Combination of checkpoint inhibition and IDO1 inhibition together with standard radiotherapy or chemoradiotherapy in newly diagnosed glioblastoma. A phase 1 clinical and translational trial.

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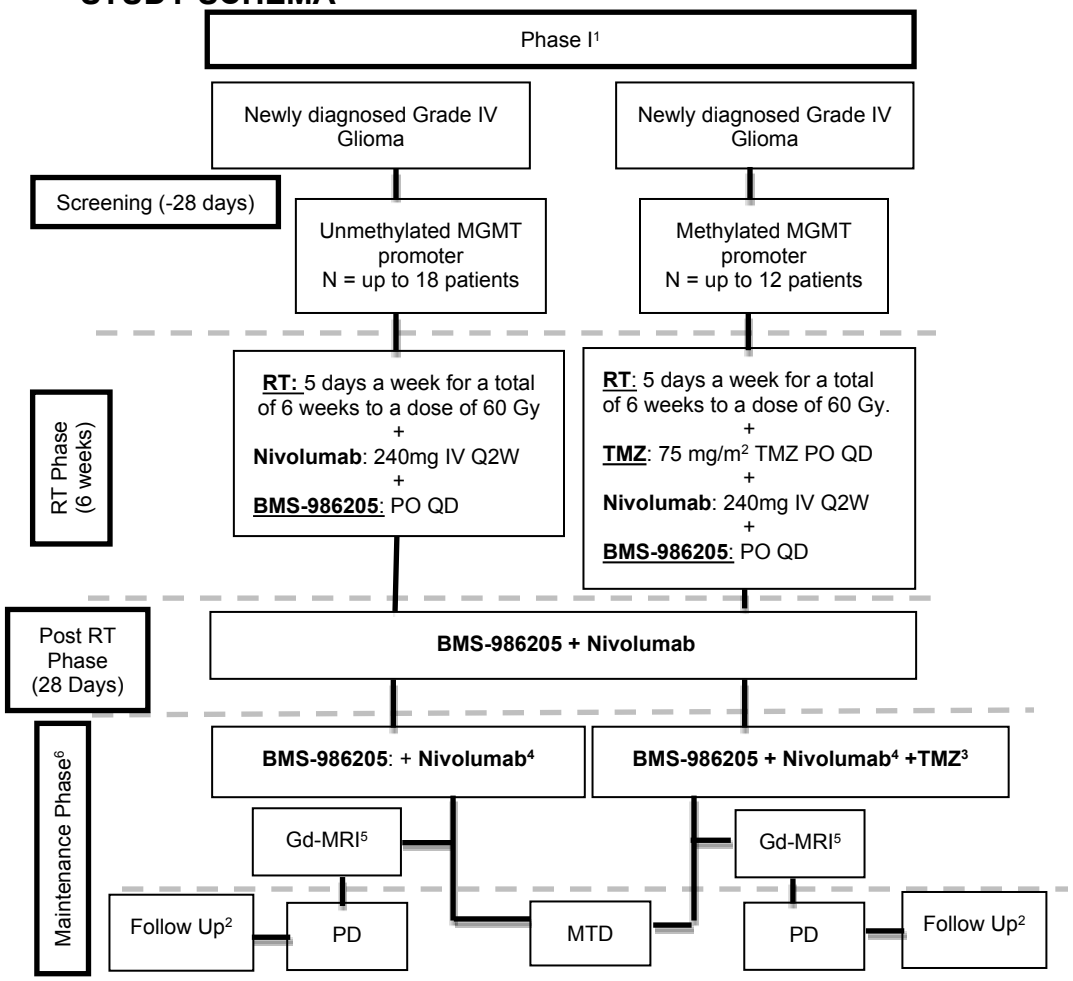
http://cancer.northwestern.edu/research/clinical-trials-office/index.html

LIST OF ABBREVIATIONS

AE	Adverse Event
ALT	Alanine Aminotransferase
ALC	Absolute Lymphocyte Count
AST	Aspartate Aminotransferase
BUN	Blood Urea Nitrogen
CBC	Complete Blood Count
CMP	Comprehensive Metabolic Panel
CR	Complete Response
CT	Computed Tomography
CTCAE	Common Terminology Criteria for Adverse Events
DLT	Dose Limiting Toxicity
DSMC	Data and Safety Monitoring Committee
GBM	Glioblastoma
H&PE	History & Physical Exam
IV (or iv)	Intravenously
KPS	Karnofsky Performance Scale
MTD	Maximum Tolerated Dose
ORR	Overall Response Rate or Objective Response Rate
OS	Overall Survival
PD	Progressive Disease
PFS	Progression Free Survival
PO (or p.o.)	Per os/by mouth/orally
RT	Radiotherapy/Radiation Therapy
SAE	Serious Adverse Event
SGOT	Serum Glutamic Oxaloacetic Transaminase
SPGT	Serum Glutamic Pyruvic Transaminase
TMZ	Temozolomide
TTFields	Tumor Treating Fields

STUDY SCHEMA



1. Determination of MTD for MGMT unmethylated cohort will occur first, followed by determination of MTD for MGMT methylated cohort.
2. Follow up: Patients will be contacted every 3 months either by clinic visit or by phone to monitor survival
3. TMZ during Maintenance Phase will be given 200 mg/m^2 QD for 5 days every 28 days for a total of 6 cycles. Nivolumab and BMS-986205 treatment will continue beyond 6 cycles as indicated.
4. Beginning at Cycle 6 of the Maintenance Phase, nivolumab will be given at 480mg Q4W IV.
5. Gd-MRI will occur every 8 weeks during Maintenance Phase beginning on C1D1.
6. Patients will be given the option to begin TTFields treatment at the beginning of the Maintenance Phase. Patients who choose not to utilize TTFields will not be required to do so.

NU Study Number: NU 18C02
BMS Study Number: CA017-075

STUDY SUMMARY

Title	Combination of checkpoint inhibition and IDO1 inhibition together with standard radiotherapy or chemoradiotherapy in newly diagnosed glioblastoma. A phase 1 clinical and translational trial.
Version	October 13, 2022
Study Design	This is a multi center, open-label, uncontrolled, Phase I study
Study Center(s)	Northwestern University and Northwestern Memorial Healthcare (West Region)
Objectives	The primary objective of the study is to explore feasibility and toxicity of a novel combination of immunomodulating therapy together with standard radiotherapy in newly diagnosed glioblastoma patients. After determination of the MTD, this regimen will be explored for efficacy in patients with MGMT promoter unmethylated tumors. It will also to be explored in conjunction with TMZ/RT → TMZ chemoradiotherapy in patients with MGMT promoter methylated tumors.
Sample Size	18-30 patients (explore 3 dose levels or a maximum of 18 patients with unmethylated tumors and 2 dose levels with up to 12 patients with methylated tumors.)
Diagnosis & Key Eligibility Criteria	**Inclusion Criteria:** • Newly diagnosed, histologically confirmed diagnosis of any grade IV glioma with documentation of MGMT methylation status. The histological diagnosis can be obtained either from a brain biopsy or from a neurosurgical resection of the tumor. • Tumor tissue specimens from the GBM surgery or biopsy for central pathology review and exploratory analysis of immunocorrelative studies, if available • For subjects who had undergone tumor resection, preoperative Gd-MRI and immediate postoperative Gd-MRI performed within <72 hours after surgery or biopsy is recommended. If CT scans were performed perioperatively, an MRI should be performed before initiation of study treatment. **Exclusion Criteria:** • Patients with an active, known or suspected autoimmune disease. • History of recent prior malignancy. Subjects with curatively treated cervical carcinoma in situ or basal cell carcinoma of the skin, or subjects who have been free of other malignancies for ≥2 years are eligible for this study. See section 3.0 for the full list of eligibility criteria.

Treatment Plan	Patients with unmethylated MGMT promotor GBM will receive RT for 6 weeks in combination with nivolumab (240mg) Q2W and BMS-986205 PO QD. Following completion of RT, patients will enter the Maintenance Phase during which they will continue to receive nivolumab and BMS-986205. Beginning at Cycle 6, nivolumab dosing will change to 480mg Q4W. In addition, patients will initiate TTFields approximately 4 weeks after the completion of RT. Patients who choose not to utilize TTFields will not be required to do so. Following the establishment of the phase 2 dose, another phase 1 cohort for patients with methylated MGMT promoter will be opened. This cohort will add TMZ concomitant with RT as well as adjuvant TMZ to the study regimen. In addition, patients will initiate TTFields approximately 4 weeks after the completion of RT. Patients who choose not to utilize TTFields will not be required to do so. Treatment will continue until disease progression or unacceptable AEs.
Statistical Methodology	In this phase 1 trial, statistical analyses will be descriptive. Based on landmark analysis of historical control data for unmethylated tumors we estimate the 1-yr survival (OS12) at 50%. If this regimen proves safe and tolerable, further investigations in a randomized phase II trial will likely be proposed. **Safety and tolerability** The worst value of each hematological/biochemical category and Adverse Events will be identified and graded for each patient. Frequencies and percentages of each category will be tabulated per arm. A table with grade 3/4 frequencies and percentages will be provided. Summaries for Serious and Related Adverse Events will also be presented.

1 INTRODUCTION – BACKGROUND & RATIONALE

1.1 Glioblastoma

Gliomas account for 40-70% of all primary brain tumors. Glioblastoma (GBM) is highly malignant infiltrating the brain extensively, and creating a local immunosuppressed microenvironment. The clinical course of GBM is almost invariably fatal, with a median survival of only a few months if untreated. Treatment of these tumors is hampered by several factors, including genomic instability, which is common to many malignant tumors.

The general treatment strategy for primary disease includes surgery, radiotherapy (RT), and chemotherapy with temozolomide (TMZ). Despite these available treatment options, people with GBM have poor prognoses, with a median survival time of 14-20 months and a 5-year survival rate of <10% (1). Major prognostic factors for survival are age and performance status at the time of diagnosis.

1.1.1 Standard treatment regimen in GBM

The standard of care for newly diagnosed GBM is based on the results of the phase III trial EORTC 26981-22981 & NCIC CE.3 with 573 randomized patients. This trial demonstrated that the addition of TMZ chemotherapy to RT increased median survival from 12 to 14.6 months, and 2-year survival rate from 10 to 26%(2).

This treatment regimen consists of TMZ (75 mg/m^2 daily) administered concomitantly to RT for 6 weeks (60 Gy), followed by maintenance therapy of 6 cycles TMZ (beginning 4 weeks after the end of RT; 150-200mg/m² for 5 days every 4 weeks). Results showed a hazard ratio for survival was 0.63 (95% confidence interval [CI] = 0.52, 0.75; log-rank *P*< 0.0001) indicating a 37% reduction in the risk of death for patients treated with RT/TMZ compared to RT alone as initial therapy. Median survival was 14.6 months (95% CI = 13.2, 16.8 months) for RT/TMZ versus 12.1 months (95% CI = 11.2, 13.0 months) for RT alone. The 2-year survival rate was 26.5% (95% CI = 21.2%, 31.7%) for RT/TMZ compared with 10.4% (95% CI = 6.8%, 14.1%) for RT alone. Median PFS was 6.9 months (95% CI = 5.8, 8.1 months) for RT/TMZ and 5.0 months (95% CI = 4.2, 5.5 months) for RT alone.

Safety data from EORTC/NCIC study confirmed a good tolerance and safety of the combination of TMZ plus RT. During concomitant RT/TMZ, Grade 3 or 4 neutropenia was documented in 12 (4%) subjects, and grade 3 or 4 thrombocytopenia occurred in 9 (3%) subjects. Overall, 19 (7%) patients experienced any Grade 3 or 4 hematologic toxicity. During maintenance TMZ, 14% of subjects experienced any Grade 3 or 4 hematologic toxicity, 4% developed Grade 3 or 4 neutropenia, and 11% developed Grade 3 or 4 thrombocytopenia. During radiotherapy, severe infections were observed in 6 (2%) patients in the RT arm and in 9 (3%) patients in the RT/TMZ arm; during adjuvant TMZ therapy, severe infections were reported in 12 (5%) patients. Toxicities related to TMZ are summarized in Table 1 (from Lukas & Mrugala, 2017).

Glioblastoma with MGMT promoter methylation are likely to benefit from TMZ chemotherapy. Patients with MGMT promoter unmethylated GBM are unlikely to benefit from TMZ chemotherapy (3). In turn, it is appropriate to limit TMZ use to the MGMT promoter methylated population (4).

The utilization of TTFields, as described in the randomized phase II EF-14 trial, in addition to the standard of care as described above has been shown to further increase OS, PFS, and landmark survival in this patient population (5). This has been shown without any impairment in health related quality of life with the addition of TTFields (6). While TTFields are included in the NCCN guidelines as a level 1 recommendation, their utilization by patients with appropriate indications has not been universal. However, the degree of compliance by those who elect to utilize TTFields has been high (7). In turn, many contemporary trials for newly diagnosed glioblastoma leave the decision to patients. This is a valid approach, particularly in light of the low toxicity profile of TTFields and low likelihood for overlapping toxicities with the investigational agents.

Grade III/IV toxicities	EORTC/NCIC[13] investigational arm	RTOG 0525[18] control arm	RTOG 0825[35] control arm during chemoradiotherapy	RTOG 0825[35] control arm during maintenance therapy
Leukopenia	7%	6%	2.3%	6%
Lymphopenia	NA	15%	9%	13.4%
Neutropenia	7%	7%	3.7%	5.1%
Thrombocytopenia	12%	10%	7.7%	11.7%
Anemia	1%	1%	0.3%	1.3%
Fatigue	13%	3%	2.7%	9%
Rash/dermatologic	3%	NA	NA	NA
Infection	7%	NA	NA	NA
Nausea/vomiting	2%	1%	0.3%	1.7%

NA, not available.

1.1.2 Immunosuppression and high-grade gliomas

Glioblastoma is associated with an immune suppressed tumor microenvironment. Two important contributors to this are the indoleamine 2,3 dioxygenase 1 (IDO) enzymatic pathway and the programmed death 1 (PD-1) and programmed death ligand 1 (PD-L1) interactions leading to T cell exhaustion (8, 9).

1.1.2.1 **IDO1 expression correlates with worse GBM patient survival.**

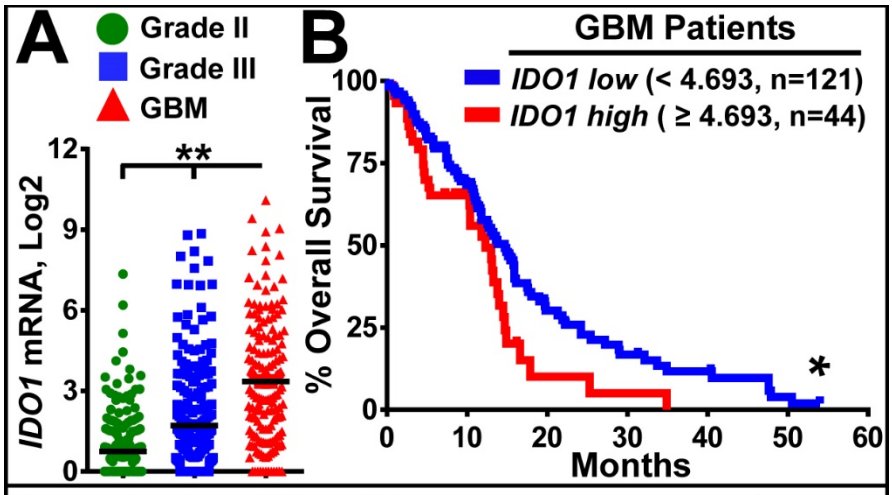


Figure 1. High IDO1 mRNA expression is correlates with decreased human GBM patient survival. (A) Hi-RNA Seq. data for 642 patient-resected glioma were analyzed from the TCGA for IDO1 mRNA expression. **(B)** GBM patient tumors were further stratified into low (blue) and high (red) IDO1-expressing samples and correlated with overall survival. *P<0.01; **P<0.001 Zhai…Wainwright, 2017; Clinical Cancer Research

IDO1 is an inducible enzyme involved in converting tryptophan (Trp) into kynurenine (Kyn) (10, 11), which suppresses T-cell function and increases immunotolerance of tumor (12-14). IDO1 mRNA increases with glioma grade (Fig. 1A), and high IDO1 levels are associated with decreased overall survival (OS) in glioma patients (Fig. 1B) (15). The IDO1 gene has several IFNɣ response elements, and the tumor tropism of IFNɣ-producing T-cells appears to stimulate IDO1 expression in GBM (see experimental results below). Increased numbers of T-cells in GBM, as indicated by intratumoral T-cell marker detection, correlates with decreased patient survival (Fig. 2).

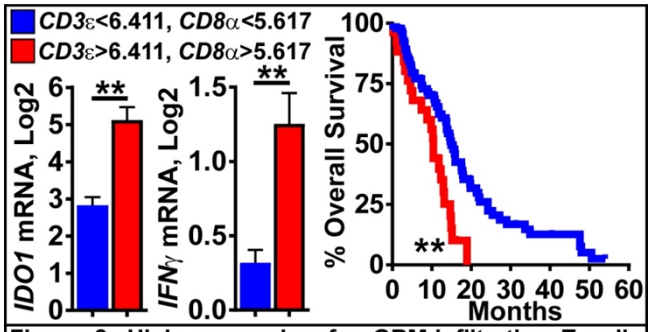


Figure 2. High expression for GBM-infiltrating T cells correlates with decreased human GBM patient survival. Hi-RNA Seq. data for 123 patient-resected GBM from the TCGA were stratified for CD3ε and CD8α expression followed by IDO1 and IFNγ mRNA expression or correlation with overall GBM patient survival. **P<0.01 Zhai…Wainwright, 2017; Clinical Cancer Research

1.1.2.2 **Tumor-infiltrating T-cells are primarily responsible for increased IDO1 expression in human GBM.**

Human T-cell tropism for intracranial GBM patient-derived xenografts (PDX) has been observed in humanized mouse tumor models, in which severely immunocompromised mice are engrafted with human immune cells and immune cell producing tissues, prior to engraftment with human tumor (16). Results from depleting the humanized mice of $CD4^+$ and $CD8^+$ T-cells show that the presence versus absence of these T-cells is directly correlated with tumor IDO1 mRNA abundance, as their depletion decreases intratumoral *IDO1* mRNA levels (P<0.001, respectively: Fig. 3A).

Interestingly, human *IDO1* mRNA is undetectable in intracranial GBM PDX isolated from T-cell-deficient mice. Expression of the T-cell-specific marker, *CD3E*, as well as the T-cell effector cytokine, IFNɣ, is readily detectable in intracranial tumors established in humanized mice, but is absent or decreased in the majority of engrafted GBM when humanized mice are depleted of human T-cells. We have demonstrated that IFNɣ potently induces IDO1 in GBM cells (Fig. 3B), and T-cells: GBM co-cultures confirm that *IDO1* is induced by activated T lymphocytes in an IFNγ-dependent manner (Fig. 3C; *P*<0.001). Taken together, these results indicate that tumor-infiltrating T-cells directly increase immunosuppressive IDO1 in GBM.

1.2 Intervention Background & Overview

1.2.1 BMS-986205

The enzyme indoleamine 2,3-dioxygenase 1 (IDO1) catalyzes the degradation of tryptophan along the kynurenine pathway and is frequently expressed in human malignancies. In healthy humans, high IDO1 expression is found in the placenta, the mucosa of the female genital tract, the lungs, and the lymphoid organs (1). The activity of IDO1 induces an immunosuppressive microenvironment in tissues by inhibiting T-cell function through local depletion of the essential amino acid tryptophan and through generation of active kynurenine pathway metabolites (2). High IDO1 expression in cancers is correlated with more aggressive tumor progression and shorter patient survival time in most cancer types (3). Tumor IDO1 transcript is elevated in patients with metastatic melanoma and renal cell carcinoma (RCC) after treatment with the anti-programmed death receptor 1

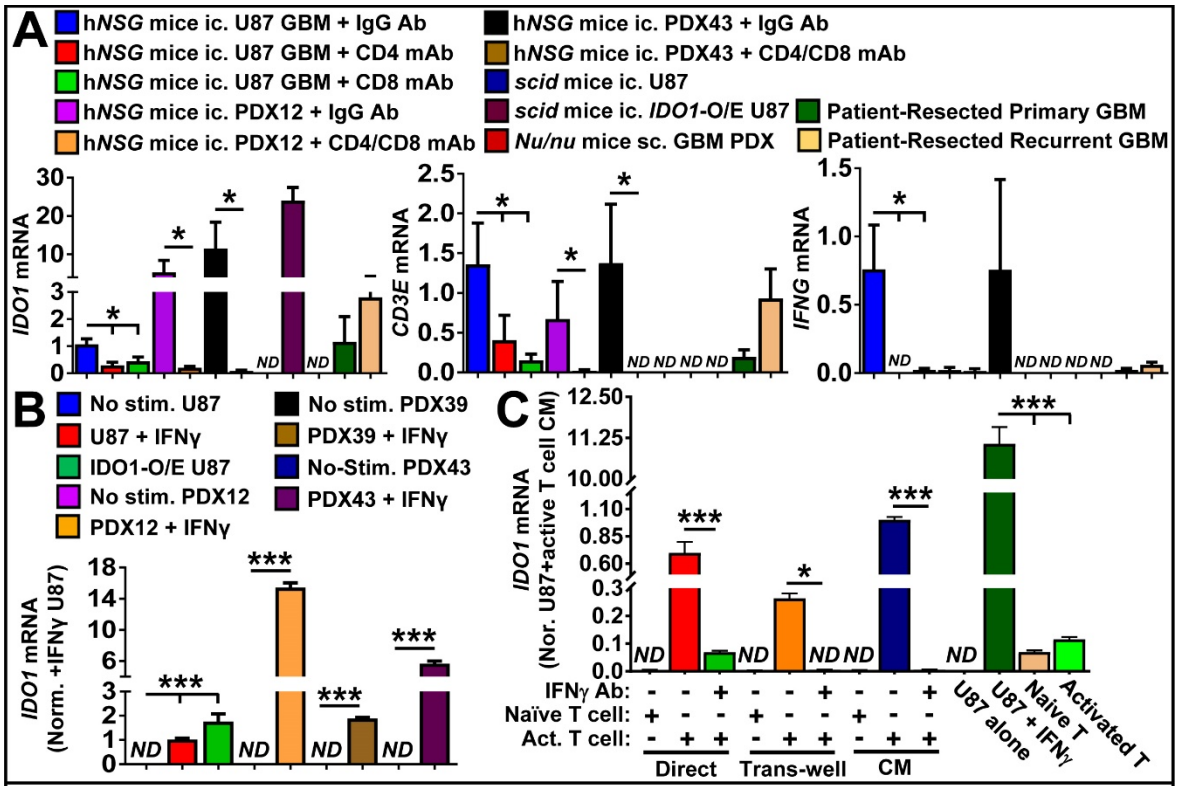


Figure 3. GBM-infiltrating T cells increase intratumoral IDO1 expression. (A) Humanized immunocompetent (h*NSG; NSG-SGM3-BLT*) and *scid* mice were intracranially-engrafted 2×10^5 U87 GBM cells ± overexpressing human IDO1 cDNA (IDO1-O/E), human patient-derived GBM xenografts (PDX) 12 or 43, ± treatment with CD4 and/or CD8 T cell-depleting mAb. GBM was isolated and analyzed for human IDO1, CD3e and IFNg mRNA levels. Subcutaneously (sc.)-engrafted PDX in nude (nu/nu) mice, as well as patient-resected GBM, were also included in the analysis. **(B)** *In vitro* expression analysis of human *IDO1* mRNA in different GBM cells with or without human interferon-gamma (IFNγ) treatment. (**C**) Detection of human *IDO1* mRNA in the human GBM-T cell co-culture system, *in vitro*. Human *IDO1* mRNA levels were analyzed in U87 GBM cells under different treatment conditions, or naïve and activated T cells were analyzed in isolation and measured by real-time RT-PCR. **P*<0.05, ****P*<0.001, *ND*=Not Detectable. Zhai…Wainwright, 2017; Clinical Cancer Research

(PD1) antibody nivolumab (4, 5). In the mouse tumor model, IDO1 is a critical resistance mechanism in antitumor T-cell immunotherapy targeting the cytotoxic T lymphocyte antigen-4 (CTLA-4) with a neutralizing antibody (6). These observations suggest that IDO1 is a mechanism that contributes to tumor escape from host immune surveillance. Therefore, inhibition of IDO1 using pharmaceutical agents may diminish the immunosuppressive tumor microenvironment and achieve more durable responses and greater patient survival benefits, particularly when used in combination with other cancer immunotherapy agents, such as nivolumab and ipilimumab. BMS-986205 (FLX287 or F-1287) is a potent and selective oral IDO1 inhibitor.

Comprehensive background information on non-clinical pharmacology, pharmacokinetics (PK) and toxicology can be found in the Investigator Brochure.

1.2.1.1 **Pharmacokinetics of BMS-986205 Preclinical evaluations**
BMS-986205 is a selective inhibitor of IDO1 without activity on IDO2 or TDO, other enzymes in the Trp metabolism pathway. Once daily dosing is supported by preclinical studies. PD has been demonstrated in *in vitro* models at single nM concentrations (17).

Preclinical studies have not yet shown penetration of the blood brain barrier (BBB) by BMS-986205, however the BBB is a dynamic partial barrier which is deemed to evolve throughout the course of disease. It is deemed that radiotherapy facilitates movement across the BBB. Additionally, the activity of immunotherapies in the non-target organ may have a favorable effect in the target organ. Further, there is no data to suggest that IDO1 enzyme inhibitors must enter the brain for their synergistic effects with concurrent PD-1 blockade and radiotherapy. It is entirely possible that IDO1 enzyme inhibitors act solely on lymph node cells (outside of the brain) and that control the development and maturation of immune cells that subsequently are recruited to brain tumors (18).

1.2.1.2 **Clinical evaluations.**
BMS-986205 is currently being investigated in an international multi-center phase 1/2a trial. The starting dose of BMS-986205 was 25 mg daily with the final dose of 400 mg daily. In this study a BMS-986205 monotherapy lead-in of two weeks was followed by combination therapy with BMS-986205 and nivolumab 240 mg IV every two weeks. The MTD was established at 200 mg based on the safety and tolerability profile and incidence of dose-limiting toxicities (DLTs). Among DLT-evaluable subjects who completed a 2-week monotherapy lead-in of BMS-986205 followed by 4 weeks of combination therapy with nivolumab, the following DLTs were observed: 0/7 at 25 mg BMS-986205, 0/8 at 50 mg, 1/9 at 100 mg (Grade 3 autoimmune hepatitis leading to treatment discontinuation), 3/12 at 200 mg (Grade 3 fatigue and Grade 3 anemia leading to dose reduction, Grade 3 AST and ALT elevations, and Grade 3 anemia leading to dose reduction), and 2/4 at 400 mg (initial Grade 2 transaminases increased progressing to Grade 3, and Grade 2 fatigue and anemia leading to > 25% of BMS-986205 doses missed and requiring dose reduction). The BMS-986205 dose of 400 mg was the MAAD and exceeded the established target toxicity profile based on Bayesian Logistic Regression Method (38.8% posterior probability that the true DLT rate is in the range of excessive toxicity, exceeding the limit of 35%). Except for the transaminase elevation at the dose of 400 mg, all other DLTs occurred during the combination therapy period. Based on

these results, BMS-986205 at 200 mg is the MTD in combination with nivolumab.

Treatment-related adverse events (AEs) of all grades were seen in 50.6% of patients receiving BMS-986205 plus nivolumab. Only 12.3% of patients exhibited grade 3-4 treatment related AEs There has been 1 treatment-related death due to myocarditis prior to the clinical data cutoff date (15-Nov-2017), which occurred during combination with nivolumab, and 2 additional treatment related deaths due to Stevens-Johnson syndrome and hepatic failure, both of which occurred after the clinical data cutoff date.

Part 2 (Dose Expansion) is currently enrolling and is assessing the preliminary efficacy of BMS-986205 in combination with nivolumab in specific malignant disease populations. BMS-986205 is being administered at 100 mg QD in all cohorts. It is also administered at 200 mg QD in select cohorts in order to obtain further safety, PK, and PD information among the BMS-986205 doses. Nivolumab is administered at either 240 mg Q2W or 480 mg every 4 weeks (Q4W).

Pharmacokinetic studies reveal that human plasma concentrations of BMS-986205 exceed levels expected to inhibit IDO1 based upon the in vitro experiments. At 25 mg daily, trough levels exceed the IC50. At 50 mg daily trough levels exceed the IC90. Dose-dependent decreases in serum Kyn levels are also noted. Approximately60% reduction on day 15 in mean serum Kyn levels was noted in doses ≥100 mg daily. There is also a dose-dependent decrease in intra-tumoral (non-CNS tumors) Kyn levels (19).

1.2.1.3 **Dose Justification**

All participants randomized will receive BMS-986205 starting at a dose of 50 mg PO QD in combination with nivolumab 240 Q2W (and beginning at cycle 6 of the maintenance phase, nivolumab dose will be 480mg Q4W). The selection of the dose and schedule for BMS 986205 is primarily based on available data from the ongoing Phase 1/2, first-in-human Study CA017003.

While 200 mg QD was the maximum tolerated dose (MTD) established in dose escalation of BMS-986205 in combination with nivolumab, preliminary PK, PD, and safety data support the selection of 50 mg QD. At 100 mg, preliminary PK data indicated that average trough plasma levels of BMS-986205 exceeded the in vitro human whole blood IC90. Significant and sustained inhibition of serum kynurenine levels was observed at all dose levels. PK-pharmacodynamic analysis of BMS-986205 exposure and kynurenine inhibition further suggests the effects to plateau at doses starting at 100 mg QD. Maximum inhibition of serum kynurenine levels was predicted to be similar at 100 mg QD and 200 mg QD. Marked but variable inhibition of intratumoral kynurenine levels was also observed at both dose levels.

The preliminary safety data presented herein from Study CA017-003 indicate that BMS-986205 is safe and tolerable at both 100 mg QD and 200 mg QD. The data suggest a more favorable tolerability profile at 100 mg, with fewer participants experiencing treatment-related ≥ Grade 3 AEs (10.9% at 100 mg QD [n=303] versus 23.5% at 200 mg QD [n=68]) and TRAEs requiring dose discontinuation (3.6% versus 5.9%, respectively) in participants receiving the 100 mg QD dose.

Furthermore, treatment-related Grade 3 anemia was reported in 0.3% of participants receiving the 100 mg dose versus 4.4% of participants receiving the 200 mg dose, and hepatic events may also occur more frequently at 200 mg compared to 100 mg (see Section 7.1.2 of the Investigator Brochure). Lastly, the only methemoglobin elevation over 10% occurred in a participant receiving 200 mg, while the peak methemoglobin reported in the 100 mg group was 6%.

No formal evaluation of efficacy between the 100 and 200 mg dose was included in the study or planned for future studies, but responses have been seen in participants treated with both doses when combined with nivolumab.

1.2.1.4 **Safety**

Preliminary analysis of safety results from Study CA017003, the first-in-human, Phase 1/2a dose escalation and cohort expansion study in advanced malignant tumors have revealed a favorable safety profile. Treatment-related adverse events (TRAEs) have generally been of low grade and are manageable. Per Investigator Brochure v. 6 (01-29-2020), the most commonly reported TRAEs (in > 10% of participants) during combination therapy with nivolumab were fatigue (17.2%) and nausea (13.2%). Grade 3 and 4 TRAEs have been reported in approximately 17% of participants receiving the combination. Treatment-related SAEs were reported in 9.4% of patients treated with BMS-986205 and nivolumab.There has been 1 treatment-related death due to myocarditis , which occurred during combination with nivolumab, and 2 additional deaths due to Stevens-Johnson syndrome and hepatic failure Furthermore, the 100 mg once daily (QD) dose of BMS 986205 in combination with nivolumab appears to have a safety profile similar to that reported for nivolumab monotherapy, except for anemia and methemoglobinemia, which may be related to p-chloroaniline production.

Metabolism of BMS-986205 produces a p-chloroaniline metabolite, which is associated with the formation of methemoglobin as well as with hemolytic anemia. As of 24-Oct-2019, there have been no clinically significant metHb events at the 100 mg dose level of BMS-986205, and the highest reported metHb value was 16% in a participant receiving 200 mg of BMS-986205; no other participants had reported metHb levels over 10%, none have required specific treatment for methemoglobinemia, and there have been no treatment discontinuations due to methemoglobinemia. Anemia and hemolytic anemia have also occurred infrequently (1% and 0.3% of participants receiving combination therapy with nivolumab, respectively) and responded to dose holding, reductions, and other standard clinical measures. Entry criteria and monitoring parameters were developed in an attempt to reduce the risk of the occurrence and impact of methemoglobin-related toxicity. Participants with cytochrome b5 reductase and G6PD deficiencies are excluded due to the increased risk of methemoglobinemia and hemolysis, respectively.

**All information above references BMS-986205 Investigator Brochure v. 6 (01-29-2020). Please refer to the most recent Investigator Brochure for a current listing of adverse events and toxicities.*

1.2.1.5 **Efficacy**

Preliminary efficacy data are available from a 13-Oct-2017 data cutoff date from select cohorts from Part 2 (Cohort Expansion) of Study CA017-003, in which BMS-986205 was administered with nivolumab in subjects with advanced malignancies. Objective responses have been observed in subjects with bladder, cervical, SCCHN, pancreatic, DLBCL, melanoma, NSCLC, renal, triple negative breast, and endometrial cancers. Mature but preliminary aggregate data have been presented for bladder and cervical cancers as follows:

- In a cohort of 25 previously treated advanced bladder cancer subjects, 8 partial responses (7 confirmed) led to an objective response rate of 32.0%, with a disease control rate of 44.0%. The overall response rate (ORR) was 40% for participants with 1 prior therapy (n=15) and 20% for participants with 2 or more prior therapies (n=10). The ORR was 46.2% for PD-L1 positive participants (tumor PD-L1 expression ≥ 1%; n=13), and 22.2% for PD-L1 negative participants (tumor PD-L1 expression <1%; n=9).
- In a cohort of 22 previously treated advanced cervical cancer subjects, 3 partial responses (1 confirmed) led to an objective response rate of 13.6%, with a disease control rate of 63.6%. The ORR was 18.2% for participants with 1 prior therapy (n=11) and 29.1% for participants with 2 or more prior therapies (n=11). The ORR was 25.0% for PD-L1 positive participants (tumor PD-L1 expression ≥ 1%; n=12), and 0% for PD-L1 negative participants (tumor PD-L1 expression < 1%; n=7).

Additional details can be found in the investigator's brochure.

Study conduct. Based on the nonclinical and clinical results available to date, the conduct of the study is regarded as justifiable at the planned dose ranges. The study shall be discontinued in the event of new findings that indicate that a relevant deterioration of the risk-benefit relationship is probable.

This trial will be conducted in compliance with the protocol, International Conference on Harmonisation (ICH) Note for Guidance on Good Clinical Practice (GCP) (ICH, Topic E6, 1996) and applicable regulatory requirements.

1.2.2 **Nivolumab**

1.2.2.1 **Mechanism of Action**

Cancer immunotherapy rests on the premise that tumors can be recognized as foreign rather than as self and can be effectively attacked by an activated immune system. An effective immune response in this setting is thought to rely on immune surveillance of tumor antigens expressed on cancer cells that ultimately results in an adaptive immune response and cancer cell death. Meanwhile, tumor progression may depend upon acquisition of traits that allow cancer cells to evade immunosurveillance and escape effective innate and adaptive immune responses (20-22). Current immunotherapy efforts attempt to break the apparent tolerance of the immune system to tumor cells and antigens by either introducing cancer antigens by therapeutic vaccination or by modulating regulatory checkpoints of the immune system. T-cell stimulation is a complex process involving the integration of numerous positive as well as negative co-stimulatory signals in addition to antigen recognition by the T-cell receptor (TCR)(23). Collectively, these signals govern the balance between T-cell activation and tolerance.

PD-1 is a member of the CD28 family of T-cell co-stimulatory receptors that also includes CD28, CTLA 4, ICOS, and BTLA (24). PD-1 signaling has been shown to inhibit CD-28-mediated upregulation of IL-2, IL-10, IL-13, interferon-γ (IFN-γ) and Bcl-xL. PD-1 expression also been noted to inhibit T cell activation, and expansion of previously activated cells. Evidence for a negative regulatory role of PD-1 comes from studies of PD-1 deficient mice, which develop a variety of autoimmune phenotypes (25). These results suggest that PD-1 blockade has the potential to activate anti-self T-cell responses, but these responses are variable and dependent upon various host genetic factors. Thus, PD-1 deficiency or inhibition is not accompanied by a universal loss of tolerance to self-antigens.

In vitro, nivolumab (BMS-936558) binds to PD-1 with high affinity (EC50 0.39-2.62 nM), and inhibits the binding of PD-1 to its ligands PD-L1 and PD-L2 (IC50 ±1 nM). Nivolumab binds specifically to PD-1 and not to related members of the CD28 family such as CD28, ICOS, CTLA-4 and BTLA. Blockade of the PD-1 pathway by nivolumab results in a reproducible enhancement of both proliferation and IFN-γ release in the mixed lymphocyte reaction (MLR). Using a CMV re stimulation assay with human PBMC, the effect of nivolumab on antigen specific recall response indicates that nivolumab augmented IFN-γ secretion from CMV specific memory T cells in a dose-dependent manner versus isotype-matched control. In vivo blockade of PD-1 by a murine analog of nivolumab enhances the anti-tumor immune response and result in tumor rejection in several immunocompetent mouse tumor models (MC38, SA1/N, and PAN02) (26).

1.2.2.2 Justification of Dose

The nivolumab dose of 240 mg every 2 weeks (Q2W) was selected based on clinical data and modeling and simulation approaches using population PK (PPK) and exposure-response analyses of data from studies in multiple tumor types (melanoma, non-small-cell lung cancer [NSCLC], and renal cell carcinoma [RCC]) where body weight normalized dosing (mg/kg) has been used.

PPK analyses have shown that the PK of nivolumab is linear with proportional exposure over a dose range of 0.1 to 10 mg/kg, and no differences in PK across ethnicities and tumor types were observed. Nivolumab clearance and volume of distribution were found to increase as the body weight increases, but less than proportionally with increasing weight, indicating that mg/kg dosing represents an over-adjustment for the effect of body weight on nivolumab PK. The PPK model previously developed using data from NSCLC subjects has recently been updated, using data from 1544 subjects from 7 studies investigating nivolumab in the treatment of melanoma, NSCLC, and RCC. In this dataset, the median (minimum - maximum) weight was 77 kg (35 - 160 kg) and thus, an approximately equivalent dose of 3 mg/kg for an 80 kg subject, nivolumab 240 mg Q2W was selected for future studies. To predict relevant summary exposures of nivolumab 240 mg Q2W, the PPK model was used to simulate nivolumab 3 mg/kg Q2W and 240 mg Q2W. In the simulations, the simulated patient populations consisted of 1000 subjects per treatment arm randomly sampled from aforementioned pooled database of cancer subjects. Because no differences in PK were noted across ethnicities and tumor types, these simulated melanoma and

NSCLC data will be applicable to subjects with other tumor types. The simulated measure of exposure of interest, time-averaged concentrations (Cavgss) for 240 mg Q2W are predicted to be similar for all subjects in reference to 80 kg subjects receiving 3 mg/kg Q2W.

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

At 6 months after initiating the Maintenance Phase, subjects will be switched from nivolumab 240 mg every 2 weeks to nivolumab 480 mg every 4 weeks (Q4W), which provides a more convenient dosing regimen for subjects. Based on PK modeling and simulations, administration of nivolumab 480 mg Q4W will be started after steady state is achieved with 240 mg Q2W and is predicted to provide Cavgss similar to 240 mg Q2W. While 480 mg Q4W is predicted to provide greater (approximately 20%) maximum steady state concentrations and lower (approximately 10%) steady state trough concentrations, these exposures are predicted to be within the exposure ranges observed exposures at doses up to 10 mg/kg Q2W used in the nivolumab clinical program, and are not considered to put participants at increased risk. Similar to the nivolumab 240 mg Q2W dosing regimen, the exposures predicted following administration of nivolumab 480 mg Q4W, are on the flat part of the exposure-response curves for previously investigated tumors, melanoma and NSCLC, and are not predicted to affect efficacy. Based on these data, nivolumab 480 mg Q4W is expected to have similar efficacy and safety profiles to nivolumab 240 mg Q2W.

1.2.3 Temozolomide

1.2.3.1 Pharmacokinetics

TMZ is rapidly and completely absorbed after oral administration; peak plasma concentrations occur in 1 hour. Food reduces the rate and extent of TMZ absorption. Mean peak plasma concentration and AUC decreased by 32% and 9%, respectively, and Tmax increased 2-fold (from 1.1 to 2.25 hours) when TMZ was administered after a modified high-fat breakfast. TMZ is rapidly eliminated with a mean elimination

half-life of 1.8 hours and exhibits linear kinetics over the therapeutic dosing range. TMZ has a mean apparent volume of distribution of 0.4 L/kg (%CV=13%). It is weakly bound to human plasma proteins; the mean percent bound of drug-related total radioactivity is 15%.

