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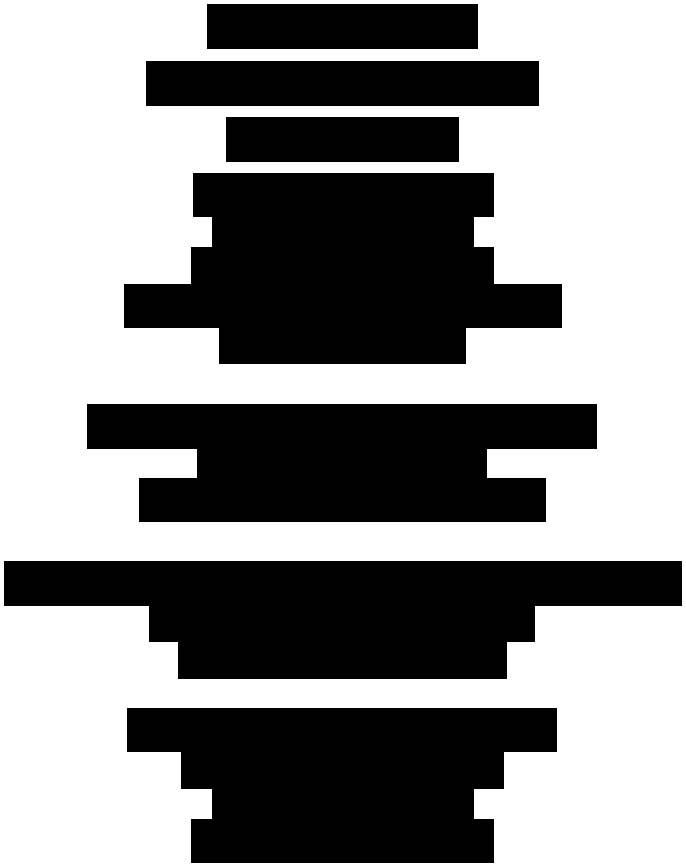
Clinical Protocol CA209143

A Randomized Phase 3 Open Label Study of Nivolumab versus Bevacizumab and a Safety Study of Nivolumab or Nivolumab in Combination with Ipilimumab in Adult Subjects with Recurrent Glioblastoma (GBM)

(CheckMate 143: CHECKpoint pathway and nivoluMAb clinical Trial Evaluation 143)



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Replace all previous version(s) of the protocol with this revised protocol and please provide a copy of this revised protocol to all study personnel under your supervision, and archive the previous versions.

DOCUMENT HISTORY

Document	Date of Issue	Summary of Change
Revised Protocol 07	16-Nov-2016	Incorporates Amendment(s) 13
Amendment 13	16-Nov-2016	• Updated Section 3.3.1 bullets d and e to clarify 5 half lives and converted weeks of contraception to months. • Updated Section 12 references • Updated Appendix 2 Algorithms for Management of Side Effects for Nivolumab Subjects to based upon updates to safety profile
Revised Protocol 06	15-Sep-2016	Incorporates Amendment(s) 10
Amendment 10	15-Sep-2016	• Removes efficacy interim analysis for superiority of the primary endpoint of OS • Updates sample size to 369 randomized subjects based on actual enrollment
Revised Protocol 05	23-Feb-2016	Incorporates Amendment(s) 09
Amendment 09	23-Feb-2016	The main purpose of this amendment is to modify the timing of interim (IA) and final (FA) analyses based on external data suggesting delayed separation of overall survival Kaplan-Meier curve and a long-lasting plateau at the end of survival curve. Timing of IA is based on achieving relatively high power (>75%) and ensuring that overall survival data is mature (~ 30% or less censoring for OS). Results from ipilimumab and nivolumab studies have demonstrated long term survival benefit in patients treated with immuno-oncology drugs observed as a long-lasting plateau towards the end of survival curve. Data from these studies have also suggested delayed effect observed as late separation of survival curves between experimental and treatment arms. Both long-term survival benefit and delayed onset of benefit may be attributed to immuno-oncology drugs based on their mechanism of action. Data from different immunotherapy compound supports this phenomenon in recurrent GBM population. As the original timing for the interim analysis (at 215 events) will be reached very shortly, this amendment should be implemented immediately, prior to receipt of IRB/IEC/HA approval. This amendment applies to all subjects enrolled.
[redacted]	[redacted]	[redacted]
Revised Protocol 04	27-Feb-2015	Incorporates Amendment(s) 07
Amendment 07	27-Feb-2015	• Increase sample size of Cohort by 120 subjects to 340 • Change from 2 planned interim analyses to a single interim analysis at 80% of the total number of events • Added clarification to allow collection of OS data outside the protocol specified windows
Revised Protocol 03	15-Aug-2014	Incorporate Amendment 05
Amendment 05	15-Aug-2014	[redacted] • Added clarification for allowing resection for assessment of progression/pseudoprogression

Document	Date of Issue	Summary of Change
		• Added central neruopathic review of tumor samples obtained after biopsy or resection in subjects for whom determination of progression versus pseudoprogression can not determined • Changed confirmation of progression to be 12 weeks rather than 8 weeks after initial radiologic progression for subjects who meet criteria for continuation of study treatment • Added table to summarize assessment of best overall response (BOR) • Combined site specific amendment for Cohort 1b into global protocol
Revised Protocol 02	15-Jul-2014	Incorporate Amendment 04 and Administrative Letter 01
Amendment 04	15-Jul-2014	• Updated title of protocol • Added selection of dose and study design for Cohort 2: Since evaluation of a second dosing regimen for the combination therapy is on-going, the randomized portion of this study (Cohort 2) will be limited to nivolumab monotherapy versus bevacizumab randomized in a 1:1 ratio. Study design, rationale for dose selection, study hypothesis, study objectives, and statistical considerations updated accordingly. • Added details for Cohort 1b (US sites only) • Clarified inclusion that required a measurable lesion at baseline is limited to Cohort 1 and 1b; • Clarified the interval of time after surgical resection to be ≥ 28 days for inclusion; • Clarified interval of time for baseline MRI to be 21 days instead of 28 days • Clarified exclusion of active, known or suspected autoimmune disease • Clarified exception to the exclusion of prior treatment with carmustine wafer to be limited to treatment administered as first line treatment and at least 6 months prior to randomization ; • Replaced exclusion of prior aspirin or clopidogrel or equivalent to be “use of anticoagulants that would place subject at significant risk for bleeding”; • Clarified guidance for continued treatment with nivolumab for subjects that discontinued combination nivolumab + ipilimumab • Clarified monitoring of glucose, amylase, and lipase following Grade 3 abnormalities [redacted] • Clarified assessment of best overall response (BOR)
[redacted]	[redacted]	[redacted]

Document	Date of Issue	Summary of Change
Revised Protocol 01	10-Dec-2013	Incorporate Amendment 01
Amendment 01	10-Dec-2013	• Adds 12-lead ECG at screening and as clinically indicated while on treatment; • Clarifies guidance regarding corticosteroid use during the study; • Includes guidance on the use of PPI or H2 blockers for patients on chronic steroids; • Excludes patients with a history of gastrointestinal diverticulitis. • Corrects inconsistencies in the statistical considerations section
Original Protocol	01-Nov-2013	Not applicable

SYNOPSIS

Clinical Protocol CA209143

Protocol Title: A Randomized Phase 3 Open Label Study of Nivolumab versus Bevacizumab and a Safety Study of Nivolumab or Nivolumab in Combination with Ipilimumab in Adult Subjects with Recurrent Glioblastoma (GBM)

(CheckMate 143: CHECKpoint pathway and nivoluMAb clinical Trial Evaluation 143)

Investigational Product(s), Dose and Mode of Administration, Duration of Treatment with Investigational Product(s):

- Nivolumab (BMS-936558) monotherapy administered IV over 60 minutes at 3 mg/kg every 2 weeks until progression or
- Nivolumab administered IV over 60 minutes at 1 mg/kg combined with ipilimumab administered IV over 90 minutes at 3 mg/kg every 3 weeks for 4 doses followed by nivolumab administered IV over 60 minutes at 3 mg/kg every 2 weeks until progression (Cohort 1 only) or
- Nivolumab administered IV over 60 minutes at 3 mg/kg combined with ipilimumab administered IV over 90 minutes at 1 mg/kg every 3 weeks for 4 doses followed by nivolumab administered IV over 60 minutes at 3 mg/kg every 2 weeks until progression (Cohort 1b only) or
- Bevacizumab monotherapy administered IV at 10 mg/kg every 2 weeks until progression (Cohort 2 only)

Study Phase: 3

Research Hypothesis: Treatment with nivolumab monotherapy will improve overall survival (OS) as compared with bevacizumab in subjects with first recurrence of glioblastoma (GBM) treated with prior radiotherapy and temozolomide (Cohort 2).

This study also includes two safety lead-in groups (Cohort 1 and 1b, selected US sites only) to evaluate the tolerability of nivolumab monotherapy and nivolumab in combination with ipilimumab. Enrollment to Cohort 2 (efficacy) will begin after the safety evaluation of nivolumab monotherapy of Cohort 1.

Objectives:

Primary Objectives:

Cohort 1 and 1b: To evaluate the safety and tolerability of nivolumab and nivolumab in combination with ipilimumab

Cohort 2: To compare the overall survival (OS) of nivolumab versus bevacizumab.

Secondary Objectives (Cohort 2):

- To compare the overall survival rate at 12 months (OS[12]) of nivolumab versus bevacizumab
- To compare progression free survival (PFS) of nivolumab versus bevacizumab
- To compare the objective response rate (ORR) of nivolumab versus bevacizumab

Exploratory Objectives: Exploratory objectives are listed in Section 1.3.3 of the protocol**.**

Study Design: This is a randomized, open-label, multicenter, phase 3 study of nivolumab monotherapy versus bevacizumab and a safety study of nivolumab and nivolumab in combination with ipilimumab therapy in adult (≥ 18 years) subjects with a first recurrence of glioblastoma (GBM). Subjects must have received previous first line treatment with radiotherapy and temozolomide. Since the use of nivolumab and ipilimumab has not previously been studied in subjects with GBM, a safety lead-in (Cohort 1) consisting of 20 subjects will be enrolled and randomized to treatment with either Arm N (nivolumab monotherapy) or Arm N+I (nivolumab combined with ipilimumab). The tolerability and safety assessment of each arm will occur after all randomized subjects have completed four doses or have discontinued dosing prior to completing four doses. In order to better characterize preliminary safety

and tolerability for the combination therapy, an additional, non-randomized safety cohort (Cohort 1b) to evaluate an alternate dosing regimen for the combination therapy (nivolumab 3mg/kg + ipilimumab 1 mg/kg every 3 weeks for 4 cycles followed by nivolumab 3 mg/kg thereafter) was initiated based on a site specific amendment to the protocol for selected US sites only. Information from Cohort 1 and Cohort 1b will provide a basis for dose selection for future studies in subjects with GBM.

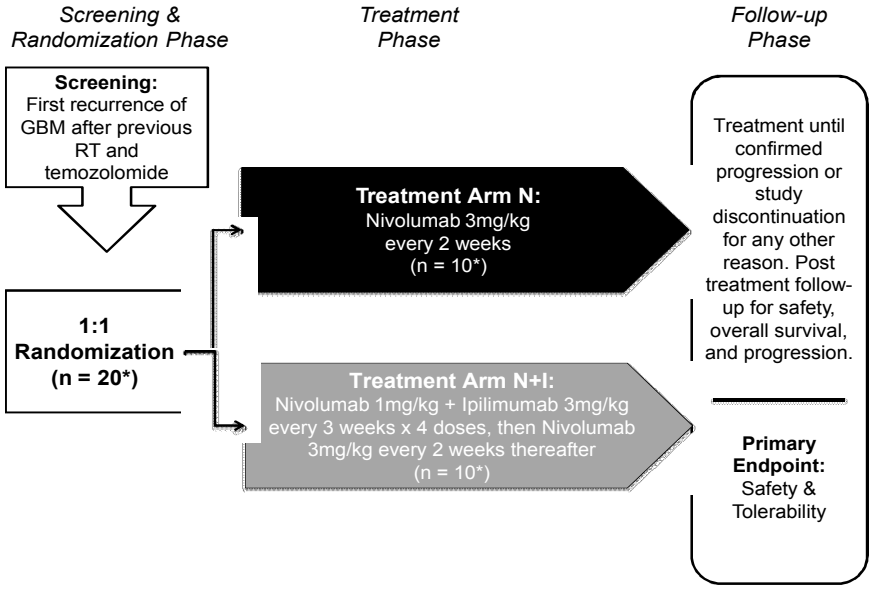
Enrollment in Cohort 2 was planned to begin after safety and tolerability of the safety lead-in had been evaluated and determination regarding which treatments arms (Arm N and/or Arm N+I) will be studied. Treatment with nivolumab monotherapy in Cohort 1 met the protocol prespecified safety and tolerability profile (less than one-third of subjects required permanent discontinuation due to treatment related adverse events prior to receiving 4 doses of treatment) to advance to Cohort 2, the randomized portion of the trial to compare nivolumab monotherapy versus bevacizumab. Since evaluation of a second dosing regimen for the combination therapy is on-going, the randomized portion of this study (Cohort 2) will be limited to nivolumab monotherapy versus bevacizumab. Evaluation of the efficacy of nivolumab+ipilimumab combination therapy will be evaluated separately, once there is sufficient data from Cohort 1 and Cohort 1b to select the appropriate dose to advance (either nivolumab 3 mg/kg + ipilimumab 1 mg/kg or nivolumab 1 mg/kg + ipilimumab 3 mg/kg) into a randomized study.

All subjects in Cohort 1, 1b, and 2 will be followed for safety and tolerability, tumor progression, and overall survival. Tumor progression or response endpoints will be assessed using the Radiologic Assessment in Neuro-Oncology (RANO) criteria. Treatment with study medication will continue until confirmed tumor progression, unacceptable toxicity, or other discontinuation criteria, whichever occurs first. A Data Safety Monitoring Committee will meet regularly during the study to ensure that subject safety is carefully monitored.

Figure 1: Study Design

Cohort 1 (selected US Sites only) – Safety Lead-In

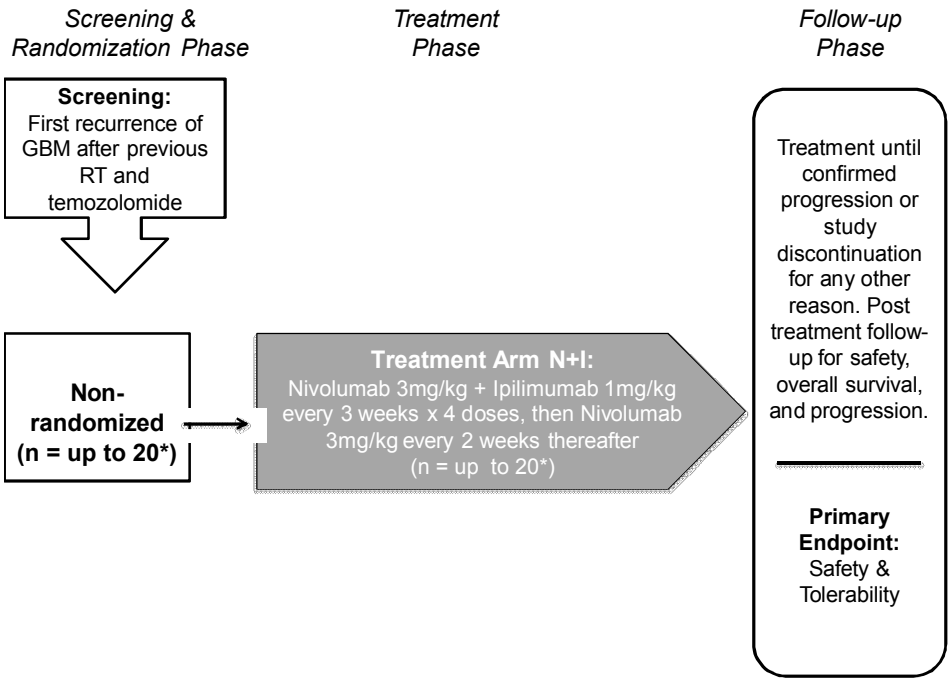
- Primary endpoint: Tolerability of N and N + I in subjects with recurrent GBM
- Demonstration of acceptable tolerability before advancing to Cohort 2



*Cohort 1 will randomize 20 subjects in a 1:1 fashion to assess the tolerability and safety of the investigational agents and suitability of advancing the treatment arms to Cohort 2, the randomized efficacy phase of the study (Section 3.1.1). The tolerability and safety assessment of each arm will occur after all subjects have completed four doses or have discontinued dosing prior to completing four doses.

Cohort 1b (selected US Sites only): Safety evaluation of combination of nivolumab 3mg/kg + ipilimumab 1mg/kg

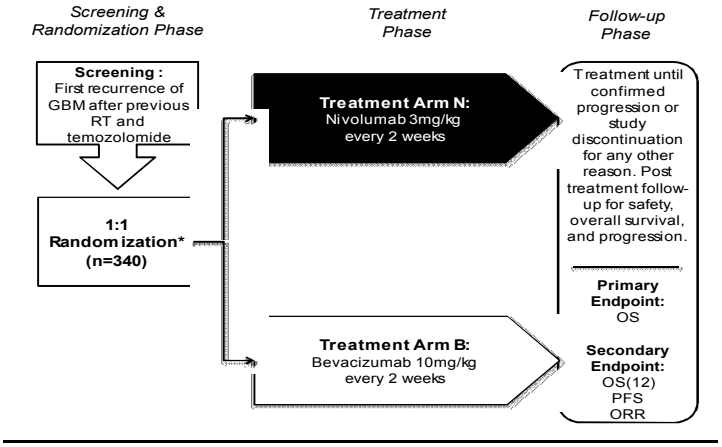
- Primary endpoint: Tolerability and safety of N+ I combination arm in subjects with recurrent GBM



*Cohort 1b will be non-randomized with up to 20 subjects treated at US sites only.

Cohort 2 – Randomized, 2-Arm: Safety and Efficacy

- Primary endpoint: Overall Survival; Secondary endpoints: OS(12), PFS, and ORR
- 1:1 Randomization



*Randomization will be stratified by presence of a measureable lesion at baseline (Y/N)

Study Population: Subjects must meet all eligibility criteria specified in Sections 3.3.1and 3.3.2 of the protocol, including the following:

Inclusion criteria:

a) Men and women, age ≥ 18 years old at the time of screening

b) Histologically confirmed diagnosis of World Health Organization Grade IV malignant glioma (glioblastoma or gliosarcoma)

c) Previous first line treatment with at least radiotherapy and temozolomide

d) Documented first recurrence of GBM by diagnostic biopsy or contrast enhanced magnetic resonance imaging (MRI) performed within 21 days of randomization per RANO criteria.

e) If first recurrence of GBM is documented by MRI, an interval of at least 12 weeks after the end of prior radiation therapy is required unless there is either: i) histopathologic confirmation of recurrent tumor, or ii) new enhancement on MRI outside of the radiotherapy treatment field

f) Karnofsky performance status of 70 or higher

Exclusion criteria:

a) More than one recurrence of GBM

b) Presence of extracranial metastatic or leptomeningeal disease

c) Subjects with active, known or suspected autoimmune disease. Subjects with vitiligo, type I diabetes mellitus, residual hypothyroidism due to autoimmune condition only requiring hormone replacement, psoriasis not requiring chronic and systemic immunosuppressive treatment, or conditions not expected to recur in the absence of an external trigger are permitted to enroll.

d) Previous bevacizumab or other VEGF or anti-angiogenic treatment (Cohort 2 only)

Study Assessments: The primary endpoint of Cohort 1 and 1b is tolerability and safety. The tolerability and safety assessment of each arm will occur after the last randomized subject has completed four doses or has discontinued dosing prior to completing four doses. The primary endpoint of Cohort 2 is overall survival (OS). Overall survival is defined as the time from randomization to the date of death from any cause. OS will be followed continuously while subjects are on the study drug and every 3 months via in-person or phone contact after subjects discontinue the study drug. All randomized subjects will be evaluated. Secondary endpoints for Cohort 2 are OS(12), PFS, and ORR. Subjects will be assessed for response by imaging (contrast enhanced MRI) beginning at end of week 6 and 12 and continuing every 8 weeks until disease progression is documented or treatment is discontinued (whichever occurs later). The RANO criteria will be used by the investigator to assess response and radiological progression.

Statistical Considerations:

Sample Size: In Cohort 1, a total of 20 subjects will be randomized to either nivolumab or nivolumab combined with ipilimumab in a 1:1 ratio. In Cohort 1b, up to 20 subjects will be treated with an alternative dosing regimen for the combination therapy of nivolumab and ipilimumab. Although the sample sizes are not based on statistical power considerations, data from these subjects will provide toxicity and dosing information on administration of nivolumab and nivolumab in combination with ipilimumab to subjects with recurrent GBM. The tolerability criteria described in the protocol used to advance to Cohort 2 will be based on drug-related adverse events leading to permanent discontinuation.

In Cohort 2, 369 subjects were randomized to the two treatment arms in a 1:1 ratio stratified by presence of a measurable lesion at baseline (yes/no).

Results from clinical trials in immunotherapies including Ipilimumab and Nivolumab have demonstrated long-term survival benefit in patients treated with immuno-oncology drugs observed as a long-lasting plateau towards the end of survival curve. Data from these studies have also suggested delayed effect observed as late separation of survival

curves between experimental and treatment arms. This may be attributed to the mechanism of action of immuno-oncology drugs.

Based on observations from these studies, following key assumptions are considered appropriate for this study design:

- 4- month delayed separation of OS curves between nivolumab and bevacizumab
- Bevacizumab Arm: OS follows exponential distribution with median of 9.2 months
- Nivolumab Arm: 10% "cure rate" (long-term survival) and exponential distribution with a median of 13.7 months after first four months for "non-cured" nivolumab subjects.

Final Analysis of OS will be conducted when at least 300 deaths have been observed among 369 randomized subjects. There will be no interim analysis for efficacy.

Given the observed accrual of 369 randomized subjects and survival assumptions stated above, simulations were conducted using piecewise exponential model for treatment group which closely approximates the assumed cure rate model for nivolumab. Based on these simulations, power at FA will be 92% based on this model.

In case target number of OS events is not met for FA 25 months after last patient is randomized, FA will be conducted. Follow-up of 25 months is considered ample for mature OS curve. Alpha will be adjusted appropriately to control overall type I error rate to 5%.

Endpoints: The primary endpoint of Cohorts 1 and 1b is tolerability and safety. The primary endpoint of Cohort 2 is overall survival (OS). The secondary endpoints for Cohort 2 are OS(12), PFS, and ORR. PFS and ORR will be determined by the investigator per RANO criteria. OS(12) will be measured by the Kaplan-Meier curve.

Analyses: In Cohort 2, the distribution of OS in all randomized subjects will be compared in arms N vs B. The Kaplan-Meier product-limit method will be used to estimate the survival curve in each arm, including medians and its 95% CI, OS rates at 6, 9, 12, and 18 months. The HR and the corresponding two-sided (1-adjusted α) % CIs will be estimated in a Cox proportional hazards model with treatment arm as a single covariate. Stratification factors will be the presence of a measurable lesion at baseline (yes/no) as entered into the IVRS.

The comparison of OS (12) will be based on a two-sided Z test. The comparison of PFS will be based on a two-sided log-rank test stratified by presence of a measureable lesion at baseline (yes/no). The comparison of ORR will be based on a two-sided Fisher's exact test. The detail of the testing procedure will be specified in the statistical analysis plan.

TABLE OF CONTENTS

1 INTRODUCTION AND STUDY RATIONALE

The purposes of this study are to: 1) evaluate the safety and tolerability of nivolumab and nivolumab in combination with ipilimumab in subjects diagnosed with recurrent glioblastoma (GBM) in a safety lead-in group (Cohort 1, 1b) and 2) to evaluate the safety, tolerability, and efficacy of nivolumab versus standard of care treatment (bevacizumab) in subjects diagnosed with recurrent GBM in a randomized trial (Cohort 2). It is predicted that nivolumab will improve overall survival (OS) as compared with bevacizumab in subjects with recurrent GBM previously treated with first line radiotherapy and temozolomide.

This is the first study examining monoclonal antibodies targeting immune checkpoint inhibitors in subjects with recurrent GBM. To ensure that nivolumab monotherapy and nivolumab in combination with ipilimumab is tolerable, a safety lead-in cohorts (Cohort 1, 1b) evaluating the tolerability of two different treatment regimens was initiated prior to advancing a treatment arm into Cohort 2. Cohort 1 (selected US sites only**)** examined in a randomized fashion, the safety and tolerability of nivolumab monotherapy dosed at 3 mg/kg every 2 weeks or nivolumab 1 mg/kg + ipilimumab 3 mg/kg every 3 weeks for four doses, then nivolumab 3mg/kg every 2 weeks thereafter. Cohort 1b (selected US sites only**)** examined, in a non-randomized fashion, the safety and tolerability of (nivolumab 3 mg/kg + ipilimumab 1 mg/kg every 3 weeks for four doses, then nivolumab 3mg/kg every 2 weeks thereafter). (Note: Cohort 1b was initiated after enrollment in Cohort 1 was completed via a site specific protocol amendment, now incorporated in the global protocol).

Treatment with nivolumab monotherapy in Cohort 1 met the protocol prespecified safety and tolerability profile (less than one-third of subjects required permanent discontinuation due to treatment related adverse events prior to receiving 4 doses of treatment) to advance to Cohort 2, the randomized portion of the study to compare nivolumab monotherapy versus bevacizumab. Since evaluation of a dosing regimen for the combination therapy is on-going in Cohort 1 and 1b, Cohort 2 was designed to evaluate nivolumab monotherapy versus bevacizumab. Evaluation of the efficacy of nivolumab+ipilimumab combination therapy will be evaluated separately, once there is sufficient data from Cohort 1 and Cohort 1b to select the appropriate combination dosing to advance into a randomized study.

Nivolumab dosing in Cohort 2 is based upon preliminary clinical experience in subjects with recurrent GBM from Cohort 1 and prior experience in the treatment of other tumor types (eg, melanoma). Subjects in the nivolumab arm will receive 3 mg/kg every 2 weeks, and subjects in the bevacizumab arm will be dosed at 10 mg/kg every 2 weeks. Subjects will continue to receive study medication until confirmed tumor progression, unacceptable toxicity, or other discontinuation criteria as described in Section 3.5, whichever comes first. Upon discontinuation of treatment, subjects will enter a follow-up phase to gather information on overall survival.

This study will also provide data regarding progression free survival, objective response rate, [redacted] Subjects in the combination arms who discontinue nivolumab + ipilimumab due to treatment related adverse events prior to completing

the fourth dose may begin nivolumab 3 mg/kg every 2 weeks with prior approval of the Sponsor (see Section 3.5).

1.1 Study Rationale

1.1.1 Summary of Investigational Agents

Immune checkpoint blockade is a rapidly advancing therapeutic approach in the field of immuno-oncology and treatment with investigational agents targeting this mechanism has induced regressions in several types of cancer. Cytotoxic T-lymphocyte–associated antigen 4 (CTLA-4) and programmed death 1 (PD-1) receptor are two important cellular targets that play complementary roles in regulating adaptive immunity. Whereas PD-1 contributes to T-cell exhaustion in peripheral tissues, CTLA-4 inhibits at earlier points in T-cell activation. In preclinical models, combined blockade of PD-1 and CTLA-4 achieved more pronounced antitumor activity than blockade of either pathway alone.[1]

Nivolumab (BMS-936558; anti-PD-1 monoclonal antibody) is a fully human monoclonal immunoglobulin (Ig) G4 antibody that binds to the PD-1 cell surface membrane receptor, a negative regulatory molecule expressed by activated T and B lymphocytes. Inhibition of the interaction between PD-1 and its ligands promote immune responses and antigen-specific T cell responses to both foreign and self antigens. PD-1 receptor blockade by nivolumab is a new approach for immunotherapy of tumors. Results from a Phase 1/2 study (CA209003)[2] indicate that nivolumab is active in multiple tumor types. Nivolumab 3 mg/kg monotherapy is currently being studied in phase 3 clinical trials in advanced melanoma, renal cell carcinoma (RCC) and non-small cell lung carcinoma (NSCLC).

Ipilimumab is a fully humanized IgG1 monoclonal antibody (mAb) binding to the anti-cytotoxic T-cell lymphoma-4 antigen (CTLA-4). Ipilimumab is an approved therapy for metastatic melanoma [Yervoy® Prescribing Information, 2011] and has demonstrated improved overall survival as monotherapy and in combination with dacarbazine.[3,4] Ipilimumab has been studied in combination with multiple standard of care (SOC) therapies including chemotherapy for squamous and non-squamous NSCLC and radiotherapy for hormone resistant prostate cancer.[5] Phase 3 studies are ongoing in NSCLC, small cell lung carcinoma (SCLC), and prostate carcinoma.

In vitro combinations of nivolumab plus ipilimumab increase IFN-γ production 2- to 7-fold over either agent alone in a mixed lymphocyte reaction. In a murine melanoma vaccine model, blockade with either CTLA-4 or PD-1 antibodies increased the proportion of CTLA-4 and PD-1-expressing CD4/CD8 tumor infiltrating T effector cells, and dual blockade increased tumor infiltration of T effector cells and decreased intratumoral T regulatory cells, as compared to either agent alone.[6]

In the Phase 1 dose escalation study CA209004, the combination of nivolumab and ipilimumab has been studied in subjects with unresectable or metastatic melanoma. In this study, a safe dose level for the combination of ipilimumab and nivolumab was established for the treatment of advanced melanoma. At this dose level, 3 mg/kg ipilimumab plus 1 mg/kg nivolumab, an

objective response rate of 53% was observed. This regimen is currently being studied in an ongoing global, randomized phase 3 study in advanced melanoma, CA209067.[7] The combination of nivolumab with ipilimumab is also currently being investigated in NSCLC (study CA209012)[8], and metastatic clear cell renal cell carcinoma (mRCC) (study CA209016[9]).

