence of 1p/19q co-deletion. Within the new classification system, all oligodendrogliomas contain *IDH1* or *IDH2* mutations and also contain a balanced translocation with loss of both the entire 1p and 19q arms. Astrocytomas can have *IDH* mutant or *IDH* wildtype phenotypes. Astrocytomas do not contain a 1p/19q co-deletion, but may have loss of *ATRX* which is more commonly seen in the IDH mutant variant. *IDH1* or *IDH2* mutations are now tested as part of the standard of care evaluation of patients with gliomas as their histological classification depends on this molecular analyses. The tumor grade remains a histologic determination based on mitotic figures and nuclear atypia, proliferation indices and the presence or absence of necrosis and endovascular proliferation.[15]

A large scale genetic analysis of gliomas in 2008 found that *IDH1* and, less commonly, *IDH2* mutations are present in over 70% of WHO Grade II and III astrocytomas and oligodendrogliomas and in many secondary glioblastomas arising from these lower grade tumors. IDH mutations likely represent driving mutations in these tumors. All IDH mutations are somatic, missense and heterozygous and occur at codon 132 in the IDH1 gene or codon 172 in the IDH2 gene, 90% of mutations involving IDH1 R132H. IDH mutant tumors are associated with a significant increase in median overall survival compared to IDH wildtype tumors.[1]

There is no established standard of care for the initial treatment of IDH mutant grade II and III gliomas; however, surgery, radiotherapy, chemotherapy with temozolomide or procarbazine/lomustine/vincristine (PCV) or a combination are all accepted treatments.[16-18] Glioblastomas are all treated with a combination of chemoradiotherapy with temozolomide regardless of IDH mutation status. Recurrence is almost universal and the prognosis of recurrent high grade glioma is dismal with a median overall survival of only 8-10 months.[2] At the time of recurrence, treatment options are limited, and there is no accepted standard of care for either IDH

mutant or wildtype tumors. Clinical trials of IDH inhibitors aimed at this subpopulation of subjects have been disappointing. For example, a trial of AG-120, an orally available IDH1 inhibitor in 20 subject with IDH1 mutant positive recurrent glioma showed no objective responses.[3]

PD-1 and PD-L1 inhibitors have revolutionized the treatment of many cancers and are FDA-approved for use in advanced melanoma, non-small cell lung cancer, renal cell carcinoma, relapsed classical Hodgkin's lymphoma, head and neck squamous cell carcinoma and urothelial carcinoma. Early phase trials of PD1 or PDL1 inhibitors in recurrent gliomas have been underwhelming. The majority of these studies have occurred in molecularly unselected subjects. In a small study of 16 subjects with recurrent glioblastoma treated with atezolizumab, only 1 subject (6%) had a partial response (Lukas et al, 2015 Society for Neuro-oncology meeting). Among 40 subjects with recurrent glioblastoma treated with nivolumab, a PD1 inhibitor, or nivolumab in combination with ipilimumab, a CTLA4 inhibitor, no objective radiographic responses were reported.[4] Checkmate 143 randomized 369 recurrent glioblastoma subjects to either nivolumab (n=184) or bevacizumab (n=185). The ORR was 8% in the nivolumab arm and 23% in the bevacizumab arm but the median duration of response was longer in the nivolumab (11.1 months) compared to bevacizumab (5.3 months). The primary endpoint of this was OS and the median was 9.8 months in the nivolumab and 10 months in the bevacizumab arm. [19] Of note, Checkmate 143 excluded subjects with IDH mutations.

Multiple studies across various cancers including bladder, melanoma, lung, and colorectal cancer have demonstrated that a hypermutated phenotype is associated with response to immunotherapeutic agents.[6-9] Hypermutated phenotypes are often associated with mutations in DNA replication and repair genes including mismatch repair genes. It is thought that tumors with a high mutational burden have more neoantigens which is important for the activity of anti-PD-1 therapies.[20,21]

In comparison to other cancer types with a robust response to immunotherapy such as melanoma and non-small cell lung cancer associated with smoking, untreated gliomas have a relatively small mutational burden. A recent study by Dr. Rabadan at Columbia University involved whole exome and transcriptome analyses of untreated and recurrent tumors from 114 subjects with glioblastomas. Among the 114 untreated tumors, the average number of somatic mutations was 60. In comparison, the average number of mutations in subjects with non-small cell lung cancer who achieved durable clinical benefit from PD-1 inhibitors was 302 vs. 148 in subjects who did not achieve a durable benefit. One exception to this is in glioblastomas arising in children with a rare germline cancer syndrome, biallelic mismatch repair deficiency (bMMRD). These tumors tend to have a high mutational burden (mean of 17,740 mutations compared to <100 in untreated glioblastomas and other gliomas). Two subjects with glioblastoma associated with bMMRD were treated with anti-PD1 inhibitor with dramatic clinical and radiographic responses.[20]

It has long been reported that the use of alkylating agents in gliomas is associated with a risk of higher-grade transformation and development of a hypermutated genotype with MSH6 mutations; however, the incidence in unselected subjects is very rare.[10,11] A recent study

investigated mutations induced by temozolomide by comparing pre and post-temozolomide glioblastoma specimens.[22] In IDH mutant low grade gliomas that progressed after temozolomide, six out of ten subjects recurred with hypermutated tumors.[23] Consistent with results from IDH mutant low grade gliomas that transformed to high-grade gliomas following temozolomide, an IDH1 mutated secondary glioblastoma subject showed a dramatically increased number of somatic mutations compared with the matched temozolomide naïve tumor (4848 vs. 119). This case also had mutations in mismatch repair genes PMS1 and MSH5. In contrast, none of the 20 subjects with IDH1 wild type glioblastoma showed any increase in the total or temozolomide-associated mutations in recurrent tumors when compared to initial tumors.[22] In Dr. Rabadan's study, almost all subjects received an alkylating agent prior to progression with temozolomide being the most common. Of 21 IDH mutant tumors, 9 (43%) developed a hypermutated recurrent tumor (>500 mutated genes/tumor) at recurrence. In comparison, only 8 of 93 (9%) IDH wildtype tumors developed a hypermutated tumor at recurrence (Fisher's exact test P=0.0005).

Preliminary data from Columbia University suggests that PD-1 inhibitors may be more effective in treating recurrent IDH1 mutant gliomas with previous exposure to alkylating agents. A cohort of 9 subjects with recurrent high grade gliomas (6 glioblastoma, 1 anaplastic oligodendroglioma, 2 anaplastic astrocytoma) with IDH1 mutation (8 with IDH1 R132H and 1 with IDH1 R132G mutations) previously treated with alkylating agents were treated with a PD-1 inhibitor alone (N = 4) or a PD-1 inhibitor in combination with re-irradiation (N = 5). Among these 9 subjects, 5 had a partial response (2 in the PD-1 only group; 3 in the PD-1 + re-irradiation group), 1 had stable disease for over 6 months (PD-1 + re-irradiation) and 3 had progressive disease (2 in the PD-1 only group, 1 in PD-1 + re-irradiation group). The overall response rate was 55% which is in stark contrast to other studies of PD-1 inhibitors in unselected subjects which have shown largely negative results. A recent study of the PD-L1 inhibitor durvalumab in recurrent glioblastoma previously exposed to temozolomide included 31 subjects, 4 with an IDH1 mutation, 22 IDH wild-type and 5 unknown. The 6 month progression free survival (PFS) rate was 20% (N=6) and the median PFS was 13.9 weeks (95% CI, 8.1-24.0). Of the 6 subjects with a response, 3 had IDH1 wildtype and 3 had IDH mutant tumors. There were 4 subjects with a response and 2 of them had IDH mutations meaning that 50% of subjects with IDH mutant tumors had a response to treatment (Reardon, et al. Society for Neuro-oncology 2016).

This provides a compelling scientific rationale for the current study evaluating nivolumab as a treatment option for recurrent glioma in subjects with IDH mutant tumors previously exposed to alkylating agents.

We hypothesize that this select group of subjects will have a clinical meaningful benefit from nivolumab in comparison to historical controls with an improved overall response rate as well as an improved median PFS, median OS, and durability of response.

4 INVESTIGATIONAL AGENT

4.1 Product Development

Nivolumab (Opdivo®) is a human monoclonal antibody (HuMAb; immunoglobulin G4 [IgG4]-S228P) that targets the PD-1 cluster of differentiation 279 (CD279) cell surface membrane receptor. PD-1 is a negative regulatory molecule expressed by activated T and B lymphocytes.[24] Binding of PD-1 to its ligands, PD-L1 and PD-L2, results in the down-regulation of lymphocyte activation. Inhibition of the interaction between PD-1 and its ligands promotes immune responses and antigen-specific T-cell responses to both foreign antigens as well as self-antigens. Nivolumab is expressed in Chinese hamster ovary cells and is produced using standard mammalian cell cultivation and chromatographic purification technologies. The clinical study product is a sterile solution for parenteral administration.Nivolumab is being investigated both as monotherapy and in combination with chemotherapy, targeted therapies, and other immunotherapies, in an array of solid and hematologic malignancies.

Nivolumab is approved in multiple countries including the US, Japan, and the European Union (EU) for treatment of previously treated, unresectable or metastatic melanoma and previously treated, metastatic squamous NSCLC, previously treated advanced bladder cancer, previously treated relapsed Classical Hodgkin's Lymphoma after hematopoetic stem cell transplant, previously treated recurrent or progressive squamous cell carcinoma of the head and neck, and additionally in the US for treatment of previously treated, unresectable or metastatic urothelial cell carcinoma and adult and pediatric (12 years and older) participants with microsatellite instability-high (MSI-H) or mismatch repair deficient (dMMR) metastatic colorectal cancer.

4.2 Preclinical Data

Nivolumab Mechanism of Action

Cancer immunotherapy rests on the premise that tumors can be recognized as foreign rather than as self and can be effectively attacked by an activated immune system. An effective immune response in this setting is thought to rely on immune surveillance of tumor antigens expressed on cancer cells that ultimately results in an adaptive immune response and cancer cell death. Meanwhile, tumor progression may depend upon acquisition of traits that allow cancer cells to evade immunosurveillance and escape effective innate and adaptive immune responses.[25-27]

Current immunotherapy efforts attempt to break the apparent tolerance of the immune system to tumor cells and antigens by either introducing cancer antigens by therapeutic vaccination or by modulating regulatory checkpoints of the immune system. T-cell stimulation is a complex process involving the integration of numerous positive as well as negative co-stimulatory signals in addition to antigen recognition by the T-cell receptor (TCR).[28] Collectively, these signals govern the balance between T-cell activation and tolerance.

PD-1 is a member of the CD28 family of T-cell co-stimulatory receptors that also includes CD28, CTLA-4, ICOS, and BTLA.59 PD-1 signaling has been shown to inhibit CD-28-mediated

upregulation of IL-2, IL-10, IL-13, interferon g (IFN g) and Bcl-xL. PD-1 expression has also been noted to inhibit T-cell activation, and expansion of previously activated cells. Evidence for a negative regulatory role of PD-1 comes from studies of PD-1 deficient mice, which develop a variety of autoimmune phenotypes.[24] These results suggest that PD-1 blockade has the potential to activate anti-self T-cell responses, but these responses are variable and dependent upon various host genetic factors. Thus, PD-1 deficiency or inhibition is not accompanied by a universal loss of tolerance to self-antigens.

In vitro, nivolumab (BMS-936558) binds to PD-1 with high affinity (EC50 0.39-2.62 nM), and inhibits the binding of PD-1 to its ligands PD-L1 and PD-L2 (IC50 ± 1 nM). Nivolumab binds specifically to PD-1 and not to related members of the CD28 family such as CD28, ICOS, CTLA-4, and BTLA. Blockade of the PD-1 pathway by nivolumab results in a reproducible enhancement of both proliferation and IFN-γ release in the mixed lymphocyte reaction (MLR). Using a cytomegalovirus (CMV) restimulation assay with human peripheral blood mononuclear cells (PBMC), the effect of nivolumab on antigen specific recall response indicates that nivolumab augmented IFN-γ secretion from CMV specific memory T-cells in a dose-dependent manner versus isotype-matched control. In vivo blockade of PD-1 by a murine analog of nivolumab enhances the anti-tumor immune response and results in tumor rejection in several immunocompetent mouse tumor models (MC38, SA1/N, and PAN02).[29]

While the extent of tumor penetration is currently unknown for nivolumab, a fully human IgG monoclonal antibody, in participants with a primary brain tumor or in participants with brain metastasis, it is expected that adequate levels are achieved to yield effects. Antibodies have been reported to pass the BBB with a cerebrospinal fluid (CSF) to serum ratio of approximately 0.3%.[30] Higher BBB permeability and greater drug exposures were observed in brain tumor than in normal brain due to breakdown of the BBB and possibly increased intratumoral angiogenesis.[31] Therefore, nivolumab is expected to be able to pass the BBB in participants with brain tumors. Receptor occupancy data demonstrated that nivolumab binds to a majority of PD-1 receptors (≥ 90%) in the circulation at low-dose level (0.3 mg/kg) with a lasting effect (≥ 8 cycles), and this effect is maintained at doses greater than 0.3 mg/kg. Thus, even though only a small percentage of circulating nivolumab could cross the BBB and become available in CSF, given the high potency and high affinity of nivolumab, it is still expected that nivolumab would block the interaction between PD-1 and PD-L1, thereby exhibiting an anti-tumor effect in brain tumors.

4.3 Clinical Data

Clinical Pharmacokinetics
The PK of nivolumab were studied in participants over a dose range of 0.1 to 10 mg/kg administered as a single dose or as multiple doses of nivolumab every 2 or 3 weeks. The geometric mean (% CV%) clearance (CL) was 9.5 mL/h (49.7%), geometric mean volume of distribution at steady state (Vss) was 8.0 L (30.4%), and geometric mean elimination half-life (t1/2) was 26.7 days (101%). Steady-state concentrations of nivolumab were reached by 12 weeks when administered at 3 mg/kg Q2W, and systemic accumulation was approximately 3-fold. The exposure to nivolumab increased dose proportionally over the dose range of 0.1 to 10

mg/kg administered every 2 weeks. The clearance of nivolumab increased with increasing body weight. The PPK analysis suggested that the following factors had no clinically important effect on the CL of nivolumab: age (29 to 87 years), gender, race, baseline LDH, and PD-L1. A PPK analysis suggested no difference in CL of nivolumab based on age, gender, race, tumor type, baseline tumor size, and hepatic impairment.

Although Eastern Cooperative Oncology Group status, baseline glomerular filtration rate, albumin, and body weight had an effect on nivolumab CL, the effect was not clinically meaningful. When nivolumab was administered in combination with ipilimumab, the CL of nivolumab was increased by 24%, whereas there was no effect on the clearance of ipilimumab. Additionally, PPK and exposure response analyses have been performed to support use of 240 mg Q2W dosing in addition to the 3 mg/kg Q2W regimen. Using the PPK model, exposure of nivolumab at 240 mg was identical to a dose of 3 mg/kg for participants weighing 80 kg, which was the approximate median body weight in nivolumab clinical trials. Full details on the clinical pharmacology aspects of nivolumab can be found in the Investigator Brochure.

Nivolumab Safety Summary
Nivolumab has been studied in over 8,600 participants and is approved in multiple indications. Extensive details on the safety profile of nivolumab are available in the Investigator Brochure, and will not be repeated herein.

Overall, the safety profile of nivolumab monotherapy as well as combination therapy is manageable and generally consistent across completed and ongoing clinical trials with no maximum tolerated dose reached at any dose tested up to 10 mg/kg. Most AEs were low-grade (Grade 1 to 2) with relatively few related high-grade (Grade 3 to 4) AEs. There was no pattern in the incidence, severity, or causality of AEs with respect to nivolumab dose level. A pattern of immune-related AEs has been defined, for which management algorithms have been developed; these are provided in Appendix 1. Most high-grade events were manageable with the use of corticosteroids or hormone replacement therapy (endocrinopathies) as instructed in these algorithms. For additional material, see the nivolumab Investigator Brochure. Additional details on the safety profile of nivolumab, including results from other clinical studies, are also available in the nivolumab IB.

Nivolumab Clinical Activity Summary
Nivolumab has demonstrated clinical activity either as monotherapy or in combination with ipilimumab in several tumor types, including NSCLC, melanoma, squamous cell carcinoma of the head and neck, classical Hodgkin's lymphoma and RCC. The majority of responses were durable and exceeded 6 months. In randomized, controlled studies, nivolumab monotherapy demonstrated statistically significant improvement in OS over standard of care in participants with advanced or metastatic melanoma and in participants with advanced or metastatic NSCLC. In randomized, controlled studies, nivolumab in combination with ipilimumab demonstrated statistically significant improvement in PFS and ORR over ipilimumab monotherapy in participants with advanced or metastatic melanoma.

Full details on the clinical efficacy aspects of nivolumab can be found in the Investigator

Brochure.

Overall Risk/Benefit Assessment

Participants with progressive or recurrent IDH mutant gliomas represent an area of substantial unmet medical need. Additionally, there is no accepted standard of care for recurrent IDH mutant gliomas and none of the treatment options are curative. Therefore the development of new approaches is needed.

Nivolumab has demonstrated a manageable safety profile in > 8600 participants across all clinical trials. The most common AEs included fatigue, rash, pruritus, diarrhea, and nausea. The AE profile for nivolumab monotherapy does not appear to be dose dependent and appears to be similar across a range of solid tumors studied. This manageable toxicity profile makes nivolumab a suitable therapeutic option in this older participant population. Together the data suggest a positive benefit-risk potential, supporting a Phase 2 study to further assess the efficacy and safety of nivolumab in progressive or recurrent IDH mutant gliomas.

Rationale for Nivolumab Dose Selection
Nivolumab will be given 240 mg every 2 weeks (Q2W) IV for 8 cycles followed by 480 mg every 4 weeks (Q4W), for a total of 2 years of treatment duration or until progressive disease, unacceptable toxicity, or withdrawal of consent. The infusion duration for both dosing regimens will be 30 minutes.

The nivolumab dose of 240 mg Q2W was selected based on clinical data and modeling and simulation approaches using population pharmacokinetics (PPK) and exposure-response analyses of data from studies in multiple tumor types (melanoma, non-small-cell lung cancer [NSCLC], and renal cell carcinoma [RCC]) where body weight-normalized dosing (mg/kg) has been used. PPK analyses have shown that the PK of nivolumab is linear with proportional exposure over a dose range of 0.1 to 10 mg/kg, and no differences in PK across ethnicities and tumor types were observed. Nivolumab clearance and volume of distribution were found to increase as the body weight increases, but less than proportional with increasing weight, indicating that mg/kg dosing represents an over-adjustment for the effect of body weight on nivolumab PK.

The PPK model previously developed using data from NSCLC participants has recently been updated, using data from 1,544 participants from 7 studies investigating nivolumab in the treatment of melanoma, NSCLC, and RCC. In this dataset, the median (minimum - maximum) weight was 77 kg (35 - 160 kg) and thus, with an approximately equivalent dose of 3 mg/kg for an 80-kg participant, nivolumab 240 mg Q2W was selected for future studies. To predict relevant summary exposures of nivolumab 240 mg Q2W, the PPK model was used to simulate nivolumab 3 mg/kg Q2W and 240 mg Q2W. In the simulations, the simulated patient populations consisted of 1,000 participants per treatment arm randomly sampled from aforementioned pooled database of cancer participants. Because no differences in PK were noted across ethnicities and tumor types, these simulated melanoma and NSCLC data will be applicable to participants with other tumor types. The simulated measure of exposure of interest, time-averaged concentrations (Cavgss) for 240 mg Q2W are predicted to be similar for all participants in reference to 80-kg

participants receiving 3 mg/kg Q2W.