1.2.3.2 **Metabolism and Elimination**

TMZ is spontaneously hydrolyzed at physiologic pH to the active species, 3-methyl-(triazen-1-yl)imidazole-4-carboxamide (MTIC) and to TMZ acid metabolite. MTIC is further hydrolyzed to 5-amino-imidazole-4-carboxamide (AIC), which is known to be an intermediate in purine and nucleic acid biosynthesis and to methylhydrazine, which is believed to be the active alkylating species. Cytochrome P450 enzymes play only a minor role in the metabolism of TMZ and MTIC. Relative to the AUC of TMZ, the exposure to MTIC and ACI is 2.4% and 23%, respectively. About 38% of the administered TMZ total radioactive dose is recovered over 7 days; 37.7% in urine and 0.8% in feces. The majority of the recovery of radioactivity in urine is as unchanged TMZ (5.6%), AIC (12%), TMZ acid metabolite (2.3%), and unidentified polar metabolites(s) (17%). Overall clearance of TMZ is about 5.5 L/hr/m2.

1.2.3.3 **Special Populations**

Creatinine Clearance

Population pharmacokinetic analysis indicates that creatinine clearance over the range of 36-130 mL/min/m2 has no effect on the clearance of TMZ after oral administration. The pharmacokinetics of TMZ have not been studied in patients with severely impaired renal function (CLcr < 36 mL/min/m2). Caution should be exercised when TMZ is administered to patients with severe renal impairment. TMZ has not been studied in patients on dialysis.

Hepatically Impaired Patients

In a pharmacokinetic study, the pharmacokinetics of TMZ in patients with mild to moderate hepatic impairment (Child's-Pugh Class I-II) were similar to those observed in patients with normal hepatic function. Caution should be exercised when TMZ is administered to patients with severe hepatic impairment.

Gender

Population pharmacokinetic analysis indicates that women have an approximately 5% lower clearance (adjusted for body surface area) for TMZ than men. Women have higher incidences of Grade 4 neutropenia and thrombocytopenia in the first cycle of therapy than men.

Age

Population pharmacokinetic analysis indicates that age (range 19-78 years) has no influence on the pharmacokinetics of TMZ.

1.2.4 **Tumor Treating Fields (TTFields)**

1.2.4.1 **Background**

TTFields are a device which received FDA approval for the treatment of newly diagnosed GBM in 2015. They are comprised of a set of arrays applied directly to the shaved scalp. These arrays create low voltage medium-frequency (200 kHz) alternating electrical fields. These alternating electrical fields have been shown in preclinical models to lead to decreased tumor cell proliferation and increased tumor cell death (27).

Preliminary data supports that there may be some additive effect when combined with PD-1 antibodies (28).

Treatment is typically initiated ~4 weeks after the completion of RT, at the time of the first adjuvant TMZ cycle. The arrays are worn over the course of the day to maximize treatment exposure. Patients may take breaks where arrays are taken off in addition to time periods when they are changing arrays (approximately every 3 days), bathing, etc. Treatment with TTFields is continued until no longer efficacious or no longer tolerable.

1.2.4.2 **Efficacy**

TTFields have demonstrated safety and efficacy in the treatment of recurrent GBM (29) and more recently newly diagnosed GBM (5). The randomized phase III EF-14 trial demonstrated improved OS, PFS, and landmark survival extending to 5 years for the treatment group receiving TTFields in addition to the standard of care (5). This was seen without any additional impairment in health related quality of life (6).

1.2.4.3 **Toxicity**

The primary additional toxicity noted with TTFields were low grade (grade 1/2) cutaneous toxicities noted in approximately ½ of patients (30). No additional toxicities were noted beyond those associated with standard temozlomide chemotherapy were noted in the phase 3 trial evaluating their use in newly diagnosed GBM patients (5).

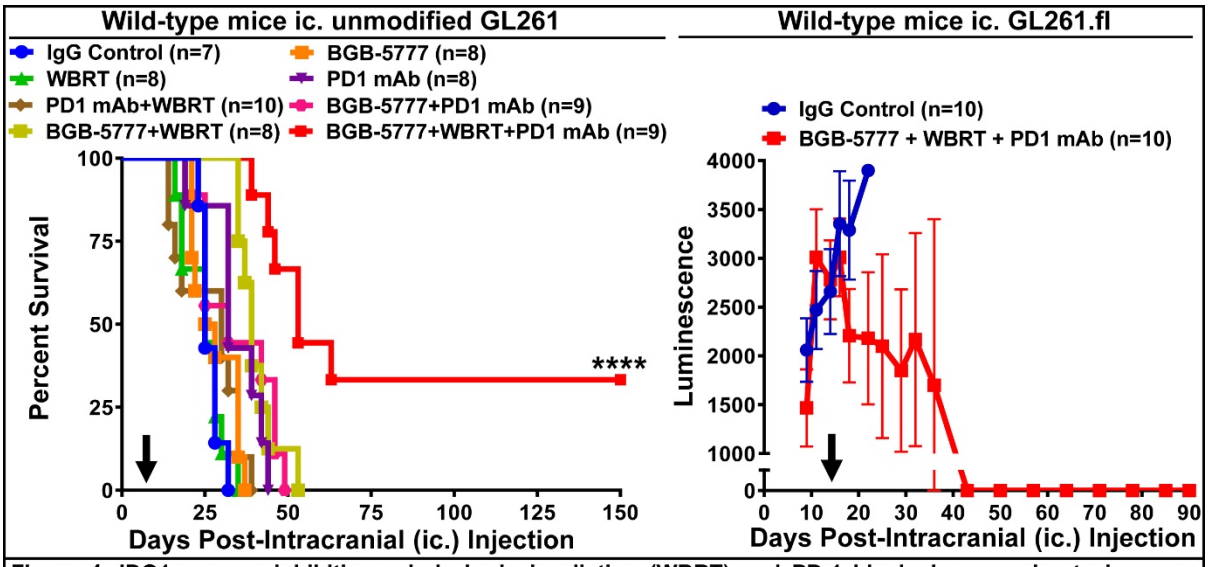


Figure 4. IDO1 enzyme inhibition, whole brain irradiation (WBRT) and PD-1 blockade synergize to increase survival in mice with well-established intracranial glioblastoma (GBM). 6-8 week old C57BL/6 mice were intracranially-injected (ic.) 2×10^5 syngeneic **(Left Panel)** unmodified or **(Right Panel)** luciferase (.fl) reporter-expressing mouse GBM (GL261) cells. Treatment with 100mg/kg IDO1 inhibitor (IDO1i; BGB-5777; oral gavage once/day ≥ 30 days total), WBRT (2Gy/day × 5 days total), and/or PD-1 mAb (J43; Loading dose=500ug, followed by 3× maintenance doses=200µg) began at 14 days post-GL261 cell injection (black arrow). Average tumor growth in mice engrafted GL261.fl tumors was measured by bioluminesence using an IVIS Spectrum imager after intraperitoneally-injecting mice with D-Luciferin (150 mg/kg). ****P<0.001

1.3 Rationale for the Current Study

1.3.1 Summary of Findings from Previous Studies

1.3.1.1 Nonclinical Studies

GBM immunotherapy requires a combinatorial approach. Brain-penetrant IDO1 inhibitors have been tested in immunocompetent mice with syngeneic intracranial GBM. As a single agents they have shown no effect on outcome (Fig. 4). Consistent with these preclinical findings,

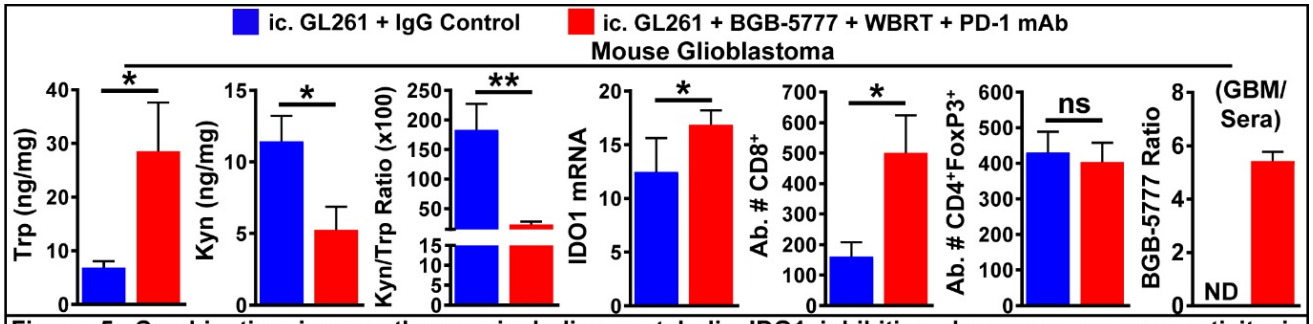


Figure 5. Combination immunotherapy including metabolic IDO1 inhibition decreases enzyme activity in mouse GBM. 6-8 week old C57BL/6 mice were intracranially-injected (ic.) 2×10^5 syngeneic mouse GBM (GL261) cells expressing mouse IDO1 cDNA (IDO1). Beginning at day 14 after injection, mice were treated with whole brain radiotherapy (RT), BGB-5777 (IDO1 inhibitor) and PD-1 mAb (dosing schedule identical as that described in Fig. 3A,B). Analyses was performed at 3 weeks post-ic. **P*<0.05 ***P*<0.01. ND=not detectable. ns=not significant.

initial clinical experience with other IDO inhibitors used as single agent did not exert clinical antitumor activity (31, 32).

Similarly, PD1 inhibition alone or radiotherapy alone, nor the combination of RT with PD1 affected tumor growth in the C57BL6-GL261 model. However, the triple combination of RT with simultaneous IDO1 and PD-1 blockade greatly reduce the growth of intracranial GBM and improve the survival of engrafted mice, even curing some animals (Fig. 4).

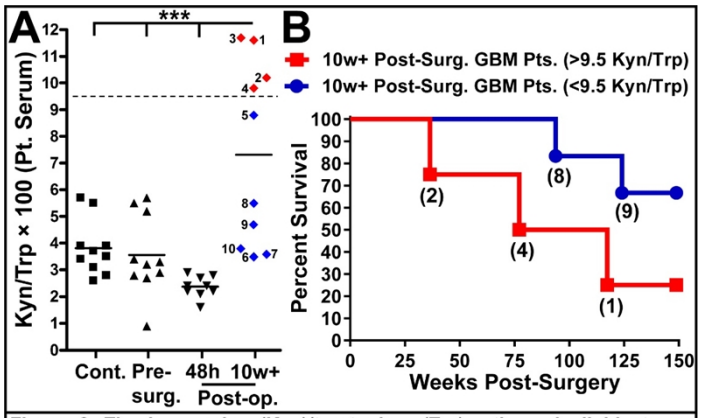


Figure 6. The kynurenine (Kyn)/tryptophan (Trp) ratio and glioblastoma (GBM) patient survival. Peripheral blood was collected from non-tumor bearing individuals as controls (Cont; squares), GBM patients prior to surgical resection (Presurg; upright triangles), or 48 hour (48h; upside down triangles) and ≥ 10 week (10w+; diamonds) post-surgically resected GBM patients (n=10 patients/ group). The serum was analyzed for the **(A)** Kyn/Trp ratio. Each patient of the 10w+ GBM cohort was color-coded and assigned a tracking number from 1–10 (A). **(B)** Kaplan-Meier survival of the 10w+ GBM patient cohort is stratified as ≥ 9.5 (red line) or ≤ 9.5 (blue line) Kyn/Trp ratio. ****P*<0.0001 Zhai…Wainwright, 2015; Journal of Clinical Neuroscience.

Preclinical results also show that the three-agent combination therapy leads to increased intratumoral Trp, decreased Kyn, and a dramatic decrease in the Kyn/Trp ratio (Fig 5). Importantly, IDO1 mRNA expression is higher in treated tumors, confirming inhibition of IDO1 activity, rather than expression.

T-cell-driven IDO1 upregulation provides a novel therapeutic intervention strategy. A plausible explanation for the failure of single agent checkpoint inhibition in GBM is that the patient's T-cells increase IDO1 activity (Fig. 3), both systemically (Fig. 6) and within the tumor (Fig. 7). Experiments suggest that RT-associated immune activation combined with PD-1 blockade and concomitant IDO1 inhibition results in substantial survival benefit to immunocompetent mice with syngeneic intracranial tumor (Fig. 4).

A model of T cell-driven IDO1 upregulation and therapeutic intervention strategy (Figure 8). Immunotherapy has yet to show a clinically measurable effect in GBM (Fig. 9). One reason for the lack of efficacy may be related to the enhancement of immunosuppressive IDO1 expression (Figs. 1,2) in human GBM by tumor-infiltrating T cells (Fig. 3). IDO1 metabolism is increased peripherally (Fig. 6) and intratumorally (Fig. 7). Combination therapy experiments confirm that, the immune-suppression inducing effects of radiotherapy and PD-1 blockade can be countered, at least in-part, by simultaneously administering an IDO1 enzyme inhibitor (Figs. 4,5). Given that IDO1 inhibition is well-tolerated in patients, the data support a clinical trial combining RT with PD-1 and IDO1 blockade.

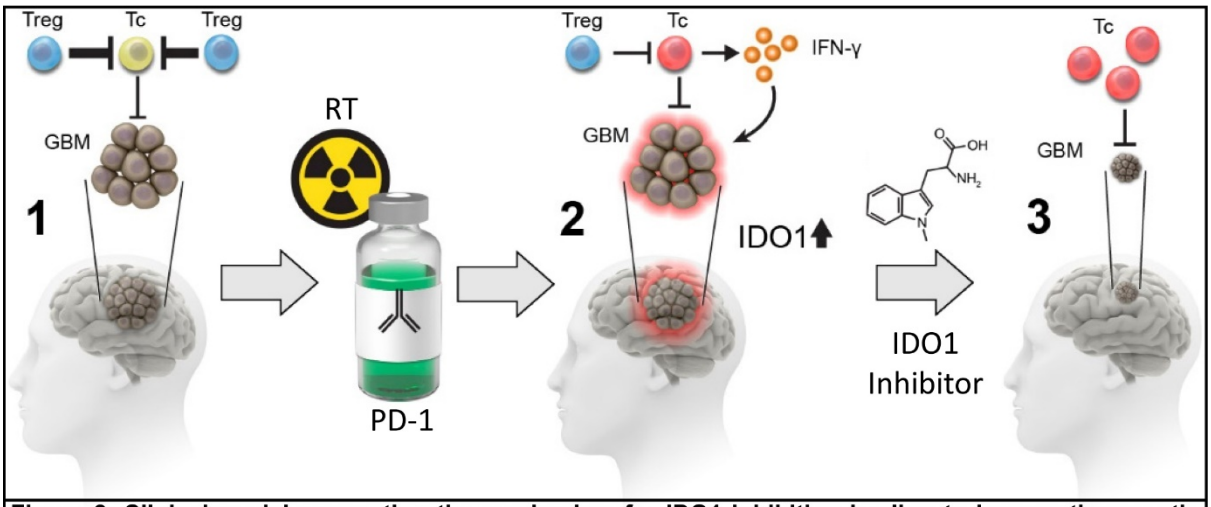


Figure 8. Clinical model suggesting the mechanism for IDO1 inhibition leading to immunotherapeutic efficacy in a glioblastoma (GBM) patient. (1) A GBM patient possesses an impaired antitumor immune response. **(2)** The GBM patient is treated with concurrent radiotherapy (RT) and systemic PD-1 mAb. **(3)** The combination of radiation and immune checkpoint inhibition enhances Tc effector function, leading to higher intratumoral IFNγ levels which **(4)** increases IDO1 expression/metabolic activity. **(5)** Further treatment with IDO1 enzyme blockade counters the T cell-induced IDO1 activity, **(6)** promoting productive GBM immunity and durable rejection of the neoplasm. Tc=cytolytic T cell ($CD8^+$); Treg=regulatory T cell ($CD4^+CD25^+FoxP3^+$)

1.3.1.2 **Clinical Studies**

Trp catabolism is altered in GBM patients and decreased by IDO1 pathway inhibition. IDO1 expression is increased in GBM, leading to immunosuppression via increased production of Kyn (16, 33, 34). Since T-cell infiltration stimulates IDO1 expression, we investigated IDO1 in the circulating immune cells of patients. Fig. 5A shows that median OS for GBM patients with a high Kyn/Trp ratio is 40% less compared to GBM patients with lower ratios (Fig. 6B).

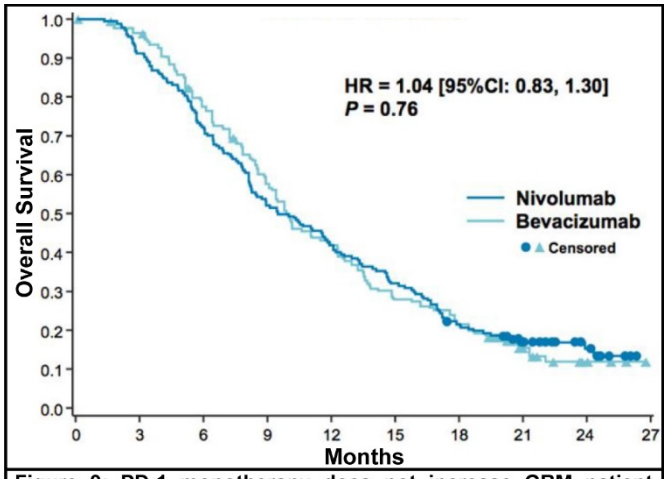


Figure 9: PD-1 monotherapy does not increase GBM patient survival. OS of recurrent GBM patients treated with nivolumab (n=184) or bevacizumab (n=185). Reardon *et al.*, 2017; Neuro-Oncol.

Single agent immunotherapy does not improve GBM patient survival. Checkpoint inhibitors have demonstrated promise in large phase III clinical trials for patients diagnosed with melanoma (35) non-small cell lung (36) and renal cell (37) cancers. While the combination of

nivolumab with radiotherapy and TMZ appears to be safe and well tolerated (38), a phase III clinical trial in recurrent GBM patients treated with nivolumab compared to bevacizumab has failed to demonstrate improved survival (Fig. 9) (39). Similarly, vaccine-based immunotherapeutic approaches, including rindopepimut and HSPPC-96 tumor associated (8, 40), did not show improved outcomes in randomized clinical trials. There is a critical need to understand why these immunotherapies did not work in GBM patients despite supportive preclinical results and, more importantly, how to successfully apply immunotherapy treatments for this disease.

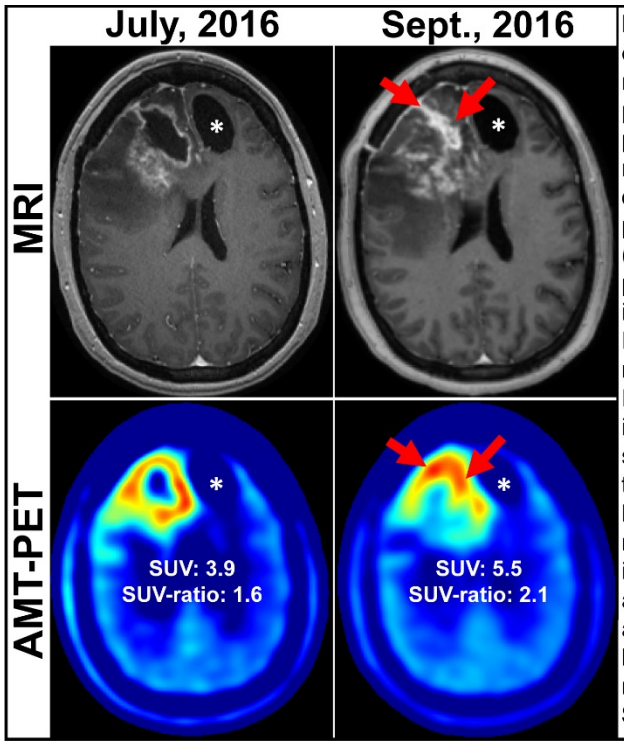


Figure 7. Intracranial imaging of tryptophan metabolism in recurrent glioblastoma (GBM) patient tumors. Recurrent GBM patients underwent magnetic resonance imaging (MRI) and α-[^{11}C]-methyl-L-tryptophan-positron emission tomography (AMT-PET). Initial imaging was prior to initiating IDO1 pathway inhibitor, indoximod (*D*1-MT). Images were repeated after 2 months on treatment with the IDO1 pathway inhibitor. Red indicates greater AMT-PET signal suggesting higher tryptophan concentration and less conversion to kynurenine metabolites. The white asterisk indicates the resection cavity and the red arrows indicate areas of increased enhancement but decreased tryptophan metabolism.
SUV= standardized uptake value

Trp catabolism can be monitored in GBM patients. In a clinical trial (NCT02052648) for treating recurrent GBM (rGBM) patients with the IDO1 inhibitor indoximod, Trp metabolism was imaged pretreatment and on treatment via PET using α-[11C]-methyl-L-Trp (AMT) (41). Figure 7 shows an example in which MRI confirmed the presence of rGBM in the left frontal lobe, with overlapping AMT-PET Trp prior to treatment with the IDO1 inhibitor. Two months after continuous indoximod, MRI indicated increased enhancement but also increased lesional Trp, which is indicative of decreased tumor Trp metabolism. This may be indicative of inhibition of the IDO-mediated conversion of Trp to Kyn. This demonstrates that AMT-PET can be used to monitor tumor response to IDO1 inhibition. However, it still requires further validation.

1.3.2 Clinical Trial Design

1.3.2.1 Introduction and Rationale

Patients newly diagnosed with GBM have a poor prognosis and the standard established by the Phase III EORTC/NCIC trial provides a clinically meaningful survival benefit for subjects newly diagnosed with GBM (2). However, tumor invariably recurs leading to patient death. Therefore a large, unmet need remains for developing new treatments based on the recently established treatment regimen.

The preclinical rationale for this three-agent combination has been outlined above. Patients with GBM lacking *MGMT* promoter methylation do not benefit from TMZ chemotherapy. This allows to withhold this immunosuppressive agent in favor of novel therapeutic agents (3). The combination of RT with immune checkpoint inhibitors has already proven

safe in large phase I-III clinical trials (NCT02667587; NCT03192943). This phase I prospective clinical trial will explore dose, safety and toxicity of concurrent RT, TTFields, the PD-1 mAb nivolumab and IDO1 enzyme inhibitor BMS-986205. Tumor tissue from initial resection and at recurrence (in patients undergoing repeat surgery) will be quantified for subtypes of tumor-infiltrating lymphocytes, PD1 expression, Trp and Kyn levels, Ki67 and TUNEL staining.

1.3.2.2 **Patient population and design**

Patients with histologically confirmed newly diagnosed GBM with unmethylated MGMT gene promoter (MGMT status will be determined centrally by pyrosequencing) are eligible. Once the MTD and a recommended phase II dose have been established, a second cohort of patients with MGMT methylated tumors (GBM) also receiving concomitant TMZ will be explored. Other standard inclusion criteria include a Karnofsky performance status ≥70 and adequate hematological, kidney and liver function. Patients with a history of autoimmune disease are excluded. Patients should be on a minimal and stable dose of steroids, if needed at all.

As of Protocol Amendment 10 (dated 9-03-2021), only IDH wildtype GBM is eligible (See Inclusion Criteria 3.1.2). Only IDH wildtype patients have been enrolled on the study. Preclinical modeling of this approach was studied exclusively within the study context of GBM IDH wildtype models. In addition, limitation of the clinical trial to GBM IDH wildtype will allow for a more homogenous patient population providing greater clarity of the outcomes for the secondary and exploratory endpoints.

A classic 3+3 dose escalation will be used in this trial. Patients will receive concomitant RT (30x2 Gy, 60 Gy total), nivolumab (240 mg every 2 weeks), and the IDO1 inhibitor (PO, QD). After completion of RT, patients will continue both nivolumab and IDO1 inhibitor combination, if tolerated until tumor progression. The doses of radiation and nivolumab have been previously established and will remain constant, while the IDO1 inhibitor dose will be increased stepwise, depending on toxicity. The IDO inhibitor is currently being investigated in combination with nivolumab in a phase I trial of solid tumors not including GBM (NCT03192943). The MTD has been established at 200 mg in combination with nivolumab based on the safety and tolerability profile and incidence of dose-limiting toxicities (DLTs). While 200 mg QD was the MTD established in dose escalation of BMS-986205 in combination with nivolumab, preliminary PK, PD, and safety data support the selection of 100 mg QD when utilized concurrently with nivolumab. In the current study we will employ a starting dose of 50 mg QD as we are initiating BMS-986205 concurrently with nivolumab and RT. If 0/3 patients experience treatment-related dose-limiting toxicity (DLT), the dose will be escalated to the next level. If DLT toxicity is observed in 1/3 patients, 3 additional patients will be enrolled at that dose. The MTD is defined as the dose for which at most 1 patient develops DLT; the recommended phase II dose would be the MTD.

Once the recommended phase II dose has been established in patients with MGMT unmethylated tumors, and pending preliminary indications of safety and response to treatment in the unmethylated group, a cohort of patients with methylated MGMT gene promoter will be treated, starting one dose level below the recommended phase II dose and then

escalated up to the recommended phase II dose. These patients will also receive concomitant TMZ chemotherapy. Prior experience with another IDO1 inhibitor, indoximod, together with TMZ has shown good tolerance with no added toxicity (NCT02052648) (41). Nivolumab in conjunction with TMZ and RT also appears tolerable (38). DLT will be established during the TMZ/RT phase, and separately for the maintenance phase (with a different TMZ schedule) after cycles 1 and 2.

Both cohorts of patients will receive TTFields beginning in the adjuvant phase approximately 4 weeks after completion of radiation. Approximately 30% of patients with newly diagnosed GBM are informed about TTFields and only 36% of these patients decide to pursue their utilization, despite the significant improvement in survival associated with their use (7). Acknowledging that there is significant variability between neuro-oncology clinical practices as well as variability in patients' acceptance of the utilization of TTFields, patients will be allowed to decline the use of TTFields. It was felt that this approach is most representative of contemporary clinical practice. It was also felt important to offer TTFields to all patients due to the survival advantage associated with their use. As toxicity is minimal their addition should not substantially increase risk to patients.

The purpose of the current phase I study is to investigate the tolerability and activity of the combination of nivolumab with BMS-986205 with radiotherapy. For patients with MGMT promoter methylation TMZ, both concomitant with radiotherapy and adjuvant, will be included. The current study is an exploratory, uncontrolled, and open study. A secondary endpoint is the overall survival. Survival is the preferred endpoint with delayed responses expected with immunotherapies. Overall survival will be calculated according to Kaplan-Meier with specific estimates examined at 12 months.

As secondary endpoints the progression free survival and response rate will also be assessed. The evaluation of progression of disease will be based on radiological and neurological criteria as well as steroid use. In addition, the influence of prognostic factors, like extent of surgery, performance status, or age will be addressed by subgroup analyses. In the case of major differences with regard to a number of prognostic factors, a matched-pair analysis might be performed with the EORTC data.

An independent review will be performed on all relevant Gd-MRI scans, and an independent pathologist will confirm the histopathological diagnosis. Central pathologic review will occur only after trial enrollment. Patients with diagnoses other than glioblastoma will be censored in the efficacy analyses.

The planned treatment period was up to 2 years. Protocol Amendment 10 (dated 9-03-2021), revised the treatment period so it is now for as long as the patient receives clinical benefit (for the study drugs BMS-986205 & nivolumab). This change was made as a few patients were benefiting from the treatment and approaching the 2 year limit. Patients will remain on treatment as long as they are not experiencing toxicity requiring removal from study or progression of disease.

Antitumor effect of immunotherapeutic approaches may become evident and measurable only many months after initiation of therapy. Thus, occasionally initial tumor progression can be observed radiologically. Thus, patients with slowly progressing disease may continue therapy even in the presence of formal PD if the investigator believes that there is a benefit for the patient. Analyses based upon radiographic endpoints (i.e. response rate, PFS) will be performed utilizing the RANO and iRANO criteria (42).

A detailed clinical study report will be established within 8 months after inclusion of the last patient.

1.3.2.3 **Anticipated Results and Interpretation**
Based on our preclinical data, we anticipate durable responses and prolonged OS when treated with RT, TTFields, nivolumab and IDO1 inhibitor compared with historical controls. We also expect GBM patients with MGMT methylation will experience improved OS when treated with TMZ/RT and TTFields combined with nivolumab/IDO1 inhibitor.

2 OBJECTIVES

2.1 Primary Objective

2.1.1 To determine the safety and tolerability of nivolumab in combination with BMS-986205 and radiation in newly diagnosed MGMT promoter unmethylated glioblastoma and MGMT promoter methylated glioblastoma.

2.2 Secondary Objectives

2.2.1 Descriptive survival analyses (OS and OS12) in patients with MGMT unmethylated and MGMT methylated promoter.

2.2.2 PFS and PFS6 in patients with MGMT unmethylated and MGMT methylated promoter.

2.2.3 Radiographic response rates (RR) as determined by RANO and iRANO criteria in patients with MGMT unmethylated and MGMT methylated promoter.

2.3 Exploratory Objectives

2.3.1 Determine the T-cell changes that occur in GBM treated with nivolumab in combination with BMS-986205 and radiation.

2.3.2 Correlate T-cell changes and IDO1 expression with patient outcomes.

2.3.3 Investigate GBM patient levels of distress, before, during, and after treatment with trimodal radiation, anti-PD-1 mAb and IDO1 enzyme inhibitor.

2.3.4 Assess whether tumor-associated α-[11C]-methyl-L-Trp (AMT) uptake on PET imaging is correlated with treatment response and other outcomes.

3 PATIENT ELIGIBILITY

The target population for this study is patients with newly diagnosed grade IV Glioma. This will be a multi-center trial conducted at Northwestern University Northwestern Memorial Healthcare (West Region) is a participating site.

A total of 18-30 patients will be needed for this Phase I trial. Approximately 6 potentially eligible patients are seen per month, and it is anticipated that at least 2 per month will be accrued. Potential patients may be referred to the Principal Investigator (PI) at Northwestern University, Dr. Rimas Lukas, at (312) 695-0990.

Eligibility will be evaluated by the study team according to the following criteria. Eligibility waivers are not permitted. Subjects must meet all of the inclusion and none of the exclusion criteria to be registered to the study. Study treatment may not begin until a subject is registered. Please refer to Section 11 for complete instructions regarding registration procedures.

3.1 Inclusion Criteria

3.1.1 Patients must have a newly diagnosed histologically confirmed diagnosis of any grade IV Glioma with documentation of MGMT methylation status. The histological diagnosis can be obtained either from a brain biopsy or from a neurosurgical resection of the tumor.

Note: Study enrollment is to be within 6 weeks from diagnostic surgery or biopsy.

Note: Pyrosequencing will be performed to determine MGMT methylation status as SOC. MGMT methylation status from outside institution will be accepted for registration and will be confirmed at Northwestern Memorial Hospital.

3.1.2 Patients must have confirmed IDH wildtype glioblastoma per immunohistochemistry or next generation sequencing.

3.1.3 Patients must be age ≥ 18 years.

3.1.4 Patients must exhibit a Karnofsky performance score of ≥70% (See Appendix B).

3.1.5 Stable or decreasing dose of steroids for ≥7 days prior to registration.
*Note: Patients must be **off** of all steroids at the time of initiation of study treatment (D#1).*

3.1.6 Patients must have adequate organ and bone marrow function at registration, as defined below:

Absolute neutrophil count	≥1500/mm^3
Platelets	≥100,000/mm^3
Creatinine or creatinine clearance	≤1.5 times upper limit of normal or ≥ 60 mL/min
Hemoglobin	≥10 mg/dL *Blood transfusion allowed.*
Total bilirubin	≤1.5 times upper limit of normal
AST(SGOT)/ALT(SPGT)	≤2.5 times above upper limit of normal
Alkaline phosphatase	≤2.5 times above upper limit of normal

3.1.7 Females of child-bearing potential (FOCBP) and males must agree to use adequate contraception prior to study entry, for the duration of study participation, and for 5 months following completion of therapy (See Appendix C). Should a female patient become pregnant or suspect she is pregnant while participating in this study, she should inform her treating physician immediately.

Due to the potential interaction with study drug(s), contraceptions that use hormones are not considered to be highly effective for FOCBP participants in this study.

NOTE: A FOCBP is *any woman* (regardless of sexual orientation, having undergone a tubal ligation, or remaining celibate by choice) who meets the following criteria:

- *Has not* undergone a hysterectomy or bilateral oophorectomy

Has had menses at any time in the preceding 12 consecutive months (and therefore has not been naturally postmenopausal for > 12 months)

3.1.8 Males who are sexually active with FOCBP must agree to follow instructions for method(s) of contraception (see Appendix C) for the duration of treatment with study treatment plus 7 months after the last dose of the study treatment (i.e., 90 days [duration of sperm turnover] plus the time required for nivolumab to undergo approximately 5 half-lives). In addition, male participants must be willing to refrain from sperm donation during this time.

Male participants with partners who are FOCBP are required to use a condom for study duration and until end of relevant systemic exposure defined as 7 months after the end of study treatment. This criteria applies to azoospermic males as well.

3.1.9 FOCBP must have a negative serum pregnancy test within 14 days of registration on study and within 24 hours of beginning study treatment.

3.1.10 Clinically normal cardiac function without history of ischemic heart disease in the past 6 months and not clinically significant 12 lead ECG (as determined by treating investigator).

3.1.11 Patients must have recovered from the effects of surgery, postoperative infection, and other complications before study registration.

3.1.12 Patients must have the ability to understand and the willingness to sign a written informed consent prior to registration on study.

3.2 Exclusion Criteria

3.2.1 Patients who have had chemotherapy for any cancer within 2 years prior to entering the study are not eligible.

3.2.2 Patients who have received brain radiation therapy (RT) are not eligible.

3.2.3 Patients may not be receiving any other investigational agents. Patients may not have received an investigational agent within the past 30 days prior to the initiation of study treatment.

3.2.4 Patients with a condition requiring systemic treatment with either corticosteroids or other immunosuppressive medications are not eligible.

Note: Inhaled or topical steroids, and adrenal replacement steroid doses ≥10 mg daily prednisone equivalent, are permitted in the absence of active autoimmune disease.

3.2.5 Patients with an active, known or suspected autoimmune disease are not eligible. Patients with type I diabetes mellitus, hypothyroidism only requiring hormone

replacement, skin disorders (such as vitiligo, psoriasis, or alopecia) not requiring systemic treatment, or conditions not expected to recur in the absence of an external trigger are permitted to enroll.

3.2.6 Participants with a personal or family (i.e., in a first-degree relative) history or presence of cytochrome b5 reductase deficiency (previously called methemoglobin reductase deficiency) or other diseases that puts them at risk of methemoglobinemia are not eligible. All participants will be screened for methemoglobin levels prior to registration.

3.2.7 Participants with a history of G6PD deficiency or other congenital or autoimmune hemolytic disorders are not eligible. All participants will be screened for G6PD levels prior to registration.

3.2.8 Participants with active interstitial lung disease (ILD) / pneumonitis or with a history of ILD / pneumonitis requiring steroids are not eligible.

3.2.9 Patients who have a history of allergic reactions attributed to compounds of similar chemical or biologic composition to nivolumab, temozolomide or BMS-986205 are not eligible.

3.2.10 Patients who have had prior treatment with an anti-PD-1, anti-PD-L1, anti-PD-L2, anti-CTLA-4 antibody, or any other antibody or drug specifically targeting T-cell co-stimulation or checkpoint pathways are not eligible.

3.2.11 Patients who have had prior treatment with BMS-986205 or any other IDO1 inhibitors are not eligible.

3.2.12 Patients who have received treatment with botanical preparations (e.g., herbal supplements or traditional Chinese medicines) intended for general health support or to treat the disease under study within 14 days prior to initiation of treatment are not eligible.

3.2.13 Patients who have an uncontrolled intercurrent illness including, but not limited to any of the following, are not eligible:

- Hypertension that is not controlled on medication
- Ongoing or active infection requiring systemic treatment
- Symptomatic congestive heart failure
- Unstable angina pectoris
- Cardiac arrhythmia
- Psychiatric illness/social situations that would limit compliance with study requirements
- Any other illness or condition that the treating investigator feels would interfere with study compliance or would compromise the patient's safety or study endpoints

3.2.14 Female patients who are pregnant or nursing are not eligible.

3.2.15 Patients who have quantitative or qualitative G6PD assay results suggesting underlying G6PD deficiency are not eligible.

3.2.16 Patients who have blood methemoglobin > ULN, assessed in an arterial or venous blood sample or by co-oximetry are not eligible.

3.2.17 Patients with a concurrent illness, including severe infection, which may jeopardize the ability of the subject to receive the procedures outlined in this protocol with reasonable safety are not eligible.

3.2.18 Concomitant use of strong inhibitors of CYP3A4/1A2 within 1 week or 5 half-lives (whichever is longer) or strong inducers of CYP3A4/1A2 within 2 weeks or 5 half-lives (whichever is longer) is not permitted (Please refer to Section 4.5.2, and Appendix E).

3.2.19 Patients with a placement of Gliadel® wafer at surgery are not eligible.

3.2.20 Patients who are unable to undergo Gd-MRI are not eligible.

3.2.21 Patients with current known alcohol dependence or drug abuse are not eligible.

3.2.22 Patients with a history or presence of hypersensitivity or idiosyncratic reaction to methylene blue are not eligible.

3.2.23 Patients with a prior history of serotonin syndrome are not eligible.

3.2.24 Known history of positive test for human immunodeficiency virus (HIV) or known acquired immunodeficiency syndrome (AIDS).

3.2.25 Patients who have any positive test result for hepatitis B virus or hepatitis C virus indicating presence of virus, e.g., Hepatitis B surface antigen (HBsAg, Australia antigen) positive, or Hepatitis C antibody (anti-HCV) positive (except if HCV RNA negative) are not eligible.

3.2.26 Patients with the presence of any familial, sociological or geographical condition potentially hampering compliance with the study protocol and follow-up schedule are not eligible; those conditions should be assessed with the patient before registration in the trial.

3.2.27 Patients with major medical illnesses or psychiatric impairments that in the investigator's opinion will prevent administration or completion of protocol therapy are not eligible.

4 TREATMENT PLAN

4.1 Overview

This is a multi center, open-label, uncontrolled, Phase I study conducted in subjects with newly diagnosed grade IV Glioma.

Approximately 18-30 patients will be enrolled. Up to 18 unmethylated MGMT patients will be enrolled initially using a classic 3+3 dose escalation design to determine MTD (see section 4.3). Once the MTD for unmethylated MGMT patients is determined, a cohort of patients with methylated MGMT gene promoter will be treated, starting one dose level below the recommended MTD and then escalated up to the recommended MTD. These patients will also receive concomitant TMZ chemotherapy.

For both cohorts, there will be a 4-week screening period, after which subjects will begin study treatment. All patients will receive radiation therapy for 5 days a week for a total of 6 weeks to a dose of 60 Gy. Details of the radiation regimen can be found in section 4.2.4. Patients will also receive nivolumab at 240mg IV Q2W and BMS-986205 PO QD in combination with RT beginning on Day 1.

Patients will be treated with a dose escalation plan for BMS-986205 based on a 3+3 study design.

Upon completion of RT, there will be a post RT phase (28 days) followed by a Maintenance Phase. Patients will continue to receive nivolumab in combination with BMS-986205 during both the post RT and Maintenance Phases. Beginning at Cycle 6, nivolumab dosing will change to 480mg IV Q4W.

Nivolumab and BMS-986205 will be administered for the entire course of the trial, or until progression or unacceptable AEs. There is no particular order in which treatment should be administered.

Patients who have disease progression per iRANO criteria or clinical decline, may have the option to re-start treatment if they undergo standard of care surgery, and their tumor tissue shows on pathologic review that that there is no evidence of significant tumor and the changes on MRI were likely treatment related. The patient will be advised of the pathology results and that they may not derive any further benefit from re-starting therapy. The patient will need to re-sign the informed consent prior to starting therapy.

4.2 Treatment Administration

<table>
<tr><th colspan="6">Treatment Administration Summary</th></tr>
<tr><th>Agent</th><th>Dose</th><th>Route</th><th>Schedule</th><th>Cycle Length</th><th>Supportive Therapies</th></tr>
<tr><td>BMS-986205</td><td>Phase I starting dose 50 mg (see 4.3 for escalation)</td><td>PO</td><td>QD</td><td rowspan="5">RT Phase: 6 weeks

Maintenance Phase: 28 Days</td><td>As Needed</td></tr>
<tr><td>Nivolumab</td><td>240mg

480mg (Beginning at Cycle 6 of Maintenance Phase)</td><td>IV</td><td>Q2W

Q4W (Beginning at Cycle 6 of Maintenance Phase)</td><td>As Needed</td></tr>
<tr><td rowspan="2">Temozolomide (in MGMT promoter methylated cohort)</td><td>75 mg/m^2 during RT</td><td rowspan="2">PO</td><td>QD</td><td rowspan="2">As Needed</td></tr>
<tr><td>200mg/m^2 4 weeks after completion of RT</td><td>QD for 5 days every 4 weeks (for a total of 6 cycles)</td></tr>
<tr><td>TTFields</td><td>N/A</td><td>Directly applied to shaved scalp</td><td>Continuous with intermittent breaks as needed</td><td>28 days (TTFields to begin during Maintenance Phase)</td><td>As Needed</td></tr>
</table>

4.2.1 **BMS-986205**

Treatment will be administered on an outpatient basis. Patients will receive a supply of BMS-986205 and will be instructed to take the dose at approximately the same time every day following a meal. Patients should avoid grapefruit and Sevile oranges and their juices due to the potential for CYP3A4 inhibition. Missed doses can be taken within 12 hours, otherwise patients should skip that dose and take the dose the following day. BMS-986205 tablets may not be crushed. Patients will be instructed to swallow the tablets whole, in rapid succession, without chewing them. If vomiting occurs during the course of treatment, no re-dosing of the patient is allowed before the next scheduled dose. Patients will be given a drug diary and should bring back any pill containers to monitor compliance.

