Safety and efficacy study of retifanlimab and epacadostat in combination with radiation and bevacizumab in patients with recurrent gliomas

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Study Drug(s): Epacadostat
(Retifanlimab)
Bevacizumab (Avastin)

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Principal Investigator Signature Page

Principal Investigator (printed):

Name of Institution:

PI Signature *Date*

By my signature, I agree to personally supervise the conduct of this study and to ensure its conduct in compliance with the protocol, informed consent, IRB/HRPO procedures, the Declaration of Helsinki, ICH Good Clinical Practices guidelines, and the applicable parts of the United States Code of Federal Regulations or local regulations governing the conduct of clinical studies.

STATEMENT OF COMPLIANCE

The trial will be carried out in accordance with International Conference on Harmonisation Good Clinical Practice (ICH GCP) and the following:

- United States (US) Code of Federal Regulations (CFR) applicable to clinical studies (45 CFR Part 46, 21 CFR Part 50, 21 CFR Part 56, 21 CFR Part 312, and/or 21 CFR Part 812)

National Institutes of Health (NIH)-funded investigators and clinical trial site staff who are responsible for the conduct, management, or oversight of NIH-funded clinical trials have completed Human Subjects Protection and ICH GCP Training.

The protocol, informed consent form(s), recruitment materials, and all participant materials will be submitted to the Institutional Review Board (IRB) for review and approval. Approval of both the protocol and the consent form must be obtained before any participant is enrolled. Any amendment to the protocol will require review and approval by the IRB before the changes are implemented to the study. In addition, all changes to the consent form will be IRB-approved; a determination will be made regarding whether a new consent needs to be obtained from participants who provided consent, using a previously approved consent form.

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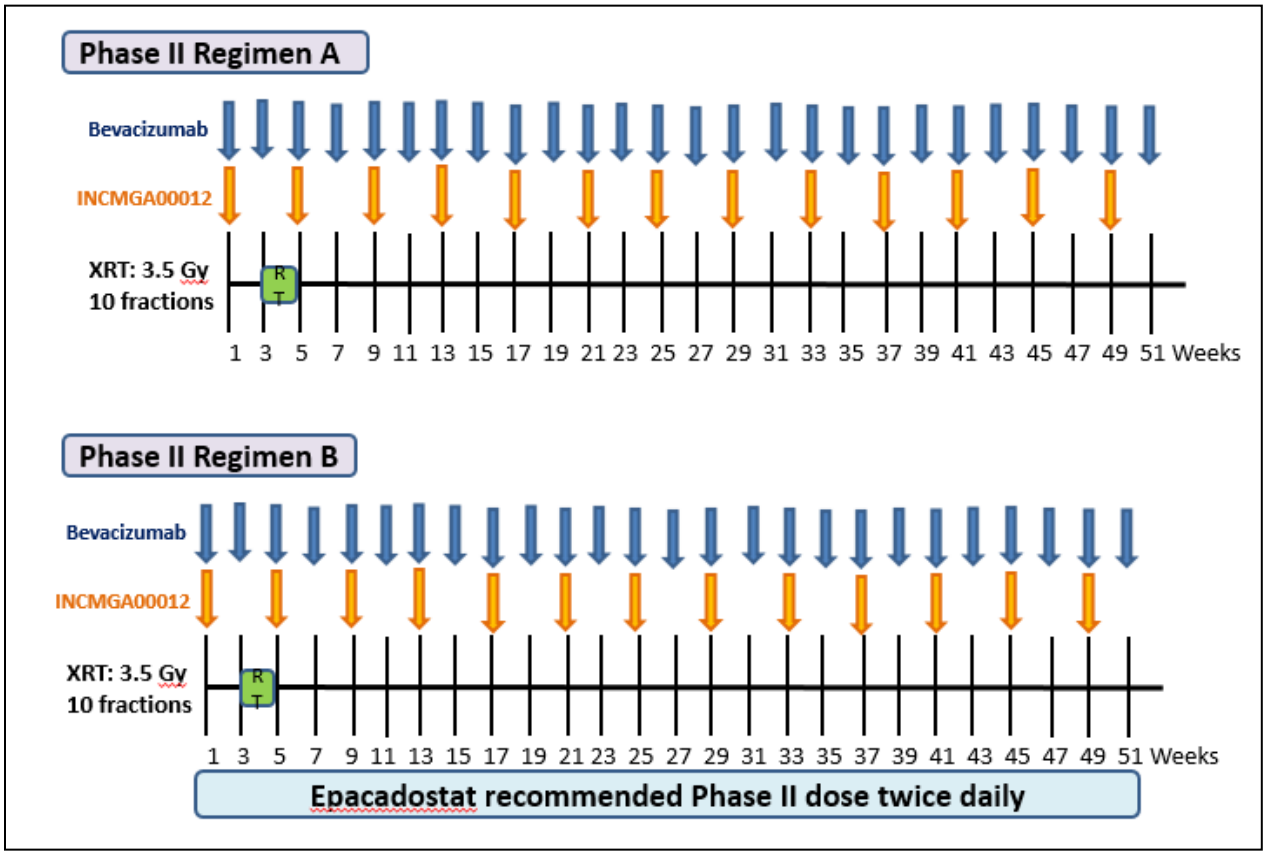
SCHEMA



Epacadostat*	Retifanlimab	Bevacizumab	Radiation Therapy
400 mg PO Twice daily	500 mg IV Q4W	10 mg/kg IV Q2W	3.5 Gy x 10 fx (during C1)

*** Regimen B only**

At time of activation, the study will enroll patients to Regimen A. When 23 patients have enrolled to Regimen A, completed the evaluation period for intolerable toxicity (refer to Section 5.2), and not exceeded the boundary "b" as specified in the table of Section 15.2, Regimen B will open to enrollment.

Glossary of Abbreviations

AE	Adverse event
ALT (SGPT)	Alanine transaminase (serum glutamate pyruvic transaminase)
AML	Acute myeloid leukemia
ANC	Absolute neutrophil count
AST (SGOT)	Aspartate transaminase (serum glutamic oxaloacetic transaminase)
B-HCG	Beta human chorionic gonadotropin
BMT	Bone marrow transplant
CBC	Complete blood count
CFR	Code of Federal Regulations
CNS	Central nervous system
CR	Complete response
CRc	Cytogenetic complete remission
CRi	Complete remission incomplete
CRm	Morphologic complete remission
CRF	Case report form
CST	Central standard time
CT	Computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
CTEP	Cancer Therapy Evaluation Program
DLT	Dose limiting toxicity
DNA	deoxyribonucleic acid
DSM	Data and Safety Monitoring
DSMC	Data Safety Monitoring Committee
ECG (or EKG)	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
EDTA	ethylenediaminetetraacetic acid
FDA	Food and Drug Administration
FISH	fluorescent in situ hybridization
FWA	Federal wide assurance
GCP	Good Clinical Practice
HHS	Department of Health and Human Services
HIV	Human Immunodeficiency Virus
HRPO	Human Research Protection Office (IRB)
IND	Investigational New Drug
IRB	Institutional Review Board
MDS	Myelodysplastic syndrome
MM	Multiple myeloma
MRI	Magnetic resonance imaging
MTD	Maximum tolerated dose
NCCN	National Cancer Center Network

NCI	National Cancer Institute
NIH	National Institutes of Health
NSCLC	Non-small cell lung cancer
OHRP	Office of Human Research Protections
ORR	Overall response rate
OS	Overall survival
PBMC	Peripheral blood mononuclear cell
PD	Progressive disease
PI	Principal investigator
PR	Partial response
PSA	Prostate-specific antigen
QASMC	Quality Assurance and Safety Monitoring Committee
RECIST	Response Evaluation Criteria in Solid Tumors (Committee)
RFS	Relapse free survival
RR	Response rate
SAE	Serious adverse event
SCC	Siteman Cancer Center
SCT	Stem cell transplant
SD	Stable disease
TSH	Thyroid stimulating hormone
TTP	Time to progression
UPN	Unique patient number
US	Ultrasound
VEGF	Vascular endothelial growth factor
WBC	White blood cell (count)

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1.0 BACKGROUND AND RATIONALE

1.1 Glioblastoma

Glioblastoma (GBM) is the most common and aggressive form of brain tumor in adults. Despite maximal surgical resection, irradiation and chemotherapy, median overall survival (OS) remains at <15 months for newly diagnosed patients and only 30 weeks for recurrent patients, emphasizing the need for novel treatments [1;2].

Indoleamine 2,3 dioxygenase 1 (IDO1) is an inducible and rate-limiting enzyme that catabolizes tryptophan (Trp) into kynurenine (Kyn). Although not normally expressed and/or found at very low levels in the CNS parenchyma, IDO1 is rapidly increased upon inflammatory stimulus. IDO1 has been demonstrated to be expressed at elevated levels in ~90% of patients with malignant glioma [3]. In addition, high IDO mRNA and protein expression levels correlate with reduced overall patient survival [4;5]. The selective nature of IDO1 expression in malignant glioma provides a higher potential for targeting specificity.

1.2 Inhibition of Indoleamine 2,3-Dioxygenase 1 as a Target for Cancer

Recent interest has focused on the role of IDO1 as a mechanism of induction of tolerance to malignancy [6]. Indoleamine 2,3-dioxygenase 1 is a heme-containing, monomeric oxidoreductase that catalyzes the degradation of the essential amino acid tryptophan to N-formyl-kynurenine. Kynurenine can be subsequently metabolized through a series of enzymatic steps to nicotinamide adenine dinucleotide. Indoleamine 2,3-dioxygenase 1 is the first rate-limiting enzyme in one of the breakdown pathways of tryptophan. In another pathway, tryptophan hydroxylase catalysis of tryptophan leads to the formation of serotonin and melatonin.

The expression and activity profiles of IDO1 are distinct from those of tryptophan dioxygenase, an enzyme predominantly expressed in liver that catalyzes the same enzymatic reaction as IDO1 and maintains proper tryptophan balance in response to dietary uptake. In contrast to tryptophan dioxygenase, IDO1 is expressed in a variety of tissues, with particularly high levels found in areas of contact with potential sources of immune challenge (eg, gut, respiratory tract, placenta, spleen), consistent with a role for regulating tryptophan metabolism in a local microenvironment [7]. Within the immune system, IDO1 activity is specifically induced in cells such as DCs and macrophages at localized sites of inflammation [8].

Indoleamine 2,3-dioxygenase 1–driven oxidation of tryptophan results in a strong inhibitory effect on the development of T-cell–mediated responses by blocking T-cell activation and inducing T-cell apoptosis [9]. Both the reduction in local tryptophan levels and the production of tryptophan catabolites that are inhibitory to cell proliferation contribute to the immunosuppressive effects [10]. Indoleamine 2,3-dioxygenase 1 activity also promotes the differentiation of naive T cells to cells with a regulatory phenotype (Treg) [11]. Because increased Treg activity has been shown to promote tumor growth and

Treg depletion has been shown to allow an otherwise ineffectual antitumor immune response to occur [12], IDO1 expansion of Treg may provide an additional mechanism whereby IDO1 could promote an immunosuppressive environment.

The biological relevance of IDO1 inhibition to immune tolerance was first demonstrated when it was shown that treating mice with a small molecule inhibitor of the IDO1 pathway, 1 methyl tryptophan, could break the tolerogenic state that protects allogeneic concepti from the maternal immune system [13]. A critical role for IDO1 in immunomodulation has been confirmed in numerous animal models, including models of allograft tolerance, inflammation, and cancer [7]. While IDO1 inhibition can exacerbate disease in models of autoimmune disorders [7], IDO1 null mice show no evidence of susceptibility to developing spontaneous autoimmunity or alterations in immune system development [9], suggesting that IDO1 inhibition, in a therapeutic setting, may produce minimal side effects in subjects without pre-existing autoimmune conditions.

Within the context of cancer, there are several lines of evidence to suggest that IDO1 is a key regulator of the immunosuppressive mechanisms responsible for tumor escape from immune surveillance. Several groups have demonstrated that blockade of IDO1 activity can directly influence the ability of tumor-bearing animals to reject tumors [14, 15]. In addition, studies with 1-methyl-tryptophan demonstrate that IDO1 inhibition dramatically increases the efficacy of various chemotherapeutic agents (eg, platinum compounds, taxane derivatives, cyclophosphamide) without increased toxicity [15]. Although the specific mechanisms responsible for this potentiation remain to be fully elucidated, the effects were not observed in T-cell–deficient animals, suggesting that the results may be the consequence of the disablement of immunosuppressive mechanisms that exist within the tumor microenvironment.

Based on studies examining serum levels of tryptophan and kynurenine, IDO1 appears to be chronically activated in patients with cancer, and IDO1 activation correlates with more extensive disease [16, 17]. Indoleamine 2,3-dioxygenase 1 has subsequently been found to be overexpressed by a wide variety of human tumor cell types, as well as by the DCs that localize to the tumor-draining lymph nodes [14, 18]. Increased expression of IDO1 in tumor cells has been shown to be an independent prognostic variable for reduced overall survival (OS) in subjects with melanoma, ovarian, colorectal, and pancreatic cancers [19-24].

Together, these results suggest that the IDO1 pathway is a key regulatory element responsible for the induction and maintenance of tumor immune tolerance. Small molecule inhibitors of IDO1 may provide an innovative and tractable method to treat malignancies either alone or in combination with chemotherapeutics and/or immunotherapy-based strategies.

1.3 Epacadostat

Epacadostat (INCB024360) is a novel, potent, and selective inhibitor of the IDO1 enzyme and can induce T cell−dependent antitumor immunity in a murine tumor model via the

ability to block regulatory T cell activity and promote dendritic cell maturation and function.[49]. A Phase 1 monotherapy study in subjects with advanced solid tumors is complete and showed epacadostat monotherapy was generally well-tolerated at doses of up to 700 mg twice daily (BID). The most common adverse events (AEs) were Grade 1 or 2 fatigue and gastrointestinal disturbances. No responses were observed; however, 7 out of 52 subjects had stable disease (SD) for at least 16 weeks [49].

Phase 1 data for the epacadostat-pembrolizumab combination in advanced cancers have also been reported [50]. Patients received escalating doses of oral epacadostat (25, 50, 100, or 300 mg) twice per day plus intravenous pembrolizumab 2 mg/kg or 200 mg every 3 weeks. Sixty-two patients were enrolled and received one or more doses of study treatment. The maximum tolerated dose of epacadostat in combination with pembrolizumab was not reached. The most common treatment-related adverse events (TRAEs) were: fatigue (36%), rash (36%), arthralgia (24%), pruritus (23%), and nausea (21%) occurring in > 20%. Grade 3/4 TRAEs were reported in 24% of patients. Seven patients (11%) discontinued study treatment because of TRAEs. No TRAEs led to death. In Phase 1, objective responses (per Response Evaluation Criteria in Solid Tumors [RECIST] version 1.1) occurred in 12 (55%) of 22 patients with melanoma and in patients with non–small-cell lung cancer, renal cell carcinoma, endometrial adenocarcinoma, urothelial carcinoma, and squamous cell carcinoma of the head and neck. The pharmacokinetics of epacadostat was comparable to historical controls for monotherapies.

Preliminary results for the combination of epacadostat with nivolumab have also recently been reported [51]. In that study, participants with no prior IDO or checkpoint inhibitor treatment (other than first line CTLA-4 inhibitor) received epacadostat in escalating doses along with standard doses of nivolumab. The most common treatment-related TEAEs at the RP2D of epacadostat 100 mg BID PO in combination with nivolumab 240 mg Q2W IV were rash (25% overall, 10% ≥ Grade 3), fatigue (23%, no ≥ Grade 3), nausea (19%, no ≥ Grade 3), pruritus (16%, 3% ≥ Grade 3), diarrhea (12%, no ≥ Grade 3), and increased AST (12%, 3% ≥ Grade 3). Dose interruption (26%) or dose reduction (4%) were needed only for a minority of participants, and discontinuation due to TEAE occurred in only 6% of participants.

Interim results of a Phase 3 randomized, double-blind, placebo-controlled study of pembrolizumab in combination with epacadostat 100 mg BID or placebo in participants with unresectable or metastatic melanoma (ECHO-301/KEYNOTE-252) have been reported (52). This study enrolled 706 patients (randomized 1:1) with dual primary endpoints of PFS and OS but was stopped when the external Data Monitoring Committee determined that the primary endpoint of PFS was not met and the endpoint of OS was also unlikely to reach statistical significance. The safety profile was consistent with that observed in previously reported studies of epacadostat in combination with pembrolizumab (52).

