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TITLE: *An Open-Label Phase II Study of Nivolumab or Nivolumab/Ipilimumab in Adult Participants With Progressive/Recurrent Meningioma*

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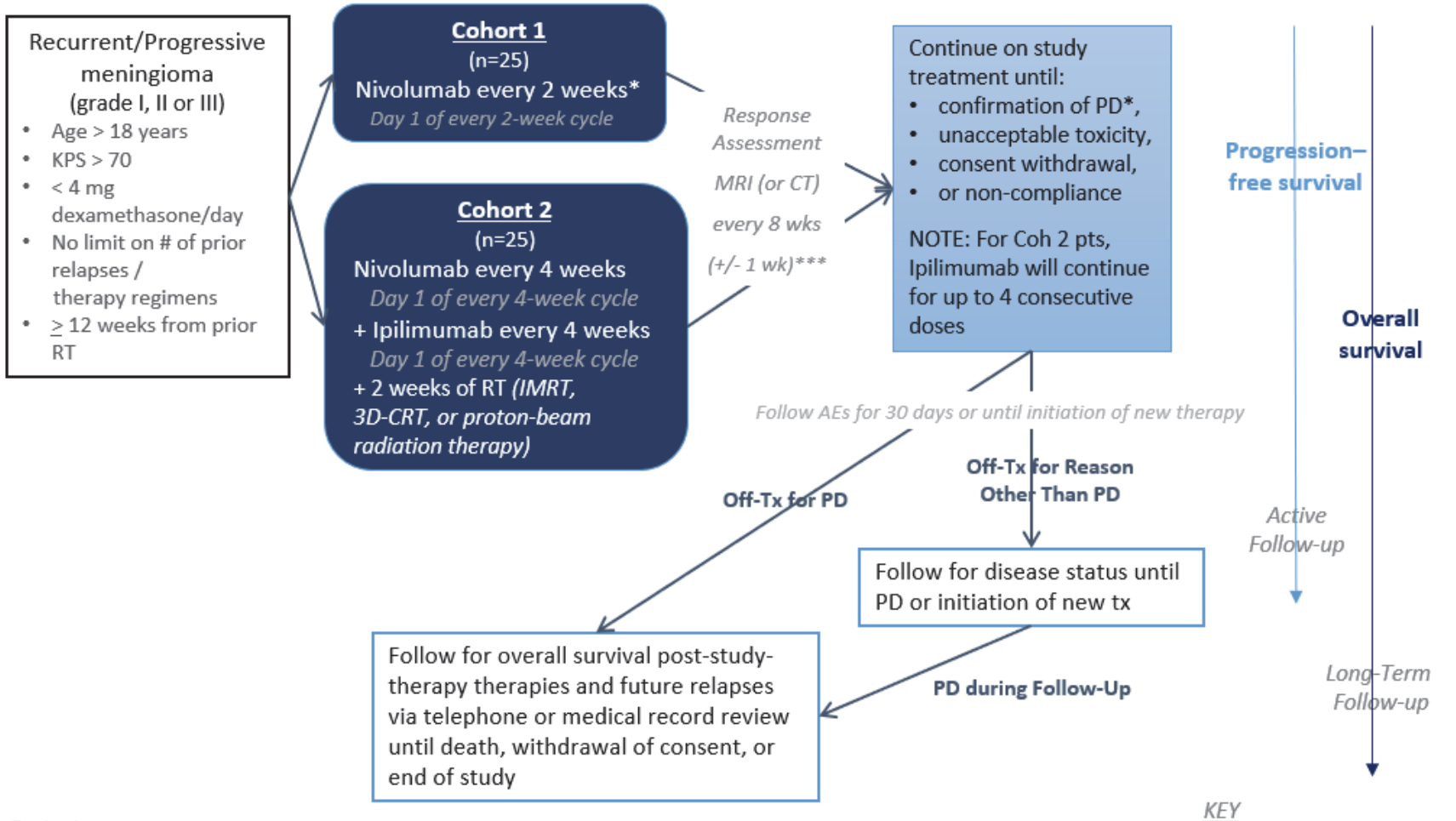
STUDY SCHEMA



Footnotes:

** NOTE: Cohort 2 participants with new areas of progression can remain on-study to receive additional RT per protocol; See Sections 5.2.5 and 5.6*

*** See Section 11.4 re: confirmation of progression (treatment beyond initial radiologic assessment of disease progression)*

*** Primary Endpoint = PFS6

KEY

Cycles = 14 days (Coh 1) & 28 days (Coh 2)
KPS = Karnofsky Performance Score
RT = Radiation Therapy
IMRT = intensity-modulated radiation therapy
3D-CRT = 3-dimensional conformal radiation therapy
PD = Progressive Disease
AEs = Adverse Events
Off-Tx = Off-Treatment

TRIAL SUMMARY

Abbreviated Title	Nivolumab for Progressive/Recurrent Meningioma
Trial Phase	II
Clinical Indication	Progressive/recurrent meningioma
Trial Type	Interventional
Type of control	No treatment control
Route of administration	Intravenous
Trial Blinding	Unblinded, open-label
Treatment	Cohort 1: Nivolumab monotherapy (240 mg every 2 weeks) *NOTE: Participants who have received active study therapy for >/= 6 months will be allowed the option to adjust their Nivolumab dosing schedule from 240 mg once every 2 weeks (-2/+5 days) to 480 mg once every 4 weeks (+/- 1 week).* Cohort 2: External Beam RT (IMRT, 3D-CRT, or proton-beam radiation therapy), followed by 4 cycles of Nivolumab (3 mg/kg every 3 weeks) + Ipilimumab (1 mg/kg every 3 weeks), followed by Nivolumab monotherapy (480 mg every 4 weeks). A safety lead-in is included for Cohort 2.
Number of trial subjects	Approximately 25 patients will be enrolled in each cohort
Estimated duration of trial	The Principal Investigator estimates that the trial will require approximately 42 months from the time the first participant of each cohort signs the informed consent until the last participant's last visit.
Duration of Participation	Each participant will participate in the trial from the time the participant signs the Informed Consent Form (ICF) through the final protocol-specified contact. After a screening phase (assessments within 14 days of first dose), eligible participants will receive treatment during each dosing cycle. • Cohort 1: Nivolumab every 2 weeks • Cohort 2: External Beam RT (IMRT, 3D-CRT, or proton-beam radiation therapy) followed by 4 cycles of Nivolumab + Ipilimumab (dosing every 3 weeks), followed by Nivolumab monotherapy (dosing every 4 weeks). Treatment with study therapy will continue until: documented confirmed disease progression; unacceptable adverse event(s)*; intercurrent illness that prevents further administration of treatment; investigator's decision to withdraw the participant; participant withdraws consent; pregnancy of the participant; noncompliance with trial treatment or procedure requirements. After the end of treatment, each participant will be followed for 30 days for adverse event monitoring (serious adverse events will be collected until 100 days after the end of treatment or the start of new anti-cancer treatment, whichever comes first). Participants who discontinue for reasons other than disease progression will have post-treatment follow-up for disease status until disease progression, withdrawing consent, or becoming lost to follow-up. All participants will be followed by telephone or medical record review for overall survival until death, withdrawal of consent, or the end of the study. ** NOTE: Cohort 2 participants may proceed with nivolumab monotherapy dosing every 4 weeks if ipilimumab is considered toxic.*