BMS-986205 will be administered daily during the radiation phase, during the 4 week interval between radiation and the first post-radiation MRI, and will continue on the same schedule in the adjuvant phase.

The dose of BMS-986205 during the phase 1 trial will be delineated for each dosing cohort.

4.2.2 **Nivolumab**

All patients in the study will receive nivolumab. Nivolumab will be administered IV every 2 weeks on Day 1 and Day 15 of each cycle (Day 1 is the same day as the 1st dose of radiation). Nivolumab will be infused over 30 minutes. No premedication is required. Nivolumab will be dosed at 240 mg per dose.

Nivolumab will be administered every 2 weeks during the radiation phase, during the 4 week interval between radiation and the first post-radiation MRI, and will continue on the same schedule in the Maintenance phase.

Participants should receive nivolumab at a dose of 240 mg as a 30 minute infusion on Day 1 and Day 15 of each treatment cycle until progression, unacceptable toxicity, withdrawal of consent, the study ends, or until Q4W dosing begins, whichever occurs first. Beginning with at cycle 6 of the Maintenance Phase, participants should receive nivolumab at a dose of 480 mg as a 30 minute infusion every 4 weeks (± 2 days) until progression, unacceptable toxicity, withdrawal of consent, or the study ends, whichever occurs first.
There will be no dose escalations or reductions of nivolumab allowed.
Participants may be dosed no less than 12 days from the previous dose during q2w cycles.

Participants should be carefully monitored for infusion reactions during nivolumab administration. If an acute infusion reaction is noted, participants should be managed according to Section 4.4.2.

4.2.3 **Temozolomide**

The dose of TMZ for MGMT methylated patients is from the standard of care as described in the EORTC/NCIC phase III trial.

4.2.3.1 **Temozolomide During Concomitant Radiation Therapy**
Only the MGMT promoter methylated cohorts will receive TMZ. They will receive it concomitantly with radiation and in up to 6 maintenance cycles after radiation.

TMZ will be administered continuously from day 1 ±2 days of radiotherapy to the last day of radiation at a daily (7 days a week) oral dose of 75 mg/m2 for a maximum of 49 days, as per standard practice.

The dose will be determined using the body surface area (BSA) calculated at baseline. The BSA will be calculated from the height obtained at the pretreatment visit and the weight obtained at the visit immediately before the first day of treatment. Capsules of TMZ are available in 5, 20, 100, and 250 mg. The daily dose will be rounded to the nearest 5 mg, which is standard of care. The exact dose administered should be recorded in the medical record.

Patients will be instructed to swallow the capsules whole, in rapid succession, without chewing them. If vomiting occurs during the course of treatment, no re-dosing of the patient is allowed before the next scheduled dose. The capsules should be taken on an empty stomach, therefore a minimum of 2 hours after a meal and with no food ingestion for 1 hour after TMZ administration.

Prophylaxis with a 5-HT3 antagonist is recommended prior to administration of the first few TMZ doses and should be administered orally 30 to 60 minutes before TMZ treatment.

4.2.3.2 **Post-Radiation Temozolomide**
Only the MGMT promoter methylated cohorts will receive post-radiation TMZ.

The start of the first maintenance cycle will be scheduled 28 days ± 3 days after the last day of radiotherapy. The start of all subsequent maintenance cycles (2-6) will be scheduled every 4 weeks (28 days ± 2 days) after the first daily dose of TMZ of the preceding cycle. TMZ will be administered orally once per day for 5 consecutive days (days 1-5) of a 28-day cycle. The starting dose for the first cycle will be 200 mg/m^2/day. Prior to each treatment cycle with TMZ a complete blood count (CBC) will be obtained (within 72 hours prior to dosing).

The dose will be determined using the BSA calculated at the beginning of each treatment cycle. The BSA will be calculated from the height obtained at baseline and from the weight obtained at the visit immediately before each cycle. Capsules of TMZ are available in 5, 20, 100, and 250 mg. The daily dose will be rounded to the nearest 5 mg. The exact dose administered should be recorded in the medical record.

Patients will be instructed to swallow the capsules whole, in rapid succession, without chewing them. If vomiting occurs during the course of treatment, no re-dosing of the patient is allowed before the next scheduled dose. The capsules should be taken on an empty stomach, therefore a minimum of 2 hours after a meal and with no food ingestion for 1 hour after TMZ administration.

Antiemetic prophylaxis with a 5-HT3 antagonist is strongly recommended and should be administered 30 to 60 minutes before TMZ administration.

Duration of treatment. Patients will be treated with post-radiation TMZ for 6 cycles unless there is evidence of tumor progression or treatment related toxicity.

4.2.4 **Radiation Therapy**

4.2.4.1 **Dose Specifications and Schedule**

Radiotherapy must begin within ≤ 6 weeks (42 days) of surgery. A treatment fraction of 2Gy will be delivered daily, 5 days per week, for 6 weeks, yielding a cumulative dose of 60Gy to the target volume.

4.2.4.2 **Technical Factors**

Treatment will be delivered with three-dimensional conformal radiotherapy (3D-CRT) or intensity-modulated radiotherapy (IMRT) utilizing megavoltage machines capable of beam energies of at least 6MV. Selection of photon-energies will depend on dose-distribution optimization. Source-to-axis distance (SAD) or source-to-skin distance (SSD) must be at least 80cm. IMRT methods may include fixed-gantry beam delivery, helical tomotherapy or volumetic modulated arc therapy (VMAT). Electron therapy is not permitted.

4.2.4.3 **Localization, Simulation, and Immobilization**

The patient shall be treated in a reproducible supine or other appropriate position utilizing a thermoplastic mask and headrest. A planning CT scan of the cranial contents (with ≤ 3.0mm slice thickness) will be fused with both pre- and post-operative MRI.

4.2.4.4 **Treatment Planning/Target Volumes**

Electronic fusion with the post-operative MRI is required for target volume definition while pre-operative imaging may be utilized for correlation and identification of tumor extent.

4.2.4.5 **Initial Target Volume**

For the first phase of treatment, gross tumor volume 1 (GTV1) will be defined to include: contrast enhancing disease + surgical cavity + surrounding edema. This will undergo a 2-cm uniform volumetric expansion to create clinical target volume 1 (CTV1), which may be reduced around natural barriers to tumor growth such as falx, skull, and ventricles, etc. Planning treatment volume 1 (PTV1) will be created to account for set-up and reproducibility errors by an additional expansion of 3 to 5 mm depending on localization method. This may not be reduced to modify organ at risk (OAR) dosing. The initial target volume will be treated to 46 Gy in 23 fractions.

4.2.4.6 **Boost Target Volume**

For the second phase of treatment, GTV2 will be defined to include: contrast enhancing disease + surgical cavity. This will undergo a 2-cm uniform volumetric expansion to create CTV2, which may be reduced around natural barriers to tumor growth such as falx, skull, and ventricles, etc. PTV2 will be created to account for set-up and reproducibility errors by an additional expansion of 3 to 5 mm depending on localization method. This may not be reduced to modify OAR dosing. The boost target volume will be treated to 14 Gy in 7 fractions.

4.2.4.7 **Dosing Guidelines**

Dosing will be normalized such that 95% of the PTV (D95%) should be covered by 100% of the prescription dose. An acceptable variation is that of D95% being covered by 95% of the prescription dose. Dose homogeneity optimization should ensure that D10% is < 63Gy (variation

acceptable: 63-65.12Gy) and that D0.03cc ≤ 64 (variation acceptable: 64-66Gy).

4.2.4.8 **Dose Limitation to Critical Structures**
The following OARs must be defined: (1) Lenses, (2) Retinae, (3) Optic nerves, (4) Optic chiasm, and (5) Brainstem.

The optic nerves, optic chiasm and brainstem will undergo a uniform volumetric expansion by 3mm to create the corresponding planning risk volume (PRV) which shall be utilized for dose constraints. These OARs should adhere to the following maximal point dose constraints (defined as a volume greater than 0.03cc): lenses = 7Gy; retinae = 50Gy; optic nerves = 55Gy; optic chiasm = 55Gy, brainstem = 60Gy.

4.2.5 **Tumor Treating Fields (TTFields)**
TTFields will be initiated approximately 4 weeks after the completion of RT. They will be initiated only after the post-RT MRI is completed. Some delay between the completion of the post-RT MRI and initiation of TTFields will be allowable to allow for accommodation of the logistical aspects of initiating TTFields which are outside of the treating physicians' control.

TTFields will be applied to the shaved scalp. They will be reapplied as need (typically approximately every 3 days). A cycle of TTFields will be defined as 28 days. If a patient utilizes TTFields for even a minimal amount of time during a cycle they will be recorded as having utilized TTFields for that respective cycle. Duration of therapy with TTFields will be indefinite, as long as there is no tumor growth and the TTFields prove tolerable.

If patients elect to refrain from utilizing TTFields they will be able to continue with on study treatment.

4.3 BMS-986205 Dose Escalation

The table below summarizes the dose levels. A dose level -1 is included in the event that level 1 is determined to be too toxic.

Dose Escalation Scheme		
Dose Level	**BMS-986205**	**# of Patients^**
Level -1	25 mg	3-6
Level 1*	50 mg	3-6
Level 2	100 mg	3-6
*Starting dose level ^A minimum of 3 patients will be treated per cohort; a total of 6 patients should be treated at whichever dose level is determined to be the MTD.		

A standard "3+3" dose escalation design will be utilized. Initially, 3 patients will be enrolled at the starting dose (level 1), after which enrollment will be temporarily suspended until all 3 patients complete the DLT evaluation period (defined as the duration of RT (6 weeks)). Once all 3 patients complete the DLT period and toxicity data has been submitted, the Data and Safety Monitoring Committee (DSMC) will review the data and confirm the presence or absence of any DLTs (defined below). The following rules will be used at each dose level to determine whether or not to proceed to the next dose level:

Dose Level	Dose	Number of patients	Number of DLTs	Outcome
-1	25 mg	3	0 or 1 of 3	Additional 3 slots will be added
			2+ of 3	Study will be closed to further accrual and the regimen of BMS-986205 + Nivolumab will be considered too toxic at any dose
		3-6	1 of 6	Dose level will be declared MTD
			2+ of 6	Study will be closed to further accrual and the regimen of BMS-986205 + Nivolumab will be considered too toxic at any dose
1	50 mg	3	0 of 3	Proceed to the next dose level
			1 of 3	Additional 3 slots will be added
			2+ of 3	De-escalation to level -1 will occur.
		3-6	1 of 6	Escalation will proceed to the next level
			2+ of 6	De-escalation to level -1 will occur.
2	100 mg	3	0 of 3	Additional 3 slots will be added.
			1 of 3	Additional 3 slots will be added.
			2+ of 3	The previous level will be declared the maximum tolerated dose (MTD)
		3-6	1 of 6	Dose level will be declared MTD
			2+ of 6	Previous level will be declared the MTD.

NOTE: Whichever dose level is declared the MTD must have 6 total patients treated at that level, however this number could be expanded at discretion of PI and funding sponsor. For example, if 3 patients are treated at level 2 and 0 patients experience DLT, an additional 3 patients will enroll at that level (with 0 or 1 DLT observed in 6 total patients) in order to declare level 2 the MTD. Further, if 2+ patients experience a DLT at dose level 2, additional 3 patients will be added to dose level 1 prior to being declared the MTD.

Note: intrapatient dose escalation will not be allowed.

4.3.1 **Dose Limiting Toxicity**

Dose Limiting Toxicities will be monitored for a period of 6 weeks.

A Dose-Limiting Toxicity is defined below and considered possibly, probably, or definitely-related to BMS-986205 or the combination of BMS-986205 and nivolumab, excluding known TMZ-related hematological toxicities (in the MGMT promoter methylated cohorts treated with TMZ). For certain events it may be difficult to attribute a toxicity exclusively to the investigational agent or the standard treatment, e.g. overlapping toxicity: nausea and vomiting or enhancing effects. The AE will be described as detailed as possible and the investigators and BMS will subsequently attempt to identify events that apply specifically attributable to BMS-986205 and/or nivolumab. If patient experiences a dose-limiting toxicity, they will be removed from the study.

4.3.1.1 **Nonhematologic Dose-Limiting Toxicity (DLT):**
Hepatic Nonhematologic DLT

Any of the following events will be considered a hepatic DLT:

- Any ≥ Grade 3 elevation of AST, ALT, or total bilirubin
- Grade 2 AST or ALT with symptomatic liver inflammation (e.g., right upper quadrant tenderness, jaundice, pruritus)
- AST or ALT > 3× ULN and concurrent total bilirubin > 2× ULN without initial findings of cholestasis (elevated serum alkaline

phosphatase, e.g., findings consistent with Hy's law or FDA definition of potential drug-induced liver injury [DILI])*

*Note that this special category of DLT uses ULN rather than Common Toxicity Criteria Grade for definition.

Nonhepatic Nonhematologic DLT
Any of the following events will be considered a nonhepatic nonhematologic DLT:

- Grade 2 episcleritis, uveitis, or iritis
- Any other Grade 2 eye pain or blurred vision that does not respond to topical therapy and does not improve to Grade 1 severity within 2 weeks OR requires systemic treatment
- Grade 2 myocarditis
- Grade 3 pneumonitis, bronchospasm, neurologic toxicity, hypersensitivity reaction, or infusion reaction of any duration requires discontinuation
- Any Grade 3 nondermatologic, nonhepatic, nonhematologic toxicity will be considered a DLT with the following specific EXCEPTIONS:
    - Grade 3 or Grade 4 electrolyte abnormalities that are not complicated by associated clinical adverse experiences, last less than 48 hours and either resolve spontaneously or respond to conventional medical intervention
    - Grade 3 nausea, vomiting, or diarrhea that lasts less than 48 hours and either resolves spontaneously or responds to conventional medical intervention
    - Isolated Grade 3 elevation of amylase or lipase not associated with clinical or radiographic evidence of pancreatitis
    - Isolated Grade 3 fever not associated with hemodynamic compromise (e.g., hypotension, clinical or laboratory evidence of impaired end-organ perfusion)
    - Grade 3 endocrinopathy that is well-controlled by hormone replacement
    - Grade 3 tumor flare (defined as pain, irritation, or rash that localizes to site of known or suspected tumor)
    - Grade 3 fatigue
    - Grade 3 infusion reaction that returns to Grade 1 in less than 6 hours

Dermatologic DLT

- Grade 3 rash if no improvement (i.e., resolution to ≤ Grade 1) after a 1- to 2-week infusion delay. Subjects who have not experienced a Grade 3 drug-related skin AE may resume treatment in the presence of Grade 2 skin toxicity.
- Grade 4 rash of any duration
- Grade 4 dermatologic toxicity
- For all dermatologic DLTs, if the dermatologic toxicity is assessed as due to TTFields and not nivolumab, BMS-986205, or TMZ, TTFields will be on hold and systemic therapies can continue at the discretion of the treating physician and PI.

Hematologic DLT

- Methemoglobin levels ≥ 15%

- Grade 4 neutropenia ≥ 5 days in duration
- Grade 4 thrombocytopenia or Grade 3 thrombocytopenia with bleeding, or any requirement for platelet transfusion
- Grade ≥ 3 febrile neutropenia for 48 hours
- Grade ≥ 3 hemolysis (i.e., requiring transfusion or medical intervention such as steroids)
- Grade 4 anemia not explained by underlying disease

Other DLT

- Grade 3 or higher non-dermatologic, non-hepatic, non-hematologic toxicity
- Grade 4 lab abnormalities. With sufficient justification, you may specify that certain abnormalities will be excluded.

If one of the initial phase I subjects is withdrawn for reasons other than those mentioned above, the subject can be replaced. Patients receiving a dose of BMS will be evaluable for toxicity. Another patient should be added if a patient withdraws study treatment prior to completing DLT period.

In addition to the above mentioned reasons for discontinuing the study, subjects will be monitored carefully for AEs related to the administration of nivolumab and BMS-986205, and the following early safety stopping rules will be applied:

- The phase I component of the study will initially enroll only MGMT promoter unmethylated patients. The cohort of MGMT promoter methylated patients will only begin accruing after a phase II dose of BMS-986205 has been established (See below).

- During the phase I component of the study, the first 3 subjects in the MGMT promoter unmethylated cohort enrolled will be monitored with additional care for a period of 6 weeks (6 weeks of radiation). If no more than 1 Dose-Limiting Event occurs with the first 3 subjects during the 6-week observation period, subject enrollment is to continue.

- Once the phase II dose of BMS-986205 has been established in MGMT promoter unmethylated patients, 3 patients in the MGMT promoter methylated cohort will be treated at that dose. If there is a Dose-Limiting Event, the cohort will be expanded by 3 patients (i.e. total 3-6 patients at that dosing cohort).

- The phase II MGMT promoter unmethylated and MGMT promoter methylated cohorts will run simultaneously. The MGMT promoter unmethylated phase II cohort will begin accruing once the phase I MGMT promoter unmethylated study has been completed and a phase 2 dose of BMS-986205 has been established. The phase II MGMT promoter methylated cohort will begin accruing after the phase I MGMT promoter methylated study has been completed and a phase II dose of BMS-986205 has been established for the MGMT promoter methylated patients.

4.4 Toxicity Management & Dose Delays/Modifications

Any patient who receives at least one dose of nivolumab or BMS-986205 will be evaluable for toxicity endpoints. Each patient will be assessed for the development of toxicity according to the timeframe referenced in the Schedule of Events table. Toxicity will be assessed according to Common Terminology Criteria for Adverse Events (CTCAE) version 5.0.

As immunotherapies can be associated with delayed toxicities subjects will be queried regarding potential toxicities at each off study follow up call.

Modifications should be made to the causing agent and other therapies may continue as permitted per protocol.

4.4.1 BMS-986205

The dosing cohorts of BMS-986205 is based upon the phase II dose determined in the phase I trial for solid tumors (NCT03192943) as discussed in Section 1. The MTD has been established at 200 mg in combination with nivolumab based on the safety and tolerability profile and incidence of dose-limiting toxicities (DLTs). While 200 mg QD was the MTD established in dose escalation of BMS-986205 in combination with nivolumab, preliminary PK, PD, and safety data support the selection of 100 mg QD.

4.4.1.1 Holding Dose

BMS-986205 should be delayed for the following:

- Clinically significant elevations in methemoglobin (generally 10% with a normal hemoglobin level) with any associated Grade 3 AE (hypoxia, dyspnea, confusion, etc.) attributable to sustained elevations of methemoglobin and not attributable to another etiology
- QTcF > 500 msec confirmed by at least 1 repeat ECG and at least 60 msec above baseline

4.4.1.2 Dose reduction

Doses of BMS-986205 should be reduced one dose level for the following AEs attributable to study therapy that do not otherwise meet criteria for discontinuation:

- Grade 3 fatigue, nausea, vomiting, or anemia related to study treatment.

  Note: dose can be reduced without being held.
- Clinically significant elevations in methemoglobin (generally 10%, with a normal hemoglobin level) with any associated Grade 3 AE (hypoxia, dyspnea, confusion, etc.) attributable to sustained elevations of methemoglobin and not attributable to another etiology
- QTcF > 500 msec confirmed by at least 1 repeat ECG and at least 60 msec above baseline

Dose modification and interruption of BMS-986205 may occur in the setting of lower grade AEs and/or be more conservative than indicated above based on the clinical judgment of the investigator and in consultation with the PI. For an AE requiring dose modification, BMS-986205 should be interrupted to allow improvement of the AE, even if the AE does not otherwise meet criteria for dose delay.

Re-escalation of BMS-986205 will not be permitted once the dose of BMS-986205 has been reduced for a participant.

Only one dose reduction is permitted. The participant must discontinue BMS-986205 if a subsequent dose reduction of BMS-986205 is required.

4.4.1.3 **Methemoglobinemia**

Detection of Methemoglobinemia

BMS-986205 may produce a p-chloroaniline metabolite. P-chloroaniline has been associated with the production of methemoglobin. Symptoms of methemoglobinemia are related to the lack of oxygen delivery to tissues and are proportional to the fraction of methemoglobin, as described below for participants with normal hemoglobin levels.

Symptoms associated with elevations of methemoglobin are as follows:

- 0% to 10% - Usually asymptomatic
- 10% to 20% - Cyanosis without other symptoms
- 20% to 50% - Headache, dyspnea, lightheadedness (possibly syncope), weakness, confusion, palpitations, chest pain
- 50% to 70% - Coma, seizures, arrhythmias; acidosis
- >70% - Usually death

Note that participants with anemia may experience symptoms at lower methemoglobin percentages than listed above, depending on the degree of anemia.

Increasing levels of methemoglobin may confound the results of standard pulse oximeters, with values of around 85% reported consistently as methemoglobin levels increase, regardless of the true oxygen saturation.

When methemoglobinemia is suspected, part of the diagnostic work-up includes evaluation for other disorders that can present with a similar clinical picture, including cardiac and pulmonary disease. A fresh peripheral blood sample (either venous or arterial) should be sent for evaluation of methemoglobin levels; methemoglobin levels may vary with storage of blood.

Treatment of Methemoglobinemia Associated with BMS-986205

The following management recommendations are intended as guidelines for the investigator and may be modified based on institutional practices or local standard of care, as appropriate.

Initial care includes supportive measures and the administration of supplemental oxygen. In mild cases, recovery often occurs simply by interrupting the administration of the offending medication. Concomitant medication lists should be reviewed for medications besides study treatment which can cause methemoglobinemia.

Further treatment is generally indicated when the methemoglobin level is above 20% or is associated with symptoms.

Intravenous methylene blue is the first-line antidotal agent and works by restoring the oxygen carrying capacity of hemoglobin by reduction of methemoglobin from its oxidized state. It is given as a 1% solution at a dose of 1 to 2 mg/kg. Most participants require only 1 dose, and symptoms should resolve within 1 hour. Methylene blue may confound

the interpretation of methemoglobin levels detected by co-oximetry; alternative methods should be used after treatment with methylene blue if methemoglobin level monitoring is required. Methylene blue should be used with caution in participants with concurrent use of serotonergic psychiatric medications, as this could increase the risk of serotonin syndrome.

Exchange transfusion and hyperbaric oxygen treatment are second-line options for participants with severe methemoglobinemia whose condition does not respond to methylene blue or who cannot be treated with methylene blue. Participant transfer should occur when life-threatening methemoglobinemia that is refractory to treatment occurs in a facility that cannot provide the appropriate critical care.

4.4.1.4 **Discontinuation of BMS-986205**

BMS-986205 treatment should be permanently discontinued for the following:

- Any event requiring discontinuation of nivolumab
- Any event requiring more than 1 dose reduction of BMS-986205
- Any AE, laboratory abnormality, or intercurrent illness which, in the judgment of the investigator, presents a substantial clinical risk to the participant with continued BMS 986205 dosing
- For participants who delay BMS-986205 but continue nivolumab, any dose delay of BMS 986205 lasting > 12 weeks will result in the discontinuation of BMS 986205 only and participants may continue treatment with nivolumab
- Any occurrence of serotonin syndrome

4.4.2 **Nivolumab**

The dose of nivolumab was determined based on nonclinical and clinical information as described in Section 1.2.

There will be no dose modifications of nivolumab. Nivolumab can be held up to 12 weeks. After 12 weeks, resumption of nivolumab will require discussion with PI.

Participants who require delay of nivolumab should be re-evaluated as clinically indicated, and resume nivolumab dosing at time of next cycle when re-treatment criteria are met.

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

- Participants may resume treatment in the presence of grade 2 fatigue
- Participants who have not experienced a grade 3 drug-related skin AE may resume treatment in the presence of grade 2 skin toxicity
- For participants with grade 2 AST, ALT and/or total bilirubin abnormalities, dosing may resume when laboratory values return to grade 0-1
- Participants with persistent grade 1 pneumonitis after completion of a steroid taper over at least 1 month may be eligible for retreatment if discussed with, and approved by, the PI.
- Participants with drug-related endocrinopathies adequately controlled with only physiologic hormone replacement may resume treatment.

Please refer to the table below for further guidelines for holding/restarting therapy.

Dosing Guidelines for Drug-Related Adverse Events for Nivolumab

Toxicity	Severity	Dose Modification
Diarrhea/Colitis	Grade 2/3 diarrhea or colitis	Withhold dose[1]
	Grade 4 diarrhea or colitis	Permanently discontinue
Pneumonitis	Grade 2 pneumonitis	Withhold dose[1]
	Grade 3/4 pneumonitis	Permanently discontinue
Hepatitis	Aspartate aminotransferase (AST)/or alanine aminotransferase (ALT) more than 3 and up to 5 times the upper limit of normal or total bilirubin more than 1.5 and up to 3 times the upper limit of normal	Withhold dose[1]
	AST or ALT more than 5 times the upper limit of normal or total bilirubin more than 3 times the upper limit of normal	Permanently discontinue
Hypophysitis	Grade 2/3 hypophysitis	Withhold dose[1]
	Grade 4 hypophysitis	Permanently discontinue
Adrenal Insufficiency	Grade 2 adrenal insufficiency	Withhold dose[1]
	Grade 3/4 adrenal insufficiency	Permanently discontinue
Type 1 Diabetes Mellitus	Grade 3 hyperglycemia	Withhold dose[1]
	Grade 4 hyperglycemia	Permanently discontinue
Nephritis and Renal Dysfunction	Serum creatinine more than 1.5 and up to 6 times the upper limit of normal	Withhold dose[1]
	Serum creatinine more than 6 times the upper limit of normal	Permanently discontinue
Skin	Grade 3 rash or suspected Stevens-Johnson syndrome (SJS) or toxic epidermal necrolysis (TEN)	Withhold dose[1]
	Grade 4 rash or confirmed SJS or TEN	Permanently discontinue
Encephalitis	New-onset moderate or severe neurologic signs or symptoms	Withhold dose[1]
	Immune-mediated encephalitis	Permanently discontinue
Other	Other Grade 3 adverse reaction: First occurrence Recurrence of same Grade 3 adverse reaction	Withhold dose[1] Permanently discontinue
	Life-threatening or Grade 4 adverse reaction	Permanently discontinue
	Requirement for 10mg per day or greater prednisone or equivalent for more than 12 weeks	Permanently discontinue
	Persistent Grade 2 or 3 adverse reactions lasting 12 weeks or longer	Permanently discontinue

1. Resume treatment when adverse reaction returns to Grade 0 or 1.

4.4.2.1 **Treatment of Nivolumab-related Infusion Reactions**

Since nivolumab contains only human immunoglobulin protein sequences, it is unlikely to be immunogenic and induce infusion or hypersensitivity reactions. However, if such a reaction were to occur, it might manifest with fever, chills, rigors, headache, rash, pruritus, arthralgias, hypotension, hypertension, bronchospasm, or other allergic-like reactions. Please refer to the table below for management of infusion reactions.

Immunotherapy agents such as nivolumab are associated with AEs that can differ in severity and duration compared to other therapeutic classes of medications. Early recognition and management of AEs associated with nivolumab can mitigate severe toxicity. Corticosteroids are the primary therapy for drug-related AEs. Management algorithms have been developed to assist investigators in assessing and managing nivolumab associated AEs, which can be found in Appendix D of this protocol. The guidance provided in these algorithms should not replace the Investigator's medical judgment.

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

Nivolumab Infusion Reactions		
NCI CTCAE Grade	**Treatment**	**Premedication at subsequent dosing**
Grade 1 Mild reaction; infusion interruption not indicated; intervention not indicated	Remain at bedside and monitor patient until recovery from symptoms.	The following prophylactic pre-medications are recommended for future infusions: • Diphenhydramine 50 mg (or equivalent) and/or • Acetaminophen 325 to 1000 mg at least 30 minutes before additional nivolumab administrations
Grade 2 Moderate reaction requires therapy or infusion interruption but responds promptly to symptomatic treatment [eg, antihistamines, non-steroidal anti- inflammatory drugs, narcotics, corticosteroids, bronchodilators, IV fluids]; prophylactic medications indicated for < 24 hours	Stop the nivolumab infusion, begin an IV infusion of normal saline, and treat the patient with diphenhydramine 50 mg IV (or equivalent) and/or acetaminophen 325 to 1000 mg; Remain at bedside and monitor patient until resolution of symptoms. Corticosteroid and/or bronchodilator therapy may also be administered as appropriate. If the infusion is interrupted, then restart the infusion at 50% of the original infusion rate; if no further complications ensue after 30 minutes, the rate may be increased to 100% of the original infusion rate.	For future infusions, the following prophylactic pre-medications are recommended: • Diphenhydramine 50 mg (or equivalent) and/or • Acetaminophen 325 to 1000 mg should be administered at least 30 minutes before nivolumab infusions. • If necessary, corticosteroids (up to 25 mg of SoluCortef or equivalent) may be used.

Nivolumab Infusion Reactions		
NCI CTCAE Grade	**Treatment**	**Premedication at subsequent dosing**
	Monitor patient closely. If symptoms recur, then no further nivolumab will be administered at that visit.	
Grades 3 or 4 Severe reaction, 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	Immediately discontinue nivolumab infusion. Begin an IV infusion of normal saline and treat the patient as follows: Recommend bronchodilators, epinephrine 0.2 to 1 mg of a 1:1000 solution for subcutaneous administration or 0.1 to 0.25 mg of a 1:10,000 solution injected slowly for IV administration, and/or diphenhydramine 50 mg IV with methylprednisolone 100 mg IV (or equivalent), as needed. Patient should be monitored until the Investigator is comfortable that the symptoms will not recur. Nivolumab will be permanently discontinued. Investigators should follow their institutional guidelines for the treatment of anaphylaxis. Remain at bedside and monitor patient until recovery of the symptoms In case of late-occurring hypersensitivity symptoms (eg, appearance of a localized or generalized pruritus within 1 week after treatment), symptomatic treatment may be given (eg, oral antihistamine or corticosteroids	No subsequent dosing

4.4.3 Combination Nivolumab and BMS-986205

4.4.3.1 Treatment Delay

BMS-986205 and Nivolumab administration should be delayed for the following:

- Grade 2 non-skin, drug-related AE, with the exception of fatigue, nausea, vomiting and anemia. If determined by the treating investigator and PI to definitely be due to TTFields (device-related) and unrelated to BMS-986205 and unrelated to nivolumab treatment with BMS-986205 and nivolumab may continue.
- Grade 2 drug-related creatinine, AST, ALT and/or Total Bilirubin abnormalities
- Grade 3 skin, drug-related AE. If determined by the treating investigator and PI to definitely be due to TTFields (device-related) and unrelated to BMS-986205 and unrelated to nivolumab treatment with BMS-986205 and nivolumab may

continue. TTF would be held until the toxicity resolves to ≤grade 1.

- Grade 3 drug-related fatigue, nausea, vomiting, and anemia
- Grade 3 drug-related laboratory abnormality, with the following exceptions:
  - Grade 3 lymphopenia or asymptomatic amylase or lipase elevations do not require dose delay
  - Grade > 3 AST, ALT, Total Bilirubin will require dose discontinuation
  - Any AE, laboratory abnormality, or intercurrent illness which, in the judgment of the investigator, warrants delaying the dose of study medication

Participants may continue to receive Nivolumab during dose delays of BMS-986205 for elevations of methemoglobin and associated events, as well as QT prolongations. For participants with methemoglobin elevations with associated Grade 3 AEs, if contribution of Nivolumab to the associated AE cannot be ruled out (e.g., a participant with dyspnea in whom pneumonitis has not yet been ruled out), Nivolumab dosing should be delayed as well. See Section 4.4.1.2 for management of methemoglobinemia.

If BMS-986205 dosing is delayed, dose reduction may be necessary.

If dosing is resumed after a delay, BMS-986205 may be resumed as soon as the criteria to resume treatment are met. Nivolumab should be resumed as soon as possible after criteria to resume treatment are met, but may be resumed later than BMS-986205 given the differences in each drug's administration.

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

4.4.3.2 Treatment Discontinuation

Should the treating physician decide to discontinue treatment given suspicion for a drug-related side effect, the side effect should be attributed to one study drug to the best of the physician's ability. Based on attribution, patients may discontinue single study drug and continue other treatments if outside of DLT period for up to 12 weeks.

BMS-986205 and Nivolumab treatment should be permanently discontinued for the following:

- Any Grade 2 drug-related uveitis, eye pain or blurred vision that does not respond to topical therapy and does not improve to Grade 1 severity within the time frame permitted for dose delays OR requires systemic treatment
- Any event requiring more than 1 dose reduction of BMS-986205 requires discontinuation of BMS-986205 only
- Any Grade 3 non-skin, drug-related AE lasting > 7 days or recurs, with the following exceptions for laboratory abnormalities, drug-related uveitis, pneumonitis, bronchospasm, neurologic toxicity, hypersensitivity reactions, infusion reactions, and endocrinopathies:

- Grade 3 drug-related uveitis, pneumonitis, bronchospasm, neurological toxicity, hypersensitivity reaction, or infusion reaction of any duration requires discontinuation.
- Grade 3 drug-related endocrinopathies, adequately controlled with only physiologic hormone replacement do not require discontinuation. Adrenal insufficiency requires discontinuation regardless of control with hormone replacement.
- Grade 3 drug-related laboratory abnormalities do not require treatment discontinuation except:
- Grade 3 drug-related thrombocytopenia > 7 days or associated with bleeding requires discontinuation
- Grade 3 drug-related AST, ALT or total bilirubin requires discontinuation*
- Concurrent AST or ALT > 3 x ULN and total bilirubin > 2x ULN

* In most cases of Grade 3 AST or ALT elevation, study treatment(s) will be permanently discontinued. If the investigator determines a possible favorable benefit/risk ratio that warrants continuation of study treatment(s), a discussion between the investigator and the PI Sponsor Medical Monitor/designee must occur.

- Any Grade 4 drug-related AE or laboratory abnormality (including but not limited to creatinine, AST, ALT, or Total Bilirubin), except for the following events which do not require discontinuation:
  - Grade 4 neutropenia < 7 days
  - Grade 4 lymphopenia or leukopenia or asymptomatic amylase or lipase
  - Isolated Grade 4 electrolyte imbalances/abnormalities that are not associated with clinical sequelae and are corrected with supplementation/appropriate management within 3 calendar days of their onset
  - Grade 4 drug-related endocrinopathy AEs, such as, hyper- or hypothyroidism, or glucose intolerance, which resolve or are adequately controlled with physiologic hormone replacement (corticosteroids, thyroid hormones) or glucose-controlling agents, respectively, may not require discontinuation after discussion with and approval from the PI Sponsor Medical Monitor/designee.
- Any AE, laboratory abnormality, or intercurrent illness which, in the judgment of the investigator, presents a substantial clinical risk to the participant with continued BMS-986205 and Nivolumab dosing
- Any event that leads to delay in dosing lasting > 12 weeks from the previous dose requires discontinuation, with the following exceptions:
  - Dosing delays to allow for prolonged steroid tapers to manage drug-related AEs are allowed.
  - Dosing delays lasting > 12 weeks from the previous dose that occur for non-drug-related reasons may be allowed if approved by the PI Sponsor Medical Monitor/designee.

Prior to re-initiating treatment in a participant with a dosing delay lasting > 10 weeks in which the prescribing physician believes that the patient may benefit from continuation of therapy, the PI/DSMC must be

consulted. Tumor assessments should continue as per protocol even if dosing is delayed. Periodic study visits to assess safety and laboratory studies should also continue every 4 weeks or more frequently if clinically indicated during such dosing delays.

For participants who delay BMS-986205 but continue Nivolumab, any dose delay of BMS-986205 lasting > 12 weeks will result in the patients being taken off study treatment.

In the case of pregnancy, the investigator must immediately notify the PI/QAM of this event via the NU CTO SAE Form. In most cases, the study drug will be permanently discontinued in an appropriate manner. Please contact the PI and DSMC within 24 hours of awareness of the pregnancy. If the investigator determines a possible favorable benefit/risk ratio that warrants continuation of study drug, a discussion with the PI must occur.

4.4.3.3 **Resuming Treatment (BMS-986205 and Nivolumab)**

Participants may resume treatment with study treatments when the drug-related AE(s) resolve to

- Grade < 1 or baseline value, with the following exceptions:
  - Participants may resume treatment in the presence of Grade 2 fatigue.
  - Participants who have not experienced a Grade 3 drug-related skin AE may resume treatment in the presence of Grade 2 skin toxicity.
- For participants with Grade 2 AST, ALT and/or Total Bilirubin abnormalities, dosing may resume when laboratory values return to baseline and management with corticosteroids, if needed, is complete.
- Participants with combined AST/ALT AND total bilirubin values meeting discontinuation
- Parameters should have treatment permanently discontinued.
- Drug-related pulmonary toxicity, diarrhea or colitis must have resolved to baseline before treatment is resumed. Participants with persistent Grade 1 pneumonitis after completion of a steroid taper over at least 1 month may be eligible for retreatment if discussed with and approved by PI Sponsor Medical Monitor/designee.

Participants with drug-related endocrinopathies adequately controlled with only physiologic hormone replacement may resume treatment after consultation with BMS Medical
Monitor/designee. Adrenal insufficiency requires discontinuation regardless of control with hormone replacement.

For participants who have BMS-986205 held for elevations of methemoglobin, dosing may resume when the methemoglobin levels have decreased to below the institutional ULN and any associated AEs have resolved to Grade < 1 or baseline value. Dose modification of BMS-986205 should be considered when resuming after a delay

4.4.4 **Temozolomide**

During either phase of temozolomide, there may be a need for a delay or discontinuation of TMZ or a reduction in dose.

4.4.4.1 **Dose Reduction – Concomitant With Radiation**

Need for delay or discontinuation of TMZ administration or reduction in TMZ dose will be evaluated weekly according to hematologic and non-hematologic AEs, as specified below. If the administration of TMZ has to be interrupted, the radiotherapy will proceed normally. Missed doses of TMZ will not be made up at the end of radiotherapy. The total number of days and total dose of TMZ will be recorded on the appropriate eCRF.

Note: If radiotherapy has to be temporarily interrupted for technical or medical reasons unrelated to the TMZ administration, then treatment with daily TMZ should continue. If radiotherapy has to be permanently interrupted then treatment with daily TMZ should stop.

4.4.4.2 **Dose Reduction – Post-Radiation Treatment (Adjuvant)**

Need for delay or discontinuation of TMZ administration or reduction in TMZ dose will be evaluated weekly according to hematologic and non-hematologic AEs, as specified below. The total number of days and total dose of TMZ will be recorded on the appropriate eCRF.

Should adjuvant TMZ need to be delayed, BMS-986205 and Nivolumab may be continued as long as the treating investigator deems the AE not related to the specific drug.

4.4.4.3 **Withhold TMZ treatment**

If one or more of the following are observed:

- ANC < 1.0 x 10^9/ L
- Platelet count < 100 x 10^9/L
- Grade 3 non-hematologic AE (except alopecia, nausea and vomiting while on maximal antiemetic therapy, and fatigue)
  Note: Any duration of grade 3 vomiting should require holding dose of TMZ (grade 3 vomiting requires tube feeding, TPN, or hospitalization).

TMZ treatment will be withheld until all of the following conditions are met:

- ANC ≥ 1.0 x 10^9/L
- Platelet count ≥ 100 x 10^9/L
- Grade ≤ 1 non-hematologic AE (except alopecia, nausea and vomiting, and fatigue)

In case of hematologic AE as defined above, a complete blood count (CBC) should be performed at least twice weekly. In case of non-hematologic AE, the patient should be assessed at least weekly with relevant laboratory test(s) and any other appropriate methods of evaluation. As soon as all of the above conditions are met, the administration of TMZ will resume at the same dose as used initially. A reduction in TMZ dose may also be appropriate per the investigator's discretion (see section 4.4.4.5).

4.4.4.4 **Discontinue TMZ treatment**

If one or more of the following are observed:

- ANC < 0.5 x 109/L (Grade 4)
- Platelet count < 10 x 10^9/L (Grade 4)
- Grade 3 or 4 non-hematologic AE (except alopecia, nausea and vomiting unless the patient has failed maximal antiemetic therapy, and fatigue)

Note: Patients who experience Grade 3 or 4 nausea and vomiting and has failed maximal antiemetic therapy for up to 3 days will be discontinued from TMZ treatment.

4.4.4.5 **Reduction in TMZ Dose**

In the event of AEs of grade 3 or higher that are possibly, probably, or definitely related to TMZ or if the investigator deems it appropriate, a reduction in dose may be warranted. Investigator should use clinical judgement for decision to dose reduce TMZ. Guidance for dose reduction can be found in the following table.