1.1.2 Background Information

Glioblastoma (GBM) is the most frequent primary brain tumor in adults and accounts for approximately 60 - 70% of all malignant gliomas.[10] The peak incidence of GBM occurs between 45 to 70 years of age and the tumors are more common in men (National Cancer Institute, 2010). GBMs are associated with a particularly aggressive clinical course with high morbidity and mortality. Despite standard first-line treatment with neurosurgery, radiation therapy (RT) and temozolomide, median survival is approximately 12 - 15 months and nearly all cases recur.[11]

Treatment options for recurrent GBM are complicated by side effects and limited efficacy. Therapies for recurrent GBM include repeated neurosurgical resection, radiation therapy, chemotherapy and supportive care. Repeated irradiation becomes more difficult and potential toxicity includes brain necrosis, progressive cerebral edema and persistent neurologic impairment.[12] As such, repeated irradiation to the brain is offered to a small minority of patients with recurrent GBM.[11] Nitrosureas, carboplatin, etoposide and irinotecan, or a combination of these agents are common salvage agents administered to recurrent GBM patients.[13,14,15,16,17,18] Bevacizumab, an anti-vascular growth factor (VEGF) mAb, was approved for the treatment of recurrent GBM in 2009. The approval for bevacizumab for recurrent GBM was based on two single arm clinical trials, AVF3708g and NCI 06-C-0064E. AVF3708g was an open label, multicenter, non-comparative, parallel group study, designed to evaluate the efficacy and safety of bevacizumab monotherapy and bevacizumab plus irinotecan in patients with previously treated glioblastoma. A total of 167 patients were enrolled (85 in the bevacizumab arm, 82 in the bevacizumab plus irinotecan arm). The efficacy of bevacizumab was demonstrated using response assessment based on WHO radiographic criteria. Responses were observed in 25.9% (95% CI:17.0%, 36.1%) of the patients. Median duration of response was 4.2 months (95% CI: 3.0, 5.7 months). The NCI06-C-0064E was a single arm, single site, NCI sponsored study of bevacizumab for patients with previously treated gliomas. A total of 56 patients with high-grade glioma were enrolled in this study. Objective responses observed in this study were 19.6% (95% CI; 10.9%, 31.3%), using the same response criteria as in AVF708g. Median duration of response observed was 3.9 months (95% CI: 2.4, 17.4).[19] Prior to the advent of antiangiogenic agents for GBM, few treatment options were available for recurrent GBM. Single agent irinotecan (CPT-11), a topoisomerase 1 inhibitor used in the relapsed setting, produces response rates of ≤ 15%. In recurrent GBM, PFS-6 rates typically range from 9% to 21%, and median OS is ≤ 30 weeks.[19]

There is an urgent need for novel treatment interventions to improve clinical outcomes and quality of life for patients suffering from GBM. Given the recent benefits in overall survival achieved with immunotherapeutics in melanoma and prostate cancer, researchers have posited

that immunotherapy approaches may offer promise in other difficult to treat cancers such as GBM.[20] Immunologic factors have clinically been associated with gliomas: a reduced risk of gliomas and longer survival is observed in patients with elevated IgE levels compared to those with normal levels.[21,22,23,24] In addition, immune checkpoint receptors such as program death-ligand (PD-L)1/B7-H1/CD274, a transmembrane receptor ligand and negative regulator of T-cell signaling, have been reported to be upregulated in gliomas.[25,26] Studies have also suggested an association between malignancy grade of astrocytic tumors and tumor cell PD-L1 expression.[27,28] Additionally use of an inhibitor of PD-L1 in mouse glioma models suggests benefit in combination with radiation therapy.[29]

Although the efficacy of check point inhibitors such as nivolumab and ipilimumab have not previously been studied in GBM, a multicenter Phase 2 study to evaluate the response of brain tumor metastases to ipilimumab was previously performed (CA184042). Subjects (N = 71) with advanced Stage IV melanoma and measureable active brain metastases were randomized to ipilimumab monotherapy. The study demonstrated that ipilimumab had clinical activity in subjects with melanoma brain metastases - with some subjects showing prolonged clinical responses, disease control, and prolonged survival (see Section 1.1.3). Ipilimumab did not cause unexpected neurological toxicity in subjects with brain metastases.

The mechanistic rationale supporting 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. The immune surveillance functions by aborting the emergence of tumors as they arise and/or causing tumor shrinkage. Tumor progression may depend upon acquisition of traits that allow cancer cells to evade immune surveillance and an effective immune response. This evasion may occur by exploiting any of the checkpoints that control the regulatory immune response, including display of antigens and control of costimulatory pathways that affect the proliferation of cells involved in immunity. 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 (either directly by stimulation of immune cells by antibodies directed to receptors on T and B cells or indirectly by cytokine manipulation). T-cell stimulation is a complex process involving the integration of numerous positive, as well as negative, costimulatory signals in addition to antigen recognition by the T-cell receptor (TCR). Collectively, these signals govern the balance between T-cell activation and tolerance to antigens.

Programmed death receptor-1 (PD-1, CD279), a 55 kD type I transmembrane protein, is a member of the CD28 family of T-cell costimulatory receptors that also includes CD28, CTLA-4, ICOS, and BTLA.2. PD-1 contains an intracellular membrane proximal immunoreceptor tyrosine inhibitory motif (ITIM) and a membrane distal immunoreceptor tyrosine-based switch motif (ITSM). Two ligands specific for PD-1 have been identified: PD-L1 (B7-H1/CD274) and PD-L2

(B7-DC/CD273). PD-L1 and PD-L2 have been shown to down-regulate T cell activation upon binding to PD-1 in both murine and human systems. PD-1 delivers a negative signal by the recruitment of SHP-2 to the phosphorylated tyrosine residue in the ITSM in its cytoplasmic region. PD-1 is primarily expressed on activated T cells, B cells, and myeloid cells. Further evidence for a negative regulatory role of PD-1 comes from studies of PD-1-deficient mice. PD1-deficient mice develop various autoimmune phenotypes, including dilated cardiomyopathy, a lupus-like syndrome with arthritis and nephritis, and accelerated diabetes mellitus. The emergence of these autoimmune phenotypes is dependent upon the genetic background of the mouse strain and many of these phenotypes emerge at different times and show variable penetrance. In addition to the phenotypes of null mutations, PD-1 inhibition by antibody-mediated blockade in several murine models has been found to play a role in the development of autoimmune diseases such as encephalomyelitis, graft-versus-host disease, and type I diabetes. Taken together, 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.

Preclinical animal models of tumors have shown that blockade by PD-1 by monoclonal antibodies (mAbs) can enhance the anti-tumor immune response and result in tumor rejection. Antitumor activity by PD-1 blockade functions in PD-L1-positive tumors as well as in tumors that are negative for the expression of PD-L1. This suggests that host mechanisms (ie, expression of PD-L1 in antigen-presenting cells) limit the antitumor response. Consequently, both PD-L1 positive and negative tumors may be targeted using this approach. In humans, constitutive PD-L1 expression is normally limited to macrophage-lineage cells, although expression of PD-L1 can be induced on other hematologic cells as well, including activated T cells. However, aberrant expression of PD-L1 by tumor cells has been reported in a number of human malignancies. PD-L1 expressed by tumor cells has been shown to enhance apoptosis of activated tumor-specific T cells in vitro. Moreover, the expression of PD-L1 may protect the tumor cells from the induction of apoptosis by effector T cells.

Based upon the mechanistic rationale discussed above and promising results from a preliminary clinical study (CA209004) using the combination of nivolumab and ipilimumab in subjects with unresectable or metastatic melanoma, CA209143 is the first study to examine the safety and efficacy of nivolumab as a single agent or in combination with ipilimumab in subjects with recurrent GBM.

1.1.3 Summary of Results from the Ipilimumab and Nivolumab Programs

1.1.3.1 Preclinical Summary of Nivolumab Combined with Ipilimumab

Preclinical data indicate that the combination of PD-1 and CTLA-4 receptor blockade may improve antitumor activity. In vitro combinations of nivolumab plus ipilimumab increase IFN-γ production 2- to 7-fold over either agent alone in a mixed lymphocyte reaction. Increased antitumor activity of the combination was also observed in 3 of 5 syngeneic murine cancer models. In a murine melanoma vaccine model, blockade with either CTLA-4 or PD-1 antibodies

increased the proportion of CTLA-4 and PD-1-expressing CD4/CD8 tumor infiltrating T effector cells, and dual blockade increased tumor infiltration of T effector cells and decreased intratumoral T regulatory cells, as compared to either agent alone.[30]

In a 4-week toxicity study of nivolumab in combination with ipilimumab conducted in cynomolgus monkeys demonstrated that the combination of nivolumab and ipilimumab resulted in dose-dependent gastrointestinal (GI) toxicity. Histologic findings included inflammatory changes in the large intestine, which increased in incidence and severity in a dose-dependent manner. GI toxicity/colitis was not observed in cynomolgus monkeys administered nivolumab alone, but was observed in monkeys receiving ipilimumab. Nivolumab in combination with ipilimumab was also associated with lymphoid hypocellularity of the cortex and/or medulla of the thymus and with acinar cell degranulation in the pancreas. Additional findings included interstitial mononuclear cell infiltrates in the kidneys, portal mononuclear cell infiltrates in the liver and myeloid hypercellularity in the bone marrow. Nivolumab in combination with ipilimumab at the high-dose level (ie, 50 mg/kg and 10 mg/kg, respectively) was associated with the death of 1 animal, attributed to acute gastric dilatation without histopathological evidence of colitis upon pathology evaluation of the GI tract.

1.1.3.2 Summary of Safety

Ipilimumab Monotherapy

Ipilimumab 3 mg/kg is globally approved for advanced melanoma based on the results of a phase 3 study, MDX010-20. In MDX010-20, the ipilimumab monotherapy arm was administered 3mg/kg ipilimumab every 3 weeks for four doses. In this arm, there were 79% drug related adverse events, with 21% being Grade 3/4 and 2% (3/131) Grade 5. The most frequent adverse events of interest were rash (30%), pruritus (33%), diarrhea (33%), colitis (8%), endocrine disorders (9%), AST/ALT increased (2%), and hepatitis (1%). Any grade immune related adverse events were 60% and the Grade 3/4 immune related adverse events for the same cohort was 13% with the most frequent adverse events being diarrhea (5%), colitis (5%), rash (2%), and endocrine disorders (3%).

Additional details on the safety profile of ipilimumab, including results from other clinical studies, are available in the ipilimumab Investigator Brochure (IB).

Nivolumab Monotherapy

CA209003 is an ongoing Phase 1 open label, multiple dose escalation study in 306 subjects with select previously treated advanced solid tumors, including melanoma, RCC, NSCLC, colorectal cancer, and hormone-refractory prostate cancer. Subjects received nivolumab at doses of 0.1, 0.3, 1, 3, or 10 mg/kg intravenously every 2 weeks, up to a maximum of 2 years of total therapy. As of 18-Mar-2013, a total of 306 melanoma subjects were treated with nivolumab in the dose range of 0.1 - 10 mg/kg.

No maximal tolerated dose was identified in CA209003. The incidence, severity and relationship of AEs were generally similar across dose levels and tumor types. Nivolumab related AEs of any grade occurred in 75.2% of subjects. Of the 306 treated subjects, 303 (99.0%) subjects have at

least 1 reported AE regardless of causality. The most frequently reported AEs were fatigue (54.9%), decreased appetite (35.0%), diarrhea (34.3%), nausea (30.1%), and cough (29.4%). Treatment-related AEs were reported in 230 (75.2%) of the 306 subjects. The most frequently reported treatment-related AEs were fatigue (28.1%), rash (14.7%), diarrhea (13.4%), and pruritus (10.5%). Most treatment-related AEs were low grade. Treatment-related high grade (Grade 3-4) AEs were reported in 52 (17.0%) of subjects. The most common treatment-related high grade AEs were fatigue (2.3%) and diarrhea (1%).

Drug-related SAEs occurred in 11.5% of subjects. Grade 3-4 drug-related SAEs reported in at least 2 subjects included: diarrhea (3 subjects, 1.0%), pneumonitis (3 subjects, 1.0%), pneumonia (2 subjects, 0.7%) and lipase increased (2 subjects, 0.7%).

Select AE categories (events with a potential inflammatory mechanism requiring more frequent monitoring and/or unique intervention such as immunosuppressants and/or endocrine replacement therapy) include: GI AEs, pulmonary AEs, renal AEs, hepatic AEs, skin AEs, and endocrinopathies. In addition, select AEs include a category for infusion reactions. Each category is composed of a discrete set of preferred terms, including those of greatest clinical relevance. These select AEs are considered events of interest based on the mechanism of action and were previously referred to as immune-related AEs or immune-mediated AEs.

The 10 mg/kg cohort had numerically greater frequency of high-grade select AEs including the subcategories of endocrinopathies, GI, pulmonary, and infusion reactions (Table 1.1.3.2-1). Most high grade events resolved following the treatment guidelines for the treatment of pulmonary events, GI events, hepatic events, renal events, and endocrine events, respectively.

Table 1.1.3.2-1: Treatment-related Select Adverse Events by Treatment - All CTC Grades Reported in at Least 10 Treated Subjects in CA209003

Preferred Term	0.1 mg/kg n=17		0.3 mg/kg n=18		1 mg/kg n=86		3 mg/kg n=54		10 mg/kg n=131		Total N=306	
	Any Grade	Grade 3-4	Any Grade	Grade 3-4	Any Grade	Grade 3-4	Any Grade	Grade 3-4	Any Grade	Grade 3-4	Any Grade	Grade 3-4
Any Select AE	**8 (47)**	**1 (5.9)**	**9 (50)**	**0**	**42 (49)**	**3 (4)**	**23 (43)**	**2 (4)**	**58 (44)**	**13 (10)**	**140 (46)**	**19 (6)**
Any Endocrinopathies	**4 (24)**	**0**	**2 (11)**	**0**	**9 (11)**	**0**	**4 (7)**	**0**	**10 (8)**	**3 (2)**	**29 (10)**	**3 (1)**
Endocrinopathies Thyroid	3 (18)	0	2 (11)	0	9 (11)		4 (7)	0	8 (6)	2 (2)	26 (9)	2 (1)
Blood TSH increased	2 (12)	0	1 (6)	0	2 (2)	0	2 (4)	0	4 (3)	1 (1)	11 (4)	1 (0.3)
Hypothyroidism	1 (6)	0	1 (6)	0	5 (6)	0	1 (2)	0	3 (2)	1 (1)	11 (4)	1 (0.3)
Any Skin AEs	**3 (18)**	**0**	**5 (28)**	**0**	**27 (31)**	**0**	**12 (22)**	**0**	**28 (21)**	**1 (1)**	**75 (25)**	**1 (0.3)**
Rash	3 (18)	0	3 (17)	0	20 (23)	0	5 (9)	0	14 (11)	0	45 (15)	0
Pruritus	0	0	1 (6)	0	15 (17)	0	3 (6)	0	13 (10)	1 (1)	32 (11)	1 (0.3)
Any GI AE	**1 (6)**	**0**	**2 (11)**	**0**	**19 (22)**	**0**	**7 (13)**	**0**	**14 (11)**	**3 (2)**	**43 (14)**	**3 (1)**
Diarrhea	1 (6)	0	2 (11)	0	19 (22)	0	6 (11)	0	13 (10)	3 (2)	41 (13)	3 (1)
Any hepatic AE	**0**	**0**	**2 (11)**	**0**	**8 (9)**	**0**	**3 (6)**	**2 (4)**	**5 (4)**	**2 (2)**	**18 (6)**	**4 (1)**
ALT increased	0	0	1 (6)	0	6 (7)	0	1 (2)	0	3 (2)	**1 (1)**	11 (4)	1 (0.3)
Any Pulmonary AE	1 (6)	**0**	1 (6)	**0**	**6 (7)**	**3 (4)**	**2 (4)**	**0**	**7 (5)**	**3 (2)**	**17 (6)**	**6 (2)**
Pneumonitis	1 (6)	0	1 (6)	0	4 (5)	2 (2)	1 (2)	0	6 (5)	2 (2)	12 (4)	4 (1)
Other Select AE	**0**	**0**	1 (6)	**0**	**3 (4)**	**0**	**3 (6)**	**0**	**8 (6)**	**2 (2)**	**15 (5)**	**2 (1)**
Infusion-related reaction	0	0	1 (6)	0	3 (4)	0	3 (6)	0	5 (4)	0	12 (4)	0

Abbreviations: ALT: alanine aminotransferase, TSH: thyroid stimulating hormone
Source: Preliminary data, MDX1106-03. Clinical data cut-off date: 18-Mar-2013

Treatment-related AEs leading to discontinuation were reported in 32 (10.5%) of the 306 treated subjects on CA209003. The most frequent of these were pneumonitis (8 subjects; 2.6%) and colitis (3 subjects; 1.0%).There were 3 (1%) drug related deaths; each occurred after development of pneumonitis.

The phase 3 dose for nivolumab monotherapy is 3 mg/kg. Additional details on the safety profile of nivolumab, including results from other clinical studies, are also available in the BMS-936558 (nivolumab) IB.

Nivolumab Combined with Ipilimumab

As of 15-Feb-2013, ascending doses of nivolumab have been studied as monotherapy in sequence with ipilimumab (N = 33) or in combination with ascending doses of ipilimumab (N = 53) in a Phase 1 study CA209004 of 86 subjects with unresectable or metastatic melanoma.

In the sequential cohorts, 1 mg/kg and 3 mg/kg nivolumab cohorts have been studied. Subjects were required to have prior ipilimumab and their last treatment must have occurred within 4 - 12 weeks. As such, based on ipilimumab pharmacokinetics, pharmacodynamically active ipilimumab was present at the outset of treatment in all subjects. Based on this, the monotherapy safety profile in the sequential cohorts was expected to differ from the monotherapy safety profile reported in CA209003. Therefore, the most relevant safety data for nivolumab monotherapy is from CA209003 (described above). The pooled safety data from CA209004 is only provided below for reference.

In each of the combination cohorts in this multi-arm study, ipilimumab was administered once every 3 weeks for 4 doses with nivolumab administered once every 3 weeks for 8 doses. Starting at week 24, ipilimumab and nivolumab were administered once every 12 weeks for 8 doses. The three initial dose escalation cohorts consisted of Cohort 1 (nivolumab 0.3 mg/kg plus ipilimumab 3 mg/kg; n = 14), Cohort 2 (nivolumab 1 mg/kg plus ipilimumab 3 mg/kg; n = 17) and Cohort 3 (nivolumab 3 mg/kg plus ipilimumab 3 mg/kg; n = 6). The study was subsequently amended to include Cohort 2a which evaluated nivolumab 3 mg/kg plus ipilimumab 1 mg/kg (n = 16). Safety data were pooled to summarize the overall findings.

At least one AE, regardless of whether they were attributed to the therapy, has been reported in 81 (94.2%) of the 86 subjects (Table 1.1.3.2-2). A numerically higher number of subjects in the combination therapy treatment groups experienced severe AEs, regardless of causality and treatment related, than those in the monotherapy treatment group.

In the combination treatment groups, the following DLTs were observed during the dose escalation in the combination cohorts:

- Cohort 1: Grade 3 elevated AST/ALT (1 subject);
- Cohort 2 : Grade 3 uveitis (1 subject) and Grade 3 elevated AST/ALT (1 subject);
- Cohort 3: Grade 4 elevated lipase (2 subjects) and Grade 3 elevated lipase (1 subject).

Based on these data, Cohort 2 was identified as the maximum tolerated dose (MTD) and Cohort 3 exceeded the MTD.

The most frequent treatment related AEs were rash (54.7%), pruritus (47.2%) and fatigue (37.7%). The most frequently reported treatment related severe AEs in the combination group were lipase and AST elevation (13.2% each), ALT elevation (11.3%), followed by diarrhea (5.7%) and rash (3.8%).

Treatment related serious adverse events (SAEs) were reported in 49% of patients in the combination treated subjects (N = 53) and were most frequently severe SAEs were: AST elevation (13.2%), ALT elevation (11.3%), lipase elevation (5.7%) and diarrhea, colitis and renal failure (3.8% each). Ten of the 53 (18.9%) treated subjects in the combination cohort discontinued therapy due treatment-related adverse events, the most frequent of which were ALT, AST elevation, lipase elevation, renal failure or pneumonitis. No drug-related deaths were reported.

Table 1.1.3.2-2: Summary of Adverse Events Reported in ≥ 10% of Subjects Treated with Nivolumab in Combination with Ipilimumab Compared to Sequential Nivolumab Monotherapy

	No. of Subjects (N)							
	Combination Therapy n=53				Sequential (Nivo Monotherapy) n=33			
	Regardless of Causality		Treatment-related		Regardless of Causality		Treatment-related	
Preferred Term	Any Grade	Grade 3-4	Any Grade	Grade 3-4	Any Grade	Grade 3-4	Any Grade	Grade 3-4
Any AE	**52 (98.1)**	**38 (71.7)**	**49 (92.5)**	**28 (52.8)**	**29 (87.9)**	**11 (33.4)**	**24 (72.7)**	**6 (18.2)**
Rash	32 (60.4)	3 (5.7)	29 (54.7)	2 (3.8)	7 (21.2)	0	3 (9.1)	0
Fatigue	31 (58.5)	0	20 (37.7)	0	12 (36.4)	14 (42.4)	3 (9.1)	0
Pruritus	28 (52.8)	1 (1.9)	25 (47.2)	0	6 (18.2)		6 (18.2)	0
Diarrhea	22 (41.5)	3 (5.7)	18 (34.0)	3 (5.7)	4 (12.1)	0	3 (9.1)	0
Cough	19 (35.8)	0	7 (13.2)	0	8 (24.2)	0	2 (6.1)	0
Nausea	19 (35.8)	1 (1.9)	11 (20.8)	0	6 (18.2)	0	1 (3.0)	0
Pyrexia	18 (34.0)	0	11 (20.8)	0	6 (18.2)	0	0	0
Headache	18 (34.0)	0	6 (11.3)	0	3 (9.1)	0	0	0
AST increased	13 (24.5)	8 (15.1)	11 (20.8)	7 (13.2)	1 (3.0)	0	0	0
Vomiting	13 (24.5)	3 (5.7)	6 (11.3)	1 (1.9)	1 (3.0)	0	0	0
ALT increased	12 (22.6)	7 (13.2)	11 (20.8)	6 (11.3)	1 (3.0)	0	1 (3.0)	0
Abdominal pain	11 (20.8)	0	5 (9.4)	0	1 (3.0)	1 (3.0)	0	0
Arthralgia	11 (20.8)	0	4 (7.5)	0	7 (21.2)	1 (3.0)	3 (9.1)	0
Lipase increased	11 (20.8)	9 (17.0)	10 (18.9)	7 (13.2)	4 (12.1)	2 (6.1)	4 (12.1)	2 (6.1)
Constipation	10 (18.9)	0	0	0	4 (12.1)	0	1 (3.0)	0
Back pain	9 (17.0)	0	0	0	4 (12.1)	0	0	0
Decreased appetite	9 (17.0)	0	5 (9.4)	0	3 (9.1)	0	1 (3.0)	0

Table 1.1.3.2-2: Summary of Adverse Events Reported in ≥ 10% of Subjects Treated with Nivolumab in Combination with Ipilimumab Compared to Sequential Nivolumab Monotherapy

	No. of Subjects (N)							
	Combination Therapy n=53				Sequential (Nivo Monotherapy) n=33			
	Regardless of Causality		Treatment-related		Regardless of Causality		Treatment-related	
Preferred Term	Any Grade	Grade 3-4	Any Grade	Grade 3-4	Any Grade	Grade 3-4	Any Grade	Grade 3-4
Dyspnea	9 (17.0)	1 (1.9)	3 (5.7)	0	3 (9.1)	1 (3.0)	0	0
Chills	9 (17.0)	0	3 (5.7)	0	2 (6.1)	0	0	0
Amylase increased	9 (17.0)	3 (5.7)	8 (15.1)	3 (5.7)	1 (3.0)	1 (3.0)	1 (3.0)	1 (3.0)
Pain in extremity	7 (13.2)	0	0	0	2 (6.1)	0	0	0

Abbreviations: AE: adverse event, ALT: alanine aminotransferase, AST: aspartate aminotransferase
Source: Preliminary data, MDX1106-04. Clinical cut-off date 15-Feb-2013.

Treatment-related AEs of Special Interest: A greater number of treatment-related select AEs including pulmonary AEs, GI AEs, hepatic AEs, endocrinopathy, skin AEs, renal AEs, and others, provided in Table 1.1.3.2-3, were reported in subjects treated with nivolumab + ipilimumab combination therapy than in sequential nivolumab monotherapy.

The most frequently reported treatment-related select AEs in the combination therapy group included rash, pruritus, diarrhea, AST increased, and ALT increased. With the exception of hepatic AEs, the events were reported were Grade 1-2. Isolated cases of pneumonitis and uveitis were observed, a finding that is consistent with previous experience with monotherapy.

The most frequently reported treatment-related select AEs in the monotherapy treatment group were pruritus, rash, and diarrhea; all were Grade 1-2.

Table 1.1.3.2-3: Summary of Treatment-related Events of Special Interest Reported in at Least 2 Subjects Treated with Nivolumab in Combination with Ipilimumab Compared to Sequential Nivolumab Monotherapy

	No. of Subjects (N)			
	Combination Therapy n=53		Sequential (Nivo Monotherapy) n=33	
Preferred Term	**Any Grade**	**Grade 3-4**	**Any Grade**	**Grade 3-4**
Any pulmonary AEs	**3 (5.7)**	**1 (1.9)**	**1 (3.0)**	**0**
Pneumonitis	3 (5.7)	1 (1.9)	1 (3.0)	0
Any GI AE	**20 (37.7)**	**5 (9.4)**	**3 (9.1)**	**0**
Colitis	5 (9.4)	2 (3.8)	0	0
Diarrhea	19 (35.8)	3 (5.7)	3 (9.1)	0
Any hepatic AE	**12 (22.6)**	**8 (15.1)**	**1 (3.0)**	**0**
ALT increased	11 (20.8)	6 (11.3)	1 (3.0)	0
AST increased	11 (20.8)	7 (13.2)	0	0
Any endocrinopathy	**7 (13.2)**	**1 (1.9)**	**3 (9.1)**	**1 (3.0)**
Adrenal insufficiency	2 (3.8)	0	1 (3.0)	1 (3.0)
Hyperthyroidism	2 (3.8)	0	0	0
Hypophysitis	2 (3.8)	1 (1.9)	2 (6.1)	1 (3.0)
Hypothyroidism	2 (3.8)	0	2 (6.1)	1 (3.0)
Thryoiditis	3 (5.7)	0	0	0
Any skin AE	**37 (69.8)**	**2 (3.8)**	**8 (24.2)**	**0**
Pruritus	25 (47.2)	0	6 (18.2)	0
Rash	29 (54.7)	2 (3.8)	3 (9.1)	0
Any Renal AE	**3 (5.7)**	**3 (5.7)**	**0**	**0**
Blood creatinine increased	3 (5.7)	3 (5.7)	0	0

Table 1.1.3.2-3: Summary of Treatment-related Events of Special Interest Reported in at Least 2 Subjects Treated with Nivolumab in Combination with Ipilimumab Compared to Sequential Nivolumab Monotherapy				
	No. of Subjects (N)			
	Combination Therapy n=53		Sequential (Nivo Monotherapy) n=33	
Preferred Term	Any Grade	Grade 3-4	Any Grade	Grade 3-4
Renal failure acute	2 (3.8)	2 (3.8)	0	0
Other	1 (1.9)	0	0	0
Infusion-related reaction	1 (1.9)	0	0	0

Abbreviations: AE: adverse event, ALT: alanine aminotransferase, AST: aspartate aminotransferase, ipi: ipilimumab, nivo: nivolumab

Source: Preliminary data, MDX1106-04. Clinical cut-off date 15-Feb-2013.

Adverse Event Management Algorithms

Because of the potential for clinically meaningful nivolumab or ipilimumab related AEs requiring early recognition and prompt intervention, management algorithms have been developed for suspected pulmonary toxicity, GI, hepatotoxicity, endocrinopathy, skin toxicity, neurological toxicity and nephrotoxicity. The algorithms recommended for utilization in CA209143 are contained in Appendix 2.

1.1.3.3 Summary of Clinical Activity

Ipilimumab Monotherapy

In melanoma, two completed Phase 3 studies have demonstrated clinically meaningful and statistically significant survival benefit in advanced melanoma. The completed Phase 3 study MDX010-20 demonstrated improved survival in pre-treated advanced melanoma. The study compared the overall survival (OS) of ipilimumab (3 mg/kg) plus a melanoma-specific vaccine (gp100) to that of gp100 alone. A second comparison defined the OS of ipilimumab alone vs gp100 alone. Both comparisons demonstrated statistically significant improvements in OS ($p = 0.0004$ and 0.0026, respectively). The median OS was 10, 10.1, and 6.4 months, for ipilimumab plus gp100, ipilimumab monotherapy, and gp100 monotherapy, respectively. The objective response rate was 5.7% (95% CI: 3.7, 8.4), 10.9% (95% CI: 6.3, 17.4), and 1.5% (95% CI: 0.2, 5.2) on the ipilimumab arm, the ipilimumab plus gp100 arm, and the gp100 arm, respectively.

The completed Phase 3 study CA184024 demonstrated improved survival in treatment-naive melanoma. The study compared the OS of ipilimumab (10 mg/kg) plus dacarbazine vs dacarbazine plus placebo. OS was improved in the ipilimumab plus dacarbazine group compared to the dacarbazine plus placebo group (11.2 months vs 9.1 months, respectively, HR 0.72, $p < 0.001$). The objective response rate was 15.2% on the ipilimumab plus dacarbazine arm compared to 10.3% on the dacarbazine plus placebo arm.

The approved ipilimumab regimen in advanced melanoma is 3 mg/kg ipilimumab monotherapy.

Nivolumab Monotherapy

In CA209003 (MDX1106-03), the clinical activity of nivolumab was demonstrated in a variety of tumor types and across a range of doses (0.1 mg/kg, 0.3 mg/kg, 1 mg/kg, 3 mg/kg, 10 mg/kg). As of the clinical cut-off date of 05-Mar-2013, a total of 306 subjects with melanoma, RCC, and NSCLC have been treated with nivolumab. All subjects initiated treatment at least one year prior to analysis. A response of either CR or PR, as determined by investigator assessed tumor evaluations based on modified RECIST 1.0, has been reported at all dose levels.

Among 107 patients with advanced melanoma who received nivolumab, the preliminary objective response rate was 33/107 (31%). Responses occurred at each dose level, with 6/17 (35%), 5/18 (28%), 11/35 (31%), 7/17 (41%), and 4/20 (20%) melanoma subjects responding at 0.1, 0.3, 1, 3, and 10 mg/kg, respectively. Duration of response range from 24.1 to 48.7+, 18.4 to 66.3+, 32.4 to 108.1+, 40.1+ to 115.4+, and 73.9 to 117.0+ months in melanoma subjects treated at 0.1, 0.3, 1, 3, and 10 mg/kg, respectively. An additional 7% of melanoma subjects had stable disease for 24 weeks or longer. Across dose levels, melanoma subjects achieved a median overall survival of 16.8 months (95% CI: 12.5, 31.6), with a 2-year overall survival rate of 43%.