Nivolumab is safe and well tolerated up to 10-mg/kg Q2W dose level. Adverse events (AEs) have been broadly consistent across tumor types following monotherapy and have not demonstrated clear dose-response or exposure-response relationships. Additionally, the simulated median and 95th prediction interval of nivolumab summary exposures across body weight range (35 kg to 160 kg) are predicted to be maintained below the corresponding observed highest exposure experienced in nivolumab, ie, 95th percentile following nivolumab 10 mg/kg Q2W from clinical study CA209003. Thus, while participants in the lower body weight ranges would have greater exposures than 80-kg participants, the exposures are predicted to be within the range of observed exposures at doses (up to 10 mg/kg Q2W) used in the nivolumab clinical program, and are not considered to put participants at increased risk. For participants with greater body weights, the simulated ranges of exposures are also not expected to affect efficacy, because the exposures predicted following administration of 240 mg Q2W are on the flat part of the exposure-response curves for previously investigated tumors in melanoma and NSCLC. Given the similarity of nivolumab PK across tumor types and the similar exposures predicted following administration of 240 mg compared to 3 mg/kg, it is expected that the safety and efficacy profile of 240 mg nivolumab will be similar to that of 3 mg/kg nivolumab. Thus nivolumab 240 mg every 2 weeks over 30 minutes for the first 4 months will be used in this study.

After 8 cycles of treatment, participants will be switched from nivolumab 240 mg Q2W to nivolumab 480 mg Q4W from Cycle 9, which provides a more convenient dosing regimen for participants. Based on PK modeling and simulations, administration of nivolumab 480 mg Q4W will be started after steady state is achieved with 240 mg Q2W and is predicted to provide Cavgss similar to 240 mg Q2W. While 480 mg Q4W is predicted to provide greater (approximately 20%) maximum steady state concentrations and lower (approximately 10%) steady state trough concentrations, these exposures are predicted to be within the exposure ranges observed at doses up to 10 mg/kg Q2W used in the nivolumab clinical program, and are not considered to put participants at increased risk. Similar to the nivolumab 240 mg Q2W dosing regimen, the exposures predicted following administration of nivolumab 480 mg Q4W are on the flat part of the exposure-response curves for previously investigated tumors in melanoma and NSCLC, and are not predicted to affect efficacy. Based on these data, nivolumab 480 mg Q4W is expected to have similar efficacy and safety profiles to nivolumab 240 mg Q2W.

Rationale for Nivolumab 30-minute Infusion

Long infusion times place a burden on participants and treatment centers. Establishing that nivolumab can be safely administered using shorter infusion times of 30 minutes duration in participants will diminish the burden provided no change in safety profile. Previous clinical studies show that nivolumab has been administered safely over 60 minutes at doses ranging up to 10 mg/kg over long treatment duration. In Study CA209010, (a Phase 2, randomized, double blinded, dose-ranging study of nivolumab in participants with advanced/metastatic clear cell RCC) a dose association was observed for infusion site reactions and hypersensitivity reactions (1.7% at 0.3 mg/kg, 3.7% at 2 mg/kg, and 18.5% at 10 mg/kg). All the events were Grade 1-2 and were manageable. An infusion duration of 30 minutes for 240-mg and 480-mg doses of nivolumab (~ 60% of the dose provided at 10 mg/kg) is not expected to present safety concerns

compared to the prior experience at 10-mg/kg nivolumab dose infused over a 60-minute duration.

5 STUDY DESIGN

5.1 General Design

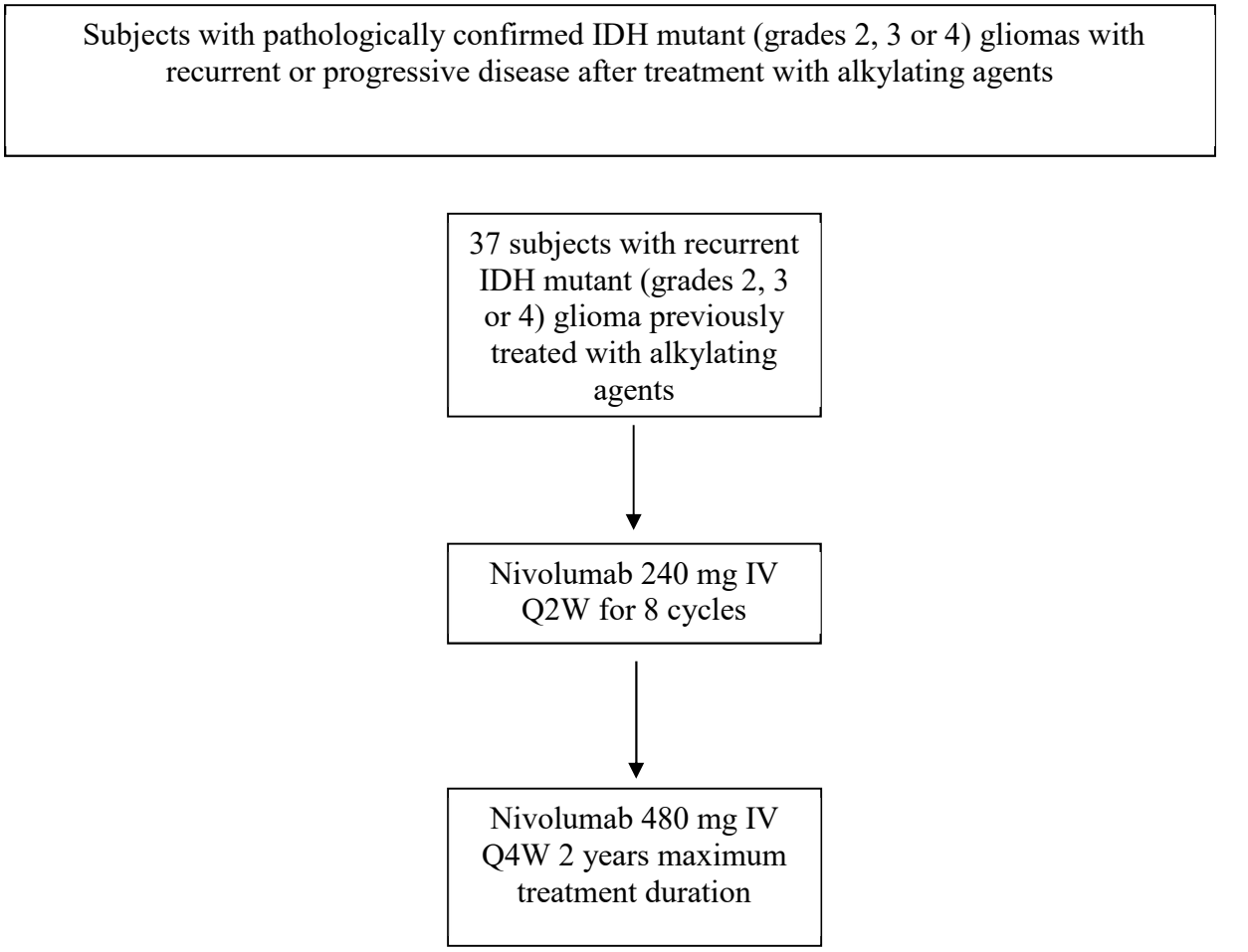
This is a Phase 2, open-label, single-arm study to estimate the safety and efficacy of nivolumab in participants with recurrent or progressive IDH mutated glioma after exposure to alkylating agents. Nivolumab 240 mg will be given every 2 weeks for 8 cycles. Beginning with Cycle 9, nivolumab 480 mg will be given every 4 weeks for a total therapy duration of 2 years, or until progressive disease, unacceptable toxicity, or withdrawal of consent. Nivolumab will be administered as a 30-minute infusion. A finite treatment duration with immune therapies in this participant population remains an area of ongoing research; therefore the treatment duration chosen was 2 years.

The study will further characterize safety and evaluate the antitumor activity of nivolumab in participants with recurrent IDH mutant glioma who progressed after or did not respond to alkylating agents.

The primary endpoint is ORR, and will be analyzed 6 months after the last participant's first treatment in the trial.

The study design schematic is presented in Figure 5.1-1.

Figure 5.1-1: Study design schematic



5.2 Primary Objective

- To evaluate the objective response rate (partial and complete responses) to nivolumab of recurrent or progressive IDH mutant (grades 2, 3 or 4) gliomas with prior exposure to alkylating agents.

5.3 Secondary Objectives

- To determine progression-free and overall survival
- To determine duration of response (DOR)

5.4 Exploratory Objectives

- To correlate response rate to nivolumab with mutational load analyses and specific tumor mutations
- To study clonal evolution of the tumor cell populations in IDH mutated gliomas undergoing therapy whenever tumor tissue is available
- To evaluate the longitudinal changes in the IDH mutant metabolite product 2-hydroxyglutarate (2HG) using magnetic resonance spectroscopy
- To evaluate spatial profiling of PD-1/PD-L1 interaction in IDH mutated gliomas and response to nivolumab
- To assess neurologic functioning in using Neurologic Assessment in Neuro-Oncology (NANO)

5.5 Correlative Studies Background

Relationship between nivolumab response and molecular evolution of the glioma cell population (Exploratory)

Current models of PD-1/PD-L1 pathway blockade in solid tumors tie strong therapeutic response to somatic mutational load, and particularly the expression and presentation of tumor neo-antigens.[8] We will perform whole exome sequencing to evaluate the genomic frequency and pattern of mutations, as well as the clonality of the tumor cell population, using tumor tissue resected prior to nivolumab treatment (initial diagnosis and post-alkylating agent whenever tissue is available). If subsequent surgeries for tumor recurrence are done following treatment with nivolumab, the clonal evolution of these tumors will be studied through computational modeling, as developed by the team of our collaborator, Dr. Raul Rabadan, in the Dept. of Systems Biology at Columbia University Medical Center.

Spatial profiling of PD-1/PD-L1 interaction in gliomas (Exploratory)

PD-1 and PD-L1 therapies have produced dramatic anti-cancer responses; however, selecting patients who will receive the most clinical benefit remains a challenge. PD-1 and PD-L1 expression in tumors does not always correlate with clinical response. Recent studies have demonstrated that characterizing the density of PD-1 positive lymphocytes in close proximity to PD-L1 expressing tumor cells may be a better measure of adaptive immune response rather than PD-1 expression alone.[32] In a study using pathway analysis across 60 melanoma cell lines, those with MHC-II expression had signitures consistent with PD-1 signalling, T-cell receptor signalling, and allograft rejection. Confirmation studies using samples from patients with melanoma treated with anti-PD-1 demonstrated that those with MHC-II expression on tumor

cells had an improved therapeutic response, increased progression-free survival, and increased overall survival times.[33] This interaction may be a useful biomarker to predict response to PD-1 inhibitors in patients with IDH-mutant gliomas..

2-hydroxyglutarate (2HG) magnetic resonance spectroscopy (Exploratory)
Mutations in IDH result in excess production of the metabolite 2-hydroxyglutarate (2HG), which can be measured non-invasively through magnetic resonance spectroscopy (MRS). 2HG MRS does not require any further gadolinium contrast and can be easily incorporated to standard of care MRI scans at baseline and every 8 weeks assessments while the patients are on-treatment without any further risk to participants. 2HG MRS can be useful longitudinally as a pharmacodynamic marker of antitumor activity and also may be useful in differentiating true tumor progression from pseudoprogression.

Neurologic Assessment in Neuro-Oncology (Exploratory)
Neurologic Assessment in Neuro-Oncology (NANO) scale is an objective and quantifiable metric of neurologic function evaluable during a routine physical examination. The scale has excellent overall reliability, inter-observer agreement, and is easily performed. The NANO scale is a quantifiable evaluation of 9 relevant neurologic domains that provides an objective clinician-reported outcome of neurologic function.[34]

5.6 Safety Assessments

At screening, a medical history will be obtained to capture relevant underlying conditions. The screening examinations should include weight, height, Karnofsky status, blood pressure (BP), heart rate (HR), and temperature.

Screening local laboratory assessments should be done within 14 days prior to treatment assignment and are to include: CBC with differential, chemistry panel including LFTs (ALT, AST, TBILI, ALP), amylase, lipase, uric acid, BUN or serum urea level, creatinine, Ca, Na, K, Cl, Mg, albumin, phosphate, LDH, glucose, and thyroid panel including TSH, T3, and free T4.

Pregnancy tests for WOCBP must be performed within 24 hours prior to the initial administration of study drug and every cycle thereafter.

The following screening local laboratory assessments should be done within 28 days prior to treatment: Hepatitis B and C testing (HBV sAg and HCV Ab or HCV RNA).

While on-study the following local laboratory assessments are to be done within 3 calendar days prior to each dose: CBC with differential, LFTs (ALT, AST, TBILI, ALP), BUN or serum urea level, creatinine, Ca, Mg, Na, K, Cl, phosphate, LDH, uric acid, amylase, lipase, albumin, glucose.

Thyroid function testing (TSH with reflexive T3 and fT4) is to be done every 3 infusions starting on C3D1 followed by C6D1 etc. for participants receiving nivolumab at 240 mg Q2W, then every 2 infusions starting at C9D1 followed by C11D1 etc. for participants receiving nivolumab at 480 mg Q4W (every other infusion).

On treatment pregnancy tests should be performed as per the schedule in the time and events table (Table 12.1-2).

Participants will be evaluated for safety if they have received any study drug. Toxicity assessments will be continuous during the treatment phase as well as during the first 2 safety follow-up visits. Once participants reach the survival follow-up phase, either in-person visits or documented telephone calls to assess the participant's status are acceptable.

Adverse events and laboratory values will be graded according to the NCI CTCAE version 4.03.

The start and stop time of the study therapy infusions and any interruptions or infusion rate reductions should be documented.

Physical examinations are to be performed as clinically indicated. If there are any new or worsening clinically significant changes since the last exam, report changes on the appropriate non-serious or SAE page.

On treatment local laboratory assessments are to be completed within 3 calendar days prior to dosing.

Additional measures, including non-study required laboratory tests, should be performed as clinically indicated or to comply with local regulations. Laboratory toxicities (eg, suspected drug induced liver enzyme evaluations) will be monitored during the follow-up phase via on site/local labs until all study drug-related toxicities resolve, return to baseline, or are deemed irreversible.

If a participant shows pulmonary-related signs (hypoxia, fever) or symptoms (eg, dyspnea, cough, fever) consistent with possible pulmonary AEs, the participant should be immediately evaluated to rule out pulmonary toxicity, according to the suspected pulmonary toxicity management algorithm (Appendix 1) and in the nivolumab Investigator Brochure.

Some of the assessments referred to in this section may not be captured as data in the eCRF. They are intended to be used as safety monitoring by the treating physician. Additional testing or assessments may be performed as clinically necessary or where required by institutional or local regulations.

Imaging Assessment for the Study

Radiographic tumor assessments will be performed with brain MRI with and without gadolinium and with 2HG MR spectroscopy as part of the standard of care every 8 weeks from C1D1 for up to 2 years while on-treatment or until progression of disease. In the follow-up period, subjects who discontinue treatment for a reason other than disease progression will continue to undergo tumor assessments at timepoints dicated per standard of care but RANO

assessments must be completed and documented on these scans. Follow-up scans should continue until disease progression or start of subsequent anti-cancer therapy, whichever occurs first. (Table 12.2: On-treatment procedures and Table 12.3: Follow up Assessments)

All efforts should be made to obtain brain MRI scans with 2HG MR spectroscopy. Sites unable to perform 2HG MR spectroscopy may have this requirement waived upon discussion with and approval by the CUMC PI. Additionally, if it is not feasible to obtain 2HG MR spectroscopy for a particular paitent at any specific timepoint, this requirement may be waived upon discussion with and approval by the CUMC PI.

5.7 Number of Participants

A sample size of 33 evaluable participants will be needed to assess the preliminary efficacy of this regimen. We expect to accrue a total of 37 participants across all sites to account for a 10% of participants who may be deemed unevaluable for the primary endpoint.

6 PARTICIPANT SELECTION AND WITHDRAWAL

Study Population

For entry into the study, the following criteria MUST be met.

6.1 Inclusion Criteria

0.1. Participants must have signed and dated an IRB/IEC approved written informed consent form in accordance with regulatory and institutional guidelines. This must be obtained before the performance of any protocol-related procedures that are not part of normal patient care.

0.2. Participant must be willing and able to comply with scheduled visits, treatment schedule, laboratory tests, and other requirements of the study.

0.3. Participant must be 18 years of age or older

0.4. Participants with pathologically confirmed grade 2, 3 or 4 gliomas with IDH mutation (confirmed by IDH R132H immunohistochemistry or IDH1/IDH2 next generation sequencing) who have progressive tumor and have had previous exposure to alkylating agents.

1.5. Participants must have measurable disease, defined as at least one enhancing tumor lesion that can be accurately measured in at least one dimension as ≥ 10mm x 10mm on brain MRI. See 13.2 Disease Parameters for more information regarding evaluation of measurable disease. Patients with non-enhancing measureable disease may be eligible upon discussion with and approval by the CUMC PI.

1.6. Documentation of availability of sufficient baseline tumor for analysis, defined as a minimum of 20 unstained slides or equivalent quantity of frozen tumor or FFPE tumor block.

1.7. KPS of 60 and above

1.8. Adequate bone marrow, kidney and liver function as defined below:

i) White blood count (WBC) ≥ 3000/uL

ii) Neutrophils ≥ 1500/uL
iii) Absolute lymphocyte count ≥ 500/uL
iv) Platelets ≥ $100x10^3$/uL
v) Hemoglobin ≥ 9.0g/dL
vi) Serum creatinine ≤ 1.5x upper limit of normal (ULN) or calculated creatinine clearance > 50 mL/min (using the Cockcroft-Gault formula)

~~1.~~9. Female CrCl = (140 - age in years) x weight in kg x 0.85 72 x serum creatinine in mg/dL
~~2.~~10. Male CrCl = (140 - age in years) x weight in kg x 1.00 72 x serum creatinine in mg/dL
~~2.~~11. vi) Aspartate aminotransferase (AST) and alanine aminotransferase (ALT) ≤ 3.0 x ULN
~~3.~~12. vii) Total bilirubin (TBILI) ≤ 1.5 x ULN (except participants with Gilbert Syndrome who must have a total bilirubin level of < 3.0xULN)
~~6.~~13. Women of childbearing potential (WOCBP) must have a negative serum or urine pregnancy test (minimum sensitivity 25 IU/L or equivalent units of human chorionic gonadotropin) within 24 hours prior to the start of study drug
~~6.~~14. Women must not be pregnant or breastfeeding
~~6.~~15. WOCBP must agree to follow instructions for method(s) of contraception for the duration of study treatment with nivolumab and 5 months after the last dose of study treatment (i.e., 30 days (duration of ovulatory cycle) plus the time required for the investigational drug to undergo approximately five half-lives.)
~~6.~~16. Males who are sexually active with WOCBP must agree to follow instructions for method(s) of contraception for the duration of study treatment with nivolumab and 7 months after the last dose of study treatment (i.e., 90 days (duration of sperm turnover) plus the time required for the investigational drug to undergo approximately five half- lives.)
~~6.~~17. Azoospermic males are exempt from contraceptive requirements. WOCBP who are continuously not heterosexually active are also exempt from contraceptive requirements, but still must undergo pregnancy testing as described in this section.
~~6.~~18. Investigators shall counsel WOCBP, and male participants who are sexually active with WOCBP, on the importance of pregnancy prevention and the implications of an unexpected pregnancy. Investigators shall advise on the use of highly effective methods of contraception, which have a failure rate of < 1% when used consistently and correctly.
~~6.~~19. At a minimum, participants must agree to use 1 highly effective method of contraception as listed in Appendix 2.