Patient Temozolomide Dose Level	Temozolomide Dose Modification
Level 1 (starting dose): 200 mg/m^2 QD PO	↓ 150 mg/m^2 QD PO
Level -1: 150 mg/m^2 QD PO	↓ 100 mg/m^2 QD PO
Level -2: 100 mg/m^2 QD PO	↓ 75 mg/m^2 QD PO
Level -3: 75 mg/m^2 QD PO	↓ 50 mg/m^2 QD PO
Level -4: 50 mg/m^2 QD PO	Discontinue

4.4.5 **Radiation Toxicity**

Acute

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

Early Delayed

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

Late Delayed

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

4.4.5.1 **Treatment Delays**

Radiation will be delayed or interrupted if the platelet count is < 20,000 or if the patient's treating physician notes a delay or interruption of the radiation would be in the patient's best interest. Radiation will not begin or resume until the platelet count is ≥ 20,000. Hematologic toxicities should be rated on a scale of 0-5 as defined in the NCI Common Terminology Criteria for Adverse Events (CTCAE) version 5.0 (See Appendix A).

4.4.6 **Tumor Treating Fields (TTFields)**
Holding treatment
If patient develops grade 2 or 3 skin toxicity related to TTFields, TTFields will be held until this resolves to ≤grade 1 at which point they will be resumed per the treating physician's discretion. If patient develops grade 4 skin toxicity related to TTFields, TTFields will be held until this resolves to ≤grade 1. At that point the decision regarding whether to resume will be made by the treating investigator and the PI.

4.5 Concomitant Medications/Treatments

Any concomitant medication or therapy that becomes necessary during the study and any changes in concomitant medication or therapy must be recorded in the corresponding section of the CRF, noting generic drug name, dose, duration, and indication.

Prior chemotherapy, anticonvulsants, and systemic steroid use for treatment of GBM should be documented in the CRF.

Concomitant medications at study entry will be documented on the CRF. Subjects may take any concomitant medications, with the exception of those listed below.

4.5.1 Prohibited Concomitant Medication and Therapy

- Chemotherapy
  Chemotherapy after registration and prior to the first day of treatment on study or chemotherapy at any time during the study. Use of a Gliadel® wafer is also excluded, when placed at surgery.

- Investigational Agents
  None within 4 weeks prior to the first day of treatment on study or at any time during the study. The exception to this are medications for quality of life improvement with no presumed efficacy in treating cancer.

- Biological Agents
  None within 4 weeks prior to the first day of treatment on study or biologic agents other than nivolumab at any time during the study.

- Strong inhibitors of CYP3A4 and/or CYP1A2 or strong inducers of CYP3A4 and/or CYP1A2 (See Appendix E)

- Immunosuppressive agents

- Immunosuppressive doses of systemic corticosteroids (exceptions apply)

- Any concurrent anti-neoplastic therapy (i.e., chemotherapy, hormonal therapy, immunotherapy, extensive, non-palliative radiation therapy, or standard or investigational agents for treatment of malignancy)

- Any botanical preparation (e.g. herbal supplements or traditional Chinese medicines) intended to treat the disease under study or provide supportive care. Please see restrictions on use of marijuana in Section 4.5.2.

- Prophylactic antimicrobial therapy (Note: treatment for Pneumocystis carinii prophylaxis is allowed. See section 4.5.4.2)

4.5.2 **Concomitant Medications/Treatments that are not recommended**
Restricted therapies are not prohibited, but are not recommended; Investigators should consider possible benefit/risk implications of enrolling and treating participants in whom the following are clearly medically indicated:

- Grapefruit and Seville oranges and their juices can inhibit CYP3A4 and should not be consumed while on study.
- Concurrent use of moderate inhibitors or inducers of CYP3A4 and/or CYP1A2 may affect the systemic exposure of BMS-986205. See Appendix E for a list of CYP3A4 and CYP1A2 modulators.
- Concurrent smoking (tobacco, marijuana, etc.) may induce CYP1A2 and decrease the systemic exposure of BMS-986205.
- Caution is warranted when consuming marijuana by means other than smoking as it may lead to increased exposure of BMS-986205 through interaction with metabolic enzymes.
- Caution is warranted when administering BMS-986205 to participants taking drugs that are highly dependent on CYP3A4 or CYP2B6 for metabolism.
- Caution is warranted when administering BMS-986205 to patients taking drugs that may be associated with QT prolongation. See Appendix F for a list of common medications associated with QT prolongation.
- Caution is warranted when administering BMS-986205 to patients taking drugs that are patient to extensive intestinal efflux by P-gp/BCRP. See Appendix H for a list of common P-gp/BCRP substrates.
- In vitro solubility data indicate that BMS-986205 has decreased solubility with increasing pH. Until further data are available, patients should try to avoid taking proton pump inhibitors. H2 antagonists and short-acting antacid agents, such as Maalox® or TUMS®, may be taken, but it is recommended that these not be taken 4 hours before or 4 hours after dosing of BMS-986205.
- Caution is warranted when using other agents known to cause methemoglobinemia (see Appendix G). Dapsone, topical anesthetics, and antimalarial drugs are the most likely agents that may cause methemoglobinemia and these drugs should only be used after discussion with the PI.
- BMS-986205 should be administered following a meal
- Participants must be on a stable or decreasing dose of steroids ≤4mg of decadron for 7 days prior to initiating study treatment [not consent] and be **off** of all steroids at the time of initiation of study treatment (D#1).

4.5.3 **Other Restrictions and Precautions**
Use caution and monitor for symptoms of serotonin syndrome in participants receiving concurrent serotonergic psychiatric medications and/or tryptophan supplements. The development of serotonin syndrome has been associated with exposure to another investigational agent that inhibits the IDO1 enzyme. No case of serotonin syndrome has been observed with administration of BMS-986205. Given the possibility of a class effect, there is a theoretical risk that BMS-986205 could cause an increase in serotonin levels in the brain that might trigger serotonin syndrome when administered in combination with serotonergic agents or tryptophan supplements. Use caution and monitor for symptoms of serotonin syndrome in participants receiving concurrent serotonergic psychiatric medications and/or tryptophan supplements. BMS-986205 should be

discontinued in any participant who develops serotonin syndrome, whether considered related to BMS-986205 or not.

4.5.4 **Permitted Concomitant Medication and Therapy for which specific dose requirements are necessary**
The following medications are permitted with the indicated dosing requirements.

4.5.4.1 **Anticonvulsants**
These are allowed

4.5.4.2 **Pneumocystis carinii prophylaxis**
A prophylaxis against P. carinii (jiroveci) pneumonia is allowed during RT (and until 4 weeks thereafter) in all patients. Both corticosteroid therapy and continuous TMZ therapy induce lymphocytopenia. Subjects receiving any of these drugs or both concomitantly are at an increased risk for opportunistic infections. One of the following treatments should be considered:

- Pentamidine inhaltations Once every 4 weeks
- Trimethoprim-sulfamethoxazole (Bactrim forte®) 1 tablet/3x per week

Prophylaxis, while not mandated, should continue until subjects have fully recovered from any lymphocytopenia (CTC Grade ≤1), or have a CD4 count > 200/µL

4.5.4.3 **Antiemetic**
The prophylactic use of a 5-HT3-antagonsist is strongly recommended before the TMZ administration.

4.6 Duration of Therapy
Patients may continue to receive cycles of treatment until any of the following occur:

- Disease progression per iRANO
- Development of an inter-current illness that prevents further administration of treatment
- Unacceptable adverse event(s)
- Patient decides to withdraw from either study treatment or the study as a whole
- The treating investigator determines that the patient should be taken off treatment for any reason (i.e. changes in condition, inability to comply with study treatment or procedures)
- Patient becomes pregnant

4.6.1 **Continuation of Investigational Therapy**
Subjects who complete 34 weeks of treatment without progression will be offered the opportunity, in agreement with the responsible investigator, to continue therapy beyond Week 34 as long as it will be of benefit to the patient.

4.7 Duration of Follow Up
Once patients come off of treatment, they will return for a follow up visit 30 days (±3 days) after last dose of treatment. Patients removed from study for unacceptable treatment-related adverse event(s) will be followed until resolution or stabilization of the adverse event

Patients will be contacted every 3 months to monitor survival until patient's withdraw consent or death.

4.8 Removal of Subjects from Study Treatment and/or Study as a Whole

Patients can be taken off the study treatment and/or study as a whole at any time at their own request, or they may be withdrawn at the discretion of the investigator for safety, behavioral or administrative reasons. The reason(s) for discontinuation must be clearly documented on the appropriate eCRF and may include:

- Patient voluntarily withdraws from treatment (follow-up permitted)
- Patient withdraws consent (no follow-up permitted)
- Patient is unable to comply with protocol requirements
- Patient demonstrates disease progression
- Patient experiences unacceptable toxicity
- Treating physician determines that continuation on the study would not be in the patient's best interest
- Patient becomes pregnant
- Patient develops a second malignancy that requires treatment which would interfere with this study
- Patient becomes lost to follow-up (LTF)

In case of premature discontinuation of study drug by a subject, the investigations scheduled for the End of Treatment Visit should be performed, if possible. In any case, the appropriate CRF section must be completed. Subjects who fail to return for final assessments will be contacted by the site in an attempt to have them comply with the protocol. Follow-up will include 2 telephone calls followed by a certified letter.

It is important to obtain follow-up data on any subject withdrawn because of an AE or SAE. Every effort must be made to undertake protocol-specified safety follow-up (see Section 7.3). Upon occurrence of an intolerable AE, the Investigator will confer with BMS.

4.9 Patient Replacement

Any patient who signs consent and is registered for the trial but does not receive study treatment may be replaced.

Patients who withdraw from the study prior to completion of study treatment due to progression of disease (PD), unacceptable AEs, or death will not be replaced.

5 STUDY PROCEDURES

5.1 Table 5-1: Study Procedures

	Screening	On Treatment										Off Treatment	
Time Period	Baseline (-28 Days*)	RT		Post RT Phase				Maintenance Phase[23]				EOT[24]	Follow-up[25]
				Cycle -1				Cycle 1+					
		Week 1 Day 1	Weeks 1-6	Day 1 (±2 days)	Day 8 (±2 days)	Day 15 (±2 days)	Day 21 (±2 days)	Day 1 (±2 days)	Day 8 (±2 days)	Day 15 (±2 days)	Day 21 (±2 days)		
Assessment or Activity													
Informed Consent	X							**See Table 5-2 for Maintenance Phase Procedures**					
Medical history	X											X	
Physical exam[1]	X	X[5]	X[2, 5]	X		X						X	
Review Concomitant Medications, Steroid use	X	X[5]	X[5]	X		X						X	
KPS	X	X		X		X						X	
Neurological Exam[4]	X	X[4]		X									
Toxicity assessment		X[5]	X[5]	X		X						X	
Gd-MRI	X											X	
AMT PET (Optional)[26]	X											X[26]	X[26]
CBC with diff	X	X[7,3]	X[3]	X	X[8]	X	X[8]					X	
Chemistry panel	X	X[7,3]	X[3]	X		X						X	
TSH, free T3 and Free T4	X			X								X	
Urinalysis	X	X[7]		X									
G6PD	X												
Methemoglobin	X			X									
Pregnancy test[9]	X		X[9]	X									
Focal RT[10]		X	X										
EKG	X												
Dispense BMS-986205[11]		X		X									
Nivolumab[12]		X	X[12]	X		X							
Temozolomide[13]		X[14]	X[14]										
TTFields[16]													
Review Drug Diary			X	X		X						X	
Questionnaire[17]	X												X
Tumor Tissue Collection	X[18]											X[19]	
Blood Collection[20]	X----------X[21]			X								X	
Stool Sample[22]	X----------X[21]												
Survival status													X

* Unless otherwise noted.

1. Includes vital signs (pulse, blood pressure) and height (baseline only) and weight.
2. Vitals will be taken prior to each infusion with nivolumab (weeks 1, 3, and 5 of RT).
3. To be performed on Day 1 of each week 1-6 during RT.

4. Baseline exam to be performed within 28 days of registration. Must be repeated on Day 1 of treatment if not within 7 days of beginning treatment. The neurologic examination will include assessment of vision, speech, cranial nerves II through XII, and mental status as well as cerebellar, sensory, and motor function.
5. To be performed every 2 weeks during RT beginning at Week 1 Day 1.
6. To be performed every 8 weeks beginning at cycle 1 of the Maintenance Phase. After 2 years of treatment, may be performed per treating investigator discretion. An independent review will be performed on all relevant Gd-MRI scans, and an independent pathologist will confirm the histopathological diagnosis.
7. If completed 72hrs prior to Week 1 Day 1 of RT, labs do not need to be repeated on Week 1 Day 1.
8. CBC + diff only for MGMT Methylated Cohort on Days 8 and 21 of Cycles 1-6 in Maintenance Phase (can be done locally). CBC + diff performed only on day 1 beginning at Cycle 7 of the Maintenance Phase.
9. Serum test for females of child-bearing potential to be performed within 14 days of registration and repeated within 24 hours prior to first dose of study treatment, and every 4 weeks while on treatment.
10. A treatment fraction of 2Gy will be delivered daily, 5 days per week, for 6 weeks, yielding a cumulative dose of 60Gy to the target volume.
11. BMS-986205 will be dispensed to patients at Week 1 Day 1 and Week 5 Day 1 of RT, Day 1 of Post-RT Phase, and on Day 1 of each cycle during Maintenance Phase. Patients will be instructed to take the dose of study drug PO QD.
12. Nivolumab will be administered Q2W (±2 days) at 240mg by IV (During RT: Weeks 1, 3 & 5. During the Maintenance Phase: Days 1 and 15 of each cycle). Beginning at Cycle 6 of the Maintenance Phase, nivolumab will be dosed at 480mg by IV Q4W (Day 1 of each cycle beginning at cycle 6).
13. TMZ only for MGMT promotor methylated cohort
14. TMZ will be administered continuously during RT phase at a daily oral dose of 75 mg/m^2 for a maximum of 49 days, as per standard practice.
15. Post RT, TMZ will be administered PO QD at 200 mg/m^2 for 5 consecutive days (days 1-5) of a 28-day cycle beginning at Cycle 2 and continue for 6 cycles.
16. Patients will be given the option to begin TTFields treatment at the beginning of the Maintenance Phase. Patients who choose not to utilize TTFields will not be required to do so.
17. Patients will complete questionnaires at baseline/pretreatment (any time prior to Day 1 of RT), up to 1 week prior to each MRI follow-up (see footnote #5), and every 3 months during follow up. Patients will receive paper forms to complete and return to the study team. Data from the paper forms will be entered into NOTIS by the study team.
18. If available, tumor tissue specimens from the GBM surgery or biopsy must be available for central pathology review and exploratory analysis of immunocorrelative studies.
19. If a patient has progression of disease and undergoes further surgery, they will have the option of allowing fresh tissue to be analyzed.
20. Research blood (2 heparinized tubes with 10ml each) will be collected at baseline, on day 1 of post RT, and at each MRI time point (every 8 weeks starting at cycle 1 day 1 of the Maintenance Cycle). Research blood will only be collected for up to 2 years of treatment, and the end of treatment visit.
21. Baseline sample can be collected at any time between consent and Week 1 Day 1 of RT prior to any treatment.
22. Optional stool sample collected at baseline and on C1D1 of maintenance phase.
23. In Maintenance Phase, 1 cycle = 28 Days.
24. End of treatment visit will occur 30 days (±3 days) of last dose of treatment.
25. Patients will be followed (either by routine clinic visit or by phone call) every 3 months until patients withdraws consent or death.
26. AMT PET is an optional study, and will be performed by Wayne State University Investigators, at the PET Center in the Children's Hospital of Michigan. Scans will occur at baseline (prior to RT and systemic therapy but after standard of care surgery), 4 weeks after completing RT and systemic therapy (D1 of Maintenance phase), and at tumor progression or after 1 year of starting RT and systemic therapy. See Section 9.6 for more details.

5.2 Table 5-2: Study Procedures During Maintenance Phase

Time Period	On Treatment													Off Treatment	
	Maintenance Phase[23]														
	Cycle 1				Cycles 2-5				Cycle 6				Cycle 7+	EOT[24]	Follow-up[25]
	Day 1 (±2 days)	Day 8 (±2 days)	Day 15 (±2 days)	Day 21 (±2 days)	Day 1 (±2 days)	Day 8 (±2 days)	Day 15 (±2 days)	Day 21 (±2 days)	Day 1 (±2 days)	Day 8 (±2 days)	Day 15 (±2 days)	Day 21 (±2 days)	Day 1 (±2 days)		
Assessment or Activity															
Informed Consent														**See table 5-1 for Off Treatment Procedures**	
Medical history															
Physical exam[1]	X		X		X		X		X				X		
Review Concomitant Medications, Steroid use	X		X		X		X		X				X		
KPS	X		X		X		X		X				X		
Neurological Exam[4]	X				X				X				X		
Toxicity assessment	X		X		X		X		X				X		
Gd-MRI	X[6]				X[6]				X[6]				X[6]		
AMT PET (Optional)[26]	X[26]														
CBC with diff	X	X[8]	X	X[8]	X	X[8]	X	X[8]	X	X[8]		X[8]	X		
Chemistry panel	X		X		X		X		X				X		
TSH, Free T3, Free T4	X				X				X				X		
Urinalysis	X				X										
G6PD															
Methemoglobin	X				X				X				X		
Pregnancy test[9]	X				X				X				X		
Focal RT[10]															
EKG	X[6]				X[6]				X[6]				X[6]		
Dispense BMS-986205[11]	X				X				X				X		
Nivolumab[12]	X		X		X		X		X[12]				X		
Temozolomide[13]	X[14]				X[14]				X[15]						
TTFields[16]	X														
Review Drug Diary	X		X		X		X		X				X		
Questionnaire[17]	X[17]				X[17]				X[17]				X[17]		
Tumor Tissue Collection															
Blood Collection[20]	X[20]				X[20]				X[20]				X[20]		
Stool Sample[22]	X														
Survival status															

1. Includes vital signs (pulse, blood pressure) and height (baseline only) and weight.
2. Vitals will be taken prior to each infusion with nivolumab (weeks 1, 3, and 5 of RT).
3. To be performed on Day 1 of each week 1-6 during RT.
4. Baseline exam to be performed within 28 days of registration. Must be repeated on Day 1 of treatment if not within 7 days of beginning treatment. The neurologic examination will include assessment of vision, speech, cranial nerves II through XII, and mental status as well as cerebellar, sensory, and motor function.
5. To be performed every 2 weeks during RT beginning at Week 1 Day 1.

6. To be performed every 8 weeks beginning at cycle 1 of the Maintenance Phase. After 2 years of treatment, may be performed per treating investigator discretion. An independent review will be performed on all relevant Gd-MRI scans, and an independent pathologist will confirm the histopathological diagnosis.
7. If completed 72hrs prior to Week 1 Day 1 of RT, labs do not need to be repeated on Week 1 Day 1.
8. CBC + diff only for MGMT Methylated Cohort on Days 8 and 21 of Cycles 1-6 in Maintenance Phase (can be done locally). CBC + diff performed only on day 1 beginning at Cycle 7 of the Maintenance Phase.
9. Serum test for females of child-bearing potential to be performed within 14 days of registration and repeated within 24 hours prior to first dose of study treatment, and every 4 weeks while on treatment.
10. A treatment fraction of 2Gy will be delivered daily, 5 days per week, for 6 weeks, yielding a cumulative dose of 60Gy to the target volume.
11. BMS-986205 will be dispensed to patients at Week 1 Day 1 and Week 5 Day 1 of RT, Day 1 of Post-RT Phase and on Day 1 of each cycle during Maintenance Phase. Patients will be instructed to take the dose of study drug PO QD.
12. Nivolumab will be administered Q2W (±2 days) at 240mg by IV (During RT: Weeks 1, 3 & 5. During the Maintenance Phase: Days 1 and 15 of each cycle). Beginning at Cycle 6 of the Maintenance Phase, nivolumab will be dosed at 480mg by IV Q4W (Day 1 of each cycle beginning at cycle 6).
13. TMZ only for MGMT promotor methylated cohort
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15. Post RT, TMZ will be administered PO QD at 200 mg/m^2 for 5 consecutive days (days 1-5) of a 28-day cycle beginning at Cycle 2 and continue for 6 cycles.
16. Patients will be given the option to begin TTFields treatment at the beginning of the Maintenance Phase. Patients who choose not to utilize TTFields will not be required to do so.
17. Patients will complete questionnaires at baseline/pretreatment (any time prior to Day 1 of RT), up to 1 week prior to each MRI follow-up (see footnote #5), and every 3 months during follow up. Patients will receive paper forms to complete and return to the study team. Data from the paper forms will be entered into NOTIS by the study team.
18. If available, tumor tissue specimens from the GBM surgery or biopsy must be available for central pathology review and exploratory analysis of immunocorrelative studies.
19. If a patient has progression of disease and undergoes further surgery, they will have the option of allowing fresh tissue to be analyzed.
20. Research blood (2 heparinized tubes with 10ml each) will be collected at baseline, on day 1 of post RT, and at each MRI time point (every 8 weeks starting at cycle 1 day 1 of the Maintenance Cycle).Research blood will only be collected for up to 2 years of treatment, and the end of treatment visit.
21. Baseline sample can be collected at any time between consent and Week 1 Day 1 of RT prior to any treatment.
22. Optional stool sample collected at baseline and on C1D1 of maintenance phase.
23. In Maintenance Phase, 1 cycle = 28 Days.
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25. Patients will be followed (either by routine clinic visit or by phone call) every 3 months until patients withdraws consent or death.
26. AMT PET is an optional study, and will be performed by Wayne State University investigators, at the PET Center in the Children's Hospital of Michigan. Scans will occur at baseline (prior to RT and systemic therapy but after standard of care surgery), 4 weeks after completing RT and systemic therapy (D1 of Maintenance phase), and at tumor progression or after 1 year of starting RT and systemic therapy. See Section 9.6 for more details.

6 ENDPOINT ASSESSMENT

6.1 Definitions

Clinical activity will be assessed by Gd-MRI, neurologic examination, and steroid use, as outlined in the following table.

6.1.1 Clinical Evaluation Criteria

iRANO

Clinical Status	Clinical Activity Assessments		
	Neuroimaging Gd-MRI	**Neurologic Examination**	**Steroid Use**
CR [1]	• Disappearance of all enhancing tumor, and • No new lesions.	Stable or improved compared to the most recent neurologic examination.	None
PR[1]	• ≥50% reduction in the sum of the products of the largest perpendicular diameters compared to the baseline sum, • No worsening of an evaluable lesion(s), and • No new lesions.	Stable or improved compared to the most recent neurologic examination	• Same or lower dose compared to the dose at previous scan, and • Dose is stable for ≥72 hours prior to each scan.
PD[2]	• ≥25% increase in the sum of the product of the largest perpendicular diameters compared to the smallest prior sum, • Worsening of an evaluable lesion(s), or • Any new lesion(s).	Worsening compared to the most recent neurologic examination[3].	NA
SD	Neither response (CR or PR) nor PD		

1 To qualify as a CR or PR, all 3 criteria (neuroimaging, neurologic examination, and steroid use) must be met. In addition, neuroimaging must be confirmed within 31 days ± 3 days.

2 Subjects with PD may remain in the study according to the criteria presented below.

3 Worsening overall performance and/or neurologic decline felt to be attributable to underlying disease despite lack of radiographic evidence of PD. Such subjects may be classified as PD upon discussion between the Coordinating Investigator and the subject's primary neuro-oncologist, if necessary.

Progressive Disease: Study treatment is to be discontinued at disease progression as determined by iRANO unless continuation is judged in the patient's best interest by the treating physician (after agreement with the PI and BMS). The following iRANO criteria (42) are to be considered when making assessments of PD.

- Repeat scan required to confirm radiographic PD for patients without significant clinical worsening
- ≥4 wks minimal time interval for confirmation of progression for patients without significant clinical decline
- Further immunotherapy treatment allowed after initial radiographic progression
- A new lesion does NOT define progression
- Radiological or clinical deterioration to causes other than tumor progression (pseudoprogression) may warrant treatment discontinuation, and will not be considered PD

RANO

Clinical Status	Clinical Activity Assessments					
	T1 gadolinium enhancing disease	**T2/FLAIR**	**New Lesion**	**Corticosteroids**	**Clinical Status**	**Requirement for response**
CR	None	Stable or ↓	None	None	Stable or ↑	All
PR	≥ 50% ↓	Stable or ↓	None	Stable or ↓	Stable or ↑	All
SD	< 50% ↓ but < 25% ↑	Stable or ↓	None	Stable or ↓	Stable or ↑	All
PD	≥ 25% ↑	↑	Present[1]	n/a	↓	Any[1]

1 Progression occurs when this criterion is present

↓ = decreased, ↑ = increased,

CR = complete response, PR = partial response, SD = stable disease, PD = progressive disease If PD is unclear based on white matter changes, patients may be kept on trial

6.2 Primary Endpoint

To determine the safety and tolerability of nivolumab in combination with BMS-986205 and radiation in newly diagnosed MGMT promoter unmethylated glioblastoma and MGMT promoter methylated glioblastoma.

Any patient who has received a dose of therapy will be evaluable for this safety endpoint.

6.3 Secondary Endpoints

Patients who have completed the RT phase and have initiated treatment in Cycle 1 of the Maintenance Phase are evaluable.

6.3.1 Descriptive survival analyses (OS and OS12) in patients with MGMT unmethylated and MGMT methylated promoter.

One-year survival rate (probability of surviving 1 year or more from start of study treatment).

Median survival time (median time from start of study treatment to death).

6.3.2 PFS and PFS6 in patients with MGMT unmethylated and MGMT methylated promoter.

Six-month PFS rate (percentage of subjects who survived 6 months without disease progression)

Median time to disease progression (median time from first treatment on study to documented disease progression).

6.3.3 Radiographic response rates (RR) as determined by iRANO criteria in patients with MGMT unmethylated and MGMT methylated promoter.

Radiographic response rates (RR) as determined by RANO criteria in patients with MGMT unmethylated and MGMT methylated promoter.

Response rate (percentage of subjects who achieve PR or CR according to the iRANO criteria).

Median duration of response (number of days from the first diagnosed PR or CR to PD), if applicable.

6.4 Exploratory Endpoints

6.4.1 Determine the T-cell changes that occur in GBM treated with nivolumab in combination with BMS-986205 and radiation.

6.4.2 Correlate T-cell changes and IDO1 expression with patient outcomes.

6.4.3 Investigate GBM patient levels of distress, before, during, and after treatment with trimodal radiation, anti-PD-1 mAb and IDO1 enzyme inhibitor using the 'Beck Depression Inventory' (see Appendix K) and the 'Emotional Distress-Anxiety' inventory of the PROMIS (see Appendix L) questionnaires.

6.4.4 Correlation between AMT-PET responses and MRI responses, survival, and PFS in newly diagnosed MGMT promoter unmethylated and MGMT promoter methylated glioblastoma treated with nivolumab in combination with BMS-986205 and radiation.

- AMT-PET correlation with OS
- AMT-PET correlation with radiographic response on MRI
- Tumor immune-correlates
- Serum immune-correlates
- Molecular pathology correlates

Exploratory endpoints will be compared at baseline, with each MRI and at the end of treatment visit. Patients who have completed the RT phase and have initiated treatment in Cycle 1 of the Maintenance Phase are evaluable.

7 ADVERSE EVENTS

This study will be conducted in compliance with the Data Safety Monitoring Plan (DSMP) of the Robert H. Lurie Comprehensive Cancer Center of Northwestern University. The level of risk attributed to this study requires High Intensity Monitoring, as outlined in the DSMP. In addition, the study will abide by all safety reporting regulations, as set forth in the Code of Federal Regulations.

7.1 Adverse Event Monitoring

Adverse event data collection and reporting, which are required as part of every clinical trial, are done to ensure the safety of subjects enrolled in the studies as well as those who will enroll in future studies using similar agents. Adverse events are reported in a routine manner at scheduled times during a trial (see Section 5 for time points). In addition, certain adverse events must be reported in an expedited manner to allow for optimal monitoring and patient safety and care.

All patients experiencing an adverse event, regardless of its relationship to study drug, will be followed until:

- the adverse event resolves or the symptoms or signs that constitute the adverse event return to baseline;
- any abnormal laboratory values have returned to baseline;

- there is a satisfactory explanation other than the study drug for the changes observed; or
- death.

7.2 Definitions & Descriptions

7.2.1 Adverse Event

An adverse event (AE) is any untoward medical occurrence in a patient receiving study treatment and which does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of an experimental intervention, whether or not related to the intervention.

Recording of AEs should be done in a concise manner using standard, acceptable medical terms. In general, AEs are not procedures or measurements, but should reflect the reason for the procedure or the diagnosis based on the abnormal measurement. Preexisting conditions that worsen in severity or frequency during the study should also be recorded (a preexisting condition that does not worsen is not an AE). Further, a procedure or surgery is not an AE; rather, the event leading to the procedure or surgery is considered an AE.

If a specific medical diagnosis has been made, that diagnosis or syndrome should be recorded as the AE whenever possible. However, a complete description of the signs, symptoms and investigations which led to the diagnosis should be provided. For example, if clinically significant elevations of liver function tests are known to be secondary to hepatitis, “hepatitis” and not “elevated liver function tests” should be recorded. If the cause is not known, the abnormal test or finding should be recorded as an AE, using appropriate medical terminology (e/g/ thrombocytopenia, peripheral edema, QT prolongation).

7.2.2 Severity of AEs

All non-hematologic adverse events will be graded according to the NCI Common Terminology Criteria for Adverse Events (CTCAE) version 5.0. The CTCAE v5 is available at https://ctep.cancer.gov/protocoldevelopment/electronic_applications/ctc.htm

If no CTCAE grading is available, the severity of an AE is graded as follows:

- Grade 1: Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated.
- Grade 2: Moderate; minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental activities of daily living*.
- Grade 3: Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self care activities of daily living**.
- Grade 4: Life-threatening consequences; urgent intervention indicated.
- Grade 5: Death related to AE

*Instrumental activities of daily living refer to preparing meals, shopping for groceries or clothes, using the telephone, managing money, etc.
**Self care activities of daily living refer to bathing, dressing and undressing, feeding self, using the toilet, taking medications, and not bedridden.

7.2.3 **Serious Adverse Events (SAEs)**

All SAEs, regardless of attribution, occurring from time of signed informed consent, through 100 days after the last administration of study drug, must be reported upon discovery or occurrence.

An SAE is defined in regulatory terminology as any untoward medical occurrence that:

- **Results in *death*.**
  If death results from (progression of) the disease, the disease should be reported as event (SAE) itself.
- **Is life-threatening.**
  The patient was at risk of death at the time of the event; it does not refer to an event that hypothetically might have caused death if it were more severe.
- **Requires in-patient hospitalization or prolongation of existing hospitalization for ≥ 24 hours.**
- **Results in persistent or significant disability or incapacity.**
- **Is a congenital anomaly/birth defect.**
- **Is an important medical event.**

  Any event that does not meet the above criteria, but that in the judgment of the investigator jeopardizes the patient, may be considered for reporting as a serious adverse event. The event may require medical or surgical intervention to prevent one of the outcomes listed in the definition of "Serious Adverse Event".

  For example: allergic bronchospasm requiring intensive treatment in an emergency room or at home; convulsions that may not result in hospitalization; development of drug abuse or drug dependency.

  Hospitalization
  For reports of hospitalization, it is the sign, symptom or diagnosis which led to the hospitalization that is the serious event for which details must be provided.

  Any event requiring hospitalization or prolongation of hospitalization that occurs during the study must be reported as a serious adverse event, except hospitalizations for the following:

- Hospitalizations not intended to treat an acute illness or adverse event (e.g., social reasons such as pending placement in long-term care facility)
- Hospitalizations for routine blood transfusions, hospitalization for an elective or diagnostic procedure, or surgery for a pre-existing condition that has not worsened, are not considered SAEs. (Emergency room visits that do not result with admission are not considered as SAEs).
- Hospitalizations or prolongation of hospitalization for ≤24 hours.

7.2.4 **Unanticipated Problems Involving Risks to Subject or Others**

A UPIRSO is a type of SAE that includes events that meet ALL of the following criteria:

- Is *unanticipated* in terms of nature, severity, or frequency
- Places the research subject or others at a different or *greater risk of harm*
- Is deemed to be *at least possibly related* to participation in the study.

7.2.5 Overdose

An overdose is defined as the accidental or intentional administration of any dose of a product that is considered both excessive and medically important. All occurrences of overdose must be reported as an SAE.

7.2.6 Pregnancy

In the case of pregnancy, the investigator must immediately notify the PI/QAM of this event via the NU CTO SAE Form. In most cases, the study drug will be permanently discontinued in an appropriate manner. Please contact the PI and DSMC within 24 hours of awareness of the pregnancy.

7.3 Adverse Event Reporting

7.3.1 Routine Reporting

All routine adverse events, such as those that are expected, or are unlikely or definitely not related to study participation, are to be reported on the appropriate eCRF. Routine AEs will be reviewed by the Data and Safety Monitoring Committee (DSMC) according to the study's phase and risk level, as outlined in the DSMP.

7.3.2 Determining if Expedited Reporting is Required

This includes all events that occur within 100 days of the last dose of protocol treatment. Any event that occurs more than 100 days after the last dose of treatment and is attributed (possibly, probably, or definitely) to the agent(s) must also be reported accordingly.

1) Identify the type of adverse event using the NCI CTCAE v 5.0.
2) Grade the adverse event using the NCI CTCAE v 5.0.
3) Determine whether the adverse event is related to the protocol therapy. Attribution categories are as follows:
   - Definite: AE is clearly related to the study treatment.
   - Probable: AE is likely related to the study treatment.
   - Possible: AE may be related to the study treatment.
   - Unlikely: AE not likely to be related to the study treatment.
   - Unrelated: AE is clearly NOT related to the study treatment.
4) Determine the prior experience of the adverse event.
   Expected events are those that have been previously identified as resulting from administration of the agent. An adverse event is considered unexpected, for expedited reporting purposes only, when either the type of event or the severity of the event is not listed in:
   - the current protocol
   - the drug package insert
   - the current Investigator's Brochure

7.3.3 Expedited Reporting of SAEs/Other Events

Sponsor and Investigator will reconcile the clinical database SAE cases (case level only) transmitted to BMS Global Pharmacovigilance (Worldwide.Safety@bms.com). Frequency of reconciliation should be every 3 months and prior to the database lock or final data summary. BMS GPV&E will email, upon request from the Investigator, the GPV&E reconciliation report. Requests for reconciliation should be sent to aepbusinessprocess@bms.com. The data elements listed on the GPV&E reconciliation report will be used for case identification purposes. If the Investigator determines a case was not transmitted to BMS GPV&E, the case should be sent immediately to BMS.

7.3.3.1 **Reporting to the Northwestern University QAM/DSMC**

All SAEs must be reported to the assigned QAM within 24 hours of becoming aware of the event. Completion of the NU CTO SAE Form, provided as a separate document, is required.

The completed form should assess whether or not the event qualifies as a UPIRSO. The report should also include:

- Protocol description and number(s)
- The patient's identification number
- A description of the event, severity, treatment, and outcome (if known)
- Supportive laboratory results and diagnostics
- The hospital discharge summary (if available/applicable)

All SAEs will be reported to, and reviewed by, the DSMC at their next meeting.

7.3.3.2 **Reporting to the Northwestern University IRB**

- Any death of an NU subject that is unanticipated in nature and at least possibly related to study participation will be promptly reported to the NU IRB within 24 hours of notification.
- Any death of an NU subject that is actively on study treatment will be reported to the NU IRB within 5 working days of notification (regardless of whether or not the event is possibly related to study treatment)
- Any death of a non-NU subject that is unanticipated and at least possibly related and any other UPIRSOs will be reported to the NU IRB within 5 working days of notification.

7.3.3.3 **Reporting to the FDA**

The FDA will be notified within 7 calendar days of any SAE that is associated with study treatment, is unexpected, and is fatal or life-threatening. The Principal Investigator will notify the FDA with the assistance of a Quality Assurance Monitor.

The FDA will be notified within 15 calendar days of any SAE that is associated with the study treatment, unexpected, and serious but *not fatal or life-threatening*. This includes any previous SAEs that were not initially deemed reportable, but are later determined to meet the criteria for reporting (i.e. by the DSMC).

All other SAEs will be reported on an annual basis as part of the annual FDA report.

7.3.3.4 **Reporting to BMS**

SAE reports (including pregnancy and death by any cause), regardless of attribution will be reported within 24 hours/1 business day to BMS Global Safety (using the NU CTO SAE Form and referencing the BMS study number, CA017-075). The assigned study coordinator will facilitate all reporting to BMS Global Safety and email QA a copy of the report upon completion. BMS Global Safety can be notified at:

Email Address: Worldwide.Safety@BMS.com
Fax: +1 609-818-3804

7.3.3.5 **Adverse Events of Special Interest (AEOSI)**
Adverse events of special interest (AEOSI) requiring **expedited** regulatory reporting by the investigator have been defined. These are:

1. Hemophagocytic lymphohistiocytosis (HLH; also known as histiocytosis haematophagic)
2. Drug reaction with eosinophilia and systemic symptoms (DRESS) syndrome
3. In addition, all potential DILI (drug induced liver injury) are to be expedited for regulatory reporting.

All AEOSIs, regardless of causal association, will be submitted to the FDA and BMS.

8 DRUG INFORMATION

8.1 BMS-986205

8.1.1 Other names
N/a

8.1.2 Classification - type of agent
Selective IDO Inhibitor

8.1.3 Mode of action
BMS-986205 is a selective inhibitor of the IDO1 enzyme. Inhibition of IDO1 inhibits the conversion of Trp to the immunosuppressive kyn.

8.1.4 Storage and stability
BMS will provide BMS-986205 in open-label supplies to the trial site. Study personnel will provide patients at the site with labeled bottles containing study drug. Patients will be instructed to keep a log of the date and time which they take BMS-986205.

BMS-986205 must be carefully stored at the study site, safely and separately from other drugs.

BMS-986205 tablets should be stored at 2°C to 30°C (36°F to 86°F) in a tightly-closed container protected from light.

8.1.5 Protocol dose specifics
Patients will take BMS-986205 at prescribed dose PO once a day with meal. If patients miss taking their dose by ≥12 hours they should skip that dose and take the dose the following day. BMS-986205 tablets may not be crushed.

8.1.6 Preparation
No preparation is required.

8.1.7 Route of administration for this study
PO

8.1.8 Incompatibilities
There are no contraindications or limitations with concurrent medications. Please refer to the current Investigator Brochure for up to date information.

Preliminary reaction phenotyping studies with human liver microsomes indicated that BMS-986205 was primarily metabolized by CYP3A4; therefore, the plasma concentrations of BMS-986205 may be affected by compounds that modulate the activity of this enzyme. Because of this, Concomitant use of strong inducers or

inhibitors of CYP3A4 is prohibited and moderate inducers or inhibitors of CYP3A4 should be used with caution.

BMS-986205 has a low potential to inhibit CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19 and UGT1A1 in vivo, given the predicted Cmax at the projected efficacious dose and high plasma protein binding (> 99.9%). Results from in vitro results indicate BMS-986205 does not induce CYP1A2 and CYP2B6. Because most hormonal contraceptives are metabolized by CYP3A4, hormonal contraceptives may not be effective when co-administered with BMS-986205. Therefore, further investigation on induction potential of CYP3A4 is warranted.

BMS-986205 has a low potential to inhibit human transporters including OATP1B1, OATP1B3, BSEP, MATE1 and OCT1 in vivo. BMS-986205 has been shown to be an inhibitor of P-gp/BCRP and could alter the absorption and distribution of compounds that are substrates of these transporters. As the potential for drug interactions exists, subjects will be prohibited from the use of strong inhibitors of CYP3A4 within 1 week or 5 half-lives (whichever is longer) or strong inducers of CYP3A4 within 2 weeks or 5 half-lives (whichever is longer) of starting BMS-986205. As grapefruit and Seville oranges and their juices can inhibit CYP3A4, they should be avoided while on study. Caution is warranted when administering BMS-986205 to subjects taking drugs that are highly dependent on CYP3A4 for metabolism or drugs that are subject to extensive intestinal efflux by P-gp/BCRP. In addition, as BMS-986205 exhibits pH-dependent solubility, subjects should try to avoid taking proton pump inhibitors until further data are available. H2 antagonists and short-acting antacid agents, such as Maalox® or TUMS®, may be taken, but it is recommended that these not be taken 4 hours before or 4 hours after dosing of BMS-986205.

8.1.9 **Availability & Supply**

BMS-986205 will be provided to the study site in individually labeled bottles in 3 drug forms (25mg, 50mg and 100mg tablets). These will be stored in the investigational pharmacy and will be provided to the patient on day of study visit on a monthly basis by the trial coordinator.

The information on the labels will be in accordance with all applicable regulatory requirements. Each bottle label will state the drug name and the amount of the drug contained in the bottle, dose of each tablet, batch number, storage conditions, sponsor's and manufacturer's name, dosing instructions, and a notice that it is limited to investigational use. The vials will be numbered consecutively. The study and bottle number will be documented in the drug accountability log in the pharmacy.