Refer to the epacadostat investigator brochure (IB) for detailed information concerning the available pharmacology, toxicology, drug metabolism, clinical studies, and AE profile of the investigational product (IP).

1.3.1 Potential Risks from Epacadostat

Monotherapy

In the Phase 1 clinical study in subjects with refractory solid tumors (INCB 24360-101), epacadostat was well tolerated at doses ranging from 50 mg QD to 700 mg BID. Twenty-five (48.1%) of the 52 subjects administered epacadostat had a single SAE. The most frequently reported SAEs were disease progression (4 subjects, 7.7%), followed by abdominal pain, nausea, and hypoxia (3 subjects each, 5.8%). Treatment-emergent adverse events (TEAEs) were reported in all subjects. The most commonly reported treatment-related TEAEs were fatigue and nausea (25 subjects, 48.1%). The incidence and severity of fatigue were not dose-related. Two DLTs occurred: 1 DLT of radiation pneumonitis at the 300 mg dose level and 1 DLT of fatigue at the 400 mg BID dose level.

Combination Therapy

Phase 1/2 data for the epacadostat-pembrolizumab combination in advanced melanoma have also been reported (53). Dose interruption or reduction due to TEAEs occurred in 25% and 11% of participants, respectively. Four participants discontinued treatment due to TEAEs (arthralgia, 2 participants; autoimmune hepatitis and increased lipase, 1 participant each). Treatment-related SAEs of arthralgia, autoimmune hepatitis, and colitis (1 participant each) were manageable with standard supportive care. No treatment-related deaths were reported. Immune-related TEAEs were assessed as AEs of special interest and included hypothyroidism (4 events, no ≥ Grade 3), severe skin reactions (4 events, 3 ≥ Grade 3), colitis (2 events, both ≥ Grade 3), uveitis (2 events, no ≥ Grade 3), and autoimmune hepatitis (1 event, which was ≥ Grade 3). The RP2D selected for further development was epacadostat 100 mg BID PO with pembrolizumab 200 mg Q3W IV.

Preliminary results for the combination of epacadostat with nivolumab have also recently been reported (51). In that study, participants with no prior IDO or checkpoint inhibitor treatment (other than first line CTLA-4 inhibitor) received epacadostat in escalating doses along with standard doses of nivolumab. The most common treatment-related TEAEs at the RP2D of epacadostat 100 mg BID PO in combination with nivolumab 240 mg Q2W IV were rash (25% overall, 10% ≥ Grade 3), fatigue (23%, no ≥ Grade 3), nausea (19%, no ≥ Grade 3), pruritus (16%, 3% ≥ Grade 3), diarrhea (12%, no ≥ Grade 3), and increased AST (12%, 3% ≥ Grade 3). Dose interruption (26%) or dose reduction (4%) were needed only for a minority of participants, and discontinuation due to TEAE occurred in only 6% of participants.

A potential concern of IDO1 inhibition is an increase in serotonin levels that could precipitate a cluster of AEs termed serotonin syndrome (SS) when administered as a single agent or in combination with other serotonergic agents. This rare syndrome has been associated with some monoamine oxidase inhibitors (MAOIs) such as

meperidine, linezolid, or methylene blue, and combinations of serotonergic drugs [25]. The clinical manifestations of SS range from barely perceptible to lethal.

Based on studies in the rat, epacadostat exhibits apparent limited penetration across the blood brain barrier and is likely not associated with significant effects on tryptophan metabolism in the brain that might impact brain serotonin levels. Furthermore, epacadostat did not increase the brain extra extracellular fluid concentrations (ECF) of serotonin levels in the rat microdialysis study when administered alone (25 mg/kg) or in combination with linezolid (100 mg/kg), a monoamine oxidase inhibitor (MAOI) (54). Thus preclinical data suggest that SS is unlikely following treatment with either epacadostat alone or in combination with MAOIs such as linezolid (54).

As of 29 OCT 2018, 4 participants treated across the entire epacadostat program have had events reported as serotonin syndrome or symptoms of serotonin syndrome; episodes were confounded, mild in severity, and transient (3 of 4 resolved with dose interruption while the other resolved following study treatment discontinuation). One of the 4 participants had an event of serotonin syndrome that was reported as a serious (medically important) event by the investigator. These AEs were not clinically substantiated by the sponsor to represent true events of serotonin syndrome.

Additional details regarding specific benefits and risks of epacadostat for participants in this clinical study may be found in the accompanying Investigator's Brochure and ICF.

1.3.2 **Justification for Dose**

The dose of epacadostat will be 400 mg BID to optimally inhibit IDO1 in combination with PD-1 pathway inhibition. Epacadostat 100 mg BID as monotherapy achieves an exposure that exceeds the IC50 at steady state and epacadostat 400 mg BID and greater (as monotherapy) achieve exposures that exceed the IC90 at steady state in peripheral blood.

INCMGA0012-102 (ClinicalTrials.gov Identifier: NCT03589651) is a Phase 1b study to evaluate the safety and tolerability of combination of epacadostat and INCMGA0012, an anti-PD-1 antibody, in participants with advanced solid tumors. Thirty-one participants received retifanlimab 500 mg Q4W plus epacadostat. Four dose levels of epacadostat were studied (100 mg BID, 400 mg BID, 600 mg BID and 900 mg BID).

All participants experienced an adverse event (AE). Sixteen participants (52%) experienced an AE that was considered related to epacadostat.

Three participants had a DLT, all of which were Grade 3 maculo-papular rash that were considered related to retifanlimab and epacadostat and resulted in

discontinuation of epacadostat. One DLT occurred at the epacadostat 400 mg BID dose level, and 2 DLTs occurred at the epacadostat 900 mg BID dose level. Two of the events also led to discontinuation of retifanlimab (epacadostat dose levels of 400 mg BID and 900 mg BID). None of the DLTs were serious, and 2 of the 3 events had recovered at the time of data cutoff. The dose of 600 mg BID was established as the maximum tolerated dose (MTD) of epacadostat in combination with retifanlimab.

Twelve participants received retifanlimab in combination with epacadostat at the MTD of 600 mg BID. Six of these participants (50%) experienced an AE related to epacadostat. One of these participants experienced a Grade 3 (CTCAE v.5.0) AE which was maculopapular rash and fever. Other AEs related to epacadostat at this dose were nausea, fatigue, dyspepsia, hypothyroidism, rash, pruritus, and diarrhea. Nine participants received retifanlimab in combination with epacadostat 400 mg BID. Four of these participants (44%) experienced an AE related to epacadostat. One of these was a Grade 3 maculopapular rash. Other AEs related to epacadostat reported at this dose included nausea, fatigue, fever, diarrhea, and dyspepsia.

Three participants received retifanlimab in combination with epacadostat 100 mg BID. One of them experienced an AE of Grade 1 anorexia that was noted as related to epacadostat.

No significant drug related laboratory abnormalities have been reported at any dose level.

Serious AEs have been reported in 6 of the 31 participants (19%). Only 1 participant had an SAE noted as related to epacadostat, which was the event of fever and maculopapular rash.

1.4 Radiation Therapy

Radiation therapy (RT) is the main treatment for malignant gliomas. Besides directly inducing tumor cell death, RT has an immunomodulatory effect. RT delivered in multiple fractions over several days increases tumor immunogenicity compared to a single high-dose RT [26, 28]. Ionizing radiation has also been shown to enhance uptake of tumor antigens by dendritic cells and their activation, as well as migration of the activated effector T cells back to the tumor. Thus RT could potentially enhance and complement the action of different immunotherapy agents [29]. Expression of PD-1 and PD-L1 is found in the microenvironment of most high grade gliomas [30]. In addition, recent studies suggest RT increases PD-L1 expression [31-33] and IDO expression (Figure 1, 2 and 3) [34; 35; Ciorba M, unpublished data]. Numerous clinical trials were conducted or on-going to test the combination of immunotherapy with various radiation dosing and fractions [36].

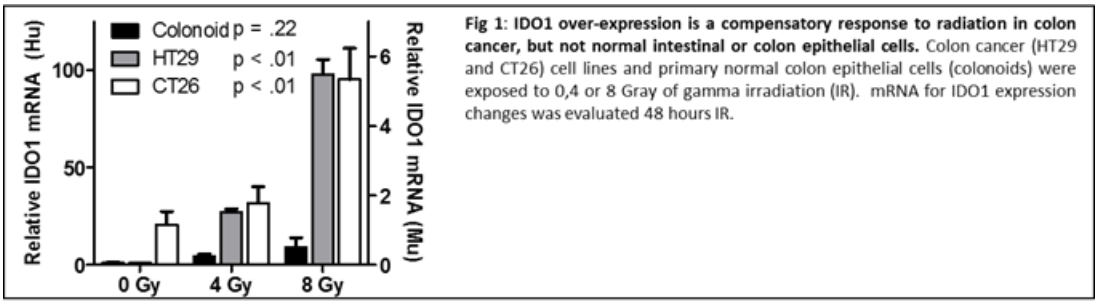

Fig 1: IDO1 over-expression is a compensatory response to radiation in colon cancer, but not normal intestinal or colon epithelial cells. Colon cancer (HT29 and CT26) cell lines and primary normal colon epithelial cells (colonoids) were exposed to 0,4 or 8 Gray of gamma irradiation (IR). mRNA for IDO1 expression changes was evaluated 48 hours IR.

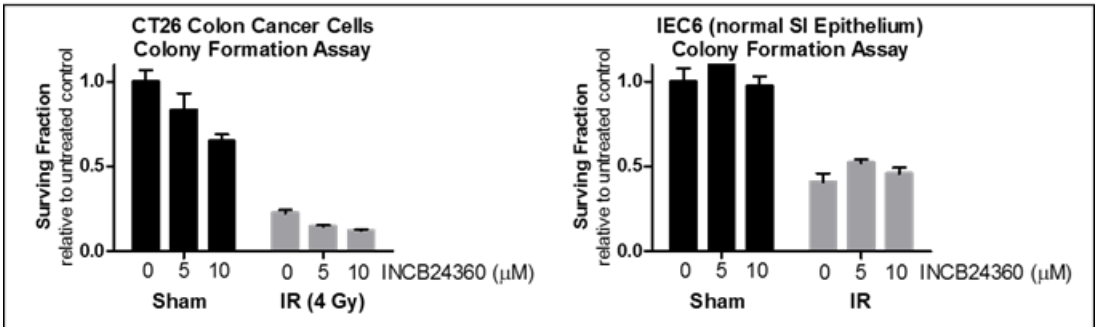

Fig 2: Epacadostat (INCB24360) enhances the tumor cytotoxicity of radiation in vitro, but does not augment radiation toxicity to normal epithelial cells. A colony forming assay was performed with 1000 cells derived from colon cancer (CT26) or the normal normal intestinal epithelium (IEC6). Cells incubated in 0, 5 or 10 μM of epacadostat 1 hour prior either Sham (no irradiation) or 4 Gy gamma irradiation (IR). Colony counts are reported as compared to dual controls (Sham IR and 0 μM epacadostat).

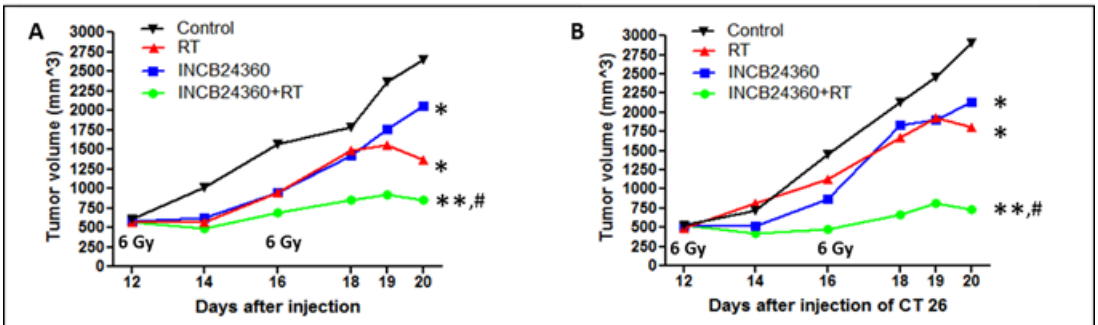

Fig 3: Epacadostat (INCB24360) enhances the anti-tumor efficacy of radiation at local and distant tumor sites. 8 Week old female BalbC mice were inoculated with 1x10^6 CT26 tumor cells in bilateral hind legs. Treatment groups are as per legend with N=5/group. 6 Gy of localized radiation (1 hind limb only) was applied on day 12 and 16. Epacadostat was administered at 300 mg/kg daily by oral gavage. Tumors were measured daily using digital calipers. * p<0.05 vs Control. ** p<0.01 vs Control. # p<0.05 vs RT or INCB24360 alone.

Retifanlimab is a humanized anti-PD-1 monoclonal antibody directed against the negative immunoregulatory human cell surface receptor programmed cell death 1 (PD-1). retifanlimab binds to and inhibits PD-1 and its downstream signaling pathways. This may restore immune function through the activation of T cells and cell-mediated immune responses against tumor cells. This may result in both T-cell activation and the induction of T-cell-mediated immune responses against tumor cells. PD-1 checkpoint inhibition has been studied in gliomas. A recent study has shown that re-irradiation using hypofractionated RT (HFRT) in combination with anti-PD1 antibody and bevacizumab (VEGF antibody) is safe and well tolerated in patients with recurrent high grade gliomas [37]. The addition of IDO inhibitor to CTLA-4 and PD-L1 decreased tumor-infiltrating Tregs and this triple combination was associated with a high survival rate in a mouse model of glioma [38]. Most recently, preclinical murine models showed significantly improved survival by combining IDO inhibitor with RT and anti-PD1 antibody [Ladomersky E et al., 2018].

1.4.1 **Justification for Retifanlimab Dose**

Retifanlimab will be administered at 500 mg Q4W. The selection of this dose was based on modeling of clinical PK data from the first-in-human monotherapy study, INCMGA00012-101 (NCT03059823), in which 37 participants were treated at doses of 1 mg/kg Q2W, 3 mg/kg Q2W, 3 mg/kg Q4W, 10 mg/kg Q2W, and 10 mg/kg Q4W.

A simulation was conducted to investigate the use of weight-based and fixed doses for retifanlimab with the aim of targeting a steady-state trough concentration of approximately 21 μg/mL, which is the median trough concentration for pembrolizumab 200 mg Q3W (55). The median retifanlimab exposure and distribution around the median at 500 mg Q4W were similar to 7 mg/kg Q4W in the simulated population, which justified clinical exploration in an expansion cohort of the INCMGA0012-101 study.

Based on the flat exposure-response relationships for efficacy and safety from pembrolizumab and nivolumab, both weight–based and flat dose regimens are considered appropriate for administration of retifanlimab. The 500 mg Q4W dose was selected to maintain a steady-state trough serum concentration of ≥ 21 μg/mL in clinical trials and to provide additional flexibility in monotherapy or combinations (eg, chemotherapy) while maintaining this schedule.

Combination with Epacadostat
As of December 13th 2021 a total of 100 participants with advanced solid tumors have been treated with epacadostat in combination with retifanlimab in Studies INCMGA 0012-102 and 204.

The most frequently reported TEAEs were nausea (30.0%), decreased appetite (25.0%), fatigue (24.0%), abdominal pain and anemia (18.0% each), and rash maculo-papular (17.0%). Serious TEAEs were reported for 39 participants (39.0%). The most frequently reported serious TEAEs were dyspnea (6.0%), rash maculo-papular (5.0%), and pleural effusion (3.0%). Treatment-emergent AEs led to discontinuation of epacadostat for 16 participants (16.0%). The most frequently reported TEAE leading to discontinuation of epacadostat was rash maculo-papular (7.0%).

The MTD of epacadostat in combination with retifanlimab 500 mg was determined to be 600 mg BID. Epacadostat 900 mg BID exceeded the MTD based on the occurrence of Grade 3 maculopapular rash in 2 of 3 participants during the DLT evaluation period. Overall, the following DLTs were reported:
• 400 mg BID: 1 DLT of Grade 3 rash maculo-papular
• 600 mg BID: 1 DLT of Grade 3 rash maculo-papular, 1 DLT of Grade 3 dermatitis acneiform, 1 DLT of Grade 3 abdominal pain

• 900 mg BID: 2 DLTs of Grade 3 rash maculo-papular.