6.2 Exclusion Criteria

~~0.~~1. Participants with an active, known, or suspected autoimmune disease.
~~0.~~2. Participants with type I diabetes mellitus, hypothyroidism only requiring hormone replacement, skin disorders (such as vitiligo, psoriasis, or alopecia) not requiring systemic treatment, or conditions not expected to recur in the absence of an external trigger are permitted to enroll.

6.3. Participants with a condition requiring systemic treatment with either corticosteroids (> 10 mg daily prednisone equivalent) or other immunosuppressive medications within 14 days of start of study treatment. Inhaled or topical steroids, and adrenal replacement steroid doses > 10 mg daily prednisone equivalent, are permitted in the absence of active autoimmune disease. Dose of dexamethasone ≤ 4 mg/day or equivalent is allowed at the study entry for brain tumor edema.[35,36] Participants are permitted the use of topical, ocular, intra-articular, intranasal, and inhalational corticosteroids (with minimal systemic absorption). A brief (less than 3 weeks) course of corticosteroids for prophylaxis (eg, contrast dye allergy) or for treatment of non-autoimmune conditions (eg, delayed-type hypersensitivity reaction caused by a contact allergen) is permitted. Participants who have received chemotherapy or experimental agents within 4 weeks (except for 6 weeks for nitrosoureas and 23 days for temozolomide) and radiotherapy within 12 weeks of the first dose of the study treatment.

6.4. Prior use of PD-1, PD-L1, or CTLA-4 inhibitors or exposure to other checkpoint inhibitors.

6.5. Prior exposure to bevacizumab or other VEGF or VEGFR inhibitors.

6. Any positive test for hepatitis B virus or hepatitis C virus indicating acute or chronic infection, and/or detectable virus

6.7. History of severe allergy or hypersensitivity to nivolumab components

Eligibility criteria for this study have been carefully considered to ensure the safety of the study participants and that the results of the study can be used. It is imperative that participants fully meet all eligibility criteria.

6.3 Definition of Women of Childbearing Potential

WOCBP is defined as any female who has experienced menarche and who has not undergone surgical sterilization (hysterectomy or bilateral oophorectomy) and is not postmenopausal. Menopause is defined as 12 months of amenorrhea in a woman over age 45 years in the absence of other biological or physiological causes. In addition, females under the age of 55 years must have a serum follicle stimulating hormone (FSH) level > 40 mIU/mL to confirm menopause. Females treated with hormone replacement therapy (HRT) are likely to have artificially suppressed FSH levels and may require a washout period in order to obtain a physiologic FSH level. The duration of the washout period is a function of the type of HRT used. The duration of the washout period below are suggested guidelines and the investigators should use their judgement in checking serum FSH levels:

- 1 week minimum for vaginal hormonal products (rings, creams, gels)
- 4 week minimum for transdermal products
- 8 week minimum for oral products

Other parenteral products may require washout periods as long as 6 months. If the serum FSH level is > 40 mIU/ml at any time during the washout period, the woman can be considered postmenopausal.

6.4 MRI Contraindication

MRI imaging of the brain will be performed per the frequency specified in the protocol, which is in line with the accepted standard of care for patients with gliomas. Investigators may obtain additional follow-up MRI scans as medically indicated. For other locally performed imaging, it is the local imaging facility's responsibility to determine, based on participant attributes (eg, allergy history, diabetic history, and renal status), the appropriate imaging modality, and contrast regimen for each participant. Imaging contraindications and contrast risks should be considered in this assessment. Participants with renal insufficiency should be assessed as to whether or not they should receive contrast, and if so, what type and dose of contrast is appropriate. Specific to MRI, participants with severe renal insufficiency (ie, estimated glomerular filtration rate < 30 mL/min/1.73 m^2) are at increased risk of nephrogenic systemic fibrosis. MRI contrast should not be given to this participant population, who should be excluded from the study. In addition, participants with surgically implanted devices (pacemaker, deep brain stimulator, metallic implants, etc.) incompatible with MRI should not undergo such imaging techniques. The local imaging facility and investigator should determine the appropriate precautions or guidelines that should be instituted for participants with tattoos, body piercings, or other body art.

The ultimate decision to perform MRI in an individual participant in this study rests with the site radiologist, and the investigator.

6.5 Concomitant Treatments

Prohibited and/or Restricted Treatments
The following medications are prohibited during the study (unless utilized to treat a drug-related AE):

- Immunosuppressive agents
- Immunosuppressive doses of systemic corticosteroids, except in participants treated with dexamethasone is permitted for management of brain edema.
- Any concurrent anti-neoplastic therapy (ie, chemotherapy, hormonal therapy, immunotherapy, radiation therapy, tumor treatment fields (TTFields) or standard or investigational agents for treatment of gliomas).

6.6 Corticosteroids Restrictions and Precautions

Participants with a condition requiring systemic treatment with either corticosteroids (> 10 mg daily prednisone equivalent) or other immunosuppressive medications within 14 days of treatment assignment are excluded. Inhaled or topical steroids, and adrenal replacement steroid doses > 10 mg daily prednisone equivalent, are permitted in the absence of active autoimmune disease.

Participants are permitted the use of topical, ocular, intra-articular, intranasal, and inhalational corticosteroids (with minimal systemic absorption). Adrenal replacement steroid doses > 10 mg daily prednisone are permitted. A brief (less than 3 weeks) course of corticosteroids for

prophylaxis (eg, contrast dye allergy) or for treatment of non-autoimmune conditions (eg, delayed-type hypersensitivity reaction caused by a contact allergen) is permitted. Treatment with dexamethasone is permitted for brain edema.

6.7 Inclusion of Women and Minorities

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

Accrual Targets					
Ethnic Category	**Sex/Gender**				
	Females		**Males**		**Total**
Hispanic or Latino	2	+	3	=	5
Not Hispanic or Latino	15	+	17	=	32
Ethnic Category: Total of all participants	17	+	20	=	37
Racial Category					
American Indian or Alaskan Native	0	+	0	=	0
Asian	0	+	1	=	1
Black or African American	2	+	2	=	4
Native Hawaiian or other Pacific Islander	0	+	0	=	0
White	15	+	17	=	32
Racial Category: Total of all participants	17	+	20	=	37

6.8 Participant Recruitment

Participants will be recruited from investigator or co-investigator clinical practices and other referring physicians.

6.9 Early Withdrawal of Subjects

When and How to Withdraw Subjects

Discontinuation of Subjects following any Treatment with Study Drug
Participants MUST discontinue investigational product (and non-investigational product at the discretion of the investigator) for any of the following reasons:

- Participant's request to stop study treatment
- Participant repetitive and significant non-compliance

- Disease progression, except as described in Section 13.3
- Unacceptable toxicity, see Section 8.5
- Any clinical AE, laboratory abnormality, or intercurrent illness which, in the opinion of the investigator, indicates that continued participation in the study is not in the best interest of the participant, see Section 8.5
- Pregnancy
- Termination of the study
- Loss of ability to freely provide consent through imprisonment or involuntarily incarceration for treatment of either a psychiatric or physical illness
- This study has a progression-free and overall survival endpoint; therefore participants discontinuing study treatment will remain on study for documentation of progression and death.

In the case of pregnancy, the investigator must immediately notify Sponsor or designee of this event. In most cases, the study drug(s) will be permanently discontinued in an appropriate manner. Please contact the Sponsor or designee within 24 hours of awareness of pregnancy. If the investigator determines a possible favorable benefit/risk ratio that warrants continuation of study drug, a discussion between the investigator and the Sponsor or designee must occur.

All participants who discontinue study drug should comply with protocol specified follow-up procedures as outlined in Section 12.3. The only exception to this requirement is when a participant withdraws consent for all study procedures including post-treatment study follow-up or loses the ability to consent freely (ie, is imprisoned or involuntarily incarcerated for the treatment of either a psychiatric or physical illness).

If study drug is discontinued prior to the participant's completion of the study, the reason for the discontinuation must be documented in the subject's medical records and entered on the appropriate case report form (CRF) page.

Data Collection and Follow-up for Withdrawn Participants

Post Study Drug Study Follow-up
In this study, OS is a secondary endpoint. Post study follow-up is of critical importance and is essential to preserving subject safety and study integrity. Participants who discontinue study drug must continue to be followed every 3 months after the second off-nivolumab follow-up visit, for collection of outcome and/or survival follow-up data as required and in line with Section 12.3 until death or study conclusion. Survival follow-up may be accomplished by visit or phone contact.

Withdrawal of Consent
Participants who request to discontinue study drug will remain in the study and must continue to be followed for protocol specified follow-up procedures. The only exception to this is when a subject specifically withdraws consent for any further contact with him/her or persons previously authorized by participant to provide this information. Participants should notify the investigator of the decision to withdraw consent from future follow-up **in writing**, whenever possible. The withdrawal of consent should be explained in detail in the medical records by the investigator, as

to whether the withdrawal is from further treatment with study drug only or also from study procedures and/or post treatment study follow-up, and entered on the appropriate CRF page. In the event that vital status (whether the subject is alive or dead) is being measured, publicly available information should be used to determine vital status only as appropriately directed in accordance with local law.

Lost to Follow-Up

All reasonable efforts must be made to locate participants to determine and report their ongoing status. This includes follow-up with persons authorized by the subject as noted above. Lost to follow-up is defined as the inability to reach the subject after a minimum of 3 documented phone calls, faxes, or emails as well as lack of response by subject to 1 registered mail letter. All attempts should be documented in the participant's medical records. If it is determined that the participant has died, the site will use permissible local methods to obtain the date and cause of death. If investigator's use of third-party representative to assist in the follow-up portion of the study has been included in the participant's informed consent, then the investigator may use a Sponsor-retained third-party representative to assist site staff with obtaining participant's contact information or other public vital status data necessary to complete the follow-up portion of the study. The site staff and representative will consult publicly available sources, such as public health registries and databases, in order to obtain updated contact information. If after all attempts, the participant remains lost to follow-up, then the last known alive date as determined by the investigator should be reported and documented in the participant's medical records.

7 REGISTRATION PROCEDURES

7.1 CUMC Research Participant Registration

Confirm eligibility as defined in the section entitled Criteria for Participant Eligibility.

Obtain informed consent, by following procedures defined in section entitled Informed Consent Procedures, along with applicable institutional policies and federal regulations.

Only Investigators/Research personnel properly trained and delegated to consent participants for this protocol will participate in the consenting process. Furthermore, properly delegated/trained Physician Investigators (e.g., MD, MD PhD) are required to sign/verify a protocol specific Eligibility Checklist for each participant enrolled on the study, in addition to providing the relevant source documentation confirming participant eligibility.

All participants must be centrally registered through the Central Registration Office within Herbert Irving Comprehensive Cancer Center at CUMC prior to initiation of study treatment.

Registration hours are available Monday through Friday from 9:00am – 5:00pm EST (excluding holidays and weekends). Same day participant registrations (and after hour registrations) will be accommodated on a case by case basis provided that the study team has expressed all time

sensitive registration concerns/cases in a timely manner to the Central Registration Office.

CPDM Central Registration Procedures (CUMC only):
Within 48 hours of obtaining consent (excluding holidays and weekends), a completed/signed IRB approved informed consent HIPAA form, and demographics forms must be submitted to the CPDM Central Registration Office via an email to CPDMRegistration@cumc.columbia.edu or fax to (212) 304-6330, with the subject line "AAAR6354 Pending Subject Registration Request (PHI)". Upon receipt, applicable participant information as well as a "pending eligibility" status will be entered into HICCC's institutional database. This status will remain until further source documentation is made available to confirm overall participant eligibility. Required materials for all pending registration submissions are as follows:

- Completed/signed IRB approved/stamped Informed Consent Forms.
- The completed/signed IRB approved HIPAA Authorization form
- Completed/signed CPDM ICF checklist
- Completed/signed HICCC personal census form
- Completed/signed CPDM Demographics Note to File

In order to confirm eligibility status, Investigators/designees (e.g., study specific Clinical Research Coordinator/Research Nurse, etc.) must submit the following documentation to the Central Registration Office via email or fax:

- The completed/signed study specific Eligibility Checklist (signed by an Physician level Investigator)
- Copies of source documentation necessary for each item to be verified on the CPDM specific Eligibility Checklist, including but not limited to:
    - Copy of required laboratory test and procedure reports (e.g., hematology, serum chemistry, pregnancy test when applicable, MRI reports, CT/bone scans, etc.)
    - Copy of pathology and surgical reports
    - Copy of clinic note(s) or other appropriate medical records capturing the consent process information, along with providing source documentation of any other items needed for screening/eligibility that are not captured in other source document forms (e.g., positive investigator statements of unique eligibility items not captured via other direct source documentation, concomitant medication lists, etc.)
    - Protocol deviation/waiver approvals (if applicable)

- **Please note**: subject line of email or fax should include the following: "AAAR6354 Complete Subject Registration Request (PHI)".

Upon receipt of the above mentioned documentation, participant eligibility information will be verified by a qualified Central Registration Registrar. If any questions arise during the review process, queries in the form of emails will be addressed to the applicable study team personnel for clarification prior to enrollment. All applicable finalized registration/eligibility information will then be entered into HICCC's institutional CTMS database by the Central Registration Registrar. Upon completion, an official participant registration notification email will be sent to the PI/research team which will include eligibility/enrollment status, as well as participant ID information. Protocol therapy may not be initiated prior to receipt of this notification from the Central Registration Office.

All screen fail/ineligible participants, as well as participant's who withdraw consent prior to enrollment/initiation of protocol therapy must be submitted to the Central Registration office in a manner analogous to the procedures noted above. Applicable source documentation will be required within the corresponding submissions.

8 TREATMENT PLAN

8.1 Agent Administration

Treatment will be preferentially administered on an outpatient basis. Reported adverse events and potential risks for nivolumab are described in Section 8.2. Appropriate dose modifications for nivolumab are described in Section 9. No investigational or commercial agents or therapies other than those described below may be administered with the intent to treat the participant's malignancy.

Agent	Dose	Route	Schedule	Cycle Length
Nivolumab	240mg	IV over 30 minutes (±7 minutes) infusion	Cycle 1-8	2 weeks (14 days)
	480mg		Cycle 9 – end of study	4 weeks (28 days)

8.1.1 Prophylactic Agent(s)

There are no prophylactic regimens required prior to administration of nivolumab.

8.2 General Concomitant Medication and Supportive Care Guidelines

Management Algorithms for Immuno-Oncology Agents

Immuno-oncology (I-O) agents are associated with AEs that can differ in severity and duration than AEs caused by other therapeutic classes. Nivolumab is considered an I-O agent in this protocol. Early recognition and management of AEs associated with I-O agents may mitigate severe toxicity. Management algorithms have been developed to assist investigators in assessing and managing the following groups of AEs:

- Gastrointestinal
- Renal
- Pulmonary
- Hepatic
- Endocrinopathy
- Skin
- Neurological

The above algorithms are found in the nivolumab Investigator Brochure and Appendix 1 of this protocol.

Treatment of Nivolumab-Related Infusion Reactions

Since nivolumab contains only human immunoglobulin protein sequences, it is unlikely to be immunogenic and induce infusion or hypersensitivity reactions. However, if such a reaction were to occur, it might manifest with fever, chills, rigors, headache, rash, pruritus, arthalgias, hypotension, hypertension, bronchospasm, or other allergic-like reactions. All Grade 3 or 4 infusion reactions should be reported within 24 hours and reported as an SAE if it meets the criteria. Infusion reactions should be graded according to National Cancer Institute (NCI) CTCAE v4.03 guidelines.

Treatment recommendations are provided below and may be modified based on local treatment standards and guidelines, as appropriate:

For Grade 1 symptoms (mild reaction; infusion interruption not indicated; intervention not indicated):

- Remain at bedside and monitor participant until recovery from symptoms. The following prophylactic premedications are recommended for future infusions: diphenhydramine 50 mg (or equivalent) and/or acetaminophen/paracetamol 325 to 1000 mg at least 30 minutes before additional nivolumab administrations.

For Grade 2 symptoms (moderate reaction required therapy or infusion interruption but responded promptly to symptomatic treatment [eg, antihistamines, non-steroidal anti inflammatory drugs, narcotics, corticosteroids, bronchodilators, IV fluids]; prophylactic medications indicated for ≤ 24 hours):

- Stop the nivolumab infusion, begin an IV infusion of normal saline, and treat the participant with diphenhydramine 50 mg IV (or equivalent) and/or acetaminophen/paracetamol 325 to 1000 mg; remain at bedside and monitor participant until resolution of symptoms. Corticosteroid and/or bronchodilator therapy may also be administered as appropriate. If the infusion is interrupted, then restart the infusion at 50% of the original infusion rate when symptoms resolve; if no further complications ensue after 30 minutes, the rate may be increased to 100% of the original infusion rate. Monitor participant closely. If symptoms recur, then no further nivolumab will be administered at that visit.
- For future infusions, the following prophylactic premedications are recommended: diphenhydramine 50 mg (or equivalent) and/or acetaminophen/paracetamol 325 to 1000 mg should be administered at least 30 minutes before nivolumab infusions. If necessary, corticosteroids (up to 25 mg of hydrocortisone or equivalent) may be used.

For Grade 3 or 4 symptoms (Grade 3: severe reaction, prolonged [ie, not rapidly responsive to symptomatic medication and/or brief interruption of infusion], recurrence of symptoms following initial improvement, hospitalization indicated for other clinical sequelae [eg, renal impairment, pulmonary infiltrates]; Grade 4: life threatening, pressor or ventilatory support indicated):

- Immediately discontinue infusion of nivolumab. Begin an IV infusion of normal saline and treat the participant as follows: Recommend bronchodilators, epinephrine 0.2 to 1 mg of a 1:1000 solution for subcutaneous administration or 0.1 to 0.25 mg of a 1:10,000 solution injected slowly for IV administration, and/or diphenhydramine 50 mg IV with methylprednisolone 100 mg IV (or equivalent), as needed. Participant should be monitored until the investigator is comfortable that the symptoms will not recur. Nivolumab will be permanently discontinued. Investigators should follow their institutional guidelines for the treatment of anaphylaxis. Remain at bedside and monitor participant until recovery of the symptoms.

In case of late-occurring hypersensitivity symptoms (eg, appearance of a localized or generalized pruritus within 1 week after treatment), symptomatic treatment may be given (eg, oral antihistamine or corticosteroids).

8.3 Duration of Therapy

In the absence of treatment delays due to adverse events, treatment may continue for 28 cycles or until one of the following criteria applies:

- Disease progression
- Intercurrent illness that prevents further administration of treatment
- Unacceptable adverse events(s)

- Participant decides to withdraw from the study
- General or specific changes in the participant's condition render the participant unacceptable for further treatment in the judgment of the investigator

8.4 Duration of Follow Up

After coming off study treatment, participants will be followed as per the local standard of care for brain imaging until removal from study or until death, whichever occurs first. Reference Section 12.3 for more information regarding follow up requirements.

8.5 Criteria for Removal from Study Drug

Participants will be removed from study when any of the criteria listed below or in section 6.9 applies. The reason for study removal and the date the participant was removed will be documented in the Case Report Form.