From the documentation on the study drug packaging, it shall be possible to retrace the composition and pharmaceutical quality according to the current Good Manufacturing Practice guidelines.

A supply of BMS986205 may be ordered from by completing a Drug Request Form provided by BMS. The first request may take place upon screening of the first patient. Allow 5 business days for shipment of drug from BMS receipt of the Drug Request Form. Drug is protocol specific, but not patient specific. All drug product will be shipped by courier in a temperature-controlled container. It is imperative that only drug product designated for this protocol number be used for this study.

Drug re-supply request form should be submitted electronically 10 business days before the expected delivery date. Deliveries will be made Tuesday through Friday. When assessing need for resupply, keep in mind the number of vials used per treatment dose, and that shipments may take 14 business days from receipt of request. Drug is not patient-specific.

At the end of the study period, Bristol-Myers Squibb Company will not continue to supply study drug to subjects/investigators unless the Sponsor-Investigator chooses to extend their study. The investigator is responsible to ensure that the subject receives appropriate standard of care or other appropriate treatment in the independent medical judgement of the Investigator to treat the condition under study.

8.1.10 **Side effects**

Among subjects receiving BMS-986205 at doses ranging from 25 to 400 mg, 201 (50.6%) had treatment related AEs reported. The majority of these TRAEs were Grade 1 or Grade 2 in severity. The most common treatment related AEs (occurring in > 5% of subjects) occurring in this group were fatigue (14.1%), nausea (11.1%), decreased appetite (9.1%), AST increased (7.6%), and ALT increased (7.1%). Treatment related AEs reported in ≥ 2% of subjects are presented below.

Treatment related AEs Occurring in ≥ 2% of Subjects During BMS-986205 and Nivolumab Combination Treatment in Study CA017-003

	Grade					Total
Preferred Term (%)	**1**	**2**	**3**	**4**	**5**	**(N = 397)**
Total subjects with AEs, regardless of causality	61 (15.4)	65 (16.4)	113 (28.5)	31 (7.8)	71 (17.9)	341 (85.9)
Total subjects with a TRAE	86 (21.7)	65 (16.4)	43 (10.8)	6 (1.5)	1 (0.3)	201 (50.6)
Fatigue	33 (8.3)	21 (5.3)	2 (0.5)	0	0	56 (14.1)
Nausea	35 (8.8)	7 (1.8)	2 (0.5)	0	0	44 (11.1)
Decreased appetite	24 (6.0)	11 (2.8)	1 (0.3)	0	0	36 (9.1)
AST increased	17 (4.3)	6 (1.5)	7 (1.8)	0	0	30 (7.6)
ALT increased	10 (2.5)	13 (3.3)	5 (1.3)	0	0	28 (7.1)
Hepatobiliary disorders[a]	2 (0.5)	1 (0.3)	13 (3.3)	3 (0.8)	0	19 (4.8)
Pyrexia	14 (3.5)	2 (0.5)	0	0	0	16 (4.0)
Diarrhoea	11 (2.8)	4 (1.0)	1 (0.3)	0	0	16 (4.0)
Rash	11 (2.8)	3 (0.8)	2 (0.5)	0	0	16 (4.0)
Pruritus	15 (3.8)	0	0	0	0	15 (3.8)
Vomiting	13 (3.3)	2 (0.5)	0	0	0	15 (3.8)
Asthenia	7 (1.8)	5 (1.3)	0	0	0	12 (3.0)
Headache	9 (2.3)	2 (0.5)	0	0	0	11 (2.8)
Transaminases increased	7 (1.8)	2 (0.5)	1 (0.3)	1 (0.3)	0	11 (2.8)

Anemia	3 (0.8)	3 (0.8)	4 (1.0)	0	0	10 (2.5)
Arthralgia	9 (2.3)	0	0	0	0	9 (2.3)
Infusion related reaction	3 (0.8)	6 (1.5)	0	0	0	9 (2.3)
Rash maculo-paular	4 (1.0)	2 (0.5)	2 (0.5)	0	0	8 (2.0)

Grade 3 treatment related AEs were reported in 43 (10.8%) subjects. Those occurring in > 2 subjects were AST increased (n = 7); ALT increased (n = 5); autoimmune hepatitis, hepatitis, and anemia (n = 4 each); hypophosphatemia (n = 3); and hepatocellular injury, pneumonitis, hyponatremia, lipase increased, rash, rash maculo-papular, fatigue, and nausea (n = 2 each). Grade 4 treatment related AEs were reported in 6 (1.5%) subjects and were autoimmune hepatitis (n = 2) and hepatitis acute, transaminases increased, gamma-glutamyltransferase (GGT) increased, embolism, and dyspnea (n = 1 each). The Grade 4 dyspnea event was associated with myocarditis. Treatment related AEs leading to discontinuation of BMS-986205 or BMS-986205 and nivolumab during combination treatment were reported in 15 (3.8%) subjects and are presented below. The most commonly reported treatment related AEs leading to discontinuation were due to hepatobiliary events (1.5% of subjects).

Treatment related AEs Leading to Discontinuation During BMS-986205 and Nivolumab Combination Treatment in Study CA017-003

Preferred Term (%)	**1**	**2**	**3**	**4**	**5**	**(N = 397)**
Total subjects with an event	0	5 (1.3)	6 (1.5)	3 (0.8)	1 (0.3)	15 (3.8)
Pneumonitis	0	1 (0.3)	2 (0.5)	0	0	3 (0.8)
Autoimmune hepatitis	0	0	2 (0.5)	1 (0.3)	0	3 (0.8)
Hepatitis	0	0	1 (0.3)	0	0	1 (0.3)
Diarrhoea	0	1 (0.3)	0	0	0	1 (0.3)
Fatigue	0	1 (0.3)	0	0	0	1 (0.3)
Lethargy	0	1 (0.3)	0	0	0	1 (0.3)
Nausea	0	1 (0.3)	0	0	0	1 (0.3)
Uveitis	0	1 (0.3)	0	0	0	1 (0.3)
Liver injury	0	0	1 (0.3)	0	0	1 (0.3)
Rash	0	0	1 (0.3)	0	0	1 (0.3)
Embolism	0	0	0	1 (0.3)	0	1 (0.3)
Hepatitis acute	0	0	0	1 (0.3)	0	1 (0.3)
Myocarditis	0	0	0	0	1 (0.3)	1 (0.3)

Treatment-related SAEs were reported in 28 (7.1%) subjects treated with BMS-986205 and nivolumab. The most commonly reported treatment-related SAEs were due to hepatobiliary events (3% of subjects). An additional 2 SAEs of Hemophagic Lymphohistiocytosis (HLH) and Drug reaction with eosinophilia and systemic symptoms (DRESS) syndrome were reported after the clinical cutoff date (15-Nov-2017) and are being considered adverse events of special interest.

There were 101 deaths reported during combination treatment with BMS-986205

and nivolumab, the majority of which were due to reasons not related to study therapy: disease progression (n = 85), unknown causes (n = 2), other causes not related to treatment (n = 10; including episodes of septic shock/sepsis, lactic acidosis, infections, cardiac arrest, myocardial infarction, thrombolic event), and status indicating death (n = 3).

There was 1 treatment-related death reported as of the 15-Nov-2017 clinical cutoff date due to Grade 5 myocarditis. Myocarditis was diagnosed based on lack of other positive diagnostic findings supporting an alternative diagnosis. In addition, there were another 2 treatment-related deaths reported after the clinical data cutoff date. A subject with diffuse large B cell lymphoma was treated with 100 mg BMS-986205 and nivolumab 240mg Q2W, and developed mucositis and rash after 34 days of study treatment, which progressed to Grade 5 Stevens-Johnson syndrome despite treatment with corticosteroids and infliximab. Another subject with non-small cell lung cancer was treated with BMS-986205 100 mg daily and nivolumab 480 mg every 4 weeks and developed grade 3 transaminitis and elevated bilirubin 141 days after study medications were initiated. He was treated with corticosteroids 1.5 mg/kg with subsequent addition of mycophenolic acid since the bilirubin did not respond to steroids alone. He died approximately 25 days later of grade 5 hepatic failure.

8.1.11 **Return and Retention of Study Drug**
At the conclusion of the study, unused drug will be destroyed according to the institution's drug destruction policy.

8.2 Nivolumab

8.2.1 **Other names**
ONO-4538, BMS-936558, or MDX1106, Opdivo

8.2.2 **Classification**
Human IgG4 anti-PD-1 monoclonal antibody

8.2.3 **Mode of action**
Nivolumab acts as an immunomodulator by blocking ligand activation of the programmed cell death 1 (PD-1) receptor on activated T cells anti-PD1.

8.2.4 **Storage and stability**
Nivolumab solution for infusion is a sterile, non-pyrogenic single-use, isotonic aqueous solution. Vials must be stored in a secure, limited-access location at 2 to 8 degrees C (36 to 46 degrees F) and protected from light, freezing, and shaking. The product is a clear to opalescent solution, which may contain proteinaceous and extraneous particulates.

Note: discard the vial if the solution is cloudy, discolored or contains extraneous particulate matter other than a few translucent-to-white, proteinaceous particles.

The product is intended for IV administration. The drug product can be further diluted with normal saline in IV containers made of polyvinyl chloride (PVC) or non-PVC material. Opened or accessed vials should be immediately used to prepare the infusion solution in the IV bag and the infusion solution should be immediately administered.

After preparation, store the Nivolumab infusion either:

- at room temperature for no more than 8 hours from the time of preparation. This includes room temperature storage of the infusion in the IV container and time for administration of the infusion or

- under refrigeration at 2°C to 8°C (36°F to 46°F) for no more than 24 hours from the time of infusion preparation.
- Do not freeze.

8.2.5 **Protocol dose**

Nivolumab will be given at 240mg Q2W. At the beginning of Cycle 6 of the Maintenance Phase, nivolumab will be given at 480mg Q4W.

8.2.6 **Preparation and administration**

- Nivolumab should be prepared in a laminar flow hood or safety cabinet using standard precautions for the safe handling of intravenous agents applying aseptic technique.
- Visually inspect the drug product solution for particulate matter and discoloration prior to administration. Discard if solution is cloudy, if there is pronounced discoloration (solution may have a pale-yellow color), or if there is foreign particulate matter other than a few translucent-to-white amorphous particles.
- Mix by gently inverting several times. Do not shake.
- Aseptically withdraw the required volume of nivolumab solution into a syringe, and dispense into an IV bag.
- If multiple vials are needed for a subject, it is important to use a separate sterile syringe and needle for each vial to prevent problems such as dulling of needle tip, stopper coring, repeated friction of plunger against syringe barrel wall.
- Do not enter into each vial more than once. Do not administer as an IV push or bolus injection.
- When the dose is based on patient weight (ie, mg/kg), nivolumab injection can be infused undiluted (10 mg/mL) or diluted with 0.9% Sodium Chloride Injection, USP or 5% Dextrose Injection, USP to protein concentrations as low as 0.35 mg/mL.
- When the dose is fixed (eg, 240 mg, 480mg), nivolumab injection can be infused undiluted or diluted so as not to exceed a total infusion volume of 160 mL.

8.2.7 **Route of administration**

Intravenous infusion. Do not administer as an IV push or bolus injection. Administer nivolumab 240 mg as an intravenous infusion over 30 (-10/+15) minutes through a 0.2-micron to 1.2-micron pore size, low-protein binding (polyethersulfone membrane) in-line filter. Beginning at Cycle 6 of the Maintenance Phase, nivolumab will be given at 480mg as an intravenous infusion over 30 (-5/+15) minutes. At the end of the infusion period, flush the line with a sufficient quantity of approved diluents. Nivolumab injection is to be administered as an IV infusion.

8.2.8 **Incompatibilities**

No incompatibilities between nivolumab injection and polyvinyl chloride (PVC), DEHP (di[2-ethylhexyl]phthalate), non-PVC/non-DEHP (di[2-ethylhexyl]phthalate) IV components, or glass bottles have been observed. Nivolumab should not be infused concomitantly in the same intravenous line with other medicinal products.

8.2.9 **Availability & Supply**

Nivolumab will be supplied by the study as 100 mg/Vial (10 mg/mL) clear to opalescent, colorless to pale yellow liquid in 10-cc Type 1 flint glass vials

stoppered with butyl stoppers and sealed with aluminum seals. May contain particles.

A supply of nivolumab may be ordered from by completing a Drug Request Form provided by BMS. The first request may take place upon screening of the first patient. Allow 5 business days for shipment of drug from BMS receipt of the Drug Request Form. Drug is protocol specific, but not patient specific. All drug product will be shipped by courier in a temperature-controlled container. It is imperative that only drug product designated for this protocol number be used for this study.

Drug re-supply request form should be submitted electronically 10 business days before the expected delivery date. Deliveries will be made Tuesday through Friday. When assessing need for resupply, keep in mind the number of vials used per treatment dose, and that shipments may take 14 business days from receipt of request. Drug is not patient-specific.

At the end of the study period, Bristol-Myers Squibb Company will not continue to supply study drug to subjects/investigators unless the Sponsor-Investigator chooses to extend their study. The investigator is responsible to ensure that the subject receives appropriate standard of care or other appropriate treatment in the independent medical judgement of the Investigator to treat the condition under study.

8.2.10 **Side effects**

Related side effects reported in subjects receiving nivolumab alone were:
Very Frequent – Expected to occur in more than 20% of people (more than 20 out of 100 people): Fatigue (50%), Dyspnea (38%), Musculoskeletal pain (36%), Rash (21%), Increased AST (28%), Increase alkaline phosphatase (22%), Hyponatremia (25-38%)
Frequent - Expected to occur in 10% to 20% of people (10 to 20 out of 100 people): Pruritus (19%), Cough (17%), URI (11%), Peripheral edema (10%), Increased ALT (16%), Hyperkalemia (15%)
Not Frequent – Expected to occur in less than 10% of people (less than 10 out of 100 people): ventricular arrhythmia, iridocyclitis, infusion related reactions, increased amylase, increased lipase, dizziness, peripheral and sensory neuropathy, exfoliative dermatitis, erythema multiforme, vitiligo, psoriasis
Deaths thought to be related to nivolumab when given alone were reported in approximately 0.5% of subjects treated (approximately 1 out 200 people).

For the most recent safety update, please refer to the current Investigator's Brochure or Study Agent Prescribing Information.

8.2.11 **Monitoring of dose administration**

Participants are seen by their study doctor and research nurse before each dose of nivolumab (every 2 weeks or every 4 weeks beginning at Cycle 6 of the Maintenance Phase). Safety evaluations at this time include a physical exam, vital signs, performance status assessment, and safety laboratory tests. The study team will continuously monitor participants for treatment side effects. Participants are instructed to inform their study doctor right away if they notice or feel anything different so the study doctor can check for side effects. The study doctor may be able to provide treatment for side effects. The study doctor may temporarily hold the study drug to reduce side effects. The study doctor will permanently stop the study drug if side effects are too severe and/or long lasting.

All participants will be followed for side effects for 12 weeks from their last dose of nivolumab.

8.2.12 **Return and Retention of Study Drug Monitoring of dose administration**
The clinical study team will be responsible for keeping accurate records of the clinical supplies received from suppliers. Upon completion or termination of the study, all unused and/or partially used investigational product will be destroyed at the site per institutional policy. It is the Investigator's responsibility to arrange for disposal of all empty containers, provided that procedures for proper disposal have been established according to applicable federal, state, local and institutional guidelines and procedures, and provided that appropriate records of disposal are kept.

8.3 Temozolomide

8.3.1 **Other names**
TMZ, Temodar, Temodal

8.3.2 **Classification - type of agent**
Alkylating Agent

8.3.3 **Mode of action**
TMZ is an alkylating chemotherapy which adds methyl groups to key locations on DNA including the O6 guanine, N7 guanine, and N3 adenine, which proves cytotoxic to tumor cells. Activity of the DNA repair enzyme methylguanine methyltransferase (MGMT) markedly decreases the efficacy of TMZ. MGMT activity is controlled by methylation of its promoter, with unmethylated patients gleaning minimal benefit, at best, from TMZ (3).

8.3.4 **Storage and stability**
The capsules are packaged in amber glass bottles and should be stored at 25°C. Temperature excursions between 15 and 30°C are permissible. Refer to the commercially labeled bottles for expiration dating.

8.3.5 **Protocol dose specifics**
Only patients in the MGMT methylated promotor cohort will take TMZ.

During radiation therapy (the first 6 weeks of treatment) subjects in the MGMT promoter methylated cohorts will also receive an oral (p.o.) daily dose of 75 mg/m^2 TMZ.

Four weeks after the end of RT therapy, subjects will continue with concomitant, maintenance TMZ at a dose of 200 mg/m^2 daily for 5 days every 4 weeks for a total of 6 cycles.

8.3.6 **Preparation**
TMZ will be obtained commercially from the patient's local or specialty pharmacy.

8.3.7 **Route of administration for this study**
PO

8.3.8 **Incompatibilities**
TMZ is contraindicated in patients who have a history of a hypersensitivity reaction to any of its components or to DTIC.

8.3.9 **Availability & Supply**
As TMZ is being obtained commercially it will not be stored at the investigational

site.

8.3.10 **Side effects**
Hematologic: Thrombocytopenia, leukopenia, myelodysplastic syndrome
Gastrointestinal: Nausea, vomiting, anorexia
Hepatic: Elevated liver enzymes (reversible)
Skin: Rash
Neurologic: Convulsions, weakness on one side of the body, abnormal coordination, paralysis
Other: Constipation, diarrhea, stomatitis, fatigue, decreased performance status, headache

8.3.11 **Nursing implications**
Patients will be instructed to swallow the capsules whole, in rapid succession, without chewing them. If vomiting occurs during the course of treatment, no re-dosing of the patient is allowed before the next scheduled dose. The capsules should be taken on an empty stomach, therefore a minimum of 2 hours after eating and with no food consumption for at least 1 hour after temozolomide administration.

8.4 Tumor Treating Fields

8.4.1 **Other names**
Optune, NovoTTF™-200A System (Optune delivers Tumor Treating Fields [TTF])

8.4.2 **Classification**
Medical Device-Tumor Treating Fields (TTF).

8.4.3 **Mode of action**
Tumor treating fields mechanism of action: (A) Disruption of the formation of the mitotic spindle in metaphase, and (B) Positive dielectrophoresis during anaphase.

The antimitotic effect of TTFields Therapy might be expected to damage the replication of rapidly dividing normal cells within the body (bone marrow, small intestine mucosa).

*The TTFields Devic*e is a portable battery-operated device that produces TTFields within the human body using surface electrodes (transducer arrays). The NovoTTF Therapy is delivered to the patient by means of surface transducer arrays that are electrically insulated, so that resistively coupled electric currents are not delivered to the patient. All the treatment parameters are pre-set by Novocure so there are no electrical output adjustments available to the patient. The patient must learn to apply and change transducer arrays and change and recharge depleted device batteries and to connect to an external electrical outlet.

8.4.4 **Storage and Stability**
The device and all related all related equipment will be stored at the patient's home at room temperature.

8.4.5 **Protocol dose**
TTField treatment will be offered to the patient at the beginning of the Maintenance Phase. All patients will be required to shave their heads to initiate array placement and TTField therapy. Array placement will be performed based on the transducer array map calculated during treatment planning.

8.4.6 **Preparation and administration**

Treatment with the device will be continuous with breaks allowed for personal needs (eg. showering, array exchange). Patients must use the device for at least 18 hours a day on average.

Treatment Planning: Transducer array layout will be determined based on the location of the patient's tumor(s) on MRI. NovoTALTM software supplied by Novocure for layout planning may be used by study investigators who previously received training by a Novocure representative and wish to use it on this trial. All other investigators will be required to send the baseline MRI scans to Novocure for NovoTAL array layout planning within one day of submitting the prescription and an array layout will be supplied prior to treatment start. The investigator may modify the transducer array layout at any time during the trial based on radiological data analysis and clinical considerations.

Patient training: Patients on the study will be trained on the technical aspects of using the device by a Novocure Device Support Specialist either in their home or at the investigator's office, as dictated by the investigator. Patients will receive an instructional call from Novocure prior to training to highlight important items such as the need to shave the head and to answer any technical or logistics questions the patient or caregiver may have.

8.4.7 **Route of administration**

Tumor treating fields through transducer arrays electrodes on bare scalp.

8.4.8 **Incompatibilities**

- Patients with active implanted medical device, a skull defect (such as, missing bone with no replacement), a shunt or bullet fragments. Examples of active electronic devices include deep brain stimulators, spinal cord stimulators, vagus nerve stimulators, pacemakers, defibrillators, and programmable shunts.
- Patients with known to be sensitive to conductive hydrogels like the gel used on electrocardiogram (ECG) stickers or transcutaneous electrical nerve stimulation (TENS) electrodes.
- Patients with programmable VP shunts and patients with vagal nerve stimulators.

8.4.9 **Contraindications**

Do not use Optune if you have an active implanted medical device, a skull defect (i.e., missing bone with no replacement) or bullet fragment(s). Examples of active electronic devices include deep brain stimulators, spinal cord stimulators, vagus nerve stimulators, pacemakers, defibrillators, and programmable shunts. Use of the Optune together with implanted electronic devices has not been tested and may theoretically lead to malfunctioning of the implanted device. Use of the Optune together with skull defects or bullet fragments has not been tested and may possibly lead to tissue damage or render the Optune ineffective.

Do not use the Optune if you are known to be sensitive to conductive hydrogels like the gel used on electrocardiogram (ECG) stickers or transcutaneous electrical nerve stimulation (TENS) electrodes. In this case, skin contact with the electrode gel used with the Optune may commonly cause increased redness and itching, and rarely may even lead to severe allergic reactions such as shock and respiratory failure.

8.4.10 **Availability & Supply**

Patients will receive the Optune device through a commercial prescription process.

8.4.11 **Side effects**

Treatment with the Optune is not expected to cause any serious side effects. However, it is possible that treatment may cause any of the following:

- Local warmth and tingling “electric” sensation beneath the transducer array
- Allergic reaction to the adhesive or to the gel
- Skin irritation or skin breakdown
- Infection at the sites of transducer array contact with the skin
- Transducer array overheating leading to pain and/or local skin burns
- Headache
- Fatigue
- Malaise
- Muscle twitching
- Fall, if the system interferes with walking

8.4.12 **Nursing Implications**

Patients should only use Optune under the supervision of a physician properly trained in use of the device. All technical training on the device will be done by a Novocure representative called a Device Support Specialist. He/she will deliver the equipment directly to the patient and train the patient and any caregivers on the all the practicalities of using the device. An instructional manual regarding the device will be provided to the patient. All medical management will be done by the PI and nursing staff. While using Optune, the following skin care guidelines should be closely adhered to:

- If the skin beneath the transducer arrays is inflamed, a high potency topical steroid should be prescribed to the patient. The patient or caregiver should apply the ointment after removing the arrays, removing remaining array adhesive from the skin with baby oil and cleaning the skin with medical alcohol. The ointment should be left on the skin for at least 30 minutes prior to washing the skin with a mild soap and applying a new set of arrays.
- At each array replacement, the new set of arrays should be shifted by approximately 2 cm compared to the previous layout so that the array discs are placed between the areas of skin irritation. At the next array replacement, the arrays should be shifted back to their original location.
- If the epidermis is breached (skin erosions, punctate lesions, cuts, open sores etc.) an antibiotic ointment (e.g. mupirocin) should be prescribed and used in place of the topical steroid treatment. Any evidence of infection should result in bacterial cultures being taken.
- There will be no “dose” adjustments to the device for adverse events.
- Reasons for breaks in treatment for longer than 24 hours will be documented in the CRFs. The maximum duration of treatment break allowed for adverse events related to NovoTTF Therapy is 8 weeks (9 weeks for patients who switch to the 3–week treatment schedule after Cycle 4).

9 CORRELATIVES/SPECIAL STUDIES

Patients must provide a sample of tumor tissue from GBM surgery or biopsy at baseline, if available (no minimum requirement). If patient undergoes surgery following disease progression, providing tumor tissue for analysis is optional. Patients will undergo a blood draw at baseline, every 8 weeks during the Maintenance Phase beginning at Cycle 1 Day 1, and at the End of Treatment Visit. An optional stool sample may be collected at baseline and at Cycle 1 Day 1 of the Maintenance Phase.

Correlative Samples - Details for Lab Manual					
Correlative study (sample type) *e.g. Pharmacokinetics (blood)*	Archival Tissue	Fresh Tissue	Blood	Blood	Stool
Mandatory or Optional	Optional	Optional	Mandatory	Mandatory	Optional
Timing (+/- windows)	Baseline and If patient undergoes surgery following disease progression	If patient undergoes surgery following disease progression	Baseline (prior to first dose of study treatment), on day 1 of post RT, and every 8 weeks during the Maintenance Phase beginning on Cycle 1 Day 1 (±2 days), and at the end of treatment visit.	Baseline (prior to first dose of study treatment), on day 1 of post RT, and every 8 weeks during the Maintenance Phase beginning on Cycle 1 Day 1 (±2 days), and at the end of treatment visit.	Baseline (prior to first dose of study treatment) and Cycle 1 Day 1 of Maintenance Phase
Volume Needed (blood only)	n/a	n/a	10 ml	10 ml	n/a
Tube type needed (blood only)	n/a	n/a	Sodium Heparinized tubes	Sodium Heparinized tube	n/a
Tissue thickness and/or # slides (tissue only)	5um, 10 slides		n/a	n/a	n/a
Processing center (e.g. PCF-CTU)	PCF-CTU & CNS Tumor Tissue bank	CNS Tumor Tissue bank	CNS Tumor Tissue bank	CNS Tumor Tissue bank	PCF-CTU
Sample handling/processing instructions	PCF-CTU will obtain archival tissue samples and will deliver to CNS Tumor Bank		Samples will be delivered to Kristen L Lauing, PhD in Dr. Derek Wainwright's laboratory.	Samples will be delivered to Kristen L Lauing, PhD in Dr. Derek Wainwright's laboratory	Globe Scientific Self-Standing Transport Tube with Screw Cap and Spoon
Storage needs	Stored at –20°C in Wainwright Labuntil analysis	Stored at –20°C in Wainwright Labuntil analysis	Stored at –80°C in CNS Tumor Bank until analysis	Stored at –80°C in CNS Tumor Bank until analysis	Stored at –80°C in PCF-CTU until analysis
Analysis center	Wainwright Lab Cardinal Bernardin Cancer Center Loyola University Chicago, Health Sciences Division 2160 S. First Ave., Bldg. 112, Rooms 208 and 210 Maywood IL 60153	Wainwright Lab Cardinal Bernardin Cancer Center Loyola University Chicago, Health Sciences Division 2160 S. First Ave., Bldg. 112, Rooms 208 and 210 Maywood IL 60153	Wainwright Lab Cardinal Bernardin Cancer Center Loyola University Chicago, Health Sciences Division 2160 S. First Ave., Bldg. 112, Rooms 208 and 210 Maywood IL 60153	Wainwright Lab Cardinal Bernardin Cancer Center Loyola University Chicago, Health Sciences Division 2160 S. First Ave., Bldg. 112, Rooms 208 and 210 Maywood IL 60153	Wainwright Lab Cardinal Bernardin Cancer Center Loyola University Chicago, Health Sciences Division 2160 S. First Ave., Bldg. 112, Rooms 208 and 210 Maywood IL 60153
Assay methodology	tryptophan/kynurenine levels and for gene expression profile analysis	tumor-infiltrating lymphocytes (TIL),	evaluation of activated peripheral lymphocytes	Peripheral blood analysis for gene expression, tryptophan metabolism and cytokine abundance	high-throughput next-generation Illumina MiSeq sequencing

9.1 Sample Collection Guidelines

Please refer to the Laboratory Manual for instructions on Sample Collection.

9.2 Sample Processing, Storage, and Shipment

Please refer to the Laboratory Manual for instructions on sample processing, storage and shipment.

9.3 Assay Methodology

9.3.1 Tissue

Tumor tissue removed at surgery will be used to extract tumor-infiltrating lymphocytes (TIL), myeloid cells including macrophages, microglia, DCs, MDSCs, as well as CD45highCD3- cells that do not possess traditionally-defined characteristics, tryptophan/kynurenine levels and for gene expression profile analysis. In addition, fresh frozen and formalin fixed paraffin embedded tissue will be banked for analysis. Extracted TILs will be used to evaluate the tumor infiltrative lymphocyte population by flow cytometry and paraffin embedded tissue will be used to evaluate TILs in situ by immunohistochemistry. If a patient has progression of disease and undergoes further surgery, they will have the option of allowing tissue to be analyzed for the above.

9.3.2 Blood

Blood, prior to, and after treatment initiation, will be collected for baseline evaluation of activated peripheral lymphocytes. Once patients are off study, there will be an optional blood draw during surgery, prior to restarting treatment and on the day of each MRI scan with extraction and banking of peripheral blood leukocytes (PBL).

PBLs and plasma will be separated with SepMate isolation tubes.

PBLs obtained prior to drug administration will be studied by flow cytometry to identify relative populations of CD8 T cells (CD3+, CD8+, PD1+/-), CD4 T cells (CD3+, CD8+, PD1+/-), regulatory T cells (CD4+, CD25+, FoxP3+), and suppressive monocytes (CD45+, CD11b+, PD-L1+). Repeat assessment of PBL markers will be determined by flow cytometry of subsequent samples taken on the day of surgery, post operatively and then on MRI days. Additionally, TILs extracted from patient tissue will be evaluated for relative populations of activated CD8 T cells (CD3+, CD8+, IFN-g+, PD1+/-), activated CD4 T cells (CD3+, CD8+, IFN-g+, PD1+/-), regulatory T cells (CD4+, CD25+, FoxP3+), and suppressive monocytes (CD45+, CD11b+, CD163+, PD-L1+). Double-labeled tissue immunofluorescence can also be performed on FFPE sections to obtain immune effector cell counts, reported as # cells / 10 hpf. Optimized labeling schemes include: CD8/IFN-g, CD4/IFN-g, CD8/PD-1, CD4/PD-1, CD68/PD-L1, and GFAP/PD-L1 (to identify PD-L1 + tumor cells). Banked PBLs, TILs and FFPE tissue from prior patients treated without the study drug will serve as comparative controls.

PBLs will also undergo gene expression analysis for IDO1, PD-L1, among other immunomodulatory factors that may change during treatment.

Plasma will be collected and stored for downstream analysis of tryptophan and kynurenine levels via HPLC, as well as for serum catecholeamine and cytokine levels including epinephrine (43), norepinephrine (43), and cortisol (44), as well as stress-related cytokines, MCP-1(45) and IL-6.

9.3.3 **Stool**
An optional stool sample will be collected at baseline and at the beginning of the Maintenance Phase (Cycle 1 Day 1) to study the effect of the microbiome on outcomes with this immunotherapeutic approach.

9.3.4 **Characterize tumor and immune response to RT, PD-1 mAb and IDO enzyme inhibition in GBM patients.**
Preclinical results show a marked survival advantage in GBM-bearing mice treated with a combination of RT and PD-1/IDO1 inhibition, with some mice even experiencing cure of tumor. Analyses of circulating and intratumoral immune cells will be performed. Orthotopic PDX models will be established.

Clinical trial correlative analyses. GBM tissue and blood samples from the operating room and clinic will be collected and processed for: (i) standard neuropathological and immunohistochemical analyses (Biospecimen Core), for ii) genomic and transcriptomic profiling of analytes from frozen material (Tempus, Chicago, IL), and (iii) immunocorrelative and targeted molecular analyses (Wainwright laboratory). As patients have been selected initially for resectability of their tumors and will be closely followed, we estimate that approx. 30 to up to 50% of patients may undergo repeat surgery at tumor progression. This will allow for paired comparison of the initial tumor samples with their respective recurrent tumors developing under therapy.

9.4 Specimen Banking

Samples will be stored in the Wainwright Lab. Please see the Lab Manual for specific instructions regarding specimen banking.

9.5 Patient Questionnaires

These questionnaires will investigate GBM patient levels of distress, before, during, and after treatment with trimodal radiation, anti-PD-1 mAb and IDO1 enzyme inhibitor**.** Biobehavioral stressors may mitigate the benefits of trimodal immunotherapy. Both patient-reported and physiologic stress measures will be investigated. Patients will complete online questionnaires using the Patient-Reported Outcomes Measurement Information System (PROMIS) to evaluate psychosocial and behavioral factor impact before, during, and after immunotherapeutic treatment. Blood levels for epinephrine, norepinephrine, cortisol, and stress-associated cytokines, in addition to T cell and monocyte expression and localization for glucocorticoid and catecholamine receptors, will be evaluated, before, during, and after treatment.

This project will use a non-randomized pre-test and post-test design, with participants serving as their own controls for assessing psychosocial and biobehavioral measures. Sampling will be obtained at baseline/pretreatment (any time prior to Day 1 of RT), 1 week prior to each MRI follow-up, and every 3 months during follow up. Patient email addresses will be requested at time of consent. A paper copy of the questionnaires will be available if needed (see appendices K and L).

The following patient report measures will be used:

- 'Beck Depression Inventory' as well as the 'Emotional Distress-Anxiety' inventory of the PROMIS measure. The PROMIS measures are a series of open access questionnaires used to evaluate general or specific areas of health and well-being. They are well validated and precise. Specific profile domains of emotional distress, and anxiety will be used to target known problems in the brain tumor population and minimize the burden of form completion. Each form can be completed in the privacy and comfort of a participant's home. Patients will be given a paper form for the PROMIS

measures. When completed, the data from the form will be entered into a secure NOTIS database by the study team. Paper forms will be secured in a locked room with access given to authorized study personnel only. Report data will be downloaded by the study team and reviewed with the patient during the visit.

- Blood draws will be obtained and separated into sera and blood cells for quantification of:
    - Distress-associated hormones including epinephrine (43), norepinephrine (43), and cortisol (44), as well as stress-related cytokines, MCP-1(45) and IL-6(44).
    - Glucocorticoid receptor and beta adrenergic receptor expression level in/on $CD8^+$ cytolytic T cells, $CD4^+FoxP3^-$ helper T cells, and $CD4^+CD25^+FoxP3^+$ immunosuppressive regulatory T cells, and $CD3^-$ monocytes.

9.6 AMT-PET Study

AMT-PET will be offered to all patients in the study (participation is optional), and we estimate performing PET imaging in about half of the patients, both prior to treatment and after RT + nivolumab + BMS-986205 +/- temozolomide combination therapy. A baseline AMT-PET will be performed after surgery or biopsy when histologic diagnosis has been established and before starting RT and systemic therapy. Follow up AMT-PET will be performed approximately 4 weeks after the completion of combined RT + IDOi + anti-PD-1 antibody. This imaging study will be correlated with the 4 week post-radiation MRI. After 1 year or at tumor progression another AMT-PET may be performed. The quantitative or semi-quantitative PET-response after the end of radiotherapy (+ nivolumab and BMS-986205) will be correlated with patient outcome.

9.6.1 AMT-PET

AMT is an analog of Trp, and AMT-PET quantifies intratumoral Trp metabolism based on the amount of radiolabeled AMT in tumor. Importantly, unlike alternative amino acid PET tracers, AMT is not incorporated into protein. Both contrast-enhancing and non-enhancing gliomas have increased AMT uptake, and increased trapping in glioma tissue is associated with elevated elevated IDO1, as confirmed by surgical resection of tumor and accompanying IHC, following treatment. Detailed volumetric analysis has demonstrated that increased AMT uptake on PET is not confined to the area of contrast enhancement in high-grade gliomas, and often extends to non-enhancing tissue subsequently shown to have tumor cell infiltration (proven by targeted biopsy and analysis of biopsied tissue). AMT-PET can accurately differentiate RT injury from tumor recurrence. The study described is being performed to assess whether tumor-associated α-[11C]-methyl-L-Trp (AMT) uptake on PET imaging is correlated with treatment response and survival outcomes.

9.6.2 **AMT-PET Scanning Protocol**

PET studies will be performed using the GE Discovery STE PET/CT scanner, located in the PET Center, Children's Hospital of Michigan, Wayne State University, Detroit. The scanner has a 15 cm field of view and generates 47 image planes with a slice thickness of 3 mm. The reconstructed image resolution is 7.5 ± 0.4 mm (isotropic), and images from this scanner will be iteratively reconstructed (2 iterations, 16 subsets, 8 mm axial smoothing). The AMT tracer is synthesized using a standard method. The procedure for AMT PET scanning has also been described previously. In brief, patients will fast for 6 hours prior to AMT PET. This decreases risk of aspirating gastric contents, and also ensures stable plasma Trp and large neutral amino acid levels during the study. In females of child-bearing age, a urine pregnancy test will be performed before scanning. A venous line will be established for injection of AMT (0.1 mCi/kg) as a slow bolus. A second venous line will be established for collection of timed blood samples (0.5 mL/sample, collected at 0, 20, 30, 40, 50 and 60 min after AMT injection). Blood radioactivity data will be used for Patlak graphical analysis.

In order to quantify AMT, cardiac volume will first be quantified via a 5-minute computerized tomography (CT) scan, using very low power (10mA, 80 keV) for attenuation correction. Following injection of AMT, a 20-minute dynamic PET scan of the heart will be performed (sequence: 12x10 s, 3x60 s, and 3x300 s) in 2D-mode in order to obtain the left ventricular (LV) blood input function. Continuation of the blood input function beyond the initial 20 minutes is then achieved using venous blood samples obtained during brain scanning. Twenty-five minutes after tracer injection, a 5-minute CT scan of the brain will be followed by a 35-min dynamic emission PET scan of the brain (7 x 5 minutes) in high-sensitivity 3D mode. Measured attenuation correction will be applied to the AMT PET images of the heart, whereas computed attenuation correction will be used to correct the brain images. Plasma will be isolated from a blood sample by centrifugation, and plasma samples will be counted in a NaI well counter cross-calibrated to the PET scanner in order to obtain the blood input function.

PET scans will be collected digitally, both raw images and processed images (color-coded, co-registered with MRI). These scans will be mailed by the Wayne State University Study Team on a CD to the NU study team at this address:

c/o Rimas Lukas, MD
710 N. Lake Shore Drive
Abbott Hall 1114
Chicago, IL 60611

Co-registration of PET and MRI image volumes

Multimodal image co-registration and analysis will be done by 3D Slicer software (www.slicer.org). Images will be co-registered with pre- and post-contrast axial T1 MR images, T2 and FLAIR images (acquired at Northwestern or local institution within 7 days of planned AMT-PET and transferred for Dr. Juhasz's access at WSU) using the Fast Rigid Registration module. Fused images will be automatically resliced and resampled. MRI abnormalities (T2/FLAIR, T1 post-gadolinium) will be delineated semi-automatically, and the volumes of interest (VOI) will be used as regions for quantitative assessment of AMT uptake and kinetic parameters.

Quantitative assessment of AMT tumor uptake

The AMT uptake in VOIs, defined on MRI will be characterized in the following ways: 1) Standardized uptake values (SUVs): the SUV calculation relates tracer concentration in tissue to the dose injected and the subject's mass (SUV= tissue

concentration in ROI [uCi/cc]/injected dose per weight [mCi/kg]). Since all subjects receive the same injected dose based upon weight (0.1 mCi/kg), the SUV images will be directly obtained by averaging the last four frames of the dynamic brain image sequence during which time there is the highest metabolic product. 2) Patlak analysis: In order to quantify unidirectional AMT uptake and metabolism in tumors non-invasively, a Patlak graphical analysis will be performed using the LV arterial input function and the dynamic brain sequence (7 x 5 min consecutive frames starting 25 min post-injection). The Patlak graphical analysis is based on a well-validated equation described in previous studies and provides the following parameters: K-complex, VD, and k3. In case of irreversible trapping of Trp metabolites, the slope parameter (k3VD) corresponds to the previously described K-complex, reflecting the unidirectional uptake of tracer into tissue. In the case of AMT, the value of the K-complex is thought to be proportional to the Trp metabolism via the Kyn pathway in tumor tissue (or serotonin in non-tumoral brain). In order to distinguish the effects of Trp transport from Trp metabolism, the intercept of the Patlak plot, termed VD' (=eVD), and the ratio between slope and intercept termed k3' (= k3/e) will be also assessed.

Comparison of AMT kinetic parameters between baseline and follow-up AMT-PET images
Baseline and follow-up (on treatment) AMT-PET images will be co-registered, together with corresponding (clinically acquired) MR images. VOIs created on the baseline images will be transferred to the post-treatment images to make sure that AMT uptake and kinetic parameters will be measured repeatedly in the same tumor volume for comparison. AMT SUV and kinetic parameters (K, VD, k3) will be calculated from the post-treatment PET images, and compared to corresponding baseline values.

All exploratory analyses will be considered hypothesis generating only and formal statistical significance will not be assessed.

9.6.3 Patient Reimbursement for Travel

Participants will be compensated for travels costs, including automobile mileage, airfare, hotel and taxi fees, and meals. The maximum amount of money that can be reimbursed per patient is $750 per each AMT-PET performed.

Reimbursement will be given in the form of a check. Participants will be instructed to keep all their receipts in order to receive reimbursement.

Free parking is available at the Children’s Hospital of Michigan. Participants will be given a handout with directions and a map to CHM and areas to park around the hospital.