Five participants (5.0%) had fatal TEAEs: acute respiratory distress syndrome and COVID-19 pneumonia (1 participant), and ascites, cardiovascular disorder, respiratory failure, and thrombocytopenia (1 participant each). None of the fatal TEAEs were considered related to epacadostat.

1.5 Bevacizumab

Bevacizumab, a monoclonal antibody against the vascular endothelial growth factor (VEGF), is the most commonly used treatment for recurrent and progressive malignant gliomas either alone or in combination with other therapy including RT [39-41]. Additionally, bevacizumab is effective in the treatment of cerebral radiation necrosis [42] and is less immunosuppressive than steroids. A recent large randomized phase II study (RTOG 1205) comparing hypofractionated re-irradiation of 35 Gy in 10 fractions with bevacizumab versus bevacizumab alone for recurrent GBM has successfully completed accrual (NCT01730950). Bevacizumab plus re-irradiation is safe and well-tolerated. Although no benefit has been shown in OS, clinically meaningful improvement in PFS has been demonstrated (Tsien C et al. 2019). Therefore, in this study, bevacizumab will be co-administered with epacadostat and retifanlimab to reduce the risk of cerebral edema from re-irradiation and the need for steroids.

1.6 Study Rationale

Collectively, there is strong preclinical evidence for the combination of IDO inhibitor, RT and anti-PD1 therapy in patients with recurrent grade 4 gliomas with very limited treatment options.

In this study, we propose to combine retifanlimab with RT and bevacizumab with or without epacadostat in the treatment of recurrent grade 4 glioma. We hypothesize that this combination provides a powerful synergy between RT and immune modulators to produce more robust anti-tumor immune response, induce tumor regression and improve overall survival.

1.7 Correlative Studies Background

One hallmark of poor prognosis grade 4 glioma, such as GBM, is the infiltration and accumulation of immunosuppressive and tumor-promoting regulatory T cells (Tregs) [27]. Both clinical and preclinical data confirm that IDO expression increases the recruitment of Tregs and inhibits the activation of effector T cells [5]. Administration of an IDO inhibitor might reverse this process. Therefore, serum Kyn/Trp level will be tested to evaluate the on-target effect of epacadostat. T cell phenotype will be tested to evaluate the effect of epacadostat. We plan to combine retifanlimab with epacadostat for potential synergic effect. Thus tumor mutation burden and PD-L1/PD-L2 expression will be tested.

2.0 OBJECTIVES

2.1 Primary Objective

To evaluate overall survival at 9 months (OS-9) of recurrent grade 4 glioma patients treated with the combination of retifanlimab, RT, and bevacizumab with or without epacadostat.

2.2 Secondary Objectives

1. To determine progression-free survival (PFS) of recurrent grade 4 glioma patients treated with the combination of RT, retifanlimab, and bevacizumab with or without epacadostat.
2. To evaluate neurologic functions of recurrent grade 4 glioma patients treated with the combination of RT, retifanlimab, and bevacizumab with or without epacadostat using the Neurologic Assessment in Neuro-Oncology (NANO) scale.
3. To evaluate the safety and toxicity of the combination of RT, retifanlimab, and bevacizumab with or without epacadostat in patients with recurrent grade 4 glioma.

2.3 Correlative Objectives

1. To assess the anti-glioma immune response before and after retifanlimab or/and epacadostat including assessment of immune cells phenotyping, function and activation in the pre-/post-treatment blood.
2. To evaluate serum Kyn/Trp ratio as a surrogate of IDO1 enzymatic activity.
3. To evaluate mRNA expressions of IDO1, IDO2, TDO and PD-L1 pre- and post- study treatment.

2.4 Exploratory Objectives

1. To evaluate the correlation between serum Trp and Kyn levels in patients and the association with treatment response and overall survival after epacadostat treatment.
2. To evaluate the correlation between intratumoral expression of IDO and the frequency of glioma cell-specific cytotoxic T cells, Tregs, treatment response and overall survival.
3. To evaluate tumor infiltrating lymphocytes (CD4, CD8, Treg, effector cells etc) in the tumor tissue pre- and post retifanlimab or/and epacadostat treatment (if available).
4. To explore tissue and blood biomarkers that may predict tumor response to epacadostat in combination with RT and retifanlimab.
5. To test tumor mutation burden by a validated comprehensive genomic profiling and PD-L1/PD-L2 expression on tumor/immune cells by IHC.

3.0 PATIENT SELECTION

3.1 Inclusion Criteria

1. Recurrent WHO grade 4 glioblastoma or gliosarcoma, including molecular features of glioblastoma and WHO grade 4 astrocytoma or WHO grade high grade glioma.

2. Other GBM variants and "secondary GBM" are allowed. All grade 4 gliomas that have relapsed more than once may be included, as the prognosis of multiply recurrent grade 4 glioma patients may not differ based on IDH mutation status.

3. Disease must have recurred, and patient must be a candidate for re-irradiation and bevacizumab. Any number of recurrences is allowed.

4. Patients must have measurable disease per RANO criteria (section 12.3). Lesions will be considered measurable when they are bi-dimensional with clearly defined margins of ≥ 5 mm in two perpendicular diameters.

5. Prior transient use of bevacizumab for cerebral edema or radiation necrosis is allowed without a washout period. Prior bevacizumab use is permitted if used for treatment of disease if administered more than 4 months prior to registration.

6. At least 18 years of age.

7. Karnofsky performance status ≥ 60% (see Appendix A)

8. Normal bone marrow and organ function as defined below:
   a. Absolute neutrophil count ≥ 1,000/mcL
   b. Platelets ≥ 75,000/mcL
   c. Hemoglobin ≥ 9.0 g/dL or > 5.6 mmol/L (transfusion is acceptable to meet this criterion)
   d. Serum creatinine ≤ 1.5 x ULN or creatinine clearance ≥ 60 mL/min/1.73 m^2 by Cockcroft-Gault for patients
   e. Serum total bilirubin ≤ 1.5 ULN
   f. AST(SGOT)/ALT(SGPT) ≤ 2.5 x IULN
   g. INR or PT ≤ 1.5 x IULN unless subject is receiving anticoagulant therapy as long as PT or PTT is within therapeutic range of intended use of anticoagulants
   h. aPTT ≤ 1.5 x IULN unless subject is receiving anticoagulant therapy as long as PT or PTT is within therapeutic range of intended use of anticoagulants

   At least 28 days from any major surgery such as craniotomy and surgical wound is fully healed, and at least 14 days from LITT or biopsy. Prior to surgery, there must be imaging evidence of measurable progressive disease (PD) per RANO criteria as noted above.
9. Women of childbearing potential and men must agree to use highly effective contraception (hormonal or barrier method of birth control, abstinence) prior to study entry and for the duration of study participation. Should a woman become pregnant or suspect she is pregnant while participating in this study, she must inform her treating physician immediately.

10. Ability to understand and willingness to sign an IRB approved written informed consent document (or that of legally authorized representative, if applicable).

11. Prior use of the Optune device is allowed, without a washout period. However, concurrent Optune use is not permitted while on treatment for this trial.

3.2 Exclusion Criteria

1. Currently receiving any other investigational agents.

2. A history of allergic reactions attributed to compounds of similar chemical or biologic composition to epacadostat, retifanlimab, bevacizumab, or other agents used in the study.

3. Dexamethasone dose > 4 mg daily at the time of registration (higher dose of steroid for symptom control is allowed during the study).

4. History of intracranial abscess within 6 months prior to start of study therapy.

5. Has active autoimmune disease or syndrome (i.e. moderate or severe rheumatoid arthritis, moderate or severe psoriasis, multiple sclerosis, active inflammatory bowel disease) that has required systemic treatment in the past 2 years (i.e. with use of disease-modifying agents, corticosteroids, or immunosuppressive drugs) or who are receiving systemic therapy for an autoimmune or inflammatory disease (i.e. with use of disease modifying agents, corticosteroids, or immunosuppressive drugs). Replacement therapy (e.g., thyroxine, insulin, or physiologic corticosteroid replacement therapy for adrenal or pituitary insufficiency) is not considered a form of systemic treatment. Subjects are permitted to enroll if they have vitiligo, resolved childhood asthma/atopy, type I diabetes mellitus, residual hypothyroidism due to autoimmune condition only requiring hormone replacement, psoriasis not requiring systemic treatment, or conditions not expected to recur in the absence of an external trigger.

6. Has a severe acute or chronic medical condition including immune colitis, inflammatory bowel disease (may be enrolled at the discretion of the PI), immune pneumonitis, or laboratory abnormalities that may increase the risk associated with study participation or study treatment administration or may interfere with the interpretation of study results and, in the judgment of the investigator, would make the patient inappropriate for entry into this study.

7. Has had an allogeneic tissue/solid organ transplant.

8. Has an active infection requiring intravenous antibiotic therapy.

9. Has a known history of active tuberculosis (TB; bacillus tuberculosis).

10. Has received prior therapy with an anti-PD-1, anti-PD-L1, anti-PD-L2, or IDO inhibitor.

11. If a patient is enrolled to regimen B, they are prohibited from receiving monoamine oxidase inhibitors (MAOIs) or drug which has significant MAOI activity (meperidine, linezolid, methylene blue) within the 21 days before screening.

12. If a patient is enrolled to regimen B, the use of any UGT1A9 inhibitor from screening through follow-up period, including acitretin, amitriptyline, androsterone, cyclosporine, dasatinib, diclofenac, diflunisal, efavirenz, erlotinib, estradiol (17-beta), flutamide, gefitinib, gemfibrozil, glycyrrhetinic acid, glycyrrhizin, imatinib, imipramine, ketoconazole, linoleic acid supplements, mefenamic acid, mycophenolic acid, niflumic acid, nilotinib, phenobarbital, phenylbutazone, phenytoin, probenecid, propofol, quinidine, ritonavir, sorafenib, sulfinpyrazone, valproic acid, and verapamil is prohibited.

13. If a patient is enrolled to regimen B, the use of probiotics from screening through end of treatment is prohibited.

14. If a patient is enrolled to regimen B, the use of warfarin is prohibited. If anti-coagulation is needed during the conduct of the study and non-warfarin regimens are not feasible, the participant must discontinue study therapy.

15. Chronic use of systemic antibiotics (> 14 days) unless medical monitor review and approval.

16. Any history of serotonin syndrome (SS) after receiving serotonergic drugs.

17. Has uncontrolled HIV (HIV 1/2 antibodies). Well-controlled HIV is defined as CD4+ count > 300 cells, undetectable viral load, and receiving HAART/ART. Study specific HIV testing is not required for patients who do not have any prior history of HIV.

18. Has uncontrolled active hepatitis B (e.g., HBsAg reactive or HBV DNA detected by quant RT PCR) or hepatitis C (e.g. HCsAg reactive or HCV RNA [qualitative or quantitative] is detected).

19. Uncontrolled intercurrent illness including, but not limited to, clinically significant (i.e. active) cardiovascular disease: cerebral vascular accident/stroke (< 6 months prior to enrollment), myocardial infarction (< 60 months prior to enrollment), congestive heart failure (≥ NYHA class II), unstable angina pectoris, or serious cardiac arrhythmia requiring medication.

20. History or presence of an abnormal electrocardiogram (ECG) that, in the investigator's opinion, is clinically meaningful. Screening QTc interval > 480 msec will require investigator's evaluation on patient's eligibility. Subjects with left bundle branch block are excluded.

21. Presence of a gastrointestinal condition that may affect drug absorption.

22. Receipt of live attenuated vaccine within 30 days before the first dose of study treatment. Examples of live vaccines include, but are not limited to, the following: measles, mumps, rubella, chicken pox, yellow fever, rabies, Bacillus Calmette-Guérin (BCG), and typhoid vaccine. Seasonal influenza vaccines for injection are generally killed virus vaccines and are allowed; however, intranasal influenza vaccines (e.g. FluMist) are live attenuated vaccines and are not allowed.

23. Pregnant and/or breastfeeding. Women of childbearing potential must have a negative pregnancy test prior to the start of study treatment.

3.3 Inclusion of Women and Minorities

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

4.0 REGISTRATION PROCEDURES

Patients must not start any protocol intervention prior to registration through the Siteman Cancer Center.

The following steps must be taken before registering patients to this study:

1. Confirmation of patient eligibility by Washington University
2. Registration of patient in the Siteman Cancer Center OnCore database
3. Assignment of unique patient number (UPN)

Once the patient has been entered in the Siteman Cancer Center OnCore database, the WUSM coordinator will forward verification of enrollment and the UPN via email.

4.1 Confirmation of Patient Eligibility

Confirm patient eligibility by collecting the information listed below and scanning and emailing it to the research coordinator listed in the *Siteman Cancer Center Clinical Trials Core Protocol Procedures for Secondary Sites* packet at least one business day prior to registering patient:

1. Your name and contact information (telephone number, fax number, and email address)
2. Your site PI's name, the registering MD's name, and your institution name
3. Patient's race, sex, and DOB
4. Three letters (or two letters and a dash) for the patient's initials
5. Currently approved protocol version date
6. Copy of signed consent form (patient name may be blacked out)

7. Planned date of enrollment
8. Completed eligibility checklist, signed and dated by a member of the study team
9. Copy of appropriate source documentation confirming patient eligibility

4.2 Patient Registration in the Siteman Cancer Center OnCore Database

Registrations may be submitted Monday through Friday between 8am and 5pm CT. Urgent late afternoon or early morning enrollments should be planned in advance and coordinated with the Washington University research coordinator. Registration will be confirmed by the research coordinator or his/her delegate by email within one business day. Verification of eligibility and registration should be kept in the patient chart.

All patients at all sites must be registered through the Siteman Cancer Center OnCore database at Washington University.

4.3 Assignment of UPN

Each patient will be identified with a unique patient number (UPN) for this study. Patients will also be identified by first, middle, and last initials. If the patient has no middle initial, a dash will be used on the case report forms (CRFs). All data will be recorded with this identification number on the appropriate CRFs.

4.4 Patient Allocation

At time of activation, the study will enroll patients to Regimen A. When 23 patients have been enrolled to Regimen A, completed the evaluation period for intolerable toxicity (refer to Section 5.2), and not exceeded the boundary "b" as specified in the table of Section 15.2, Regimen B will open to enrollment.

4.5 Screen Failures

Screen failures are defined as participants who consent to participate in the clinical trial but are not subsequently entered in the study. A minimal set of screen failure information is required to ensure transparent reporting of screen failure participants, to meet the Consolidated Standards of Reporting Trials (CONSORT) publishing requirements and to respond to queries from regulatory authorities. Minimal information includes demography, screen failure details, eligibility criteria, and any serious adverse event (if applicable).

5.0 TREATMENT PLAN

5.1 Agent Administration

Retifanlimab will be given intravenously over the course of 30 to 60 minutes at a dose of 500 mg on Day 1 of each 28-day cycle. In order to mitigate infusion-related reactions,

patients must be premedicated with an antihistamine and with acetaminophen prior to the first 4 infusions of retifanlimab. Premedications should be administered for subsequent retifanlimab doses based upon clinical judgment and presence/severity of prior infusion reactions.

Bevacizumab will be given intravenously at a dose of 10 mg/kg on Days 1 and 15 of each 28-day cycle. The first infusion will be over the course of 90 minutes; the second infusion will be over the course of 60 minutes; if tolerated, all subsequent infusions may be over 30 minutes.

At time of activation, the study will enroll patients to Regimen A. When 23 patients have been enrolled to Regimen A, completed the evaluation period for intolerable toxicity (refer to Section 5.2), and not exceeded the boundary "b" as specified in the table of Section 15.2, Regimen B will open to enrollment.

Patients enrolled to Regimen B will receive epacadostat. Epacadostat will be administered orally at 400 mg BID. If the 400 mg BID dose is determined to be intolerable during the first cycle of treatment (by continuous toxicity monitoring as described in Section 15.2), the patient must be discontinued from treatment with epacadostat. No dose reduction below 400 mg BID is permitted. Patients enrolled prior to Amendment 8 were enrolled at a starting dose of epacadostat 600 mg BID. Patients beyond cycle 1 of treatment at the time of Amendment 8 were instructed to continue at this dose and will follow the protocol guidelines regarding dose reduction. Patients currently in cycle 1 of treatment at the time of Amendment 8 were instructed to dose reduce to 400 mg BID.