Nivolumab Combined with Ipilimumab

As of 15-Feb-2013, in the combination cohorts of CA209004, ipilimumab was administered once every 3 weeks for 4 doses with nivolumab administered once every 3 weeks for 8 doses. Starting at week 24, ipilimumab and nivolumab were administered once every 12 weeks for 8 doses. The three initial dose-escalation cohorts consisted of Cohort 1 (nivolumab 0.3 mg/kg plus ipilimumab 3 mg/kg; n = 14), Cohort 2 (nivolumab 1.0 mg/kg plus ipilimumab 3 mg/kg; n = 17) and Cohort 3 (nivolumab 3.0 mg/kg plus ipilimumab 3 mg/kg; n = 6). Later, the study was amended to include Cohort 2a which evaluated nivolumab 3 mg/kg plus ipilimumab 1 mg/kg (n = 15).

In the combination cohorts, across all dose levels (N = 53), confirmed objective responses according to modified WHO criteria were observed in 21 of 52 patients (40%; 95% CI, 27 to 55) who had a response that could be evaluated. In addition, 4 patients had an objective response according to immune-related response criteria and 2 had an unconfirmed partial response. These patients were not included in the calculation of objective response rates. In the 1 mg/kg nivolumab + 3 mg/kg ipilimumab group, the ORR was 53% (see Table 1.1.3.3-1)

Table 1.1.3.3-1: Objective Response Rate and Progression Free Survival 24 Weeks Rate in Melanoma Subjects - MDX1106-04						
Treatment Group[a]	**Nivo Dose (mg/kg)**	**N**	**ORR**	**95% CI of ORR**	**PFS at 24 weeks (%)**	**95% CI of PFS**
Nivo + 3 Ipi	0.3	14	3 (21)	5 - 51	43	17 - 69
Nivo + 3 Ipi	1.0	17	9 (53)	28 - 77	58	34 - 82
Nivo + 1 Ipi	3.0	15	6 (40)	16 - 68	59	26 - 92
Nivo + 3 Ipi	3.0	6	3 (50)	12 - 88	50	10 - 90

[a] Subjects received ipilimumab immediately prior to study entry, within 4 - 12 weeks of initiating nivolumab monotherapy on the protocol.

Abbreviations: CI: confidence interval, Ipi: ipilimumab, Nivo: nivolumab, ORR: objective response rate, PFS: progression-free survival

Source: Preliminary data, MDX1106-04. Clinical cut-off date 15-Feb-2013.

After noting that several patients had very deep responses (approaching complete response), a post hoc analysis of the number of patients with tumor reduction of 80% or more was done. This depth of response was uncommon in published studies of ipilimumab or nivolumab.[31,32] A total of 16 out of 52 evaluable patients had tumor reduction of 80% or more at 12 weeks, including 5 with a complete response.

In the combination cohorts, overall evidence of clinical activity (conventional, unconfirmed, or immune-related response or stable disease for ≥ 24 weeks) was observed in 65% of patients (95% CI, 51 to 78). Responses were ongoing in 19 of 21 patients who had a response, with the duration ranging from 6.1 to 72.1 weeks at the time of data analysis.[33]

1.1.3.4 Summary of Clinical Trial Experience with Ipilimumab in Brain Metastases

CA184042 evaluated ipilimumab monotherapy (ipilimumab 10 mg/kg) among subjects with advanced Stage IV melanoma and active brain metastases. Measurable lesions in the brain were required for enrollment into this trial, so that CNS-specific efficacy and safety of ipilimumab could be assessed. The primary endpoint of the study was disease control rate (DCR) by mWHO. However, in addition to mWHO, the immune related response (irRC) criteria were used to facilitate capture of response beyond progression (by mWHO). Subjects in this study were classified by treatment arm based on whether or not they were corticosteroid free (Arm A) or corticosteroid dependent (Arm B). In this way, the study was designed to capture response data (both in brain and non-CNS lesions) in subjects who were and were not receiving concurrent treatment with high doses of corticosteroid (to reduce tumor-related edema). Ipilimumab has an indirect mechanism of action which augments T-cell immunity and may result in tumor volume increase in some patients before objective response. Since tumor volume increase may precede an objective response, subjects with brain metastases could be at risk for additional CNS complications. Therefore, in order to elucidate the risk of ipilimumab administration in subjects

with brain metastases, a secondary endpoint of the study was to characterize CNS-specific AEs as a part of the overall safety assessment.

The primary endpoint, global DCR by mWHO criteria, was 17.6% (9 or 51 treated subjects) in the corticosteroid-free Arm A and 4.8% (1 of 21 treated subjects) in the corticosteroid-dependent Arm B. Objective response (all PR) was observed in 5 (9.8%) out of 51 subjects in Arm A and 1 (4.8%) out of 21 subjects in Arm B. The best objective response rate in the brain was comparable to that observed in the non-CNS compartment, suggesting that ipilimumab treatment of patients with melanoma can induce clinical activity in the CNS. The duration of response observed in Arm A (median of 10.4 months both by mWHO and irRC) was consistent with that observed in other ipilimumab studies and longer than observed for other therapies commonly used to treat brain metastases in patients with melanoma metastatic to the brain: temozolomide (median duration of response = 2 months).

The OS rates observed in Arm A of this study (26% at year-2) is consistent with survival data observed in other ipilimumab monotherapy (10 mg/kg) studies, and appear favorable to the survival recorded in historical studies where 2-year survival is approximately 10%.[25] Cross-study comparisons should be interpreted with caution, due to its retrospective nature and due to the fact that the population of the two studies may be meaningfully different (corticosteroid in-dependent versus. all comers, respectively). Consistency of the CA184042 results with comparable Phase 2 studies suggests that patients with brain metastases from metastatic melanoma may similarly benefit from ipilimumab as do patients without brain metastases. Interpretation of OS in corticosteroid-dependent subjects is complicated by their poor prognosis at the start of ipilimumab treatment and the possibility that the use of steroids may interfere with ipilimumab efficacy. Nevertheless, survival at 2 years was observed in 2 out of 21 corticosteroid-dependent subjects (Arm B).

A total of 55 subjects died, almost all with a primary cause of disease. One subject in Arm A died due to study drug toxicity. SAEs (any grade and regardless of causality) were reported for 36 subjects (70.6%) in Arm A and 16 subjects (76.2%) in Arm B. The most frequently reported SAE (all grades) was disease progression observed in 16 subjects (31.4%) in Arm A and 10 subjects (47.6%) in Arm B. The other frequently reported SAEs (any grade) were diarrhea in Arm A (7 subjects, 13.7%) and convulsions in Arm B (3 subjects, 14.3%). Adverse events, regardless of causality and intensity, were reported for 50 subjects (98.0%) in Arm A and 21 subjects (100.0%) in Arm B. The most common Grade 3-4 AEs reported for subjects in Arm A included diarrhea and fatigue, each occurring in 6 subjects (11.8%). Drug-related AEs (any grade) leading to discontinuation were reported for 6 subjects (11.8%) in Arm A and for 3 subjects (14.3%) in Arm B. One subject in Arm A discontinued treatment due to ipilimumab-related CNS symptoms (cerebral hemorrhage).

There was a higher frequency of irAEs (regardless of etiology or intensity) reported for Arm A (34 subjects, 66.7%) compared to Arm B (13 subjects, 61.9%), as well as a higher frequency of Grade 3 irAEs reported for Arm A (12 subjects [23.5%] in Arm A and 2 subjects [9.5%] in Arm B). There were no reported events of Grade 4 or 5. The presence of corticosteroids in subjects in Arm B as well as the lower median number of doses (3 in Arm A vs 2 in Arm B) due

to rapidly progressing disease, as well as the low sample size may be contributing factors to these observations. The most frequently reported irAEs were those affecting the GI tract (diarrhea) and skin (rash and pruritus).

The safety profile of ipilimumab observed in CA184042 was consistent with the safety profile of ipilimumab observed in subjects with similar stages of disease but without brain metastases.14 Ipilimumab-related central neurologic AEs (any grade) were reported in 7 (13.7%) subjects in Arm A and 2 (9.5%) subjects in Arm B. The use of ipilimumab in subjects with brain metastases did not appear to induce unexpected neurological toxicity.

Overall, administration of ipilimumab in CA184042 demonstrated clinical activity in subjects with melanoma brain metastases - with prolonged clinical responses, disease control, and prolonged survival, in some subjects. 2-year survival rates for corticosteroid-independent subjects (Arm A) in the context of historical data, eg,, subjects treated at the same dose of ipilimumab, are favorable. Ipilimumab did not cause unexpected neurological toxicity in subjects with brain metastases.

1.1.4 Rationale to Support Dose/Schedule of Nivolumab Combined with Ipilimumab

In CA209004, the 3 mg/kg nivolumab plus 3 mg/kg ipilimumab dosing regimen exceeded the maximum tolerated dose per protocol. In CA209004, while both Cohort 2 (1 mg/kg nivolumab plus 3 mg/kg ipilimumab) and Cohort 2a (3 mg/kg nivolumab plus 1 mg/kg ipilimumab) had similar Week 24 PFS rate, a dose of 3 mg/kg of ipilimumab every 3 weeks for a total of four doses and 1 mg/kg nivolumab every 3 weeks for four doses followed by nivolumab 3 mg/kg every 2 weeks until progression was chosen. Based on preliminary data, this group had a numerically higher ORR than Cohort 2a, although the significance of this difference is not clear.

The rationale for maximizing the ipilimumab dose over the nivolumab dose is primarily based on a well defined dose and exposure response for ipilimumab (10 mg/kg > 3 mg/kg > 0.3 mg/kg). In contrast, analysis of nivolumab monotherapy across dose ranges of 1 mg/kg to 10 mg/kg reveals similar clinical activity with no clear evidence of dose or exposure response. Therefore, the selection of 3 mg/kg of ipilimumab (Cohort 2) may be more clinically impactful than selection of 3 mg/kg of nivolumab (Cohort 2a).

Based on the clinical activity in CA209004, the majority of responses to the combination of nivolumab and ipilimumab occur in the first 12 weeks. Nivolumab 3 mg/kg monotherapy treatment every two weeks until progression was studied in CA209003 and was associated with durable responses. Thus starting at week 12, which is after the completion of the four doses of combined nivolumab and ipilimumab, nivolumab at 3 mg/kg will be administered every two weeks until confirmed tumor progression, unacceptable toxicity, or other discontinuation criteria, whichever occurs first.

Study CA209143 will use the same dose and schedule as that in Cohort 2 of CA209004 for the first 12 weeks (nivolumab 1 mg/kg plus ipilimumab 3 mg/kg) followed by nivolumab 3 mg/kg every 2 weeks until confirmed tumor progression, unacceptable toxicity, or other discontinuation criteria, whichever occurs first. This is the same regimen currently being studied in the

phase 3 study in advanced melanoma, CA209067 and in ongoing studies in RCC and NSCLC. In CA209067 and in this current protocol, ipilimumab will be limited to 4 doses in the first 12 weeks since this is the currently approved dosing regimen.

To ensure that nivolumab monotherapy and nivolumab in combination with ipilimumab is tolerable, a safety lead-in cohorts (Cohort 1 and 1b) evaluating the tolerability of both treatment regimens were to be completed prior to the start of Cohort 2. Approximately 20 subjects were enrolled and randomized to treatment with either Arm N (nivolumab monotherapy) or Arm N+I (nivolumab 1 mg/kg combined with ipilimumab 3mg/kg). In Cohort 1b, up to 20 subjects will be treated to treatment Arm N+I_1b (nivolumab 3 mg/kg combined with ipilimumab 1mg/kg). The criteria for determining tolerability are provided in Section 3.1.1.

In order to better characterize preliminary safety and tolerability for the combination therapy, an additional, non-randomized safety cohort (Cohort 1b) to evaluate an alternate dosing regimen for the combination therapy (nivolumab 3 mg/kg + ipilimumab 1 mg/kg every 3 weeks for 4 cycles followed by nivolumab 3 mg/kg thereafter) was initiated based on a site specific amendment to the protocol for selected US sites. This dosing regimen is currently being studied in two ongoing clinical trials in lung and renal cell cancer (CA209012, CA209016), and has demonstrated an acceptable AE profile to date. Information from subjects treated with combination therapy in Cohort 1 and Cohort 1b will provide a basis for dose selection for future studies in subjects with GBM.

Treatment with nivolumab monotherapy in Cohort 1 met the protocol prespecified safety and tolerability profile (less than one-third of subjects required permanent discontinuation due to treatment related adverse events prior to receiving 4 doses of treatment) to advance to Cohort 2, the randomized portion of the study to compare nivolumab monotherapy versus bevacizumab. Since evaluation of a second dosing regimen for the combination therapy is on-going, the randomized portion of this study (Cohort 2) will be limited to nivolumab monotherapy versus bevacizumab. Evaluation of the efficacy of nivolumab+ipilimumab combination therapy will be evaluated separately, once there is sufficient data from Cohort 1 and 1b to select the appropriate combination dose to advance into a randomized study (either nivolumab 3 mg/kg + ipilimumab 1 mg/kg or nivolumab 1 mg/kg + ipilimumab 3 mg/kg).

1.1.5 Rationale for Permitting Continued Treatment in Cases of Suspected Progressive Disease

Accumulating clinical evidence indicates some subjects treated with immune system stimulating agents may develop progression of disease (by conventional response criteria) before demonstrating clinical objective responses and/or stable disease. This phenomenon was observed in approximately 10% of subjects in the Phase 1 study of nivolumab and has also been reported for ipilimumab monotherapy.[34] Two hypotheses have been put forth to explain this phenomenon. First, enhanced inflammation within tumors could lead to an increase in tumor size which would appear as enlarged index lesions and as newly visible small non-index lesions. Over time, both the malignant and inflammatory portions of the mass may then decrease leading to overt signs of clinical improvement. Alternatively, in some individuals, the kinetics of tumor growth may

initially outpace anti-tumor immune activity. With sufficient time, the anti-tumor activity will dominate and become clinically apparent. Therefore, subjects initially meeting radiologic criteria for disease progression (see Section 5.4.2) will be allowed to continue study therapy until a second radiologic confirmation of progression performed approximately 12 weeks later as long as the following criteria are met: 1) the subject experiences investigator-assessed clinical benefit and 2) the subject is tolerating the study treatment.

For the purposes of this protocol, tumor response will be based upon the Radiologic Assessment in Neuro-Oncology (RANO) criteria[35] described in Section 5.4.2.

[redacted]

1.1.8 Rationale for Investigational Treatment Arm for Cohort 2

At the completion of the Cohort 1 safety lead-in the protocol was amended to reflect the determination of the treatment arms for Cohort 2. The tolerability criteria used to advance to Cohort 2 was based on drug related adverse events leading to permanent discontinuation (listed in Section 4.3.5) and included the following:

- If no more than one-third of the subjects in a given treatment arm permanently discontinue study medication prior to completing four doses due to treatment related adverse events then this dose cohort will be deemed as tolerable and enrollment in Cohort 2 may proceed.
- If more than one-third of subjects in a treatment arm permanently discontinue study medication prior to completing four doses due to treatment-related adverse events, then the safety and tolerability of that treatment arm will be reviewed with the DMC prior to randomizing any additional subjects. A decision will be made by the sponsor whether to continue enrollment or advance either treatment arm into Cohort 2.

Treatment with nivolumab monotherapy in Cohort 1 met the protocol prespecified safety and tolerability profile to advance to Cohort 2, the randomized portion of the study to compare nivolumab monotherapy versus bevacizumab. Since evaluation of a second dosing regimen for the combination therapy is on-going, the randomized portion of this study (Cohort 2) will be limited to nivolumab monotherapy versus bevacizumab. Evaluation of the efficacy of nivolumab+ipilimumab combination therapy will be evaluated separately, once there is sufficient data from Cohort 1 and Cohort 1b to select the appropriate combination dose to advance (either nivolumab 3 mg/kg + ipilimumab 1 mg/kg or nivolumab 1 mg/kg + ipilimumab 3 mg/kg).

1.2 Research Hypothesis

Treatment with nivolumab monotherapy will improve overall survival (OS) as compared with bevacizumab in subjects with first recurrence of glioblastoma (GBM) treated with prior radiotherapy and temozolomide (Cohort 2).

This study also includes two safety lead-in groups (Cohort 1 and 1b, selected US sites only) to evaluate the tolerability of nivolumab monotherapy and nivolumab in combination with ipilimumab. Enrollment to Cohort 2 (efficacy) will begin after the safety evaluation of nivolumab monotherapy of Cohort 1.

1.3 Objectives(s)

1.3.1 Primary Objectives

Cohort 1 and 1b (Safety Lead-in):

- To evaluate the safety and tolerability of nivolumab and nivolumab in combination with ipilimumab

Cohort 2:

- To compare the overall survival (OS) of nivolumab versus bevacizumab.

1.3.2 Secondary Objectives (Cohort 2)

- To compare the overall survival rate at 12 months (OS[12]) of nivolumab versus bevacizumab
- To compare progression free survival (PFS) of nivolumab versus bevacizumab
- To compare the objective response rate (ORR) of nivolumab versus bevacizumab

1.3.3 Exploratory Objectives

- To evaluate progression free survival (PFS) and objective response rate (ORR) of nivolumab and nivolumab in combination with ipilimumab (Cohort 1 and 1b)
- To evaluate the safety of nivolumab and bevacizumab (Cohort 2, only)

[redacted]

[redacted]

- To describe steroid sparing effects in glioblastoma subjects treated with nivolumab, nivolumab plus ipilimumab, or bevacizumab)

[redacted]

1.4 Product Development Background

As of Mar-2013, approximately 723 subjects have been treated with nivolumab in completed and ongoing phase 1-2 studies assessing pharmacokinetics (PK), clinical activity, and safety. Nivolumab is currently being studied in multiple Phase 3 studies in squamous and non-squamous non-small cell lung cancer (NSCLC), malignant melanoma, and renal (clear) cell carcinoma (RCC). Nivolumab is being investigated both as monotherapy and in combination with chemotherapies and other immunotherapies.

Ipilimumab is an approved therapy for metastatic melanoma[36] and has demonstrated improved overall survival as monotherapy and in combination with dacarbazine.[3,4] An extensive clinical development program for ipilimumab, encompassing more than 12,700 subjects in several cancer types in completed and ongoing studies, as well as a compassionate use program have been conducted. Ipilimumab has been studied in combination with multiple standard of care (SOC) therapies including chemotherapy for squamous and non-squamous NSCLC and radiotherapy for hormone resistant prostate.[5] Phase 3 studies are ongoing in NSCLC, SCLC, and prostate carcinoma.

Please refer to the Nivolumab and Ipilimumab Investigator Brochure for additional information.

1.5 Overall Risk/Benefit Assessment

GBM is a particularly invasive and aggressive brain tumor with high mortality and morbidity despite current treatments. Adverse sequelae associated with repeated brain tissue resection and radiation therapy in subjects with recurrent GBM further complicates the management of this tumor type. The significant unmet clinical need for subjects and preclinical data suggesting involvement of immunologic factors in GBM disease course (see Study Rationale 1.1) support the investigation of checkpoint inhibitors for therapeutic potential.

Nivolumab monotherapy has demonstrated clinical activity across several tumor types, including advanced melanoma, NSCLC, and RCC. Nivolumab has demonstrated a manageable safety profile in patients > 700 subjects across all clinical trials. The most common AEs included fatigue, rash, pruritus, diarrhea, and nausea. The AE profile for nivolumab monotherapy does not appear to be dose dependent and appears to be similar across a range of solid tumors studied.

Ipilimumab 3 mg/kg is approved for use in the US (advanced melanoma) and in the EU (for previously treated advanced melanoma) based on overall survival benefit in randomized trials. Furthermore, clinical activity with ipilimumab has been observed in subjects with NSCLC, SCLC, and prostate carcinoma. The efficacy of ipilimumab in these tumor types is being investigated in ongoing phase 3 studies. The currently approved dose for ipilimumab in

melanoma subjects is 3 mg/kg every 3 weeks for up to 4 doses. Ipilimumab has demonstrated a manageable safety profile and treatment guidelines for immune related adverse events are established based on > 12,000 subjects treated in clinical trials.

The combination of nivolumab and ipilimumab has the potential for increased benefit compared to both ipilimumab monotherapy and nivolumab monotherapy. In Study CA209004, 53% of the subjects with advanced melanoma treated at the dose level of nivolumab 1 mg/kg combined with ipilimumab 3 mg/kg had an objective response, the majority of which had deep tumor reduction of 80% or more. This deep response compares favorably to results with 3 mg/kg ipilimumab monotherapy or nivolumab monotherapy and is the basis for an ongoing randomized phase 3 study in advanced melanoma (CA209067). Studies investigating the efficacy and safety of nivolumab in combination with ipilimumab are ongoing in NSCLC and RCC.

The combination of nivolumab and ipilimumab also has the potential for increased frequencies of adverse events compared to ipilimumab monotherapy or nivolumab monotherapy. The most common (reported at > 10% incidence) treatment related AEs are fatigue, rash, pruritus, diarrhea, lipase increased, pyrexia, ALT increase, AST increased, amylase increased and vitiligo. This class of AEs is expected for the combination of nivolumab and ipilimumab based on the known AE profile of each drug alone. In addition, many of the Grade 3-4 adverse events were laboratory in nature (ie LFTs, lipase, amylase), were without clinical sequalae and have been manageable and reversible following intervention dose delays or with systemic steroid treatment. However, these AEs have the potential to be fatal if not detected early and managed per the established algorithm and fatal AEs have been reported for both ipilimumab and nivolumab monotherapy. As of June 2013, one subject died because of a study treatment related adverse event (toxic epidermal necrolysis, TEN) in the nivolumab + ipilimumab development program. Fatal TEN has previously been reported for ipilimumab monotherapy.

Across multiple tumors, 3 mg/kg nivolumab monotherapy has demonstrated a tolerable AE profile in hundreds of subjects and that appears to be independent of tumor type. The combination of 1 mg/kg nivolumab + 3 mg/kg ipilimumab has demonstrated an acceptable AE profile in melanoma and is currently in phase 3. The same regimen is currently being studied in RCC and NSCLC. The combination of 3 mg/kg nivolumab + 1 mg/kg ipilimumab has also demonstrated an acceptable AE profile and is currently being studied in two ongoing clinical trials in lung and renal cell cancer (CA209012 and CA209106). The following safety measures have been employed to ensure safety of the subjects in this current study:

- Initial safety lead-in cohorts to establish the safety and tolerability of the investigational agents in subjects with recurrent GBM before proceeding to Cohort 2
- Toxicity monitoring will help to ensure the subjects' safety in Study CA209143, including frequent safety conference calls during safety lead-in cohorts with investigators and representatives of the sponsor.
- A BMS medical safety team (MST) routinely reviews safety signals across the entire nivolumab program, including all ongoing combinations with ipilimumab.
- Regular or ad hoc safety and efficacy reviews by an independent DMC (Section 7)

In conclusion, the overall risk-benefit assessment for Study CA209143 justifies the conduct of the study. The study aims to compare the overall survival of nivolumab versus bevacizumab in a Phase 3 randomized, open-label study in subjects with recurrent GBM. Evaluating nivolumab monotherapy versus bevacizumab in subjects with recurrent GBM will also potentially generate efficacy signals as a basis for a further clinical development earlier in the treatment of GBM. In addition, the study will provide information about the safety and tolerability of two dosing regimens nivolumab in combination with ipilimumab to provide a basis for dose selection for future studies in subjects with GBM.

2 ETHICAL CONSIDERATIONS

2.1 Good Clinical Practice

This study will be conducted in accordance with Good Clinical Practice (GCP), as defined by the International Conference on Harmonisation (ICH) and in accordance with the ethical principles underlying European Union Directive 2001/20/EC and the United States Code of Federal Regulations, Title 21, Part 50 (21CFR50).

The study will be conducted in compliance with the protocol. The protocol and any amendments and the subject informed consent will receive Institutional Review Board/Independent Ethics Committee (IRB/IEC) approval/favorable opinion prior to initiation of the study.

All potential serious breaches must be reported to BMS immediately. A serious breach is a breach of the conditions and principles of GCP in connection with the study or the protocol, which is likely to affect, to a significant degree, the safety or physical or mental integrity of the subjects of the study or the scientific value of the study.

Personnel involved in conducting this study will be qualified by education, training, and experience to perform their respective tasks.

This study will not use the services of study personnel where sanctions have been invoked or where there has been scientific misconduct or fraud (eg, loss of medical licensure, debarment).

2.2 Institutional Review Board/Independent Ethics Committee

Before study initiation, the investigator must have a written and dated approval/favorable opinion from the IRB/IEC for the protocol, consent form, subject recruitment materials (eg, advertisements), and any other written information to be provided to subjects. The investigator or BMS should also provide the IRB/IEC with a copy of the Investigator Brochure or product labeling information to be provided to subjects and any updates.

The investigator or BMS should provide the IRB/IEC with reports, updates and other information (eg, expedited safety reports, amendments, and administrative letters) according to regulatory requirements or institution procedures.

2.3 Informed Consent

Investigators must ensure that subjects are clearly and fully informed about the purpose, potential risks, and other critical issues regarding clinical studies in which they volunteer to participate.

In situations where consent cannot be given to subjects, their legally acceptable representatives are clearly and fully informed about the purpose, potential risks, and other critical issues regarding clinical studies in which the subject volunteers to participate.

BMS will provide the investigator with an appropriate (ie, Global or Local) sample informed consent form which will include all elements required by ICH, GCP and applicable regulatory requirements. The sample informed consent form will adhere to the ethical principles that have their origin in the Declaration of Helsinki.

Investigators must:

1) Provide a copy of the consent form and written information about the study in the language in which the subject is most proficient prior to clinical study participation. The language must be non-technical and easily understood.
2) Allow time necessary for subject or subject's legally acceptable representative to inquire about the details of the study.
3) Obtain an informed consent signed and personally dated by the subject or the subject's legally acceptable representative and by the person who conducted the informed consent discussion.
4) Obtain the IRB/IEC's written approval/favorable opinion of the written informed consent form and any other information to be provided to the subjects, prior to the beginning of the study, and after any revisions are completed for new information.
5) If informed consent is initially given by a subject's legally acceptable representative or legal guardian, and the subject subsequently becomes capable of making and communicating his or her informed consent during the study, consent must additionally be obtained from the subject.
6) Revise the informed consent whenever important new information becomes available that is relevant to the subject's consent. The investigator, or a person designated by the investigator, should fully inform the subject or the subject's legally acceptable representative or legal guardian, of all pertinent aspects of the study and of any new information relevant to the subject's willingness to continue participation in the study. This communication should be documented.

The confidentiality of records that could identify subjects must be protected, respecting the privacy and confidentiality rules applicable to regulatory requirements, the subjects' signed ICF and, in the US, the subjects' signed HIPAA Authorization.

The consent form must also include a statement that BMS and regulatory authorities have direct access to subject records.

Subjects unable to give their written consent (eg, stroke or subjects with or severe dementia) may only be enrolled in the study with the consent of a legally acceptable representative. The subject must also be informed about the nature of the study to the extent compatible with his or her understanding, and should this subject become capable, he or she should personally sign and date the consent form as soon as possible. The explicit wish of a subject who is unable to give his or her written consent, but who is capable of forming an opinion and assessing information to

refuse participation in or to be withdrawn from, the clinical study at any time should be considered by the investigator.

The rights, safety, and well-being of the study subjects are the most important considerations and should prevail over interests of science and society.

3 INVESTIGATIONAL PLAN

3.1 Study Design and Duration

This is a randomized, open-label, multicenter, phase 3 study of nivolumab monotherapy versus bevacizumab and a safety study of nivolumab and nivolumab in combination with ipilimumab in adult (≥ 18 years) subjects with a first recurrence of glioblastoma (GBM) after treatment with radiotherapy and temozolomide. Since the use of nivolumab and ipilimumab has not previously been studied in subjects with GBM, a safety lead-in (Cohort 1) consisting of approximately 10 subjects in each of two treatment arms will be enrolled and randomized to treatment with either Arm N (nivolumab monotherapy) or Arm N+I (nivolumab combined with ipilimumab). Tolerability and safety of a treatment arm will be determined after all subjects in the arm have completed four doses or have discontinued dosing prior to completing four doses. A safety evaluation of Cohort 1 will be conducted for each arm based on criteria described in Section 4.3.5, Enrollment to Cohort 1 will be limited to selected US sites.

In order to better characterize preliminary safety and tolerability for the combination therapy an additional, non-randomized safety cohort (Cohort 1b) to evaluate an alternate dosing regimen for the combination therapy (nivolumab 3mg/kg + ipilimumab 1 mg/kg every 3 weeks for 4 cycles followed by nivolumab 3 mg/kg thereafter) was initiated based on a site specific amendment to the protocol for selected US sites. This dosing regimen is currently being studied in two ongoing clinical trials in lung and renal cell cancer (CA209012, CA209016) and has demonstrated an acceptable AE profile to date. Evaluation of the efficacy of nivolumab+ipilimumab combination therapy will be evaluated separately Information from subjects treated with combination therapy in Cohort 1 and Cohort 1b will provide a basis for dose selection for future studies in subjects with GBM.

Enrollment in Cohort 2 was planned to begin after safety and tolerability of the safety lead-in had been evaluated and determination regarding which treatments arms (Arm N and/or Arm N+I) will be studied. Treatment with nivolumab monotherapy in Cohort 1 met the protocol prespecified safety and tolerability profile (less than one-third of subjects required permanent discontinuation due to treatment related adverse events prior to receiving 4 doses of treatment) to advance to Cohort 2, the randomized portion of the study to compare nivolumab monotherapy versus bevacizumab. Since evaluation of a second dosing regimen for the combination therapy is on-going, the randomized portion of this study (Cohort 2) will be limited to nivolumab monotherapy versus bevacizumab. Evaluation of the efficacy of nivolumab+ipilimumab combination therapy will be evaluated separately, once there is sufficient data from Cohort 1 and 1b to select the appropriate dose to advance (either nivolumab 3 mg/kg + ipilimumab 1 mg/kg or nivolumab 1 mg/kg + ipilimumab 3 mg/kg) into a randomized study.