TABLE OF CONTENTS

1. OBJECTIVES

We hypothesize that inhibition of PD-1 signaling will generate meaningful anti-tumor benefit and will be well tolerated for progressive/recurrent meningioma patients. We propose to initially evaluate Nivolumab in an open-label, phase II study for patients with recurrent atypical or anaplastic meningioma. The study has been amended to include a second cohort (cohort 2) of participants where the combination of nivolumab plus ipilimumab is evaluated following administration of radiation therapy. Enrollment to cohort 2 will commence upon completion of enrollment to the original cohort (cohort 1) of participants treated with nivolumab monotherapy. In addition, the study has been amended to include patients with grade 1 meningioma that have progressed after prior radiation therapy based on the lack of effective therapies for these patients and their decreased outcome.

1.1 Study Design

This open-label Phase 2 study will evaluate nivolumab among adult (≥ 18 years of age) participants with progressive/recurrent grade I, II or III meningioma. The initial cohort of participants (cohort 1) will receive nivolumab monotherapy. Cohort 2 participants will receive nivolumab plus ipilimumab following radiation therapy. All participants will be followed for safety and tolerability, tumor progression and survival. Safety and tolerability will be evaluated by adverse event assessments that will be documented at each visit throughout the study using the Common Terminology Criteria for Adverse Events (CTCAE) Version 4.0 grading system. Tumor progression or response endpoints will be assessed using Immunotherapy Radiologic Assessment in Neuro-Oncology criteria (iRANO) criteria as described in Section 11.2. Treatment with study medication will continue until confirmed tumor progression, unacceptable toxicity or other discontinuation criteria as described in Section 11, whichever comes first.

The study design schematic is presented in Figure 1.

1.2 Primary Objectives

1.2.1 To evaluate the anti-tumor activity as measured by progression-free survival at six months (PFS-6) for single-agent nivolumab (cohort 1) or nivolumab plus ipilimumab following radiation therapy among patients with recurrent/progressive grade I, II or III meningioma.

1.3 Secondary Objectives

1.3.1 To evaluate the safety and tolerability of single-agent nivolumab and nivolumab plus ipilimumab after radiation therapy among patients with recurrent/progressive grade I, II or III meningioma

1.3.2 To evaluate additional measures of anti-tumor activity of single-agent nivolumab and nivolumab plus ipilimumab after radiation therapy among patients with recurrent/progressive grade I, II or III meningioma including median PFS, median overall survival (OS) and objective response rate (ORR).

1.4 Exploratory Objectives

1.4.1 Correlatives:

1.4.1.1 To evaluate correlative biomarkers of systemic immune response among patients with recurrent/progressive grade I, II or III meningioma treated with study therapy.

1.4.1.2 To evaluate archival tumor expression of PD-L1 and PD-1 expressing tumor infiltrating lymphocytes.

1.4.1.3 To evaluate archival tumor expression of immune gene expression signature.

1.4.2 To evaluate neurologic function among patients with recurrent/progressive grade I, II or III meningioma treated with study therapy using the Neurologic Assessment in Neuro-Oncology (NANO) scale.

1.4.3 To evaluate change in tumor growth rate as measured by volumetric analysis

1.4.3.1 To determine if there is a difference in tumor growth rates before and after treatment that would allow detection of treatment efficacy.

1.4.3.2 To determine if there are pre-treatment predictors of treatment response using radiomic analysis

2. BACKGROUND

This phase II study is designed to evaluate the anti-tumor benefit and safety of inhibition of PD-1 signaling among patients with progressive grade II-III meningioma. Specifically, the primary objective of this study is to evaluate the anti-tumor activity of nivolumab monotherapy and nivolumab plus ipilimumab after radiation therapy among patients with progressive grade I-III meningioma as measured by progression-free survival at six months (PFS-6). Secondary objectives include to 1) evaluate the safety and tolerability of nivolumab monotherapy and nivolumab plus ipilimumab after radiation therapy in subjects with progressive/recurrent meningioma; and 2) evaluate additional measures of anti-tumor activity of nivolumab monotherapy and nivolumab plus ipilimumab after radiation therapy among subjects with progressive/recurrent meningioma including median PFS, median overall survival (OS) and overall radiographic response rate (ORR). We hypothesize that nivolumab will have meaningful anti-tumor benefit and will be well tolerated among subjects with progressive/recurrent meningioma.