Epacadostat is an oral medication that will be taken twice a day every day without regard to food during each 28-day cycle. If a dose is missed by more than 4 hours, then that dose should be skipped and the next dose should be taken at the next scheduled time point. All BID doses will be taken in the morning and evening, approximately 12 hours apart.

The drugs may be given in any order on Day 1 of each cycle; however, for patients enrolled to Regimen B, the dose of epacadostat should be taken as close to the regularly scheduled 12-hour dosing interval as possible.

Ten fractions of radiation therapy will be given at a dose of 3.5 Gy per fraction as per RTOG 1205 study. The gross tumor maximum diameter (to be irradiated) to be </= 6cm in the first 6 patients. Additionally, if more than 1 target is irradiated, then the sum of all the target maximum diameters should be </= 6cm in the first 6 patients. For subsequent patients (patients enrolled after the first 6), no more than 3 separate targets for RT is allowed.

Retifanlimab and bevacizumab (with or without epacadostat) will be started approximately two weeks before the first day of radiation therapy (+/-3 days window). This means that RT may start anywhere between Cycle 1 Day 12 and Cycle 1 Day 18. Depending on scheduling, it is possible that RT may extend into Cycle 2 of retifanlimab and bevacizumab (with or without epacadostat).

Additionally, for patients being treated on either regimen who have surgical intervention, including laser ablation, for a radiographically progressing tumor but the final pathology demonstrates a predominant immune-mediated reaction or treatment-related effect, with no obvious progression of tumor, such subjects will be deemed not to have progressed and be allowed to resume assigned study treatment at a time deemed safe by the treating physician, but no later than 8 weeks from the surgery

5.2 Toxicity and Response Evaluations

All patients who receive any study treatment are evaluable for toxicity. Patients are evaluated from first receiving study treatment until a 90-day follow up after the conclusion of treatment or death.

Toxicity evaluations for "intolerable toxicity" (as defined in Section 15.2) will take place in each patient in both regimens from first dose of study treatment until 28 days after last dose of Cycle 2 treatment; for patients enrolled in Regimen A, this is Cycle 3 Day 1 (28 days after the C2D1 dose of retifanlimab), and for patients enrolled in Regimen B, this is Cycle 3 Day 28 (28 days after the C2D28 dose of epacadostat).

Patients must receive at least one dose of study treatment to be evaluable for intolerable toxicities. If a patient decides to drop out of the study during the first cycle for reasons other than treatment-related toxicity, the patient is not evaluable for intolerable toxicities and will be replaced.

All patients are evaluable for disease response unless they discontinue treatment prior to completion of Cycle 2 and have not had any disease assessment.

Brain MRI with and without contrast (or CT head with and without contrast if participants cannot get MRI) will be obtained every 2 cycles to assess disease response. A baseline image should be obtained within 4 weeks prior to initiation of study treatment.

5.3 General Concomitant Medication and Supportive Care Guidelines

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

Patients are prohibited from receiving the following therapies while in screening for and enrolled in this trial:

- Investigational agents other than retifanlimab and epacadostat
- Any anticancer medications, including chemotherapy or biologic therapy other than the study medications. Note: denosumab is permitted.
- Radiation therapy beyond what is described in this protocol (note: radiation therapy to a symptomatic solitary lesion or to the brain may be allowed at the investigator's discretion)

- Oncologic surgery for tumor control
- Administration of live attenuated vaccines within 30 days prior to the first dose of treatment and while participating in the trial. Examples of live vaccines include, but are not limited to, the following: measles, mumps, rubella, chicken pox, yellow fever, rabies, BCG, and typhoid vaccine. Seasonal influenza vaccines for injection are generally killed virus vaccines and are allowed; however, intranasal influenza vaccines (eg, FluMist®) are live attenuated vaccines and are not allowed.
- If a patient is enrolled to Regimen B, then the use of the anticonvulsant carbamazepine (a UGT1A9 inducer) is discouraged. Because there is a potential interaction that could result in lower epacadostat exposures, an alternative to carbamazepine should be used, if possible.
- Warfarin
- If a patient is enrolled to Regimen B, then any MAOI or drug associated with significant MAOI activity agents is prohibited from 21 days prior Day 1 through 2 weeks after the final dose of epacadostat. This includes, but is not limited to, hydrazines (example phenelzine), meperidine, caroxazone, linezolid, echinopsidine, methylene blue, furazolidone, tranylcypromine, brofaromine, metralindole, minaprine, moclobemide, pirlindole, toloxatone, lazabemide, pargyline, rasagiline, selegiline.
- If a patient is enrolled to Regimen B, then the use of any UGT1A9 inhibitor, including acitretin, amitriptyline, androsterone, cyclosporine, dasatinib, diclofenac, diflunisal, efavirenz, erlotinib, flutamide, gefitinib, gemfibrozil, glycyrrhetinic acid glycyrrhizin, imatinib, imipramine, ketoconazole (systemic), linoleic acid supplements, mefenamic acid, mycophenolic acid, niflumic acid, nilotinib, phenobarbital, phenylbutazone, phenytoin, probenecid, quinidine, ritonavir, sorafenib, sulfinpyrazone, valproic acid, and verapamil is prohibited.
- If a patient is enrolled to Regimen B, then the use of probiotics is prohibited.

Patients who, in the assessment by the investigator, require the use of any of the aforementioned treatments for clinical management should be removed from the trial.

5.3.1 **Procedure for Subjects Exhibiting Serotonin Syndrome**

There is a rare chance that epacadostat could cause an increase in serotonin levels in the brain that might trigger serotonin syndrome (SS) [25], when administered in combination with other serotonergic agents. The clinical manifestations of SS range from barely perceptible to lethal; onset is rapid (within 12 hours of drug[s] administration). Selective serotonin reuptake inhibitors (SSRIs), selective serotonin/norepinephrine reuptake inhibitors (SNRIs), and MAOIs are permitted in the study. Due to the results of the preclinical study specifically evaluating the effect of epacadostat on the brain ECF concentrations of serotonin with linezolid described above by Zhang et al (54), and the clinical experience with related medications (eg., SSRIs/SNRIs) that suggest that SS is low risk, the use of MAOIs is not prohibited in the current study.

Serotonin syndrome usually manifests with autonomic changes, mental status changes, and neurological findings. These mild, moderate, and severe signs and symptoms of SS (summarized in the table below) should be evaluated in the context of possible comorbid conditions as well. Due to its uniqueness, a neurology consult is strongly recommended to diagnose or confirm serotonin syndrome or to rule out other etiologies.

The following procedures will be implemented if participants exhibit the signs/symptoms of SS, including tremor; hyperreflexia; spontaneous, ocular, or inducible clonus; together with agitation, fever, diaphoresis, or muscle rigidity:

- Immediately interrupt study treatment (defined as retifanlimab +/- epacadostat).
- Immediately interrupt any SSRI, SNRI or MAOI administration.
- Provide appropriate medical management of the participant until all signs/symptoms are resolved (eg, IV fluids and/or sympathomimetic amines for hypotension, benzodiazepines for agitation, administration of 5-hydroxytryptamine antagonists such as cyproheptadine).
- If participant chooses to remain in the study, restart study treatment after the SSRI, SNRI or MAOI has been discontinued, no sooner than 5 half-lives have elapsed for the specific SSRI or SNRI in question, and after resolution of signs/symptoms of SS. The SSRI or SNRI dosing MAY NOT be restarted.
- If participant chooses to withdraw from the study, or must restart treatment with SSRI, SNRI, or MAOI the participant should be scheduled for a Follow-up Visit. Treatment with SSRI, SNRI or MAOI may be initiated 2 weeks after resolution of signs and symptoms of SS.
- If a participant had experienced moderate or severe unconfounded SS in the opinion of the investigator, without concomitant SSRI, SNRI or MAOI usage, or serotonergic concomitant medications, only non epacadostat study administration may be resumed; epacadostat treatment should be permanently discontinued.

Signs and Symptoms of Serotonin Syndrome

Seriousness	Autonomic signs	Neurological signs	Mental status	Other
Mild	Afebrile or low-grade fever Tachycardia Mydriasis Diaphoresis or shivering	Intermittent tremor Akathisia Myoclonus Mild hyperreflexia	Restlessness Anxiety	
Moderate	Increased tachycardia Fever (up to 41°C) Diarrhea with hyperactive bowel sounds	Hyperreflexia Inducible clonus Ocular clonus (slow continuous lateral eye movements) Myoclonus	Easily startled Increased confusion Agitation and hypervigilance	Rhabdomyolysis Metabolic acidosis Renal failure Disseminated intravascular coagulopathy

	Diaphoresis with normal skin color			(secondary to hyperthermia)
Severe	Temperature often more than 41 °C (Secondary to increased tone)	Increased muscle tone (lower limb > upper) Spontaneous clonus Substantial myoclonus or hyperreflexia	Delirium Coma	As above

Source: [Boyer, E. W. 2005 (25)]

5.3.1 Guidelines for Management of Suspected Infusion Reactions

Grade	Description[a]	Treatment	Subsequent Infusions
1	Mild reaction; infusion interruption not indicated; intervention not indicated.	Monitor vital signs closely until medically stable.	Premedication with acetaminophen/paracetamol and a histamine blocker should be considered for participants who have had previous systemic reactions to protein product infusions or when recommended by institutional policy.
2	Requires infusion interruption but responds promptly to symptomatic treatment (eg, antihistamines, NSAIDS, narcotics, IV fluids); prophylactic medications indicated for ≤ 24 hours.	**First occurrence:** Stop infusion and initiate appropriate medical measures (eg, IV fluids, antihistamines NSAIDS, acetaminophen/paracetamol, narcotics, per institutional preferences). Monitor vital signs until medically stable. If symptoms resolve within 1 hour, infusion may be resumed at 50% of the original infusion rate. **Subsequent occurrences (after recommended prophylaxis):** Permanently discontinue study treatment.	Premedicate at least 30 minutes before infusion with antihistamines (eg, diphenhydramine 50 mg PO) and acetaminophen/ paracetamol (500-1000 mg PO). Additional supportive measures may be acceptable (per institutional preference) but should be discussed with medical monitor. Next infusion should start at 50% of the original infusion rate. If no reaction, rate of infusion can be increase by 25% every 15 minutes until a rate of 100% has been reached. Subsequent infusions can begin at 100%.
3 or 4	**Grade 3:** 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.	Stop infusion and initiate appropriate medical therapy (eg, IV fluids, antihistamines NSAIDS, acetaminophen/ paracetamol, narcotics, oxygen, pressors, epinephrine, corticosteroids, per institutional preferences). Monitor vital signs frequently until medically stable. Hospitalization may be indicated.	Permanently discontinue study treatment.

[a] Per NCI CTCAE v5.0, appropriate resuscitation equipment should be available at the bedside and a physician readily available during the period of study treatment administration.

5.4 Women of Childbearing Potential

Women of childbearing potential (defined as women with regular menses, women with amenorrhea, women with irregular cycles, women using a contraceptive method that precludes withdrawal bleeding, or women who have had a tubal ligation) are required to have a negative serum pregnancy test within 14 days prior to the first dose of the study treatment.

Female and male patients (along with their female partners) are required to use a highly effective contraception, including one barrier method, during participation in the study and for 4 months following the last dose of study treatment.

If a patient is suspected to be pregnant, study treatment should be immediately discontinued. In addition, a positive urine test must be confirmed by a serum pregnancy test. If it is confirmed that the patient is not pregnant, the patient may resume treatment.

If a female patient or female partner of a male patient becomes pregnant during therapy or within 4 months after the last dose of study treatment, the investigator must be notified in order to facilitate outcome follow-up.

5.5 Duration of Therapy

5.5.1 Treatment Duration

If at any time the constraints of this protocol are considered to be detrimental to the patient's health and/or the patient no longer wishes to continue protocol therapy, the protocol therapy should be discontinued and the reason(s) for discontinuation documented in the case report forms.

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

- Documented and confirmed disease progression (subjects in Regimen B may continue on study treatment after demonstrating progression if they are deriving clinical benefit in the opinion the treating MD)
- Death
- Adverse event(s) that, in the judgment of the investigator, may cause severe or permanent harm or which rule out continuation of study drug
- General or specific changes in the patient's condition render the patient unable to receive further treatment in the judgment of the investigator
- Suspected pregnancy
- Serious noncompliance with the study protocol
- Lost to follow-up
- Patient withdraws consent
- Investigator removes the patient from study
- The Siteman Cancer Center decides to close the study

Treatment may continue for a maximum of two years if none of the criteria listed above are met. Patients who prematurely discontinue treatment for any reason will be followed as indicated in the study calendar.

5.5.2 Treatment Beyond Progression

Subjects on regimen B may continue on study after demonstrating progression as long as they are deriving clinical benefit in the opinion of the treating physician

provided the following criteria are met

- Participant signs the treatment beyond progression consent
- The Washington University PI is notified

Participants who remain on treatment after disease progression will follow all procedures as described in section 10.0

The subject who remain on despite progression will be removed from study treatment when any of the below criteria are met:

- Persistent progression per iRANO criteria on imaging 6 months after the initial scans showing progressive disease
- Clinical decline with KPS <60 for greater than 2 months
- Persistent increased dexamethasone use for 2 months (>100% baseline use)
- Patient is no longer deriving clinical benefit in the opinion of treating physician
- Patient has completed 2 years of treatment
- Any criteria described in section 5.5.1 are met

5.6 Duration of Follow-up

After coming off treatment, patients will return for a 30-day follow-up visit preferably in person but a telephone or video visit is acceptable if a patient's functional status precludes an in-person visit, with an extended safety follow-up at 90 days after last retifanlimab administration (which may be performed via a site visit or via a telephone or video call with subsequent site visit required if any concerns are noted during the call). They will then be followed, when study treatment is completed, for 2 years or until death, whichever occurs first. Follow-up will take place as per routine care, and data on progression and survival will be collected when 2 years has elapsed. Patients removed from study for unacceptable adverse events will be followed until resolution or stabilization of the adverse event.

6.0 DOSE DELAYS/DOSE MODIFICATIONS

Please note that if a patient must discontinue retifanlimab (for patients in Regimen A) or both retifanlimab and epacadostat (for patients in Regimen B), s/he must be removed from study (but may continue bevacizumab off study). Otherwise, if any single drug must be discontinued, the patient may remain on study and continue treatment. In some circumstances, it may be necessary to temporarily interrupt both study treatments as a result of AEs that may have an unclear relationship to study drug. If an interruption is necessary, treatment holds and modifications may be made at the discretion of the PI and/or treating physician.

6.1 Dose Holds for Epacadostat

Any interruptions of > 2 weeks or for LFT abnormalities must be discussed with the medical monitor before resuming treatment. Treatment with both study drugs should be withheld for drug-related Grade 4 hematologic toxicities, non-hematological toxicity ≥ Grade 3 (including laboratory abnormalities), and severe or life-threatening AEs.

Epacadostat will be administered as a flat dose of 400 mg BID. Epacadostat may be held and restarted at the same dose level provided that fewer than 22 days have elapsed since start of dose hold. Patients unable to tolerate this flat dose or unable to restart at the same dose level after 21 days on 400 mg BID dosing will discontinue epacadostat but may remain on retifanlimab monotherapy.

Dosing interruptions may be permitted in the case of medical/surgical events or logistical reasons not related to study therapy (eg, elective surgery, unrelated medical events, subject vacation, and/or holidays). The reason for interruption should be documented in the subject's study record.

6.2 Procedures for Participants Exhibiting Immune-Related Adverse Events

Adverse events of a potential immunologic etiology, or irAEs, may be defined as AEs of unknown etiology, associated with drug exposure and consistent with an immune phenomenon. Immune-related AEs may be predicted based on the nature of the compounds, their mechanism of action, and reported experience with immunotherapies that have a similar mechanism of action. Special attention should be paid to AEs that may be suggestive of potential irAEs. An irAE can occur shortly after the first dose or several months after the last dose of treatment.

If an irAE is suspected, efforts should be made to rule out neoplastic, infectious, metabolic, toxin or other etiologic causes before labeling an AE as an irAE.

Recommendations for management of specific immune-mediated AEs known to be associated with other PD-1 inhibitors (eg, pembrolizumab, nivolumab) are detailed in the table below. Algorithms for evaluation of selected immune toxicities that have previously been attributed to PD-1 inhibitors and management guidelines for irAEs not detailed elsewhere in the protocol should follow the ASCO or ESMO Clinical Practice Guidelines (56, 57).