9.6.4 Communication Plan

If there is an eligible patient, the NU study team will contact the Wayne State University Investigator (Dr. Juhasz Csaba). The PET Center will need a signed NU consent form, eligibility verification for the AMT PET study (includes clinical and imaging records), and patient contact information. This information will be provided by the NU study team via encrypted email.

Dr. Juhasz will inform Angela Wigeluk (Lead technologist) and her colleagues (PET Center staff), who will check the PET schedule and give possible dates for the scan.

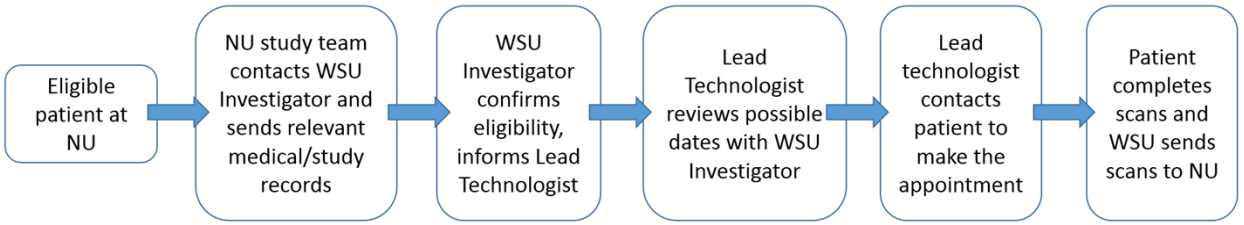
Once the AMT-PET scan is scheduled by the PET Center staff, a technologist or a nurse from the WSU PET Center will call the patient to confirm the appointment, and give instructions and directions to the PET Center.

Patients will complete an additional PET consent form at the CHM PET Center before the scan.

PET images will be sent electronically from Dr. Juhasz's office to NU investigators after image processing. The images will be mailed on CDs to the address listed in Section 9.6.2.

Angela Wigeluk is the primary contact for the PET Center and can be contacted by patients if there are any questions about the AMT PET study. Her contact information and the other PET Center/WSU study contacts are listed in Section 9.6.5.

Communication Plan Diagram



9.6.5 Wayne State University PET Center Personnel and Contact Information

Investigator
Csaba Juhasz, MD, PhD
Phone: 313-966-5136
Email: csaba.juhasz@wayne.edu

Lead Technologist
Angela Wigeluk
Phone: 313-993-3849
Email: wigeluka@karmanos.org

Regulatory Coordinator
Lynda Ferguson
Phone: 313-993-0006
Email: fergusol@karmanos.org

PET Center
Children's Hospital of Michigan
3901 Beaubien St.
Detroit, MI 48201
Fax: 313-966-9228

10 STATISTICAL CONSIDERATIONS

10.1 Study Design/Study Endpoints

In this phase 1 trial, statistical analyses will be descriptive. Based on landmark analysis of historical control data for unmethylated tumors we estimate the 1-yr survival (OS12) at 50%. For methylated tumors the prognosis is somewhat more favorable, and a benefit may only be observed after > 2 years. All statistical analyses of data from this cohort including survival will be considered descriptive and exploratory.

10.1.1 Primary Variable

Phase I

- Safety
- Dosing

10.1.2 Secondary Variables

- 1-year survival rate (probability of surviving 1 year or more from start of study treatment).
- Median survival time (median time from time of first treatment to death).
- Response rate (percentage of subjects who achieve PR or CR according to the iRANO criteria).
- Response rate (percentage of subjects who achieve PR or CR according to the RANO criteria).
- Median duration of response (number of days from the first diagnosed PR or CR to PD or death), if applicable.
- 6-month PFS rate (probability of disease progression or death from any cause occurring 6 months or later from start of study treatment)
- Median time to disease progression (median time from first treatment on study to documented disease progression or death from any cause).

10.1.3 **Safety Variables**

- Incidence and type of AEs
- Vital signs
- Laboratory values
- Neurologic exam
- KPS

10.1.4 **Further Variables of Interest**

- Tumor immune-correlates
- Serum immune-correlates
- Molecular pathology correlates
- Patient distress correlates
- AMT-PET correlation with overall survival
- AMT-PET correlation with radiographic response on MRI
- AMT-PET correlation with tumor and serum immune-correlates

10.2 Analysis sets

10.2.1 **Intention-to-treat (Full analysis set)**

The intention-to-treat population includes all subjects who have received at least 1 i.v. administration of nivolumab or one oral dose of BMS-986205.

10.2.2 **Per protocol**

The per protocol population includes all intention-to-treat subjects who meet the following criteria:

- Complete 12 months of infusion with nivolumab and 12 months of oral BMS-986205 unless drug is discontinued due to disease progression, death, or study drug related unacceptable AEs in which case the subject will not be required to complete 12 months of treatment.

- Do not miss more than 2 consecutive doses of nivolumab or 4 consecutive weeks of BMS-986205 *and* do not miss a total of 7 doses of nivolumab or 30 doses of BMS-986205 during the first 12 months of the study or prior to disease progression, death, or study drug related unacceptable adverse events whichever occurs first.

Subjects who do not meet the above criteria may continue in the study but are considered not evaluable. Subjects with major protocol violations that would likely affect the clinical activity of study drug may also be excluded from the per protocol population. Such decision should be made prior to database lock and the primary analysis.

10.2.3 **Safety**
The safety population includes all subjects who have received at least 1 i.v. administration of nivolumab or one oral dose of BMS-986205, which is same as the intention-to-treat population.

10.2.4 **Subgroups**
Following subgroups will be analyzed descriptively:

- Age, (Patients <65 years old and patients ≥65 years old)
- performance score,
- extent of resection, if applicable.

10.3 Sample Size and Accrual
We will recruit 18-30 patients in this Phase I study depending on dose findings.

Based on landmark analysis of historical control data for unmethylated tumors we estimate the 1-yr survival (OS12) at 50%. For methylated tumors the prognosis is somewhat more favorable, and a benefit may only be observed after > 2 years. All statistical analyses of data from this cohort including survival will be considered descriptive and exploratory.

10.4 Data Analyses Plans
All statistical analyses pertaining to the proposed studies will be performed under the supervision of Dr. Denise Scholtens, PhD (Associate Director of Biostatistics for the RHLCCC Quantitative Data Sciences Core). In general, for continuous variables, data will be presented as mean (SD) or mediation (range, interquartile range) and categorical variables will be summarized with tables of frequencies and counts. Exploratory overall survival and PFS curves will be generated via Kaplan-Meier method. Statistical analyses will be performed using R-3.6.1 (https://cran.r-project.org/).

10.4.1 **General considerations**
Analyses of primary and secondary target variables will be performed using the intention-to-treat and the per protocol populations, with the intention-to-treat population being the primary analysis set. All analyses of safety and tolerability will be performed using the safety population.

Point estimates and the 95% confidence interval will be provided for all primary and secondary target variables. Safety and tolerability data will be summarized descriptively using tables of frequencies and counts.

Handling of drop outs and missing data

Subjects who terminated the study prior to the 12-month time point will be considered failure to achieve 12-month survival. For response rate calculations, the best response during the observed period will be used.

For time-to-event analyses, missing data will be treated as censored at the time of last follow-up if the event (death or progression) is not observed.

Analyses of the safety data will be performed using all observed data.

MGMT unmethylated and methylated groups

All statistical analyses will be performed separately for MGMT unmethylated and methylated patient groups

10.4.2 **Primary analysis**

The primary analyses for this Phase I study will be descriptive. Dose-limiting toxicities will be monitored as described above to conduct of the 3+3 design. All dose-limiting toxicities and adverse events will be tabulated.

10.4.3 **Secondary analyses**

Survival time is defined as the number of days between date of study enrollment and date of death. Subjects for whom death is not observed will be censored at the time when the subject is last known to be alive. The survival curve will be plotted using the Kaplan-Meier method. Median survival time and the 95% confidence interval will be presented for each study group and 1-year overall survival will be estimated. The 95% confidence intervals will be obtained by Greenwood's formula.

Tumor response will be reported as CR, PR, SD, PD, or unknown (UNK) according to the iRANO criteria and RANO criteria (42). A responder is defined as a subject whose best response during the study is either complete (CR) or partial (PR). The response rate will be calculated as the percentage of responders, and similarly, the 95% confidence interval will be calculated using the exact binomial method, if data allow.

Time to disease progression is defined as the number of days between date of study enrollment and date of first assessment of PD during the study or until death from any cause, whichever occurs first. Subjects without disease progression and are alive will be censored at the time when the subject is last known to be non-progressing. Similar to overall survival analyses, the Kaplan-Meier curve will be plotted and median time to disease progression and the 95% confidence interval will be calculated. 6-month progression free survival will also be estimated. Since tumor assessment will only be performed periodically (every 8 weeks), the Kaplan-Meier estimate (estimated probability that a subject is progression-free at a specific time) and its 95% confidence interval will be provided at the end of each 8-week period.

For subjects who achieve PR or CR during the study, duration of objective response measures the number of days from the first objective assessment of PR or CR to PD or death from any cause following a confirmed PR or CR. Subjects who achieve PR or CR but for whom subsequent PD is not observed during the study will be censored at the time when the subject is last known to be non-progressing. Each duration and censoring information will be provided in a data listing.

10.4.4 **Exploratory analyses**

Exploratory analyses will include non-parametric Spearman correlations and 95%CIs between tumor immune correlates, serum immune correlates and molecular pathology correlates. Non-parametric summaries of continuous variables by categorical groups, or contingency tables for comparisons of categorical variables will also be used.

In addition, non-parametric summaries of patient distress measures with clinical outcomes will also be explored using either Spearman correlations or non-parametric summaries of continuous measures across groups, as appropriate.

While sample size may preclude formal interpretation of results, correlations between AMT-PET responses and MRI responses with time-to-event outcomes will be explored using Cox proportional hazards regression models. If appropriate, we will include the use of time-varying covariates in these models to allow for changes in response status over time. Exploratory analyses evaluating correlations between AMT-PET responses and tumor and serum-immune correlates will also be performed.

10.4.5 **Safety analyses**

Drug safety and tolerability will be evaluated by descriptively summarizing AEs, laboratory assessments, vital signs, and ECG assessments using tables of frequencies and counts for categorical variables and means (sds) or medians (ranges, interquartile ranges) for continuous variables.

11 STUDY MANAGEMENT

11.1 Institutional Review Board (IRB) Approval and Consent

It is expected that the IRB will have the proper representation and function in accordance with federally mandated regulations. The IRB should approve the consent form and protocol.

In obtaining and documenting informed consent, the investigator should comply with the applicable regulatory requirement(s), and should adhere to Good Clinical Practice (GCP) and to ethical principles that have their origin in the Declaration of Helsinki.

Before recruitment and enrollment onto this study, the patient will be given a full explanation of the study and will be given the opportunity to review the consent form. Each consent form must include all the relevant elements currently required by the FDA Regulations and local or state regulations. Once this essential information has been provided to the patient and the investigator is assured that the patient understands the implications of participating in the study, the patient will be asked to give consent to participate in the study by signing an IRB approved consent form.

Prior to a patient's participation in the trial, the written informed consent form should be signed and personally dated by the patient and by the person who conducted the informed consent discussion.

11.2 Amendments

The Principal Investigator will formally initiate all amendments to the protocol and/or informed consent. All amendments will be subject to the review and approval of the appropriate local, institutional, and governmental regulatory bodies, as well as by BMS.

11.3 Registration Procedures

For potential patients for this phase I study, study teams are asked to inform the QAM of the date and time that the patient will need to be registered (croqualityassurance@northwestern.edu).

BEFORE a patient can be treated on study, please complete and submit the following items to confirm eligibility and receive an identification number:

- Patient's signed and dated informed consent form (upload to NOTIS and keep original hard copy in a secure location/study chart)
- Eligibility checklist (signed and dated by the treating physician – upload to NOTIS)
- Eligibility eCRF (complete in NOTIS)
- Copy of the pathology report (upload to NOTIS)

The QAM will review all source documentation required to confirm eligibility that is readily available in the patient's electronic medical record (EMR). Any information that is not available in the EMR must be de-identified and emailed to the QAM. Once the QAM confirms the patient is eligible, he or she will register the patient, assign a subject identification number, provide a cohort assignment, and send a confirmation of

registration to involved personnel. Registration will then be complete and the patient may begin study treatment.

11.4 Data Submission

Once a subject is confirmed and registered to the study, eCRFs should be submitted according to the study procedure table. Generally, all data for phase I patients during the time period patients are evaluated for Dose Limiting Toxicities (DLTs) must be submitted on a weekly basis.

11.5 Instructions for Participating Sites

Before the study can be initiated at any site, the following documentation must be provided to the Clinical Trials Office at Northwestern University (as applicable):

- Completed feasibility assessment(s) to verify site's capacity to support a Northwestern sponsored trial
- Signed copy of Northwestern University's Data Participating Site Acknowledgement which details data submission guidelines
- Draft consent form for review and approval prior to submission to the local IRB
- A copy of the official IRB approval letter for the protocol and informed consent
- A copy of the IRB approved informed consent
- Pertinent credentials (CVs, MLs, CITI & GCP Training and FDFs) for the local PI and any sub-investigators who will be involved in the study at the site
- Form FDA 1572 appropriately filled out and signed with appropriate supporting certifications

Additional activities may be required prior to site activation (i.e. contract execution, study-specific training, and delegation of authority log). Full requirements will be outlined in the study start-up packet upon successful completion of a feasibility assessment.

11.6 Data Collection and Record Keeping

We will take measures to minimize the unauthorized release of confidential information. All personal identifying information will be removed from the clinical database, specimens tracking systems, as well as the headers of the raw NGS data files. They will be replaced with the unique study number generated through the Northwestern Oncology Trial Information System (NOTIS). A key will be established that links the unique study number to the patient's name and medical record number. That key will only be accessible to study personnel with access to the protocol in NOTIS. This will allow the combination, only when needed, of data from various sources e.g. combining genetic information with clinical (i.e. response to treatment, survival, etc.).

NOTIS will be used to develop the case report forms (CRFs) and to populate them with data. The study coordinator at each participating institution will be responsible for entering data into NOTIS. All sites will be trained by a member of the Northwestern University study team to use NOTIS.

11.7 Data Management and Monitoring/Auditing

This study will be conducted in compliance with the Data Safety Monitoring Plan (DSMP) of the Robert H. Lurie Comprehensive Cancer Center of Northwestern University (please refer to NOTIS for additional information). The level of risk attributed to this study requires high-intensity monitoring, as outlined in the DSMP. The assigned QAM, with oversight

from the Data and Safety Monitoring Committee, will monitor this study in accordance with the study phase and risk level.

11.8 Adherence to the Protocol

Except for an emergency situation in which proper care for the protection, safety, and well-being of the study patient requires alternative treatment, the study shall be conducted exactly as described in the approved protocol.

11.8.1 Emergency Modifications

Investigators may implement a deviation from, or a change of, the protocol to eliminate an immediate hazard(s) to trial subjects without prior IRB approval.

For any such emergency modification implemented, an IRB modification form must be completed within 5 business days of making the change, and the QAM must be notified within 24 hours of such change.

11.8.2 Other Protocol Deviations

All other deviations from the protocol must be reported to the assigned QAM using the appropriate form.

A protocol deviation is any unplanned variance from an IRB approved protocol that:

- Is generally noted or recognized after it occurs.
- Has no substantive effect on the risks to research participants.
- Has no substantive effect on the scientific integrity of the research plan or the value of the data collected.
- Did not result from willful or knowing misconduct on the part of the investigator(s).

A protocol deviation may be considered an instance of Promptly Reportable Non-Compliance (PRNC) if it:

- Has harmed or increased the risk of harm to one or more research participants.
- Has damaged the scientific integrity of the data collected for the study.
- Results from willful or knowing misconduct on the part of the investigator(s).
- Demonstrates serious or continuing noncompliance with federal regulations, State laws, or University policies.

11.9 Investigator Obligations

The Principal Investigator is responsible for the conduct of the clinical trial at the site in accordance with Title 21 of the Code of Federal Regulations and/or the Declaration of Helsinki. The PI is responsible for personally overseeing the treatment of all study patients. The PI must assure that all study site personnel, including sub-investigators and other study staff members, adhere to the study protocol and all FDA/GCP/NCI regulations and guidelines regarding clinical trials both during and after study completion.

The Principal Investigator at each institution or site will be responsible for assuring that all the required data will be collected, entered onto the appropriate eCRFs, and submitted within the study-specific timeframes. Periodically, monitoring visits may be conducted and the Principal Investigator will provide access to his/her original records to permit verification of proper entry of data. The study may also be subject to routine audits by the Audit Committee, as outlined in the DSMP.

11.10 Publication Policy

All potential publications and/or data for potential publications (e.g. manuscripts, abstracts, posters, clinicaltrials.gov releases) must be approved in accordance with the policies and processes set forth in the Lurie Cancer Center DSMP. For trials that require high intensity monitoring, the assigned QAM will prepare a preliminary data summary (to be approved by the DSMC) no later than 3 months after the study reaches its primary completion date (the date that the final subject is examined or receives an intervention for the purposes of final data collection for the primary endpoint). If the investigator's wish to obtain DSMC-approved data prior to this point (or prior to the point dictated by study design), the PI must send a written request for data to the QAM which includes justification. If the request is approved, data will be provided no later than 4 weeks after this request approval. The data will be presented to the DSMC at their next available meeting, and a final, DSMC-approved dataset will be released along with any DSMC decisions regarding publication. The investigators are expected to use only DSMC-approved data in future publications. The investigators should submit a copy of the manuscript to the biostatistician to confirm that the DSMC-approved data are used appropriately. Once the biostatistician gives final approval, the manuscript may be submitted to external publishers.

11.11 Discontinuation of Study

Although BMS has every intention of completing the study, BMS reserves the right to discontinue the study at any time for clinical or administrative reasons. Reasons for terminating the study may include:

- Occurrence of intolerable drug-related AEs unknown to date with respect to their nature, severity, and duration.
- Unexpected incidence of known AEs.
- Medical or ethical reasons affecting the continued performance of the study.
- Difficulties in the recruitment of subjects.
- Cancellation of drug development.

In case of early study discontinuation investigators will be recompensated for expenses incurred.

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APPENDICES

Appendix A: Common Terminology Criteria for Adverse Events V5.0 (CTCAE)

The descriptions and grading scales found in the revised NCI Common Terminology Criteria for Adverse Events (CTCAE) version 5.0 will be utilized for adverse event reporting. (https://ctep.cancer.gov/protocoldevelopment/electronic_applications/ctc.htm)

Appendix B: Karnofsky Performance Scale (KPS)

Points	Description
100	Normal, no complaints, no evidence of disease
90	Able to carry on normal activity
80	Normal activity with effort; some signs or symptoms of disease
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/her needs
50	Requires considerable assistance and frequent medical care
40	Disabled; requires special care and assistance
30	Severely disabled; hospitalization indicated. Death not imminent
20	Very sick; hospitalization necessary; active support treatment necessary
10	Moribund; fatal processes progressing rapidly
0	Dead

Appendix C: Female Participants of Child Bearing Potential Definitions and Methods of Contraception

Female of Child Bearing Potential (FOCBP)

A woman is considered fertile following menarche and until becoming post-menopausal unless permanently sterile. Permanent sterilization methods include hysterectomy, bilateral salpingectomy, and bilateral oophorectomy.

Women in the following categories are not considered FOCBP

- Premenarchal
- Premenopausal female with 1 of the following:
  - Documented hysterectomy
  - Documented bilateral salpingectomy
  - Documented bilateral oophorectomy

Note: Documentation can come from the site personnel's review of the participant's medical records, medical examination, or medical history interview.

- Postmenopausal female
  - A postmenopausal state is defined as 12 months of amenorrhea in a woman over age 45 years in the absence of other biological or physiological causes. In addition, females under the age of 55 years must have a serum follicle stimulating hormone, (FSH) level > 40 mIU/mL to confirm menopause.

CONTRACEPTION GUIDANCE FOR FEMALE PARTICIPANTS OF CHILD BEARING POTENTIAL

One of the highly effective methods of contraception listed below is required during study duration and until the end of relevant systemic exposure, defined as 5 months after the end of study treatment.*

Note: Hormone-based contraceptives are <u>not</u> considered highly effective methods of contraception for FOCBP participants in Arms, which include BMS986205 IDO.

Highly Effective Contraceptive Methods That Are User Dependent *Failure rate of <1% per year when used consistently and correctly.*[a]
• **Not in Arms, which include BMS986205 IDO:** Combined (estrogen- and progestogen-containing) hormonal contraception associated with inhibition of ovulation[b] – oral – intravaginal – transdermal

- **Not in Arms, which include BMS986205 IDO.** Progestogen-only hormonal contraception associated with inhibition of ovulation[b]
  - oral
  - injectable

Highly Effective Methods That Are User Independent

- **Not in Arms, which include BMS986205 IDO.** Implantable progestogen-only hormonal contraception associated with inhibition of ovulation [b]
- **Not in Arms, which include BMS986205 IDO.** Hormonal methods of contraception including oral contraceptive pills containing a combination of estrogen and progesterone, vaginal ring, injectables, implants and intrauterine hormone-releasing system (IUS)[c]
- Intrauterine device (IUD)[c]
- Bilateral tubal occlusion

- Vasectomized partner

A vasectomized partner is a highly effective contraception method provided that the partner is the sole male sexual partner of the FOCBP and the absence of sperm has been confirmed. If not, an additional highly effective method of contraception should be used.

- Sexual abstinence

Sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the study drug. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the study and the preferred and usual lifestyle of the participant.

- It is not necessary to use any other method of contraception when complete abstinence is elected.
- FOCBP participants who choose complete abstinence must continue to have pregnancy tests, as specified in Section 2.
- Acceptable alternate methods of highly effective contraception must be discussed in the event that the FOCBP participants chooses to forego complete abstinence

NOTES:

[a] Typical use failure rates may differ from those when used consistently and correctly. Use should be consistent with local regulations regarding the use of contraceptive methods for participants participating in clinical studies.

[b] Hormonal contraception may be susceptible to interaction with the study drug, which may reduce the efficacy of the contraceptive method. Hormonal contraception is permissible only when there is sufficient evidence that the IMP and other study medications will not alter hormonal exposures such that contraception would be ineffective or result in increased exposures that could be potentially hazardous. In this case, alternative methods of contraception should be utilized.

[c] Intrauterine devices and intrauterine hormone releasing systems are acceptable methods of contraception in the absence of definitive drug interaction studies when hormone exposures from intrauterine devices do not alter contraception effectiveness. The absence of such interactions is not known for BMS-986205 when administered with nivolumab. Therefore,

for participants of child-bearing potential who receive these 2 medications, intrauterine hormone releasing systems are not acceptable methods of contraception.

Unacceptable Methods of Contraception*
• Male or female condom with or without spermicide. Male and female condoms cannot be used simultaneously • Diaphragm with spermicide • Cervical cap with spermicide • Vaginal Sponge with spermicide • Progestogen-only oral hormonal contraception, where inhibition of ovulation is not the primary mechanism of action • Periodic abstinence (calendar, symptothermal, post-ovulation methods) • Withdrawal (coitus interruptus). • Spermicide only • Lactation amenorrhea method (LAM)

*** Local laws and regulations may require use of alternative and/or additional contraception methods.**

CONTRACEPTION GUIDANCE FOR MALE PARTICIPANTS WITH PARTNER(S) OF CHILD BEARING POTENTIAL.

Male participants with female partners of childbearing potential are eligible to participate if they agree to the following during the treatment and until the end of relevant systemic exposure.

- Inform any and all partner(s) of their participation in a clinical drug study and the need to comply with contraception instructions as directed by the investigator.
- Male participants are required to use a condom for study duration and until end of relevant systemic exposure defined as 7 months after the end of study treatment.
- Female partners of males participating in the study to consider use of effective methods of contraception until the end of relevant systemic exposure, defined as 7 months after the end of treatment in the male participant.
- Male participants with a pregnant or breastfeeding partner must agree to remain abstinent from penile vaginal intercourse or use a male condom during each episode of penile penetration during the treatment and until 7 months after the end of study treatment.
- Refrain from donating sperm for the duration of the study treatment and until 7 months after the end of study treatment.

COLLECTION OF PREGNANCY INFORMATION

Guidance for collection of Pregnancy Information and outcome of pregnancy on the Pregnancy Surveillance Form is provided in the Pregnancy Surveillance Form-Quick Reference Guide.

Appendix D: Management Algorithms

These general guidelines constitute guidance to the Investigator and may be supplemented by discussions with the Medical Monitor representing the Sponsor. The guidance applies to all immuno-oncology agents and regimens.

A general principle is that differential diagnoses should be diligently evaluated according to standard medical practice. Non-inflammatory etiologies should be considered and appropriately treated.

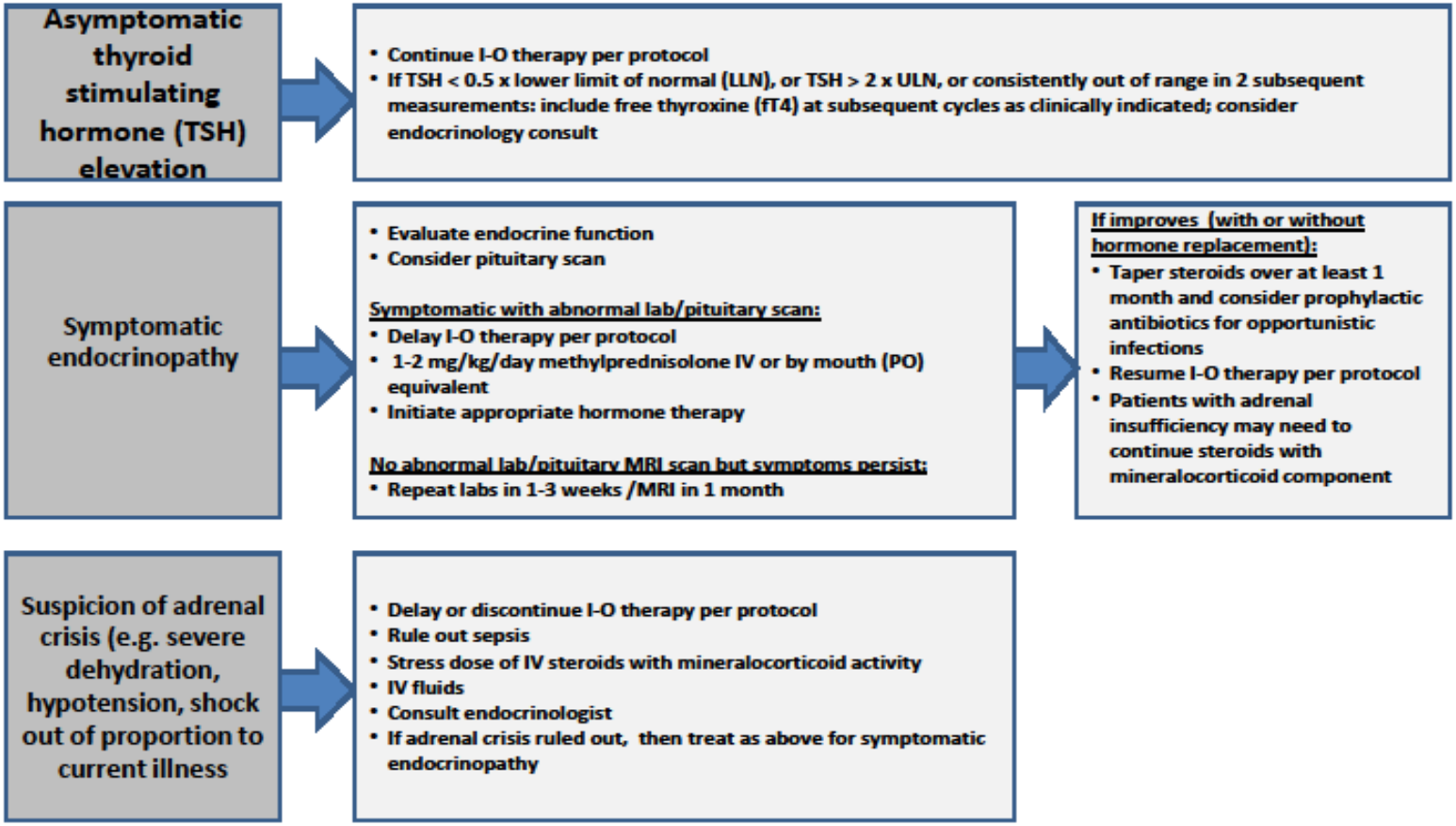
Corticosteroids are a primary therapy for immuno-oncology drug-related adverse events. The oral equivalent of the recommended IV doses may be considered for ambulatory patients with low-grade toxicity. The lower bioavailability of oral corticosteroids should be taken into account when switching to the equivalent dose of oral corticosteroids.

Consultation with a medical or surgical specialist, especially prior to an invasive diagnostic or therapeutic procedure, is recommended.

The frequency and severity of the related adverse events covered by these algorithms will depend on the immuno-oncology agent or regimen being used.

Endocrinopathy Management Algorithm

Rule out non-inflammatory causes. If non-inflammatory cause, treat accordingly and continue I-O therapy. Consider visual field testing, endocrinology consultation, and imaging.



Patients on IV steroids may be switched to an equivalent dose of oral corticosteroids (e.g. prednisone) at start of tapering or earlier, once sustained clinical improvement is observed. Lower bioavailability of oral corticosteroids should be taken into account when switching to the equivalent dose of oral corticosteroids.

GI Adverse Event Management Algorithm

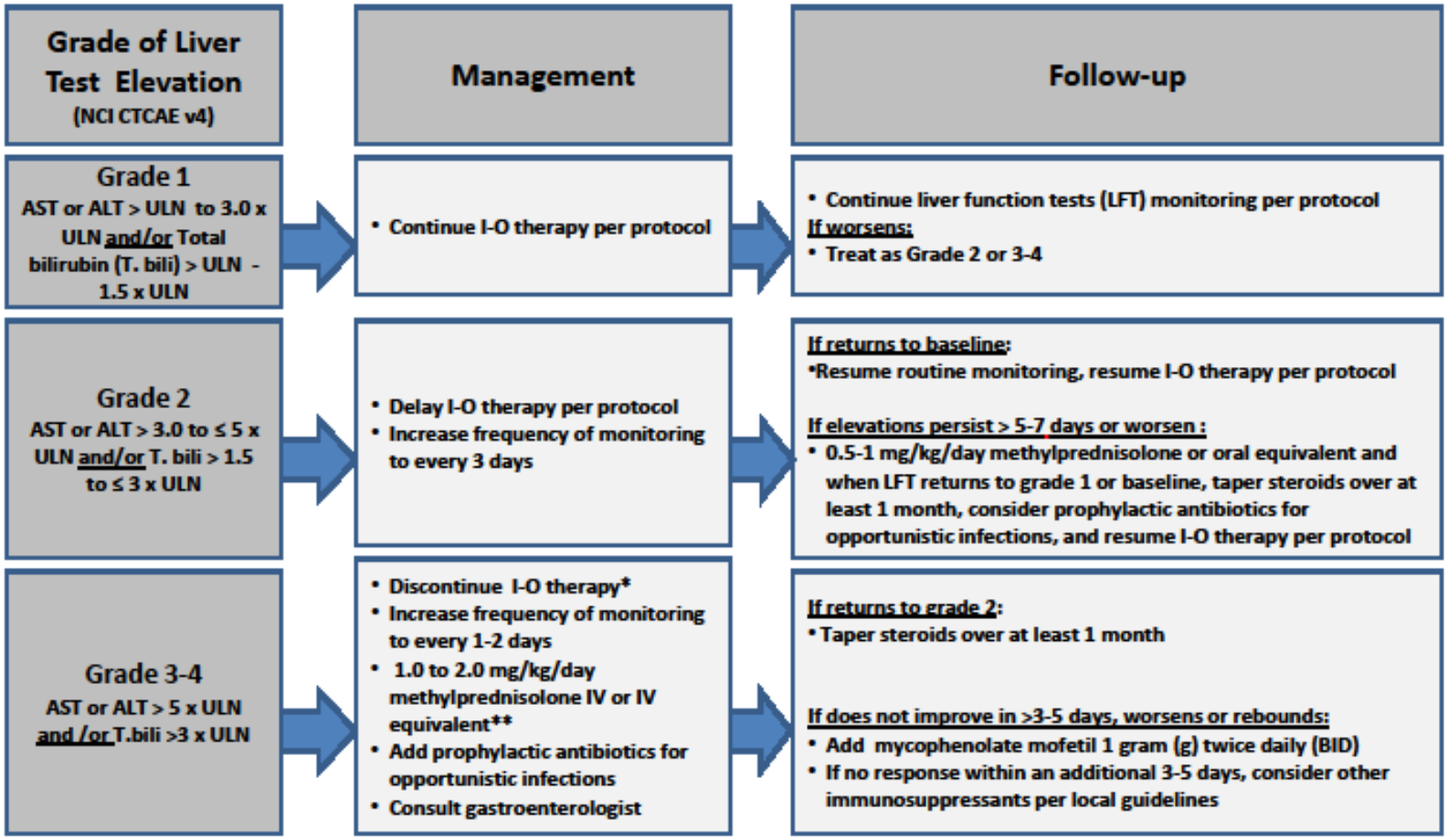
Rule out non-inflammatory causes. If non-inflammatory cause is identified, treat accordingly and continue I-O therapy. Opiates/narcotics may mask symptoms of perforation. Infliximab should not be used in cases of perforation or sepsis.

Grade of Diarrhea/ Colitis (NCI CTCAE v4)	Management	Follow-up
Grade 1 Diarrhea: < 4 stools/day over baseline; Colitis: asymptomatic	• Continue I-O therapy per protocol • Symptomatic treatment	• Close monitoring for worsening symptoms. • Educate patient to report worsening immediately If worsens: • Treat as Grade (G) 2 or 3/4
Grade 2 Diarrhea: 4-6 stools per day over baseline; IV fluids indicated <24 hours (hrs); not interfering with ADL Colitis: abdominal pain; blood in stool	• Delay I-O therapy per protocol • Symptomatic treatment	If improves to grade 1: • Resume I-O therapy per protocol If persists > 5-7 days or recur: • 0.5-1.0 mg/kg/day methylprednisolone or oral equivalent • When symptoms improve to grade 1, taper steroids over at least 1 month, consider prophylactic antibiotics for opportunistic infections, and resume I-O therapy per protocol. If worsens or persists > 3-5 days with oral steroids: • Treat as grade 3/4
Grade 3-4 Diarrhea (G3): ≥7 stools per day over baseline; incontinence; IV fluids ≥24 hrs; interfering with activities of daily living (ADL) Colitis (G3): severe abdominal pain, medical intervention indicated, peritoneal signs G4: life-threatening, perforation	• Discontinue I-O therapy per protocol • 1.0 to 2.0 mg/kg/day methylprednisolone IV or IV equivalent • Add prophylactic antibiotics for opportunistic infections • Consider lower endoscopy	If improves: • Continue steroids until grade 1, then taper over at least 1 month If persists > 3-5 days, or recurs after improvement: • Add infliximab 5 mg/kg (if no contraindication). Note: Infliximab should not be used in cases of perforation or sepsis

Patients on IV steroids may be switched to an equivalent dose of oral corticosteroids (e.g. prednisone) at start of tapering or earlier, once sustained clinical improvement is observed. Lower bioavailability of oral corticosteroids should be taken into account when switching to the equivalent dose of oral corticosteroids.

Hepatic Adverse Event Management Algorithm

Rule out non-inflammatory causes. If non-inflammatory cause, treat accordingly and continue I-O therapy. Consider imaging for obstruction.



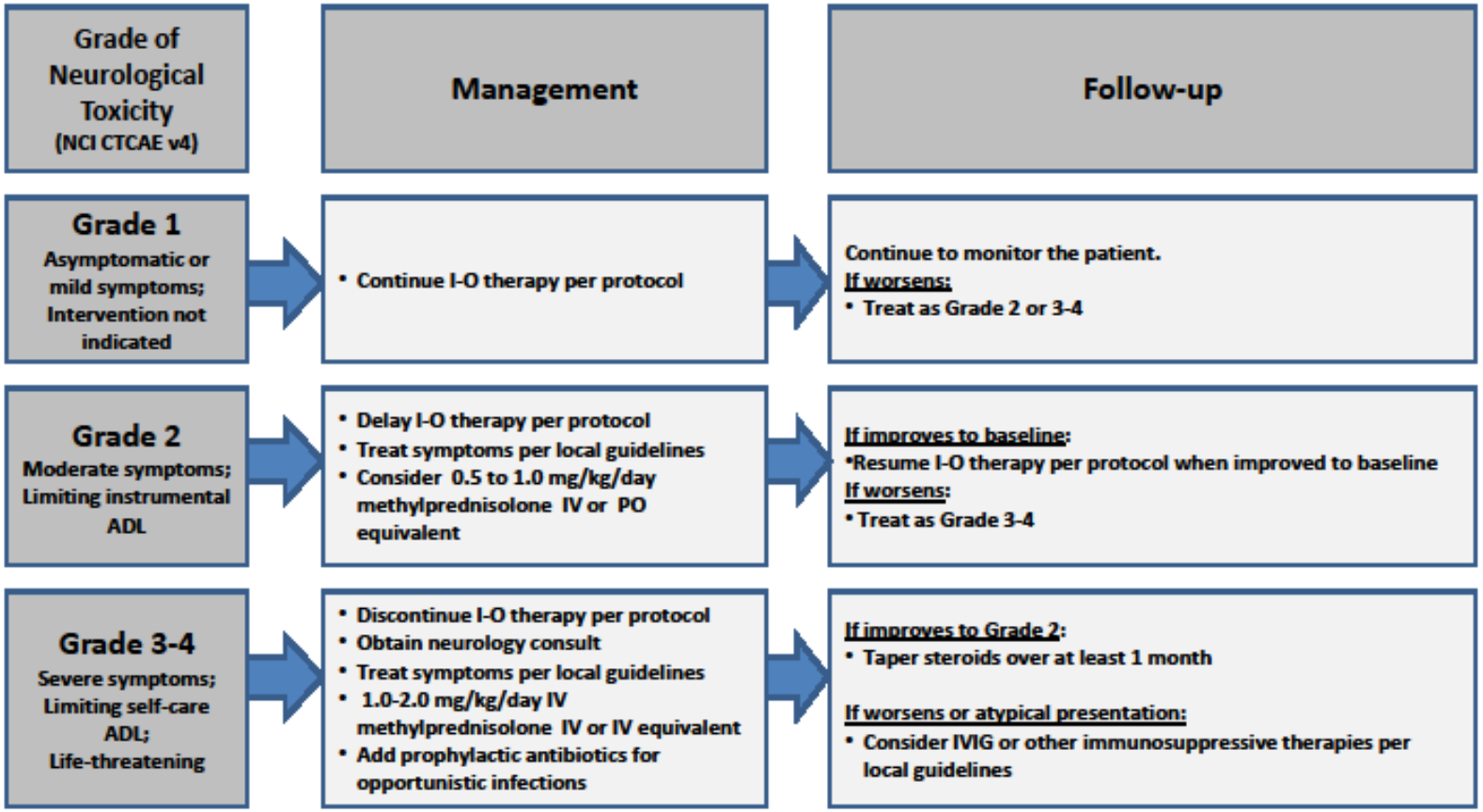
Patients on IV steroids may be switched to an equivalent dose of oral corticosteroids (e.g. prednisone) at start of tapering or earlier, once sustained clinical improvement is observed. Lower bioavailability of oral corticosteroids should be taken into account when switching to the equivalent dose of oral corticosteroids.

*I-O therapy may be delayed rather than discontinued if AST/ALT ≤ 8 x ULN and T.bili ≤ 5 x ULN.

**The recommended starting dose for grade 4 hepatitis is 2 mg/kg/day methylprednisolone IV.

Neurological Adverse Event Management Algorithm

Rule out non-inflammatory causes. If non-inflammatory cause, treat accordingly and continue I-O therapy.



Patients on IV steroids may be switched to an equivalent dose of oral corticosteroids (e.g. prednisone) at start of tapering or earlier, once sustained clinical improvement is observed. Lower bioavailability of oral corticosteroids should be taken into account when switching to the equivalent dose of oral corticosteroids.