2.1 Study Disease: Meningioma

Meningiomas are the most common primary central nervous system tumor among adults. Approximately 23,000 cases are diagnosed annually in the United States.(4) Meningiomas arise from meningothelial arachnoid cap cells associated with the leptomeningeal surface of the central nervous system. Most occur in the supratentorial compartment, while about 12% arise along the spinal cord. Approximately 9% of patients present with multifocal lesions.(5) In population based studies, meningiomas represent greater than 20% of primary intracranial neoplasms in adults.(4) Their incidence increases with age and there is predominance in women with a female/male ratio of 2:1. They are also more common among African Americans than Caucasians.(6) Predisposing risk factors include neurofibromatosis type 2 (NF-2) and prior exposure to cranial irradiation.(7, 8)

The World Health Organization (WHO) classifies meningiomas into three main categories based on histopathologic findings including: grade I (benign); grade II (atypical); and grade III (anaplastic) meningiomas. Atypical (WHO grade II) meningiomas account for up to 20% of all meningiomas, and are distinguished by either an elevated mitotic rate (≥ 4 mitoses/high power field) or increased cellularity. Anaplastic (WHO grade III) meningiomas account for up to 3% of

cases and are defined by the presence of either frank anaplastic features or a markedly elevated mitotic index (≥ 20 mitoses/high power field).
Although most meningiomas are grade I and can be initially treated with surgery and/or radiation, effective therapy for those that recur or are either grade II (atypical) or grade III (anaplastic) remains elusive.(9-13) Six thousand patients are estimated to require additional treatment following meningioma recurrence annually in the United States.(14)

Initial therapy for symptomatic or growing meningiomas is maximum safe resection while radiation therapy is usually reserved for atypical or anaplastic meningiomas or inoperable and progressive grade I tumors.(15, 16) Nonetheless, radiotherapy approaches, although initially effective in many cases, are not curative, and are associated with a spectrum of significant late sequela including cognitive decline, neuroendocrine deficiency, strokes and second malignancies.(17)

Effective therapy for meningiomas that recur following radiation therapy has not been identified. In particular, overall outcome for patients with progressive grade II and III meningiomas remains particularly poor with most series reporting 5-year survival rates of 28-61%.(18, 19) A recent meta-analysis of all salvage medical therapies evaluated for patients with atypical and anaplastic meningiomas that recur after surgery and radiation, revealed a weighted average PFS-6 rate of 26% (95% CI: 19.3-32.7%).(20) Similarly, meta-analysis data from the literature evaluating treatment of grade 1 meningioma patients who progressed after initial radiation therapy report a median PFS-6 of 29% (95% CI: 20.3%, 37.7%) and median overall survival of 7-13 months following administration of salvage therapy.(20) Results of several trials evaluating a wide variety of chemotherapy agents have been disappointing(15) although hydroxyurea has demonstrated modest anti-tumor activity in some series.(21, 22) Targeted therapies that inhibit specific activators of dysregulated cell signaling pathways, such as the epidermal growth factor receptor (EGFR) or platelet derived growth factor receptor (PDGFR) have also proven ineffective in clinical trials to date among non-enriched meningioma patients.(23, 24) In addition, hormonal-based therapies have also proven ineffective.(25, 26) Most recently, therapeutic efforts have utilized anti-angiogenic agents for progressive meningiomas based on the observation that levels of vascular endothelial growth factor (VEGF) and VEGF receptor increase with increasing meningioma grade and provide prognostic significance.(27) Two retrospective series report modest therapeutic benefit associated with bevacizumab, a humanized monoclonal antibody against VEGF, for patients with progressive meningiomas.(28, 29) In addition, a recently reported single arm phase II study of sunitinib, an oral VEGFR tyrosine kinase inhibitor, demonstrated modest anti-tumor activity among patients with recurrent atypical and anaplastic meningiomas.(30) In summary, effective treatment of meningiomas that progress following surgery and radiotherapy have not been defined and patients with such tumors remain a major unmet need in modern day oncology. A recent meta-analysis of all salvage medical therapies evaluated for surgery and radiation refractory, recurrent atypical and anaplastic meningiomas revealed a weighted average PFS-6 rate of 26% (95% CI: 19.3-32.7%) and 29% for those with progressive grade I tumors.(20) The poor PFS-6 rate for progressive grade I meningiomas, which is negligibly better than that of grade II or III tumors, indicates that effective therapies for progressive grade I meningiomas are not available. In addition, a subset of grade I meningiomas may transform to grade II or III at recurrence. Based on these considerations, patients with progressive grade I meningiomas are therefore appropriate to consider for treatment with promising salvage therapies in prospective clinical trials, and other clinical trials are doing so (NCT03279692). The current clinical trial has therefore been amended to include patients with grade I meningiomas that have progressed after prior surgery and

radiotherapy. Novel therapeutic strategies are desperately needed for patients with progressive/recurrent grade I-III meningioma.

2.2 IND Agent: Nivolumab

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) indicate that nivolumab is active in multiple tumor types. Nivolumab 3 mg/kg monotherapy is currently being studied in advanced clinical trials in advanced melanoma, glioblastoma, renal cell carcinoma (RCC), gastric cancer, head and neck carcinoma, nasopharyngeal carcinoma and various subtypes of lung cancer (Bristol Myers Squibb; unpublished data). Nivolumab was approved by the US FDA for advanced melanoma on December 22, 2014 based on an objective response rate of 40% which was maintained for more than six months in approximately one-third of patients.(2) On March 4, 2015, Nivolumab was approved by the US FDA for patients with advanced squamous non-small cell lung cancer (NSCLC) who have progressed on or after platinum-based chemotherapy.(3) This approval was based on data from the phase III CheckMate-017 study in which nivolumab improved OS by 3.2 months compared to docetaxel. Among the 272 patients enrolled on this study, treatment with nivolumab improved OS by 41% (9.2 vs 6.0 months; HR = 0.59; p=0.00025). The FDA approval for squamous NSCLC was supported by data from a single-arm phase II study in which heavily pretreated patients achieved a median OS of 8.2 months and the ORR was 15%. In this study, 26% of patients achieved stable disease for at least six months and tumor PD-L1 expression did not correlate with response.

2.2.1 Product Development Background

Nivolumab is FDA approved for the treatment of metastatic melanoma among adults who have progressed on ipilumimab and a BRAF inhibitor as well as advanced stage squamous NSCLC that has recurred after platinum-based chemotherapy. 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) and further detailed information regarding the clinical safety of nivolumab for each of these indications is provided in the Investigator's Brochure and as detailed below. Nivolumab is being investigated both as monotherapy and in combination with chemotherapies and other immunotherapies.