Immune-Related Adverse Event	Toxicity Grade or Conditions (CTCAE v5.0)	Action Taken With retifanlimab and Epacadostat	AE Management With Corticosteroid and/or Other Supportive Care Therapies
Pneumonitis	Grade 1	No action.	None.
	Grade 2	Withhold until ≤ Grade 1.	• Administer systemic corticosteroids per local practice followed by taper. • Evaluate participants with suspected pneumonitis with radiographic imaging and initiate corticosteroid treatment. • Add prophylactic antibiotics for opportunistic infections.
	Grades 3 or 4, or recurrent Grade 2	Permanently discontinue.	
Diarrhea/colitis	Grade 1	No action.	None.
	Grades 2 or 3	Withhold until ≤ Grade 1.	• Consider prompt initiation of standard anti-diarrheal agents. • Administer systemic corticosteroids per local practice followed by taper. • Consider prophylactic antibiotics per local practice. • Consider gastrointestinal consultation and performing endoscopy to rule out colitis.
	Grade 4 or recurrent Grade 3	Permanently discontinue.	
AST/ALT elevation and/or increased bilirubin/Hepatitis	Grade 1	No action.	None.
	Grade 2	Withhold until ≤ Grade 1.	• Administer systemic corticosteroids per local practice followed by taper. • Consider monitoring liver enzymes weekly (or more frequently) until liver enzyme value returns to baseline or is stable.
	Grade 3 or 4, or in participants with liver metastasis with baseline Grade 2 elevation of AST or ALT, hepatitis with AST or ALT increases ≥ 50% and lasts ≥ 1 week	Permanently discontinue.	
Endocrinopathies Type 1 diabetes mellitus Hyperglycemia Hyperthyroidism Hypothyroidism Hypophysitis Adrenal insufficiency	Grades 1 and 2	No action.	None.
	Grades 3 and 4 hyperthyroidism	No action.	For hypothyroidism, initiate thyroid replacement hormones (eg, levothyroxine or liothyronine) per standard of care.
	Grades 3 or 4	Withhold until ≤ Grade 1. May restart retifanlimab if endocrinopathy has improved to ≤ Grade 2 and is controlled with hormone replacement, if indicated, and steroid taper is complete.	• For Type 1 diabetes mellitus, initiate insulin replacement therapy. • For hyperglycemia, administer antihyperglycemic. • For hyperthyroidism, treat with nonselective beta-blockers (eg, propranolol) or thionamides as appropriate. • For hypophysitis or adrenal insufficiency, administer corticosteroids and initiate hormonal replacements as clinically indicated.
Nephritis and renal dysfunction	Grade 1	No action.	None.
	Grade 2	Withhold until ≤ Grade 1.	Administer corticosteroids per local practice followed by taper.
	Grade 3 or 4	Permanently discontinue.	

Immune-Related Adverse Event	**Toxicity Grade or Conditions (CTCAE v5.0)**	**Action Taken With** retifanlimab **and Epacadostat**	**AE Management With Corticosteroid and/or Other Supportive Care Therapies**
Rash	Grade 1	No action.	None.
	Grade 2	No action.	Manage with topical steroids with or without drug interruption.
	Grade 3[i)] or persistent Grade 2 (≥ 2 weeks) or suspected Stevens-Johnson syndrome or toxic epidermal necrolysis	Withhold until ≤ Grade 1.	Administer corticosteroids per local practice followed by taper.
	Grade 4 or confirmed Stevens-Johnson syndrome or toxic epidermal necrolysis	Permanently discontinue.	
Myocarditis	Grade 2	Withhold until ≤ Grade 1.	• Treatment with systemic corticosteroids should be initiated (initial dose of 1-2 mg/kg per day of prednisone or equivalent). Taper as appropriate. • Management of cardiac symptoms according to standard of care and with guidance from cardiology. Consider cardiac MRI and myocardial biopsy for diagnosis.
	Grades 3 or 4	Permanently discontinue.	
All other irAEs	Grade 3 or intolerable/ persistent Grade 2	Withhold until ≤ Grade 1.	Based on severity of AE, administer corticosteroids.
	Recurrent Grade 3	Consider discontinuation.	
	Grade 4	Permanently discontinue.	

6.3 Dose Modifications for Bevacizumab

There are no recommended dose reductions. Discontinue bevacizumab for:

- Gastrointestinal perforations, fistula formation in the gastrointestinal tract, intra-abdominal abscess, fistula formation involving an internal organ
- Wound dehiscence and wound healing complications requiring medical intervention
- Serious hemorrhage (i.e., requiring medical intervention)
- Severe arterial thromboembolic events
- Live-threatening (grade 4) venous thromboembolic events, including pulmonary embolism
- Hypertensive crisis or hypertensive encephalopathy
- Posterior Reversible Encephalopathy Syndrome (PRES)
- Nephrotic syndrome

Temporarily suspend bevacizumab for:

- At least 4 weeks prior to elective major surgery
- Severe hypertension not controlled with medical management
- Severe proteinuria
- Severe infusion reactions

6.4 Dose Modifications for Radiation Therapy

There are no protocol-mandated radiation therapy dose modifications. Dosing may be adjusted at the discretion of the treating radiation oncologist.

7.0 REGULATORY AND REPORTING REQUIREMENTS

The entities providing oversight of safety and compliance with the protocol require reporting as outlined below. Please refer to Appendix D for definitions and Appendix E for a grid of reporting timelines.

Adverse events will be tracked from time of consent through 90 days following the last day of treatment. All adverse events must be recorded on the toxicity tracking case report form (CRF) with the exception of:

- Baseline adverse events, which shall be recorded on the medical history CRF

Refer to the data submission schedule in Section 11 for instructions on the collection of AEs in the EDC.

Reporting requirements for Washington University study team may be found in Section 7.1. Reporting requirements for secondary site study teams participating in Washington University-coordinated research may be found in Section 7.2.

7.1 Sponsor-Investigator Reporting Requirements

7.1.1 Reporting to the Human Research Protection Office (HRPO) at Washington University

Reporting will be conducted in accordance with Washington University IRB Policies.

Pre-approval of all protocol exceptions must be obtained prior to implementing the change.

7.1.2 Reporting to the Quality Assurance and Safety Monitoring Committee (QASMC) at Washington University

The Washington University Sponsor-Investigator (or designee) is required to notify the QASMC of any unanticipated problems involving risks to participants or others occurring at WU or any BJH or SLCH institution that has been reported to and acknowledged by HRPO. (Unanticipated problems reported to HRPO and withdrawn during the review process need not be reported to QASMC.)

QASMC must be notified within **10 days** of receipt of IRB acknowledgment via email to qasmc@wustl.edu. Submission to QASMC must include the myIRB form and any supporting documentation sent with the form.

For events that occur at secondary sites, the Washington University Sponsor Investigator (or designee) is required to notify the QASMC within 10 days of Washington University notification via email to qasmc@wustl.edu. Submission to QASMC must include either the myIRB form and supporting documentation or (if not submitted to myIRB) the date of occurrence, description of the event, whether the event is described in the currently IRB approved materials, the event outcome, determination of relatedness, whether currently enrolled participants will be notified, and whether the informed consent document and/or any study procedures will be modified as a result of this event.

7.1.3 Reporting to Incyte

The Principal Investigator (PI) must report all Serious Adverse Events (SAEs) to Incyte within 24 hours of learning of an event, regardless of the PI's causality assessment. This notification should be provided on a completed Serious Adverse Event (SAE) form. SAE reporting for each subject begins the day the informed consent is signed by the patient and within 90 days after subject has completed or discontinued from the study or has taken last dose of the study drug, or as described in the protocol.

SAEs, occurring using Incyte study drug, are reported in accordance with the effective protocol. SAEs occurring with any other commercial drug are reported to

the manufacturer of that drug in accordance with regulations and protocol.

Initial SAEs and/or subsequent follow-up reports should be reported via email to SafetyReporting@Incyte.com or fax (+) 1-866-981-2057. SAE reports should be for a single subject. SAE forms should be sent with a cover sheet and any additional attachments.

All adverse event information is reported to Incyte on the Principal Investigator's/Institution's Adverse Event Report Form, or a CIOMS-I or MedWatch Form FDA 3500A, or on an Adverse Event Report Form which may be provided by Incyte upon request. The Principal Investigator does not provide medical records (e.g., discharge summary) to Incyte, unless specifically requested.

7.1.3.1 Reporting Pregnancy

An "Initial Pregnancy Report" or equivalent must be completed in full and emailed to SafetyReporting@Incyte.com or faxed to (+) 1-866-981-2057 within 24 hours of discovery of a pregnancy of a subject who has taken the Incyte product or the pregnancy of a partner for a subject who has taken the Incyte product. The "Follow-up Pregnancy Report Form" or equivalent must be completed and emailed to SafetyReporting@Incyte.com or faxed to (+) 1-866-981-2057 within 30 days after delivery, so that Incyte is provided with information regarding the outcome of the pregnancy. If the pregnancy results in any events which meet the serious criteria (i.e., miscarriage or termination), the SAE reporting process needs to be followed and the timelines associated with a SAE should be followed.

7.1.4 Reporting to the FDA

The conduct of the study will comply with all FDA safety reporting requirements. **PLEASE NOTE THAT REPORTING REQUIREMENTS FOR THE FDA DIFFER FROM REPORTING REQUIREMENTS FOR HRPO/QASMC.** It is the responsibility of the Washington University Sponsor-Investigator to report to the FDA as follows:

- Report any unexpected fatal or life-threatening suspected adverse reaction (refer to Appendix D for definitions) no later than **7 calendar days** after initial receipt of the information.
- Report a suspected adverse reaction that is both serious and unexpected (SUSAR, refer to Appendix D) no later than **15 calendar days** after it is determined that the information qualifies for reporting. Report an adverse event (refer to Appendix D) as a suspected adverse reaction only if there is evidence to suggest a causal relationship between the drug and the adverse event, such as:
    - A single occurrence of an event that is uncommon and known to be strongly associated with drug exposure

    - One or more occurrences of an event that is not commonly associated with drug exposure but is otherwise uncommon in the population exposed to the drug
    - An aggregate analysis of specific events observed in a clinical trial that indicates those events occur more frequently in the drug treatment group than in a concurrent or historical control group
- Report any findings from epidemiological studies, pooled analysis of multiple studies, or clinical studies that suggest a significant risk in humans exposed to the drug no later than **15 calendar days** after it is determined that the information qualifies for reporting.
- Report any findings from animal or in vitro testing that suggest significant risk in humans exposed to the drug no later than **15 calendar days** after it is determined that the information qualifies for reporting.
- Report any clinically important increase in the rate of a serious suspected adverse reaction of that listed in the protocol or IB within **15 calendar days** after it is determined that the information qualifies for reporting.

Submit each report as an IND safety report in a narrative format or on FDA Form 3500A or in an electronic format that FDA can process, review, and archive. Study teams must notify the Siteman Cancer Center Protocol Development team of each potentially reportable event within 1 business day after initial receipt of the information, and must bring the signed 1571 and FDA Form 3500A to the Siteman Cancer Center Protocol Development team no later than 1 business day prior to the due date for reporting to the FDA.

Each notification to FDA must bear prominent identification of its contents ("IND Safety Report") and must be transmitted to the review division in the Center for Drug Evaluation and Research (CDER) or in the Center for Biologics Evaluation and Research (CBER) that has responsibility for review of the IND. Relevant follow-up information to an IND safety report must be submitted as soon as the information is available and must be identified as such ("Follow-up IND Safety Report").

7.1.5 Reporting to Secondary Sites

The Washington University Sponsor-Investigator (or designee) will notify the research team at each secondary site of all unanticipated problems involving risks to participants or others that have occurred at other sites within **10 working days** of the occurrence of the event or notification of the Sponsor-Investigator (or designee) of the event. This includes events that take place both at Washington University and at other secondary sites, if applicable. Refer to Section 16.0 (Multicenter Management) for more information.

7.2 Secondary Site Reporting Requirements

The research team at each secondary site is required to promptly notify the Washington

University Sponsor-Investigator and designee of all serious adverse events (refer to Appendix D, Section D) within **1 working day** of the occurrence of the event or notification of the secondary site's PI of the event. This notification may take place via email if there is not yet enough information for a formal written report (using FDA Form 3500a (MedWatch) and Washington University's cover sheet (Appendix F)). A formal written report must be sent to the Washington University Sponsor-Investigator and designee within **4 calendar days** (for fatal or life-threatening suspected adverse reactions) or **11 calendar** days (for serious unexpected adverse reactions) of the occurrence of the event or notification of the secondary site's PI of the event.

The research team at a secondary site is responsible for following its site's guidelines for reporting applicable events to its site's IRB according to its own institutional guidelines. The research team at Washington University is responsible for reporting all applicable events to the FDA and Incyte as needed.

Washington University pre-approval of all protocol exceptions must be obtained prior to implementing the change. Local IRB approval must be obtained as per local guidelines. Washington University IRB approval is not required for protocol exceptions occurring at secondary sites.

7.3 Exceptions to Expedited Reporting

Events that do not require expedited reporting as described in Section 7.1 include:

- planned hospitalizations
- hospitalizations < 24 hours
- respite care
- events related to disease progression

Events that do not require expedited reporting must still be captured in the EDC.

8.0 PHARMACEUTICAL INFORMATION

8.1 Epacadostat

8.1.1 Epacadostat Description

Epacadostat is an inhibitor of the enzyme indoleamine 2,3-dioxygenase 1 (IDO1) that is proposed for development for the treatment of malignant diseases. Its chemical name is (***Z***)-*N*-(3-bromo-4-fluorphenyl)-*N'*-hydroxy-4-(2-(sulfamoylamino)ethylamino)-1,2,5-oxadiazole-3-carboximidamide. It has a molecular formula of $C_{11}H_{13}BrFN_7O_4S$ and a molecular weight of 438.23.

8.1.2 Clinical Pharmacology

Epacadostat represents a novel, potent, and selective inhibitor of the enzyme

indoleamine 2,3-dioxygenase 1 (IDO1) in both human tumor cells and human dendritic cells (DCs).

8.1.3 Pharmacokinetics and Drug Metabolism

After oral dose administration in the fasted state, the peak plasma concentration of epacadostat was typically attained at 2 hours post-dose. Epacadostat was eliminated with a geometric mean terminal disposition half-life of 2.9 hours.

Systemic accumulation after BID administration increased the mean epacadostat Cmax and AUC0-t by 16% and 33%, respectively, suggesting an effective half-life of 4 to 6 hours.

8.1.4 Supplier(s)

Epacadostat will be supplied by Incyte.

8.1.5 Dosage Form and Preparation

Epacadostat is available as 100mg tablets or 300 mg tablets packaged in high-density polyethylene bottles.

8.1.6 Storage and Stability

Epacadostat drug product should be stored at ambient conditions (59°F-86°F).

8.1.7 Administration

Refer to Section 5.1.

8.2 Retifanlimab

8.2.1 Retifanlimab Description

Retifanlimab is a humanized, hinge-stabilized, IgG4κ monoclonal antibody that recognizes human PD-1. Retifanlimab contains a human IgG4 Fc domain to limit effector function while retaining neonatal Fc receptor binding to extend circulating half-life. Retifanlimab is designed to target PD-1–expressing cells, including T cells, and to sustain/restore their effector function by blocking checkpoint inhibitory interactions between PD-1 and its 2 ligands, PD-L1 and PD-L2.

8.2.2 Clinical Pharmacology

Consistent with its intended mechanism of action and functional properties, retifanlimab has been shown to inhibit the binding of PD L1 and PD L2 to PD-1, to disrupt the PD-1/PD-L1 inhibitory axis, and to enhance IFN γ secretion in SEB-

stimulated human PBMCs with activity comparable to pembrolizumab and nivolumab replicas.

8.2.3 Supplier

Retifanlimab will be supplied by Incyte.

8.2.4 Dosage Form and Preparation

Retifanlimab will be provided in a glass vial for single use. Each vial will be labeled as required per country requirement.

8.2.5 Storage and Stability

Retifanlimab drug product must be stored at 2°C to 8°C until use. It must be stored upright and protected from light.

8.2.6 Administration

Refer to Section 5.1.

8.3 Bevacizumab (Avastin)

8.3.1 Bevacizumab Description

Bevacizumab is a recombinant humanized monoclonal IgG1 antibody that binds to and inhibits the biologic activity of human vascular endothelial growth factor (VEGF) in in vitro and in vivo assay systems. It as an approximate molecular weight of 149 kD. It is produced in a mammalian cell (Chinese Hamster Ovary) expression system in a nutrient medium containing the antibiotic gentamicin.