Treatment Discontinuation Criteria for Nivolumab

Nivolumab treatment should be permanently discontinued for the following:

- Any Grade 2 drug-related uveitis, eye pain, or blurred vision that does not respond to topical therapy and does not improve to Grade 1 severity OR requires systemic treatment
- Any Grade 3 non-skin, drug-related AE lasting > 7 days, with the following exceptions for laboratory abnormalities, drug-related uveitis, pneumonitis, bronchospasm, hypersensitivity reactions, infusion reactions, and endocrinopathies:
    - Grade 3 drug-related uveitis, pneumonitis, bronchospasm, hypersensitivity reaction, or infusion reaction of any duration requires discontinuation
    - Grade 3 drug-related endocrinopathies adequately controlled with only physiologic hormone replacement do not require discontinuation
    - Grade 3 drug-related laboratory abnormalities do not require treatment discontinuation except:
        - Grade 3 drug-related thrombocytopenia > 7 days or associated with bleeding requires discontinuation
        - Grade >3 drug-related AST, ALT, or TBILI requires discontinuation*
        - Concurrent AST or ALT > 3xULN and TBILI > 2xULN

* In most cases of Grade 3 AST or ALT elevation, study drug(s) will be permanently discontinued. If the investigator determines a possible favorable benefit/risk ratio that warrants

continuation of study drug(s), a discussion between the principal investigator and the treating physician must occur.

- Any Grade 4 drug-related AE or laboratory abnormality, except for the following events which do not require discontinuation:
    - Grade 4 neutropenia ≤ 7 days
    - Grade 4 lymphopenia or leukopenia
    - Isolated Grade 4 amylase or lipase abnormalities that are not associated with symptoms or clinical manifestations of pancreatitis
    - Isolated Grade 4 electrolyte imbalances/abnormalities that are not associated with clinical sequelae and are corrected with supplementation/appropriate management within 72 hours of their onset
    - Grade 4 drug-related endocrinopathy AEs, such as adrenal insufficiency, ACTH deficiency, hyper- or hypothyroidism, or glucose intolerance, which resolve or are adequately controlled with physiologic hormone replacement (corticosteroids, thyroid hormones) or glucose-controlling agents, respectively, may not require discontinuation after discussion with and approval from the principal investigator
- Any event that leads to delay in dosing lasting > 8 weeks from the previous dose requires discontinuation, with the following exceptions:
    - Dosing delays to allow for prolonged steroid tapers to manage drug-related AEs are allowed. Tumor assessments should continue as per protocol even if dosing is delayed. Periodic study visits to assess safety and laboratory studies should also continue every 6 weeks or more frequently if clinically indicated during such dosing delays.
    - Dosing delays lasting > 8 weeks from the previous dose that occur for non-drug-related reasons may be allowed if approved by the principal investigator. Prior to re-initiating treatment in a participant with a dosing delay lasting > 8 weeks, the principal investigator must be consulted. Tumor assessments should continue as per protocol even if dosing is delayed. Periodic study visits to assess safety and laboratory studies should also continue every 6 weeks or more frequently if clinically indicated during such dosing delays.
- Any AE, laboratory abnormality, or intercurrent illness which, in the judgment of the investigator, presents a substantial clinical risk to the participant with continued nivolumab dosing

9 DOSING DELAYS/DOSE MODIFICATIONS

Dose Modifications for Nivolumab

Dose modifications are not allowed for nivolumab.

Dose Delay Criteria for Nivolumab

Tumor assessments should continue per protocol schedule, even if dosing is delayed. Treatment delays will be recorded, but the total duration of therapy will be up to two years, regardless of the number of cycles. Nivolumab administration should be delayed for the following:

- Any Grade ≥ 2 non-skin, drug-related AE, with the following exception:
  - Grade 2 drug-related fatigue or laboratory abnormalities do not require a treatment delay
- Grade 2 drug-related creatinine, AST, ALT, or TBILI abnormalities
- Any Grade 3 skin, drug-related AE
- Any Grade 3 drug-related laboratory abnormality (excluding AST, ALT, or TBILI), with the following exceptions for lymphopenia or asymptomatic amylase or lipase:
  - Grade 3 lymphopenia does not require dose delay
  - Any Grade ≥ 3 drug-related amylase or lipase abnormality that is not associated with symptoms or clinical manifestations of pancreatitis does not require dose delay

- Any AE, laboratory abnormality, or intercurrent illness which, in the judgment of the investigator, warrants delaying the dose of study medication

Participants who require delay of nivolumab should be re-evaluated weekly or more frequently if clinically indicated, and resume nivolumab dosing when re-treatment criteria are met.

Criteria to Resume Dosing for Nivolumab

Participants may resume treatment with study drug when the drug-related AE(s) resolve to Grade ≤ 1 or baseline value, with the following exceptions:

- Participants may resume treatment in the presence of Grade 2 fatigue.
- Participants who have not experienced a Grade 3 drug-related skin AE may resume treatment in the presence of Grade 2 skin toxicity.
- For participants with Grade 2 AST, ALT, or TBILI elevations, dosing may resume when laboratory values return to baseline and management with corticosteroids, if needed, is complete.
- Participants with combined Grade 2 AST/ALT AND TBILI values meeting discontinuation parameters should have treatment permanently discontinued.

- Drug-related pulmonary toxicity, diarrhea, or colitis must have resolved to baseline before treatment is resumed. Participants with persistent Grade 1 pneumonitis after completion of a steroid taper over at least 1 month may be eligible for retreatment.
- Participants with drug-related endocrinopathies adequately controlled with only physiologic hormone replacement may resume treatment after consultation with the principal investigator.

Recommended Dose Modifications for Nivolumab

Event	Severity*	Dose modification
Colitis	Grade 2 or 3 diarrhea or colitis	Withhold dose[a]
	Grade 4 diarrhea or colitis	Permanently discontinue
Pneumonitis	Grade 2 pneumonitis	Withhold dose[a]
	Grade 3 or 4 pneumonitis	Permanently discontinue
Hepatitis	Aspartate aminotransferase (AST)/or alanine aminotransferase (ALT) more than 3 and up to 5 times the upper limit of normal or total bilirubin more than 1.5 and up to 3 times the upper limit of normal	Withhold dose[a]
	AST or ALT more than 5 times the upper limit of normal or total bilirubin more than 3 times the upper limit of normal	Permanently discontinue
Hypophysitis	Grade 2 or 3 hypophysitis	Withhold dose[a]
	Grade 4 hypophysitis	Permanently discontinue
Adrenal insufficiency	Grade 2 adrenal insufficiency	Withhold dose[a]
	Grade 3 or 4 adrenal insufficiency	Permanently discontinue
Type 1 Diabetes Mellitus	Grade 3 hyperglycemia	Withhold dose[a]
	Grade 4 hyperglycemia	Permanently discontinue
Nephritis and renal dysfunction	Serum creatinine more than 1.5 and up to 6 times the upper limit of normal	Withhold dose[a]
	Serum creatinine more than 6 times the upper limit of normal	Permanently discontinue
Skin	Grade 3 rash or suspected Stevens-Johnson syndrome (SJS) or toxic epidermal necrolysis (TEN)	Withhold dose[a]
	Grade 4 rash or confirmed SJS or TEN	Permanently discontinue
Encephalitis	New-onset moderate or severe neurologic signs or symptoms	Withhold dose[a]
	Immune-mediated encephalitis	Permanently discontinue
Other	Other Grade 3 adverse reaction: 1. First occurrence 2. Recurrence of same Grade 3 adverse reactions	1. Withhold dose[a] 2. Permanently discontinue
	Life threatening or Grade 4 adverse reaction	Permanently discontinue

	Requirement for 10 mg per day or greater prednisone or equivalent for more than 12 weeks	Permanently discontinue
	Persistent Grade 2 or 3 adverse reactions lasting 12 weeks or longer	Permanently discontinue
*Toxicity was graded per National Cancer Institute Common Terminology Criteria for Adverse Events. Version 4.0 (NCI CTCAE v4). [a] Resume treatment when adverse reaction returns to Grade 0 or 1.		

10 ADVERSE EVENTS: LIST AND REPORTING REQUIREMENTS

10.1 Adverse Event

An adverse event (AE) is any untoward or unfavorable medical occurrence in a human participant, including abnormal sign, symptom or disease, temporally associated with the participant's participation in research, whether or not considered related to the participant's participation in the research. Abnormal results of diagnostic procedures are considered to be adverse events if the abnormality:

- results in study withdrawal
- is associated with a serious adverse event
- is associated with clinical signs or symptoms
- leads to additional treatment or to further diagnostic tests
- is considered by the investigator to be of clinical significance

Immune-mediated adverse events (IMAEs) are AEs consistent with an immune-mediated mechanism or immune-mediated component for which non-inflammatory etiologies (eg, infection or tumor progression) have been ruled out. IMAEs can include events with an alternate etiology which were exacerbated by the induction of autoimmunity. Information supporting the assessment will be collected on the participant's CRF.

We will be reporting AEs to regulatory authorities and ethics committees according to local applicable laws including FDA Code of Federal Regulations 21 CFR Parts 312 and 320.

All AEs must be documented as related or unrelated to study treatment and graded per CTCAE 4.03.

10.2 Serious Adverse Event

Adverse events are classified as serious or non-serious. A serious adverse event is any AE that is:

- fatal
- life-threatening
- requires inpatient hospitalization/prolongation of existing hospitalization. NOTE:The following hospitalizations are not considered SAEs:

  - A visit to the emergency room or other hospital department < 24 hours, that does not result in admission (unless considered an important medical or life-threatening event)
  - Elective surgery, planned prior to signing consent
  - Admissions as per protocol for a planned medical/surgical procedure
  - Routine health assessment requiring admission for baseline/trending of health status (eg, routine colonoscopy)
  - Medical/surgical admission other than to remedy ill health and planned prior to entry into the study. Appropriate documentation is required in these cases.
  - Admission encountered for another life circumstance that carries no bearing on health status and requires no medical/surgical intervention (eg, lack of housing, economic inadequacy, caregiver respite, family circumstances, administrative reason)
  - Admission for administration of anticancer therapy in the absence of any other SAEs (applies to oncology protocols)
- results in persistent or significant disability or incapacity
- a congenital anomaly or birth defect
- an important medical event

Important medical events are those that may not be immediately life threatening, but are clearly of major clinical significance. They may jeopardize the participant, and may require intervention to prevent one of the other serious outcomes noted above. For example, drug overdose or abuse, a seizure that did not result in inpatient hospitalization or intensive treatment of bronchospasm in an emergency department would typically be considered serious. Potential drug-induced liver injury (DILI) is also considered an important medical event. (See Section 10.10 for the definition of potential DILI.)

All adverse events that do not meet any of the criteria for serious events should be regarded as non-serious adverse events (AE).

Non-serious Adverse Event Collection and Reporting

Non-serious Adverse Events (AE) are to be provided to BMS in aggregate via interim or final study reports as specified in the agreement or, if a regulatory requirement [eg, IND US trial] as part of an annual reporting requirement.

Non-serious AE information should be collected from the start of a placebo lead-in period or other observational period intended to establish a baseline status for the subjects.

The collection of non-serious AE information should begin following consent. All non-serious adverse events (not only those deemed to be treatment-related) should be collected continuously during the treatment period and for a minimum of 100 days following the last dose of study treatment. Non-serious AEs should be followed to resolution or stabilization, or until it has been

determined that the study treatment or participation is not the cause, or reported as SAEs if they become serious. Follow-up is also required for non-serious AEs that cause interruption or discontinuation of study drug and for those present at the end of study treatment as appropriate.

10.3 Unanticipated Problem

An unanticipated problem is any incident, experience or outcome involving risks to participants or others in any human subjects research that meets all of the following criteria:

- Unexpected (in terms of nature, severity or frequency) given (a) the research procedures that are described in the IRB-approval protocol and informed consent document, and (b) the characteristics of the participant population being studied;
- Related or possibly related to participation in such research (e.g., there is a reasonable possibility that the incident, experience or outcome may have been caused by the procedures involved in such research); and
- Suggests that the research places participants or others at a greater risk of harm (including physical, psychological, economic or social harm) than was previously known or recognized.

10.4 Adverse Event Reporting Period

The study period during which adverse events must be reported starts on the day of consent and continues for at least 100 days following the last administration of study drug.

Baseline/Preexisting Condition

A baseline/preexisting condition is one that is present at the start of the study. A preexisting condition should be recorded as an adverse event if the frequency, intensity, or if the character of the condition worsens during the study period.

General Physical Examination Findings

At screening, any clinically significant abnormality should be recorded as a preexisting condition. At the end of the study, any new clinically significant findings/abnormalities that meet the definition of an adverse event must also be recorded and documented as an adverse event.

Post-study Adverse Event

All unresolved adverse events should be followed by the investigator until the events are resolved, the participant is lost to follow-up, or the adverse event is otherwise explained. At the last scheduled visit, the investigator should instruct each participant to report any subsequent event(s) that the participant, or the participant's personal physician, believes might reasonably be related to participation in this study.

Abnormal Laboratory Values

A clinical laboratory abnormality should be documented as an adverse event if any one of the following conditions is met:

- The laboratory abnormality is not otherwise refuted by a repeat test to confirm the abnormality
- The abnormality suggests a disease and/or organ toxicity

- The abnormality is of a degree that requires active management or meets criteria for a SAE (e.g., change of dose, discontinuation of the drug, more frequent follow-up assessments, further diagnostic investigation, etc.).

Hospitalization, Prolonged Hospitalization or Surgery
Any adverse event that results in hospitalization or prolonged hospitalization should be documented and reported as a serious adverse event unless specifically instructed otherwise in this protocol. Any condition responsible for surgery should be documented as an adverse event if the condition meets the criteria for an adverse event.

Neither the condition, hospitalization, prolonged hospitalization, nor surgery are reported as an adverse event in the following circumstances:

- Hospitalization or prolonged hospitalization for diagnostic or elective surgical procedures for a preexisting condition. Surgery should **not** be reported as an outcome of an adverse event if the purpose of the surgery was elective or diagnostic and the outcome was uneventful.
- Hospitalization or prolonged hospitalization required to allow efficacy measurement for the study.
- Hospitalization or prolonged hospitalization for therapy of the target disease of the study, unless it is a worsening or increase in frequency of hospital admissions as judged by the clinical investigator.

10.5 Recording of Adverse Events
At each contact with the participant, the investigator must seek information on adverse events by specific questioning and, as appropriate, by examination. Information on all adverse events should be recorded immediately in the source document, and also in the appropriate adverse event module of the case report form (CRF). All clearly related signs, symptoms, and abnormal diagnostic procedures results should recorded in the source document, though should be grouped under one diagnosis.

All adverse events occurring during the study period must be recorded. The clinical course of each event should be followed until resolution, stabilization, or until it has been determined that the study treatment or participation is not the cause. Serious adverse events that are still ongoing at the end of the study period must be followed up to determine the final outcome. Any serious adverse event that occurs after the study period and is considered to be possibly related to the study treatment or study participation should be recorded and reported immediately.

10.6 Reporting of Serious Adverse Events
The Reference Safety Information in the Investigator Brochure serves as a reference to determine expectedness of SAEs for expedited reporting.

All Serious Adverse Events (SAEs) that occur following the subject's consent through 100 days after last dose of study drugmust be reported to BMS Worldwide Safety, whether related or not

related to study drug. If applicable, SAEs must be collected that relate to any later protocol-specified procedure (eg, a follow-up skin biopsy).

Following the subject's consent, all SAEs, whether related or not related to study drug, are collected, including those thought to be associated with protocol-specified procedures. The investigator should report any SAE occurring after these aforementioned time periods, which is believed to be related to study drug or protocol-specified procedure.

- An SAE report should be completed for any event where doubt exists regarding its seriousness;
    - If the investigator believes that an SAE is not related to study drug, but is potentially related to the conditions of the study (such as withdrawal of previous therapy or a complication of a study procedure), the relationship should be specified in the narrative section of the SAE Report Form.
    - If the BMS safety address is not included in the protocol document (eg, multicenter studies where events are reported centrally), the procedure for safety reporting must be reviewed/approved by the BMS Protocol Manager. Procedures for such reporting must be reviewed and approved by BMS prior to study activation.
- An appropriate SAE form, such as the HICCC DSMC SAE Form, (e.g. ex-US = CIOMS form or USA = Medwatch form) should be used to report SAEs to BMS . The BMS protocol ID number must be included on whatever form is submitted by the Sponsor/Investigator.
    - The CIOMS form is available at: http://www.cioms.ch/index.php/cioms-form-i
    - The MedWatch form is available at: https://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM048334.pdf
    - Worldwide.Safety@bms and aepbusinessprocess@bms.com

In accordance with local regulations, BMS will notify investigators of all reported SAEs that are suspected (related to the investigational product) and unexpected (ie, not previously described in the IB). An event meeting these criteria is termed a Suspected, Unexpected Serious Adverse Reaction (SUSAR). Investigator notification of these events will be in the form of a SUSAR Report.

- Other important findings which may be reported by BMS as an Expedited Safety Report (ESR) include: increased frequency of a clinically significant expected SAE, an SAE considered associated with study procedures that could modify the conduct of the study, lack of efficacy that poses significant hazard to study subjects, clinically significant safety finding from a nonclinical (eg, animal) study, important safety recommendations from a study data monitoring committee, or sponsor decision to end or temporarily halt a clinical study for safety reasons.

- Upon receiving an ESR from BMS, the investigator must review and retain the ESR with the IB. Where required by local regulations or when there is a central IRB/IEC for the study, the sponsor will submit the ESR to the appropriate IRB/IEC. The investigator and IRB/IEC will determine if the informed consent requires revision. The investigator should also comply with the IRB/IEC procedures for reporting any other safety information.
- In addition to the Sponsor Investigator's responsibility to report events to their local HA, suspected serious adverse reactions (whether expected or unexpected) shall be reported by BMS to the relevant competent health authorities in all concerned countries according to local regulations (either as expedited and/or in aggregate reports).

SAEs, whether related or not related to study drug, and pregnancies must be reported to BMS within 24 hours (excluding holidays and weekends). SAEs must be recorded on either CIOMS, MedWatch form, or institutional equivalent & pregnancies must be reported on a Pregnancy Surveillance Form or can be submitted on the aforementioned SAE form to BMS.

- **SAE Email Address:** Worldwide.Safety@BMS.com and aepbusinessprocess@bms.com
- **SAE Facsimile Number:** +1 609-818-3804
- If only limited information is initially available, follow-up reports are required. (Note: Follow-up SAE reports should include the same investigator term(s) initially reported.)
- If an ongoing SAE changes in its intensity or relationship to study drug or if new information becomes available, a follow-up SAE report should be sent within 24 hours (excluding holidays and weekends) to BMS (or designee) using the same procedure used for transmitting the initial SAE report.
- All SAEs should be followed to resolution or stabilization.

IRB Notification by Sponsor-Investigator

Reports of all events (including follow-up information) that meet the definition of an unanticipated problem posing risk to participants or others must be submitted to the IRB within one week (5 business days) following the occurrence of the unanticipated problem or the principal investigator's acquiring knowledge of the unanticipated problem in accordance with IRB policy. Additionally, the sponsor-investigator will submit a summary of all Unanticipated problems that occurred since the beginning of the study at the time of continuing review. Copies of each report and documentation of IRB notification and receipt will be kept in the Regulatory binder.

DSMC Reporting by the Sponsor Investigator

Serious adverse events not constituting unanticipated problems are to be reported to the HICCC DSMC. Reporting should occur within 24 hours of knowledge of the SAE occurring at our institution or affiliate sites.

Reporting to Drug Manufacturer by Sponsor-Investigator

The Sponsor-Investigator will report to investigational agent manufacturer any serious adverse

events that meet the reporting criteria to the Institutional Review Board as described in section 10.4 within 24 hours of becoming aware of it, so that these reports can be evaluated and included in the Investigator's Brochure and for IND safety submissions per regulations. Reporting will occur by sending the reporting form along with any additional documentation sent to the regulatory authorities.

At the time of IRB renewal or at the request of the manufacturer, the Sponsor- Investigator will submit a summary of all Serious Adverse Events that have occurred inclusive of all sites to manufacturer.