2.2.2 Clinical Pharmacokinetics

The pharmacokinetics of nivolumab was studied in subjects over a dose range of 0.1 to 10 mg/kg administered as a single dose or as multiple doses of nivolumab over 2 or 3 weeks. The geometric mean (% CV%) clearance (CL) was 9.5 mL/h (49.7%), geometric mean volume of distribution at steady state (Vss) was 8.0 L (30.4%), and geometric mean elimination half-life (t1/2) was 26.7 days (101%). Steady-state concentrations of nivolumab were reached by 12 weeks when administered at 3 mg/kg Q2W, and systemic accumulation was approximately 3-fold. The exposure to nivolumab increased dose proportionally over the dose range of 0.1 to 10 mg/kg administered every 2 weeks. The clearance of nivolumab increased with increasing body weight. The PPK analysis suggested that the following factors had no clinically important effect on the CL of nivolumab: age (29-87 years), gender, race, baseline LDH, PD-L1. A PPK analysis suggested no difference in CL of nivolumab based on age, gender, race, tumor type, baseline tumor size and hepatic impairment.
Although ECOG status, baseline glomerular filtration rate (GFR), albumin, body weight, and mild hepatic impairment had an effect on nivolumab CL, the effect was not clinically meaningful. When nivolumab is administered in combination with ipilimumab, the CL of nivolumab was increased by 24%, whereas there was no effect on the clearance of ipilimumab. Additionally, PPK and exposure response analyses have been performed to support use of 240 mg Q2W in addition to the 3 mg/kg Q2W regimen. Using the PPK model, exposure of nivolumab at 240 mg flat dose was identical to a dose of 3 mg/kg for subjects weighing 80 kg, which was the approximate median body weight in nivolumab clinical trials.

2.2.3 Clinical Efficacy

Nivolumab has demonstrated durable responses exceeding 6 months as monotherapy and in combination with ipilimumab in several tumor types, including NSCLC, melanoma, RCC and some lymphomas. In confirmatory trials, nivolumab as monotherapy demonstrated a statistically significant improvement in OS as compared with the current standard of care in subjects with advanced or metastatic NSCLC and in subjects with unresectable or metastatic melanoma. Nivolumab in combination with ipilimumab improved PFS and ORR over ipilimumab alone in subjects with unresectable or metastatic melanoma.

2.2.4 Clinical Safety

The overall safety experience with nivolumab, as a monotherapy or in combination with other therapeutics, is based on experience in approximately 8600 subjects treated to date.

For monotherapy, the safety profile is similar across tumor types and is manageable with no MTD reached at any dose tested up to 10 mg/kg. There is no pattern in the incidence, severity, or causality of AEs to nivolumab dose level. Most AEs were low-grade (Grade 1-2) with relatively few related high-grade (Grade 3-4) AEs. In Phase 3 controlled studies, the safety profile of nivolumab monotherapy is acceptable in the context of the observed clinical efficacy, and manageable using established safety guidelines. Clinically relevant AEs typical of stimulation of the immune system were infrequent and manageable by delaying or stopping nivolumab treatment and timely immunosuppressive therapy or other supportive care.

In several ongoing clinical trials, the safety of nivolumab in combination with other therapeutics such as ipilimumab, cytotoxic chemotherapy, anti-angiogenics, and targeted therapies is being

explored. Most studies are ongoing and, as such, the safety profile of nivolumab combinations continues to evolve. The safety profile of nivolumab combination therapy varies with the agent combined with nivolumab, but is generally consistent with the safety profiles observed with either agent alone and, in some cases, both frequency and severity of AEs were greater than that observed with either agent alone. The most advanced combination under development is nivolumab plus ipilimumab in subjects with unresectable or metastatic melanoma. Results to date suggest that the safety profile of nivolumab plus ipilimumab combination therapy is consistent with the mechanisms of action of nivolumab and ipilimumab. The nature of the AEs is similar to that observed with either agent used as monotherapy; however, both frequency and severity of AEs are increased with the combination. For nivolumab monotherapy and combination therapy, most high-grade events were manageable with use of corticosteroids or hormone replacement therapy (endocrinopathies).

Please refer to the Nivolumab Investigator Brochure for additional information.

2.2.5 Rationale for Nivolumab Dose

The nivolumab dose of 240 mg every 2 weeks (Q2W) for cohort 1 was selected based on clinical data and modeling and simulation approaches using population PK (PPK) and exposure-response analyses of data from studies in multiple tumor types (melanoma, non-small-cell lung cancer [NSCLC], and renal cell carcinoma [RCC]) where body weight normalized dosing (mg/kg) has been used.

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

Nivolumab is safe and well tolerated up to 10 mg/kg Q2W dose level. Adverse events have been broadly consistent across tumor types following monotherapy and have not demonstrated clear dose-response or exposure-response relationships. Additionally, the simulated median and 95th prediction interval of nivolumab summary exposures across body weight range (35 - 160 kg) are predicted to be maintained below the corresponding observed highest exposure experienced in nivolumab ie, 95th percentile following nivolumab 10 mg/kg Q2W from clinical study CA209003. Thus, while subjects in the lower body weight ranges would have greater exposures than 80 kg subjects, the exposures are predicted to be within the range of observed exposures at doses (up to 10 mg/kg Q2W) used in the nivolumab clinical program, and are not considered to put subjects at

increased risk. For subjects with greater body weights, the simulated ranges of exposures are also not expected to affect efficacy, because the exposures predicted following administration of a 240 mg Q2W are on the flat part of the exposure-response curves for previously investigated tumors, melanoma and NSCLC. Given the similarity of nivolumab PK across tumor types and the similar exposures predicted following administration of 240 mg flat dose compared to 3 mg/kg, it is expected that the safety and efficacy profile of nivolumab 240 mg Q2W will be similar to that of nivolumab 3 mg/kg Q2W. Thus a flat dose of nivolumab 240 mg every 2 weeks will be used this study for cohort 1. For cohort 2 in which nivolumab is combined initially with ipilimumab, the dose will be 3 mg/kg once every 3 weeks in combination with ipilimumab for four doses and then administered at 480 mg flat dosing once every four weeks until study therapy discontinuation.