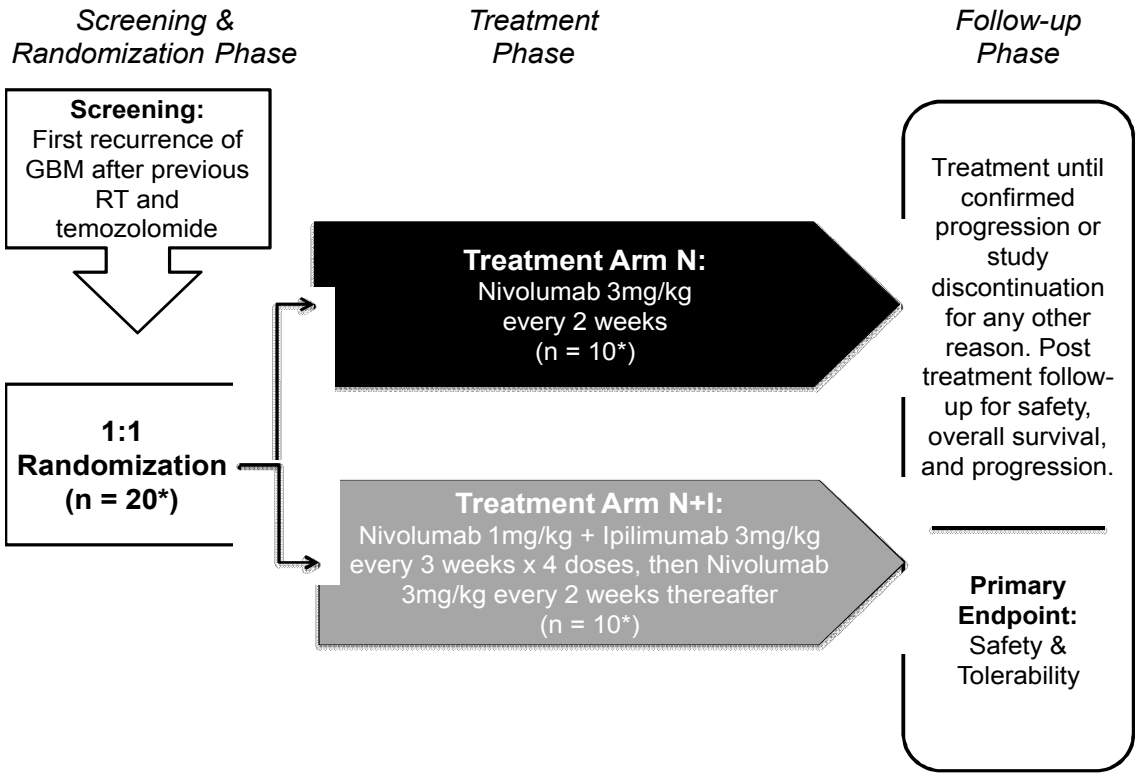
All subjects in Cohort 1, 1b, and 2 will be followed for safety and tolerability, tumor progression, and overall survival. Tumor progression or response endpoints will be assessed using Radiologic Assessment in Neuro-Oncology criteria (RANO) described in Section 5.4.2. Treatment with study medication will continue until confirmed tumor progression, unacceptable toxicity, or other discontinuation criteria as described in Section 3.5, whichever comes first. A Data Safety Monitoring Committee (DMC) will meet regularly during the study to ensure that subject safety is carefully monitored.

The study design schematic is presented in Figure 3.1-1.

Figure 3.1-1: Study Design Schematic

Cohort 1 – Safety Lead-In:

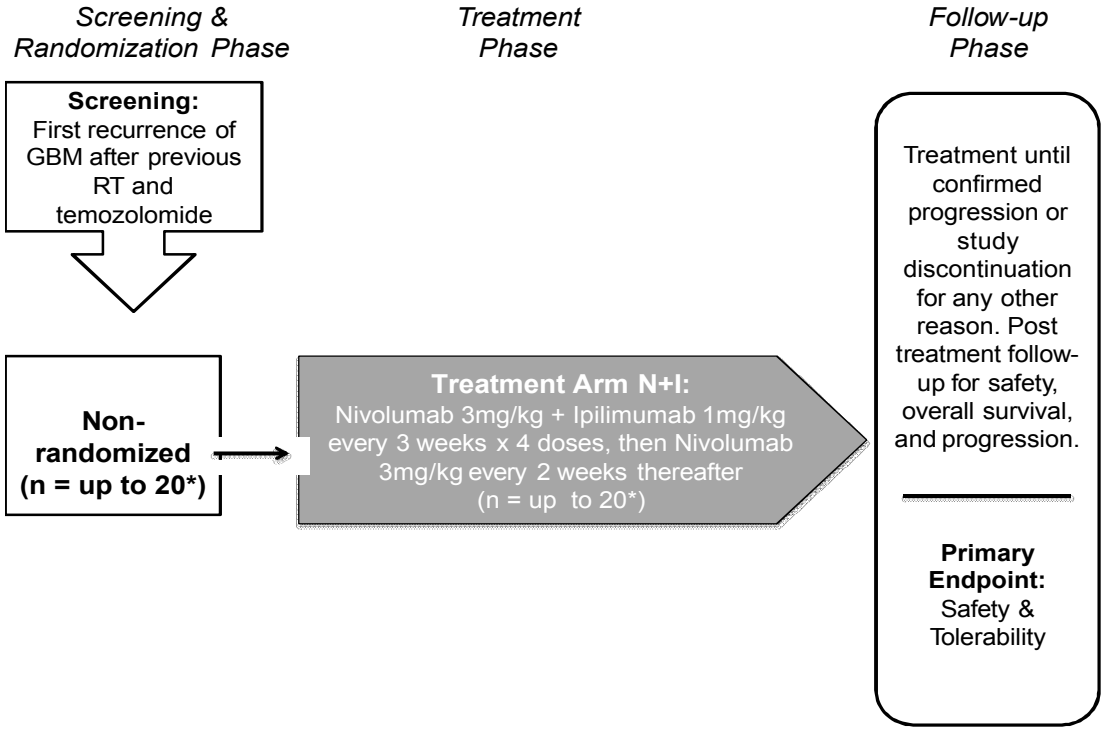
- Primary endpoint: Tolerability and safety of N and N + I in subjects with recurrent GBM
- Demonstration of acceptable tolerability and safety before advancing to Cohort 2



*Cohort 1 will randomize 20 subjects in a 1:1 fashion to assess the tolerability and safety of the investigational agents and suitability of advancing the treatment arms to Cohort 2, the randomized efficacy phase of the study (Section 3.1.1). The tolerability and safety assessment of each arm will occur after the last randomized subject has completed four doses or has discontinued dosing prior to completing four doses.

Cohort 1b: Safety evaluation of combination of nivolumab 3mg/kg + ipilimumab 1mg/kg

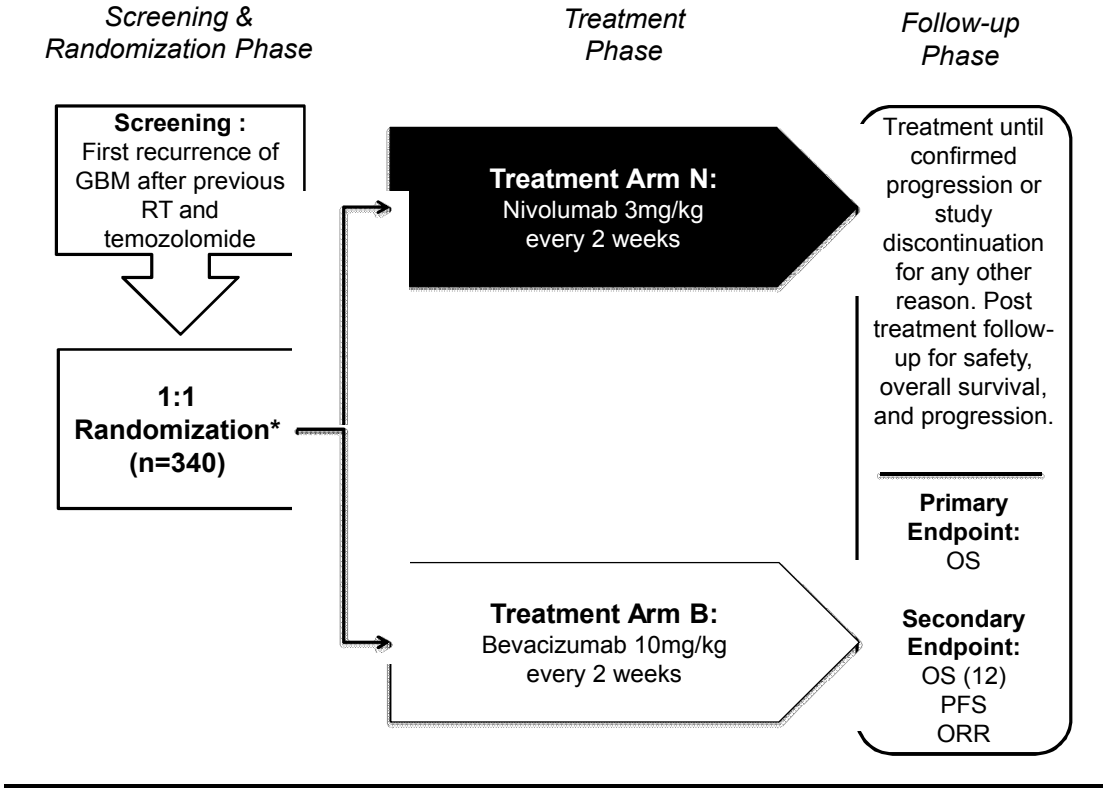
- Primary endpoint: Tolerability and safety of N+ I combination arm in subjects with recurrent GBM



*Cohort 1b will be non-randomized with up to 20 subjects treated at selected US sites only.

Cohort 2 – Randomized, 2-Arm:

- Primary endpoint: Overall Survival; Secondary endpoints: OS(12), PFS, and ORR
- 1:1 Randomization



This study will consist of three phases: screening, treatment, and follow up. (See Table 5.1-1, Table 5.1-2, Table 5.1-3, Table 5.1-4). After confirmed progression or study discontinuation for any other reason, study treatment will be discontinued and subjects will enter the post treatment follow-up phase to assess safety, progression and overall survival.

*Randomization will be stratified by presence of a measureable lesion at baseline (Y/N)

It is expected that enrollment and follow-up of randomized subjects (10 subjects in each arm) into Cohort 1 will take approximately 6-8 months. The total duration of Cohort 2 from the start of randomization to primary analysis of overall survival is expected to be 34 months. Additional survival follow-up may continue after the primary analysis of survival.

3.1.1 Safety Evaluation of Cohort 1 and 1b

The proposed dosing regimen for nivolumab and ipilimumab in Cohort 1 and 1b is based upon safety and tolerability data from the use of nivolumab and ipilimumab in other tumor types (see Section 1). Although the proposed dosing regimen is expected to be tolerable in subjects with GBM, this study initially included two safety lead-in cohorts (Cohort 1 and 1b) prior to initiation of the efficacy study comparing nivolumab monotherapy versus bevacizumab

(Cohort 2). Approximately 10 subjects with recurrent GBM will be randomized to each of the two investigational treatment groups in Cohort 1 (Arm N and Arm N+ I. Up to 20 subjects with recurrent GBM will be treated in Cohort 1b (Arm N+I_1b).

Tolerability and safety of a treatment arm will be determined after all subjects per arm have completed four doses or have discontinued dosing prior to completing four doses. However, tolerability beyond four doses may also be taken into consideration. All subjects will continue to be followed for safety, progression, and overall survival after discontinuation of study medication. The tolerability criteria used to advance to Cohort 2 was based on drug related adverse events leading to permanent discontinuation in the safety lead-in cohorts (listed in Section 4.3.5) and include the following:

- If no more than one-third of the subjects in a given treatment arm permanently discontinue study medication prior to completing four doses due to treatment related adverse events then this dose cohort will be deemed as tolerable and enrollment in Cohort 2 may proceed.
- If more than one-third of subjects in a treatment arm permanently discontinue study medication prior to completing four doses due to treatment-related adverse events, then the safety and tolerability of that treatment arm will be reviewed with the DMC prior to randomizing any additional subjects. A decision will be made by the sponsor whether to continue enrollment or advance either treatment arm into Cohort 2.

Treatment with nivolumab monotherapy in Cohort 1 met the protocol prespecified safety and tolerability profile detailed above to advance to a randomized study versus bevacizumab in Cohort 2. As of 27-June-2014, no subjects randomized to nivolumab discontinued due to treatment-related adverse events prior to receiving four doses of nivolumab. Since evaluation of a second dosing regimen for the combination therapy is on-going, the randomized portion of this study (Cohort 2) will be limited to nivolumab monotherapy versus bevacizumab. Evaluation of the efficacy of nivolumab+ipilimumab combination therapy will be evaluated separately, once there is sufficient data from Cohort 1 and 1b to select the appropriate dose to advance (either nivolumab 3 mg/kg + ipilimumab 1 mg/kg or nivolumab 1 mg/kg + ipilimumab 3 mg/kg) into a randomized study.

3.1.1.1 Evaluation of Risk/Benefit for a Treatment Arm that does not meet Tolerability Criteria

In the event that more than one-third of the subjects in either combination treatment arm require permanent discontinuation due to treatment related adverse events prior to receiving 4 doses of treatment, the sponsor will review the risk/benefit profile of this treatment arm with the DMC and determine whether or not to advance that arm. In this event, the DMC will review all available Cohort 1 and 1b data and recommend continuation, modification or termination of the treatment arm. The rationale for further evaluation with the DMC is that the most frequent severe drug related AEs for the combination of nivolumab and ipilimumab in melanoma have been asymptomatic and reversible (ie., LFTs and lipase laboratory changes) and there is preliminary evidence of deep and durable responses in advanced melanoma (CA209004) despite these events. In particular, any assessment of the risk/benefit of a treatment arm not meeting tolerability will be triggered if the following criteria are met:

- A majority of subjects in the treatment arm have at least stable disease or a partial tumor response
- All treatment related AEs leading to discontinuation are non-fatal, reversible and without severe sequela
- A majority of the treatment related AEs are laboratory in nature, asymptomatic, and monitorable via routine blood draws

If a decision is made to continue with a treatment arm because of a favorable risk/benefit profile (ie. non fatal AEs in subjects with at least stable disease or a partial tumor response) and despite meeting the 'not tolerable' criteria above, then the DMC and EC/IRBs must be notified, Informed Consent forms updated, and discussion of the risk/benefit must be documented with all current and future subjects who are randomized to this regimen.

3.1.2 Review of Safety

The subjects' safety will be monitored on an ongoing basis as described fully in Section 7. Safety conference calls with investigators and representatives of the sponsor will be held as necessary. An independent Data Monitoring Committee (DMC) will provide safety reviews every six months or as defined in the DMC Charter. Decisions regarding safety will be made by the sponsor in conjunction with feedback from the investigators and the DMC. In addition, a BMS medical safety team (MST) will routinely reviews safety signals across the entire nivolumab program including combination studies with ipilimumab. The DMC will meet on a regular basis at least every six months or at an ad-hoc basis as defined by the DMC charter. The DMC will review all available data (safety and efficacy) data and at the end of each meeting, will recommend continuation, modification or termination of the study protocol based upon their review.

3.1.3 Treatment beyond progression

Treatment with assigned study therapy beyond disease progression will be permitted until a second radiologic confirmation of progression 12 weeks later as long as the following criteria are met: 1) the subject experiences investigator-assessed clinical benefit and 2) the subject is tolerating the study treatment

3.1.4 Dose reductions

Dose reduction is not permitted for any reason. Dose delays for the management of study treatment related adverse events are described in Section 4.3.2. Subjects in the nivolumab + ipilimumab treatment arms who discontinue due to treatment-related adverse events prior to the fourth dose may begin nivolumab 3mg/kg every 2 weeks with approval of the Sponsor (see Section 3.5).

3.1.5 Tumor Tissue

Tumor tissue is required to be submitted for retrospective biomarker analyses. If tumor tissue is not available, a subject may be enrolled in the study with prior permission of the medical monitor.

3.1.6 Study Phases

This study will consist of three phases: screening, treatment (Cohort 1, 1b, and Cohort 2), and follow-up.

Screening Phase:

- Begins by establishing the subject's initial eligibility and signing of the informed consent form (ICF).
- Subject is enrolled using the Interactive Voice Response System (IVRS).

Treatment Phase:

- Begins with the randomization call to the IVRS. Subjects in Cohort 1 and Cohort 2 are randomly assigned to one of the treatment arms based on the study cohort. Subjects in Cohort 1b are assigned to Arm N + I_1b.
- Within 3 working days from treatment assignment, the subject must receive the first dose of study medication:
  - Arm N (nivolumab monotherapy): Nivolumab 3 mg/kg IV every two weeks.
  - Arm N+I (nivolumab + ipilimumab): Nivolumab 1 mg/kg IV combined with ipilimumab 3 mg/kg IV every three weeks for 4 doses, then nivolumab 3 mg/kg IV every two weeks (Cohort 1 only)
  - Arm N+I_1b (nivolumab + ipilimumab): Nivolumab 3 mg/kg IV combined with ipilimumab 1 mg/kg IV every three weeks for 4 doses, then nivolumab 3 mg/kg IV every two weeks (Cohort 1b only)
  - Arm B (bevacizumab) Cohort 2: Bevacizumab 10 mg/kg every 2 weeks
- Adverse event assessments will be documented at each visit throughout the study.
- [redacted]
- All of the laboratory tests and vital signs will be collected prior to study drug dosing at the time points specified in Table 5.1-2 and Table 5.1-3.
- [redacted]
- Study drug dosing may be delayed for toxicity. See Section 4.3.2.
- Treated subjects will be evaluated for response by the investigator and according to the RANO criteria. Tumor assessments will be performed beginning at the end of Week 6 (± 1 week) after first dose, at the end of Week 12 (± 1 week) and continuing every 8 weeks ± 1 week) until disease progression or treatment discontinuation, whichever occurs later.

This phase ends when the subject experiences a confirmed tumor progression, unacceptable toxicity, or other discontinuation criteria, whichever occurs first. For a complete list of reasons for treatment discontinuation, see Section 3.5.

Follow-Up Phase

- Begins when the decision to discontinue a subject from study therapy is made (no further treatment with study therapy).

- Subjects who discontinue treatment for reasons other than tumor progression will continue to have tumor assessments beginning at the end of Week 6 (± 1 week) after first dose, at the end of Week 12 (± 1 week) and then every 8 (± 1 week) weeks until disease progression or, withdrawal of consent. All radiologically determined disease progression must be confirmed by an additional confirmatory MRI scan approximately 12 weeks following the initial assessment of radiological progression. Investigators may obtain additional follow-up MRI scans prior to 12 weeks as medically appropriate.
- Subjects will be followed for drug-related toxicities until these toxicities resolve, return to baseline or are deemed irreversible. All adverse events will be documented for a minimum of 100 days after last dose.
- After completion of the first two follow-up visits, subjects will be followed every 3 months for survival.

3.1.7 Total Study Duration

It was projected that the accrual to Cohort 1 of the study would be completed within 6 months after the first subject is enrolled. Enrollment in Cohort 1 is complete. Enrollment in Cohort 1b is ongoing. Enrollment in Cohort 2 was planned to begin after a decision has been made by the sponsor regarding the safety and tolerability of the treatment arms in Cohort 1.

Treatment with nivolumab monotherapy in Cohort 1 met the protocol prespecified safety and tolerability profile to advance to Cohort 2. Since evaluation of a second dosing regimen for the combination therapy is on-going, the randomized portion of this study (Cohort 2) will be limited to nivolumab monotherapy versus bevacizumab. Evaluation of the efficacy of

nivolumab+ipilimumab combination therapy will be evaluated separately, once there is sufficient data from Cohort 1 and Cohort 1b to select the appropriate dose to advance into a randomized study.

The accrual to Cohort 2 was completed after 9 months. The final analysis for the primary objective is expected 34 months after the first subject is randomized to Cohort 2.

3.2 Post Study Access to Therapy

At the conclusion of the study, subjects who continue to demonstrate clinical benefit will be eligible to receive study drug. Study drug will be provided via an extension of the study, a rollover study requiring approval by responsible health authority and ethics committee or through another mechanism at the discretion of BMS. BMS reserves the right to terminate access to study drug if any of the following occur: a) the marketing application is rejected by responsible health authority; b) the study is terminated due to safety concerns; c) the subject can obtain medication from a government sponsored or private health program; or d) therapeutic alternatives become available in the local market.

Any subjects who are treated prior to week 13 in the nivolumab plus ipilimumab arm at the time of study closure will finish their combination and then continue their nivolumab monotherapy under the same post-study conditions as the nivolumab monotherapy arm as long as tolerability is acceptable .

The sponsor will not supply bevacizumab as a post-study crossover therapy to those subjects randomized to nivolumab or nivolumab plus ipilimumab. Therapy with bevacizumab from other sources post-study is not prohibited.

Subjects who were randomized to bevacizumab and who have not progressed at the conclusion of the study will receive bevacizumab post-study only if they continue to demonstrate clinical benefit and only if local regulations mandate that the sponsor must be the sole source of bevacizumab for these study subjects.

3.3 Study Population

For entry into the study, the following criteria MUST be met. Eligibility criteria apply to all subjects (Cohort 1, 1b, and Cohort 2), unless otherwise specified.

3.3.1 Inclusion Criteria

1. Signed Written Informed Consent

a) Written informed consent and HIPAA authorization (applies to covered entities in the USA only) obtained from the subject/legal representative prior to performing any protocol-related procedures, including screening evaluations

b) Subjects must be willing and able to comply with scheduled visits, treatment schedule, laboratory testing, and other requirements of the study, including disease assessment by MRI.

2. Target Population

a) Histologically confirmed diagnosis of World Health Organization Grade IV malignant glioma (glioblastoma or gliosarcoma)

b) Previous first line treatment with at least radiotherapy and temozolomide

c) Documented first recurrence of GBM by diagnostic biopsy or contrast enhanced magnetic resonance imaging (MRI) performed within 21 days of randomization per RANO criteria.

d) If first recurrence of GBM is documented by MRI, an interval of at least 12 weeks after the end of prior radiation therapy is required unless there is either: i) histopathologic confirmation of recurrent tumor, or ii) new enhancement on MRI outside of the radiotherapy treatment field.

e) Cohort 1 and 1b only: At least one measurable GBM lesion prior to randomization that meets the following criteria:

i) Contrast enhancing and clearly defined, bi-dimensionally measurable margins AND

ii) At least two perpendicular diameters measuring ≥ 10mm x ≥ 10mm (Note: MRI measurements will not include surgical cavity, cyst, or necrotic area)

f) An interval of ≥ 28 days and full recovery (ie, no ongoing safety issues) from surgical resection prior to randomization.

g) An interval of ≥ 4 weeks after the last administration of any other treatment for GBM.

h) Karnofsky performance status of 70 or higher (Appendix 1)

i) Life expectancy ≥ 12 weeks

j) Subject Re-enrollment: This study permits the re-enrollment of a subject that has discontinued the study as a pre-treatment failure (ie, subject has not been randomized / has not been treated). If re-enrolled, the subject must be re-consented.

3. Age and Reproductive Status

a) Men and women, age ≥ 18 years old at the time of screening

b) Women of childbearing potential (WOCBP) must have a negative serum or urine pregnancy test (minimum sensitivity 25 IU/L or equivalent units of HCG) within 24 hours prior to the start of study drug

c) Women must not be breastfeeding

d) WOCBP must agree to follow instructions for method(s) of contraception from the time of enrollment for the duration of treatment with study drug (s) plus approximately 5 half-lives of study drug (s) plus 30 days (duration of ovulatory cycle) for a total of 5 months post treatment completion for subjects enrolled to Treatment Arm Nivolumab or Nivolumab + Ipilimumab. Subjects enrolled to Treatment Arm Bevacizumab must agree to follow instructions for method(s) of contraception use for 6 months post treatment completion.

e) Men who are sexually active with WOCBP must agree to follow instructions for method(s) of contraception for the duration of treatment with study drug (s) plus

approximately 5 half-lives of study drug (s) plus 90 days (duration of sperm turnover) for a total of 7 months post-treatment completion for subjects enrolled to Treatment Arm Nivolumab or Nivolumab + Ipilimumab. Subjects enrolled to Treatment Arm Bevacizumab must agree to follow instructions for method(s) of contraception use for 6 months post treatment completion

Investigators shall counsel WOCBP and male subjects who are sexually active with WOCBP on the importance of pregnancy prevention and the implications of an unexpected pregnancy Investigators shall advise WOCBP and male subjects who are sexually active with WOCBP on the use of highly effective methods of contraception. Highly effective methods of contraception have a failure rate of < 1% per year when used consistently and correctly.

At a minimum, subjects must agree to the use of two methods of contraception, with one method being highly effective and the other method being either highly effective or less effective as listed below:

HIGHLY EFFECTIVE METHODS OF CONTRACEPTION

- Male condoms with spermicide
- Hormonal methods of contraception including combined oral contraceptive pills, vaginal ring, injectables, implants, and intrauterine devices (IUDs) such as Mirena® by WOCBP subjects or male subject's WOCBP partner.
- Nonhormonal IUDs, such as ParaGard®
- Tubal ligation
- Vasectomy.
- Complete Abstinence*

*Complete abstinence is defined as complete avoidance of heterosexual intercourse and is an acceptable form of contraception for all study drugs. Subjects who choose complete abstinence are not required to use a second method of contraception, but female subjects must continue to have pregnancy tests. Acceptable alternate methods of highly effective contraception must be discussed in the event that the subject chooses to forego complete abstinence.

LESS EFFECTIVE METHODS OF CONTRACEPTION

- Diaphragm with spermicide
- Cervical cap with spermicide
- Vaginal sponge
- Male Condom without spermicide*
- Progestin only pills by WOCBP subjects or male subject's WOCBP partner

- Female Condom*

*A male and female condom must not be used together

f) Azoospermic males and WOCBP who are continuously not heterosexually active are exempt from contraceptive requirements. However WOCBP subjects must still undergo pregnancy testing as described in these sections.

4. Physical and Laboratory Test Findings

a) Screening/Baseline laboratory values must meet the following criteria (using CTCAE v4):

i) WBC ≥ 2000/uL

ii) Neutrophils ≥ 1500/uL

iii) Platelets ≥ $100x10^3$/uL

iv) Hemoglobin ≥ 9.0 g/dL

v) Serum creatinine ≤ 1.5x ULN or creatinine clearance (CrCl) ≥ 40 mL/min (using the Cockcroft-Gault formula)

(1). Female CrCl = (140 - age in years) x weight in kg x 0.85 /72 x serum creatinine in mg/dL

(2). Male CrCl = (140 - age in years) x weight in kg x 1.00/72 x serum creatinine in mg/dL

vi) AST ≤ 3x ULN

vii) ALT ≤ 3x ULN

viii) Bilirubin ≤ 1.5x ULN (except subjects with Gilbert Syndrome, who can have total bilirubin < 3.0 mg/dL)

ix) Subjects must have resting baseline O2 saturation by pulse oximetry of ≥ 92% at rest

3.3.2 Exclusion Criteria

1. Target Disease Exceptions

a) More than one recurrence of GBM

b) Presence of extracranial metastatic or leptomeningeal disease

c) Diagnosis of secondary GBM (ie, glioblastomas that progress from low grade diffuse astrocytoma or anaplastic astrocytoma)

2. Medical History and Concurrent Diseases

a) Any serious or uncontrolled medical disorder that, in the opinion of the investigator, may increase the risk associated with study participation or study drug administration, impair the ability of the subject to receive protocol therapy, or interfere with the interpretation of study results.

b) Subjects with active, known or suspected autoimmune disease. Subjects with vitiligo, type I diabetes mellitus, residual hypothyroidism due to autoimmune condition only requiring hormone replacement, psoriasis not requiring chronic and systemic immunosuppressive treatment, or conditions not expected to recur in the absence of an external trigger are permitted to enroll.

c) Previous radiation therapy with anything other than standard radiation therapy (ie, focally directed radiation)

d) Subjects requiring escalating or chronic supraphysiologic doses of corticosteroids for control of their disease at randomization are excluded

e) Previous treatment with carmustine wafer except when administered as first line treatment and at least 6 months prior to randomization

f) Previous bevacizumab or other VEGF or anti-angiogenic treatment (Cohort 2 only)

g) Previous treatment with a PD-1 or CTLA-4 targeted therapy

h) Evidence of > Grade 1 CNS hemorrhage on the baseline MRI scan;

i) Inadequately controlled hypertension (defined as systolic blood pressure > 150 mmHg and/or diastolic blood pressure > 100 mmHg) within 28 days of first study treatment;

j) Prior history of hypertensive crisis, hypertensive encephalopathy, reversible posterior leukoencephalopathy syndrome (RPLS);

k) Prior history of gastrointestinal diverticulitis, perforation, or abscess;

l) Clinically significant (ie, active) cardiovascular disease, for example cerebrovascular accidents ≤ 6 months prior to study enrollment, myocardial infarction ≤ 6 months prior to study enrollment, unstable angina, New York Heart Association (NYHA) Grade II or greater congestive heart failure (CHF), or serious cardiac arrhythmia uncontrolled by medication or potentially interfering with protocol treatment;

m) History or evidence upon physical/neurological examination of central nervous system disease (eg, seizures) unrelated to cancer unless adequately controlled by medication or potentially interfering with protocol treatment;

n) Significant vascular disease (eg, aortic aneurysm requiring surgical repair or recent arterial thrombosis) within 6 months prior to start of study treatment. Any previous venous thromboembolism > NCI CTCAE Grade 3;

o) History of pulmonary hemorrhage/hemoptysis ≥ grade 2 (defined as ≥ 2.5 mL bright red blood per episode) within 1 month prior to randomization;

p) History or evidence of inherited bleeding diathesis or significant coagulopathy at risk of bleeding (ie, in the absence of therapeutic anticoagulation);

q) Current or recent (within 10 days of study enrollment) use of anticoagulants that, in the opinion of the investigator, would place the subject at significant risk for bleeding. Prophylactic use of anticoagulants is allowed;

r) Surgical procedure (including open biopsy, surgical resection, wound revision, or any other major surgery involving entry into a body cavity) or significant traumatic injury

within 28 days prior to first study treatment, or anticipation of need for major surgical procedure during the course of the study;

s) Minor surgical procedure (eg, stereotactic biopsy within 7 days of first study treatment; placement of a vascular access device within 2 days of first study treatment);

t) History of intracranial abscess within 6 months prior to randomization;

u) History of active gastrointestinal bleeding within 6 months prior to randomization;

v) Serious, non-healing wound, active ulcer, or untreated bone fracture;

w) Subjects unable (due to existent medical condition, eg, pacemaker or ICD device) or unwilling to have a head contrast enhanced MRI

3. Physical and Laboratory Test Findings

a) Positive test for hepatitis B virus surface antigen (HBV sAg) or detectable hepatitis C virus ribonucleic acid (HCV RNA) indicating acute or chronic infection

b) Known history of testing positive for human immunodeficiency virus (HIV) or known acquired immunodeficiency syndrome (AIDS)

NOTE: Testing for HIV must be performed at sites where mandated by local requirements.

4. Allergies and Adverse Drug Reaction

a) History of allergy to study drug components.

b) History of severe hypersensitivity reaction to any monoclonal antibody.