Pulmonary Adverse Event Management Algorithm

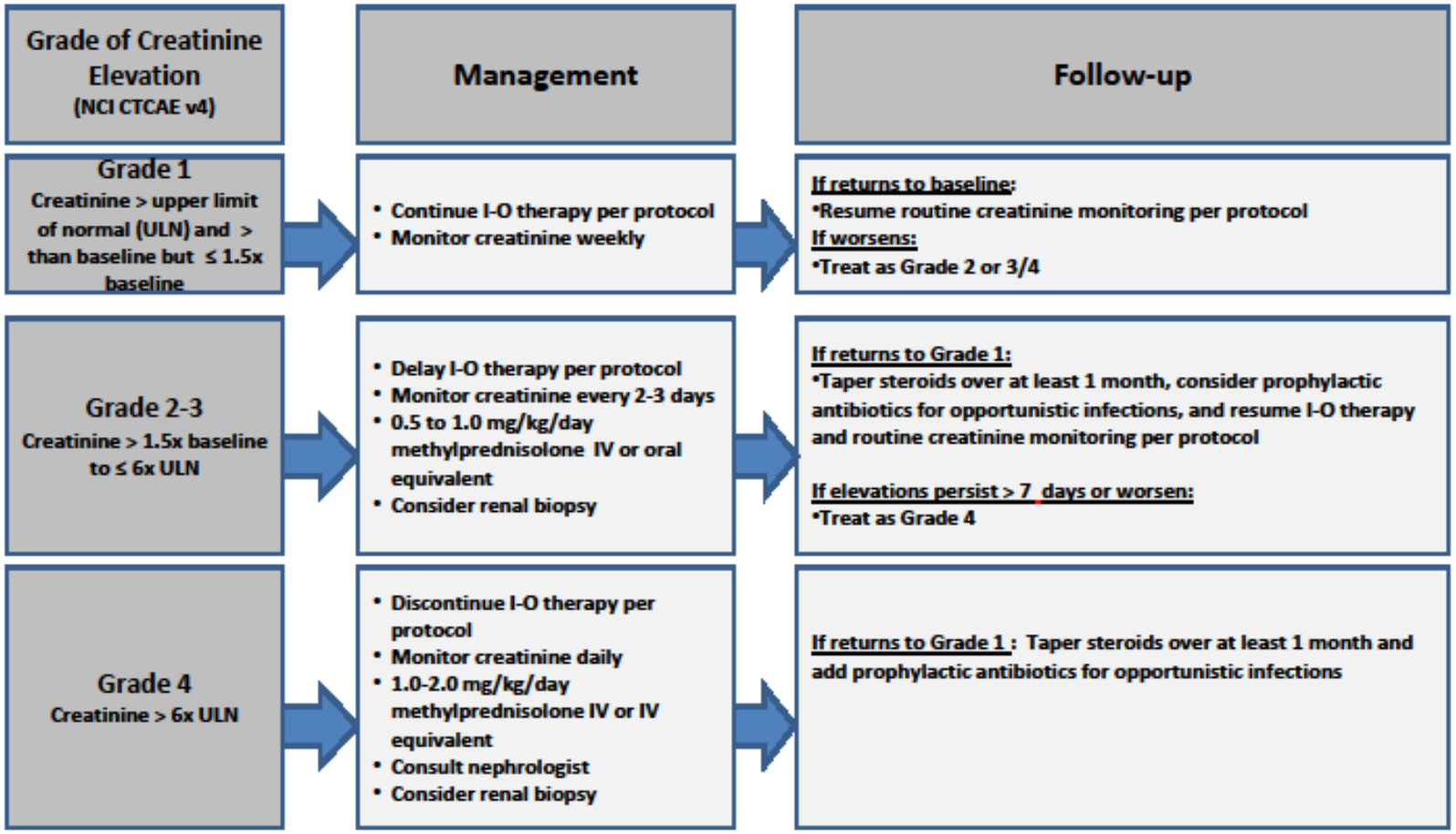
Rule out non-inflammatory causes. If non-inflammatory cause, treat accordingly and continue I-O therapy. Evaluate with imaging and pulmonary consultation.

Grade of Pneumonitis (NCI CTCAE v4)	Management	Follow-up
Grade 1 Radiographic changes only	• Consider delay of I-O therapy • Monitor for symptoms every 2-3 days • Consider Pulmonary and Infectious Disease (ID) consults	• Re-image at least every 3 weeks If worsens: • Treat as Grade 2 or 3-4
Grade 2 Mild to moderate new symptoms	• Delay I-O therapy per protocol • Pulmonary and ID consults • Monitor symptoms daily, consider hospitalization • 1.0 mg/kg/day methyl-prednisolone IV or oral equivalent • Consider bronchoscopy , lung biopsy	• Re-image every 1-3 days If improves: • When symptoms return to near baseline, taper steroids over at least 1 month and then resume I-O therapy per protocol and consider prophylactic antibiotics If not improving after 2 weeks or worsening: • Treat as Grade 3-4
Grade 3-4 Severe new symptoms; New/worsening hypoxia; Life-threatening	• Discontinue I-O therapy per protocol • Hospitalize • Pulmonary and ID consults • 2-4 mg/kg/day methylprednisolone IV or IV equivalent • Add prophylactic antibiotics for opportunistic infections • Consider bronchoscopy, lung biopsy	If improves to baseline: • Taper steroids over at least 6 weeks If not improving after 48 hours or worsening: • Add additional immunosuppression (e.g. infliximab, cyclophosphamide, intravenous immunoglobulin (IVIG), or mycophenolate mofetil)

Patients on IV steroids may be switched to an equivalent dose of oral corticosteroids (e.g. prednisone) at start of tapering or earlier, once sustained clinical improvement is observed. Lower bioavailability of oral corticosteroids should be taken into account when switching to the equivalent dose of oral corticosteroids.

Renal Adverse Event Management Algorithm

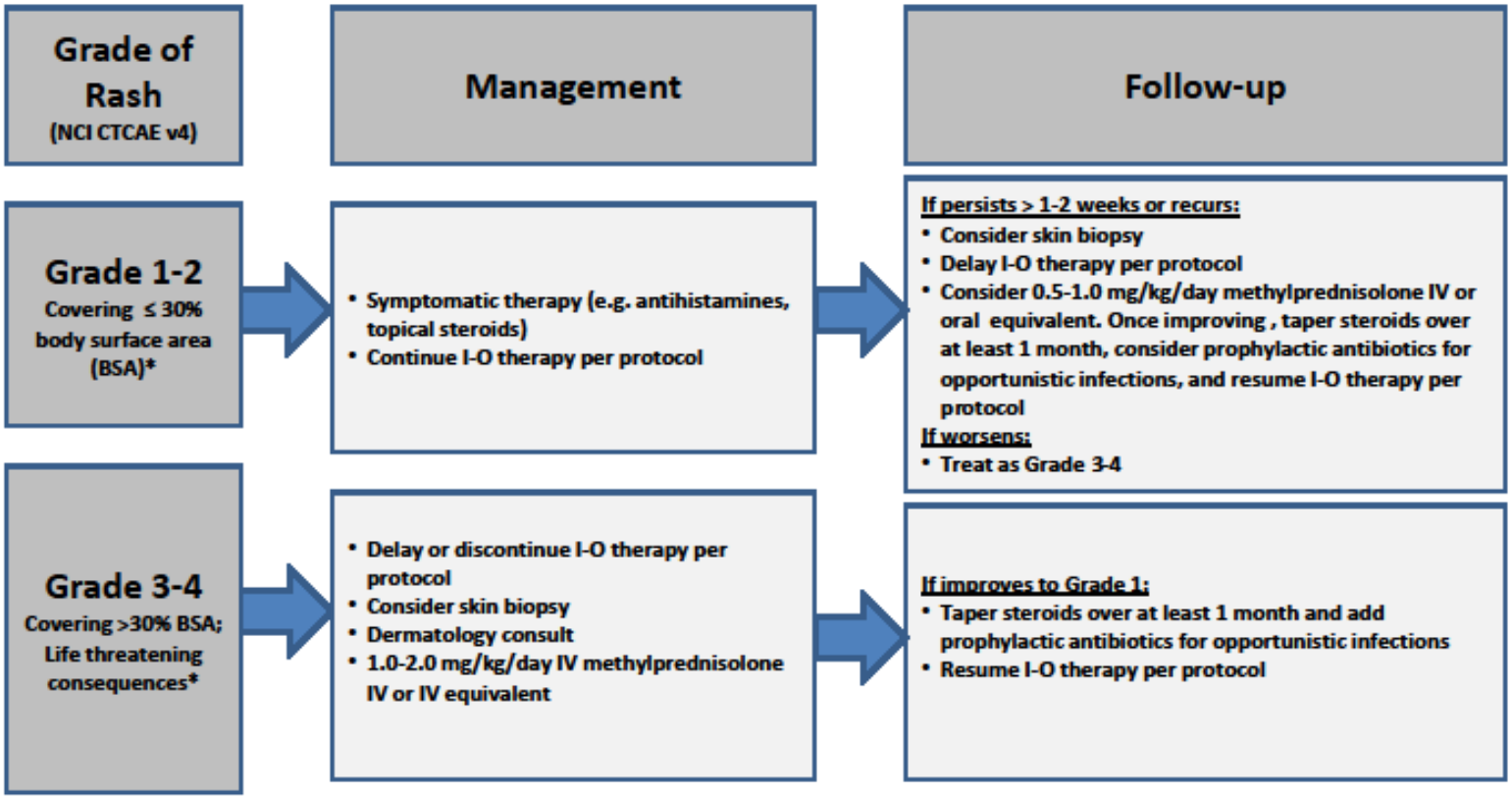
Rule out non-inflammatory causes. If non-inflammatory cause, treat accordingly and continue I-O therapy



Patients on IV steroids may be switched to an equivalent dose of oral corticosteroids (e.g. prednisone) at start of tapering or earlier, once sustained clinical improvement is observed. Lower bioavailability of oral corticosteroids should be taken into account when switching to the equivalent dose of oral corticosteroids.

Skin Adverse Event Management Algorithm

Rule out non-inflammatory causes. If non-inflammatory cause, treat accordingly and continue I-O therapy.



Patients on IV steroids may be switched to an equivalent dose of oral corticosteroids (e.g. prednisone) at start of tapering or earlier, once sustained clinical improvement is observed. Lower bioavailability of oral corticosteroids should be taken into account when switching to the equivalent dose of oral corticosteroids.
*Refer to NCI CTCAE v4 for term-specific grading criteria.

Appendix E: CYP3A4, CYP2B6 and CYP1A2 Guidance

The lists below are not meant to be all inclusive. Please consult individual drug labels for further information. Additional information is also available at:

http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/DrugInteractionsLabeling/ucm093664.htm

Table 1: Classification of In Vivo Inhibitors of CYP Enzymes

CYP Enzymes	Strong Inhibitors[a] ≥ 5-fold Increase in AUC or > 80% Decrease in CL	Moderate Inhibitors[b] ≥ 2 but < 5-fold Increase in AUC or 50-80% Decrease in CL	Weak Inhibitors[c] ≥ 1.25 but < 2-fold Increase in AUC or 20-50% Decrease in CL
CYP3A	Boceprevir, clarithromycin, conivaptan, grapefruit juice,[d] indinavir, itraconazole, ketoconazole, lopinavir/ritonavir, mibefradil,[e] nefazodone, nelfinavir, posaconazole, ritonavir, saquinavir, telaprevir, telithromycin, voriconazole	Amprenavir, aprepitant, atazanavir, ciprofloxacin, darunavir/ritonavir, diltiazem, erythromycin, fluconazole, fosamprenavir, grapefruit juice,[d] imatinib, verapamil	Alprazolam, amiodarone, amlodipine, atorvastatin, bicalutamide, cilostazol, cimetidine, cyclosporine, fluoxetine, fluvoxamine, ginkgo,[f] goldenseal,[f] isoniazid, nilotinib, oral contraceptives, ranitidine, ranolazine, tipranavir/ritonavir, zileuton
CYP1A2	ciprofloxacin, enoxacin, fluvoxamine[g], zafirlukast	methoxsalen, mexiletine, oral contraceptives	acyclovir, allopurinol, cimetidine, peginterferon alpha-2a, piperine, zileuton

Please note that this is not an exhaustive list.

[a] A strong inhibitor for a specific CYP is defined as an inhibitor that increases the AUC of a substrate for that CYP by equal or more than 5-fold.

[b] A moderate inhibitor for a specific CYP is defined as an inhibitor that increases the AUC of a sensitive substrate for that CYP by less than 5-fold but equal to or more than 2-fold.

[c] A weak inhibitor for a specific CYP is defined as an inhibitor that increases the AUC of a sensitive substrate for that CYP by less than 2-fold but equal to or more than 1.25-fold.

[d] The effect of grapefruit juice varies widely among brands and is concentration, dose, and preparation dependent. Studies have shown that it can be classified as a "strong CYP3A inhibitor" when a certain preparation was used (eg, high dose, double strength) or as a "moderate CYP3A inhibitor" when another preparation was used (eg, low dose, single strength).

[e] Withdrawn from the United States market because of safety reasons.

[f] Herbal product.

[g] Strong inhibitor of CYP1A2 and CYP2C19, and moderate inhibitor of CYP2D6 and CYP3A

Abbreviations: AUC = area under the concentration-time curve; CYP = cytochrome P450.

Table 2: Classification of In Vivo Inducers of CYP Enzymes

CYP Enzymes	Strong Inducers ≥ 80% Decrease in AUC	Moderate Inducers 50-80% Decrease in AUC	Weak Inducers 20-50% Decrease in AUC

Table 2: Classification of In Vivo Inducers of CYP Enzymes

CYP Enzymes	Strong Inducers ≥ 80% Decrease in AUC	Moderate Inducers 50-80% Decrease in AUC	Weak Inducers 20-50% Decrease in AUC
CYP3A	Avasimibe,[a] carbamazepine, phenytoin, rifampin, St. John's wort[b]	Bosentan, efavirenz, etravirine, modafinil, nafcillin	Amprenavir, aprepitant, armodafinil, echinacea,[c] pioglitazone, prednisone, rufinamide
CYP1A2		Phenytoin[d], rifampin[e], ritonavir[f], smoking, teriflunomide	

Please note that this is not an exhaustive list.

[a] Not a marketed drug.

[b] The effect of St. John's wort varies widely and is preparation dependent.

[c] Herbal product.

[d] Strong inducer of CYP3A and moderate inducer of CYP1A2, CYP2C19.

[e] Strong inducer of CYP2C19, CYP3A, and moderate inducer of CYP1A2, CYP2B6, CYP2C8, CYP2C9.

[f] Strong inducer of CYP2C19 and moderate inducer of CYP1A2, CYP2B6, CYP2C9.

Abbreviations: AUC = area under the concentration-time curve; CYP = cytochrome P450.

Table 3: Examples of Sensitive In Vivo CYP Substrates and CYP Substrates with Narrow Therapeutic Range

CYP Enzymes	Sensitive Substrates[a]	Substrates with Narrow Therapeutic Range[b]
CYP3A	Alfentanil, aprepitant, budesonide, buspirone, conivaptan, darifenacin, darunavir, dasatinib, dronedarone, eletriptan, eplerenone, everolimus, felodipine, indinavir, fluticasone, lopinavir, lovastatin, lurasidone, maraviroc, midazolam, nisoldipine, quetiapine, saquinavir, sildenafil, simvastatin, sirolimus, tolvaptan, tipranavir, triazolam, vardenafil	Alfentanil, astemizole,[c] cisapride,[c] cyclosporine, dihydroergotamine, ergotamine, fentanyl, pimozide, quinidine, sirolimus, tacrolimus, terfenadine[c]
CYP2B6	Bupropion, efavirenz	

Please note that this is not an exhaustive list.

[a] Sensitive CYP substrates refers to drugs whose plasma AUC values have been shown to increase 5-fold or higher when co-administered with a known CYP inhibitor.

[b] CYP substrates with narrow therapeutic range refers to drugs whose exposure-response relationship indicates that small increases in their exposure levels by the concomitant use of CYP inhibitors may lead to serious safety concerns (eg, Torsades de Pointes).

[c] Withdrawn from the United States market because of safety reasons.

Abbreviations: AUC = area under the concentration-time curve; CYP = cytochrome P450.

Appendix F: Medications Associated with QT Prolongation

The list below is not meant to be all inclusive. Please consult individual drug labels for further information.

quinidine, procainamide, disopyramide,
amiodarone, sotalol, ibutilide, dofetilide,
erythromycins, clarithromycin,
chlorpromazine, haloperidol, mesoridazine, thioridazine, pimozide,
cisapride, bepridil, droperidol, methadone, arsenic, chloroquine, domperidone,
halofantrine, levomethadyl, pentamidine, sparfloxacin, lidoflazine

Appendix G: Agents Known to Cause Methemoglobinemia

- Acetanilid
- p-Amino salicylic acid
- Aniline, aniline dyes
- Benzene derivatives
- Clofazimine
- Chlorates
- Chloroquine
- Dapsone
- Local anesthetic agents
- Benzocaine
- Lidocaine
- Prilocaine
- Menadione
- Metoclopramide
- Methylene blue*
- Naphthoquinone
- Naphthalene
- Nitrites
- Amyl nitrite
- Farryl nitrite
- Sodium nitrite
- Nitroglycerin
- Nitric oxide
- Nitrobenzene
- Paraquat
- Phenacetin
- Phenazopyridine
- Primaquine
- Rasburicase
- Resorcinol
- Sulfonamides

*While methylene blue is a recognized treatment for methemoglobinemia, it is an agent with oxidant potential (and may worsen the clinical situation) and in individuals with glucose-6-phosphate dehydrogenase deficiency, it may induce acute hemolysis that can further decrease oxygen delivery to the tissues. Furthermore, in high doses, methylene blue can also increase methemoglobinemia.

Appendix H: P-GP and BCRP Guidance

The list below is not meant to be all inclusive. Please consult individual drug labels for further information. Additional information is also available at:

http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/DrugInteractionsLabeling/ucm080499.htm

Table 1: Examples of In Vivo Substrates for Selected Transporters

Transporter	Gene	Substrate
P-gp	ABCB1	Aliskiren, ambrisentan, colchicine, dabigatran etexilate, digoxin, everolimus, fexofenadine, imatinib, lapatinib, maraviroc, nilotinib, posaconazole, ranolazine, saxagliptin, sirolimus, sitagliptin, talinolol, tolvaptan, topotecan
BCRP	ABCG2	Methotrexate, mitoxantrone, imatinib, irrinotecan, lapatinib, rosuvastatin, sulfasalazine, topotecan

Please note that this is not an exhaustive list.

Abbreviations: BCRP = breast cancer resistance protein; P-gp = P-glycoprotein.

Appendix I: BMS-986205 and Nivolumab Dose Delay Criteria

Table 1: BMS-986205 and Nivolumab Dose Delay and Reduction

Situation	Nivolumab delay	BMS-986205 delay	BMS-986205 Reduction after Delay
Grade 2 non-skin, drug-related AE, except fatigue, nausea, vomiting and anemia	Yes	Yes	No
Grade 2 drug-related creatinine, AST, ALT and/or Total Bilirubin abnormalities	Yes	Yes	No
Grade 3 skin, drug-related AE	Yes	Yes	No
Grade 3 drug-related laboratory abnormality (exceptions apply, consult protocol)	Yes	Yes	No
Grade 3 drug-related fatigue, nausea, vomiting, and anemia	Yes	Yes	Yes
Methemoglobin ≥ 15% or any clinically significant elevation with associated Gr 3 AE not attributable to another etiology	No	Yes	Yes
QTcF > 500 msec (and > 60 msec above baseline)	No	Yes	Yes
Other lower grade AEs (in consultation with MM)	Possibly	Possibly	Possibly

Appendix J: BMS-986205 Diagnostic Criteria for HLH and DRESS Syndrome

Table 1. Diagnostic criteria for HLH used in the HLH-2004 trial*

The diagnosis of HLH† may be established:
A. Molecular diagnosis consistent with HLH: pathologic mutations of *PRF1*, *UNC13D*, *Munc18-2*, *Rab27a*, *STX11*, *SH2D1A*, or *BIRC4*
or
B. Five of the 8 criteria listed below are fulfilled:
1. Fever ≥ 38.5°C
2. Splenomegaly
3. Cytopenias (affecting at least 2 of 3 lineages in the peripheral blood)
Hemoglobin < 9 g/dL (in infants < 4 weeks: hemoglobin < 10 g/dL)
Platelets < 100×10^3/mL
Neutrophils < 1×10^3/mL
4. Hypertriglyceridemia (fasting, > 265 mg/dL) and/or hypofibrinogenemia (< 150 mg/dL)
5. Hemophagocytosis in bone marrow, spleen, lymph nodes, or liver
6. Low or absent NK-cell activity
7. Ferritin > 500 ng/mL‡
8. Elevated sCD25 (α-chain of sIL-2 receptor)§

*Adapted from Henter et al.

†In addition, in the case of familial HLH, no evidence of malignancy should be apparent.

‡Although the HLH-2004 protocol uses ferritin > 500 ng/mL, we generally view ferritin > 3000 ng/mL as concerning for HLH and ferritin > 10 000 as highly suspicious.

§Elevations above age-adjusted, laboratory-specific normal levels (defined as > 2 SD from the mean) appear more meaningful than the original designation of > 2400 U/mL because of variations between laboratories.

Jordan et al. How I treat hemophagocytic lymphohistiocytosis. Blood. 2011;118(15):4041. Epub 2011 Aug 9

Table 2 Scoring system for classifying HSS/DRESS cases as definite, probable, possible or no case

Score	−1	0	1	2	Min.	Max.
Fever ≥ 38·5 °C	No/U	Yes			−1	0
Enlarged lymph nodes		No/U	Yes		0	1
Eosinophilia		No/U			0	2
Eosinophils			$0{\cdot}7–1{\cdot}499 \times 10^9\ L^{-1}$	$\geq 1{\cdot}5 \times 10^9\ L^{-1}$		
Eosinophils, if leucocytes $< 4{\cdot}0 \times 10^9\ L^{-1}$			10–19·9%	≥ 20%		
Atypical lymphocytes		No/U	Yes		0	1
Skin involvement					−2	2
Skin rash extent (% body surface area)		No/U	> 50%			
Skin rash suggesting DRESS	No	U	Yes			
Biopsy suggesting DRESS	No	Yes/U				
Organ involvement*					0	2
Liver		No/U	Yes			
Kidney		No/U	Yes			
Lung		No/U	Yes			
Muscle/heart		No/U	Yes			
Pancreas		No/U	Yes			
Other organ		No/U	Yes			
Resolution ≥ 15 days	No/U	Yes			−1	0
Evaluation of other potential causes						
Antinuclear antibody						
Blood culture						
Serology for HAV/HBV/HCV						
Chlamydia/mycoplasma						
If none positive and ≥ 3 of above negative			Yes		0	1
Total score					−4	9

U, unknown/unclassifiable; HAV, hepatitis A virus; HBV, hepatitis B virus; HCV, hepatitis C virus. *After exclusion of other explanations: 1, one organ; 2, two or more organs. Final score < 2, no case; final score 2–3, possible case; final score 4–5, probable case; final score > 5, definite case.

Kardaun et al., Variability in the clinical pattern of cutaneous side-effects of drugs with systemic symptoms: does a DRESS SHBr J Dermatol. 2007 Mar;156(3):609-11.

Table I. RegiSCAR DRESS validation score

Score	−1	0	1	2	Min	Max
Fever ≥ 38.5° C	No/U	Yes			−1	0
Enlarged lymph nodes		No/U	Yes		0	1
Eosinophilia		No/U			0	2
Eosinophils			700-1499/μL	≥1500/μL		
Eosinophils, if leukocytes <4000			10-19.9%	≥20%		
Atypical lymphocytes		No/U	Yes		0	1
Skin involvement					−2	2
Rash extent (>50% BSA)		No/U	Yes			
Rash suggesting DRESS	No	U	Yes			
Biopsy suggesting DRESS	No	Yes/U				
Organ involvement*					0	2
Liver		No/U	Yes			
Kidney		No/U	Yes			
Lung		No/U	Yes			
Muscle/heart		No/U	Yes			
Pancreas		No/U	Yes			
Other organ(s)		No/U	Yes			
Resolution ≥ 15 days	No/U	Yes			−1	0
Evaluation other potential causes:					0	1
ANA						
Blood culture						
Serology for HVA/HVB/HVC						
Chlamydia-/*Mycoplasma pneumoniae*						
Other serology/PCR						
If none positive and ≥ 3 of above negative			Yes			
TOTAL SCORE					−4	9

U = unknown/unclassifiable.
*After exclusion of other explanations: 1 = 1 organ, 2 = ≥ 2 organs
Final score <2: No case
Final score 2-3: Possible case
Final score 4-5: Probable case
Final score >5: Definite case

Comments on Table I:
Specifics for evaluation of diagnostic features in DRESS
Fever (−1, 0)
If core temperature is < 38.5°C (Fahrenheit 101.3): deduction of 1 point

Lymphadenopathy (0, 1)
Tender enlarged lymph nodes (>1 cm) at least at 2 different anatomic locations: 1 point

Peripheral blood:
Eosinophilia: (0, 1, 2)
- Absolute eosinophilia of 700-1500 10^9E/l: 1 point, if ≥ 1500 10^9E/l: 2 points
- If leukocyte count is < 4000 10^9E/l: % eosinophils ≥ 10%-19.9%: 1 point, eosinophils ≥ 20%: 2 points

Atypical lymphocytes: (0, 1)
If present: 1 point

Skin reaction (extent, morphology) **(−2, −1, 0, 1, 2)**
a. *Extent rash (0, 1)* If morphology is compatible with DRESS and extent eruption > 50% body surface area (BSA): 1 point
b. *Morphology rash (−1, 0, 1)*: If morphology is suggestive for DRESS: 1 point; if suggestive for a different type of reaction: deduction of 1 point; otherwise 0 points
Morphology is considered suggestive for DRESS at presence of ≥ 2 of following criteria:
- scaling/desquamation, eg, exfoliative dermatitis
- edema, especially facial edema (excluding lower leg edema)
- purpura (excluding lower leg)
- infiltration

c. Histology (−1, 0):
When histology is compatible with DRESS: 0 points; when suggestive for another diagnosis: deduction 1 point

Involvement internal organs: (0, 1, 2)
For acute involvement of each organ, 1 point is given, with a maximum of 2 points. Organ involvement is based on history, clinical investigation, medical imaging, biopsy, or other tissue/fluid investigation. Organ involvement is also calculated at presence of the following abnormal laboratory values:

Liver (0, 1)
- ALAT > 2 times upper normal limit (*UNL) on at least 2 successive dates **or**
- conjugated bilirubin > 2* UNL on at least 2 successive dates **or**
- ASAT, total bilirubin, alkaline phosphatase (AP) all > 2* UNL at least

Kidney (0, 1)
Serum creatinine more than 1.5 times above the base value for the patient on at least 2 successive dates, and/or proteinuria above 1 g/day, hematuria, decreased creatinine clearance, decreased GFR

Lungs (0, 1)
Cough and/or dyspnea in conjunction with
- evidence of interstitial involvement on imaging and/or
- abnormal broncho-alveolar lavage fluid, or biopsy and/or
- abnormal blood gases

Muscle, heart: (0, 1)
- Muscle pain and/or weakness, myocarditis (often nonspecific symptoms: hypotension, fatigue, chest pain, dyspnea, malaise, palpitations, tachycardia, cardiac dysfunction, cardiomegaly, sudden cardiac death), with
- Raised serum creatine phosphokinase (CPK) > 2*UNL
- Raised isoenzymes: CPK-3/CPK-MM (indicative for skeletal muscle), raised CPK-2/MB fraction (indicative for heart muscle involvement)
- Serum troponin T > 0.01 μg/L
- Abnormal imaging: chest X-ray/ECHO/CT/MRI/EMG including ECG: ST-T electrocardiogram abnormalities or conduction defects (ST-segment depression, T-wave inversions, or nondiagnostic ECG changes (paced or bundle branch block)
- Endomyocardial biopsy

Pancreas (0, 1):
Amylase and/or lipase ≥ 2*UNL

Other organs: spleen, thyroid gland, central nervous system, gastrointestinal tract
- Clinical symptoms and additional investigations: enlargement/imaging, including EEG
- Abnormal lab values: TSH, FT4, FT3.
- Biopsy

Duration: (−1, 0)
If the total duration of the reaction is ≤ 15 days or unknown: deduction 1 point

Exclusion of other causes, eg, infections, virus (re)activation: (0, 1)
- Hepatitis A/B/C
- *Mycoplasma-/Chlamydia pneumoniae*
- Blood cultures ≤ 3 days of index date
- Other (infections): serology, PCR, microbiological cultures
- ANA

In case of a positive result for any of these, organ involvement is reevaluated for a possible alternative cause. If ≥ 3 mentioned groups are investigated and no positive result is found, an extra point is given to express thorough investigation for alternative causes.
Viral (re)activation of EBV, CMV, and HHV6/7 are also recorded; results, however, do not influence the score.

Appendix K: Beck's Depression Inventory Questionnaire

Beck's Depression Inventory

This depression inventory can be self-scored. The scoring scale is at the end of the questionnaire.

1.
- 0 I do not feel sad.
- 1 I feel sad
- 2 I am sad all the time and I can't snap out of it.
- 3 I am so sad and unhappy that I can't stand it.

2.
- 0 I am not particularly discouraged about the future.
- 1 I feel discouraged about the future.
- 2 I feel I have nothing to look forward to.
- 3 I feel the future is hopeless and that things cannot improve.

3.
- 0 I do not feel like a failure.
- 1 I feel I have failed more than the average person.
- 2 As I look back on my life, all I can see is a lot of failures.
- 3 I feel I am a complete failure as a person.

4.
- 0 I get as much satisfaction out of things as I used to.
- 1 I don't enjoy things the way I used to.
- 2 I don't get real satisfaction out of anything anymore.
- 3 I am dissatisfied or bored with everything.

5.
- 0 I don't feel particularly guilty
- 1 I feel guilty a good part of the time.
- 2 I feel quite guilty most of the time.
- 3 I feel guilty all of the time.

6.
- 0 I don't feel I am being punished.
- 1 I feel I may be punished.
- 2 I expect to be punished.
- 3 I feel I am being punished.

7.
- 0 I don't feel disappointed in myself.
- 1 I am disappointed in myself.
- 2 I am disgusted with myself.
- 3 I hate myself.

8.
- 0 I don't feel I am any worse than anybody else.
- 1 I am critical of myself for my weaknesses or mistakes.
- 2 I blame myself all the time for my faults.
- 3 I blame myself for everything bad that happens.

9.
- 0 I don't have any thoughts of killing myself.
- 1 I have thoughts of killing myself, but I would not carry them out.
- 2 I would like to kill myself.
- 3 I would kill myself if I had the chance.

10.
- 0 I don't cry any more than usual.
- 1 I cry more now than I used to.
- 2 I cry all the time now.
- 3 I used to be able to cry, but now I can't cry even though I want to.

11.

0	I am no more irritated by things than I ever was.
1	I am slightly more irritated now than usual.
2	I am quite annoyed or irritated a good deal of the time.
3	I feel irritated all the time.

12.

0	I have not lost interest in other people.
1	I am less interested in other people than I used to be.
2	I have lost most of my interest in other people.
3	I have lost all of my interest in other people.

13.

0	I make decisions about as well as I ever could.
1	I put off making decisions more than I used to.
2	I have greater difficulty in making decisions more than I used to.
3	I can't make decisions at all anymore.

14.

0	I don't feel that I look any worse than I used to.
1	I am worried that I am looking old or unattractive.
2	I feel there are permanent changes in my appearance that make me look unattractive
3	I believe that I look ugly.

15.

0	I can work about as well as before.
1	It takes an extra effort to get started at doing something.
2	I have to push myself very hard to do anything.
3	I can't do any work at all.

16.

0	I can sleep as well as usual.
1	I don't sleep as well as I used to.
2	I wake up 1-2 hours earlier than usual and find it hard to get back to sleep.
3	I wake up several hours earlier than I used to and cannot get back to sleep.

17.

0	I don't get more tired than usual.
1	I get tired more easily than I used to.
2	I get tired from doing almost anything.
3	I am too tired to do anything.

18.

0	My appetite is no worse than usual.
1	My appetite is not as good as it used to be.
2	My appetite is much worse now.
3	I have no appetite at all anymore.

19.

0	I haven't lost much weight, if any, lately.
1	I have lost more than five pounds.
2	I have lost more than ten pounds.
3	I have lost more than fifteen pounds.

20.

0 I am no more worried about my health than usual.
1 I am worried about physical problems like aches, pains, upset stomach, or constipation.
2 I am very worried about physical problems and it's hard to think of much else.
3 I am so worried about my physical problems that I cannot think of anything else.

21.

0 I have not noticed any recent change in my interest in sex.
1 I am less interested in sex than I used to be.
2 I have almost no interest in sex.
3 I have lost interest in sex completely.

INTERPRETING THE BECK DEPRESSION INVENTORY

Now that you have completed the questionnaire, add up the score for each of the twenty-one questions by counting the number to the right of each question you marked. The highest possible total for the whole test would be sixty-three. This would mean you circled number three on all twenty-one questions. Since the lowest possible score for each question is zero, the lowest possible score for the test would be zero. This would mean you circles zero on each question. You can evaluate your depression according to the Table below.

Total Score	Levels of Depression
1-10	These ups and downs are considered normal
11-16	Mild mood disturbance
17-20	Borderline clinical depression
21-30	Moderate depression
31-40	Severe depression
over 40	Extreme depression

http://www.med.navy.mil/sites/NMCP2/PatientServices/SleepClinicLab/Documents/Beck_Depression_Inventory.pdf

Appendix L: PROMIS Emotional Distress - Anxiety

PROMIS - Ca Item Bank v1.0 - Emotional Distress - Anxiety

Emotional Distress-Anxiety

Please respond to each item by marking one box per row.

In the past 7 days…

		Never	Rarely	Sometimes	Often	Always
EDANX27	I felt something awful would happen	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
EDANX53	I felt uneasy	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
EDANX05	I felt anxious	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
EDANX12	I felt upset	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
EDANX55	I had difficulty calming down	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
EDANX01	I felt fearful	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
EDANX02	I felt frightened	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
EDANX33	I felt terrified	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
EDANX08	I was concerned about my mental health	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
EDANX47	I felt indecisive	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
EDANX18	I had sudden feelings of panic	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
EDANX26	I felt fidgety	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
EDANX07	I felt like I needed help for my anxiety	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

24 June 2016

FATIGUE – SHORT FORM 6A

Please respond to each question or statement by marking one box per row.

During the past 7 days…

		Not at all	A little bit	Somewhat	Quite a bit	Very much
HI7	I feel fatigued	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
AN3	I have trouble <u>starting</u> things because I am tired.....	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
	In the past 7 days…					
FATEXP41	How run-down did you feel on average? ...	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
FATEXP40	How fatigued were you on average?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
FATEXP35	How much were you bothered by your fatigue on average?.....	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
FATIMP49	To what degree did your fatigue interfere with your physical functioning?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

NU Study Number: NU 18C02
BMS Study Number: CA017-075

Sleep Disturbance – Short Form 8b

Please respond to each item by marking one box per row.

In the past 7 days...

		Not at all	A little bit	Somewhat	Quite a bit	Very much
Sleep108	My sleep was restless.....	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
Sleep115	I was satisfied with my sleep	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1
Sleep116	My sleep was refreshing	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1
Sleep44	I had difficulty falling asleep	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

In the past 7 days…

		Never	Rarely	Sometimes	Often	Always
Sleep87	I had trouble staying asleep.....	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
Sleep90	I had trouble sleeping.....	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
Sleep110	I got enough sleep	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1

In the past 7 days…

		Very poor	Poor	Fair	Good	Very good
Sleep109	My sleep quality was	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1

3 May 2016

Physical Function – Short Form 10b

Please respond to each question or statement by marking one box per row.

		Without any difficulty	With a little difficulty	With some difficulty	With much difficulty	Unable to do
PFA11	Are you able to do chores such as vacuuming or yard work?	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1
PFA56	Are you able to get in and out of a car?	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1
PFA21	Are you able to go up and down stairs at a normal pace?	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1
PFA53	Are you able to run errands and shop?	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1
PFA9	Are you able to bend down and pick up clothing from the floor?	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1
PFB28r1	Are you able to lift 10 pounds (5 kg) above your shoulder?	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1
		Not at all	**Very little**	**Somewhat**	**Quite a lot**	**Cannot do**
PFA1	Does your health now limit you in doing vigorous activities, such as running, lifting heavy objects, participating in strenuous sports?	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1
PFA6	Does your health now limit you in bathing or dressing yourself?	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1
PFB3	Does your health now limit you in putting a trash bag outside?	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1
PFB44	Does your health now limit you in doing moderate activities, such as moving a table, pushing a vacuum cleaner, bowling, or playing golf?	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1

PROMIS - Ca Item Bank v1.0 - Emotional Distress - Anxiety

In the past 7 days…

		Never	Rarely	Sometimes	Often	Always
EDANX30	I felt worried	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
EDANX46	I felt nervous.....	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
EDANX51	I had trouble relaxing.....	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
EDANX54	I felt tense	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
EDANX41	My worries overwhelmed me	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
EDANX03	It scared me when I felt nervous.....	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
EDANX48	Many situations made me worry	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
EDANX09	I had unpleasant thoughts that wouldn't leave my mind	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
EDANX39	I worried about dying	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

Appendix M: Summary of Changes

Amendment 1 – October 18, 2018			
Sections(s) Affected	***Prior Version***	***Amendment 1 Changes***	***Rationale***
Cover Page;	Funded by BMS	Funded by the Department of Neurosurgery, Northwestern University	BMS is no longer funding study
Cover Page; Study Schema; Study Summary; Section 1.3.2 (Clinical Trial Design); Section 2 (Objectives); Section 3 (Patient Eligibility); Section 4.1 (Treatment Overview); Section 4.2 (Treatment Administration); Section 4.2.1 (BMS-986205); Section 4.2.2 (Nivolumab); Section 4.2.3 (Temozolomide); Section 4.3 (BMS-986205 Dose Escalation); Section 6.2 (Primary Endpoint); Section 6.3 (Secondary Endpoints); Section 10 (Statistical Considerations); Section 11.3 (Registration Procedures); Section 11.4 (Data Submission)	Study written as a Phase I/IIa	Study written as a Phase I only	Due to the change in funding, this study will move forward as a Phase I only. Plans for Phase II portion to be opened separately.
Section 3 (Patient Eligibility)	"Approximately **5** potentially eligible patients are seen per month, and it is anticipated that at least **1** per month will be accrued"	"Approximately **6** potentially eligible patients are seen per month, and it is anticipated that at least **2** per month will be accrued"	Estimate of patient recruitment has been updated.
Section 3.1.6 (Inclusion Criteria); Section 3.2.4 (Exclusion Criteria)	n/a	Addition of restrictions for steroids use while on study treatment.	There is emerging data supporting abrogation of benefit of immunotherapies in patients treated with steroids. It was felt by the neurooncology community at a recent NRG meeting that it would be very reasonable to include additional restrictions for

			patients on steroids.
Section 5 (Study Procedures)	AMT-PET to be performed only in Phase II portion of the study	AMT-PET will be performed in current study, which is only Phase I	Optional AMT-PET will be performed during Phase I.
Amendment 2 – January 14, 2018			
Sections(s) Affected	***Prior Version***	***Amendment 2 Changes***	***Rationale***
Cover page	IND Holder: pending	IND Holder: Rimas Lukas, MD	Administrative change
Section 1.2.1 (BMS-986205); Section 8.1.10 (Side Effects)	Language describing ongoing clinical trials for BMS-986205	Updates to information for ongoing clinical trials for BMS-986205	Additional background information is available regarding BMS-986205
Section 1.3.2. (Clinical Trial Design); Section 4.6.1 (Continuation of investigational Therapy)	"Planned treatment period is indefinite"	"Planned treatment period is up to 2 years"	BMS recommends nivolumab treatment up to 2 years.
Section 3.1.10 (Inclusion Criteria)	n/a	Referenced the pregnancy test required within 24 hours prior to beginning study treatment	Included requirement that 24 hour pregnancy test is required prior to beginning study treatment.
Section 4.3 (BMS-986205 Dose Escalation)	n/a	Added "Further, if 2+ patients experience a DLT at dose level 2, additional 3 patients will be added to dose level 1 prior to being declared the MTD."	Included additional clarification on how DLTs will be managed prior to determining MTD.
Section 4.3.1 (Dose Limiting Toxicity); Section 4.4.3.3 (Resuming Treatment); Section 6.1 (Definitions); Section 7.3.3 (Expedited Reporting of SAEs/Other Events); Section 8.1.4 (Storage and Stability)	Referred to "the funding sponsor"	Refer to "BMS"	BMS is no longer financially supporting this trial, so the language needed to be changed
Section 4.3.1.1 (nonhematologic DLT)	"Details will be established in a protocol amendment after establishing the recommended phase II dose in the unmethylated patient population."	Removed statement about amending the protocol	Referencing a future amendment to update the MGMT promoter unmethylated Phase II dose is not needed.
Section 4.4 (Toxicity Management & Dose Delays/Modifications)	"Any patient who receives at least one dose of nivolumab **and** BMS-986205 will be evaluable for	"Any patient who receives at least one dose of nivolumab **or** BMS-986205 will be evaluable for toxicity	Clarify that a patient who receives one dose of either drug will be evaluable for toxicity

	toxicity endpoints"	endpoints"	
Section 4.4.2.1 (Dose Reduction)	n/a	Removed typo	Corrected type error in protocol
Section 4.4.2.1 (Dose Reduction); Section 4.4.3.3 (Resuming Treatment)	Referenced BMS-986205 placebo	Removed reference to BMS-986205 placebo	Corrected error. No placebo is being used in this trial.
Section 4.4.2 (Nivolumab)	• Bilirubin >1.5 - 3.0 x ULN •Alkaline Phosphatase >2.5 - 5.0 x UL	• **Grade 2** Bilirubin >1.5 - 3.0 x ULN • **Grade 2** Alkaline Phosphatase >2.5 - 5.0 x ULN • **Grade 2 AST/ALT**	Clarified and updated criteria for delaying nivolumab administration based on BMS comments.
Section 4.4.3.2 (Treatment Discontinuation)	n/a	Added "any event requiring more than 1 dose reduction of BMS-986205 **requires discontinuation of BMS-986205 only"**	Clarification that patients may continue to take nivolumab on study if BMS-986205 is discontinued.
	"For participants who delay BMS-986205 but continue Nivolumab, any dose delay of BMS-986205 lasting > 12 weeks will result in the **discontinuation of both BMS-986205 and Nivolumab**".	"For participants who delay BMS-986205 but continue Nivolumab, any dose delay of BMS-986205 lasting > 12 weeks will result in the **patients being taken off study treatment."**	Patients who discontinue BMS-986205 **and** nivolumab will be taken off study treatment.
Section 4.5.2 (Concomitant Medications/Treatments that are not recommended)	n/a	Added "Caution is warranted when administering BMS-986205 to participants taking drugs that are highly dependent on CYP3A4 or CYP2B6 for metabolism."	Additional information provided by BMS on CYP restrictions
Section 4.5.2 (Concomitant Medications/Treatments that are not recommended); Section 4.5.4 (Permitted Concomitant Medication and Therapy for which specific dose requirements are necessary)	n/a	Added clarification to steroid use "Participants must be on a stable or decreasing dose of steroids ≤4mg of decadron for 7 days prior to initiating study treatment [not consent] and be **off** of all steroids at the time of initiation of study treatment (D#1)."	To align with steroid restrictions in inclusion criteria
Section 4.5.3 (Other Restrictions and Precautions"	n/a	Included additional information on serotonin syndrome	Additional information provided by BMS
Section 5 (Study	n/a	Included X for	As indicated by