2.3 IND Agent: Ipilimumab

2.3.1 Product Development Background

Ipilimumab (BMS-734016, MDX010, MDX-CTLA4) is a fully human monoclonal immunoglobulin (Ig) G1κ specific for human cytotoxic T-lymphocyte antigen 4 (CTLA-4, cluster of differentiation [CD] 152), which is expressed on a subset of activated T cells. CTLA-4 is a negative regulator of T-cell activity. Ipilimumab is a monoclonal antibody (mAb) that binds to CTLA-4 and blocks the interaction of CTLA-4 with its ligands, CD80/CD86. Blockade of CTLA-4 has been shown to augment T-cell activation and proliferation, including the activation and proliferation of tumor-infiltrating T-effector cells. Inhibition of CTLA-4 signaling can also reduce T-regulatory cell (Treg) function, which may contribute to a general increase in T-cell responsiveness, including the anti-tumor response. Yervoy™ (ipilimumab) 3 mg/kg has been approved for use in advanced melanoma in over 47 countries, including the United States (US, 25-Mar-2011), the European Union (EU, 13-Jul 2011), and Australia (Jul-2011). In this protocol, patients on cohort 2 will receive ipilimumab at 1 mg/kg every 3 weeks for four doses in combination with nivolumab.

Yervoy 10 mg/kg is approved as adjuvant treatment of unresectable or metastatic melanoma in the US. The European Commission (EC) decision for Yervoy Type II variation extending the indication to previously untreated melanoma patients was granted on 31-Oct-2013. Yervoy is approved in the EU for the treatment of adolescents and in the US for the treatment of melanoma in pediatric patients.

2.3.2 Clinical Pharmacokinetics

The PK of ipilimumab has been extensively studied in subjects with melanoma, at the ~3-mg/kg and 10-mg/kg doses administered as a 1.5-hour IV infusion. The PK of ipilimumab was characterized by population pharmacokinetic (PPK) analysis and determined to be linear and time invariant in the dose range of 0.3 to 10 mg/kg. The population pharmacokinetics of ipilimumab was studied in 785 subjects (3,200 serum concentrations) with advanced melanoma in 4 Phase 2 studies (CA184004, CA184007, CA184008, and CA184022),(61) 1 Phase 3 study (CA184024), and 1 Phase 1 study (CA184078). The PPK analysis demonstrated that the PK of ipilimumab is linear, the exposures are dose proportional across the tested dose range of 0.3 mg/kg to 10 mg/kg, and the model parameters are time-invariant, similar to that determined by noncompartmental analyses. Upon repeated dosing of ipilimumab, administered q3w, minimal systemic accumulation was observed by an accumulation index of 1.5-fold or less, and ipilimumab steady-state concentrations were achieved by the third dose. The ipilimumab CL of 16.8 mL/h from PPK

analysis is consistent with that determined by noncompartmental PK analysis and shown in Table 5.2.1-1. The terminal T-HALF and Vss of ipilimumab calculated from the model were 15.4 days and 7.47 L, respectively, which are consistent with that determined by noncompartmental analysis. Volume of central compartment (Vc) and peripheral compartment were reported to be 4.35 L and 3.28 L, respectively, suggesting that ipilimumab first distributes into plasma volume and, subsequently, into extracellular fluid space. CL of ipilimumab and Vc were found to increase with increase in BW. However, there was no significant increase in exposure with increase in BW when dosed on a milligram/kilogram basis, supporting dosing of ipilimumab based on a weight normalized regimen. The PK of ipilimumab is not affected by age, gender, race, and immunogenicity (ADA status); concomitant use of chemotherapy; prior therapy; BW; performance status; or tumor type. Other covariates had effects that were either not statistically significant or of minimal clinical relevance.

The population pharmacokinetics of ipilimumab when administered alone or in combination with nivolumab to subjects with melanoma, non-small cell lung cancer, renal cell carcinoma, small cell lung cancer, hepatocellular carcinoma, and colorectal cancer was also assessed.(64) Ipilimumab CL when given in combination with nivolumab 3 mg/kg q3w was not significantly different from that seen with ipilimumab monotherapy. The CL of ipilimumab was higher when administered in combination with nivolumab 1 mg/kg q3w or 3 mg/kg q3w compared to ipilimumab monotherapy; however, the magnitude of these differences are not considered to be clinically relevant (< 20%). Thus, there is no apparent effect of nivolumab on the CL of ipilimumab. The CL of ipilimumab in subjects with NSCLC, RCC, HCC, and CRC was not significantly different relative to subjects with melanoma. The CL of ipilimumab was lower in subjects with SCLC relative to subjects with melanoma; however, the magnitude of the difference was not considered to be clinically relevant. Ipilimumab CL was not significantly different in the presence of anti-ipilimumab antibodies.

2.3.3 Clinical Efficacy

BMS and MDX (acquired by BMS in Sep-2009) have co-sponsored an extensive clinical development program for ipilimumab, encompassing more than 22,571 subjects (total number of subjects enrolled in ipilimumab studies) in several cancer types in completed and ongoing studies, including a compassionate use program. The focus of the clinical program is in melanoma, prostate cancer, and lung cancer, with advanced melanoma being the most comprehensively studied indication. Ipilimumab is being investigated both as monotherapy and in combination with other modalities such as chemotherapy, radiation therapy, and other immunotherapies. All studies were conducted in accordance with Good Clinical Practices, as defined by the International Conference on Harmonisation 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).

Ipilimumab Monotherapy in Melanoma, Prostate, and Cancer
Phase 3 programs are ongoing in melanoma and lung cancer. In melanoma, 4 completed Phase 3 studies (MDX010-20, CA184024, CA184029, and CA184169) have demonstrated a clinically meaningful and statistically significant survival benefit in pretreated advanced melanoma, previously untreated advanced melanoma, and adjuvant melanoma with a manageable safety profile. Studies MDX010-20 and CA184024 were completed in subjects with advanced melanoma. Study CA184029 is complete with a final clinical study report, but still has ongoing patients in follow-up.

Ipilimumab Monotherapy in mCRPC
The completed Phase 3 study (CA184043) evaluated ipilimumab in subjects with mCRPC who had progressed during or following treatment with docetaxel. Eligible subjects were randomized to a single dose of bone-directed RT, followed by either ipilimumab 10 mg/kg or placebo (799 randomized: 399 ipilimumab and 400 placebo). This study did not meet its primary endpoint of OS. The safety profile in this study was consistent with the previously defined AE profile at the same dose. A second Phase 3 study (CA184095) evaluated ipilimumab 10 mg/kg versus placebo in subjects with asymptomatic or minimally symptomatic, chemotherapy-naïve mCRPC with no visceral metastases. The study did not meet its primary endpoint of demonstrating a statistically significant prolongation of survival for the ipilimumab group (10 mg/kg) compared with the placebo group. The safety profile of ipilimumab in this study was generally consistent with the experience in other studies using 10 mg/kg ipilimumab. No new safety signals were identified in this patient population.