10.7 Reporting Process

Adverse events may be submitted on FDA Form 3500A, the HICCC DSMC Serious Adverse Event Reporting Form, or in a narrative format. If supplied as in a narrative format, the minimum information to be supplied is noted above at the beginning of section 10.5.

SAEs must be recorded on the HICCC DSMC SAE Report Form; pregnancies on a Pregnancy Surveillance Form (electronic or paper forms). These forms are to be transmitted via email or confirmed facsimile (fax) transmission to:

SAE Email Address: Worldwide.Safety@BMS.com

- **SAE Facsimile Number:** +1 609-818-3804

For studies capturing SAEs through electronic data capture, electronic submission is the required method for reporting. In the event the electronic system is unavailable for transmission, paper forms must be used and submitted immediately. When paper forms are used, the original paper forms are to remain on site.

SAE Telephone Contact (required for SAE and pregnancy reporting): Refer to Contact Information list.

If only limited information is initially available, follow-up reports are required. (Note: Follow-up SAE reports must include the same investigator term[s] initially reported.)

If an ongoing SAE changes in its intensity or relationship to study drug or if new information becomes available, the SAE report must be updated and submitted within 24 hours to BMS (or designee) using the same procedure used for transmitting the initial SAE report.

All SAEs must be followed to resolution or stabilization.

A SUSAR (Suspected, Unexpected Serious Adverse Reaction) is a subset of SAEs and will be reported to the appropriate regulatory authorities and investigators following local guidelines and requirements.

10.8 Pregnancy

If, following initiation of the study drug, it is subsequently discovered that a study participant is

pregnant or may have been pregnant at the time of study exposure, including during at approximately 5 half-lives after product administration, the investigator must immediately notify BMS of this event and complete and forward a Pregnancy Surveillance Form to BMS Designee within 24 hours of awareness of the event and in accordance with SAE reporting procedures described in Section 10.6.

Follow-up information regarding the course of the pregnancy, including perinatal and neonatal outcome and, where applicable, offspring information, must be reported on the Pregnancy Surveillance Form.

Any pregnancy that occurs in a female partner of a male study participant should be reported to BMS. Information on this pregnancy will be collected on the Pregnancy Surveillance Form.

10.9 Overdose

An overdose is defined as the accidental or intentional administration of any dose of a product that is considered both excessive and medically important. All occurrences of overdose must be reported as an SAE (see Section 10.6 for reporting details).

10.10 Potential Drug Induced Liver Injury (DILI)

Wherever possible, timely confirmation of initial liver-related laboratory abnormalities should occur prior to the reporting of a potential DILI event. All occurrences of potential DILIs, meeting the defined criteria, must be reported as SAEs (see Section 10.6 for reporting details).

Potential drug induced liver injury is defined as:

1. AT (ALT or AST) elevation > 3xULN

AND

2. Total bilirubin > 2xULN, without initial findings of cholestasis (elevated serum alkaline phosphatase),

AND

3. No other immediately apparent possible causes of AT elevation and hyperbilirubinemia including, but not limited to, viral hepatitis, pre-existing chronic or acute liver disease, or the administration of other drug(s) known to be hepatotoxic.

10.11 Other Safety Considerations

Any significant worsening noted during interim or final physical examinations, electrocardiogram, x-ray filming, any other potential safety assessment required or not required by protocol should also be recorded as a nonserious or serious AE, as appropriate, and reported accordingly.

11 PHARMACEUTICAL INFORMATION

Study Drugs

11.1 Description

Investigational Product

In this protocol, the investigational product is nivolumab (Opdivo®).

Nivolumab (also referred to as Opdivo®) is a human monoclonal antibody (HuMAb; immunoglobulin G4 [IgG4]-S228P) that targets the PD-1 cluster of differentiation 279 (CD279) cell surface membrane receptor. PD-1 is a negative regulatory molecule expressed by activated T and B lymphocytes.[24] Binding of PD-1 to its ligands, PD-L1 and PD-L2, results in the down-regulation of lymphocyte activation. Inhibition of the interaction between PD-1 and its ligands promotes immune responses and antigen-specific T-cell responses to both foreign antigens as well as self-antigens. Nivolumab is expressed in Chinese hamster ovary cells and is produced using standard mammalian cell cultivation and chromatographic purification technologies. The clinical study product is a sterile solution for parenteral administration. Nivolumab is being investigated both as monotherapy and in combination with chemotherapy, targeted therapies, and other immunotherapies, in an array of solid and hematologic malignancies.

Non-investigational Product

None.

11.2 Treatment Regimen

Nivolumab Dose and Schedule

Participants should receive nivolumab at a dose of 240 mg as a 30-minute (± 7 minutes) infusion on Day 1 of each treatment cycle for the first 8 cycles until progression, unacceptable toxicity, withdrawal of consent, or the study ends, whichever occurs first. Participants should begin study treatment within 3 calendar days of treatment assignment. Beginning with Cycle 9, participants should receive nivolumab at a dose of 480 mg as a 30-minute (± 7 minutes) infusion until progression, unacceptable toxicity, withdrawal of consent, or the study ends, whichever occurs first.

There will be no dose escalations or reductions of nivolumab allowed. Participants may be dosed no less than 12 days from the previous dose. For Q4W dosing cycles, participants may be dosed within a +/- 3-day window. Premedications are not recommended for the first dose of nivolumab.

Participants should be carefully monitored for infusion reactions during nivolumab administration. If an acute infusion reaction is noted, participants should be managed according to Section 8.2.

Doses of nivolumab may be interrupted, delayed, or discontinued depending on how well the participant tolerates the treatment. Dosing visits are not skipped, only delayed.

Information regarding infusion details for nivolumab can be found in the Investigator Brochure.

Nivolumab Treatment Beyond Progression

Evidence indicates a minority of participants treated with immunotherapy may derive clinical benefit despite initial evidence of PD,[29] for example, due to inflammatory reaction simulating progression ("tumor flare" or pseudoprogression). Pseudoprogression is well described in neuro-oncology, and refers to radiographic enlargement of tumor lesions that would be interpreted as disease progression by conventional response criteria, but upon histologic examination reveals necrosis and/or inflammation (treatment effect) and not disease progression.[29]

A similar phenomenon has been observed in various tumors when treated with immunotherapeutic agents, in which transient enlargement of lesions or appearance of new lesions is attributable to the influx of immune cells. These potential immune treatment effects complicate the evaluation of response and may lead to premature discontinuation of therapy. Furthermore, the time period to pseudoprogression or tumor flare with different immune therapies varies in different malignancies.

Participants treated with nivolumab will be permitted to continue nivolumab treatment beyond initial progressive disease, assessed by the investigator, as long as they meet the following criteria:

- Investigator-assessed clinical benefit
- Tolerance of study drug
- Treatment beyond progression will not delay an imminent intervention to prevent serious complications of disease progression (eg, severe symptoms due to brain mass effect)
- Participant provides written informed consent prior to receiving additional nivolumab treatment

All other elements of the main consent including description of reasonably foreseeable risks or discomforts, or other alternative treatment options will still apply.

A radiographic assessment/scan should be performed within 8 weeks of initial investigator-assessed progression to determine whether there has been a decrease in the tumor size or continued PD. The assessment of clinical benefit should be balanced by clinical judgment as to whether the participant is clinically deteriorating and unlikely to receive any benefit from continued treatment with nivolumab.

If the investigator considers that the nivolumab participant continues to achieve clinical benefit by continuing treatment, the participant should remain on the trial and continue to receive monitoring according to the time and events schedule in Section 12.2.

If at the radiographic assessment at 8 weeks of initial investigator-assessed progression the assessment determines continued PD but all the above criteria are met and the investigator considers the participant continues to achieve clinical benefit by continuing treatment, the participant may remain on the trial and continue to receive treatment and monitoring according to the time and events schedule in Section 12.2. Potential for clinical benefit should be balanced by clinical judgment as to whether the participant is clinically deteriorating and unlikely to receive benefit from continued treatment with nivolumab. A second radiographic assessment should be performed within 8 weeks of second investigator-assessed progression to determine whether there has been a decrease in the tumor size or continued PD. If this second 8-week radiographic assessment determines continued PD, then the participant should discontinue therapy and enter the follow-up period.

If the participant undergoes another surgery for presumed tumor progression but pathological findings are consistent with pseudoprogression, the participant will deemed to not have had tumor progression and may continue treatment with nivolumab after review with the principal investigator.

11.3 Preparation and Administration of Study Drug

Storage and Dispensing

The product storage manager should ensure that the study drug is stored in accordance with the environmental conditions (temperature, light, and humidity) in accordance with the package insert and as per investigator brochure provided by BMS for nivolumab (Opdivo®). If concerns regarding the quality or appearance of the study drug arise, the study drug should not be dispensed and BMS should be contacted immediately.

Nivolumab vials must be stored at a temperature of 2°C to 8°C and should be protected from light and freezing. If stored in a glass front refrigerator, vials should be stored in the carton. Recommended safety measures for preparation and handling of nivolumab include laboratory coats and gloves.

For details on prepared drug storage and use time of nivolumab under room temperature/light and refrigeration, please refer to the nivolumab Investigator Brochure section for "Recommended Storage and Use Conditions" and/or Pharmacy Manual.

Infusion related supplies (eg, IV bags, in-line filters, 0.9% NaCl solution) should be purchased locally.

11.4 Participant Compliance Monitoring

Treatment compliance will be monitored by drug accountability as well as participant's medical record and CRF.

11.5 Prior and Concomitant Therapy

Prior therapy
Prior treatment with alkylating agents is required inclusion criteria for this study.

Prohibited and/or Restricted Treatments

The following medications are prohibited during the study (unless utilized to treat a drug-related AE):

- Immunosuppressive agents
- Immunosuppressive doses of systemic corticosteroids. Dexamethasone is permitted for anti-edema treatment.
- Any concurrent anti-neoplastic therapy

Other Restrictions and Precautions

Participants with a condition requiring systemic treatment with either corticosteroids (> 10 mg daily prednisone equivalent) or other immunosuppressive medications within 14 days of treatment assignment are excluded. Inhaled or topical steroids, and adrenal replacement steroid doses > 10 mg daily prednisone equivalent, are permitted in the absence of active autoimmune disease.

Participants are permitted the use of topical, ocular, intra-articular, intranasal, and inhalational corticosteroids (with minimal systemic absorption). Adrenal replacement steroid doses > 10 mg daily prednisone are permitted. A brief (less than 3 weeks) course of corticosteroids for prophylaxis (eg, contrast dye allergy) or for treatment of non-autoimmune conditions (eg, delayed-type hypersensitivity reaction caused by a contact allergen) is permitted. Dexamethasone ≤ 4 mg/day or equivalent is permitted for vasogenic brain edema.

11.6 Packaging

OPDIVO® is a sterile, preservative-free, non-pyrogenic, clear to opalescent, colorless to pale-yellow liquid that may contain light (few) particles. OPDIVO® injection for intravenous infusion is supplied in single-dose vials. Cartons of Nivolumab will be provided for this study. Each carton contains: 5 vials of 100mg Nivolumab, 10 mg/mL.

11.7 Blinding of Study Drug

Not applicable

11.8 Receiving, Storage, Dispensing and Return

Receipt of Drug Supplies

Opdivo® (nivolumab) will be shipped to each local research pharmacy.

Study Drug Records

It is the responsibility of the investigator to ensure that a current disposition record of study drug (inventoried and dispensed) is maintained at the study site to include investigational product. Records or logs must comply with applicable regulations and guidelines and should include the following:

- Amount received and placed in storage area
- Amount currently in storage area
- Label identification number or batch number
- Amount dispensed to and returned by each participant, including unique participant identifiers
- Amount transferred to another area/site for dispensing or storage
- Nonstudy disposition (eg, lost, wasted)
- Amount destroyed at study site, if applicable
- Amount returned to BMS
- Retain samples for bioavailability/bioequivalence, if applicable
- Dates and initials of person responsible for IP dispensing/accountability, as per the Delegation of Authority Form.

Dispensing of Study Drug

Regular study drug reconciliation will be performed to document drug assigned, drug consumed, and drug remaining. This reconciliation will be logged on the drug reconciliation form, and signed and dated by the study team. Nivolumab will be dispensed by the research pharmacy to the infusion center team.

Return or Destruction of Study Drug

Return of Study Drug

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.

BMS must be notified of all drug destructions/disposals as detailed below.

Destruction of Study Drug

For this study, study drugs (those supplied by BMS or sourced by the investigator) such as partially used study drug containers, vials and syringes may be destroyed on site.

Any unused study drugs can only be destroyed after being inspected and reconciled by the responsible Study Monitor unless study drug containers must be immediately destroyed as required for safety, or to meet local regulations (eg, cytotoxics or biologics).

On-site destruction is allowed provided the following minimal standards are met:

- On-site disposal practices must not expose humans to risks from the drug
- On-site disposal practices and procedures are in agreement with applicable laws and regulations, including any special requirements for controlled or hazardous substances
- Written procedures for on-site disposal are available and followed. The procedures must be filed with the site's standard operating procedures and a copy provided to BMS upon request.
- Records are maintained that allow for traceability of each container, including the date disposed of, quantity disposed, and identification of the person disposing the containers. The method of disposal, ie, incinerator, licensed sanitary landfill, or licensed waste disposal vendor must be documented
- Accountability and disposal records are complete, up-to-date, and available for the Monitor to review throughout the clinical trial period If conditions for destruction cannot be met, the responsible Study Monitor will make arrangements for return of study drug. 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.
- BMS must be notified of all drug destructions.

12 STUDY CALENDAR

Baseline evaluations are to be conducted within 28 days prior to start of protocol therapy. Scans must be done ≤2 weeks prior to the start of therapy.

12.1 Table 12.1: Screening Assessments

Screening Assessments		
Procedure	**Screening Visit**	**Notes (Screening procedures are to occur within 28 days prior to first dose unless otherwise specified)**
Eligibility Assessment		
Informed Consent	X	
Inclusion/Exclusion Criteria	X	All inclusion/exclusion criteria should be assessed at screening
Medical History	X	
Prior Systemic Therapy	X	
Prior Radiation Therapy	X	
Prior Surgery	X	

Safety Assessments		
Complete Physical Exam	X	Include neurological exam
Performance Status	X	Karnofsky Performance Status
Vital Signs	X	Temperature, BP, HR
Assessment of Signs and Symptoms	X	Required for the 28 days prior to the first dose
Concomitant Medication Collection	X	Required for the 28 days prior to the first dose
Laboratory Tests	X	CBC with differential, chemistry panel including LDH, AST, ALT, ALP, albumin, TBILI, BUN or serum urea level, uric acid, creatinine, phosphate, Ca, Mg, Na, K, Cl, glucose, amylase, lipase, TSH, T3, Free T4 within 14 days prior to first dose. Hepatitis B surface antigen (HBV sAg) and Hepatitis C antibody (HCV Ab) or HCV Ribonucleic acid (RNA) within 28 days prior to first dose.
Pregnancy Test	X	For WOCBP (Refer to Section 6.3) only and must be done within 24 hours of first dose
Efficacy Assessment		
Radiographic Tumor Assessment: Gadolinium-enhanced MRI of the brain with 2HG MR Spectroscopy	X	To be performed within 14 days of the first dose
Neurologic Assessment in Neuro-Oncology (NANO) Scale	X	
Correlative Assessment		
Archival Tissue	X	Minimum of 20 unstained slides, see laboratory manual for additional details

12.2 Table 12.2: On-treatment procedures

On-treatment Procedures			
Procedure	**Cycle 1, Day 1**	**Cycle 2 and beyond, Day 1**	**Notes[1]:**
Safety Assessments			
Targeted Physical Examination	X	X	
Vital Signs	X	X	Temperature, BP, HR
Adverse Events Assessment	------Assessed Continuously------		Assessed using NCI CTCAE v. 4.03
Review of Concomitant Medications	X	X	
Physical Measurements	X	X	Includes weight
Karnofsky Status	X	X	
Laboratory Tests		X	To be done within 72 hours of dosing and

			include: CBC with differential, uric acid, BUN or serum urea level, creatinine, Mg, Ca, K, Cl, Na, amylase, lipase, glucose, phosphate, AST, ALT, TBILI, ALP, albumin, LDH Cycle 1 Day 1: Laboratory tests do not need to be repeated if performed within 14 days of the first dose
Thyroid function testing		See note	Thyroid function testing (TSH with reflexive T3 and fT4) is to be done every 3 infusions starting on C3D1 followed by C6D1 etc. for patients receiving nivolumab at 240mg Q2W, then every 2 infusions starting at C9D1 followed by C11D1 etc. for participants receiving nivolumab at 480mg Q4W (every other infusions)
Pregnancy Test (WOCBP only)	X	X	Serum or urine pregnancy test must be performed within 24 hours of C1D1 and must also be performed within 24 hours of all subsequent cycles (i.e. C2D1, C3D1, C4D1, etc.)
Efficacy Assessments			
Radiographic Tumor Assessment: Gadolinium enhanced MRI of the brain with 2HG MR spectroscopy		See note	Tumor assessments will occur every 8 weeks (±2 weeks) from C1D1 for up to 2 years while the patient is on treatment or until disease progression
Neurologic Assessment in Neuro-Oncology (NANO) Scale		See note	NANO every 8 weeks (± 7 days of each MRI)
Clinical Drug Supplies			
Administer Nivolumab	X	X	Participants should receive Nivolumab at a dose of 240mg as a 30-minute infusion on Day 1 of each treatment cycle for 8 cycles until Q4W dosing begins. Participants may be dosed

			no less than 12 days from the previous dose. For Q2W dosing cycles, participants may be dosed within a ±2 day window. Beginning with Cycle 9, participants should receive Nivolumab at a dose of 480mg as a 30-minute infusion every 4 weeks (±3 days) for a maximum 2 years of total treatment, or until PD, unacceptable toxicity, or withdrawal of consent.
Correlative Assessments			
Blood for Whole Exome Sequencing	X		Blood sample can be drawn on C1D1 or at anytime while the patient is on study, see laboratory manual for additional details
[1]All windows proposed are calendar days. Procedures must be done within 72h prior to dosing unless otherwise specified. Cycle duration is 2 weeks until 8 doses have been completed; subsequent cycles are 4 weeks in duration			

12.3 Table 12.3: Follow up Assessments

Follow up Assessments			
Procedure	**Follow ups, Visit 1 and Visit 2 (X01 & X02)***	**Survival Assessments**	**Notes**
Safety Assessments			
Targeted Physical Examination	X		
Adverse events assessment	X		Assessed using NCI CTCAE v. 4.03. Adverse events must be collected for at least 100 days following the last dose of study treatment and at both X01 and X02 follow-up visits,.
Laboratory tests	X		Required for X01: CBC with differential, uric acid, BUN or serum urea level, creatinine, Ca, Mg, K, Cl, Na, amylase, lipase, glucose, phosphate, AST, ALT, TBILI, ALP, albumin, LDH. Panel should also be performed at X02 if X01 results were abnormal and clinically

			signficiant
Pregnancy Test (WOCBP only)	X		Serum or urine pregnancy test at X01 only
Efficacy Assessments			
Radiographic tumor assessment: Gadolinium-enhanced MRI of the brain	See note	X	If the subject had disease progression on -study then no additional tumor assessments are required. If not, tumor assessments will continue to occur as per standard of care, however, RANO assessments must be completed and documented until disease progression or start or subsequent anti-cancer therapy (whichever occurs first). 2HG is not required for scans during follow-up.
Participant Status			
Participant Status	X	X	Survival follow up visits are expected to occur every 3 months after X02; May be accomplished by visit or phone contact to update survival information and assess subsequent anti-cancer therapy. Principal Investigator may request that survival data be collected on all treated participants outside of the 3-month specified window. At the time of this request, each participant will be contacted to determine their survival status unless the participant has withdrawn consent for all contact.
Subsequent Anti-Cancer Therapy	X	X	This assessment coincides with the participant status assessment performed at survival follow up vists every 3 months after X02.