8.3.2 Clinical Pharmacology

Bevacizumab binds VEGF and prevents the interaction of VEGF to its receptors (Flt-1 and KDR) on the surface of endothelial cells. The interaction of VEGF with its receptors leads to endothelial cell proliferation and new blood vessel formation in in vitro models of angiogenesis. Administration of bevacizumab to xenotransplant models of colon cancer in nude (athymic) mice caused reduction of microvascular growth and inhibition of metastatic disease progression.

8.3.3 Pharmacokinetics and Drug Metabolism

The pharmacokinetic profile of bevacizumab was assessed using an assay that measures total serum bevacizumab concentrations. Based on a population pharmacokinetic analysis of 491 patients who received 1 to 20 mg/kg of bevacizumab weekly every 2 or every 3 weeks, the estimated half-life of

bevacizumab was approximately 20 days. The predicted time to reach steady state was 100 days.

The clearance of bevacizumab varied by body weight, gender, and tumor burden.

8.3.4 **Supplier(s)**

Bevacizumab is commercially available.

8.3.5 **Dosage Form and Preparation**

Bevacizumab is a clear to slightly opalescent, colorless to pale brown, sterile, pH 6.2 solution for intravenous infusion. It is supplied in 100 mg and 400 mg preservative-free, single-use vials to deliver 4 mL or 16 mL of bevacizumab (25 mg/mL).

8.3.6 **Storage and Stability**

Bevacizumab vials are stable at 2-8ºC. They should be protected from light. Do not freeze or shake. Diluted bevacizumab solutions may be stored at 2-8ºC for up to 8 hours. Store in the original carton until time of use.

8.3.7 **Administration**

Do not administer as an IV push or bolus. Administer only as an IV infusion. The first infusion should be administered over 90 minutes. The second infusion may be administered over 60 minutes if the first infusion is tolerated; all subsequent infusions over 30 minutes if the 60-minute infusion is tolerated.

For this study, bevacizumab should be administered at a dose of 10 mg/kg on Days 1 and 15 of each 28-day cycle.

Please note that biosimilars are permitted for bevacizumab (Avastin).

8.3.8 **Special Handling Instructions**

None.

9.0 CORRELATIVE STUDIES

9.1 Peripheral Blood for PBMCs

9.1.1 **Collection of Specimens**

A total of 40 mL of blood will be collected in 5 cellular preparation tubes (8 mL

each) containing sodium heparin (CPTs) or 4 ethylenediamine tetraacetic acid (EDTA) tubes (10 mL each) for isolation of PBMCs at each of the following time points (NOTE-: +/- 7 days are allowed):

- Baseline (prior to administration of any study treatment)
- Before initiation of RT (up to 7 days prior to start of RT; may be on the same day as RT before RT treatment)
- At the end of RT and/or Cycle 2 Day 1 prior to administration of retifanlimab with or without epacadostat (end of RT will typically correspond with C2D1, but if it doesn't, either or both of these time points may be captured on a +/- 7 day window)
- Cycle 3 Day 1 prior to administration of retifanlimab with or without epacadostat(+/- 7 days).
- Cycle 5 Day 1 prior to administration of retifanlimab with or without epacadostat (+/- 7 days).
- Time of disease progression.

Additionally, ~3-10mL of plasma will be saved along with PBMC collection.

9.1.2 Handling of Specimens

Cellular preparation tubes (CPTs) can be purchased from BD Biosciences. A total of 40 mL of blood will be collected in CPTs or EDTAs and PBMCs will be collected by centrifugation per each site's standard protocol. PBMC and plasma will be saved in -80°C or liquid nitrogen for immunologic studies.

9.1.3 Shipping and Storage of Specimens

Blood samples collected at CAM should be transported at room temperature to either the Siteman Cancer Center's Tissue Procurement Core (located on the 5th floor of the BJCIH) or Dr. Matthew Ciorba's lab (located on the 10th floor of the CSRB-North Tower Annex Room 1021) at ambient temperature immediately after collection and processed immediately upon arrival.

Coded samples may be distributed from the Tissue Procurement Core and mailed to Dr. Timothy Garrett's lab at the University of Florida for processing key correlative analyses such as calculation of study specified kynurenine to tryptophan (K/T) ratio.

Blood samples that are collected at secondary sites will be transported to the site's local processing lab at ambient temperature immediately after collection and processed immediately upon arrival. At the conclusion of the study, all samples collected at the secondary site will be batch shipped to Washington University in St. Louis for final analysis. This final analysis will be performed in Dr. Matthew Ciorba's lab.

NOTE: After analysis are performed at Dr. Matthew Ciorba's Lab, selected

remaining study samples could be saved at the Siteman Cancer Center's Tissue Procurement Core (located on the 5th floor of the BJCIH) for future studies.

9.2 Peripheral Blood for Serum

9.2.1 Collection of Specimens

A total of 5 mL of blood will be collected in one red-top tube at each of the following time points:

- Baseline (up to 7 days prior to administration of any study treatment)
- Before initiation of RT (up to 7 days prior to start of RT; may be on the same day as RT before RT treatment)
- At the end of RT and/or Cycle 2 Day 1 prior to administration of retifanlimab with or without epacadostat (end of RT will typically correspond with C2D1, but if it doesn't, either or both of these time points may be captured on a +/- 7 day window)
- Cycle 3 Day 1 prior to administration of retifanlimab with or without epacadostat (+/- 7 days)
- Time of disease progression

9.2.2 Handling of Specimens

Serum will be collected via centrifugation per standard protocol. Serum will be saved in -80°C refrigerator for biomarker assays.

9.2.3 Shipping and Storage of Specimens

Samples should be stored and shipped as described in Section 9.1.3.

9.3 Tumor Tissue – Optional

9.3.1 Collection of Specimen

Any tissue (from either surgical debulking or biopsy or MLA/biopsy) available after histopathologic diagnosis of glioma will be collected for correlated studies as follows:

- Flash frozen for DNA and RNA isolation
- Fixed and embedded in paraffin for IHC
- Acutely dissociated to generate patients' primary glioma cell lines and tumor infiltrating lymphocyte cultures if adequate tissue is available.

The amount of tissue saved will be variable depending on how much is removed at the time of the standard of care procedure and how much is left over after pathology. Tissue need not be requested right away.

For patients who have a post-treatment biopsy or surgery as part of their clinical care, any tissue available for research use after it has been evaluated by pathology will be requested for this study.

9.3.2 Handling of Specimen

Tissue cryopreservation and paraffin embedding are per standard protocol. One half of the tissue will be equally divided into 2 parts: one part will be flash frozen, and the other part will be fixed and embedded in paraffin (FFPE). FFPE samples will be batch shipped to a designated laboratory (TBD) for PD-L1 IHC.

Flash frozen samples will be taken to the TPC and then sent to Matthew Ciorba's lab for RNA isolation. mRNA expressions of the biomarkers will be tested.

9.3.3 Shipping and Storage of Specimen

Brain tumor samples collected at WU should be placed in a buffered solution (e.g. PBS, a tissue culture media), transported to the Siteman Cancer Center Tissue Procurement Core at ambient temperature, and processed immediately upon arrival.

Tissue samples that are collected at secondary sites should be placed in a buffered solution (e.g. PBS, a tissue culture media) and transported to the site's local processing lab at ambient temperature after collection and processed immediately upon arrival. At the conclusion of the study, all samples collected at the secondary site will be batch shipped to Washington University in St. Louis for final analysis.

10.0 STUDY CALENDAR

Screening/baseline evaluations are to be conducted within 2 weeks prior to Day 1 of treatment. Scans must be done no more than 4 weeks prior to the start of the protocol therapy. Each cycle is 28 days. There is a +/- 7 day window for all assessments/dosing.

	Screening	**Baseline**	**Before start of RT**	**End of RT**	**Day 1 of each cycle**	**Day 15 of each cycle**	**End of every even-numbered cycle (Eg. before C3D1, C5D1, etc.)**	**End of treatment**	**Follow-up[2]**
Informed consent	X[14]								
H&P, KPS, BP, wt	X				X			X	
NANO	X						X[13]	X	
CBC	X				X	X		X	X[7]
CMP	X				X	X		X	X[7]
PT, PTT, INR	X								
Free T4 and TSH	X				X[6]				
Urine β-hCG[1]	X								
Hepatitis B and C testing	X								
UA Macro reflex to Micro	X				X	X			
Brain MRI[15]	X						X	X	
ECG[12]	X								
RT					10 fx during C1				
Epacadostat[8,9]					twice daily				
Retifanlimab[9]					X				
Bevacizumab[9]					X	X			
Blood for PBMCs		X	X	X	X[3]			X[3]	
Blood for serum		X	X	X[10]	X[11]			X[3]	
Research tissue		X ---------- X[5]						X[5]	
AE assessment		X---------- X[4]							
Survival									X

1. Women of childbearing potential only
2. Every 2 months for 2 years
3. C3D1, C5D1, time of progression
4. For 90 days after last day of treatment; the extended safety follow-up beyond 30 days after last retifanlimab administration may be performed via a site visit or via a telephone call with subsequent site visit required if any concerns are noted during the call
5. Any tissue from surgical debulking, biopsy, or MLA/biopsy available after pathology will be collected. If a post-treatment surgical procedure is performed as part of the patient's clinical care, available tissue will be requested for research purposes as well.

6. To be performed every 8 weeks (Day 1 of every odd-numbered cycle)
7. At 30-day follow-up only
8. Regimen B patients only
    9. Treatment with retifanlimab and bevacizumab (and epacadostat, if applicable) will start 2 weeks before the first day of RT; RT is intended to start on Cycle 1 Day 15 (+/- 3 days).
    10. And/or C2D1 (prior to administration of retifanlimab with or without epacadostat)
    11. C3D1 only (prior to administration of retifanlimab with or without epacadostat)
12. Subjects with left bundle branch block are excluded.
13. +/- 7 days from MRI
14. Initial consent must be completed within 6 weeks prior to Day 1 of treatment
15. The timing of MRIs should be done based on the date of C1D1 and done every 8 weeks (+/- 2 weeks) thereafter

11.0 DATA SUBMISSION SCHEDULE

Case report forms with appropriate source documentation will be completed according to the schedule listed in this section.

Case Report Form	Submission Schedule
Original Consent Form	Prior to registration
On-Study Form Medical History Form	Prior to starting treatment
Treatment Form	Every cycle
Toxicity Form	Continuous
Correlatives Form	Baseline, end of RT, C2D1, C6D1, C12D1/Time of progression
Treatment Summary Form	Completion of treatment
Follow Up Form	Every 2 months for 2 years
Tumor Measurement Form	Baseline, end of every second cycle, and end of treatment
Progression Form	Time of disease progression
Death Form	Time of death
MedWatch Form	See Section 7.0 for reporting requirements

Any queries generated by Washington University must be responded to within 28 days of receipt by the participating site. The Washington University research team will conduct a regular review of data status at all secondary sites, with appropriate corrective action to be requested as needed.

11.1 Adverse Event Collection in the Case Report Forms

All adverse events that occur beginning with start of treatment (minus exceptions defined in Section 7.0) must be captured in the Toxicity Form. Baseline AEs should be captured on the Medical History Form.

Participant death due to disease progression should be reported on the Toxicity Form as grade 5 disease progression. If death is due to an AE (e.g. cardiac disorders: cardiac arrest), report as a grade 5 event under that AE. Participant death must also be recorded on the Death Form.

12.0 MEASUREMENT OF EFFECT

12.1 Antitumor Effect – Solid Tumors

For the purposes of this study, patients will be re-evaluated for recurrence or progression every 8 (+/- 2) weeks. Response and progression will be evaluated in this study using the updated response assessment criteria for high-grade gliomas: immunotherapy Response Assessment in Neuro-Oncology (iRANO) working group guideline [44].

Criteria for Response Assessment Incorporating MRI and Clinical Factors (Adapted from [47])

Response	Criteria
Complete response	Requires all of the following: • Disappearance of all enhancing measurable and nonmeasurable disease sustained for at least 4 weeks. • No new lesions; stable or improved nonenhancing (T2/FLAIR) lesions • Patients must be off corticosteroids (or on physiologic replacement doses only) and stable or improved clinically. Note: Patients with nonmeasurable disease only cannot have a complete response; the best response possible is stable disease.
Partial response	Requires all of the following: • ≥ 50% decrease compared with baseline in the sum of products of perpendicular diameters of all measurable enhancing lesions sustained for at least 4 weeks • No progression of nonmeasurable disease • Stable or improved nonenhancing (T2/FLAIR) lesions on same or lower dose of corticosteroids compared with baseline scan; the corticosteroid dose at the time of the scan evaluation should be no greater than the dose at time of baseline scan • Stable or improved clinically. Note: Patients with nonmeasurable disease only cannot have a partial response; the best response possible is stable disease.
Stable disease	Requires all of the following: • Does not qualify for complete response, partial response, or progression • Stable nonenhancing (T2/FLAIR) lesions on same or lower dose of corticosteroids compared with baseline scan. In the event that the corticosteroid dose was increased for new symptoms and signs without confirmation of disease progression on neuroimaging, and subsequent follow-up imaging shows that this increase in corticosteroids was required because of disease progression, the last scan considered to show stable disease will be the scan obtained when the corticosteroid dose was equivalent to the baseline dose • Stable or improved clinically
Progression	Defined by any of the following: • ≥ 25% increase in sum of the products of perpendicular diameters of enhancing lesions compared with the smallest tumor measurement obtained either at baseline (if no decrease) or best response, on stable or increasing doses of corticosteroids*. The absolute increase in any dimension must be at least 5mm when calculating the products. • Significant increase in T2/FLAIR nonenhancing lesion on stable or increasing doses of corticosteroids compared with baseline scan or best response after initiation of therapy* not caused by comorbid events (e.g. radiation therapy, demyelination, ischemic injury, infection, seizures, postoperative changes, or other treatment effects)

Response	Criteria
	• Any new measureable lesion • 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. • Failure to return for evaluation as a result of death or deteriorating condition; or clear progression of nonmeasurable disease.

- NOTE. All measurable and nonmeasurable lesions must be assessed using the same techniques as at baseline.
- Abbreviations: MRI, magnetic resonance imaging; FLAIR, fluid-attenuated inversion recovery.
- Stable doses of corticosteroids include patients not on corticosteroids.

iRANO criteria for progression: Confirmation of progression on follow-up imaging 3 months after initial radiographic progression if:

1. No new or significantly worsened neurologic deficits not due to co-morbid event or concurrent medication
2. $\leq$ 6 months from initiation of immunotherapy; If follow-up imaging confirms progression, the date of actual progression should be back-dated to the date of initial radiographic progression. Note the appearance of new lesions solely does not define progressive disease$\leq$ 6 months from initiation of immunotherapy. Rather, the lesions are added to the total lesion areas for follow-up assessments.

Otherwise, progressive disease will be defined as radiographic evidence of progression with significant clinical decline that is felt to be unrelated to co-morbid event or concurrent medication, or if there is radiographic evidence of progression > 6 months after initiation of immunotherapy.

12.2 Disease Parameters

Measurable disease: Bi-dimensionally measurable lesions with clearly defined margins by MRI scan. All tumor measurements must be recorded in millimeters (or decimal fractions of centimeters).

Non-measurable or evaluable disease: Uni-dimensionally measurable lesions or lesions with margins not clearly defined such as areas of T2/FLAIR signal abnormality or poorly defined enhancing abnormality.

Note: For cystic lesions, the only measurable part is any enhancement area around the cyst that is clearly defined and bi-dimensionally measurable. The cyst itself should not be considered measurable or non-measureable disease.

Target lesions: All measurable lesions should be identified as target lesions and recorded and measured. Target lesions should be selected on the basis of their size (lesions with the longest diameter), but in addition should be those that lend themselves to reproducible repeated measurements. It may be the case that, on occasion, the largest lesion does not

lend itself to reproducible measurement in which circumstance the next largest lesion, which can be measured reproducibly should be selected. When there are too many measurable lesions, choose the largest 3 lesions as target lesions to follow. The other measurable lesions should be considered evaluable for the purpose of objective status determination.