5. Sex and Reproductive Status

a) See inclusion criteria (Section 3.3.1)

6. Other Exclusion Criteria

a) Prisoners or subjects who are involuntarily incarcerated

b) Subjects who are compulsorily detained for treatment of either a psychiatric or physical (eg, infectious disease) illness

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

3.3.3 Women of Childbearing Potential

A women of childbearing potential (WOCBP) is defined as any female who has experienced menarche and who has not undergone surgical sterilization (hysterectomy or bilateral oophorectomy) and is not postmenopausal. Menopause is defined as 12 months of amenorrhea in a woman over age 45 years in the absence of other biological or physiological causes. In addition, women under the age of 55 years must have a serum follicle stimulating hormone, (FSH) level > 40mIU/mL to confirm menopause.*

*Women treated with hormone replacement therapy, (HRT) are likely to have artificially suppressed FSH levels and may require a washout period in order to obtain a physiologic FSH level. The duration of the washout period is a function of the type of HRT used. The duration of the washout period below are suggested guidelines and the investigators should use their judgment in checking serum FSH levels. If the serum FSH level is > 40 mIU/ml at any time during the washout period, the woman can be considered postmenopausal :

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

Other parenteral products may require washout periods as long as 6 months.

3.4 Concomitant Treatments

3.4.1 Prohibited and/or Restricted Treatments

The following medications are prohibited during the study:

- Any concurrent drug or other investigational agents for treatment of GBM (ie, chemotherapy, hormonal therapy, immunotherapy, radiation therapy)
- Medications contraindicated with bevacizumab treatment (refer to the package insert, summary of product characteristics (SmPC), or similar document)

Supportive care for disease-related symptoms may be offered to all subjects on the study.

3.4.2 Other Restrictions and Precautions

Study related MRI imaging of the brain will be performed per the frequency specified in the protocol. Investigators may obtain additional follow-up MRI scans as medically indicated. For other locally performed imaging, it is the local imaging facility's responsibility to determine, based on subject attributes (eg, allergy history, diabetic history and renal status), the appropriate imaging modality and contrast regimen for each subject. Imaging contraindications and contrast risks should be considered in this assessment. Subjects with renal insufficiency should be assessed as to whether or not they should receive contrast and if so, what type and dose of contrast is appropriate. Specific to MRI, subjects with severe renal insufficiency (ie, estimated glomerular filtration rate (eGFR) < 30 mL/min/1.73m2) are at increased risk of nephrogenic systemic fibrosis. MRI contrast should not be given to this subject population. In addition, subjects with surgically implanted devices (pacemaker, deep brain stimulator, metallic implants, etc.) incompatible with MRI should not undergo such imaging techniques. The local imaging facility and investigator should determine the appropriate precautions or guidelines that should be instituted for subjects with tattoos, body piercings or other body art.

The ultimate decision to perform MRI in an individual subject in this study rests with the site radiologist, the investigator and the standard set by the local Ethics Committee.

3.4.3 Permitted Therapy

Subjects are permitted to use topical, ocular, intra-articular, intranasal, and inhalational corticosteroids (with minimal systemic absorption). Systemic corticosteroid use or physiologic replacement doses of steroids are permitted, even if > 10 mg/day prednisone equivalents, for: a) treatment-related AEs; b) sequelae of underlying GBM treatment; or c) for the treatment of non-autoimmune conditions (such as prophylaxis for contrast dye allergy, delayed-type hypersensitivity reaction caused by contact allergen). Details regarding corticosteroid use prior to and during the study will be collected (name of medication, doses utilized, start and stop dates, frequency of use, route of administration). Information regarding concomitant corticosteroid use may be analyzed with regard to study outcome measures.

Subjects requiring chronic treatment with corticosteroids should be treated with histamine-2-receptor antagonists or proton pump inhibitors as prophylaxis for potential gastrointestinal adverse reactions (ulceration, perforation, hemorrhage) unless otherwise contraindicated.

Concomitant medications are recorded at baseline and throughout the treatment phase of the study in the appropriate section of the CRF. All medications (prescriptions or over the counter medications) continued at the start of the study or started during the study and different from the study drug must be documented in the concomitant therapy section of the CRF.

3.5 Discontinuation of Subjects from Treatment

Subjects MUST discontinue investigational product (and non-investigational product at the discretion of the investigator) for any of the following reasons:

- Subject's request to stop study treatment
- Any clinical adverse event (AE), laboratory abnormality or intercurrent illness which, in the opinion of the investigator, indicates that continued participation in the study is not in the best interest of the subject
- Pregnancy (as specified in Section 6.4)
- Termination of the study by Bristol-Myers Squibb (BMS)
- Loss of ability to freely provide consent through imprisonment or involuntarily incarceration for treatment of either a psychiatric or physical (eg, infectious disease) illness
- Toxicity as specified in Section 4.3.5
- Confirmed radiological disease progression or investigator assessed clinical progression as described in Section 4.3.7

<u>For subjects treated with nivolumab in combination with ipilimumab (Cohort 1 and 1b only):</u>

- If a subject discontinues combination treatment with nivolumab + ipilimumab due to a drug-related adverse event prior to completing four doses of the combination therapy, the subject may continue treatment with nivolumab 3mg/kg every 2 weeks as long as the AE leading to discontinuation was clearly attributed to ipilimumab and not nivolumab. In such circumstances, the subject may re-start nivolumab therapy when the subject fully recovers

from the drug-related adverse event that led to discontinuation (Note: If the duration from last treatment to full recovery exceeds 42 days, the subject may re-start treatment with nivolumab only if, in the investigator's opinion, the subject was clinically benefiting from treatment and approval was obtained from the BMS medical monitor).

- In all instances discussion with the Sponsor must be documented prior to continuing nivolumab monotherapy.

All subjects who discontinue investigational product should comply with protocol specified follow-up procedures as outlined in Section 5. The only exception to this requirement is when a subject withdraws consent for all study procedures including post-treatment study follow-up or loses the ability to consent freely (ie, is imprisoned or involuntarily incarcerated for the treatment of either a psychiatric or physical illness).

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

3.6 Post Treatment Study Follow up

In this study, overall survival is a key endpoint of the study. Post treatment study follow-up is of critical importance and is essential to preserving subject safety and the integrity of the study. Subjects who discontinue study treatment must continue to be followed for collection of outcome and/or survival follow-up data as described in Table 5.1-4 until death or the conclusion of the study.

BMS may request that survival data be collected on all treated/randomized subjects outside of the protocol defined window (Table 5.1-4). At the time of this request, each subject will be contacted to determine their survival status unless the subject has withdrawn consent for all contact.

3.6.1 Withdrawal of Consent

Subjects who request to discontinue study treatment will remain in the study and must continue to be followed for protocol specified follow-up procedures. The only exception to this is when a subject specifically withdraws consent for any further contact with him/her or persons previously authorized by subject to provide this information. Subjects should notify the investigator of the decision to withdraw consent from future follow-up **in writing**, whenever possible. The withdrawal of consent should be explained in detail in the medical records by the investigator, as to whether the withdrawal is from further treatment with study drug only or also from study procedures and/or post treatment study follow-up, and entered on the appropriate CRF page. In the event that vital status (whether the subject is alive or dead) is being measured, publicly available information should be used to determine vital status only as appropriately directed in accordance with local law.

3.6.2 Lost to Follow-Up

All reasonable efforts must be made to locate subjects to determine and report their ongoing status. This includes follow-up with persons authorized by the subject as noted above. Lost to follow-up is defined by the inability to reach the subject after a minimum of three documented phone calls, faxes, or emails as well as lack of response by subject to one registered mail letter. All attempts should be documented in the subject's medical records. If it is determined that the subject has died, the site will use permissible local methods to obtain the date and cause of death.

If investigator's use of third-party representative to assist in the follow-up portion of the study has been included in the subject's informed consent, then the investigator may use a Sponsor-retained third-party representative to assist site staff with obtaining subject's contact information or other public vital status data necessary to complete the follow-up portion of the study. The site staff and representative will consult publicly available sources, such as public health registries and databases, in order to obtain updated contact information. If after all attempts, the subject remains lost to follow-up, then the last known alive date as determined by the investigator should be reported and documented in the subject's medical records.

4 TREATMENTS

Study drugs include both Non-investigational (NIMP) and Investigational Medicinal Products (IMP) and can consist of the following:

- All products, active or placebo, being tested or used as a comparator in a clinical trial.
- Study required premedication, and
- Other drugs administered as part of the study that are critical to claims of efficacy (eg, background therapy, rescue medications)
- Diagnostic agents: (such as glucose for glucose challenge) given as part of the protocol requirements must also be included in the dosing data collection.

See Table 4.1-1 Product Description for product description of nivolumab, ipilimumab, and bevacizumab.

4.1 Study Treatments

Table 4.1-1: Product Description

Product Description and Dosage Form	Potency	Primary Packaging (Volume)/ Label Type	Secondary Packaging (Qty) /Label Type	Appearance	Storage Conditions (per label)
BMS-936558-01 Solution for Injection[a]	100 mg (10 mg/mL)	10 mL vial/ Open-label	10 vials per carton/ Open-label	Clear to opalescent colorless to pale yellow liquid. May contain particles	2 to 8°C. Protect form light and freezing
Ipilimumab Solution for Injection	200 mg (5 mg/mL)	40 mL vial/Open-label	4 vials per carton/Open-label	Clear, colorless to pale yellow liquid. May contain particles	2 to 8°C. Protect from light and freezing.
Bevacizumab Solution[b] for Infusion	400 mg/vial	16mL per vial/Open-label	1 vial per carton/Open-label	Clear to slightly opalescent, colorless to pale brown liquid	2 to 8°C. Protect from light and freezing. Do not shake.

[a] Nivolumab is labeled as BMS-936558-01 Solution for Injection

[b] Bevacizumab may be obtained by the investigational sites located in the USA as local commercial product (which may be available as a different potency/package size than listed above) if local regulations allow and agreed to by BMS

4.1.1 Investigational Product

An investigational product, also known as investigational medicinal product in some regions, is defined a pharmaceutical form of an active substance or placebo being tested or used as a reference in a clinical study, including products already with a marketing authorization but used or assembled (formulated or packaged) differently than the authorized form, or used for an unauthorized indication, or when used to gain further information about the authorized form.

The investigational product should be stored in a secure area according to local regulations. It is the responsibility of the investigator to ensure that investigational product is only dispensed to study subjects. The investigational product must be dispensed only from official study sites by authorized personnel according to local regulations.

In this protocol, investigational product(s) is/are: BMS-936558 (nivolumab), ipilimumab and bevacizumab.

4.1.2 Non-investigational Product

Other medications used as support or escape medication for preventative, diagnostic, or therapeutic reasons, as components of the standard of care for a given diagnosis, may be considered as non-investigational products.

In this protocol, non-investigational product(s) is/are: Not applicable for this study

4.1.3 Handling and Dispensing

The product storage manager should ensure that the study drug is stored in accordance with the environmental conditions (temperature, light, and humidity) as determined by BMS. If concerns regarding the quality or appearance of the study drug arise, the study drug should not be dispensed and contact BMS immediately.

Investigational product documentation must be maintained that includes all processes required to ensure drug is accurately administered. This includes documentation of drug storage, administration and, as applicable, storage temperatures, reconstitution, and use of required processes (eg, required diluents, administration sets).

Infusion-related supplies (eg, IV bags, in-line filters, 0.9% NaCl solution) will not be supplied by the sponsor and should be purchased locally if permitted by local regulations.

For non-investigational product, if marketed product is utilized, it should be stored in accordance with the package insert, summary of product characteristics (SmPC), or similar.

Please refer to the current version of the Investigator Brochure and/or pharmacy reference sheets for complete storage, handling, dispensing, and infusion information for BMS-936558 (nivolumab) and ipilimumab.

4.1.3.1 Nivolumab (BMS-936558)

For details regarding drug storage, preparation, administration, and use time please refer to the BMS-936558 (nivolumab) Investigator Brochure and/or pharmacy reference sheets.

Nivolumab is to be administered as an approximately 60-minute IV infusion. At the end of the infusion, flush the line with a sufficient quantity of normal saline.

4.1.3.2 Ipilimumab

For ipilimumab storage, administration, and use time instructions, refer to ipilimumab IB and/or pharmacy reference sheets.

Ipilimumab is to be administered as an approximately 90-minute IV infusion. At the end of the infusion, flush the line with a sufficient quantity of normal saline or 5% dextrose solution.

When both study drugs are to be administered on the same day, separate infusion bags and filters must be used for each infusion. Nivolumab is to be administered first. The nivolumab infusion must be promptly followed by a saline flush to clear the line of nivolumab before starting the ipilimumab infusion. The second infusion will always be ipilimumab, and will start no sooner than 30 minutes after completion of the nivolumab infusion.

4.1.3.3 Bevacizumab

For countries in which BMS is providing packaged/labeled bevacizumab 400 mg vials, please refer to the package insert, summary of product characteristics (SmPC), or similar document for details regarding drug preparation, administration, and use time.

For countries where local sourcing of bevacizumab is permitted, product should be stored, prepared, and administered in accordance to the package insert, summary of product characteristics (SmPC), or similar document.

4.2 Method of Assigning Subject Identification

CA209143 is a randomized study. After the subject's initial eligibility is established and informed consent has been obtained, the subject must be enrolled into the study by calling an interactive voice response system (IVRS) to obtain the subject number. Every subject that signs the informed consent form must be assigned a subject number in IVRS. The investigator or designee will register the subject for enrollment by following the enrollment procedures established by BMS. The following information is required for enrollment:

- Date that informed consent was obtained
- Date of birth
- Gender at birth

Once enrolled in IVRS, enrolled subjects that have met all eligibility criteria will be ready to be randomized through the IVRS. The following information is required for subject randomization:

- Subject number
- Date of birth
- Presence of measurable lesion at baseline (yes/ no); Cohort 2 only

Subjects meeting all eligibility criteria will be randomized either in a 1:1 ratio for Cohort 1 to Arm N (nivolumab) or Arm N+I (nivolumab + ipilimumab), or in a 1:1 ratio for Cohort 2 to Arm N (nivolumab) or Arm B (bevacizumab). All subjects enrolled in Cohort 1b will be assigned to Arm N+I_1b (nivolumab + ipilimumab).

For Cohort 2, randomization will be achieved using the permuted blocks within each stratum: presence of a measureable lesion at baseline (yes/no). The randomization schedule will allocate subjects among the 2 treatment arms (nivolumab or bevacizumab) in a 1:1 ratio. A measureable lesion at baseline (yes) will be defined by at least one contrast enhancing lesion on MRI with clear borders and both diameters equal or greater than 10mm. (Note: MRI measurements will not include surgical cavity, cyst, or necrotic area.) The absence of a measureable lesion at baseline (no) will be defined as lesions that do not meet criteria for a measurable lesion. Only those subjects with measureable disease at baseline will be included in the response rate analysis and stratification will prevent against an imbalances between treatments with regard to this secondary outcome measure.

The exact procedures for using the IVRS will be detailed in the IVRS manual.

4.3 Selection and Timing of Dose for Each Subject

The dosing regimen and schedule for Arm N (nivolumab) and Arms N+I (nivolumab and ipilimumab) and Arm B (bevacizumab) are detailed in Table 4.3-1, Table 4.3-2, Table 4.3-3 and Table 4.3-4.

Table 4.3-1: Dosing Schedule for Arm N Nivolumab (BMS-936558) Monotherapy

Every 2 Week Dosing	
Day 1, Week 1	**Day 1, Week 3 and every two weeks thereafter**
3 mg/kg Nivolumab	3 mg/kg Nivolumab

Table 4.3-2: Dosing Schedule for Arm N+I (Week 1-12) Nivolumab (BMS-936558) + Ipilimumab Combination

Every 3 Week Dosing	
Day 1 **Week 1, Week 4, Week 7, Week 10**	
Cohort 1 (selected US sites): 1 mg/kg Nivolumab 3 mg/kg Ipilimumab	Cohort 1b (selected US sites) 3 mg/kg Nivolumab 1 mg/kg Ipilimumab

Table 4.3-3: Dosing Schedule for Arm N+I (Week 13 and following) Nivolumab (BMS-936558) + Ipilimumab Combination	
Every 2 Week Dosing	
Day 1 **Week 13 and every other week thereafter**	
3 mg/kg Nivolumab	

Table 4.3-4: Dosing Schedule for Arm B (Bevacizumab monotherapy)	
Every 2 Week Dosing	
Day 1 **Week 1**	**Day 1** **Week 3 and every two weeks thereafter**
10 mg/kg	10 mg/kg

Nivolumab and Ipilimumab combination:

When study drugs (nivolumab and ipilimumab) are to be administered on the same day, separate infusion bags and filters must be used for each infusion. Nivolumab is to be administered first. The second infusion will always be ipilimumab, and will start no sooner than 30 minutes after completion of the nivolumab infusion.

Dosing calculation based on weight:

The dosing calculations should be based on the body weight. If the subject's weight on the day of dosing differs by > 10% from the weight used to calculate the dose, the dose must be recalculated. All doses should be rounded to the nearest milligram.

Dosing modifications:

There will be no dose reductions allowed for the management of toxicities of individual subjects. Doses may be delayed for toxicity management.

Dosing window Arm N+I (Week 1-12): subjects may be dosed no less than 19 days between doses and no more than 3 days after the scheduled dosing date. Dose given after the 3 day window is considered a dose delay. A maximum delay of 42 days *between doses* is allowed. If dosing is delayed, both nivolumab and ipilimumab must be delayed together. If dosing is resumed after a delay, both nivolumab and ipilimumab must be resumed on the same day.

Dosing window Arm N, Arm B and Arm N+I (Week 13 and following): subjects may be dosed no less than 12 days between doses and no more than 3 days after the scheduled dosing date. Dose given after the 3 day window is considered a dose delay. A maximum delay of 42 days *between doses* is allowed.

Bevacizumab

Dose may be temporarily delayed. Refer to package insert or SmPC.

4.3.1 Antiemetic Premedications

Antiemetic premedications should not be routinely administered prior to dosing of drugs. See Section 4.3.6 for premedication recommendations following a nivolumab or ipilimumab related infusion reaction.

4.3.2 Dose Delay Criteria

Dose delay criteria specified below apply for all nivolumab or nivolumab combined with ipilimumab related adverse events (regardless of whether or not the event is attributed to nivolumab, ipilimumab, or both). Nivolumab and/or nivolumab and ipilimumab must be delayed until treatment can resume (see Section 4.3.2.)

Nivolumab and/or nivolumab and ipilimumab administration should be delayed for the following:

- Any Grade ≥ 2 non-skin, drug-related adverse event, with the following exceptions:
  - Grade 2 drug-related fatigue or laboratory abnormalities do not require a treatment delay
- Any Grade 3 skin, drug-related adverse event
- Any Grade 3 drug-related laboratory abnormality, with the following exceptions for asymptomatic amylase or lipase, AST, ALT, or total bilirubin:
  - Grade 3 amylase or lipase abnormalities that are not associated with symptoms or clinical manifestations of pancreatitis do not require a dose delay. It is recommended to consult with the BMS Medical Monitor for Grade 3 amylase or lipase abnormalities, and to assess clinically relevant laboratory tests at more frequent intervals to be determined by the investigator.
  - If a subject has a baseline AST, ALT, or total bilirubin that is within normal limits, delay dosing for drug-related Grade ≥ 2 toxicity
  - If a subject has baseline AST, ALT, or total bilirubin within the Grade 1 toxicity range, delay dosing for drug-related Grade ≥ 3 toxicity
- Any adverse event, laboratory abnormality, or intercurrent illness which, in the judgment of the investigator, warrants delaying the dose of study medication.

Bevacizumab administration should be delayed in accordance with the package insert or summary of product characteristics (SmPC).

- Bevacizumab must be held for ≥ 2 grams of proteinuria/24 hours and may resume when proteinuria is < 2 gm/24 hours. Treatment should be discontinued in subjects with nephrotic syndrome.

4.3.2.1 Management Algorithms for Immuno-Oncology Agents

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

- Gastrointestinal
- Renal
- Pulmonary
- Hepatic
- Endocrinopathies
- Skin
- Neurological

While the ipilimumab investigator brochure contains safety management algorithms for similar adverse events, the recommendations are to follow the nivolumab algorithms for immune-oncology agents (I-O) in order to standardize the safety management. Therefore, the algorithms recommended for utilization in this protocol are included in Appendix 2.

For subjects expected to require more than 4 weeks of corticosteroids or other immunosuppressants to manage an adverse event, consider recommendations provided in Appendix 2.

4.3.3 Dose Modifications

Dose reductions or dose escalations are not permitted.

4.3.4 Criteria to Resume Treatment

Criteria to resume treatment with study medication previously meeting dose delay criteria:

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

- Subjects may resume treatment in the presence of Grade 2 fatigue
- Subjects who have not experienced a Grade 3 drug-related skin AE may resume treatment in the presence of Grade 2 skin toxicity
- Subjects with baseline Grade 1 AST/ALT or total bilirubin who require dose delays for reasons other than a 2-grade shift in AST/ALT or total bilirubin may resume treatment in the presence of Grade 2 AST/ALT OR total bilirubin
- Subjects with combined Grade 2 AST/ALT AND total bilirubin values meeting discontinuation parameters (Section 4.3.5) should have treatment permanently discontinued

- Drug-related pulmonary toxicity, diarrhea, or colitis, must have resolved to baseline before treatment is resumed
- Drug-related endocrinopathies adequately controlled with only physiologic hormone replacement may resume treatment
- As permitted by the bevacizumab package insert.

If the criteria to resume treatment are met, the subject should restart treatment at the next scheduled time point per protocol.

If treatment with study medication is delayed > 6 weeks, the subject must be permanently discontinued from study therapy, except as specified in Section 4.3.5.

4.3.5 Discontinuation Criteria

Treatment with nivolumab and/or ipilimumab must be permanently discontinued for the following:

- Any Grade 2 drug-related uveitis or eye pain or blurred vision that does not respond to topical therapy and does not improve to Grade 1 severity within the re-treatment period OR requires systemic treatment
- Any Grade 3 non-skin, drug-related adverse event lasting > 7 days, with the following exceptions for drug-related laboratory abnormalities, uveitis, pneumonitis, bronchospasm, diarrhea, colitis, neurologic toxicity, hypersensitivity reactions, and infusion reactions:
  - Grade 3 drug-related uveitis, pneumonitis, bronchospasm, diarrhea, colitis, neurologic toxicity, hypersensitivity reaction, or infusion reaction of any duration requires discontinuation
  - Grade 3 drug-related laboratory abnormalities do not require treatment discontinuation except:
    - Grade 3 drug-related thrombocytopenia > 7 days or associated with bleeding requires discontinuation
    - Any drug-related liver function test (LFT) abnormality that meets the following criteria require discontinuation:
      - AST or ALT > 8 x ULN
      - Total bilirubin > 5 x ULN
      - Concurrent AST or ALT > 3 x ULN and total bilirubin > 2 x ULN
- Any Grade 4 drug-related adverse event or laboratory abnormality, except for the following events which do not require discontinuation:
  - Grade 4 amylase or lipase abnormalities that are not associated with symptoms or clinical manifestations of pancreatitis. It is recommended to consult with the BMS Medical Monitor for Grade 4 amylase or lipase abnormalities.
  - Isolated Grade 4 electrolyte imbalances/abnormalities that are not associated with clinical sequelae and are corrected with supplementation/appropriate management within 72 hours of their onset

- Any dosing interruption lasting > 6 weeks from the last dose with the following exceptions:
  - Dosing interruptions to allow for prolonged steroid tapers to manage drug-related adverse events are allowed. Prior to re-initiating treatment in a subject with a dosing interruption lasting > 6 weeks, the BMS medical monitor must be consulted. Tumor assessments should continue as per protocol even if dosing is interrupted.
  - Dosing interruptions > 6 weeks from the last dose that occur for non-drug-related reasons may be allowed if approved by the BMS medical monitor. Prior to re-initiating treatment in a subject with a dosing interruption lasting > 6 weeks, the BMS medical monitor must be consulted. Tumor assessments should continue as per protocol even if dosing is interrupted.
- Any adverse event, laboratory abnormality, or intercurrent illness which, in the judgment of the Investigator, presents a substantial clinical risk to the subject with continued nivolumab or ipilimumab dosing.

Treatment with bevacizumab must be permanently discontinued according to the updated bevacizumab package insert including the following:

- Grade 3 uncontrolled hypertension (ie, if not controlled to 150/100 mmHg with medication);
- Grade 4 hypertension including hypertensive encephalopathy;
- Grade 3 non-pulmonary and non-CNS hemorrhage (ie, bleeding diathesis; subjects receiving anticoagulation treatment);
  - Subjects who experience a repeat Grade 3 hemorrhagic event will be discontinued from receiving bevacizumab;
- Grade 4 non-pulmonary or non-CNS hemorrhage;
- Grade ≥ 1 pulmonary or CNS hemorrhage;
- Arterial thromboembolic event (any grade);
- Grade ≥ 3 congestive heart failure;
- Grade 3 proteinuria;
- GI perforation;
- Fistula (thromboembolism, any grade; Grade 4 fistula);
- Wound dehiscence (any grade –requiring medical or surgical therapy);
- Reversible posterior leukoencephalopathy (any grade,- confirmed by MRI);
- Other unspecified bevacizumab related AE's (Grade 4).

Study treatment must be discontinued upon confirmed radiological progression or clinical progression as described in Section 4.3.7, whichever occurs first.

4.3.6 Treatment of Nivolumab or Ipilimumab Related Infusion Reactions

Since nivolumab and ipilimumab 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, hypo- or hypertension, bronchospasm, or other symptoms. All Grade 3 or 4 infusion reactions should be reported within 24 hours to the BMS Medical Monitor and reported as an SAE if criteria are met. Infusion reactions should be graded according to NCI CTCAE (version 4.0) guidelines.

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

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

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

For Grade 2 symptoms: (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 or ipilimumab infusion, begin an IV infusion of normal saline, and treat the subject with diphenhydramine 50 mg IV (or equivalent) and/or paracetamol 325 to 1000 mg (acetaminophen); remain at bedside and monitor subject until resolution of symptoms. Corticosteroid or bronchodilator therapy may also be administered as appropriate. If the infusion is interrupted, then restart the infusion at 50% of the original infusion rate when symptoms resolve; if no further complications ensue after 30 minutes, the rate may be increased to 100% of the original infusion rate. Monitor subject closely. If symptoms recur then no further nivolumab or ipilimumab will be administered at that visit. Administer diphenhydramine 50 mg IV, and remain at bedside and monitor the subject until resolution of symptoms. The amount of study drug infused must be recorded on the electronic case report form (eCRF). The following prophylactic premedications are recommended for future infusions: diphenhydramine 50 mg (or equivalent) and/or paracetamol 325 to 1000 mg (acetaminophen) should be administered at least 30 minutes before additional nivolumab or ipilimumab administrations. If necessary, corticosteroids (recommended dose: up to 25 mg of IV hydrocortisone or equivalent) may be used.

For Grade 3 or Grade 4 symptoms: (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 infusion of nivolumab or ipilimumab. Begin an IV infusion of normal saline, and treat the subject as follows. Recommend bronchodilators, epinephrine 0.2 to 1 mg of a 1:1,000 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. Subject should be monitored until the investigator is comfortable that the symptoms will not recur. Nivolumab or ipilimumab will be permanently discontinued. Investigators should follow their institutional guidelines for the treatment of anaphylaxis. Remain at bedside and monitor subject until recovery from symptoms. In the 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).

4.3.7 *Treatment Beyond Initial Radiological Assessment of Disease Progression*

Standard treatment for glioblastomas (including radiation therapy and temozolomide) may result in a transient increase in tumor enhancement (pseudoprogression) in a subset of subjects that eventually subsides without any change in therapy. Pseudoprogression may be difficult to differentiate from true tumor progression and may have important implications for patient management. As described in Section 1.5, accumulating evidence also indicates that some subjects treated with immune system stimulating agents may also develop apparent progression of disease (by conventional response criteria) before demonstrating clinical objective responses and/or stable disease. [37] This phenomenon was observed in approximately 10% of subjects in the Phase 1 study of nivolumab and has also been reported for ipilimumab monotherapy.[33]

In order to minimize premature discontinuation of study medication and distinguish pseudoprogression from progressive disease, subjects initially meeting radiologic criteria for disease progression may continue receiving study medication until confirmation of progression with an MRI performed approximately 12 weeks later.

In order to continue study treatment after assessment of initial radiological progression, the following criteria must be met:

1) The subject is believed to demonstrate clinical benefit as determined by the investigator
2) The subject is tolerating study medication

Subjects with confirmed progression (approximately 12 weeks after initially assessed progression) will discontinue study medication and enter the follow up/survival phase of the study. If progression is confirmed then the date of disease progression will be the first date the subject met the criteria for progression.

In those cases in which radiologic progression cannot be differentiated from pseudoprogression and it is the investigator's opinion that a surgical resection to obtain tumor tissue for histopathology is in the subject's best interests, a surgical resection may be performed following consultation with the BMS medical monitor. Tumor biopsy samples (blocks or slides) must be

submitted for central review by a neuropathologist to minimize any inter-observer variation in the histopathologic assessment of progression versus treatment-related changes. If tumor pathology confirms progression, then the subject will be discontinued from study medication per protocol discontinuation criteria and the date of progression will be the day that it was first suspected. If tumor pathology reveals treatment-related changes and does not confirm disease progression, the subject may continue study medication. An MRI after the resection is required prior to treatment continuation. The subject will then continue all on-treatment tumor assessments as per the treatment schedule.

Central Neuropathologic Review of Tumor Samples After Biopsy or Resection

In those cases in which radiologic progression cannot be differentiated from pseudoprogression and the subject undergoes a biopsy or diagnostic surgical resection to obtain tumor tissue for histopathology analysis, representative tumor tissue samples will be reviewed locally and submitted for central review by a neuropathologist. If there is discordance between the central and local neuropathologic determination of progression versus treatment-associated changes (pseudoprogression), then a second central neuropathologic review will be performed and serve as the final adjudication of the histopathologic determination. Central review of histopathology will be blinded to the subject treatment arm assignment. Specific instructions will be provided to the investigative sites regarding the requirements for submission of tumor tissue for central neuropathologic review. If tumor tissue is not available for central neuropathology review, the reasons for not submitting tissue for central review must be clearly documented by the principle investigator and approval obtained from the BMS Medical Monitor.

4.4 Blinding/Unblinding

Not applicable.

4.5 Treatment Compliance

Treatment compliance will be monitored by drug accountability as well as the subject's medical record and eCRF.

4.6 Destruction and Return of Study Drug

4.6.1 Destruction of Study Drug

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

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

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

- On-site disposal practices must not expose humans to risks from the drug.
- On-site disposal practices and procedures are in agreement with applicable laws and regulations, including any special requirements for controlled or hazardous substances.

- Written procedures for on-site disposal are available and followed. The procedures must be filed with the site's SOPs and a copy provided to BMS upon request.
- Records are maintained that allow for traceability of each container, including the date disposed of, quantity disposed, and identification of the person disposing the containers. The method of disposal, ie, incinerator, licensed sanitary landfill, or licensed waste disposal vendor must be documented.
- Accountability and disposal records are complete, up-to-date, and available for the Monitor to review throughout the clinical trial period.