Ipilimumab in Monotherapy and Combination Therapy in Lung Cancer Activity was observed in a large Phase 2 study in lung cancer (NSCLC and SCLC; Study CA184041)(55) in combination with chemotherapy. Two Phase 3 studies evaluated ipilimumab in combination with chemotherapy in squamous NSCLC (CA184104) and SCLC (CA184156). Neither study met its primary endpoint of demonstrating a statistically significant prolongation of OS for the ipilimumab group (10 mg/kg ipilimumab/standard of care chemotherapy) over the placebo group (placebo/standard of care chemotherapy) among randomized subjects who received at least 1 dose of blinded study therapy; however, no new safety concerns were identified in the course of standard clinical safety monitoring of the 2 studies. While the types of safety events observed in subjects receiving ipilimumab do not appear to change, even in combination with other anti-cancer agents, the proportion of subjects experiencing 1 type or another irAE may be impacted by the choice of combination partner. Skin and GI irAEs predominate in monotherapy studies. In combination with DTIC (melanoma), the incidence of skin and GI irAEs was lower than expected and the incidence of hepatic irAEs was higher. In combination with paclitaxel and carboplatin (NSCLC), the incidence of all types of irAEs appeared to be numerically lower compared to the incidence observed for ipilimumab monotherapy in the Phase 2 program. In a Phase 1 study (CA184161), the concomitant administration of vemurafenib and ipilimumab in subjects with BRAF V600 mutated metastatic melanoma resulted in asymptomatic and reversible increases in aspartate aminotransferase (AST) and alanine aminotransferase (ALT), exceeding the incidence to be expected when either agent is administered as a monotherapy, leading to discontinuation of this treatment. All were reversible with dose reduction, interruption, or permanent discontinuation of the study drugs or administration of corticosteroids. In a Phase 2 study (CA184240), sequential treatment with vemurafenib followed by 10 mg/kg ipilimumab in subjects with BRAF V600-mutated metastatic melanoma was tolerable with a manageable safety profile. No significant BRAF V600 signals of hepatobiliary toxicity were reported. The benefit/risk profile of this sequence needs to be evaluated further based on individual subject characteristics and new treatment options. Ipilimumab is also being evaluated in clinical studies conducted independently by the Cancer Therapy Evaluation Program of the US NCI, as well as in several additional externally sponsored studies.

2.3.4 Clinical Safety

Ipilimumab is associated with inflammatory events resulting from increased or excessive immune activity, likely to be related to its mechanism of action. Inflammatory events were analyzed in 2 ways:

irAEs (Immune-related adverse events)
irAEs are defined as AEs that are 1) related to ipilimumab per investigator and 2) consistent with an inflammatory process. The most common treatment-related AEs associated with the use of ipilimumab were immune related (named immune-related AEs or irAEs), reflecting ipilimumab's mechanism of action. The irAEs primarily involved the GI tract (eg, diarrhea and colitis); skin (eg, pruritus and rash); and, less frequently, the liver (eg, transaminase elevations), endocrine glands (including the thyroid, pituitary and adrenal glands, manifested by hypothyroidism, hypophysitis with hypopituitarism, or adrenal insufficiency, respectively), and nervous system (eg, motor neuropathy with or without sensory neuropathy). Immune-related AEs were generally manageable using symptomatic or immuno-suppressive therapy as recommended through detailed diagnosis and management guidelines, as described in Section 7.

imARs
imARs represent the subset of events for which a nonimmune etiology could not be established and included the following specific events of clinical interest: enterocolitis, dermatitis, hepatitis, neuropathies, endocrinopathies, and other. The definition of imARs and the methodology for imAR analysis were developed jointly by BMS and the US Food and Drug Administration for the first approval of 3 mg/kg ipilimumab monotherapy in the US.

Since the imAR definition was developed after completion of the original registrational studies, imARs were originally retrospectively adjudicated by the Sponsor in a blinded fashion to investigator attribution (including for Studies MDX010-20 and CA184024). In more recent studies, imARs were adjudicated by the investigator based on the same case definitions. Importantly, case definitions for imARs should not be used as guidance for AE management, as events are assessed retrospectively, and adjudication includes consideration of the eventual outcome of the event.

2.4 Rationale

The rationale supporting immune-based therapeutic strategies to treat meningiomas is based on several factors. First, our group has recently quantitated the level of PD-L1 expression and characterized the immune infiltrate in 291 meningioma samples including 195 grade I, 73 grade II and 23 grade III tumors.(31) We noted high PD-L1 mRNA expression among 72% and 82% of grade II and III meningiomas, respectively that correlated with PD-L1 protein expression as measured by immunohistochemistry. Furthermore, grade II and III meningioma samples demonstrated decreased CD4+ and CD8+ lymphocytes while FoxP3+ cells were increased. These findings indicate that atypical and anaplastic meningiomas induce immunosuppression in the tumor microenvironment mediated by increased PD-L1 expression. Second, the potential benefit of immunotherapy approaches to treat meningioma was recently confirmed in a canine spontaneous meningioma model, which closely resembles human meningioma. In this study, median survival was significantly longer among dogs treated with immunotherapy (645 days) compared to historical controls (222 days; $p<0.05$) and only one of eleven treated dogs developed progressive tumor.(32) Third, results of recent studies provide proof of principle that targeting immune response checkpoint regulatory proteins such as cytotoxic T-lymphocyte-associated antigen-4 (CTLA-4), programmed death-1 (PD-1) and PD-1 ligand (PD-L1) can provide anti-tumor benefit against several different types of aggressive solid tumors,(33-35) including those with CNS metastases.(36, 37) Fourth, meningiomas frequently demonstrate infiltration of immune and inflammatory cells within these tumors including macrophages, microglia and lymphocytes.(38-42) Fifth, meningiomas commonly express tumor-associated antigens which

may be exploited for immune based attack.(43-45) Sixth, immunosuppression, both systemically and in the tumor microenvironment, is a key feature associated with the pathogenicity of malignant primary CNS tumors including malignant glioma as well as meningioma.(46) Finally, meningiomas have better access to the systemic immune system than tumors arising in the brain parenchyma such as gliomas because meningiomas arise external to the blood brain barrier and are thus not restricted by endothelial cell tight junctions that can limit immune cell and large molecule penetration. Meningiomas are also directly exposed to the cerebrospinal fluid space that drains into the venous circulation, thereby facilitating tumor antigen presentation to cervical lymph nodes.