* Follow-up visit 1 (X01) = 35 days (+/- 7 days) from the last dose or coincide with the date of discontinuation (+/- 7 days) if date of discontinuation is greater than 42 days after last dose, Follow-up visit 2 (XO2) = 80 days (+/- 7 days) from follow-up visit 1. Additionally, if the patient starts a subsequent anti-cancer therapy prior to X01 and/or X02, then they do not need to be completed. Survival follow-up visits should continue for all patients regardless of whether they start subsequent anti-cancer therapy.

13 MEASUREMENT OF EFFECT

13.1 Antitumor Effect

For the purposes of this study, participants should be re-evaluated for response every 8 weeks. In addition to a baseline scan, confirmatory scans should also be obtained every 8 weeks following initial documentation of objective response.

Assessment of Overall Tumor Burden

Efficacy assessment will be conducted and reported on the eCRF. For the purpose of treatment decisions in this study, tumor progression will be assessed by the treating investigator using a consistent and objective assessment of tumor response based on the Response assessment in Neuro-Oncology (RANO) Criteria. (Appendix 4).[37] Treatment post-progression and confirmation of progression per Immunotherapy Response Assessment in Neuro-Oncology (iRANO) Criteria (Appendix 5) is permitted for patients who are clinically stable.[38]

The primary efficacy endpoint is ORR per RANO. Investigator assessments will be used for the ORR, DOR, PFS and OS endpoints. Objecive responses will be confirmed by an independent expert.

Efficacy assessments will be required as follows:

- Physical Exam, AE assessment (CTCAE v.4), laboratory tests (CBC, CMP, TSH) every 2 weeks for the first 8 cycles and then every 4 weeks thereafter.
- MRI of the brain w/wo gadolinium and 2HG spectroscopy every 8 weeks.

All efforts should be made to obtain brain MRI scans with 2HG MR spectroscopy. Sites unable to perform 2HG MR spectroscopy may have this requirement waived upon discussion with and approval by the CUMC PI. Additionally, if it is not feasible to obtain 2HG MR spectroscopy for a particular paitent at any specific tumor assessment timepoint, this requirement may be waived upon discussion with and approval by the CUMC PI.

Baseline Imaging

All participants will undergo gadolinium-enhanced MRI of the brain at the timepoints specified in Table 12.1-2 for baseline assessment and on study response assessment purposes.

Investigators may obtain more frequent follow-up MRI scans as medically indicated. Local radiologic assessment of tumor measurements will be used for clinical management and investigator-assessed clinical endpoints.

Participants who are unable (due to existent medical condition, ie, pacemaker or implantable cardioverter-defibrillator device) or unwilling to have a brain MRI at baseline are excluded from the study (Section 6.4).

Participants who become unable to undergo MRI imaging after enrollment may continue in the study for assessment of OS as long as there is no safety issue which would require monitoring by MRI. Study sites will retain local access to the imaging results for safety and efficacy reading purposes. The study investigator will review the local MRI results as clinically appropriate to ensure that any potentially emergent clinical situations are addressed in a timely fashion. Clinically significant radiologic findings or changes from baseline scans will be coded as AEs or SAEs according to the criteria described below in Section 10.

On-study Assessment of Response

Radiographic study evaluations will take place as outlined in Section 12. Baseline MRI of the brain with gadolinium and 2HG spectroscopy should be performed within 14 days prior to the first dose.

13.1.1 Definitions

Evaluable for toxicity: All participants will be evaluable for toxicity from the time of their first treatment with Nivolumab

Evaluable for objective response: Only those participants who have measurable disease present at baseline, have received at least one cycle of therapy, and have had their disease re-evaluated will be considered evaluable for response. These participants will have their response classified according to the definitions stated below. (Note: Participants who exhibit objective disease progression prior to the end of cycle 1 will also be considered evaluable.)

Evaluable Non-Target Disease Response: Participants who have lesions present at baseline that are evaluable but do not meet the definitions of measurable disease, have received at least one cycle of therapy, and have had their disease re-evaluated will be considered evaluable for non-target disease. The response assessment is based on the presence, absence, or unequivocal progression of the lesions.

13.2 Disease Parameters

Assessment of Overall Tumor Burden and Measurable Disease

To serially evaluate tumor response to therapy, it is necessary to estimate the overall tumor burden at baseline and use this as a comparator for subsequent measurements. Measurable disease is defined by the presence of at least one measurable enhancing tumor lesion 10mm x 10mm in size on T1 post-contrast MRI of the brain. Patients with non-enhancing measureable disease may be eligible upon discussion with and approval by the CUMC PI.

Methods for Evaluation of Measurable Disease

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

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

Selection of Target and Non-target Lesions at Baseline:

- At baseline, all sites of disease should be classified as either measurable or non- measurable. The measurable lesions will be source for selection of target lesions for serial quantitative analysis during the study.
- Measurable and non-measurable lesions are classified according to the following characteristics:
    - Measurable Lesions
        - Contrast-enhancing (T1-weighted) lesions with clearly defined, bi-dimensionally measurable margins with minimum size of ≥ 10 mm in two perpendicular diameters.
            - In the event the MRI is performed with slices greater than 5 mm (with 0 mm skip/gap), the minimum size requirement for a measurable lesion at baseline should be two times the slice thickness.
            - It is also recommended that the same criterion be applied to a third axis, if possible, in order to consider the lesion to be a measurable lesion (e.g., visible on at least two axial slices with 5 mm thickness and 0 mm skip/gap, or two times the slice thickness).
        - Tumor around cystic or surgical cavities should generally not be considered measurable unless there is a nodular component measuring ≥ 10 × 10 mm. The cystic or surgical cavity itself should not be measured. ·
        - Measurable lesions will serve as the source of target lesions.
            - If there are multiple measurable lesions, up to 5 (at least 2) should be selected as target lesions. These lesions should generally be the largest or most reproducible tumor masses. They should lend themselves to precise anatomical re-location, tend to be the most reliably measured and be most representative of the patient's disease.

- Non-measurable Lesions
  - Non-enhancing (seen on FLAIR/T2)
  - All non-measureable enhancing lesions:
    - Smaller than 10 mm in any one diameter
    - Measurable in only one diameter
    - Not likely to be reliably visualized/measured throughout study (due to artifacts, difficult anatomy, etc.)
    - Hemorrhagic or predominantly necrotic
    - Tumor around a cyst or surgical cavity unless a nodular component > 10 × 10 mm
- Non-target Lesions
  - All measurable enhancing lesions not selected as target lesions (including those beyond upper limit of 5)
  - All non-measurable lesions

13.3 Response Criteria

For the purpose of treatment decisions in this study, tumor progression will be assessed by the treating investigator using a consistent and objective assessment of tumor response based on the Response assessment in Neuro-Oncology (RANO) Criteria (see Appendix 4).[37] Treatment post-progression and confirmation of progression per Immunotherapy Response Assessment in Neuro-Oncology (iRANO) Criteria is permitted for patients who are clinically stable (see Appendix 5).[38]

Response/Progression Categories (RANO criteria):

- **Complete response (CR).** All of the following criteria must be met:
  - Complete disappearance of all enhancing measurable and non-measurable disease sustained for at least 4 weeks. In the absence of a confirming scan 4 weeks later, this scan will be considered only stable disease.
  - No new lesions.
  - All measurable and non-measurable lesions must be assessed using the same techniques as baseline.
  - Patients must be on no steroids or on physiologic replacement doses only.
  - Stable or improved non-enhancing (T2/FLAIR) lesions
  - Stable or improved clinically, for clinical signs and symptoms present at baseline and recorded to be disease related
    Patients with residual non-measurable disease cannot have a complete response. The best response possible is stable disease.

- **Partial response (PR).** All of the following criteria must be met:

  - Greater than or equal to 50% decrease compared to baseline in the sum of products of perpendicular diameters of all measurable enhancing lesions sustained for at least 4 weeks. In the absence of a confirming scan 4 weeks later, this scan will be considered only stable disease.
  - No progression of non-measurable disease.
  - No new lesions.
  - All measurable and non-measurable lesions must be assessed using the same techniques as baseline.
  - The steroid dose at the time of the scan evaluation should be no greater than the dose at time of baseline scan.
  - Stable or improved non-enhancing (T2/FLAIR) lesions on same or lower dose of corticosteroids compared to baseline scan.
  - Stable or improved, for clinical signs and symptoms present at baseline and recorded to be disease related clinically.
  - Patients with non-measurable disease cannot have a partial response. The best response possible is stable disease.

- **Progressive disease (PD).** Any of the following criterion must be met:
  - > 25% increase in sum of the products of perpendicular diameters of enhancing lesions (over best response [smallest tumor size] or baseline if no decrease) on stable or increasing doses of corticosteroids
  - Any new enhancing measurable lesion that when added to the change in initial tumor(s) exceeds a 25% increase in cross-sectional area.
  - Clear clinical deterioration not attributable to other causes apart from the tumor (e.g. seizures, medication side effects, complications of therapy, cerebrovascular events, infection, etc.). The definition of clinical deterioration is left to the discretion of the investigator but it is recommended that a decline in the Karnofsky Performance Score (KPS) from 100 or 90 to 70 or less, a decline in KPS of at least 20 from 80 or less, or a decline in KPS from any baseline to 50 or less, for at least 7 days, be considered neurologic deterioration, unless attributable to co-morbid events or changes in corticosteroid dose.
  - Failure to return for evaluation due to death or deteriorating condition
  - Classification of progressive disease may be deferred for up to three months for patients with initial radiographic findings consistent with progressive disease (criteria a and b above) as detailed below. However, if follow-up imaging after three months confirms progression or if the patient experiences significant clinical decline at any time, the date of actual progression will be back-dated to the first date that the patient met criteria for progression and such patients should discontinue further immunotherapy.

- **Stable disease (SD).** All of the following criteria must be met:
  - Does not qualify for CR, PR, or progression.
  - All measurable and non-measurable sites must be assessed using the same techniques as baseline.
  - Stable clinically.

- **Unknown response status.** Progressive disease has not been documented and one or more measurable or non-measurable lesions have not been assessed.

Table 13.1 RANO Response Criteria Summary

	CR	PR	SD	PD#
T1 + Gd	None	≥50% decrease	<50% decrease to <25% increase	≥25% increase (including new lesions)*
T2/FLAIR	Stable/Decrease	Stable/Decrease	N/A	N/A
New Lesion	None	None	None	Present (contributing to lesion size)*
Corticosteroids	None	Stable/Decreased	Stable/Decreased	Stable/Increasing
Clinical Status	Stable or Improved	Stable or Improved	Stable or Improved	Clinical decline*
Requirment for Response	All	All	All	Any*

CR = complete response; PR = partial response; SD = stable disease; PD = progressive disease; N/A = not applicable

#: Progression occurs when any of the criteria with * is present; radiologic confirmation of progression is permitted as described below

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

The iRANO criteria call for serial radiographic evaluation of lesions with comparative analysis of changes in the area of contrast enhancement and nonenhancing component. Corticosteroid dosing and clinical status also contribute to response assessment. The guidance below is provided to facilitate assessment of tumor response by the treating investigator or responsible site staff.

Complete Response (CR): Requires all of the following:

- Complete disappearance of all enhancing measurable and non-measurable disease confirmed on consecutive scans at least four (4) weeks apart
- Stable or improved non-enhancing (T2/FLAIR) lesions,
- No new lesions,
- Off corticosteroids (or on physiologic replacement doses [up to the equivalent of 20 mg/day of hydrocortisone]), and

- Stable or improved clinical status.

Partial Response (PR): Requires all of the following:

- ≥ 50% decrease compared with baseline in the sum of the products of the diameter (SPD) of measurable enhancing target lesions confirmed on consecutive scans at least four (4) weeks apart
- No progression of non-target disease (enhancing and non-enhancing (T2/FLAIR) lesions),
- No new lesions,
- Corticosteroid dose stable (< 10% increase) or decreased, and
- Stable or improved clinical status.

Stable Disease (SD): Requires all of the following:

- Does not qualify for CR, PR or PD,
- Stable nonenhancing (T2/FLAIR) lesions
- Corticosteroid dose NOT increased by ≥ 50%, and
- Stable or improved clinical status.
- Patients with non-measurable disease only cannot be assessed as a CR. The best possible response is stable disease (SD).

Progressive Disease (PD): Defined by any of the following:

- ≥ 25% increase in the SPD of measurable enhancing (target) lesions plus > 5 mm absolute increase in the sum of the longest diameters (SLD) of target lesions compared to the best response after initiation of therapy (nadir), or baseline if the baseline is the nadir value,2
- Clear progression of enhancing non-target disease
- Significant increase in T2/FLAIR non-enhancing lesions not caused by co-morbid events (e.g., radiation therapy, demyelination, ischemic injury, infection, seizures, post-operative changes, or other treatment effects)
- Any new lesions or
- Clear clinical deterioration not attributable to other causes apart from the tumor (e.g., seizures, medication adverse effects, complications of therapy, cerebrovascular events, infection and so on) or changes in corticosteroid dose.
- Increasing steroid doses alone do not constitute PD.

Patients who have imaging findings that meet criteria for progressive disease more than 6 months from starting immunotherapy are expected to have a low likelihood of ultimately deriving clinical benefit and should discontinue therapy. For patients who have imaging findings that meet criteria for progressive disease within 6 months of starting immunotherapy including patients who develop new lesions but who do not have substantial neurological decline, confirmation of radiographic progression by follow-up MRIs should be sought following an

interval of up to 3 months after initial radiographic evidence of progressive disease to decrease the likelihood of prematurely declaring progressive disease in patients with pseudoprogression or delayed response.

Patients who develop substantial new or worsened neurological deficits not due to comorbid events or a change in co-administered medication at any time within the 3-month follow-up window should discontinue immunotherapy. For these patients, the date of actual tumor progression should be back-dated to the date when radiographic progressive disease was initially identified. Those with confirmation of further radiographic progression based on a comparison with the scan that first showed evidence of disease progression, or who develop substantial clinical decline at any time, should also be classified as having progressive disease with the date of disease progression back-dated to the first date that the patient met criteria for radiographic progression. In the event that follow-up imaging does not confirm further disease progression compared with the scan of the tumor that first showed initial progressive changes, but instead there is stabilization or reduction in tumor burden, treatment should be continued or resumed in the absence of increased corticosteroid dosing.

In addition, in uncertain cases in which acquisition of tumor histopathology by biopsy or resection is thought to be feasible, pathological assessment might be considered to clarify the cause of progressive imaging findings. If pathology confirms a predominance of recurrent tumor, the cause should be considered to be true progression. For cases where there is no evidence of a viable tumor, or where a prominence of gliosis or inflammation with restricted viable tumor is reported, the cause should be deemed consistent with treatment effect, and such patients should be classified as stable and allowed to continue therapy.

Unable to Evaluate (UE): Defined by any of the following:

- A patient's corticosteroid dosage has increased within 2 weeks of MRI assessment relative to the dose taken at the time of the previous assessment, cannot be classified as having a complete response, partial response, or stable disease and should be classified as non-evaluable at that time point. Conversely, patients who decrease corticosteroid use within 2 weeks of MRI assessment relative to the dose taken at the time of the previous assessment cannot be classified as having progressive disease and should be classified as nonevaluable.
- Radiographic changes indicative of progression are suspected due to other causes, including decreased steroid doses. Note: In contrast, if clinical deterioration occurs but is attributed to other causes, the time point response should be assessed with consideration to radiographic response and steroid use.
- Any target and/or non-target lesion present at baseline becomes unevaluable, including surgical removal of any target and/or non-target lesion. Note: PD can be determined without evaluation of all sites of disease based on the SPD for target lesions, evaluation of unequivocal progression in non-target lesions or observation of a new lesion within the available radiographic or clinical assessments.

Patients with stable or improved imaging studies, whose corticosteroid dose was increased by ≥50% should be considered unevaluable (UE). They should be observed closely. If their corticosteroid dose can be reduced back to the baseline dose, they may continue being followed for response. If further clinical deterioration related to tumor or radiographic progression becomes apparent, the date of progression should be the date when the average daily corticosteroid dosage for the seven day period increased ≥50% as compared to baseline.

Table 13.2 iRANO Response Criteria Summary

	CR	PR	SD	PD
T1 + Gd	Complete disappearance	≥50% decrease from baseline in SPD	Insufficient change in SPD to meet criteria for CR, PR or PD	≥25% increase and >5mm increase in SLD from baseline
Non-target disease: Enhancing Non-Enhancing	Stable/Decrease**	Stable/Decrease	Stable/Decrease	Increased, not due to other causes
New Lesion	None	None	None	Present
Corticosteroids	None	Stable/Decreased	Stable/Decreased	A ≥50% increase in steroid dose alone will not constitute PD (unless later confirmed PD)
Clinical Status	Stable or Improved	Stable or Improved	Stable or Improved	Clinical decline
Requiriment for Response	All of the above; Response must be confirmed on consecutive scans at least 4 weeks apart	All of the above; Response must be confirmed on consecutive scans at least 4 weeks apart	All of the above	Progression of disease occurs when PD is present in any category. For patients who have imaging findings that meet criteria for progressive disease within 6 months of starting immunotherapy, a window of up to 3 months may be allowed to confirm progression.

CR = complete response; PR = partial response; SD = stable disease; PD = progressive disease

** To qualify for CR there should be complete disappearance of enhancing non-target disease, but there can be stable or decreased residual non-enhancing FLAIR disease.

Evaluation of Target Lesions

Complete Response (CR): Disappearance of all enhancing disease (measurable and non-measurable) sustained for at least 4 weeks with stable or improved non enhancing FLAIR/T2 lesions. No new lesions. Clinically, participants must be stable or improved and not on corticosteroids exceeding physiologic replacement doses.

Partial Response (PR): 50% or more decrease of all measurable enhancing lesions sustained for at least 4 weeks with no progression of non-measurable disease and stable or improved non enhancing FLAIR/T2 lesions. No new lesions. Clinically, participants must be stable or improved and on stable or reduced dose of corticosteroids compared to baseline.

Progressive Disease (PD): 25% of more increase in enhancing lesions despite stable or increasing steroid dose, increase (significant) in non-enhancing T2/FLAIR lesions, not attributable to other non-tumour causes, or any new lesions. Clinical deterioration (not attributable to other non-tumour causes and not due to steroid decrease).

Stable Disease (SD): Does not qualify for complete response, partial response or progression with stable non-enhancing FLAIR/T2 lesions. Clinically, participants are stable and are on stable or reduced dose or corticosteroids compared to baseline.

13.4.3 Evaluation of Best Overall Response

The best overall response is the best response recorded from the start of the treatment until disease progression/recurrence (taking as reference for progressive disease the smallest measurements recorded since the treatment started). The participant's best response assignment will depend on the achievement of both measurement and confirmation criteria.

Table 13.3 For Participants with Measurable Disease

Target Lesions	Non-Target Lesions	New Lesions	Overall Response	Best Overall Response when Confirmation is Required*
CR	CR	No	CR	≥4 wks. Confirmation**
CR	Non-CR/Non-PD	No	PR	≥4 wks. Confirmation**
CR	Not evaluated	No	PR	
PR	Non-CR/Non-PD/not evaluated	No	PR	
SD	Non-CR/Non-PD/not evaluated	No	SD	documented at least once ≥4 wks. from baseline**
PD	Any	Yes or No	PD	no prior SD, PR or CR
Any	PD***	Yes or No	PD	
Any	Any	Yes	PD	

*** In exceptional circumstances, unequivocal progression in non-target lesions may be accepted as disease progression.

Note: Participants with a global deterioration of health status requiring discontinuation of treatment without objective evidence of disease progression at that time should be reported as "symptomatic deterioration." Every effort should be made to document the objective progression even after discontinuation of treatment.