Non-target lesions: All non-measurable lesions should be identified as non-target lesions and should also be recorded at baseline. Measurements of these lesions are not required, but the presence, absence, or in rare cases unequivocal progression of each should be noted throughout follow-up.

12.3 Methods for Evaluation of Measurable Disease

All measurements should be taken and recorded in metric notation using a ruler. All baseline evaluations should be performed as closely as possible to the beginning of treatment and never more than 4 weeks before the beginning of the treatment.

Clinical lesions: Clinical lesions will only be considered measurable on brain MRI when they are ≥ 5 mm diameter as assessed using a ruler.

Histology: This technique can be used to differentiate between partial responses (PR) and complete responses (CR) in rare cases when biopsy or surgical resection of a measureable lesion is clinically indicated.

Perfusion/CBV: This advanced brain MRI technique can be used as an adjunct test to determine treatment response or disease status. However, it should not be used as the primary or sole method to determine response or disease status.

Brain FDG-PET coupled with head CT or brain MRI: This advanced metabolic imaging technique can be used as an adjunct test to determine response or disease status. However it should be used as the primary or sole method of determining response or disease status.

12.3.1 Evaluation of Target Lesions

Complete Response (CR): Disappearance of all target lesions.

Partial Response (PR): ≥ 50% decrease compared with baseline in the sum of products of perpendicular diameters of all target lesions sustained for at least 4 weeks.

Progressive Disease (PD): At least a 25% increase in the sum of products of perpendicular diameters of at least 1 target lesion, taking as reference the smallest sum of products of perpendicular diameters on study (this includes the baseline sum if that is the smallest on study). The absolute increase in any dimension must be at least 5mm when calculating the products of perpendicular diameters.

Stable Disease (SD): Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as reference the smallest sum of products of perpendicular diameters while on study.

12.3.2 Evaluation of Non-Target Lesions

Complete Response (CR): Disappearance of all non-target lesions.

Non-CR/Non-PD: Persistence of one or more non-target lesion(s).

Progressive Disease (PD): Appearance of one or more new lesions and/or unequivocal progression of existing non-target lesions on stable or increasing doses of corticosteroids compared with baseline scan or best response after initiation of therapy* not caused by comorbid events (e.g. radiation therapy, demyelination, ischemic injury, infection, seizures, postoperative changes, or other treatment effects). It must be representative of overall disease status change, not a single lesion increase.

In the event of surgical intervention for clinical reasons of a radiographically progressing tumor when subsequent surgical pathology demonstrates a predominant immune-mediated reaction with no obvious progression of tumor, the subject will be deemed not progressed and allowed to resume study treatment as assigned prior to the surgery at a time deemed safe by the treating physician, but no later than 8 weeks from the surgery.

Although a clear progression of "non-target" lesions only is exceptional, the opinion of the treating physician should prevail in such circumstances, and the progression status should be confirmed at a later time by the review panel (or Principal Investigator).

12.3.3 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 patient's best response assignment will depend on the achievement of both measurement and confirmation criteria.

Summary of the iRANO Response Criteria (Adapted from [44])

Criterion	CR	PR	SD	PD
T1 gadolinium enhancing disease	None	≥ 50% ↓	< 50% ↓ but < 25% ↑	≥ 25% ↑*
T2/FLAIR	Stable or ↓	Stable or ↓	Stable or ↓	↑*

Criterion	CR	PR	SD	PD
New lesion	None	None	None	Present*
Corticosteroids	None	Stable or ↓	Stable or ↓	NA†
Clinical status	Stable or ↑	Stable or ↑	Stable or ↑	↓*
Requirement for response	All	All	All	Any*

Abbreviations: iRANO, immunotherapy Response Assessment in Neuro-Oncology; CR, complete response; PR, partial response; SD, stable disease; PD, progressive disease; FLAIR, fluid-attenuated inversion recovery; NA, not applicable.
* Progression occurs when this criterion is present.
† Increase in corticosteroids alone will not be taken into account in determining progression in the absence of persistent clinical deterioration.

12.3.4 **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). If the subject does not have an event of disease progression and the subject has not died, the subject data will be censored for duration of overall response at the date of the last disease assessment.
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.

12.3.5 **Neurological Exam and Performance Status**

Patients will be graded using the Karnofsky Performance Status scale and their neurological function evaluated as improved, stable or deteriorated in addition to objective measurement of tumor size. These parameters will be used to determine the overall response assessment.

12.3.6 **Progression-Free Survival**

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

Radiographic disease progression will be assessed using the RECIST 1.1 criteria. If the disease recurrence/progression assessment involves more than one date, the earliest date will be used as the event date. A patient will be censored at the date of

the last radiographic disease assessment indicating a lack of disease progression, if any of the following occurs before documented disease progression:

- Patient is alive and lack evidence of progression at the end of study or at the time of analysis data cut-off.
- Disease progression or death occurs right after missing data for a scheduled radiographic disease assessment (including missing the assessment or assessment results in an inevaluable status for overall response per RECIST 1.1).
- Patient receives non-protocol treatment.
- For equivocal findings of recurrence (e.g., very small and uncertain new lesions; cystic changes or necrosis in existing lesions), treatment may continue until the next scheduled assessment. If recurrence is confirmed at the next scheduled assessment, the date of recurrence should be the earlier date when recurrence was suspected.

13.0 DATA AND SAFETY MONITORING

In compliance with the Washington University Institutional Data and Safety Monitoring Plan, an independent Data and Safety Monitoring Board (DSMB) will be specifically convened for this trial to review toxicity data. A DSMB will consist of no fewer than 3 members including 2 clinical investigators and a biostatistician. DSMB members must be employed by Washington University, Barnes-Jewish Hospital, or St. Louis Children's Hospital. Like investigators, DSMB members are subject to the Washington University School of Medicine policies regarding standards of conduct. Individuals invited to serve on the DSMB will disclose any potential conflicts of interest to the trial principal investigator and/or appropriate university officials, in accordance with institution policies. Potential conflicts that develop during a trial or a member's tenure on a DSMB must also be disclosed.

Until such a time as the first secondary site enrolls its first patient, a semi-annual DSM report to be prepared by the study team will be submitted to the Quality Assurance and Safety Monitoring Committee (QASMC) semi-annually beginning six months after study activation at Washington University (if at least one patient has been enrolled) or one year after study activation (if no patients have been enrolled at the six-month mark).

The DSM report for the DSMB will be prepared by the study team with assistance from the study statistician, will be reviewed by the DSMB, and will be submitted to the QASM Committee. The DSMB must meet at least every six months beginning six months after enrollment of the first patient at a secondary site, no more than one month prior to the due date of the DSM report to QASMC. This report will include:

- HRPO protocol number, protocol title, Principal Investigator name, data coordinator name, regulatory coordinator name, and statistician
- Date of initial HRPO approval, date of most recent consent HRPO approval/revision, date of HRPO expiration, date of most recent QA audit, study status, and phase of study

- History of study including summary of substantive amendments; summary of accrual suspensions including start/stop dates and reason; and summary of protocol exceptions, error, or breach of confidentiality including start/stop dates and reason
- Study-wide target accrual and study-wide actual accrual including numbers from participating sites
- Protocol activation date at each participating site
- Average rate of accrual observed in year 1, year 2, and subsequent years at each participating site
- Expected accrual end date, accrual by site, and accrual by regimen
- Objectives of protocol with supporting data and list the number of participants who have met each objective
- Measures of efficacy
- Early stopping rules with supporting data and list the number of participants who have met the early stopping rules
- Summary of toxicities at all participating sites separated by regimens with the number of dose-limiting toxicities indicated
- Abstract submissions/publications
- Summary of any recent literature that may affect the safety or ethics of the study

Further DSMB responsibilities are described in the DSMB charter.

The study principal investigator and coordinator will monitor for serious toxicities on an ongoing basis. Once the principal investigator or coordinator becomes aware of an adverse event, the AE will be reported to the HRPO and QASMC according to institutional guidelines (please refer to Section 7.0).

Refer to the Washington University Quality Assurance and Data Safety Monitoring Committee Policies and Procedures for full details on the responsibilities of the DSMB. This is located on the QASMC website at https://siteman.wustl.edu/research/clinical-research-resources/protocol-office-prmcqasmc/.

14.0 AUDITING

As coordinating center of this trial, Washington University (via the Quality Assurance and Safety Monitoring Committee (QASMC) will monitor each participating site to ensure that all protocol requirements are being met; that applicable federal regulations are being followed; and that best practices for patient safety and data collection are being followed per protocol. Participating sites will be asked to send copies of all audit materials, including source documentation. The audit notification will be sent to the Washington University Research Patient Coordinator, who will obtain the audit materials from the participating institution.

Notification of an upcoming audit will be sent to the research team one month ahead of the audit. Once accrual numbers are confirmed, and approximately 30 days prior to the audit, a list of the cases selected for review (up to 10 for each site) will be sent to the research team. However, if

during the audit the need arises to review cases not initially selected, the research team will be asked to provide the additional charts within two working days.

Items to be evaluated include:

- Subject screening and enrollment
- Reporting of adverse events
- Maintenance of HIPAA compliance
- Completeness of regulatory documentation
- Completeness of participant documentation
- Acquisition of informed consent
- IRB documentation
- Issues of protocol adherence

Additional details regarding the auditing policies and procedures can be found at https://siteman.wustl.edu/research/clinical-research-resources/protocol-office-prmcqasmc/.

15.0 STATISTICAL CONSIDERATIONS

15.1 Overall Study Design

This is an open-label nonrandomized Phase II study on two regimens in bevacizumab-naïve recurrent or progressive grade 4 glioma patients: retifanlimab + bevacizumab+ RT (regimen A), and retifanlimab + epacadostat + bevacizumab + RT (regimen B), each with 24 efficacy evaluable patients. The study will start to enroll patients to receive regimen A while regimen B will open to enrollment later after regimen A starts or even after the completion of regimen A. The dosage of retifanlimab and epacadostat are fixed at 500mg Q4W and 400mg BID respectively, based on prior clinical trial data (INCMGA00012: NCT03059823). If a patient experiences toxicity, the next dose can be skipped to resolve the adverse event (see Section 6 for more details for the handling). The objective is not to compare the two regimens but to evaluate efficacy and safety of the two treatment regimens in parallel and to compare the efficacy of each regimen to historical controls.

To ensure patient safety in both regimens, we will perform continuous monitoring of intolerable toxicities. "Intolerable toxicity" is defined as grade 4 or higher dermatological or grade 3 or higher non-dermatological adverse events as graded by CTCAE version 5.0 that cannot be resolved within a week and are considered at least possibly related to study treatment. Patients enrolled to Regimen A will follow the toxicity monitoring described in Section 15.2. Enrollment to Regimen A will stop if the boundary "b" is crossed. Thus, Regimen A will be discontinued in a timely fashion should any excessive intolerable toxicity occur in Regimen A. See details on criteria for evaluability and the stopping boundary in Section 15.2.

Enrollment to Regimen B will begin when the first 23 (of a total 24) patients have been enrolled to Regimen A, received a cycle of treatment, completed the evaluation period for intolerable toxicity, and not exceeded the boundary "b" as specified in the table of Section

15.2 (i.e., 10 or fewer patients among the first 23 patients enrolled to Regimen A experience intolerable toxicities). Once enrollment to Regimen B starts, we will use the same table to monitor toxicity in patients enrolled to Regimen B. See details on criteria for evaluability and the stopping boundary in Section 15.2.

15.2 Early Stopping Rules for Continuous Toxicity Monitoring

"Intolerable toxicity" is defined as grade 4 or higher dermatological or grade 3 or higher non-dermatological adverse events as graded by CTCAE version 5.0 that cannot be resolved within a week and are considered at least possibly related to study treatment. Intolerable toxicity will be separately monitored for each regimen. Patients must receive at least one dose of study treatment to be evaluable for intolerable toxicities. Toxicity evaluations for "intolerable toxicity" will take place in each patient in both regimens from first dose of study treatment until 28 days after last dose of Cycle 2 treatment; for patients enrolled in Regimen A, this is Cycle 3 Day 1 (28 days after the C2D1 dose of retifanlimab) and for patients enrolled in Regimen B, this is Cycle 3 Day 28 (28 days after the C2D28 dose of epacadostat). If a patient decides to drop out of the study during the first cycle for reasons other than treatment-related toxicity, the patient is not evaluable for intolerable toxicities and will be replaced.

Intolerable toxicity will be routinely monitored after three patients are treated on a regimen, using a Bayesian Binomial-beta hierarchical model as implemented in Multc Clean (version2.1.0). The trial will stop if there is more than 0.9 likelihood that the estimated rate of intolerable toxicities (θ) is above 0.3, i.e., $\Pr(\theta \geq 0.3) > 0.9$ with the specific boundaries (b) out of total number of patients treated (n) detailed in the table below.

n # of patients (inclusive)	b stop the trial if the # patients with toxicities >= b (inclusive)
3	2-3
4-5	3-5
6-8	4-8
9-10	5-10
11-13	6-13
14-15	7-15
16-18	8-18
19-21	9-21
22-23	10-23
24	always stop with this many patients

Specifically, the trial will stop if 2 out of the first 3 patients, or 3 out of the first 5 patients, 4 out of the first 6 patients, 5 out of the first 9 patients, 6 out of the first 11 patients, 7 out of the first 14 patients, 8 out of the first 16 patients, 9 out of the first 19 patients, 10 out of the first 22 patients are observed to experience intolerable toxicities.

Accrual will be paused and the event will be reviewed by the PI and study statistician, with possible referral to the Data Safety and Monitoring Board, if a grade 5 toxicity (non-hematological, non-dermatologic, non-progression) is observed within 30 days of the last dose of INCGMA00012, bevacizumab, or epacadostat (whichever is latest).

Additionally, the study will be suspended or possibly stopped prematurely for any of the following reasons:

1. A death that is unexpected and at least probably related to epacadostat, or to the combination of radiotherapy, retifanlimab and epacadostat.
2. Anaphylactic reaction to epacadostat.
3. Any events that, in the judgment of the medical monitor, are at least probably related to epacadostat and are deemed serious enough to warrant immediate review by the data safety monitoring panel. This may include any symptomatic and/or irreversible treatment-related grade 4 pneumonitis, colitis, dermatitis, or hepatitis or any symptomatic treatment-related related grade ≥ 3 neurological toxicity or uveitis.
4. Any other safety finding assessed as related to epacadostat or its respective combinations with radiotherapy or anti-PD-1 agent that, in the opinion of the internal data safety monitoring panel, contraindicates further dosing of study subjects.

15.3 Endpoints

The primary endpoint of phase II trials for both regimen A and B is overall survival (OS). Overall survival is defined as the time interval from date of treatment start to date of first documented death event (death due to any cause) or date of censoring. If a patient has not had an event, OS will be censored at the date of last follow up. The secondary endpoints of phase II include progression-free survival (PFS), as defined from date of treatment start to date of progression of the disease or death to any cause . Patients who do not have disease progression and have not died will be censored at the date of last disease assessment.

15.4 Sample Size Justification

For the phase II trials, a total of 24 efficacy evaluable patients will be enrolled for each of regimen A and B, as justified below

The 9-month OS probability estimated from the Kaplan-Meier method of Bevacizumab naïve recurrent grade 4 glioma patients treated with bevacizumab alone is 38 %, based on the 2014 BELOB study [45]. An increase of the 9-month OS from 38% to 60% in this regimen is considered clinically relevant and warrants further investigation of regimen A and regimen B. Assuming an enrollment period of 18 months and a total duration of 30 months, based on a one-sided one-sample log rank test at a 0.1 alpha level, a total of 24 patients with 16 events at the end of study provides 89.09% power to test a favorable 9-month OS ≥60% against an unfavorable 9-month OS ≤38% in this regimen, corresponding to a hazard ratio of 0.528. (58, 59) In the event of slower than anticipated accrual, we will

extend the accrual period. The sample size was calculated under the assumption of exponential survival distribution using PASS (version 15.0.5).

15.5 Statistical Analysis

The two regimens will be analyzed separately. All data will be evaluated as observed, and no imputation method for missing values will be used. Descriptive statistics will be used to summarize the trial results, i.e., statistics for continuous variables may include mean, median, range and appropriate measures of variability such as standard deviation and inter-quartile range. Qualitative variables will be summarized by counts and percentages. The uncertainty of estimates will be assessed by confidence intervals.