This study is being amended to add a second cohort (Cohort 2) which will build on the clinical experience acquired from the treatment of patients on Cohort 1 who were treated with nivolumab monotherapy following progression after prior surgery and radiation. For patients treated on Cohort 1, we observed that nivolumab monotherapy was well tolerated and no unexpected toxicities were observed. In addition, we noted that nivolumab monotherapy was associated with modest therapeutic benefit; specifically, one particularly heavily pretreated patient who had extensive tumor burden at study enrollment achieved a dramatic near complete response while 20-25% of patients achieved stable disease (D. Reardon, personal communication). To build on these encouraging yet modest results, we plan to add a second cohort of patients who will receive radiation therapy combined with immune checkpoint therapy consisting of anti-PD-1 (nivolumab) plus anti-CTLA-4 (ipilimumab).

Several factors contribute to the rationale for adding Cohort 2 to this study. First, although radiation therapy and re-irradiation are considered a standard of care for patients with grade I, II or III meningioma, the therapeutic benefit of radiation is not durable, and most patients will progress. Second, growing data across multiple tumor indications supports the possibility that radiation therapy can enhance the therapeutic benefit associated with immune checkpoint treatment and that such combination therapy can lead to durable responses. The mechanism underlying the therapeutic benefit associated with adding radiation to immune checkpoint blockade is not clear but significant preclinical and clinical data supports the approach. Preclinical data in several solid tumor types demonstrates enhanced activity when RT is combined with either anti-PD-1 or dual blockade of PD-1 and CTLA-4,[55] while blockade of PD-1 signaling has also been associated with reversal of radiation resistance.[56] Second, radiation therapy can induce immunogenic cell death[57] which can augment antigen-specific anti-PD-1 immune responses via cross presentation of tumor antigens.[58] Third, local radiation therapy combined with immunotherapy can generate abscopal responses at distant tumor sites beyond the targeted radiation field.[61,62] This is relevant to the current study in that approximately 15% of meningioma patients will have multiple sites of disease and patients with multifocal disease are eligible to participate in this study.

The rationale for adding combination therapy with CTLA-4 and PD-1 blockade for Cohort 2 is that each of these immune checkpoints provide complementary and non-redundant mechanisms of immunosuppression; thus, we anticipate that the anti-tumor benefit associated with this combination will enhance that observed with nivolumab monotherapy for Cohort 1. CTLA-4 blocks co-stimulation required for activation of T cells and thus is a key mediator of early T cell activation as well as tolerance.[47] PD-1 is primarily expressed by T cells upon T cell receptor engagement and interaction with its ligands leads to downregulation of T cell activity[48] and exhaustion.[49] Preclinical studies confirm enhanced anti-tumor activity for combined CTLA-4 plus PD-1 blockade in cancer models[28] including malignant glioma.[50] Recent clinical studies

demonstrate a high rate of therapeutic benefit with ipilimumab plus nivolumab in patients with melanoma,[51] small cell lung cancer,[52] renal cell carcinoma[53] and melanoma brain metastases,[54] although these studies also demonstrate that combination therapy is accompanied by a higher rate of immune related adverse events. More recent trials incorporating a reduced dosing schedule of anti-CTLA-4 have been associated with a decreased rate of immune related toxicity while preserving therapeutic benefit.

In addition to the above data supporting our hypothesis that anti-PD-1 plus anti-CTLA-4 will lead to durable therapeutic benefit when combined with radiation therapy for patients with recurrent grade I, II or III meningioma, there is ample data to support our expectation that this combination regimen will be safe and associated with a tolerable toxicity profile. Although results of radiation therapy plus immune checkpoint blockade have not been reported for meningioma patients, the safety of anti-PD-1 combined with fractionated radiation therapy has been demonstrated for newly diagnosed glioblastoma patients[63] while the addition of anti-PD-1 and anti-CTLA-4 to stereotactic radiosurgery has been confirmed among patients with brain metastases.[64]

In conclusion, our study data to date for Cohort 1 demonstrates that nivolumab monotherapy is associated with encouraging but limited benefit for patients with recurrent grade II or III meningioma. Given that radiation therapy is a standard of care for these patients, and that growing data demonstrates that radiation therapy can synergize to enhance the therapeutic benefit of immune checkpoint blockade, we plan to amend the current study to add a second cohort who will receive dual anti-CTLA-4 plus anti-PD-1 immune checkpoint blockade combined with radiation therapy. We anticipate that our overall study data, evaluating both efficacy and safety of Cohorts 1 and 2, will provide a substantial basis to guide the further clinical development of immune checkpoint therapy for patients with recurrent/progressive grade I, II and III meningioma.

2.5 Overall Risk/Benefit Assessment

Recurrent/progressive grade I, II and III meningiomas are particularly aggressive brain tumors with high mortality and morbidity despite current treatments. Adverse sequela associated with repeated brain tissue resection and radiation therapy in subjects with progressive/recurrent grade II/III meningioma further complicates the management of this tumor type. The significant unmet clinical need of high-grade meningioma patients coupled with preclinical data implicating PD-1/PD-L1 mediated immunosuppression among these tumors (Section 2.3) 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 exhibits a manageable safety profile in patients including assessment of > 700 subjects enrolled across all clinical trials. The most common AEs include 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. 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.

Initial radiation therapy and re-irradiation administered via either fractionated conformal dosing schedule or via stereotactic radiosurgical boost dosing, are considered a standard of care for high-grade glioma with an acceptable rate of associated toxicity.[59] Although the addition of CTLA-4 blockade to anti-PD-1 therapy has typically been associated with a higher rate of immune related adverse events than anti-PD-1 monotherapy, the combination of nivolumab plus ipilimumab for

progressive high-grade meningioma patients has not been previously studied and thus the overall safety of this regimen in this setting is unknown. Preliminary analysis of patients treated with nivolumab monotherapy on cohort 1 of this study reveals an acceptable toxicity profile which does not appear different from that observed with anti-PD-1 therapy for other cancer indications (D. Reardon, personal communication). In addition, in this study, anti-CTLA-4 therapy is limited to only 4 doses as a strategy to decrease immune related toxicity while maintaining potential therapeutic benefit.