13.4 For patients with only non-enhancing lesions, the low-grade glioma RANO criteria will be used.

Complete response Complete response requires all the following criteria compared with the baseline scan: (1) Complete disappearance of the lesion on T2 or FLAIR imaging (if enhancement had been present, it must have resolved completely); (2) no new lesions, no new T2 or FLAIR abnormalities apart from those consistent with radiation eff ects, and no new or increased enhancement; (3) patients must be off corticosteroids or only on physiological replacement doses; and (4) patients should be stable or improved clinically

Partial response Partial response requires all of the following criteria compared with the baseline scan: (1) greater than or equal to 50% decrease in the product of perpendicular diameters of the lesion on T2 or FLAIR imaging sustained for at least 4 weeks compared with baseline; (2) no new lesions, no new T2 or FLAIR abnormalities apart from those consistent with radiation eff ects, and no new or increased enhancement; and (3) patients should be on a corticosteroid dose that should not be greater than the dose at time of baseline scan, and should be stable or improved clinically

Minor response Minor response requires the following criteria compared with baseline: (1) a decrease of the area of non-enhancing lesion on T2 or FLAIR MR imaging between 25% and 50% compared with baseline; (2) no new lesions, no new T2 or FLAIR abnormalities apart from those consistent with radiation eff ect, and no new or increased enhancement; and (3) patients should be on a corticosteroid dose that should not be greater than the dose at time of baseline scan, and should be stable or improved clinically Stable disease Stable disease is present if the changes do not qualify for complete, partial, or minor response, or progression and requires: (1) stable area of non-enhancing abnormalities on T2 or FLAIR imaging; (2) no new lesions, no new T2 or FLAIR abnormalities apart from those consistent with radiation eff ect, and no new or increased enhancement; and (3) patients should be on a corticosteroid dose that should not be greater than the dose at time of baseline scan, and should be stable or improved clinically

Progression Progression is defi ned by any of the following: (1) development of new lesions or increase of enhancement (radiological evidence of malignant transformation); (2) a 25% increase of the T2 or FLAIR non-enhancing lesion on stable or increasing doses of corticosteroids compared with baseline scan or best response after initiation of therapy, not attributable to radiation eff ect or to comorbid events; (3) defi nite clinical deterioration not attributable to other causes apart from the tumour, or decrease in corticosteroid dose; or (4) failure to return for evaluation because of death or deteriorating condition, unless caused by documented non-related disorders

~~13.6~~13.5 Duration of Response

Duration of overall response: The duration of overall response is measured from the time measurement criteria are met for CR or PR (whichever is first recorded) until the first date that recurrent or progressive disease is objectively documented (taking as reference for progressive disease the smallest measurements recorded since the treatment started).

The duration of overall CR is measured from the time measurement criteria are first met for CR until the first date that progressive disease is objectively documented.

Duration of stable disease: Stable disease is measured from the start of the treatment until the criteria for progression are met, taking as reference the smallest measurements recorded since the treatment started, including the baseline measurements.

~~13.7~~13.6 Progression-Free Survival (PFS) and Overall Survival (OS)

PFS is defined as the duration of time from start of treatment to time of progression or death, whichever occurs first.

OS is defined as the time from the first dose of nivolumab to death due to any cause. All other participants will be censored at the last date known to be alive.

~~13.8~~13.7 Response Review

For this trial where the response rate is the primary endpoint, all responses be reviewed by the Sponsor Investigator and/or designee of the study at the study's completion. Simultaneous review of the participants' files including corticosteroids usage and neurological status in conjuction with radiological images is the best approach.

~~13.9~~13.8 Unblinding Procedures

Not applicable.

14 DATA REPORTING / REGULATORY REQUIREMENTS

Adverse event lists, guidelines, and instructions for AE reporting can be found in Section 10 (Adverse Events: List and Reporting Requirements). The Data Safety Monitoring Plan is described in Section 14.3.

14.1 Data Collection

The Herbert Irving Comprehensive Cancer Center has an electronic clinical trials and data management system (CTMS) that will be used for data collection. CRFs for the study will be built into the CTMS for data entry. The system has full auditing capabilities which is web-based and housed on a server in a fully HIPAA compliant server room with restricted access and video camera monitoring. All users must login with their own application username and password. Users off campus must first access the Virtual Private Network with their assigned campus username and password and then use their application credentials. Users are only able to see study information if they are indicated as study personnel in our electronic IRB system. Users are limited to access based on the role assigned in their corresponding protocol. Subject data is

entered directly into the system, which (in the case of Columbia subjects) confirms the correct identity of subjects via an interface with the electronic medical subject index. Staff with the appropriate IRB defined roles can run reports within the system for reporting purposes.

14.2 Data Reporting

Case Report Forms will be completed for each subject enrolled into the clinical study through the CTMS. It is the investigator's responsibility for ensuring that all clinical and laboratory data entered on the corresponding CRFs are complete, accurate and authentic.

14.3 Data and Safety Monitoring Committee

The NCI-approved Data Safety and Monitoring Committee (DSMC) of the Herbert Irving Comprehensive Cancer Center (HICCC) will monitor every subject who receives treatment on this protocol for toxicity. This protocol will adhere to the policies of the currently approved HICCC Data and Safety Monitoring Plan (DSMP), which is in accordance with NCI and CUMC-IRB policy and guidelines. The committee is chair is appointed by the HICCC Director. The committee consists of HICCC faculty and staff with expertise in oncology, research pharmacy, research nursing, and data management. The DSMC convenes twice a month to review subject safety and the conduct of the trial. The PI will submit data and safety monitoring reports to the DSMC at a frequency to be determined by the DSMC based on risk to the subjects.

At the time of renewal, the study team will submit the most recent DSMC approval letter for safety review to the CUMC IRB. Any modifications that are required by the DSMC to ensure subject safety will be submitted to the IRB. All protocol deviations, violations, and eligibility waivers will be submitted to and approved by the DSMC prior to being reported to the IRB. All study data reviewed and discussed during these meetings will be kept confidential.

For multicenter research, the principal investigator will assure that there is a mechanism in place to distribute the report to all participating investigators for submission to their local IRB. The report will document that a review of data and outcomes across all centers took place on a given date. It will summarize the DSMC's review of the cumulative toxicities reported from all participating sites without specific disclosure by treatment arm. It will also inform site investigators of the study the DSMC's conclusion with respect to progress or need for modification of the protocol.

14.4 Quality Control and Quality Assurance

Independent monitoring of the clinical study for protocol and GCP compliance will be conducted periodically by the CPDM Compliance Core on behalf of the HICCC DSMC. Additionally, the Compliance Oversight Committee of the IRB at Columbia University Medical Center may audit the study at any time per institutional policies and procedures. The investigator-sponsor and Columbia University Medical Center will permit direct access of the study monitors and appropriate regulatory authorities to the study data and to the corresponding source data and documents to verify the accuracy of this data.

A risk-based approach will be used by the Compliance Core to determine the frequency, number of subject charts, and data elements to be monitored. The Compliance Coordinator will review the study status and summarize enrollment, toxicities, SAEs/UPs, dose escalation, statistical endpoints (e.g., stopping rules), etc. for the full DSMC membership at the regularly scheduled meetings.

Internal On-site Monitoring:

- Initial, recurrent, and close-out on-site monitoring visits will also be conducted at remote clinical sites, as appropriate/feasible. Other sites will have monitoring performed remotely (see below for further details).

- The study Monitoring Visit Log will be completed and signed by the monitor and the PI/CRNP/CRN and/or CRC and will be filed in the regulatory binder.

- The Compliance Coordinator will communicate with the site coordinator/Site Principle Investigator to schedule the monitoring visit and arrange for access to study materials and documentation.

- The assigned Compliance Coordinator will monitor this trial within 1 month after the first subject is enrolled and throughout the life of the study to ensure that the study is being conducted in accordance with the protocol, GCP, applicable federal and local regulations, and per all applicable SOPs. The Compliance Coordinator is responsible to notify the PI and CRNP/CRN/CRC of upcoming monitor visits and convey what information and documentation will be required for the visit(s). The Compliance Coordinator is responsible for verifying that informed consent is properly obtained, eligibility is met (via the central registration process), and all study procedures are conducted according to the study protocol. The Compliance Coordinator will also verify that the data reported in the CRF's accurately reflect source documents, that all toxicities have been reported to date, and that all SAE's/UPs/deviations/violations have been reported according to local IRB and HICCC DSMC requirements. The Compliance Coordinator will issue queries and ensure resolution in a timely and efficient manner. The Compliance Coordinator will also monitor for applicable regulatory compliance and research pharmacy compliance (if applicable) and communicate any deficiencies as appropriate.

14.5 Confidentiality

Information about study subjects will be kept confidential and managed according to the requirements of the Health Insurance Portability and Accountability Act (HIPAA). Those regulations require a signed subject authorization informing the subject of the following:

- What protected health information (PHI) will be collected from subjects in this study
- Who will have access to that information and why
- Who will use or disclose that information
- The rights of a research subject to revoke their authorization for use of their PHI.

In the event that a subject revokes authorization to collect or use PHI, the investigator, by regulation, retains the ability to use all information collected prior to the revocation of subject

authorization. For subjects that have revoked authorization to collect or use PHI, attempts should be made to obtain permission to collect at least vital status (e.g., that the subject is alive) at the end of their scheduled study period.

The subject binders will be maintained with in the CPDM offices, a secured floor within the Herbert Irving Pavilion and only the investigator and study staff will have access to the file.

14.6 Source Documents

Source data is all information, original records of clinical findings, observations, or other activities in a clinical trial necessary for the reconstruction and evaluation of the trial. Source data are contained in source documents Examples of these original documents, and data records include: hospital records, clinical and office charts, laboratory notes, memoranda, participants' diaries or evaluation checklists, pharmacy dispensing records, recorded data from automated instruments, copies or transcriptions certified after verification as being accurate and complete, microfiches, photographic negatives, microfilm or magnetic media, x-rays, participant files, and records kept at the pharmacy, at the laboratories, and at medico-technical departments involved in the clinical trial.

14.7 Case Report Forms

The study case report form (CRF) is the primary data collection instrument for the study. All data requested on the CRF must be recorded. All missing data must be explained. If a space on the CRF is left blank because the procedure was not done or the question was not asked, write "N/D". If the item is not applicable to the individual case, write "N/A".

14.8 Records Retention

Records relating to a specific research activity, including research records collected by investigators, must be maintained for at least three years after completion of the research (45 CFR 46.115(b); 21 CFR 56.115(b); 21 CFR 312.62). This minimum retention period applies whether or not any participants were enrolled in the study.

If the research is FDA regulated, records should be retained for at least two years after approval of the investigational agent by FDA; if it is not approved, records should be retained at least two years after the study is terminated and FDA is notified (note the additional requirement below for clinical research studies);

Clinical records, including consent forms that document clinical intervention or clinical diagnostic procedure research-related procedures, must be retained in medical records by the institution for at least seven years, per CUMC and NYP policy which is based on state law.

15 STATISTICAL CONSIDERATIONS

15.1 Study Design/Endpoints

This is a phase II, open label, single-arm study designed to estimate the safety and efficacy of nivolumab in participants with recurrent or progressive IDH mutant gliomas who were

previously exposed to alkylating agents. The primary endpoint is to evaluate the objective response rate (partial and complete responses) to nivolumab in these participants. Secondary endpoints include determination of progression free and overall survival and duration of response. Additonal exploratory endpoints include biomarker assessments including correlations of response rate with mutational load analysis, clonal evolution of tumor cell populations in IDH mutated gliomas undergoing therapy when tissue is available, and evaluation of longitudinal changes in the IDH mutant metabolite product 2-hydroxygluterate (2HG) using magnetic resonance spectroscopy.

15.2 Size/Accrual Rate

Based on prior hiostorical data showing an overall response rate (ORR) of 9% in recurrent high-grade gliomas (grade III and IV)[39], and 0% on the IDH inhibitor trial (AG-221)[3] we set the null hypothesis of an ORR = 10% and the alternative hypothesis of an ORR = 30%. With one-sided α=0.05 and β=0.10, a sample size of 33 evaluable participants will be needed to assess the preliminary efficacy of this regimen. We expect to accrue a total of 37 participants across all sites to account for a 10% of participants who may be deemed unevaluable for response.

We expect an accrual rate of 3 participants per month.

15.3 Stratification Factors

Not applicable

15.4 Analysis of Primary Endpoints

Objective Response Rates

Objective response rate is defined as the proportion of patients with a reduction in tumor size while on treatment with nivolumab. Overall objective response rate is the sum of participants with either a partial response or complete response. Tumor size as measured on MRIs every 8 weeks will be used to determine response rate. The initial MRI prior to starting on study will serve as a baseline for comparison. Partial and complete responses will based on RANO or criteria (See **Section 13.3**). This will be used to evaluate the direct therapeutic effect of nivolumab in IDH mutant gliomas previously exposed to aklyating agents. The objective response rate will be compared to the null hypothesis using an exact test. The null hypothesis is an objective response rate of 10% based on historical data in patients with recurrent high-grade gliomas. The objective response rate and a 95% confidence interval will be reported.

A central review of all scans collected during the course of the study for all enrolled patients will be completed by the Sponsor Investigator and/or designee to review and confirm response assessment

15.5 Analysis of Secondary Endpoints

PFS and OS

PFS is defined as the time from the first dose of nivolumab to the first documented tumor progression or death due to any cause. participants who die without a reported progression will be considered to have progressed on the date of death. Participants who did not have disease progression or die will be censored at the date of last tumor assessment. Participants who started any subsequent anti-cancer therapy without a prior reported progression will be censored at the last tumor assessment prior to initiation of the subsequent anti-cancer therapy. Participants who had surgical resection post start of study treatment will be censored at the last tumor assessment date prior to initiation of surgical resection PFS will be determined by investigator reported response based on RANO criteria.

OS is defined as the time from the first dose of nivolumab to death due to any cause. All other participants will be censored at the last date known to be alive.

PFS and OS will be presented in Kaplan Meier curves and median with 95% confidence intervals. The duration of overall response is measured from the time measurement criteria are met for CR or PR (whichever is first recorded) until the first date that recurrent or progressive disease is objectively documented. DOR will be presented as a median with 95% confidence intervals.

15.6 Analysis of Exploratory Endpoints

Mutational load analysis and tumor cell population clonalilty:
Whole exome sequencing will be performed to evaluate the genomic frequency and pattern of mutations as well as the clonality of the tumor cell population, using tumor tissue resected prior to nivolumab treatment (initial diagnosis and post-alkylating agent whenever tisusue is available). Germline DNA from peripheral blood mononuclear cells will be used as controls for each participant. None of the somatic or germline whole exome sequencing results will be returned to participants or treating physicians.

We will correlate ORR with mutational burden using chi-square or Fisher exact test as appropriate for this exploratory analyses.

If subsequent surgeries for tumor recurrence are done following treatment with nivolumab, the cloncal evolution of these tumors will be studied through computational modeling, as developed by the team of our collaborator, Dr. Raul Rabadan, in the Department of Systems Biology at Columbia University Medical Center

Imaging Biomarkers

2HG will measured non-invasively through magnetic resonance spectroscopy (MRS) added to standard of care MRI scans at baseline and every 8 week assessments. Analysis will be descriptive as this is an exploratory biomarker.

Spatial Profiling of PD-1/PD-L1 Interaction

Slides from tumor samples will be fluorescently stained with multiple immunomarkers using immunohistochemistry. Novel algorithms, developed by our collaborator Dr. Douglas Johnson at Vanderbilt University, are used to objectively quantify biomarker positive cells and their co-localization and flow cytology is used to identify these cells. A PD-1/PD-L1 interaction score is generated and this will be correlated with response to treatment.

Neurologic Assessment in Neuro-Oncology

Descriptive analyses of NANO scale and correlation with MRI will be performed.

15.7 Reporting and Exclusions

Evaluation of toxicity

All participants will be evaluable for toxicity from the time of their first treatment with the study drug.

Evaluation of response

All participants included in the study must be assessed for response to treatment, even if there are major protocol treatment deviations or if they are ineligible. Each participant will be assigned one of the following categories: 1) complete response, 2) partial response, 3) stable disease, 4) progressive disease, 5) early death from malignant disease, 6) early death from toxicity, 7) early death because of other cause, or 9) unknown (not assessable, insufficient data). [Note: By arbitrary convention, category 9 usually designates the "unknown" status of any type of data in a clinical database.]

All of the participants who met the eligibility criteria (with the possible exception of those who received no study medication) should be included in the main analysis of the response rate. Participants in response categories 4-9 should be considered to have a treatment failure (disease progression). Thus, an incorrect treatment schedule or drug administration does not result in exclusion from the analysis of the response rate. Precise definitions for categories 4-9 will be protocol specific.

All conclusions should be based on all eligible participants. Subanalyses may then be performed on the basis of a subset of participants, excluding those for whom major protocol deviations have been identified (e.g., early death due to other reasons, early discontinuation of treatment, major protocol violations, etc.). However, these subanalyses may not serve as the basis for drawing conclusions concerning treatment efficacy, and the reasons for excluding participants from the analysis should be clearly reported. The 95% confidence intervals should also be provided.

16 PROTECTION OF HUMAN SUBJECTS

This study is to be conducted in accordance with applicable government regulations and Institutional research policies and procedures.

This protocol and any amendments will be submitted to a properly constituted Institutional Review Board (IRB), in agreement with local legal prescriptions, for formal approval of the study conduct. The decision of the IRB concerning the conduct of the study will be made in writing to the investigator and a copy of this decision will be obtained before commencement of this study.

All subjects for this study will be provided a consent form describing this study and providing sufficient information for subjects to make an informed decision about their participation in this study. This consent form will be submitted with the protocol for review and approval by the IRB for the study. The formal consent of a subject, using the IRB-approved consent form, must be obtained before that subject is submitted to any study procedure. This consent form must be signed by the subject or legally acceptable surrogate, as outlined in the IRB approved protocol, and the investigator-designated research professional obtaining the consent.

17 STUDY FINANCES

17.1 Conflict of Interest

Any investigator who has a conflict of interest with this study (patent ownership, royalties, or financial gain greater than the minimum allowable by their institution, etc.) must have the conflict reviewed by the Columbia University Conflict of Interest Committee with a Committee-sanctioned conflict management plan that has been reviewed and approved prior to participation in this study. All CUMC investigators will follow the University conflict of interest policy. All other sites will follow their local conflict of interest policies.

17.2 Subject Stipends or Payments

There are no subject payments or stipends.

18 PUBLICATION PLAN

Bristol-Myers Squibb will be provided with a copy of each publication and any form of public disclosure prior to submission to a journal, publisher, meeting or presentation.

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20 APPENDICES

20.1 Appendix 1

20.2 Appendix 2: Methods of Contraception

At a minimum, subjects must agree to use one highly effective method of contraception as listed below:

HIGHLY EFFECTIVE METHODS OF CONTRACEPTION
Highly effective methods of contraception have a failure rate of < 1% when used consistently and correctly. WOCBP and female partners of male subjects, who are WOCBP, are expected to use one of the highly effective methods of contraception listed below. Male subjects must inform their female partners who are WOCBP of the contraceptive requirements of the protocol and are expected to adhere to using contraception with their partner. Contraception methods are as follows:

1) Progestogen only hormonal contraception associated with inhibition of ovulation.
2) Hormonal methods of contraception including oral contraceptive pills containing combined estrogen + progesterone, vaginal ring, injectables, implants and intrauterine devices (IUDs) such as Mirena®
3) Nonhormonal IUDs, such as ParaGard®
4) Bilateral tubal occlusion
5) Vasectomised partner with documented azoospermia 90 days after procedure
   - Vasectomised partner is a highly effective birth control method provided that partner is the sole sexual partner of the WOCBP trial participant and that the vasectomized partner has received medical assessment of the surgical success.