Procedures)		pregnancy test during RT therapy	footnote 5, pregnancy test will be performed every 4 weeks while on treatment, including during RT.
Section 6.3.1 (Secondary Endpoints); Section 10.1.2 (Secondary Variables)	Indicate timeframe for collected data from "time of study enrollment"	Indicate timeframe for collected data from "start of study treatment"	Correction of error. Data for survival will be collected starting at the time of treatment initiation.
Section 7.3.3.4 (Reporting to BMS)	n/a	"SAE reports (including **pregnancy and** death by any cause),…"	Must inform BMS of pregnancy while on study treatment
Section 7.3.3.5 (Adverse Events of Special Interest (AEOSI))	n/a	Included information on AEOSI (HLH and DRESS)	Per BMS, additional AEOSI require expedited reporting.
Section 8.1.9 (Availability and Supply)	n/a	Additional information on ordering BMS 986205	Administrative change to provide clarification on drug ordering.
Section 8.2.6 (Preparation and administration)	"When the dose is fixed (eg, 240 mg, 480mg), nivolumab injection can be infused undiluted or diluted so as not to exceed a total infusion volume of **120 mL."**	"When the dose is fixed (eg, 240 mg, 480mg), nivolumab injection can be infused undiluted or diluted so as not to exceed a total infusion volume of **160 mL."**	Update from nivolumab IB.
Section 8.2.9 (Availability and Supply)	"The initial order should be limited to 20 vials"	Removed restriction limiting order to 20 vials	Per BMS, not needed in protocol.
Section 10.3 (Sample Size and Accrual)	"We will recruit 18-30 patients in this Phase I study depending on dose findings **in the Phase I study**."	"We will recruit 18-30 patients in this Phase I study depending on dose findings."	Removed text due to redundancy
Appendix C	"Guidance for collection of Pregnancy Information and outcome of pregnancy on the Pregnancy Surveillance Form is provided in **Section 9.2.5 and the Appendix for Adverse Events and Serious Adverse Events Definitions and**	"Guidance for collection of Pregnancy Information and outcome of pregnancy on the Pregnancy Surveillance Form is provided in the **Pregnancy Surveillance Form-Quick Reference Guide."**	Clarify the location of pregnancy surveillance form

	procedures for Evaluating, Follow-up and Reporting."		
Appendix D	n/a	Included introductory language on management algorithms previously included in Appendix I	Formatting error corrected for clarity.
Appendix E	CYP3A4 and CYP2B6 Guidance	CYP3A4, CYP2B6 and CYP1A2 Guidance	Updated guidance based on information from BMS
Appendix I	n/a	BMS-986205 and Nivolumab Dose Delay Criteria	Updated information provided by BMS
Appendix J	n/a	BMS-986205 Diagnostic Criteria for HLH and DRESS syndrome	Updated information provided by BMS
Amendment 3 -- For Internal Use *SRC acknowledgement of FDA and IRB protocol changes*			
Amendment 4 - September 19, 2019			
Sections(s) Affected	***Prior Version***	***Amendment 4 Changes***	***Rationale***
Cover page; Study Schema; Study Summary; Section 1.1 (Glioblastoma and Anaplastic Astrocytoma); Section 1.3.1.1 (Nonclinical Studies); Section 1.3.2.2 (Patient population and design); Section 2.1 (Primary Objective); Section 3.1.1 (Inclusion Criteria); Section 4.1 (Overview)	Study opened to patients with newly diagnosed glioblastoma	Study opened to patients with newly diagnosed glioblastoma and anaplastic astrocytoma	To facilitate accrual which allow the study to progress more quickly into a randomized phase 2 trial.
List of Abbreviations	n/a	Include AA (anaplastic astrocytoma) and TTFields (tumor treating fields)	Administrative update
Study Schema; Study Summary; Section 1.1.1 (Standard treatment regimen in GBM); Section 1.2.4 (Tumor Treating Fields); Section 1.3.2.2 (Patient population and design); Section 1.3.2.1 (Introduction and Rationale); Section 1.3.2.3 (Anticipated Results and Interpretation); Section 3.2.22 (Exclusion Criteria); Section 4.2 (Treatment	Optune (TTFields) therapy not permitted	Optune (TTFields) is permitted beginning at Day 1 of the Maintenance Phase	Make Optune available to patients who would like to participate

Administration); Section 2.4.5 (Tumor Treating Fields); Section 4.3.1.1 (Nonhematologic Dose-Limiting Toxicity (DLT): Hepatic Nonhematologic DLT); Section 4.4.3.1 (Treatment Delay); Section 4.4.6 (Tumor Treating Fields); Section 4.5.1 (Prohibited Concomitant Medication and Therapy); Section 8.4 (Tumor Treating Fields)			
Section 1.1.2 (Immunosuppression and high-grade gliomas)	Section title "Immunosuppression and GBM"	Section title: "Immunosuppression and high-grade gliomas"	To reference both GBM and AA
Section 1.2.1.3 (Dose Justification)	Starting dose of BMS-986205 listed as 100mg	Starting dose of BMS-986205 listed as 50mg	Corrected error.
Section 1.3.2.2 (Patient population and design)	"Analyses based upon radiographic endpoints (i.e. response rate, PFS) will be performed utilizing the iRANO criteria"	"Analyses based upon radiographic endpoints (i.e. response rate, PFS) will be performed utilizing the **RANO and** iRANO criteria"	Both RANO and iRANO will be used for response analysis.
Section 2.3.3 (Exploratory Objectives); Section 5 (study Procedures); Section 6.4.3 (Exploratory Endpoints); Section 9.5 (Patient Questionnaires); Appendix K (Beck's Depression Inventory Questionnaire); Appendix L (PROMIS Emotional Distress - Anxiety)	n/a	Include an exploratory objective "Investigate GBM/AA patient levels of distress, before, during, and after treatment with trimodal radiation, anti-PD-1 mAb and IDO1 enzyme inhibitor.	Included an objective to analyze patient levels of distress using the PROMIS questionnaires.
Section 3.1.1 (Inclusion Criteria)	"Study enrollment is to be within **5 weeks** from diagnostic surgery or biopsy."	"Study enrollment is to be within **6 weeks** from diagnostic surgery or biopsy."	Increase window to allow for more patient availability
Section 3.1.2 (Inclusion Criteria); Section 3.1.3 (Inclusion Criteria)	Inclusion criteria: Tumor tissue specimens from the GBM surgery or biopsy for central pathology review and exploratory analysis of immunocorrelative studies, if available (no minimum requirement).	Criteria removed.	Both criteria were removed as they are not requirements for study enrollment, only recommendations.

	For subjects who had undergone tumor resection, preoperative Gd-MRI and immediate postoperative Gd-MRI performed within <72 hours after surgery or biopsy is recommended. If CT scans were performed perioperatively, an MRI should be performed before initiation of study treatment.		
Section 3.1.9 (Inclusion Criteria)	"Clinically normal cardiac function without history of ischemic heart disease in the past 6 months and **normal** 12 lead ECG."	"Clinically normal cardiac function without history of ischemic heart disease in the past 6 months **and not clinically significant** 12 lead ECG **(as determined by treating investigator)**."	Clarification to allow for treating physician discretion
Section 3.2.1 (Exclusion Criteria)	"Patients who have had chemotherapy within 2 years prior to entering the study are not eligible."	"Patients who have had chemotherapy **for any cancer** within 2 years prior to entering the study are not eligible."	Clarification
Section 3.2.9 (Exclusion Criteria)	"Patients with a history of recent prior malignancy are not eligible. Subjects with curatively treated cervical carcinoma in situ or non-melanoma basal cell carcinoma of the skin, or subjects who have been free of other malignancies for ≥2 years are eligible for this study."	Removed criteria	Exclusion criteria 3.2.1 was clarified to cover all previous cancer diagnoses so this was redundant.
Section 3.2.12 (Exclusion Criteria)	"Patients who have received treatment with botanical preparations (e.g., herbal supplements	"Patients who have received treatment with botanical preparations (e.g., herbal supplements or	Allow for washout period to be from time of treatment.

	or traditional Chinese medicines) intended for general health support or to treat the disease under study within 14 days prior to **registration** are not eligible."	traditional Chinese medicines) intended for general health support or to treat the disease under study within 14 days prior to **initiation of treatment** are not eligible."	
Section 3.2.24 (Exclusion Criteria)	"Note: testing for HIV must be performed at sites where mandated locally"	Removed note	This is a single institution study and HIV testing is not mandated at Northwestern.
Section 4.3 (BMS-986205 Dose Escalation)	"BMD-986205"	"BMS-986205"	Corrected typing error.
Section 4.3.1.1 (Nonhematologic Dose-limiting Toxicity (DLT)); Section 4.4.3.1 (Treatment Delay)	n/a	Include information for DLTs specific to TTFields	Clarify DLTs due to TTFields will not delay other treatments.
Section 4.4.3.2 (Treatment Discontinuation)	A dosing delay lasting > **10 weeks** from previous dose	A dosing delay lasting > **12 weeks** from previous dose	Corrected error.
Section 4.5.1 (Prohibited Concomitant Medication and Therapy)	All Prophylactic antimicrobial therapy prohibited	Prophylactic antimicrobial therapy (Note: treatment for Pneumocystis carinii prophylaxis is allowed. See section 4.5.4.2)	Clarify restrictions with Prophylactic antimicrobial therapy
Section 4.6 (Duration of Therapy)	n/a	Disease progression by **iRANO**	Clarify that therapy will continue until disease progression as determined by iRANO criteria.
Section 5 (Study Procedures)	One table for study procedures	Study procedures for Maintenance Phase have been moved into a separate table.	Tables have been split to provide clarity on timing of procedures to be performed.
	n/a	Footnote numbers were updated	Format update
	n/a	Footnote 18: clarify that blood will be collected at each MRI time point, which is "every 8 weeks starting at cycle 1 day 1)	Clarification of timing
	n/a	Footnote 5 was added to clarify timing of toxicity assessment, physical exam and conmeds during RT phase	Included for clarity.

	n/a	Added footnote 13 to clarify TMS will only be in MGMT promotor methylated cohort	Included for clarity.
	n/a	Added to footnote 8 that beginning at cycle 7 of Maintenance Phase, CBC +diff will be performed only on day 1	Once MGMT promotor methylated patients complete TMZ, they will no longer need additional CBC+diff
Section 5 (Study Procedures); Section 9 (Correlatives/Special Studies)	n/a	Added footnote 21 to allow baseline research blood and stool samples can be collected any time after consent and prior to any study treatment.	Extended the window for blood collection to reduce deviations.
Section 5.1 (Study Procedures)	n/a	Included “Post RT Phase” in procedure table	Post RT Phase was referenced in the protocol, however was not included in the procedure table.
Section 8.1.9 (Availability & Supply); Section 8.2.9 (Availability & Supply)	n/a	Included instructions for the end of study period from BMS	Required language from BMS (moved from section 8.4)
Section 9 (Correlatives/Special Studies)	n/a	Table of correlative collection information has been updated to reflect the involvement of Pathology Core Facility for collecting archival tissue samples and stool samples.	Updates to sample collection.
Section 9.3.2 (Blood)	n/a	Additional information on analysis of blood samples	Clarification of analysis plans
Section 10.4.1 (Data Analyses Plans)	“Statistical analyses will be performed using **R-3.4.3**”	“Statistical analyses will be performed using **R-3.6.1**”	Software Update
Section 10.4.4 (Exploratory Analyses)	Explanation the analyses of AMT-PET exploratory analyses	Explanation of analyses of questionnaires and correlative studies.	Analyses plans have been updated based on the change to study endpoints.
Amendment 5– December 16, 2019			
Sections(s) Affected	***Prior Version***	***Amendment 5 Changes***	***Rationale***
Coverpage	Jeffery Raizer listed as Sub-I	Jeffery Raizer removed from Sub-I list	Administrative change
Table 5-2 (Study Procedures During Maintenance Phase)	n/a	“X” added in columns for maintenance cycle for the following rows: MRI, EKG,	Administrative update for clarity and to match table with current

		temozolomide, questionnaire, and correlative blood.	footnotes
Appendix	n/a	Inserted 4 missing pages of Emotional Distress-Anxiety questionnaire in appendix of protocol. Questionnaires are in Redcap for patients completion.	Inserted missing pages, correction of administrative error.
Amendment 6 – May 1, 2020			
Sections(s) Affected	***Prior Version***	***Amendment 6 Changes***	***Rationale***
Cover Page;	n/a	Added Dr. Csaba Juhasz MD, PhD from Wayne State University to Lab Co-Investigators	Added optional AMT-PET study to the Protocol per PI request. Dr. Juhasz and his PET Center team will perform the AMT-PET scans and analyze/send data to NU for this optional exploratory study. Both contrast-enhancing and non-enhancing gliomas have increased AMT uptake. This study will assess whether AMT uptake on PET imaging is correlated with treatment response and other outcomes.
	Biostatistician: Denise Scholtens, PhD	Biostatistician: Hui Zhang, PhD	Dr. Scholtens is no longer part of the Division of Biostatistics.
1.2.1.4 Safety	The most commonly reported TRAEs (in > 10% of participants) during combination therapy with nivolumab were fatigue (14.1%) and nausea (11.1%). Grade 3 TRAEs have been reported in approximately 11% of participants receiving the combination and treatment-related	Per Investigator Brochure v. 6 (01-29-2020), the most commonly reported TRAEs (in > 10% of participants) during combination therapy with nivolumab were fatigue (17.2%) and nausea (13.2%). Grade 3 and 4 TRAEs have been reported in approximately 17% of participants receiving the combination.	Updated the numbers per IB v. 6 (01-29-2020). Removed outdated dates per Pharma sponsor feedback.

	SAEs in approximately 7%. There has been 1 treatment-related death due to myocarditis prior to the clinical data cutoff date (15-Nov-2017), which occurred during combination with nivolumab, and 2 additional deaths due to Stevens-Johnson syndrome and hepatic failure, which occurred after the clinical data cutoff date. (pg 23 IB)	Treatment-related SAEs were reported in 9.4% of patients treated with BMS-986205 and nivolumab.There has been 1 treatment-related death due to myocarditis , which occurred during combination with nivolumab, and 2 additional deaths due to Stevens-Johnson syndrome and hepatic failure Furthermore, the 100 mg once daily (QD) dose of BMS 986205 in combination with nivolumab appears to have a safety profile similar to that reported for nivolumab monotherapy, except for anemia and methemoglobinemia, which may be related to p-chloroaniline production.	
	Metabolism of BMS-986205 produces a p-chloroaniline metabolite, which is associated with the formation of methemoglobin as well as with hemolytic anemia. As of 15-Nov-2017, there have been no clinically significant metHb events at the 100 mg dose level of BMS-986205, and the highest reported metHb value was 16% in a participant receiving 200 mg of BMS-986205; no other participants had reported metHb levels over 10%, none have required	Metabolism of BMS-986205 produces a p-chloroaniline metabolite, which is associated with the formation of methemoglobin as well as with hemolytic anemia. As of 24-Oct-2019, there have been no clinically significant metHb events at the 100 mg dose level of BMS-986205, and the highest reported metHb value was 16% in a participant receiving 200 mg of BMS-986205; no other participants had reported metHb levels over 10%, none have required specific treatment for	Updated the data per IB v. 6 (01-29-2020). Added a footnote to explain that the data in the above paragraphs are based on IB v. 6 (01-29-2020), and that the most current version of the IB should be consulted.

	specific treatment for methemoglobinemia, and there have been no treatment discontinuations due to methemoglobinemia. Anemia and hemolytic anemia have also occurred infrequently (2.5% and 0.3% of participants receiving combination therapy with nivolumab, respectively) and responded to dose holding, reductions, and other standard clinical measures. Entry criteria and monitoring parameters were developed in an attempt to reduce the risk of the occurrence and impact of methemoglobin-related toxicity. Participants with cytochrome b5 reductase and G6PD deficiencies are excluded due to the increased risk of methemoglobinemia and hemolysis, respectively.	methemoglobinemia, and there have been no treatment discontinuations due to methemoglobinemia. Anemia and hemolytic anemia have also occurred infrequently (1% and 0.3% of participants receiving combination therapy with nivolumab, respectively) and responded to dose holding, reductions, and other standard clinical measures. Entry criteria and monitoring parameters were developed in an attempt to reduce the risk of the occurrence and impact of methemoglobin-related toxicity. Participants with cytochrome b5 reductase and G6PD deficiencies are excluded due to the increased risk of methemoglobinemia and hemolysis, respectively. **All information above references BMS-986205 Investigator's Brochure v. 6 (01-29-2020). Please refer to the most recent Investigator Brochure for a current listing of adverse events and toxicities.*	
1.3.1.2 Clinical Studies		Added Figure 7 and clinical information on AMT-PET in GBM patients.	Added clinical information to provide rationale for optional AMT-PET study.
2.3 Exploratory Objectives, 2.3.4	n/a	Added exploratory objective 2.3.4 "Assess whether tumor-associated α-[11C]-methyl-L-Trp	Added an objective for AMT-PET.

		(AMT) uptake on PET imaging is correlated with treatment response and other outcomes. “	
4.4.1.1 Holding Dose	QTc**B** > 500 msec confirmed by at least 1 repeat ECG and at least 60 msec above baseline	QTc**F**> 500 msec confirmed by at least 1 repeat ECG and at least 60 msec above baseline	Changed to QTc Fridericia’s formula (was previously Bazett’s) to be consistent with the rest of the Protocol.
4.4.1.2 Dose reduction	QTc**B** > 500 msec confirmed by at least 1 repeat ECG and at least 60 msec above baseline	QTc**F** > 500 msec confirmed by at least 1 repeat ECG and at least 60 msec above baseline	Changed to QTc Fridericia’s formula (was previously Bazett’s) to be consistent with the rest of the Protocol.
4.4.2 Nivolumab	Nivolumab administration should be delayed for the following (in addition to the table below) until resolution to ≤ grade 1 or baseline: •Grade 2 non-skin, drug-related adverse events (including below), with the exception of fatigue •Grade 2 Bilirubin >1.5 - 3.0 x ULN •Grade 2 Alkaline Phosphatase >2.5 - 5.0 x ULN •Grade 2 AST/ALT •Grade 3 skin, drug-related adverse event •Grade 3 drug-related laboratory abnormality, with the following exceptions: o Grade ≥ 3 lymphopenia or asymptomatic amylase or lipase elevation does not require dose delay o Grade ≥ 3 AST, ALT, total bilirubin will require dose	N/A	Deleted this section. The bulleted language for the nivolumab monotherapy dose modification contradicted some of the guidelines for the nivolumab combination therapy dose modifications. The pharma sponsor clarified that this section should be deleted, and that the table below (on page 38) should be followed in it’s place.

	discontinuation ○ Grade ≥ 3 cardiac toxicity, neurotoxicity, or pneumonitis will require dose discontinuation		
Table 5-1: Study Procedures	n/a	Added "AMT PET (Optional)[26]" as an assessment, marked at screening, EOT, and follow-up.	See rationale for AMT-PET above.
	n/a	Added "TSH, free T3, and Free T4" at baseline, Post RT Phase D1, and EOT.	Per pharma sponsor feedback, thyroid function tests are necessary for safety monitoring.
	n/a	Added footnote 26.	The footnote was added to describe when/where AMT-PET will be performed.
	n/a	Added Blood Collection at D1 of Post RT Phase.	Added per Dr. Derek Wainwright's request (lab investigator). Dr. Wainwright would like to see how the patient's blood counts respond to radiation.
	Footnote 20: Research blood (2 heparinized tubes with 10ml each) will be collected at baseline and at each MRI time point (every 8 weeks starting at cycle 1 day 1 of the Maintenance Cycle) and at the end of treatment visit.	Footnote 20: 20.Research blood (2 heparinized tubes with 10ml each) will be collected at baseline, **on day 1 of post RT**, and at each MRI time point (every 8 weeks starting at cycle 1 day 1 of the Maintenance Cycle) and at the end of treatment visit.	See rationale for additional blood sample above.
Table 5-2: Study Procedures During Maintenance Phase	n/a	Added "AMT PET (Optional)[26]" as an assessment, marked at Day 1	See rationale for AMT-PET above.
	b/a	Added "TSH, Free T3, Free T4" to every cycle D1.	Per pharma sponsor feedback, thyroid function tests are necessary for safety monitoring.
	n/a	Added footnote 26.	The footnote was added to describe

			when/where AMT-PET will be performed.
	Footnote 20: Research blood (2 heparinized tubes with 10ml each) will be collected at baseline and at each MRI time point (every 8 weeks starting at cycle 1 day 1 of the Maintenance Cycle) and at the end of treatment visit.	Footnote 20: 20.Research blood (2 heparinized tubes with 10ml each) will be collected at baseline, **on day 1 of post RT**, and at each MRI time point (every 8 weeks starting at cycle 1 day 1 of the Maintenance Cycle) and at the end of treatment visit.	See rationale for additional blood sample above
6.4 Exploratory Endpoints, 6.4.4	n/a	Added Endpoint 6.4.4: Correlation between AMT-PET responses and MRI responses, survival, and PFS in newly diagnosed MGMT promoter unmethylated and MGMT promoter methylated glioblastoma treated with nivolumab in combination with BMS-986205 and radiation. • AMT-PET correlation with OS • AMT-PET correlation with radiographic response on MRI • Tumor immune-correlates • Serum immune-correlates • Molecular pathology correlates	See rationale for adding AMT-PET study above.
7.2.3 Serious Adverse Events (SAEs)	n/a	Added a Hospitalization section: Hospitalization For reports of hospitalization, it is the sign, symptom or diagnosis which led to the hospitalization that is the serious event for which details must be	This section was added to clarify when a hospitalization is an SAE and when it isn't. This helps prevent reporting previously planned surgical and routine procedures (i.e. a craniotomy) as an

		provided. Any event requiring hospitalization or prolongation of hospitalization that occurs during the study must be reported as a serious adverse event, except hospitalizations for the following: •Hospitalizations not intended to treat an acute illness or adverse event (e.g., social reasons such as pending placement in long-term care facility) •Hospitalizations for routine blood transfusions, hospitalization for an elective or diagnostic procedure, or surgery for a pre-existing condition that has not worsened, are not considered SAEs. (Emergency room visits that do not result with admission are not considered as SAEs). •Hospitalizations or prolongation of hospitalization for ≤24 hours.	SAE.
7.3.3.3 Reporting to the FDA	N/A	Added the following line: The Principal Investigator will notify the FDA with the assistance of a Quality Assurance Monitor.	Per pharma sponsor feedback, clarified that the FDA will be notified by the PI with assistance from a QAM.
7.3.3.5 Adverse Events of Special Interest (AEOSI)	N/A	Added the following line: All AEOSIs, regardless of causal association, will be submitted to the FDA and BMS.	Per pharma sponsor feedback, clarified that all AEOSIs will be submitted to the FDA and BMS. This confusion was because the section had defined events of special interest

			that required expedited regulatory reporting. This does not mean we will not report AEOSIs beyond the three listed in this section that are of "special interest."
9 CORRELATIVES/SPECIAL STUDIES, Correlative Samples – Details for Lab Manual	Under "Timing and Blood": Baseline (prior to first dose of study treatment) and every 8 weeks during the Maintenance Phase beginning on Cycle 1 Day 1 (±2 days), and at the end of treatment visit.	Under "Timing and Blood": Baseline (prior to first dose of study treatment), **on day 1 of post RT**, and every 8 weeks during the Maintenance Phase beginning on Cycle 1 Day 1 (±2 days), and at the end of treatment visit.	See rationale above for adding additional blood sample on D1 of post RT.
9.6 AMT-PET Study	n/a	Added section 9.6 to describe the AMT-PET study including the scanning protocol, description of AMT, timing of assessments, communication plan between NU and WSU, WSU personnel contact info, and patient reimbursement.	See rationale above for AMT-PET study.
10.1.4 Further Variables of Interest	n/a	*Added three additional variables of interest:* -AMT-PET correlation with overall survival -AMT-PET correlation with radiographic response on MRI -AMT-PET correlation with tumor and serum immune-correlates	See rationale above for AMT-PET study.
10.4.4 Exploratory analyses	n/a	Added analysis plan for AMT-PET (third paragraph in section).	See rationale above for AMT-PET study.
TITLE PAGE, LIST OF ABBREVIATIONS, STUDY SCHEMA, STUTDY SUMMARY TITLE (Title Objectives, Diagnosis & Key Eligibility Criteria, Treatment Plan), 1.1 Glioblastoma ~~and Anaplastic Astrocytoma~~,	Mentioned Astrocytoma or "AA"	Removed astrocytoma or AA.	All references to astrocytoma cohort were removed. The pharma sponsor (BMS) requested we remove this cohort for two reasons: 1. The protocol primarily supports

1.2.3.3 Special Populations (Age), 1.3.1.1 GBM~~/AA~~ immunotherapy requires a combinatorial approach,1.3.2.2 Patient population and design, 2.1.1 Primary Objective, Exploratory Objectives 2.3.1 and 2.3.3, Inclusion Criteria 3.1.1, 4.1 Overview			GBM, as all the preclinical and clinical data are based on GBM models and there isn't much data in support of AA patients. 2. Due to small sample size inclusion of another subset population introduces heterogeneity into the study, which could limit interpretability of the study results.
Throughout Protocol			Editorial changes such as protocol version date, page numbers, formatting, TOC updates, etc were made throughout.
Amendment 7 – July 24, 2020			
Sections(s) Affected	***Prior Version***	***Amendment 7 Changes***	***Rationale***
Title Page		Added the West Region of NM with Dr. Sean Grimm as the Lead Investigator.	The West Region will be added as an outside site to this study.
Tables 5-1 Study Procedures and 5-2 Study Procedures in Maintenance Phase	Footnote 17: Patients will complete questionnaires at baseline/pretreatment (any time prior to Day 1 of RT), 1 week prior to each MRI follow-up (see footnote #5), and every 3 months during follow up. Patients will receive a link to complete questionnaires online via RedCAP.	Footnote 17: Patients will receive paper forms to complete and return to the study team. Data from the paper forms will be entered into NOTIS by the study team.	Due to technical issues with REDCap, paper form questionnaires will be used. Paper forms will be secured in a locked room. Data from the paper forms will be entered into NOTIS.
Table 9 Correlative/Special Studies	Previous address: 300 E Superior Street Tarry Bldg 2-725	Updated Address for Dr. Wainwright's lab: 303 E Superior St Simpson-Querrey 6-	Dr. Wainwright's lab was moved to a new location.

	Chicago, IL 60611 Lab Phone: (312) 503-5168; Office Phone: (312) 503-3161	500 Chicago, IL 60611 Lab Phone: 312-503-5168	
	Analysis center for all specimens previously said: Wainwright Lab 300 E Superior Street Tarry Bldg 2-725 Chicago, IL 60611 Lab Phone: (312) 503-5168; Office Phone: (312) 503-3161	Updated Address to: 303 E Superior St Simpson-Querrey 6-500 Chicago, IL 60611 Lab Phone: 312-503-5168	Dr. Wainwright's lab was moved to a new location, with a new address.
9.5 Questionnaires	When completed, the form data will be immediately uploaded into a secure REDCap database. Patients who do not have access to email, or do not wish to complete measures by email link, will be offered the opportunity to complete the measures on arrival into the clinic, prior to evaluation by the physician. Report data will be downloaded by the study team and reviewed with the patient during the visit.	Patients will be given a paper form for the PROMIS measures. When completed, the data from the form will be entered into a secure NOTIS database by the study team. Paper forms will be secured in a locked room with access given to authorized study personnel only. Report data will be downloaded by the study team and reviewed with the patient during the visit.	See rationale above.
Throughout Protocol			Editorial Changes (formatting, grammar, updates to Protocol Amendment version and date, etc).
Amendment 8 – November 18, 2020			
Sections(s) Affected	***Prior Version***	***Amendment 8 Changes***	***Rationale***
4.1 Overview		*Added the following*	To allow patients

		paragraph: *Patients who have disease progression per iRANO criteria or clinical decline, may have the option to re-start treatment if they undergo standard of care surgery, and their tumor tissue shows on pathologic review that that there is no evidence of significant tumor and the changes on MRI were likely treatment related. The patient will be advised of the pathology results and that they may not derive any further benefit from re-starting therapy. The patient will need to re-sign the informed consent prior to starting therapy.*	who may have experienced pseudo-progression (treatment-related inflammation) to re-start treatment.
4.4.2 Nivolumab		Removed DSMC from this paragraph: *There will be no dose modifications of nivolumab. Nivolumab can be held up to 12 weeks. After 12 weeks, resumption of nivolumab will require discussion with PI/~~DSMC~~.*	Per DSMC feedback, asked to remove them from this paragraph as they do not provide waivers.
Amendment 9 – August 16, 2021 New NM West Region PI, fixing NM West Region info on the title page, and adding Multicenter language that was omitted in error.			
Sections(s) Affected	***Prior Version***	***Amendment 9 Changes***	***Rationale***
TITLE PAGE	.	*Added the bolded and underlined text:* **<u>Participating Northwestern Medicine Network Site:</u>** **<u>Northwestern Memorial Healthcare (West Region) Participating</u>**	*Added new PI Dr. Gondi, to replace Dr. Grimm who is no longer at NM.* *Also corrected the title page information to clearly show which West Region location is participating (only Warrenville).*

		Northwestern Memorial Healthcare Location: **•Northwestern Medicine Cancer Center Warrenville 4405 Weaver Parkway Warrenville, IL 60555 Phone: 630-352-5450** **Northwestern Memorial Healthcare Principal Investigator:** **Vinai Gondi, MD Director of Research & Education Northwestern Medicine Proton Center Co-Director, Brain & Spine Tumor Center Northwestern Medicine Cancer Center Warrenville 4405 Weaver Parkway Warrenville, IL 60555 Phone: (630) 352-5350 Email: vinai.gondi@nm.org**	
STUDY SUMMARY		*Added the bolded and underlined text:* Study Center(s): Northwestern University and **Northwestern Memorial Healthcare (West Region)**	*Added West Region as a participating center. Erroneously considered West Region as part of Northwestern University in previous Amendments.*
3 PATIENT ELIGIBILITY		*Added the bolded and underlined text and deleted the strikethrough text:* This will be a **multi** ~~single~~-center trial conducted at Northwestern University. **Northwestern**	*Added West Region as a participating center. Erroneously considered West Region as part of Northwestern University in previous Amendments.*

		Memorial Healthcare (West Region) is a participating site.	
4 TREATMENT PLAN 4.1 Overview		*Added the bolded and underlined text:* This is a **multi**~~single~~ center, open-label, uncontrolled, Phase I study conducted in subjects with newly diagnosed grade IV Glioma.	*Erroneously considered West Region as part of Northwestern University in previous Amendments*
5 STUDY PROCEDURES. 5.1 Table 5-1: Study Procedures, 5.2 Table 5-2: Study Procedures During Maintenance Phase		*Added the bolded and underlined text:* Footnote 11. BMS-986205 will be dispensed to patients at Week 1 Day 1 and Week 5 Day 1 of RT, **Day 1 of Post-RT Phase**, and on Day 1 of each cycle during Maintenance Phase. Patients will be instructed to take the dose of study drug PO QD.	*Omitted Day 1 of Post-RT phase from the footnote, in error. It was marked on the study calendar.*
11.5 Instructions for Participating Sites		*Added the bolded and underlined text:* **Before the study can be initiated at any site, the following documentation must be provided to the Clinical Trials Office at Northwestern University (as applicable):** **•Completed feasibility assessment(s) to verify site's capacity to support a Northwestern sponsored trial** **•Signed copy of Northwestern University's Data Participating Site Acknowledgement which details data submission**	*Erroneously considered West Region as part of Northwestern University in previous Amendments. Added instructions for participating sites since the West Region should be considered a participating site.*

		guidelines **•Draft consent form for review and approval prior to submission to the local IRB** **•A copy of the official IRB approval letter for the protocol and informed consent** **•A copy of the IRB approved informed consent** **•Pertinent credentials (CVs, MLs, CITI & GCP Training and FDFs) for the local PI and any sub-investigators who will be involved in the study at the site** **•Form FDA 1572 appropriately filled out and signed with appropriate supporting certifications** **Additional activities may be required prior to site activation (i.e. contract execution, study-specific training, and delegation of authority log). Full requirements will be outlined in the study start-up packet upon successful completion of a feasibility assessment.**	
Throughout Protocol			Editorial Changes (formatting, grammar, updates to Protocol Amendment version and date, etc).
Amendment 10 – September 3, 2021			
Sections(s) Affected	***Prior Version***	***Amendment 10 Changes***	***Rationale***

SCHEMA, Treatment Plan		*Deleted the strikethrough text:* Treatment will ~~continue for up to 2 years~~ until disease progression or unacceptable AEs.	Patients will be allowed to continue treatment until they no longer receive clinical benefit. This decision was made because two patients on study are deriving clinical benefit from the study drugs, and are approaching the two year limit.
1.3.2.2 Patient Population and Design		*Added the bolded and underlined text:* **As of Protocol Amendment 10 (dated 9-03-2021), only IDH wildtype GBM is eligible (See Inclusion Criteria 3.1.2). Only IDH wildtype patients have been enrolled on the study. Preclinical modeling of this approach was studied exclusively within the study context of GBM IDH wildtype models. In addition, limitation of the clinical trial to GBM IDH wildtype will allow for a more homogenous patient population providing greater clarity of the outcomes for the secondary and exploratory endpoints**.	The patients that have been enrolled on the study happen to be all IDH wildtype. The PI requested we make this an inclusion criteria, as a homogenous patient population will make the endpoints clearer.
		Deleted the strikethrough text and added the bolded and underlined text: The planned treatment period was~~is~~ up to 2 years. **Protocol Amendment 10 (dated 9-03-2021), revised the treatment period so it is now for as long as the**	Patients will be allowed to continue treatment for as long as they receive clinical benefit. This decision was made because two patients on study are deriving clinical benefit from the study drugs, and are approaching the two year limit.

		patient receives clinical benefit (for the study drugs BMS-986205 & nivolumab). This change was made as a few patients were benefiting from the treatment and approaching the 2 year limit. Patients **will remain on treatment as long as they** ~~who~~ are not experiencing toxicity requiring removal from study or progression of disease ~~will remain on study treatments~~.	
3.1 Inclusion Criteria		*Added the bolded and underlined:* **3.1.2 Patients must have confirmed IDH wildtype glioblastoma per immunohistochemistry or next generation sequencing.**	See rationale above.
4.6 Duration of Therapy		*Deleted the strikethrough text:* Patients may continue to receive cycles of treatment ~~for up to 2 years or~~ until any of the following occur:	See rationale above.
4.6.1 Continuation of Investigational Therapy		*Deleted the strikethrough text:* Subjects who complete 34 weeks of treatment without progression will be offered the opportunity, in agreement with the responsible investigator, to continue therapy beyond Week 34 as long as it will be of benefit to the patient ~~up to 2 years~~.	See rationale above
5.1 + 5.2 Study Procedures		*Deleted strikethrough text, added bolded and*	Clarified that some procedures may not

		underlined text: Footnote 6: To be performed every 8 weeks beginning at cycle 1 of the Maintenance Phase. **<u>After 2 years of treatment, may be performed per treating investigator discretion.</u>** An independent review will be performed on all relevant Gd-MRI scans, and an independent pathologist will confirm the histopathological diagnosis. Footnote 20: Research blood (2 heparinized tubes with 10ml each) will be collected at baseline, on day 1 of post RT, and at each MRI time point (every 8 weeks starting at cycle 1 day 1 of the Maintenance Cycle). **<u>Research blood will only be collected for up to 2 years of treatment, and the end of treatment visit.</u>** ~~and at the end of treatment visit.~~	be repeated after 2 years of treatment (research blood). Also clarified that EKG and tumor imaging after 2 years will be performed per investigator discretion (does not need to follow 8 week schedule).
Throughout Protocol			Editorial Changes (formatting, grammar, updates to Protocol Amendment version and date, etc).

Amendment 11 – February 22, 2022			
Sections(s) Affected	***Prior Version***	***Amendment 11 Changes***	***Rationale***
TITLE PAGE & Throughout	Protocol Version Date: September 3, 2021 (Amendment 10)	Protocol Version Date: February 22, 2022	Administrative revision
4.4 Toxicity Management & Dose Delays/Modifications	"No dose reduction will be made, but delay or discontinuation of	"Need for delay or discontinuation of TMZ administration or reduction in TMZ dose	Option to reduce TMZ dose is now available

	TMZ administration will be decided weekly…"	will be evaluated weekly…"	
4.4.4 Temozolomide	[not present]	"During either phase of temozolomide, there may be a need for a delay or discontinuation of TMZ or a reduction in dose."	Option to reduce TMZ dose is now available
4.4.4.1 Dose Reduction – Concomitant With Radiation	"No dose reduction will be made, but delay or discontinuation of TMZ administration will be decided weekly according to hematologic and non-hematologic AEs, as specified below."	"Need for delay or discontinuation of TMZ administration or reduction in TMZ dose will be evaluated weekly according to hematologic and non-hematologic AEs, as specified below."	Option to reduce TMZ dose is now available for treatment concomitant with other drugs
4.4.4.2 Dose Reduction – Post-Radiation Treatment (Adjuvant)	[not present]	"Need for delay or discontinuation of TMZ administration or reduction in TMZ dose will be evaluated weekly according to hematologic and non-hematologic AEs, as specified below. The total number of days and total dose of TMZ will be recorded on the appropriate eCRF. Should adjuvant TMZ need to be delayed, BMS-986205 and Nivolumab may be continued as long as the treating investigator deems the AE not related to the specific drug."	Option to reduce TMZ dose is now available for adjuvant treatment
4.4.4.3 Withhold TMZ Treatment	"In case of non-hematologic AE, the patient should be assessed at least weekly with relevant laboratory test(s). As soon as all of the above conditions are met, the administration of TMZ will resume at the same dose as used initially."	"In case of non-hematologic AE, the patient should be assessed at least weekly with relevant laboratory test(s) and any other appropriate methods of evaluation. As soon as all of the above conditions are met, the administration of TMZ will resume at the same dose used	Option to reduce TMZ dose is now available

		initially. A reduction in TMZ dose may also be appropriate per the investigator's discretion (see section 4.4.4.5)."	
4.4.4.5 Reduction in TMZ Dose	[not present]	"In the event of AEs of grade 3 or higher that are possibly, probably, or definitely related to TMZ, a reduction in dose may be warranted. Guidance for dose reduction can be found in the following table." [table; includes information on dose de-escalation starting with a baseline dose of 200 mg/m^2 QD PO]	Specifying information on TMZ dose reduction

Amendment 12 – October 13, 2022			
Sections(s) Affected	***Prior Version***	***Amendment 12 Changes***	***Rationale***
TITLE PAGE & Throughout	Protocol Version Date: February 22, 2022	Protocol Version Date: October 13, 2022	Administrative revision
TITLE PAGE	**Lab Co-Investigators:** Derek A. Wainwright, PhD *Department of Neurosurgery* *Northwestern University*	**Lab Co-Investigators:** Derek A. Wainwright, PhD *Department of Neurosurgery* *Loyola University*	Wainwright lab is relocating to Loyola University
9 Correlatives/Special Studies	Wainwright Lab 303 E Superior St Simpson-Querrey 6-500 Chicago, IL 60611 Lab Phone: 312-503-5168	Wainwright Lab Cardinal Bernardin Cancer Center Loyola University Chicago, Health Sciences Division 2160 S. First Ave., Bldg. 112, Rooms 208 and 210 Maywood IL 60153	Wainwright lab is relocating to Loyola University