If conditions for destruction cannot be met the responsible BMS Study Monitor will make arrangements for return of study drug.

It is the investigator's responsibility to arrange for disposal of all empty containers, provided that procedures for proper disposal have been established according to applicable federal, state, local, and institutional guidelines and procedures, and provided that appropriate records of disposal are kept.

4.6.2 Return of Study Drug

If study drug will not be destroyed upon completion or termination of the study, all unused and/or partially used study drug that was supplied by BMS must be returned to BMS. The return of study drug will be arranged by the responsible BMS Study Monitor.

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.

5 STUDY ASSESSMENTS AND PROCEDURES

5.1 Flow Chart/Time and Events Schedule

Table 5.1-1: Screening Assessments (CA209143)

Procedure	Screening Visit: within 28 days of randomization	Notes
Eligibility Assessments		
Informed Consent	X	Contact IVRS to obtain study subject number. Study allows for re-enrollment of a subject that has discontinued the study as a pre-treatment failure. If re-enrolled, the subject must be re-consented and assigned a new subject number from IVRS
Inclusion/Exclusion Criteria	X	All inclusion/exclusion criteria should be assessed at screening and confirmed prior to randomization
Disease Status		
Medical History	X	
Gene methylation status		If available
Tumor Biopsy	X	Archival or fresh biopsy taken at any point prior to study treatment. Submit to central vendor. Medical monitor approval is required for subjects for whom tissue is not available.;
Safety Assessments		
Physical Examination	X	
Vital signs and oxygen saturation	X	Including BP, HR, temperature and oxygen saturation by pulse oximetry. Pulse oximetry at rest and after exertion. Obtain vital signs at the screening visit and within 72 hours prior to first dose
Physical measurements (including performance status)	X	Height and weight; Karnofsky performance status
Assessment of Signs and Symptoms	X	Within 14 days prior to randomization
Concomitant Medication collection	X	Within 14 days prior to randomization
Steroid Dose documentation	X	Within 14 days prior to randomization

Table 5.1-1: Screening Assessments (CA209143)		
Procedure	**Screening Visit: within 28 days of randomization**	**Notes**
Laboratory Tests	X	CBC w/differential; Chemistry panel including: LDH, AST, ALT, ALP, T.Bili, BUN or serum urea level, creatinine, Ca, Mg, Na, K, Cl, Glucose, amylase, lipase, TSH, Free T4, Free T3, Hep B/C(HBV sAG, HCV antibody), within 14 days prior to randomization
Urinalysis	X	Dipstick; obtain within 14 days prior to randomization
Screening 12-lead ECG	X	Within 14 days prior to randomization
Pregnancy Test (WOCPB only)	X	
[redacted]	[redacted]	[redacted]
Tumor Assessment		
Screening/Baseline Tumor Assessment	X	Within 21 days prior to randomization; Contrast-enhanced MRI.[a] The baseline MRI assessment must be performed on a MRI qualified to meet study specific acquisition parameters (see Imaging Manual).

[a] When logistically feasible, the timing of the baseline MRI should be performed as close as possible to the randomization date but no longer than 21 days before. Additionally, MRI scans performed prior to this baseline may be collected by the sponsor.

Table 5.1-2: On-Study Assessments Nivolumab (N) and Bevacizumab (B) Arms (CA209143)		
Procedure	**Day 1 Week 1 and then every 2 weeks within 3 days prior to dosing**	**Notes**
Safety Assessments		
Targeted Physical Examination	X	Perform as clinically indicated
Vital Signs and Oxygen saturation	X	Pulse oximetry at rest and after exertion.
Physical Measurements (including PS)	X	Weight and Karnofsky Performance Status (prior to each dose)
Adverse Events Assessment	Continuously	
Review of Concomitant Medications	X	
Steroid medication documentation	X	
Laboratory Tests	X	Obtain prior to each dose through Week 21 and then obtain every 4 weeks thereafter; must be collected within 72 hours prior to dose. Collect CBC w/differential; Chemistry panel including: LDH, AST, ALT, ALP, T.Bili, BUN or serum urea level, creatinine, Ca, Mg, Na, K, Cl, Glucose, amylase, lipase, TSH with reflexive Free T4, Free T3,
Urinalysis (For subjects in Arm B only)	X	Dipstick, within 72 hours prior to bevacizumab dose. Subjects with 2+ or greater proteinurea dipstick reading must undergo further assessment with a 24 hr urine collection prior to being dosed.
Pregnancy Test (WOCBP only)	X (Day 1 Week 1 and then every 4 weeks)	Obtain at the specified schedule (ie, every 4 weeks [+/-1 week]) regardless of dose delays; if collected with a dosing visit then obtain within 24 hours prior to administration of study drug: urine or serum
12-lead ECG	See note	As clinically indicated
[redacted]		
[redacted]	[redacted]	[redacted]

Table 5.1-2: On-Study Assessments Nivolumab (N) and Bevacizumab (B) Arms (CA209143)		
Procedure	**Day 1 Week 1 and then every 2 weeks within 3 days prior to dosing**	**Notes**
Exploratory Biomarker Samples		
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
Tumor sample at the time of progression or suspected progression		If a biopsy or surgical resection is performed at the time of progression or suspected progression, a tumor biopsy sample (block or slides) should be submitted for central neuropathologic review. (Note: Prior pre-study treatment archival tumor specimens may be submitted to the sponsor to aid in the histologic assessment when available).
Efficacy Assessments		
Tumor assessments	X (Day 1 Week 7)	Contrast-enhanced MRI. Week 7 and 13, Day 1 and then every 8 weeks (+/- 1 week)
[redacted]	[redacted]	[redacted]
[redacted]		
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	

Table 5.1-2: On-Study Assessments Nivolumab (N) and Bevacizumab (B) Arms (CA209143)		
Procedure	**Day 1 Week 1 and then every 2 weeks within 3 days prior to dosing**	**Notes**
[redacted]	[redacted]	[redacted]
Clinical Drug Supplies		
IVRS Randomization	X	
Administer Study Treatment	X (within 3 working days of randomization)	Nivo is administered q 2 weeks; Bevacizumab is administered q 2 weeks.

Table 5.1-3: On-Study Assessments Nivolumab+ Ipilimumab (N+I) Arm (CA209143; Cohort 1 and 1b, only)			
Procedure	**Day 1 Week 1, 4, 7, and 10 within 3 days prior to dosing**	**Day 1 Week 13 and then every 2 weeks**	**Notes**
Safety Assessments			
Targeted Physical Examination	X	X	Perform as clinically indicated
Vital Signs and Oxygen saturation	X	X	Pulse oximetry at rest and after exertion.
Physical Measurements (including PS)	X	X	Weight and Karnofsky Performance Status (prior to each dose)
Adverse Events Assessment	Continuously	→	
Review of Concomitant Medications	X	X	
Steroid Dose documentation	X	X	Within 72 hours prior to dose
Laboratory Tests	X	X (prior to dosing on Day 1 Week 13 through Day 1 Week 21 and then every 4 weeks thereafter)	Within 72 hours prior to dose. Collect CBC w/differential; Chemistry panel including: LDH, AST, ALT, ALP, T.Bili, BUN or serum urea level, creatinine, Ca, Mg, Na, K, Cl, Glucose, amylase, lipase, TSH with reflexive, Free T4, Free T3,
Pregnancy Test (WOCBP only)	X	X	Obtain at the specified schedule (ie, every 4 weeks [+/- 1 week]) regardless of dose delays; if collected with a dosing visit then obtain within 24 hours prior to administration of study drug: urine or serum; Obtain every 4 weeks (+/- 1 week) regardless of dose delays during nivo monotherapy
12-lead ECG	See note	See note	As clinically indicated
[redacted]			
[redacted]	[redacted]		[redacted]
[redacted]			
[redacted]	[redacted]		[redacted]

Table 5.1-3: On-Study Assessments Nivolumab+ Ipilimumab (N+I) Arm (CA209143; Cohort 1 and 1b, only)			
Procedure	**Day 1 Week 1, 4, 7, and 10 within 3 days prior to dosing**	**Day 1 Week 13 and then every 2 weeks**	**Notes**
[redacted]	[redacted]		[redacted]
[redacted]	[redacted]		[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
Efficacy Assessments			
Tumor assessments	X (Day 1 Week 7 only)	X	Contrast-enhanced MRI at Day 1 Week 7 and 13 and then every 8 weeks (+/- 1 week).
[redacted]			
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]		
Clinical Drug Supplies			
IVRS Randomize	X		
Administer Study Treatment	X (Nivo and Ipi on Day 1 Week 1, 4, 7, and 10); Day 1 Week 1 dose within 3 working days of randomization	X	Nivo and Ipi combination are administered q 3 weeks x 4 doses; after the 4th ipi dose, or when ipi is discontinued, nivo is administered every 2 weeks

Table 5.1-4: Follow-up Assessments (CA209143) - *For all subjects*			
Procedure	**Follow up phase[a] Visits**	**Survival Phase[b]**	**Notes**
Safety Assessments			
Targeted Physical Examination	X		
Adverse Event assessment	X		Beyond 100 days from the last dose of study therapy, subjects will be followed for ongoing drug-related adverse events until resolved, return to baseline or deemed irreversible, or until lost to follow-up, withdrawal of study consent,
Laboratory Tests	X		CBC w/differential, LFTs, BUN, creatinine and TSH for follow-up #1, repeat labs at follow-up #2 if study drug related toxicity persists.
Pregnancy test (for WOCBP)	X		
Review of Concomitant Medications	X		
[redacted]			
[redacted]	[redacted]		[redacted]
[redacted]			
[redacted]	[redacted]		
[redacted]	[redacted]	[redacted]	[redacted]
Survival Status			
Survival Status	X	X	Every 3 months (clinic visit or telephone contact), during Survival phase, include subsequent anti-cancer therapy

Table 5.1-4: Follow-up Assessments (CA209143) - *For all subjects*			
Procedure	**Follow up phase[a] Visits**	**Survival Phase[b]**	**Notes**
Efficacy Assessments			
Tumor Assessment	X	X	Only required for subjects who did not progress while on study therapy, including subjects who start subsequent anti-cancer therapy. Obtain at end of Week 6 and 12 (+/-1 week) and then every 8 weeks (+/-1 week thereafter. Tumor assessments will not be collected for subjects who are lost to follow-up or withdraw consent.

[a] Subjects must be followed for at least 100 days after last dose of study therapy. Follow-up visit #1 (FU1) occurs approximately 35 days (+/- 7 days) after last dose or coinciding with the date of discontinuation (+/- 7 days) if date of discontinuation is greater than 35 days after last dose. Follow up visit #2 (FU2) occurs approximately 80 days (+/- 7 days) after FU1.

[b] Survival visits = every 3 months from FU2

5.2 Study Materials

- NCI CTCAE version 4.0
- Nivolumab Investigator Brochure
- Ipilimumab Investigator Brochure
- Pharmacy Binder
- Laboratory manuals for collection and handling of blood [redacted] and tissue specimens;
- Site manual for operation of interactive voice response system, including enrollment/randomization worksheets
- Manual for entry of local laboratory data
- Pregnancy Surveillance Forms
- [redacted]
- Radiology scan submission manual

5.3 Safety Assessments

At baseline, a medical history will be obtained to capture relevant underlying conditions. The baseline examinations should include weight, height, Karnofsky Performance Status, BP, HR, temperature, 12-lead ECG and oxygen saturation by pulse oximetry at rest and after exertion and should be performed as noted in Table 5.1-1 Notes. Baseline signs and symptoms are those that are assessed within 14 days prior to randomization. Concomitant medications will be collected from within 14 days prior to randomization through the study treatment period (see Section 5.1).

Baseline local laboratory assessments should be done within 14 days prior to randomization to include: CBC w/differential, ANC, platelets, Hgb; Chemistry panel including ALT, AST, total bilirubin, alkaline phosphatase), BUN or serum urea level, creatinine, Ca, Mg, Na, K, Cl, LDH, glucose, amylase, lipase, TSH, Free T4, Free T3, and Hep B and C testing (HBV sAg, HCV Ab or HCV RNA) (see Table 5.1-1). Pregnancy testing for WOCBP (done locally) must be performed within 24 hours prior to the initial administration of study drug at baseline. Where required by local regulations, an HIV test must also be performed.

Subjects will be evaluated for safety if they have received any study drug. Toxicity assessments will be continuous during the treatment phase. During the safety follow-up phase (Table 5.1-4), toxicity assessments should be done in person. Once subjects reach the survival follow-up phase, either in person or documented telephone calls to assess the subject's status are acceptable.

Adverse events and laboratory values will be graded according to the NCI-CTCAE version 4.0.

On-study weight, Karnofsky performance status, and vital signs should be assessed at each on-study visit prior to dosing. Vital signs should also be taken as per institutional standard of care prior to, during and after dosing. Oxygen saturation by pulse oximetry at rest and after

exertion should be assessed at each on study visit prior to dosing. Urinalysis (dipstick) should be obtained within 72 hours prior to dose for subjects randomized to bevacizumab. The start and stop time of the nivolumab and the ipilimumab infusion and bevacizumab administration should be documented. Physical examinations are to be performed as clinically indicated. If there are any new or worsening clinically significant changes since the last exam, report changes on the appropriate non-serious or serious adverse events page.

Additional measures, including non-study required laboratory tests, should be performed as clinically indicated or to comply with local regulations. On-treatment 12-lead ECGs should be obtained if clinically indicated. Laboratory toxicities (eg, suspected drug inducted liver enzyme elevations) will be monitored during the follow-up phase via on site/local labs until all study drug related toxicities resolve, return to baseline or are deemed irreversible.

Oxygen saturation by pulse oximetry should be obtained prior to each dose of nivolumab and at any time a subject has any new or worsening respiratory symptoms. A reading at rest should be obtained at each time point. If a subject shows changes on pulse oximetry or other pulmonary related signs (eg, hypoxia, fever) or symptoms (eg, dyspnea, cough) consistent with possible pulmonary adverse events, the subject should be immediately evaluated to rule out pulmonary toxicity. An algorithm for the management of suspected pulmonary toxicity can be found in the Appendix 2.

Urinalysis should be obtained for all subjects within 72 hours prior to dose. Urinalysis will be collected on treatment only for subjects randomized to bevacizumab. Subjects with 2+ or greater proteinurea urine dipstick reading must undergo further assessment with a 24 hour collection prior to being dosed. Bevacizumab must be held for ≥ 2 grams of proteinuria/24 hours and may resume when proteinuria is < 2 gm/24 hours. Treatment should be discontinued in subjects with nephrotic syndrome.

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

5.3.1 Imaging Assessment for the Study

All subjects will receive safety, tumor measurements and volumetric Magnetic Resonance Imaging (MRI) of the head at the time points specified in Table 5.1-1, Table 5.1-2, Table 5.1-3, Table 5.1-4. Investigators may obtain more frequent follow-up MRI scans as medically indicated. All radiologic imaging from this study will be transmitted to a centralized imaging core lab for storage and may be reviewed by an Independent Radiology Review Committee (IRRC) as determined by the Sponsor. Sites will be trained in image acquisition parameters, and the submission process prior to scanning the first study subject. These guidelines will be outlined in a separate Site Imaging Manual. Any incidental findings of potential clinical relevance that are not directly associated with the objectives of the protocol should be evaluated and handled by the Study Investigator as per standard medical/clinical judgment. Study sites will retain local access to the imaging results for safety and efficacy reading purposes. The study investigator will

review the local MRI results as clinically appropriate to ensure that any potentially emergent clinical situations are addressed in a timely fashion.

Subjects who are unable (due to existent medical condition, ie, pacemaker or ICD device) or unwilling to have a head MRI at baseline are excluded from the study. Subjects who become unable to undergo MRI imaging after randomization may continue in the study for assessment of overall survival as long as there is no safety issue which would require monitoring by MRI.

Clinically significant radiologic findings or changes from baseline scans will be coded as adverse events or serious adverse events according to the criteria described below in Section 6.

Please refer to Section 5.4 for more information regarding MRIs.

5.4 Efficacy Assessments

5.4.1 Head Magnetic Resonance Imaging (MRI)

All subjects will receive efficacy assessments with brain MRI at time points specified in Table 5.1-1, Table 5.1-2, Table 5.1-3, Table 5.1-4 All MRIs should occur at +/− 7 days per scheduled visits. Investigators may obtain more frequent follow-up MRI scans as medically indicated.

Local radiologic assessment of tumor measurements will be used during the study for clinical management and investigator-assessed disease progression (see Table 5.4.2-1 and Section 4.3.7). Cases of suspected radiologic disease progression will be confirmed by an MRI performed approximately 12 weeks after the initial radiological assessment of progression.

Sites will be trained in image acquisition parameters, submission process, application of RANO criteria (as outlined in Section 5.4.2) prior to scanning the first study subject. These guidelines will be outlined in a separate Site Imaging Manual. All radiologic imaging from this study will be transmitted to a centralized imaging core lab for storage and may be reviewed by an Independent Radiology Review Committee (IRRC) as determined by the Sponsor.

5.4.2 Efficacy Assessments

The primary efficacy measure of the study is overall survival (OS). OS is defined as the time between the date of randomization and the date of death due to any cause. OS will be followed continuously while subjects are on study drug and every 3 months via in-person or phone contact during the survival follow-up phase of the study (see Section 8.3.1 and 8.4.2.1).

Investigator-assessed tumor response will be based upon published RANO criteria[35]. Tumor assessments will be performed at baseline, the end of Week 6 (Day 1 Week 7), 12 (Day 1 Week 13) (+/- 1 week), and then every 8 weeks (+/- 1 week) thereafter. Radiologic response will be assessed by comparing the pretreatment baseline and on-treatment MRI scans. Radiologic progression will be determined by using the smallest tumor measurement at either the pretreatment baseline or after initiation of study medication. Table 5.4.2-1 describes the radiologic and clinical criteria that will be used for determining tumor response.

Table 5.4.2-1:	**RANO Criteria for Response Assessment Incorporating MRI and Clinical Factors[a]**
Response	**Criteria**
Complete response	Requires all of the following: complete disappearance of all enhancing measurable and nonmeasurable disease sustained for at least 4 weeks; no new lesions; stable or improved nonenhancing (T2/FLAIR) lesions; patients must be off corticosteroids (or on physiologic replacement doses only); and stable or improved clinically. Note: Patients with nonmeasurable disease only cannot have a complete response; the best response possible is stable disease.
Partial response	Requires all of the following: ≥ 50% decrease compared with baseline in the sum of products of perpendicular diameters of all measurable enhancing lesions sustained for at least 4 weeks; no progression of nonmeasurable disease; no new lesions; stable or improved nonenhancing (T2/FLAIR) lesions on same or lower dose of corticosteroids compared with baseline scan; the corticosteroid dose at the time of the scan evaluation should be no greater than the dose at time of baseline scan; and stable or improved clinically. Note: Patients with nonmeasurable disease only cannot have a partial response; the best response possible is stable disease.
Stable disease	Requires all of the following: does not qualify for complete response, partial response, or progression; stable nonenhancing (T2/FLAIR) lesions on same or lower dose of corticosteroids compared with baseline scan. In the event that the corticosteroid dose was increased for new symptoms and signs without confirmation of disease progression on neuroimaging, and subsequent follow-up imaging shows that this increase in corticosteroids was required because of disease progression, the last scan considered to show stable disease will be the scan obtained when the corticosteroid dose was equivalent to the baseline dose.
Progression	Defined by any of the following: ≥ 25% increase in sum of the products of perpendicular diameters of enhancing lesions compared with the smallest tumor measurement obtained either at baseline (if no decrease) or best response, on stable or increasing doses of corticosteroids[*]; significant increase in T2/FLAIR nonenhancing lesions on stable or increasing doses of corticosteroids compared with baseline scan or best response after initiation of therapy[*] not cause by comorbid events (eg, radiation therapy, demyelination, ischemic injury, infection, seizures, postoperative changes, or other treatment effects); any new lesion; clear clinical deterioration not attributable to other causes apart from the tumor (eg, seizures, medication adverse effects, complications of therapy, cerebrovascular events, infection, and so on) or changes in corticosteroid dose; failure to return for evaluation as a result of death or deteriorating condition; or clear progression of nonmeasurable disease.

[a] From: Wen PY, Macdonald DR, Reardon DA, Cloughesy TF, Sorenson AG, Galanis E, et al. Updated Response Assessment Criteria for High-Grade Gliomas: Response Assessment in Neuro-Oncology Working Group; J Clin Oncol. 2010 Apr 10;28(11):1963-72.

NOTE: Radiologic interpretation guidelines, definitions and tumor measurement instructions will be provided separately. All measurable and nonmeasurable lesions must be assessed using the same techniques as at baseline.

Abbreviations: MRI, magnetic resonance imaging; FLAIR, fluid-attenuated inversion recovery

[*] Stable doses of corticosteroids include subjects not on corticosteroids

For purposes of this study, the minimum time from baseline for determination of SD will be 6 weeks.

BOR should be determined based on response designations recorded per RANO defined criteria. The subject's BOR assignment will depend on the findings of both target and non-target disease, and will also take into consideration the appearance of new lesions.

The assessments that will contributed to the evaluation of BOR include the response assessment recorded between the date of randomization and the first to occur of the following:

1) The date of objectively documented progression per RANO criteria

-OR-

2) The date of subsequent therapy

-OR-

3) The date of pathology results from diagnostic surgical resection.

Among the available response assessments, the criteria listed in Table 5.4.2-2 will be used to determine BOR.

Table 5.4.2-2: Assessment of Best Overall Response

Best Overall Response	Criteria
Complete Response (CR)	CR observed in consecutive assessments ≥ 4 weeks apart per RANO
Partial Response (PR)	PR observed in consecutive assessments ≥ 4 weeks apart per RANO
Stable Disease (SD)[a]	SD observed and does not qualify for CR or PR or Suspected PD followed with histologic results not confirming PD, and no CR PR, or SD observed
Not Evaluable (NE)	Insufficient data to determine disease progression or response
Progressive Disease (PD)	No CR, PR, or SD prior to PD

[a] To qualify for SD there must be a minimum on-treatment period of 6 weeks.

In order to distinguish potential treatment-associated pseudoprogression from progressive disease and minimize premature discontinuation of study medication, subjects who initially meet radiologic criteria for disease progression but are believed to derive clinical benefit and are tolerating study medication should continue receiving study medication until confirmation of progression with an MRI performed approximately 12 weeks later (see Section 4.3.7). If the follow-up assessment confirms that progression has occurred, the date of progression will be the date at which progression was first determined.

For purposes of this study, the minimum duration between baseline (start of treatment) and first on-study scan in order to determine BOR of SD is 6 weeks. If the minimum time is not met when SD is otherwise the best time point response, the subject's best response will depend on the

subsequent assessments. For example, a subject who has SD at a timepoint < 6 weeks and PD at a second assessment, will have a best response of PD.

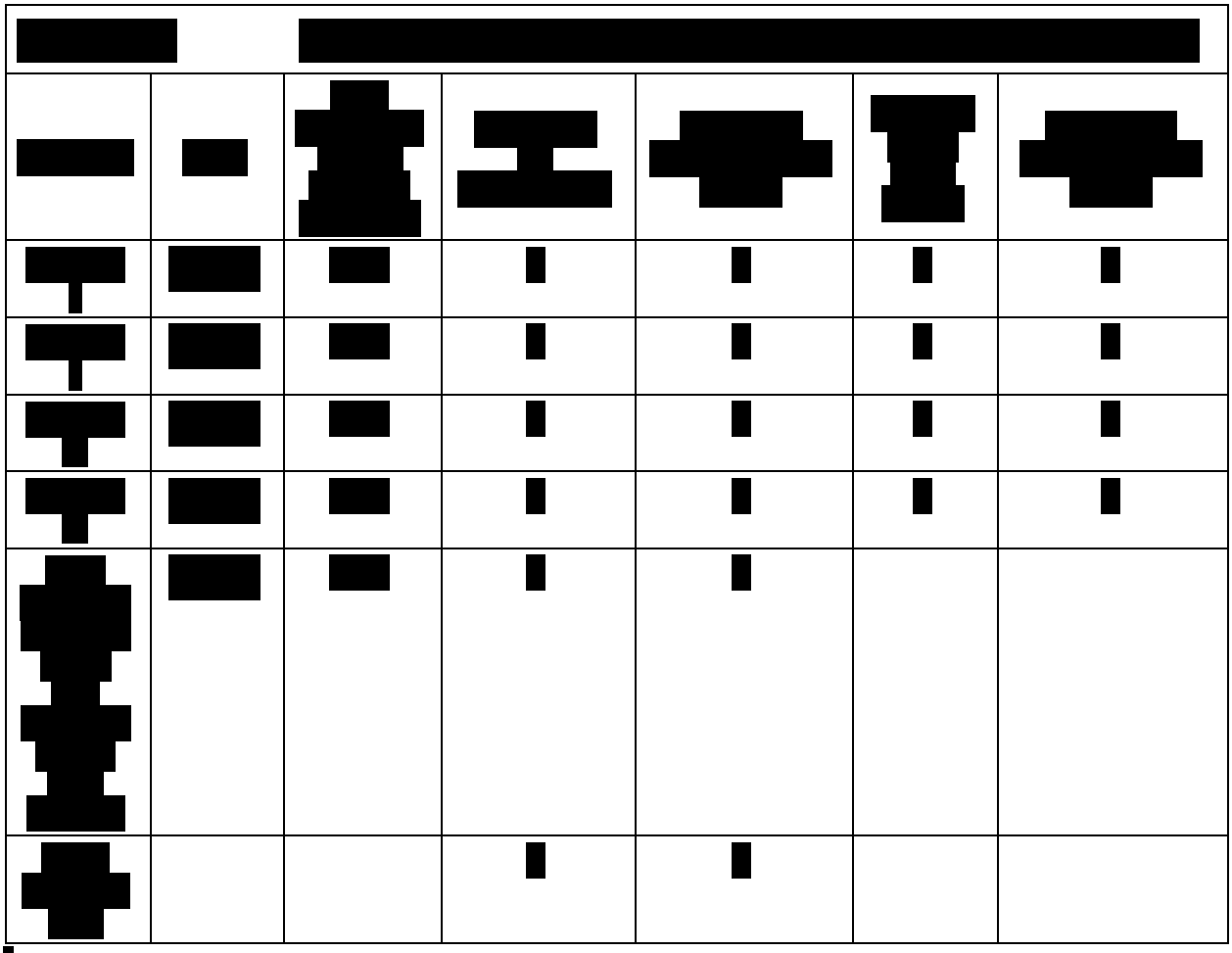
Subjects with nonmeasurable disease at baseline only cannot have a complete or partial response; these patients will be deemed non-evaluable for BOR analysis, but their disease status will be assessed (SD or PD) at each tumor assessment, and they will be included in analysis of PFS and OS. Patients who have undergone surgical resection or biopsy at the time of their first recurrence of GBM and have as a result of that procedure non-measureable disease at their baseline MRI (lesions < 10 mm x 10 mm on contrast enhancing MRI) will be followed for progression as defined in Section 8.4.2.2. If upon subsequent contrast-enhancing MRI, there are no significant signs of progression and the patient is clinically stable, the radiologic assessment will be categorized as SD.

Subjects with a complete or partial response must have that response sustained for 4 weeks. Subjects who do not qualify for complete response, partial response, or confirmed progression will be considered as stable disease for the protocol BOR analysis.

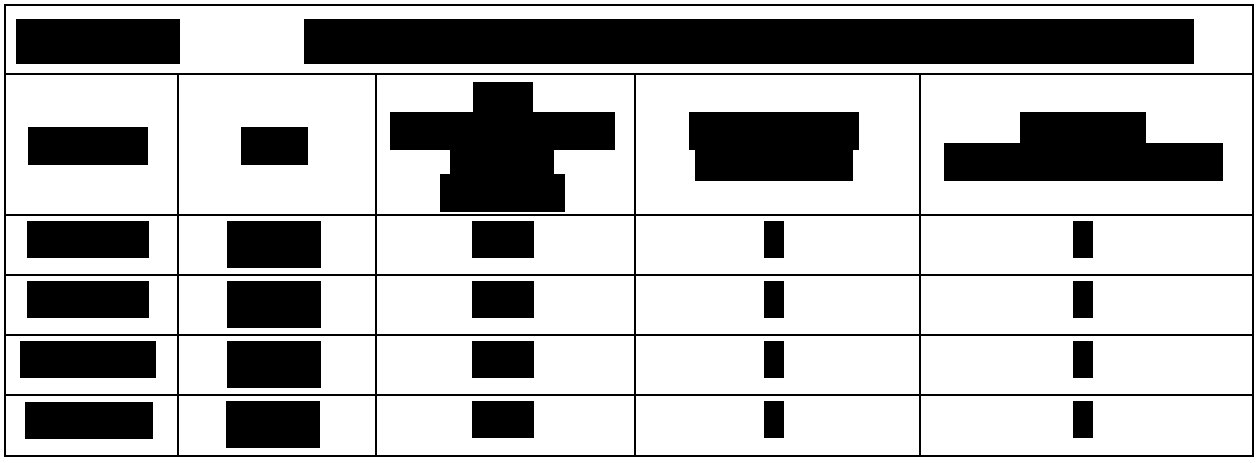
In order to distinguish potential treatment-associated pseudoprogression from progressive disease and minimize premature discontinuation of study medication, subjects who initially meet radiologic criteria for disease progression but demonstrate clinical benefit and are tolerating study medication should continue receiving study medication until confirmation of progression with an MRI performed approximately 12 weeks later (see Section 4.3.7). If the follow-up assessment confirms that progression has occurred, the date of progression will be the date at which progression was first determined.