6) Intrauterine hormone-releasing system (IUS).
7) Complete abstinence
   - Complete abstinence is defined as the complete avoidance of heterosexual intercourse (refer to Glossary of Terms)
   - Complete abstinence is an acceptable form of contraception for all study drugs and must be used throughout the duration of the study treatment (plus approximately 5 half-lives of the investigational drug plus 30 days).
   - It is not necessary to use any other method of contraception when complete abstinence is elected.
   - Subjects who choose complete abstinence must continue to have pregnancy tests, as specified in Section 12.
   - Acceptable alternate methods of highly effective contraception must be discussed in the event that the subject chooses to forego complete abstinence.
   - The reliability of sexual abstinence needs to be evaluated in relation to the duration of the clinical trial and the preferred and usual lifestyle of the subject.

UNACCEPTABLE METHODS OF CONTRACEPTION
1) Periodic abstinence (calendar, symptothermal, post-ovulation methods)
2) Withdrawal (coitus interruptus)

3) Spermicide only
4) Lactation amenorrhea method (LAM)

20.3 Appendix 3. Guidelines for Affiliate Institutions in Multicenter Studies with Columbia University as the Leading Site

1. Multi-site Communication:

The CPDM Office at CUMC provides administration, data management, and organizational support for the affiliate sites in the conduct of a multicenter clinical trial. The CPDM Multicenter Office will coordinate, at minimum, regularly scheduled conference calls with affiliate sites.
The following issues will be discussed, as appropriate:

- Enrollment information
- Adverse events (e.g., new adverse events and updates on unresolved adverse events and new safety information)
- Protocol violations
- Other issues affecting the conduct of the study

2. New Protocol Distribution, IRB Submission, Modifications, and Annual Renewals

- Protocol specific documents are distributed to affiliate sites once CUMC IRB approval has been obtained.
- The affiliate site must submit a draft of site specific revisions to protocol and/or consent form documents for review and approval by the sponsor-investigator prior to submission to the local IRB. Draft documents should be sent to the study specific email address. The site will be provided confirmation that they are approved to submit to their local IRB.
- Protocol amendments must be approved by the affiliate site's local IRB within 90 days of distribution to the site by the sponsor-investigator.

3. Regulatory Documents:

Prior to Site Initiation:
Sponsor-Investigator will ensure that proper requests are made of sites and that the following documentation is collected, prior to the initiation of an affiliate site.

- CV of PI, Co-I's and other research staff listed on FDA 1572 (signed and dated copy within 2 years)
- Medical Licenses of PI and Co-I's (current copy)
- Human subjects training certificates for PI and Co-I's
- CLIA/Laboratory Certifications for Local Laboratories listed on FDA 1572
- Local Laboratory Director's CV and License
- Local Laboratory Reference Ranges
- IRB roster or statement of compliance
- FDA Form 1572, if applicable (wet ink originals required)
- Financial Disclosure forms for all members listed on FDA 1572 (wet ink originals required)

Ongoing Regulatory Documentation: Sponsor-Investigator will ensure that proper requests are made of sites and that the following documentation is collected throughout the course of the study.

- IRB approval letters for all protocol modifications and all renewals
- IRB-approved consent forms
- Current IRB roster, if statement of compliance is not provided as part of site initiation
- FDA Form 1572, if applicable as updates are required
- Updated investigator and site information where relevant (e.g., CV, medical licensure and Financial Disclosure for new sub-investigator, local laboratory information)

Regulatory documents may be sent to the CPDM Multicenter Core at AAAR6354@lists.cumc.columbia.edu or to the following address if wet ink originals are required:

Clinical Protocol & Data Management Office
161 Fort Washington Ave.
Herbert Irving Pavilion
Mezzanine Level, M-203
New York, NY 10032

4. Site activation

Columbia University will schedule a site initiation visit (via teleconference) once IRB approval has been submitted from the affiliate site.

5. Central Registration Procedures- Affiliate Institution Research Participant Registration Process:

All Affiliate Institutions **must** register subjects with the coordinating center (CUMC) **prior** to any administration of study drug/intervention/local institution registration. Please send all Affiliate Site Registrations to AAAR6354@lists.cumc.columbia.edu. Please see instructions below:

1. Within 48 hours of obtaining consent (excluding holidays and weekends), the Affiliate Institution CRN and/or CRC is required to submit the following documents to the coordinating center's designee (CUMC Multicenter Trials Core at AAAR6354@lists.cumc.columbia.edu.). The coordinating center's designee will review the documents for accurateness, and subsequently submit the documents to the CPDM Central Registration Office via email with a request to register the patient "pending eligibility." The title of the email should read, "AAAR6354 Pending Subject Registration Request (PHI)". The following documents should be submitted with the pending registration request, as applicable:

a. Redacted Completed/signed IRB approved/stamped Informed Consent Forms, including additional study ICFs (e.g., tissue, DNA, etc.), as applicable
b. Redacted Signed HIPAA (or institutional equivalent)
c. MCT CPDM Velos Note to File form

2. The Affiliate Institution's investigator/research nurse/data manager/coordinator must contact the coordinating center's designee CUMC Multicenter Trials Corevia telephone or email to communicate the following:
   - Notify of pending registration request
   - Confirm method of registration request submission (email or fax)
   - Communicate expected time-line of registration request submission (e.g., same day, next day, within the hour, etc.)
3. To complete registration, the Affiliate Institution's investigator/research nurse/data manager/coordinator should then submit the following documents to the CUMC Multicenter Trials Core at AAAR6354@lists.cumc.columbia.edu.:
   - A signed Affiliate Site Eligibility Checklist (signed by the investigator)
   - Copies of redacted source documentation necessary for each item to be verified on the CUMC specific Eligibility Checklist, including but not limited to:
     - Copy of required laboratory test and procedure reports (e.g., hematology, serum chemistry, pregnancy test when applicable, MRI reports, CT/bone scans, etc.)
     - Copy of pathology and surgical reports
     - Copy of clinic note(s) capturing the consent process information, along with providing source documentation of any other items needed for screening/eligibility that are not captured in other source document forms. (e.g., positive investigator statements of unique eligibility items not captured via other direct source documentation, concomitant medication lists, etc.)
     - Protocol deviation/waiver approvals (if applicable)
   - **Please note**: subject line of email or fax should include the following: "AAAR6354 Complete Subject Registration Request (PHI)".
4. Upon receipt of the above mentioned documents, the designated study specific Clinical Research Coordinator will review all documents and verify patient eligibility. If any questions arise during the review process, queries in the form of emails will be addressed to the applicable affiliate site study team personnel for clarification prior to enrollment. Upon verification, the CUMC Multicenter Core will then forward all documents to the CPDM Central Registration Office for central registration (as described above). The CPDM Central Registration Registrar will review all applicable documents and communicate to the CUMC study specific designee in order to clarify any items. The CUMC study specific designee will communicate with the applicable site study team personnel for additional clarifications necessary prior to enrollment.

5. Upon receipt of the subject registration notification email, the CUMC Multicenter Core will forward the notification email (which will include the study specific patient ID) to the affiliate site's Principal Investigator, Consenting Professional, and applicable research personnel. This notification should be filed in the patient research binder accordingly. Protocol therapy **may not** be initiated prior to receipt of this notification from the coordinating center.
6. All screenfail/ineligible subjects, as well as subject's who withdraw consent prior to enrollment/initiation of protocol therapy must be submitted to the Central Registration Office in a manner analogous to the procedures noted above. Applicable source documentation will be required within the corresponding submissions.

6. Protocol Deviation/Subject Waiver request for Affiliate Sites:

The Affiliate site MUST submit a prospective deviation request to the CUMC lead PI for review and submission to the HICCC DSMC and CUMC IRB. Approvals must be obtained from all entities prior to implementation at the Affiliate site. If a prospective protocol deviation request is submitted for review (from an Affiliate site), the PI/site memo(s), HICCC DSMC approval(s) and correspondence and CUMC IRB approval letter(s)/equivalent should be forwarded to the Affiliate site for documentation. The Affiliate site is also required to obtain prospective local IRB approval as per institutional policies/procedures prior to implementing the proposed deviation. All documents and determinations must be clearly documented in the study subject's medical record, research chart and regulatory binder, as described.

Please note that the HICCC DSMC and PRMC do not approve eligibility deviations. If eligibility deviations are submitted, they will not be approved.

7. Guidelines for Affiliate Site Monitoring

On-Site MCT Monitoring:

1. Initial, recurrent, and close-out on-site monitoring visits will also be conducted at Affiliate sites, as appropriate/feasible. Other sites will have monitoring performed remotely (see below for further details).
    a. The study Monitoring Visit Log will be completed and signed by the monitor and the PI/CRNP/CRN and/or CRC and will be filed in the regulatory binder.
2. The Compliance Coordinator will communicate with the Affiliate site coordinator/Site Principle Investigator to schedule the monitoring visit and arrange for access to study materials and documentation.
3. The Compliance Coordinator will monitor IIT trials within 1 month after the first subject is enrolled at the Affiliate site and throughout the life of the study to ensure that the study is being conducted in accordance with the protocol, GCP, applicable federal and local regulations, and per all applicable SOPs. The Compliance Coordinator is responsible to notify the participating site PI and CRNP/CRN/CRC of upcoming monitor visits and convey what information and documentation will be required for the visit(s). The Compliance Coordinator is responsible for verifying that informed consent is properly

obtained, eligibility is met (via the central registration process), and all study procedures are conducted according to the study protocol. The Compliance Coordinator will also verify that the data reported in the CRF's accurately reflect source documents, that all toxicities have been reported to date, and that all SAE's/UPs/deviations/violations have been reported according to Coordinating Center, local IRB and HICCC DSMC requirements. The Compliance Coordinator will issue queries and ensure resolution in a timely and efficient manner. The Compliance Coordinator will also monitor for applicable regulatory compliance and research pharmacy compliance (if applicable) and communicate any deficiencies as appropriate.

4. An SIV (or) teleconference will be scheduled and conducted prior to study drug being made available (if applicable) and before any subjects are enrolled on a study at the Affiliate site.

MCT Remote Monitoring:

- When necessary (due to logistical constraints), Affiliate sites will be monitored remotely by a designated Compliance Coordinator. Sites will be informed of this remote monitoring process on a site by site basis.
- Affiliate sites will be monitored by the Compliance Coordinator on both a regulatory level, as well as a clinical data/source documentation review level.
- Redacted source documents (applicable to supporting the protocol specific CRF data requirements) will be sent to the designated Compliance Coordinator via fax or secure email for all subjects enrolled at Affiliate sites. Timelines for submission procedures will be defined on a case by case basis.
- The Compliance Coordinator will review all submitted redacted source documents against the data entered on the protocol specific CRFs. The Compliance Coordinator will issue queries when/if necessary.
- The Affiliate site research staff will respond to queries within 30 days. If queries remain outstanding, the Compliance Coordinator will send a delinquent query reminder for the outstanding items.
- The remote monitoring procedures will include review of applicable redacted source documentation and supporting applicable documents to determine compliance regarding:
    a. Informed consent procedures
    b. Eligibility criteria
    c. Protocol specific treatment compliance
    d. Protocol specific toxicity/outcome documentation/compliance
    e. Protocol specific schedule of events (e.g., baseline visits, pre-treatment, on study, follow-up)
    f. Participating site IRB documents (e.g., IRB amendment approvals, annual renewals, SAE/UP submissions, violation/deviation submissions, INDSR submissions, etc).
    g. Required specimen submissions (e.g., tissue specimens, research blood specimens, etc.)
    h. Pharmacy accountability records

i. Adherence to the CRF submission timeframes to CUMC (within the protocol specified timeframes)

- Affiliate site remote monitoring reports will be sent to the lead PI, HICCC DSMC, and Affiliate sites after each remote monitoring review. Reports will include information regarding data submission timeliness/accuracy, protocol adherence items, query resolution status, regulatory status, and overall Affiliate site performance. These reports will be generated by the Compliance Coordinator and reviewed with the Compliance Core Manager prior to dissemination.

8. Adverse event reporting

Sponsor reporting: Notifying participating investigators at affiliate sites of adverse events

It is the responsibility of the study sponsor to notify all affiliate sites, in a written IND safety report, of any adverse event associated with the use of the drug that is both serious and unexpected, as well as any finding from tests in laboratory animals that suggest a significant risk for human subjects. Additionally, sponsors are also required to identify in IND safety reports all previous reports concerning similar adverse events and to analyze the significance of the current event in light of the previous reports.

Serious Adverse Event Reporting

Each participating investigator is required to abide by the reporting requirements set by Columbia University Medical Center. The study must be conducted in compliance with FDA regulations, local safety reporting requirements, and reporting requirements of the principal investigator.

Participating investigators must report each serious adverse event to the Columbia University Medical Center Overall Principal Investigator within 24 hours of learning of the occurrence using the SAE Report Form. In the event that the participating investigator does not become aware of the serious adverse event **immediately** (e.g., participant sought treatment elsewhere), the participating investigator is to report the event within 24 hours after learning of it and document the time of his or her first awareness of the adverse event. Report serious adverse events by telephone, email or facsimile to:

Fabio M. Iwamoto, MD
710 West 168 Street
NY, NY 10032
Phone: 212-342-0571
Fax: 212-342-1246
Email: AAAR6354@lists.cumc.columbia.edu

The participating investigator must provide follow-up information on the serious adverse event until event resolution. Follow-up information should describe whether the event has resolved or continues, if and how the event was treated, and whether the participant will continue or

discontinue study participation.

Follow-up information is sent to the same person to whom the original SAE Report Form was sent, using a new SAE Report Form stating that this is a follow- up to the previously reported SAE and giving the date of the original report. Each re-occurrence, complication, or progression of the original event should be reported as a follow-up to that event regardless of when it occurs. The follow-up information should describe whether the event has resolved or continues, if and how it was treated, and whether the subject **continued** or withdrew from study participation or if study drug was interrupted or discontinued.

If the SAE is not previously documented in the Investigator's Brochure for the study drug (new occurrence) and is thought to be related to the investigational agent, the sponsor-investigator may urgently require further information from the investigator for reporting to Health Authorities.

Non-Serious Adverse Event Reporting

Non-serious adverse events will be reported to the Columbia University Medical Center Overall Principal Investigator on the toxicity Case Report Forms in Velos eResearch.

Reporting to the Institutional Review Board (IRB) and the Data and Safety Monitoring Committee:

All Unanticipated Problems (UPs) will be reported to the CUMC IRB. SAEs not constituting UPs will reported to the HICCC DSMC.

Each affiliate site will be responsible for safety reporting to their local IRB. Investigators are responsible for complying with their local IRB's reporting requirements, though must submit the required reports to their IRB no later than 7 calendar days following the occurrence of the UP or the Principal's Investigator's acquiring knowledge of the UP. Copies of each report and documentation of IRB notification and receipt must be included in the regulatory binder.

Expected AEs must be reported at the time of continuing review of a protocol.

Guidelines for Processing IND Safety Reports

The U.S. Food and Drug Administration (FDA) regulations require sponsors of clinical studies to notify the FDA and all participating investigators of any serious and unexpected adverse experiences that are possibly related to the investigational agent. The CUMC Principal Investigator will review all applicable IND Safety Reports and has the responsibly for forwarding the IND Safety Reports to the Affiliate Institutions. The Affiliate Institution investigators are to review, send a copy to their IRB according to their local IRB's policies and procedures, and file a copy with their regulatory documents. All Affiliate site INDSR submissions, along with IRB acknowledgment (per local policies and procedures) are to be forwarded to CUMC for placement within the trial master file.

Reporting to Hospital Risk Management

Affiliate Site investigators will report to their local Risk Management Office any subject safety reports or sentinel events that require reporting according to institutional policy.

9. Confidentiality

Each affiliate site will be assigned a site number. Each subject that signs consent should be assigned a unique code number consisting of site number followed by a number with each new subject being assigned the next sequential number (e.g., 04-10). All sites will be required to enter their data in the Velos eResearch, the Clinical Trial Management System used for all Cancer-related clinical research at CUMC. All users must login with their own application username and password. Users off campus must first access the Virtual Private Network with their assigned campus username and password and then use their application credentials.

Subject confidentiality must be maintained according to HIPAA regulations and GCP recommendations.

Except when required by law, study information shared with persons and organizations outside of Columbia University Medical Center must not identify the patient by name, social security number, address, telephone number, or any other direct personal identifier.
If the results of this research project are published or presented at a scientific or medical meeting, the patient not be identified. Otherwise, all results will be kept confidential and will not be divulged (except as required by law) without permission.

10. Data Reporting Plan

Columbia University Medical Center (CUMC) is deeply committed to research integrity and strong credibility when it comes to the discovery of new treatment concepts, implementation of new clinical research techniques, and acceptance of its researcher's findings by the medical establishment. In accord with these ethics, CUMC encourages and supports its investigators in the sharing of final research data and/or details of newly developed clinical treatments.

CUMC's policies that pertain to patient data sharing conform to CUMC IRB rules, local and state laws, and HIPAA privacy regulations. The primary reason for this is to protect the privacy of patients who participate in clinical trials. The data can be made available for continuing review by federal agencies upon request and for ongoing study safety reviews by the Principal Investigator, Statistician, Data Safety and Monitoring Board (DSMC), and, in other instances, the CUMC IRB.

Data collected during the course of this clinical trial will primarily be shared with other investigators and University staff, the IRB, FDA, and other reporting agencies, and/or transferred to other collaborators. Prior to transfer, the data collected must comply with, and must be limited by, the CUMC's guidelines for Protecting the Rights and Privacy of Human Subjects.

11. Data Acquisition and Submission

Informed consent, including HIPPA authorization, must be obtained on all subjects prior to their participation. Always keep the original signed and dated consent form, with the redacted source documents and eligibility checklist. Velos eResearch will be used as the electronic clinical trials and data management system. Affiliate sites will enter data directly into Velos eResearch via customized case report forms for the study. The research staff will generate reports from Velos eResearch to ensure timely submission of data by affiliate sites. This resource allows for the timely analysis of particular data sets for safety analysis.

12. Record Keeping and Record Retention

The Principal Investigator is required to maintain adequate records of the disposition of the drug, including dates, quantity, and use by subjects, as well as written records of the disposition of the drug when the study ends.

The Principal Investigator is required to prepare and maintain adequate and accurate case histories that record all observations and other data pertinent to the investigation on each individual administered the investigational drug or employed as a control in the investigation. Case histories include the case report forms and supporting data including, for example, signed and dated consent forms and medical records including, for example, progress notes of the physician, the individual's hospital chart(s), and the nurses' notes. The case history for each individual shall document that informed consent was obtained prior to participation in the study. Study documentation includes all CRFs, data correction forms or queries, source documents, Sponsor-Investigator correspondence, monitoring logs/letters, and regulatory documents (e.g., protocol and amendments, CHR correspondence and approval, signed patient consent forms). Source documents include all recordings of observations or notations of clinical activities and all reports and records necessary for the evaluation and reconstruction of the clinical research study. In accordance with FDA regulations, the investigator shall retain records for a period of 2 years following the date a marketing application is approved for the drug for the indication for which it is being investigated; or, if no application is to be filed or if the application is not approved for such indication, until 2 years after the investigation is discontinued and FDA is notified.