PFS and OS will be separately analyzed using the Kaplan-Meier (KM) method to estimate the empirical survival probabilities. Median PFS and OS and OS and PFS probability at 9 month will be estimated with 90% confidence interval from KM analyses. In consideration that MGMT methylated and/or IDH mutated patients exhibit better survival, MGMT promoter methylation and IDH mutation status adjusted KM curves and hazard ratio will be generated. Cox proportional hazard model will be used to estimate hazard ratio of a risk factor of interest (but not treatment since single arm) without and with adjustment for patient characteristics.

Safety is assessed through summaries of AEs, changes in laboratory test results, changes in vital signs, physical examination findings, changes in KPS, and changes in cardiac ejection fraction results. AEs will be classified by system organ class (SOC) and preferred term using the Medical Dictionary for Regulatory Activities (MedDRA); AE severities will be classified using the CTCAE criteria Version 5.0. All the safety data will be summarized as appropriate by descriptive statistics (mean, median, standard deviation etc for continuous and count/percentages for categorical variables), by grade, relationship to study drugs, patient characteristics within each regimen.

Neurologic function scores using the NANO scale will be summarized by descriptive statistics including mean, median, standard deviation, inter-quartile range and range for each regimen at each time point. Within regimen, the scores will be compared between two time points by Wilcoxon signed rank test or paired-sample t test.

For correlative studies, to assess predictive, prognostic, and pharmacodynamic exploratory biomarkers in archival and/or fresh tumor tissue and blood and their association with disease status and/or response to study treatment, logistic regression or Cox proportional hazard model will be used. Paired t-test will be used to compare the anti-glioma immune response before and after. All analyses and estimates will be conducted among all patients overall, as well as by subgroups of interest.

15.6 Populations for Analysis

- All Enrolled Subjects Analysis Set: this analysis set contains all subjects who signed an informed consent for the study
- Safety/toxicity evaluable analysis set: this analysis set contains all subjects who

receive any dose level of the drug combinations from the time of their first treatment.

- Efficacy-Evaluable Subjects: this analysis set contains all subjects who receive the study drug combinations of any of two regimens for at least 1 cycle.

16.0 MULTICENTER REGULATORY REQUIREMENTS

Washington University requires that each participating site sends its informed consent document to be reviewed and approved by the Washington University Regulatory Coordinator (or designee) prior to IRB/IEC submission.

Site activation is defined as when the secondary site has received official written documentation from the coordinating center that the site has been approved to begin enrollment. At a minimum, each participating institution must have the following documents on file at Washington University prior to study activation:

- Documentation of IRB approval of the study in the form of a letter or other official document from the participating institution's IRB. This documentation must show which version of the protocol was approved by the IRB.
- Documentation of IRB approval of an informed consent form. The consent must include a statement that data will be shared with Washington University, including the Quality Assurance and Safety Monitoring Committee (QASMC), the DSMC (if applicable), and the Washington University study team.
- Documentation of FWA, signed FDA Form 1572 (if applicable), and the CVs of all participating investigators.
- Protocol signature page signed and dated by the investigator at each participating site.

The coordinating center Principal Investigator (or designee) is responsible for disseminating to the participating sites all study updates, amendments, reportable adverse events, etc. Protocol/consent modifications and IB updates will be forwarded electronically to the secondary sites within 4 weeks of obtaining Washington University IRB approval. Activated secondary sites are expected to submit protocol/consent/IB modifications to their local IRBs within 4 weeks of receipt unless otherwise noted. Upon the secondary sites obtaining local IRB approval, documentation of such shall be sent to the Washington University study team within 2 weeks of receipt of approval. Secondary sites will also notify the Washington University study team of any regimen B subjects continuing on study past progression.

Documentation of participating sites' IRB approval of annual continuing reviews, protocol amendments or revisions, all SAE reports, and all protocol violations/deviations/exceptions must be kept on file at Washington University.

The investigator or a designee from each institution must participate in a regular conference call to update and inform regarding the progress of the trial.

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APPENDIX A: Karnofsky Performance Scale

Able to carry on normal activity and to work; no special care needed.	100	Normal no complaints; no evidence of disease.
	90	Able to carry on normal activity; minor signs or symptoms of disease.
	80	Normal activity with effort; some signs or symptoms of disease.
Unable to work; able to live at home and care for most personal needs; varying amount of assistance needed.	70	Cares for self; unable to carry on normal activity or to do active work.
	60	Requires occasional assistance, but is able to care for most of his personal needs.
	50	Requires considerable assistance and frequent medical care.
Unable to care for self; requires equivalent of institutional or hospital care; disease may be progressing rapidly.	40	Disabled; requires special care and assistance.
	30	Severely disabled; hospital admission is indicated although death not imminent.
	20	Very sick; hospital admission necessary; active supportive treatment necessary.
	10	Moribund; fatal processes progressing rapidly.
	0	Dead

APPENDIX B: Patient's Medication Diary

Today's Date: _____ Agent: Epacadostat

Cycle: _____ Study ID#: _____

INSTRUCTIONS TO THE PATIENT:

1. Complete one form for each month. Take _____mg (___capsules) of epacadostat twice daily at approximately the same times each day. Take it with a glass of water and drink the glass of water in as little time as possible. Swallow the capsules whole and do not chew the capsules.
2. Record the date, the number of capsules taken, and when you took them.
3. If you forget to take a dose within 4 hours of your regular time, then do not take that dose. Restart taking it with the next scheduled dose.
4. If you have any questions or notice any side effects, please record them in the comments section. Record the time if you should vomit.
5. Please return the forms to your physician or your study coordinator when you go to your next appointment. Please bring your unused study medications and/or empty bottles with you to each clinic visit so that a pill count can be done.

Day	Date	What time was dose taken?		# of tablets taken		Comments
		AM dose	PM dose	AM dose	PM dose	
1						
2						
3						
4						
5						
6						
7						
8						
9						
10						
11						
12						
13						
14						
15						
16						
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27						
28						

APPENDIX C: NANO Scale

8.5 Neurologic Function in Neuro-Oncology (NANO) Scale

Scoring assessment is based on direct observation and testing performed during clinical evaluation and is not based on historical information or reported symptoms.

Domain Levels of Function
Please check 1 answer for each domain

Domains	Key Considerations
Gait 0 ☐ Normal 1 ☐ Abnormal but walks without assistance 2 ☐ Abnormal and requires assistance (companion, cane, walker, etc.) 3 ☐ Unable to walk ☐ Not assessed ☐ Not evaluable	• Walking is ideally assessed by at least 10 steps
Strength 0 ☐ Normal 1 ☐ Movement present but decreased against resistance 2 ☐ Movement present but none against resistance 3 ☐ No movement ☐ Not assessed ☐ Not evaluable	• Test each limb separately • Recommend assess proximal (above knee or elbow) and distal (below knee or elbow) major muscle groups • Score should reflect worst performing area • Patients with baseline level 3 function in one major muscle group/limb can be scored based on assessment of other major muscle groups/limb
Ataxia (upper extremity) 0 ☐ Able to finger to nose touch without difficulty 1 ☐ Able to finger to nose touch but difficult 2 ☐ Unable to finger to nose touch ☐ Not assessed ☐ Not evaluable	• Non-evaluable if strength is compromised • Trunk/lower extremities assessed by gait domain • Particularly important for patients with brainstem and cerebellar tumors • Score based on best response of at least 3
Sensation 0 ☐ Normal 1 ☐ Decreased but aware of sensory modality 2 ☐ Unaware of sensory modality ☐ Not assessed ☐ Not evaluable	• Recommend evaluating major body areas separately (face, limbs and trunk) • Score should reflect worst performing area • Sensory modality includes but not limited to light touch, pinprick, temperature and proprioception • Patients with baseline level 2 function in one major body area can be scored based on assessment of other major body areas

Visual Fields

- 0 ☐ Normal
- 1 ☐ Inconsistent or equivocal partial hemianopsia (≥quadrantopsia)
- 2 ☐ Consistent or unequivocal partial hemianopsia (≥quadrantopsia)
- 3 ☐ Complete hemianopsia
- ☐ Not assessed
- ☐ Not evaluable

- Patients who require corrective lenses should be evaluated while wearing corrective lenses
- Each eye should be evaluated and score should reflect the worst performing eye

Facial Strength

- 0 ☐ Normal
- 1 ☐ Mild/moderate weakness
- 2 ☐ Severe facial weakness
- ☐ Not assessed
- ☐ Not evaluable

- Particularly important for brainstem tumors
- Weakness includes nasolabial fold flattening, asymmetric smile and difficulty elevating

Language

- 0 ☐ Normal
- 1 ☐ Abnormal but easily conveys meaning to examiner
- 2 ☐ Abnormal and difficulty conveying meaning to examiner
- 3 ☐ Abnormal. If verbal, unable to convey meaning to examiner OR non-verbal (mute/global aphasia)
- ☐ Not assessed
- ☐ Not evaluable

- Assess based on spoken speech. Non-verbal cues or writing should not be included.
- **Level 1**: Includes word finding difficulty; few paraphasic errors/neologisms/word substitutions; but able to form sentences (full/broken)
- **Level 2**: Includes inability to form sentences (<4 words per phrase/sentence); limited word output; fluent but "empty" speech.

Level of Consciousness

- 0 ☐ Normal
- 1 ☐ Drowsy (easily arousable)
- 2 ☐ Somnolent (difficult to arouse)
- 3 ☐ Unarousable/coma
- ☐ Not assessed
- ☐ Not evaluable

- None

Behavior

- 0 ☐ Normal
- 1 ☐ Mild/moderate alteration
- 2 ☐ Severe alteration
- ☐ Not assessed
- ☐ Not evaluable

- Particularly important for frontal lobe tumors
- Alteration includes but is not limited to apathy, disinhibition and confusion
- Consider subclinical seizures for significant

APPENDIX D: Definitions for Adverse Event Reporting

A. Adverse Events (AEs)

As defined in 21 CFR 312.32:

Definition: any untoward medical occurrence associated with the use of a drug in humans, whether or not considered drug-related.

Grading: the descriptions and grading scales found in the revised NCI Common Terminology Criteria for Adverse Events (CTCAE) version 5.0 will be utilized for all toxicity reporting. A copy of the CTCAE version 5.0 can be downloaded from the CTEP website.

Attribution (relatedness), Expectedness, and Seriousness: the definitions for the terms listed that should be used are those provided by the Department of Health and Human Services' Office for Human Research Protections (OHRP). A copy of this guidance can be found on OHRP's website:
http://www.hhs.gov/ohrp/policy/advevntguid.html

B. Suspected Adverse Reaction (SAR)

As defined in 21 CFR 312.32:

Definition: any adverse event for which there is a reasonable possibility that the drug caused the adverse event. "Reasonable possibility" means there is evidence to suggest a causal relationship between the drug and the adverse event. "Suspected adverse reaction" implies a lesser degree of certainty about causality than adverse reaction, which means any adverse event caused by a drug.

C. Life-Threatening Adverse Event / Life Threatening Suspected Adverse Reaction

As defined in 21 CFR 312.32:

Definition: any adverse drug event or suspected adverse reaction is considered "life-threatening" if, in the view of the investigator, its occurrence places the patient at immediate risk of death. It does not include an adverse event or suspected adverse reaction that, had it occurred in a more severe form, might have caused death.

D. Serious Adverse Event (SAE) or Serious Suspected Adverse Reaction

As defined in 21 CFR 312.32:

Definition: an adverse event or suspected adverse reaction is considered "serious" if, in the view of the investigator, it results in any of the following outcomes:

- Death
- A life-threatening adverse event

- Inpatient hospitalization or prolongation of existing hospitalization
- A persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions
- A congenital anomaly/birth defect
- Any other important medical event that does not fit the criteria above but, based upon appropriate medical judgment, may jeopardize the subject and may require medical or surgical intervention to prevent one of the outcomes listed above

E. Protocol Exceptions

Definition: A planned change in the conduct of the research for one participant.

F. Deviation

Definition: Any alteration or modification to the IRB-approved research without prospective IRB approval. The term "research" encompasses all IRB-approved materials and documents including the detailed protocol, IRB application, consent form, recruitment materials, questionnaires/data collection forms, and any other information relating to the research study.

A minor or administrative deviation is one that does not have the potential to negatively impact the rights, safety, or welfare of participants or others or the scientific validity of the study.

A major deviation is one that does have the potential to negatively impact the rights, safety, or welfare of participants or others or the scientific validity of the study.

APPENDIX E: Reporting Timelines

Expedited Reporting Timelines				
Event	**HRPO**	**QASMC**	**FDA**	**Incyte**
Serious AND unexpected suspected adverse reaction			Report no later than 15 calendar days after it is determined that the information qualifies for reporting	
Unexpected fatal or life-threatening suspected adverse reaction			Report no later than 7 calendar days after initial receipt of the information	
Unanticipated problem involving risk to participants or others	Report within 10 working days. If the event results in the death of a participant enrolled at WU/BJH/SLCH, report within 1 working day.	Report via email after IRB acknowledgment		
Serious adverse events				Report within 24 hours of learning of the event regardless of causality.
Major deviation	Report within 10 working days. If the event results in the death of a participant enrolled at WU/BJH/SLCH, report within 1 working day.			
A series of minor deviations that are being reported as a continuing noncompliance	Report within 10 working days.			
Pregnancy				Report within 24 hours of discovery
Protocol exception	Approval must be obtained prior to implementing the change			
Clinically important increase in the rate of a serious suspected adverse reaction of			Report no later than 15 calendar days after it is determined that the information qualifies for reporting	

Expedited Reporting Timelines				
Event	**HRPO**	**QASMC**	**FDA**	**Incyte**
that list in the protocol or IB				
Complaints	If the complaint reveals an unanticipated problem involving risks to participants or others OR noncompliance, report within 10 working days. If the event results in the death of a participant enrolled at WU/BJH/SLCH, report within 1 working day. Otherwise, report at the time of continuing review.			
Breach of confidentiality	Within 10 working days.			
Incarceration	If withdrawing the participant poses a safety issue, report within 10 working days. If withdrawing the participant does not represent a safety issue and the patient will be withdrawn, report at continuing review.			

Routine Reporting Timelines				
Event	**HRPO**	**QASMC**	**FDA**	**Incyte**
Adverse event or SAE that does not require expedited reporting	If they do not meet the definition of an unanticipated problem involving risks to participants or others, report summary information at the time of continuing review	Adverse events will be reported in the toxicity table in the DSM report which is typically due every 6 months.	The most current toxicity table from the DSM report is provided to the FDA with the IND's annual report.	
Minor deviation	Report summary information at the time of continuing review.			
Complaints	If the complaint reveals an unanticipated problem involving risks to participants or others OR noncompliance, report within 10 working days. If the event results in the death of a participant enrolled at WU/BJH/SLCH, report within 1			

Routine Reporting Timelines				
Event	**HRPO**	**QASMC**	**FDA**	**Incyte**
	working day. Otherwise, report at the time of continuing review.			
Incarceration	If withdrawing the participant poses a safety issue, report within 10 working days. If withdrawing the participant does not represent a safety issue and the patient will be withdrawn, report at continuing review.			

Expedited Reporting Timelines for Secondary Sites				
Event	**WU (Coordinating Center)**	**Local IRB**	**FDA**	**Incyte**
Serious AND unexpected suspected adverse reaction	Report no later than 11 calendar days after it is determined that the information qualifies for reporting.	Report all applicable events to local IRB according to local institutional guidelines.	The research team at Washington University is responsible for reporting all applicable events to the FDA as needed.	The research team at Washington University is responsible for reporting all applicable events to Incyte as needed.
Unexpected fatal or life-threatening suspected adverse reaction	Report no later than 4 calendar days after initial receipt of the information.			
Unanticipated problem involving risk to participants or others	Report no later than 4 calendar days after initial receipt of the information.			
Adverse event or SAE that does not require expedited reporting	As per routine data entry expectations			
Protocol exception	Approval must be obtained prior to implementing the change.			

APPENDIX F: Washington University Unanticipated Problem Reporting Cover Sheet

SAE COVER SHEET- Secondary Site Assessment

Washington University HRPO#:	Sponsor-Investigator:
Subject Initials:	Subject ID:
Treating MD:	Treating Site:
EVENT TERM:	Admission Date:
EVENT GRADE:	Date of site's first notification:

Treating MD Event Assessment:

Is this event **possibly, probably, or definitely** related study treatment?

☐ yes ☐ no

If yes, please list which drug (if more than one)_____

Explain _____

_____

_____ _____ _____

Physician's Name **Physician's Signature** **Date**