[redacted]

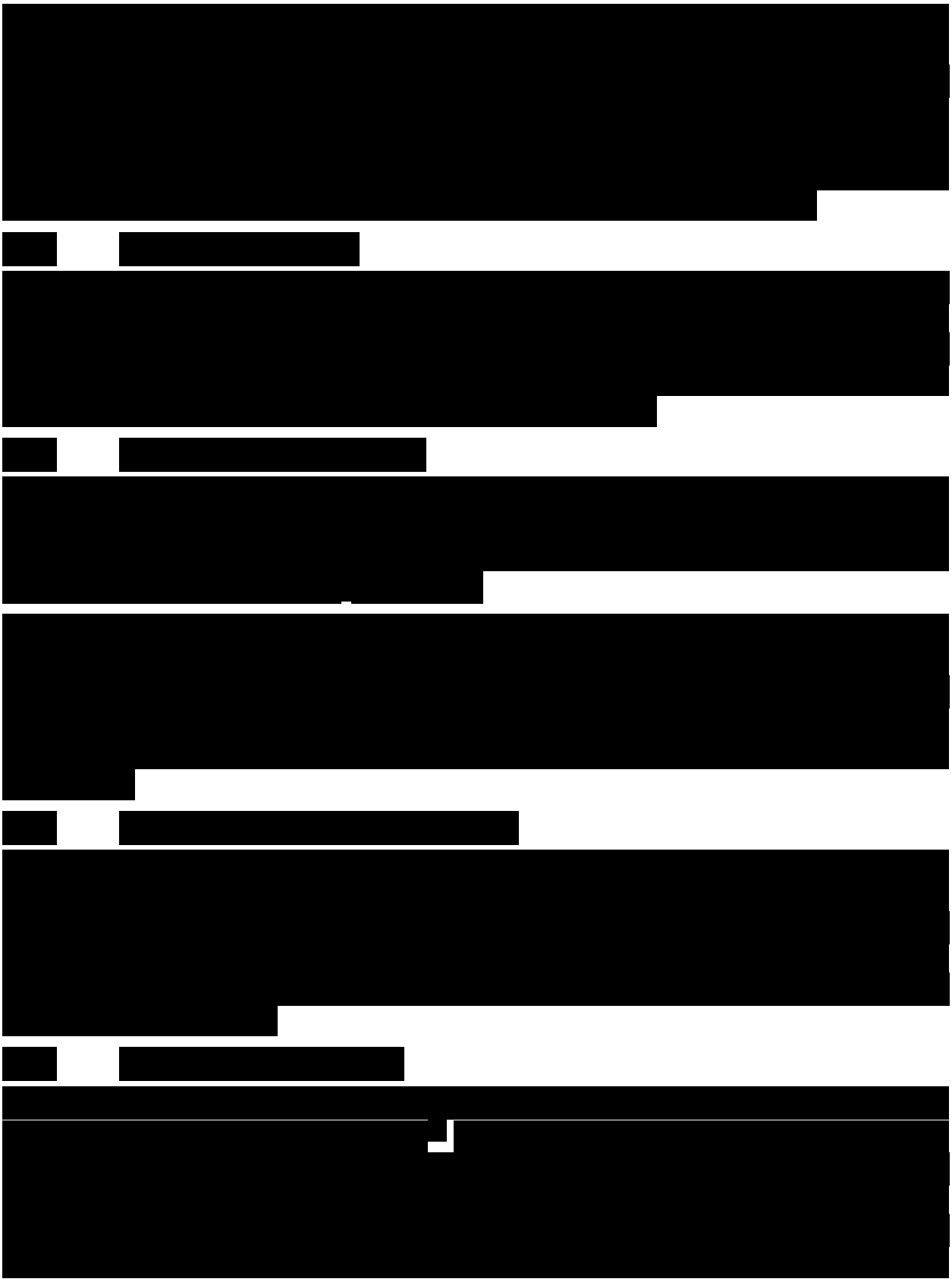
[redacted]



[redacted]



[redacted]



[redacted]

5.6.7 Tumor Samples

5.6.7.1 Tumor-Based Biomarker Measures

Tumor biopsy specimens will be obtained from consenting subjects prior to treatment with nivolumab monotherapy, nivolumab plus ipilimumab combination therapy, or bevacizumab to characterize immune cell populations and expression of selected tumor markers. Archival biopsy block or slides or fresh biopsy must be available for submission prior to randomization. If tumor tissue is not available, please contact the Medical Monitor to discuss possible inclusion of the subject in the protocol. Fresh biopsy collection prior to study therapy is preferred for subjects with accessible lesions but is not required. On-treatment biopsy samples are optional.

Fresh biopsies will be provided for biomarker analysis if accessible and deemed safe by the investigator and should be prioritized over submission of an archived sample. An archived biopsy prior to therapy is acceptable if the fresh biopsy cannot be obtained and if the archived tissue meets the defined criteria as stated below.

- An archived biopsy (block or slides) must contain tumor tissue;
- If an archived block is not available, 10 or more slides containing tumor are available for exploratory use

Whenever possible the archival tumor sample should be obtained from a time point after the subject has completed other systemic therapy (including treatment with temozolomide) and prior to randomization.

[redacted]

[redacted]

5.6.8 Tumor sample collection details

Fresh biopsy:

Fresh biopsies at baseline should be prioritized over archived samples and are strongly encouraged on-treatment.

Tumor samples obtained from bone metastases are not considered acceptable for PD-L1 testing because the PD-L1 assay does not include a decalcification step. For any cases where the only tumor tissue available is from a bone metastasis lesion, please discuss further with the study Medical Monitor.

Biopsy samples should be excisional, incisional or core needle using a gauge needle that is utilized within the institution. In general, a 16 or 18 gauge needle is used for core biopsies.

It is recommended that samples be fixed in 10% Neutral-buffered formalin for 24 – 48 hours. Tumor tissue samples should not be shipped in formalin as the temperature and length of fixation cannot be controlled during shipping.

If slides are submitted, the recommended tissue section thickness is 4 microns and the **slides must be positively charged**. Slides should be shipped refrigerated at 2-8 ^{0} C.

Sample shipments should include a completed requisition form containing collection date, collection method, primary/met, site, fixation conditions, and a copy of Pathology report, if available.

If a fresh biopsy is taken, up to 4 core biopsies are recommended. An assessment of biopsy quality by a pathologist is strongly encouraged at the time of the procedure. The tumor tissue that is obtained from these biopsies will be divided three ways in the following priority order: into

formalin for fixation and paraffin-embedding, in RNALater for RNA/DNA extraction and prepared for tumor infiltrating lymphocyte (TIL) isolation.

The investigator, in consultation with the radiology staff, must determine the degree of risk associated with the procedure and find it acceptable. Biopsies may be done with local anesthesia or conscious sedation. Institutional guidelines for the safe performance of biopsies should be followed. Excisional biopsies may be performed to obtain tumor biopsy samples. Invasive procedures that require general anesthesia should not be performed to obtain a biopsy specimen. However, if a surgical procedure is performed for a clinical indication, excess tumor tissue may be used for research purposes with the consent of the subject.

Archived biopsy:

Minimum of 1 formalin-fixed paraffin embedded (FFPE) tumor tissue block (preferred) OR minimum of 10 FFPE unstained sections are required for assessment of PD-L1 status [redacted]

[redacted]

Detailed instructions of the obtaining, processing, labeling, handling, storage and shipment of specimens will be provided in a separate Procedure Manual at the time of study initiation.

[redacted]

[redacted]

5.9 Results of Central Radiologic Assessments

The clinical management of subjects during the study protocol and secondary outcomes (PFS, ORR) will be based upon local radiologic tumor measurements and the investigator-assessed RANO response criteria described in Section 5.4. Radiologic imaging from this study will be also be transmitted to a centralized imaging core lab for storage and for potential analysis by an Independent Radiology Review Committee (IRRC) as determined by the Sponsor. The site will be informed of quality issues or need for repeat scanning via queries from the core lab.

6 ADVERSE EVENTS

An ***Adverse Event (AE)*** is defined as any new untoward medical occurrence or worsening of a preexisting medical condition in a clinical investigation subject administered an investigational (medicinal) product and that does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (such as an abnormal laboratory finding), symptom, or disease temporally associated with the use of investigational product, whether or not considered related to the investigational product.

The causal relationship to study drug is determined by a physician and should be used to assess all adverse events (AE). The casual relationship can be one of the following:

Related: There is a reasonable causal relationship between study drug administration and the AE.

Not related: There is not a reasonable causal relationship between study drug administration and the AE.

The term "reasonable causal relationship" means there is evidence to suggest a causal relationship.

Adverse events can be spontaneously reported or elicited during open-ended questioning, examination, or evaluation of a subject. (In order to prevent reporting bias, subjects should not be questioned regarding the specific occurrence of one or more AEs.)

6.1 Serious Adverse Events

A S***erious Adverse Event (SAE)*** is any untoward medical occurrence that at any dose:

- results in death
- is life-threatening (defined as an event in which the subject was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe)
- requires inpatient hospitalization or causes prolongation of existing hospitalization (see **NOTE** below)
- results in persistent or significant disability/incapacity
- is a congenital anomaly/birth defect
- is an important medical event (defined as a medical event(s) that may not be immediately life-threatening or result in death or hospitalization but, based upon appropriate medical and scientific judgment, may jeopardize the subject or may require intervention [eg, medical, surgical] to prevent one of the other serious outcomes listed in the definition above.) Examples of such events include, but are not limited to, intensive treatment in an emergency room or at home for allergic bronchospasm; blood dyscrasias or convulsions that do not result in hospitalization.) Potential drug induced liver injury (DILI) is also considered an important medical event. (See Section 6.6 for the definition of potential DILI.)

Suspected transmission of an infectious agent (eg, pathogenic or nonpathogenic) via the study drug is an SAE.

Although pregnancy, overdose, cancer, and potential drug induced liver injury (DILI) are not always serious by regulatory definition, these events must be handled as SAEs. (See Section 6.1.1 for reporting pregnancies).

Any component of a study endpoint that is considered related to study therapy (eg, death is an endpoint, if death occurred due to anaphylaxis, anaphylaxis must be reported) should be reported as SAE (see Section 6.1.1 for reporting details).

NOTE:

The following hospitalizations are not considered SAEs in BMS clinical studies:

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

6.1.1 Serious Adverse Event Collection and Reporting

Following the subject's written consent to participate in the study, all SAEs, whether related or not related to study drug, must be collected, including those thought to be associated with protocol-specified procedures. All SAEs must be collected that occur during the screening period and within 100 days of discontinuation of dosing. If applicable, SAEs must be collected that relate to any later protocol-specified procedure (eg, a follow-up skin biopsy).

The investigator should report any SAE that occurs after these time periods and that is believed to be related to study drug or protocol-specified procedure.

An SAE report should be completed for any event where doubt exists regarding its seriousness.

If the investigator believes that an SAE is not related to study drug, but is potentially related to the conditions of the study (such as withdrawal of previous therapy or a complication of a study procedure), the relationship should be specified in the narrative section of the SAE Report Form.

SAEs, whether related or not related to study drug, and pregnancies must be reported to BMS (or designee) within 24 hours. SAEs must be recorded on the SAE Report Form; pregnancies on

a Pregnancy Surveillance Form (electronic or paper forms). When using paper forms, the reports are to be transmitted via email or confirmed facsimile (fax) transmission to:

SAE Email Address: Refer to Contact Information list.

SAE Facsimile Number: Refer to Contact Information list.

For studies capturing SAEs through electronic data capture (EDC), electronic submission is the required method for reporting. The paper forms should be used and submitted immediately, only in the event the electronic system is unavailable for transmission. When paper forms are used, the original paper forms are to remain on site.

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

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

If an ongoing SAE changes in its intensity or relationship to study drug or if new information becomes available, a follow-up SAE report should be sent within 24 hours to the BMS (or designee) using the same procedure used for transmitting the initial SAE report.

All SAEs should be followed to resolution or stabilization.

6.2 Nonserious Adverse Events

A ***nonserious adverse event*** is an AE not classified as serious.

6.2.1 Nonserious Adverse Event Collection and Reporting

The collection of nonserious AE information should begin at initiation of study drug. Nonserious AE information should also be collected from the start of a placebo lead-in period or other observational period intended to establish a baseline status for the subjects.

Nonserious AEs should be followed to resolution or stabilization, or reported as SAEs if they become serious (see Section 6.1.1). Follow-up is also required for nonserious AEs that cause interruption or discontinuation of study drug and for those present at the end of study treatment as appropriate. All identified nonserious AEs must be recorded and described on the nonserious AE page of the CRF (paper or electronic).

All nonserious adverse events (not only those deemed to be treatment-related) should be collected continuously during the treatment period and for a minimum of 100 days following the last dose of study treatment.

Completion of supplemental CRFs may be requested for AEs and/or laboratory abnormalities that are reported/identified during the course of the study.

6.3 Laboratory Test Result Abnormalities

The following laboratory test result abnormalities should be captured on the nonserious AE CRF page or SAE Report Form (paper or electronic) as appropriate:

- Any laboratory test result that is clinically significant or meets the definition of an SAE

- Any laboratory test result abnormality that required the subject to have study drug discontinued or interrupted
- Any laboratory test result abnormality that required the subject to receive specific corrective therapy.

It is expected that wherever possible, the clinical rather than laboratory term would be used by the reporting investigator (eg, anemia versus low hemoglobin value).

6.4 Pregnancy

If, following initiation of the investigational product, it is subsequently discovered that a study subject is pregnant or may have been pregnant at the time of study exposure, including during at least 5 half lives after product administration, the investigator must immediately notify the BMS (or designee) Medical Monitor of this event and complete and forward a Pregnancy Surveillance Form to BMS (or designee) within 24 hours and in accordance with the SAE reporting procedures described in Section 6.1.1

In most cases, the study drug will be permanently discontinued in an appropriate manner (eg, dose tapering if necessary for subject safety).

In the rare event that the benefit of continuing study drug is thought to outweigh the risk, after consultation with BMS, the pregnant subject may continue study drug, after a thorough discussion of benefits and risk with the subject.

Protocol required procedures for study discontinuation and follow-up must be performed on the subject unless contraindicated by pregnancy (eg, x-ray studies). Other appropriate pregnancy follow-up procedures should be considered if indicated.

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

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

6.5 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 (see Section 6.1.1 for reporting details.).

6.6 Potential Drug Induced Liver Injury (DILI)

Wherever possible, timely confirmation of initial liver-related laboratory abnormalities should occur prior to the reporting of a potential DILI event. All occurrences of potential DILIs, meeting the defined criteria, must be reported as SAEs (see Section 6.1.1 for reporting details).

Potential drug induced liver injury is defined as:

1) AT (ALT or AST) elevation > 3 times upper limit of normal (ULN)

AND

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

AND

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

6.7 Other Safety Considerations

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

7 DATA MONITORING COMMITTEE AND OTHER EXTERNAL COMMITTEES

A Data Monitoring Committee will be established to provide oversight of safety and efficacy evaluation of the entire study and to provide advice to the sponsor regarding actions the committee deems necessary for the continuing protection of subjects. The DMC will be charged with assessing such actions in light of an acceptable benefit/risk profile for nivolumab and nivolumab + ipilimumab. The DMC will act in an advisory capacity to BMS and will monitor subject safety and evaluate the available efficacy data for the study. The oncology therapeutic area of BMS has primary responsibility for design and conduct of the study. The DMC will meet at least every 6 months or more frequently as needed on an ad-hoc basis. Information regarding DMC membership, responsibilities, and procedures are detailed in the DMC charter. The DMC will be informed should a safety signal emerge and may convene an ad-hoc meeting on its own initiative. The DMC will review all available data (safety and efficacy) data at each meeting. At the conclusion of each DMC meeting the committee, will provide the sponsor with a recommendation to continue, modify or terminate the study protocol based upon their review. Ultimately, decisions regarding the study protocol will be made by the sponsor in conjunction with feedback from investigators and the DMC.

8 STATISTICAL CONSIDERATIONS

8.1 Sample Size Determination

This study will include two safety lead-in groups (cohort 1 and 1b) and a randomized phase 3 (Cohort 2).

Cohort 1 consists of two arms to evaluate the tolerability and safety profile of nivolumab (N) and nivolumab in combination with ipilimumab (N+I, nivolumab 1 mg/kg + ipilimumab 3 mg/kg) in subjects with recurrent GBM. For this purpose, approximately 20 subjects will be randomized at 1:1 ratio to arm N or arm N + I. Cohort 1b was added to characterize an alternative dosing regimen for the combination therapy of nivolumab and ipilimumab (N+I_1b, nivolumab 3mg/kg

+ ipilimumab 1 mg/kg) in subjects with recurrent GBM. Cohort 1b will include up to 20 subjects treated. Although the sample sizes are not based on statistical power considerations, data from these subjects will provide toxicity and dosing information on administration of nivolumab and nivolumab in combination with ipilimumab to recurrent GBM subjects.

Cohort 2 is a randomized two arm study with primary objective to compare the overall survival (OS) of nivolumab (N) versus bevacizumab (B).

Results from Ipilimumab and Nivolumab studies[40,41,42] have demonstrated long term survival benefit in patients treated with immuno-oncology drugs observed as a long lasting plateau towards the end of survival curve. Data from these studies have also suggested delayed effect observed as late separation of survival curves between experimental and treatment arms. Both long-term survival benefit and delayed onset of benefit may be attributed to immuno-oncology drugs based on their mechanism of action. Recent data from a different immunotherapy compound also supports this observation in recurrent GBM population.[43]

Based on observations from these studies, following key assumptions are considered appropriate for this study design:

- 4-month delayed separation of OS curves between nivolumab and bevacizumab
- Bevacizumab Arm: OS follows exponential distribution with median of 9.2 months
- Nivolumab Arm: 10% "cure rate" (long-term survival) and exponential distribution with a median of 13.7 months after first four months for "non-cured" nivolumab subjects.

Final Analysis of OS will be conducted when at least 300 deaths have been observed among 369 randomized subjects. There will be no interim analysis for efficacy.

Given the observed accrual of 369 randomized subjects and survival assumptions stated above, simulations were conducted using piecewise exponential model for treatment group which closely approximates the assumed cure rate model for Nivolumab. Based on the assumptions for survival model, following hazard rate for Nivo/hazard ratio is used for simulation:

Months	**0-<4**	**4-<8**	**8-<12**	**12-<16**	**16-<20**	**20-<24**	**24-<28**	**28-<32**	**32-<36**	**36+**
Hazard rate for Nivolumab	.075	0.045	0.043	0.042	0.041	0.039	0.037	0.035	0.034	0.032
Hazard Ratio*	1.00	0.591	0.576	0.557	0.538	0.518	0.488	0.465	0.446	0.43

*Based on hazard rate for bevacizumab arm = 0.07534, which corresponds to median of 9.2 months under exponential distribution.

Based on simulations, it is expected that power at FA will be 92%, based on this model.

In case target number of OS events is not met for FA 25 months after last patient is randomized, FA will be conducted. Follow-up of 25 months is considered sample for mature OS curve.

All simulations were conducted using East v6.3.1.

Three hundred and sixty-nine (369) subjects have been randomized to the two arms (nivolumab vs bevacizumab) in a 1:1 ratio stratified by presence of a measureable lesion at baseline (yes/no) in 9 months. Details for comparison between previous and revised design are included in Table 8.1-1.

Table 8.1-1: Study Design - Original versus Revised

	Previous Design [redacted]	**Revised Design**
N randomized / Randomization	n=368 (actual)/ 1:1 (nivo: bevacizumab)	n=369 (actual)/ 1:1 (nivo: bevacizumab)
Target OS effect (90% power)	Bevacizumab: mOS = 9.2 months (follows exponential distribution) Nivolumab: mOS =Non-proportional hazards model based on following key assumptions: 4 months of delayed separation of curves 10% cure rate for nivolumab 13.7 months of mOS for 'non-cured'	Bevacizumab: mOS = 9.2 months (follows exponential distribution) Nivolumab: Non-proportional hazards model based on following key assumptions: 4 months of delayed separation of curves 10% 'cure rate' for nivolumab 13.7 months of mOS for 'non-cured' Power (based on Simulation): ~92%
Timing of OS IA (from first subject randomized)	90% OS events (27 months, 18 months after last patient randomized)	No Interim analysis
Final OS (from first subject randomized)	300 OS events (34 months, 25 months after last patient randomized)	300 OS events (34 months, 25 months after last patient randomized)

The overall survival at 12 months (OS[12]), progression free survival (PFS), and objective response rate (ORR) are secondary endpoints of Cohort 2 and will be tested using a hierarchical testing procedure in order to control a family-wise type I error of 0.05 (Section 8.4.2.2). Study will have more than 90% power to detect HR of 0.67 or lower for PFS (assuming a median PFS of 4.2 months for arm B) at the interim and final analysis and a difference of 20% or more for ORR at two-sided significance level of 0.05.

8.2 Populations for Analyses

- Enrolled subjects: All subjects who signed an informed consent form and were registered into the IVRS. This is the dataset for disposition.
- Randomized subjects: All enrolled subjects who were randomized. This is the dataset for baseline demographics and efficacy analyses of Cohort 2

- Treated subjects in Cohort 1 and 1b: All subjects in Cohort 1 and Cohort 1b who received at least one dose of study drug. This is the dataset for baseline demographics, efficacy, and safety evaluation of Cohort 1 and 1b.
- Treated subjects in Cohort 2: All randomized subjects in Cohort 2 who received at least one dose of study drug. This is the dataset for safety evaluation of Cohort 2.
- Response-Evaluable Subjects: All randomized subjects (for Cohort 2) or all treated subjects (for Cohort 1 and 1b) with measurable disease at a baseline tumor assessment.

[redacted]

8.3 Endpoints

8.3.1 Primary Endpoint(s)

The primary endpoint of Cohort 1 and 1b is safety and tolerability as described in Section 3.1.1. Tolerability and safety of a treatment arm will be determined after all subjects per arm have completed four doses or have discontinued dosing prior to completing four doses. Safety evaluation will include descriptive statistics as stated Section 8.4.3. The primary endpoint of Cohort 2 is overall survival (OS). OS is defined as the time between the date of randomization and the date of death due to any cause. A subject who has not died will be censored at the last known alive date. OS will be followed continuously while subjects are on study drug and every 3 months via in-person or phone contact during the survival follow-up phase of the study.

8.3.2 Secondary Endpoint(s) (Cohort 2)

The first secondary objective (compare OS rate at 12 months between arm N and arm B) will be measured by the endpoint of OS rate at 12 months OS(12). OS(12) is measured as the survival rate at 12 months from Kaplan-Meier curve of OS.

The second secondary objective (comparing PFS between arm N and arm B) will be measured by the endpoint of PFS. PFS is defined as the time from randomization to the date of the first documented tumor progression or death due to any cause. Subjects who die without a reported prior progression will be considered to have progressed on the date of death. Subjects who did not have disease progression or die will be censored at the date of last tumor assessment. Subjects who did not have any on study tumor assessment and did not die will be censored at the randomization date. Subjects who started any subsequent anti-cancer therapy without a prior reported progression will be censored at the last tumor assessment prior to initiation of the subsequent anti-cancer therapy which excludes the surgical resection for differentiating

radiology progression from pseudoprogression. Subjects who had surgical resection for differentiating radiologic progression from pseudoprogression and tumor pathology does not confirm disease progression will be censored at the last tumor assessment prior to initiation of the surgical resection. PFS will be determined by investigator reported response based on RANO criteria (Section 5.4.2). First tumor assessment will occur at the end of week 6 (+/- 1 week), end week 12 (+/- 1 week) and then every 8 weeks (+/- 1 week) thereafter until disease progression is documented. Subjects with nonmeasureable disease at baseline will be considered to have progressed if there is an appearance of new lesions consistent with tumor, any unequivocal increase in baseline enhancing disease, the unequivocal appearance of new tumor growth or re-growth at prior surgical sites, or clinical deterioration.[44]

The last secondary objective (comparing ORR between arm N and arm B) will be measured by the endpoint of ORR. ORR is defined as the number of subjects whose best overall response (BOR) is confirmed CR or PR divided by response evaluable subjects (Section 8.2). The best overall response (BOR) is determined once all the data for the subject is known. BOR is defined as the best response designation, as determined by investigators, recorded between the date of randomization and the date of objectively documented progression per RANO criteria (Section 5.4.2), the date of subsequent therapy, or date of surgical resection, whichever occurs first. For subjects without documented progression, subsequent therapy, or surgical resection, all available response designations will contribute to the BOR assessments. BOR will be determined by investigator reported response based on RANO criteria.

Tumor assessments will occur at the end of week 6, at end of week 12 and then every 8 weeks thereafter until disease progression is documented or the end of the study. For purposes of this protocol analysis, if a response evaluable subject discontinues from the study or receives a subsequent therapy prior to the 6 week tumor assessment, this subject will be counted in the denominator as a non-responder.

8.3.3 Exploratory Endpoint(s)

Duration of and time to response will be reported in conjunction with ORR. They are measured by the endpoints duration of response (DOR) and time to response (TTR). DOR is defined as the time between the date of first documented response (CR or PR) to the date of first documented tumor progression (per RANO criteria assessed by the investigator) or death due to any cause. For subjects who neither progress nor die, the date of progression will be censored at the same time they will be censored for the primary definition of PFS. TTR is defined as the time from randomization to the date of the first documented CR or PR per investigator reported RANO criteria (Section 5.4.2). DOR and TTR will be evaluated for responders (CR or PR) only.

[redacted]

Safety and tolerability will be measured by the incidence of adverse events, serious adverse events, deaths, and laboratory abnormalities.

[redacted]

8.4 Analyses

8.4.1 Demographics and Baseline Characteristics

Demographic and baseline characteristics will be summarized in all treated subjects by treatment group, as treated, for Cohort 1 and 1b and in all randomized subjects by treatment group, as randomized, for Cohort 2, using descriptive statistics

8.4.2 Efficacy Analyses

The analyses of primary and secondary endpoints will only include subjects who enrolled in Cohort 2. All hypothesis testing will be two-sided on a significance level of 0.05. If superiority in OS is demonstrated, a hierarchical hypothesis testing approach for the key secondary endpoints will be used to preserve a study-wise type I error rate at 0.05. The key secondary endpoints will be tested in the following hierarchical order:

1) OS(12)
2) PFS
3) ORR

The formal statistical testing for OS(12) will take place only if OS is statistically significant, the statistical testing for PFS will take place only if both OS and OS(12) are statistically significant, and the statistical testing for ORR will take place only all OS, OS(12) and PFS are statistically significant.

8.4.2.1 Analyses of Primary Endpoint

The distribution of OS in all randomized subjects will be compared in arms N vs B via two-sided, log-rank tests, stratified by presence of a measureable lesion at baseline (yes/no). The Kaplan-Meier product-limit method will be used to estimate the survival curve in each arm, including medians and its 95% CI, OS rates at 6, 9, 12 and 18 months. The HR and the corresponding two-sided 95% CIs will be estimated in a Cox proportional hazards model with

treatment arm as a single covariate stratified by presence of a measureable lesion at baseline (yes/no).

8.4.2.2 Analyses of Secondary Endpoints

The comparison of OS(12) will be based on a two-sided Z test. The comparison of PFS will be based on a two-sided log-rank test stratified by presence of a measureable lesion at baseline (yes/no). The comparison of ORR will be based on a two-sided Fisher's exact test. The detail of the testing procedure based will be specified in the statistical analysis plan.

8.4.3 Safety Analyses

Safety analyses will be performed in all treated subjects. Descriptive statistics of safety will be presented using National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) version 4.0 by treatment group. All on-study AEs, treatment-related AEs, SAEs, and treatment-related SAEs will be tabulated using worst grade per NCI CTCAE v 4.0 criteria by system organ class and preferred term. On-study lab parameters including hematology, chemistry, liver function, and renal function will be summarized using worst grade NCI CTCAE v 4.0 criteria.

[redacted]

[redacted]

8.5 Interim Analyses

No interim analysis for efficacy will be conducted for Cohort 2.

Data from Cohorts 1 and 1b will be periodically analyzed for external publications.

9 STUDY MANAGEMENT

9.1 Compliance

9.1.1 Compliance with the Protocol and Protocol Revisions

The study shall be conducted as described in this approved protocol. All revisions to the protocol must be discussed with, and be prepared by, BMS. The investigator should not implement any deviation or change to the protocol without prior review and documented approval/favorable opinion from the IRB/IEC of an amendment, except where necessary to eliminate an immediate hazard(s) to study subjects.

If a deviation or change to a protocol is implemented to eliminate an immediate hazard(s) prior to obtaining IRB/IEC approval/favorable opinion, as soon as possible the deviation or change will be submitted to:

- IRB/IEC for review and approval/favorable opinion
- BMS
- Regulatory Authority(ies), if required by local regulations

Documentation of approval signed by the chairperson or designee of the IRB(s)/IEC(s) must be sent to BMS.

If an amendment substantially alters the study design or increases the potential risk to the subject: (1) the consent form must be revised and submitted to the IRB(s)/IEC(s) for review and approval/favorable opinion; (2) the revised form must be used to obtain consent from subjects

currently enrolled in the study if they are affected by the amendment; and (3) the new form must be used to obtain consent from new subjects prior to enrollment.

If the revision is done via an administrative letter, investigators must inform their IRB(s)/IEC(s).

9.1.2 Monitoring

Representatives of BMS must be allowed to visit all study site locations periodically to assess the data quality and study integrity. On site they will review study records and directly compare them with source documents, discuss the conduct of the study with the investigator, and verify that the facilities remain acceptable.

In addition, the study may be evaluated by BMS internal auditors and government inspectors who must be allowed access to CRFs, source documents, other study files, and study facilities. BMS audit reports will be kept confidential.

The investigator must notify BMS promptly of any inspections scheduled by regulatory authorities, and promptly forward copies of inspection reports to BMS.

9.1.3 Investigational Site Training

Bristol-Myers Squibb will provide quality investigational staff training prior to study initiation. Training topics will include but are not limited to: GCP, AE reporting, study details and procedure, electronic CRFs, study documentation, informed consent, and enrollment of WOCBP.

9.2 Records

9.2.1 Records Retention

The investigator must retain all study records and source documents for the maximum period required by applicable regulations and guidelines, or institution procedures, or for the period specified by BMS, whichever is longer. The investigator must contact BMS prior to destroying any records associated with the study.

BMS will notify the investigator when the study records are no longer needed.

If the investigator withdraws from the study (eg, relocation, retirement), the records shall be transferred to a mutually agreed upon designee (eg, another investigator, IRB). Notice of such transfer will be given in writing to BMS.

9.2.2 Study Drug Records

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

- amount received and placed in storage area
- amount currently in storage area
- label identification number or batch number
- amount dispensed to and returned by each subject, including unique subject identifiers

- amount transferred to another area/site for dispensing or storage
- nonstudy disposition (eg, lost, wasted)
- amount destroyed at study site, if applicable
- amount returned to BMS
- retain samples for bioavailability/bioequivalence, if applicable
- dates and initials of person responsible for Investigational Product dispensing/accountability, as per the Delegation of Authority Form.

BMS will provide forms to facilitate inventory control if the investigational site does not have an established system that meets these requirements.

9.2.3 Case Report Forms

An investigator is required to prepare and maintain adequate and accurate case histories designed to record all observations and other data pertinent to the investigation on each individual treated or entered as a control in the investigation. Data that are derived from source documents and reported on the CRF must be consistent with the source documents or the discrepancies must be explained. Additional clinical information may be collected and analyzed in an effort to enhance understanding of product safety. CRFs may be requested for AEs and/or laboratory abnormalities that are reported or identified during the course of the study.

For sites using the BMS electronic data capture tool, electronic CRFs will be prepared for all data collection fields except for fields specific to SAEs and pregnancy, which will be reported on the paper or electronic SAE form and Pregnancy Surveillance form, respectively. Spaces may be left blank only in those circumstances permitted by study-specific CRF completion guidelines provided by BMS.

The confidentiality of records that could identify subjects must be protected, respecting the privacy and confidentiality rules in accordance with the applicable regulatory requirement(s).

The investigator will maintain a signature sheet to document signatures and initials of all persons authorized to make entries and/or corrections on CRFs.

The completed CRF, including any paper or electronic SAE/pregnancy CRFs, must be promptly reviewed, signed, and dated by the investigator or qualified physician who is a subinvestigator and who is delegated this task on the Delegation of Authority Form .For electronic CRFs, review and approval/signature is completed electronically through the BMS electronic data capture tool. The investigator must retain a copy of the CRFs including records of the changes and corrections.

Each individual electronically signing electronic CRFs must meet BMS training requirements and must only access the BMS electronic data capture tool using the unique user account provided by BMS. User accounts are not to be shared or reassigned to other individuals.

9.3 Clinical Study Report and Publications

A Signatory Investigator must be selected to sign the clinical study report.

For this protocol, the Signatory Investigator will be selected considering the following criteria:

- Subject recruitment
- Involvement in trial design

The data collected during this study are confidential and proprietary to BMS. Any publications or abstracts arising from this study require approval by BMS prior to publication or presentation and must adhere to BMS's publication requirements as set forth in the approved clinical trial agreement (CTA). All draft publications, including abstracts or detailed summaries of any proposed presentations, must be submitted to BMS at the earliest practicable time for review, but at any event not less than 30 days before submission or presentation unless otherwise set forth in the CTA. BMS shall have the right to delete any confidential or proprietary information contained in any proposed presentation or abstract and may delay publication for up to 60 days for purposes of filing a patent application.

10 GLOSSARY OF TERMS

Term	Definition
Adverse Reaction	An adverse event that is considered by either the investigator or BMS as related to the investigational product
Unexpected Adverse Reaction	An adverse reaction, the nature or severity of which is not consistent with the applicable product information (eg, Investigator Brochure for an unapproved investigational product)
Serious Adverse Event	Serious adverse event defined as any untoward medical occurrence that at any dose: results in death; is life threatening (defined as an event in which the subject was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe), requires inpatient hospitalization or causes prolongation of existing hospitalization; results in persistent or significant disability/incapacity, is a congenital anomaly/birth defect; is an important medical event (defined as a medical event(s) that may not be immediately life threatening or result in death or hospitalization but, based upon appropriate medical and scientific judgment, may jeopardize the subject or may require intervention [eg, medical, surgical] to prevent one of the other serious outcomes listed in the definition above). Examples of such events include, but are not limited to, intensive treatment in an emergency room or at home for allergic bronchospasm; blood dyscrasias or convulsions that do not result in hospitalization.). For reporting purposes only, BMS also considers the occurrence of pregnancy, overdose (regardless of association with an AE), and cancer as important medical events.

11 LIST OF ABBREVIATIONS

Term	Definition
ADL	Activities of daily living
AE	adverse event
ALT	alanine aminotransferase
ANC	absolute neutrophil count
AST	aspartate aminotransferase
BID	Twice daily
β-HCG	beta-human chorionic gonadotrophin
BMS	Bristol-Myers Squibb
BSA	Body surface area
BUN	blood urea nitrogen
CBC	complete blood count
CFR	Code of Federal Regulations
CI	confidence interval
cm	centimeter
CNS	Central nervous system
CrCl	Creatinine clearance
CRF	Case Report Form, paper or electronic
eCRF	Electronic Case Report Form
EDC	Electronic Data Capture
eg	exempli gratia (for example)
FDA	Food and Drug Administration
FSH	follicle stimulating hormone
FLAIR	Fluid-attenuated inversion recovery
fT4	Free thyroxine
G	Grade
g	Grams
GCP	Good Clinical Practice
GFR	glomerular filtration rate
HBV sAg	hepatitis B virus surface antigen

Term	Definition
HBV	hepatitis B virus
HCV	hepatitis C virus
HIV	Human Immunodeficiency Virus
HR	heart rate
HRS	hours
HRT	hormone replacement therapy
ICD	Implantable cardioverter defibrillator
ICH	International Conference on Harmonisation
ID	Infectious disease
ie	id est (that is)
IEC	Independent Ethics Committee
IMP	investigational medicinal products
IND	Investigational New Drug Exemption
I-O	Immuno-oncology
IRB	Institutional Review Board
IU	International Unit
IV	intravenous
IVIG	Intravenous immunoglobulin
kg	kilogram
L	liter
LC	liquid chromatography
LDH	lactate dehydrogenase
LFT	Liver function tests
mg	milligram
mg/kg	Milligram per kilogram
min	minute
mL	milliliter
mmHg	millimeters of mercury
MRI	Magnetic resonance image
µg	microgram

Term	Definition
N	number of subjects or observations
N/A	not applicable
[redacted]	[redacted]
NCI CTCAE v4	National Cancer Institute Common Terminology Criteria for Adverse Events version 4
NIMP	non-investigational medicinal products
NSAID	nonsteroidal anti-inflammatory drug
OS	overall survival
OS(12)	overall survival assessed at 12 months
[redacted]	[redacted]
[redacted]	[redacted]
PO	By mouth
QC	quality control
QD, qd	quaque die, once daily
RANO	Radiologic assessment in neuro-oncology
RBC	red blood cell
SAE	serious adverse event
SOP	Standard Operating Procedures
[redacted]	[redacted]
T. bili	Total bilirubin
TSH	Thyroid stimulating hormone
ULN	Upper limit of normal
WBC	white blood cell
WHO	World Health Organization
WOCBP	women of childbearing potential

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APPENDIX 1 KARNOFSKY PERFORMANCE SCALES

100	Normal; no complaints; no evidence of disease
90	Able to carry on normal activity; minor signs or symptoms of disease
80	Normal activity with effort; some sign or symptoms of disease
73	Cares for self; unable to carry on normal activity or do active work
60	Requires occasional assistance, but is able to care for most personal needs
50	Requires considerable assistance and frequent medical care
40	Disabled; requires special care and assistance
30	Severely disabled; hospitalization is indicated, although death not imminent
20	Very sick; hospitalization necessary; active support treatment is necessary
10	Moribund; fatal processes progressing rapidly
0	Dead

APPENDIX 2 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 (I-O) 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.

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.

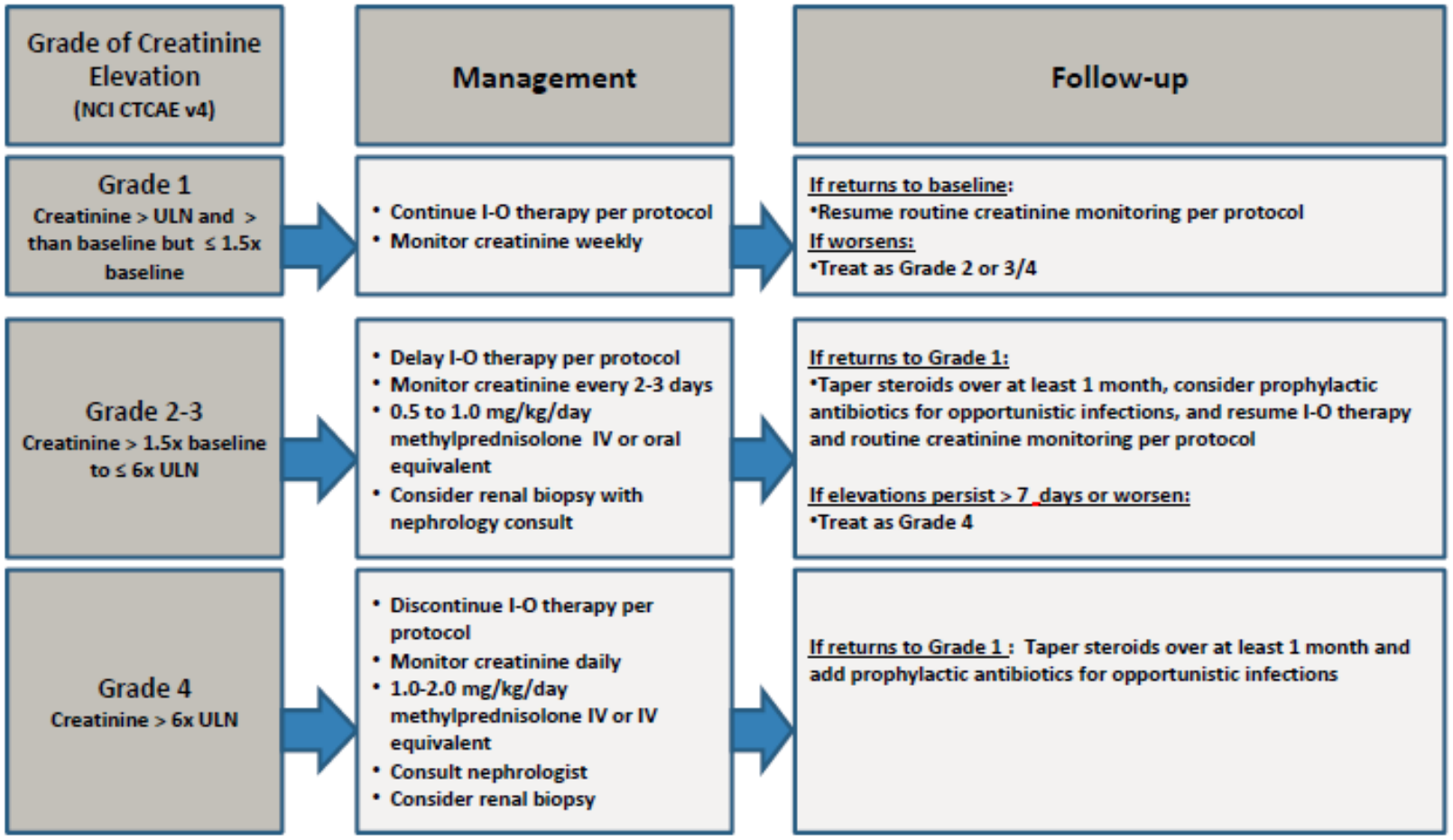
Grade of Diarrhea/ Colitis (NCI CTCAE v4)	Management	Follow-up
Grade 1 Diarrhea:< 4 stools/day over baseline; Colitis: asymptomatic	• Continue I-O therapy per protocol • Symptomatic treatment	• Close monitoring for worsening symptoms. • Educate patient to report worsening immediately If worsens: • Treat as Grade 2 or 3/4
Grade 2 Diarrhea: 4-6 stools per day over baseline; IV fluids indicated <24 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 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.

Updated 05-Jul-2016

Renal Adverse Event Management Algorithm

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

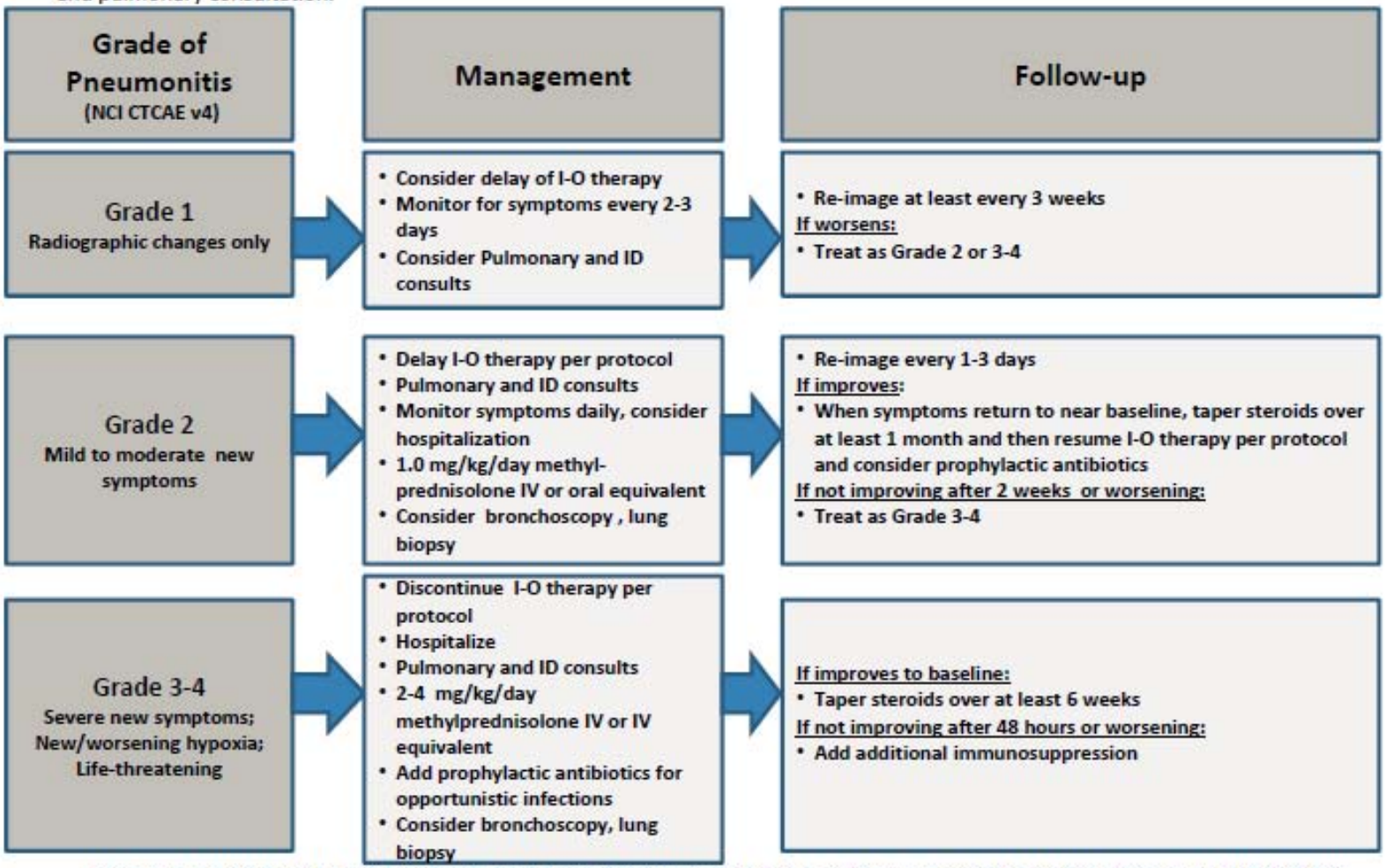


Patients on IV steroids may be switched to an equivalent dose of oral corticosteroids (e.g. prednisone) at start of tapering or earlier, once sustained clinical improvement is observed. Lower bioavailability of oral corticosteroids should be taken into account when switching to the equivalent dose of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

Updated 05-Jul-2016

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.

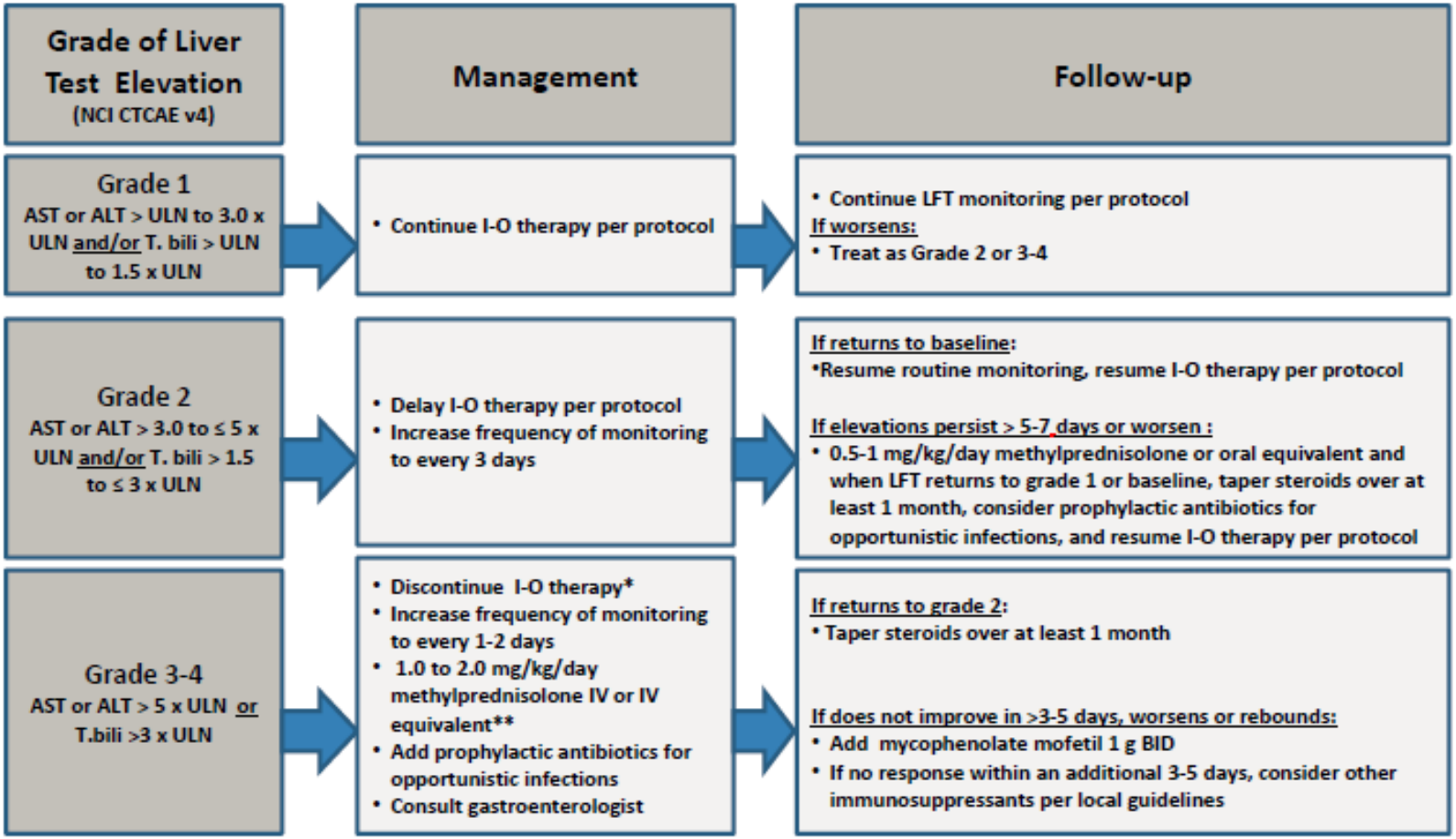


Patients on IV steroids may be switched to an equivalent dose of oral corticosteroids (e.g. prednisone) at start of tapering or earlier, once sustained clinical improvement is observed. Lower bioavailability of oral corticosteroids should be taken into account when switching to the equivalent dose of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

Updated 05-Jul-2016

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.

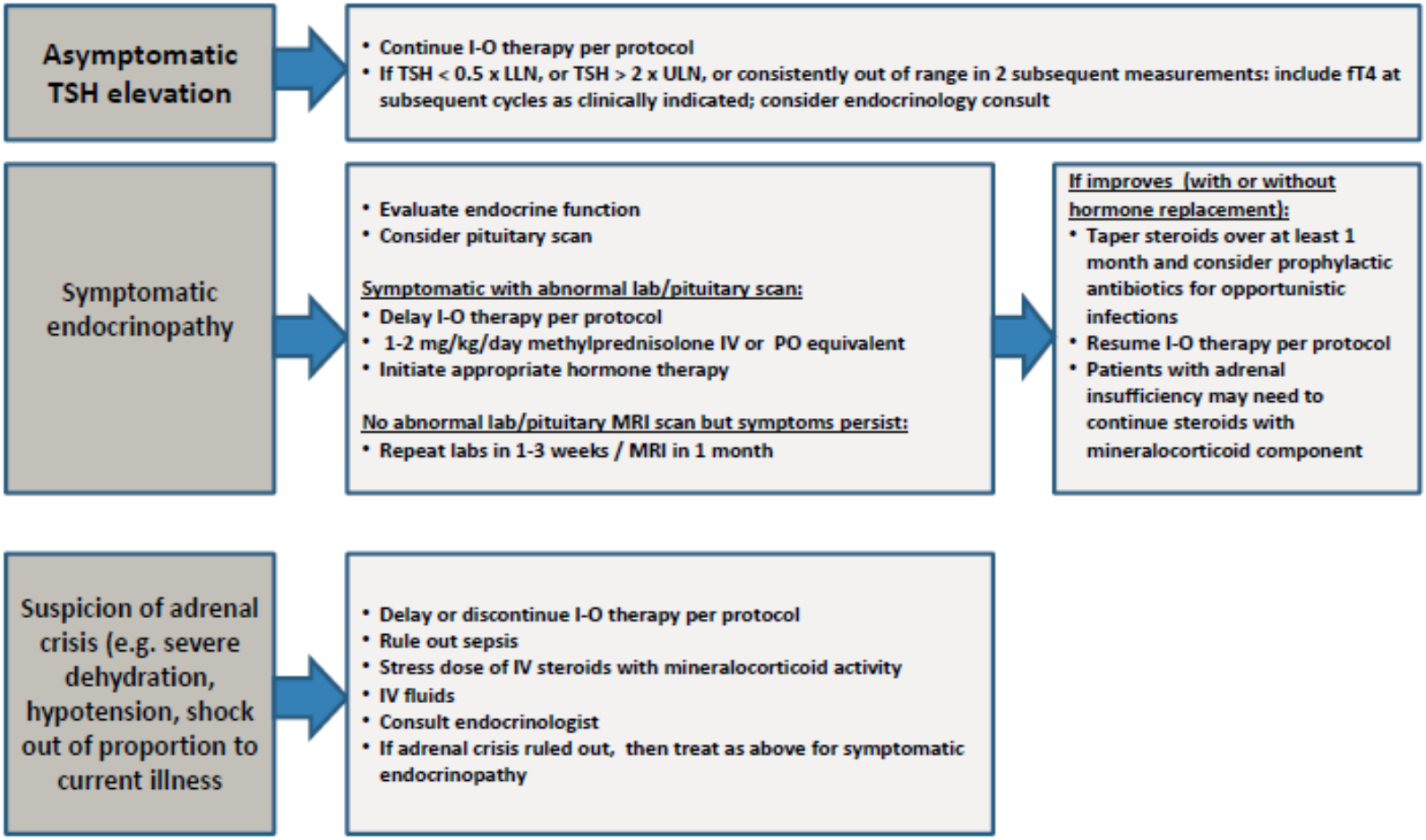
*I-O therapy may be delayed rather than discontinued if AST/ALT ≤ 8 x ULN or T.bili ≤ 5 x ULN.

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

Updated 05-Jul-2016

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.

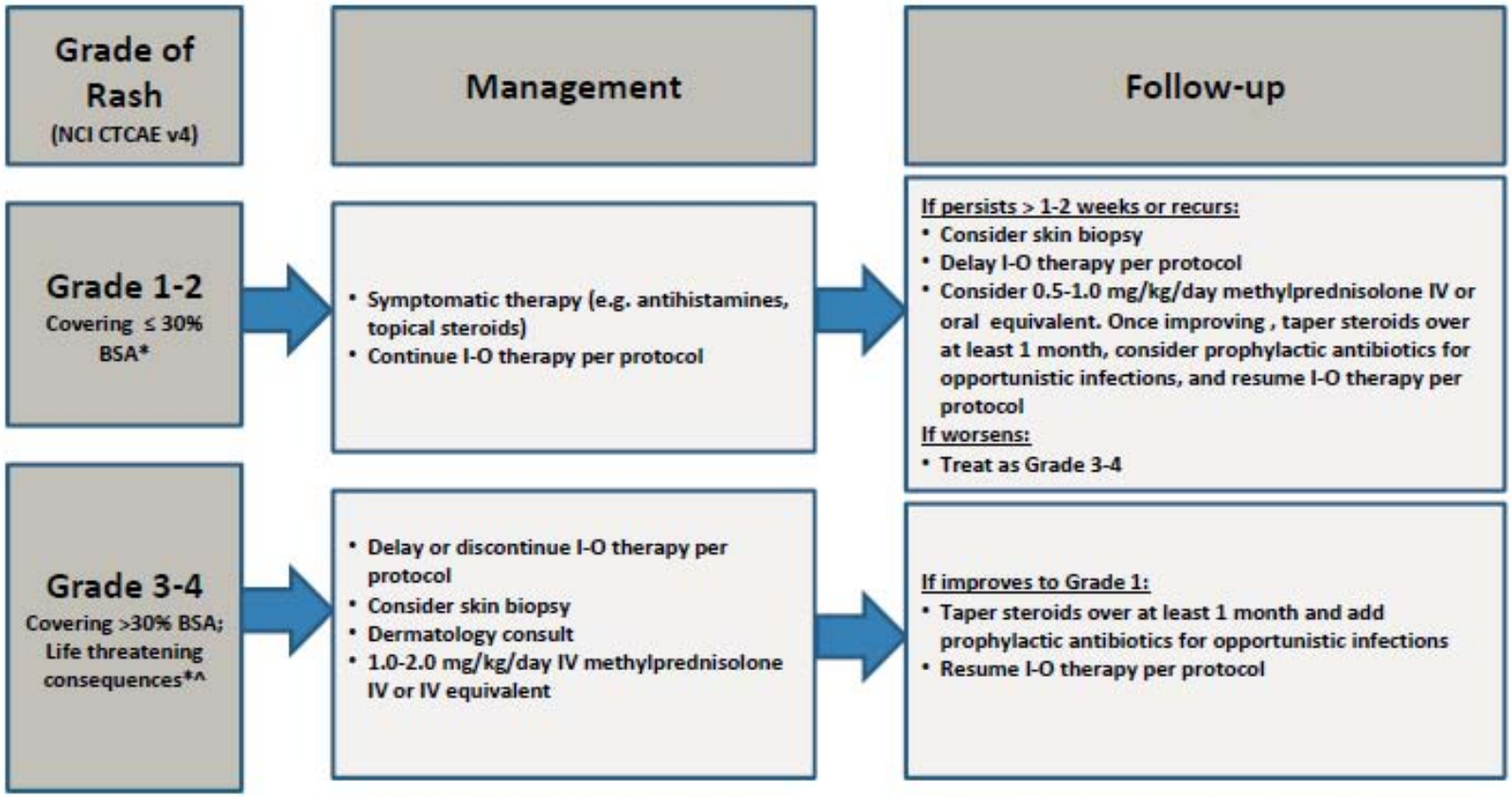


Patients on IV steroids may be switched to an equivalent dose of oral corticosteroids (e.g. prednisone) at start of tapering or earlier, once sustained clinical improvement is observed. Lower bioavailability of oral corticosteroids should be taken into account when switching to the equivalent dose of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

Updated 05-Jul-2016

Skin Adverse Event Management Algorithm

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

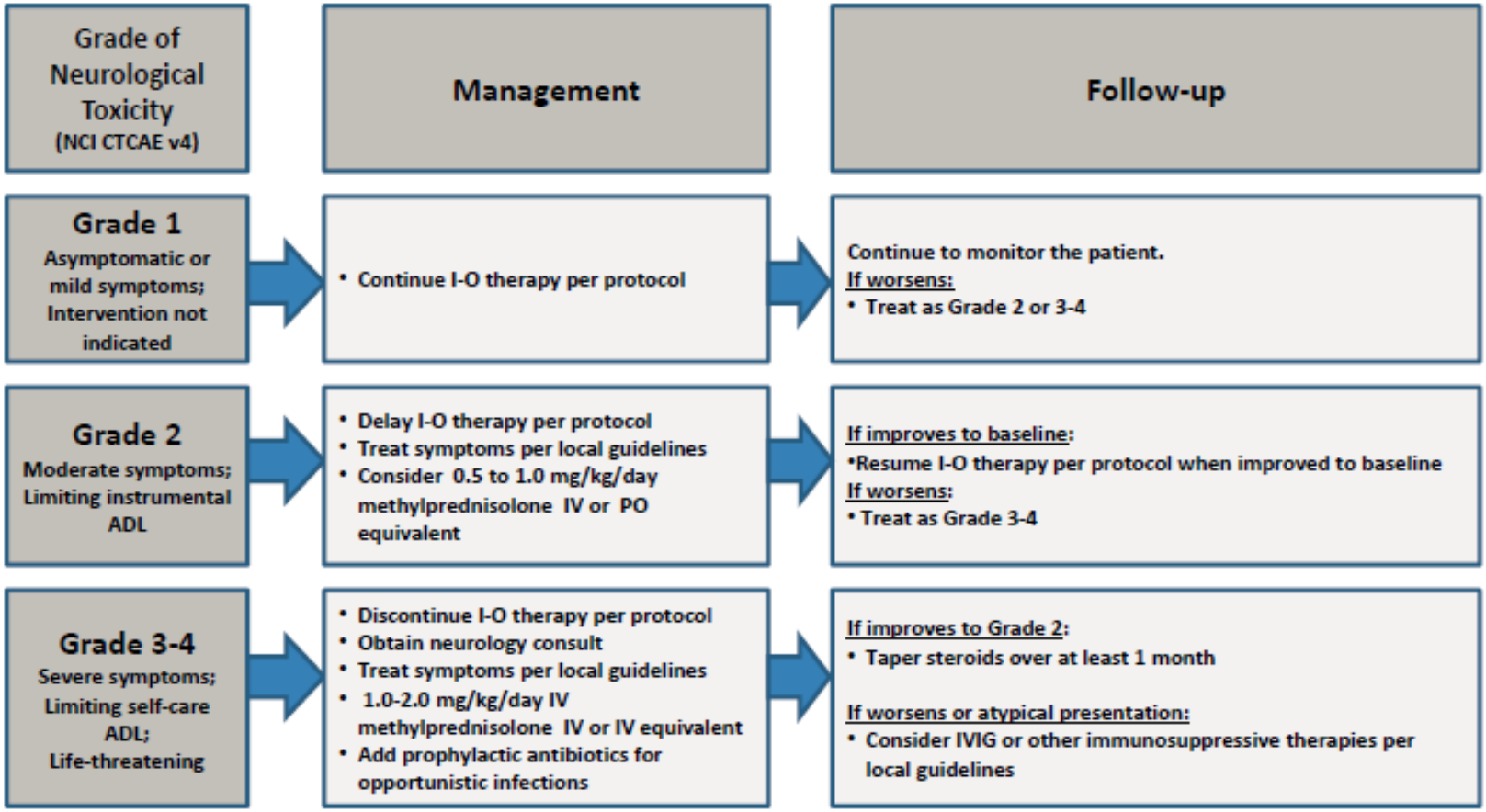


Patients on IV steroids may be switched to an equivalent dose of oral corticosteroids (e.g. prednisone) at start of tapering or earlier, once sustained clinical improvement is observed. Lower bioavailability of oral corticosteroids should be taken into account when switching to the equivalent dose of oral corticosteroids.
*Refer to NCI CTCAE v4 for term-specific grading criteria.
^If SJS/TEN is suspected, withhold I-O therapy and refer patient for specialized care for assessment and treatment. If SJS or TEN is diagnosed, permanently discontinue I-O therapy.

Updated 05-Jul-2016

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.

Updated 05-Jul-2016