2.6 Rationale and Aims for Biomarker Assessments

The biological basis of nivolumab in the treatment of oncologic disease is to modulate the immune system to both generate and restore a durable anti-tumor response leading to clearance of tumor. The clinical data generated to date supports the hypothesis that blockade of PD-1 signaling results in rejection of tumor by the host immune system.

The precise mechanisms by which nivolumab and ipilimumab exert their anti-tumor activity is unclear, however, particular cell types, such as effector T cells and regulatory T cells are critical for the anti-tumor response. The current study will explore tumor expression of PD-L1 as well as expression of an interferon- gene expression signature, which has been associated with a heightened likelihood of therapeutic benefit following anti-PD-1 therapy in other cancer indications,[65] as potential biomarkers of therapeutic benefit. Tumor material will consist of the most recently available archival sample prior to study enrollment. Archival tumor material is not required for study eligibility. In addition, if a biopsy or surgical resection is performed at the time of potential progression, a tumor sample (block or slides) should also be submitted if sufficient tumor material is available.

2.7 Rationale for Volumetric Analysis

Meningiomas account for over 25% of all primary intracranial tumors in the United States (48). While the majority of meningiomas are considered benign using histological assessment, complete surgical resection may not be possible for some of these tumors and these tumors often develop resistance to radiation treatment. Thus, several clinical trials have been performed to evaluate the role of chemotherapy in treatment of meningiomas (48)(49).

The optimal endpoint for clinical trials in meningioma is problematic. Overall survival is very long, and even progression-free survival requires long follow-up. In addition, the response rate - especially for grade I meningiomas - is low. Thus, the same criteria used to evaluate other tumor types, including high grade glioma or metastases, will not be sensitive to meningioma size change, suggesting a need to search for imaging marker that is more sensitive to subtle changes in growth behavior of tumor following treatment to provide a signal of activity following treatment. More recently, volumetric analysis of MRI has been proposed as a new method for detecting change in slowly evolving brain tumors (50). This approach has also been recommended for evaluating changes in tumor size in clinical trials of neurofibromatosis (51). For this specific disease population, a 20% volume change has been proposed to indicate a decrease or increase in tumor size.

In this exploratory analysis, we propose to perform volumetric evaluation of serial MRI data of patients enrolled in the trial. The tumor volume growth characteristics including tumor volume change and change in growth rate before and after treatment initiation will be measured. Although this analysis is exploratory, if slowing of the rate of progression is observed based on this analysis,

it will indicate that further investigation of this metric of efficacy is warranted in future study.

3. PARTICIPANT SELECTION

Screening evaluations are detailed in Study Calendar (Section 10). All assessments are to occur within 14 days of Day 1 except where otherwise noted. The participant must be thoroughly informed about all aspects of the study, including the study visit schedule and required evaluations and all regulatory requirements for informed consent. The written informed consent must be obtained from the participant prior to enrollment.

Following registration, any additional laboratory assessments obtained prior to start of treatment will not be used to re-confirm eligibility. Please refer to Section 6 Dosing Delays/Dose Modifications for toxicity management between registration and start of study treatment.

3.1 Eligibility Criteria

In order to be eligible for participation in this trial, all participants must meet the following criteria on screening examination:

3.1.1 Have histologically confirmed WHO grade I, II or III meningioma that is progressive or recurrent. Metastatic meningiomas are allowed. Participants with grade I tumors must have failed radiation therapy.

3.1.2 Prior therapy:

There is no limit on the number of prior surgeries, radiation therapy, radiosurgery treatments or systemically administered therapeutic agents.

For **Cohort 1**: Patients may have been treated with standard external beam radiation or radiosurgery in any combination, however, an interval of ≥ 12 weeks (84 days) must have elapsed from the completion of the radiation therapy to start of study therapy unless there is histopathologic confirmation of recurrent tumor or there is new enhancing tumor outside the radiation field (beyond the high dose region or the 80% isodose line). (See Inclusion Criterion 3.1.9 for RT requirements for **Cohort 2** patients.)

In addition, there must be subsequent evidence of tumor progression after completion of radiation therapy (grade I tumors only);

An interval of ≥ 28 days and full recovery (no ongoing safety issues) from surgical resection (≥ 7 days from stereotactic biopsy).

For prior systemic agents, participants must be at least 4 weeks (or 5 half-lives, whichever is shorter) from other prior cytotoxic chemotherapy (6 weeks from nitrosoureas) or biologic therapies.

3.1.3 Participants must have recovered to grade ≤ 1 or pretreatment baseline from clinically significant adverse events related to prior therapy (exclusions include but are not limited to alopecia, laboratory values listed per inclusion criteria and lymphopenia);

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

3.1.5 Have a Karnofsky performance status (KPS) ≥ 70 (Appendix A).

3.1.6 Participants must demonstrate adequate organ and marrow function as defined below (all screening labs to be performed within 14 days of treatment initiation):

- White blood cell (WBC) ≥ 2000/mm^3
- Absolute neutrophil count (ANC) ≥ 1,000/mm^3
- Platelet count ≥ 100,000/mm^3
- Hemoglobin ≥ 9 gm/dl
- AST(SGOT)/ALT(SGPT) ≤ 3 x laboratory upper limit of normal (ULN)
- Serum creatinine ≤ 1.5 X ULN
  OR creatinine clearance (measured or calculated) ≥ 60 mL/min
  for participants with creatinine levels > 1.5 X ULN
  (GFR can be used in place of creatinine or creatinine clearance)
- Total serum bilirubin ≤ 1.5 X ULN
  (except participants with Gilbert's Syndrome, who can have a total bili < 5 X ULN)
- Resting baseline oxygen saturation ≥ 92% at rest - by pulse oximetry

3.1.7 MRI (or CT if MRI contraindicated) within 14 days prior to start of study treatment Corticosteroid dose must be stable or decreasing for at least 5 days prior to the scan. If steroids are added or the steroid dose is increased between the date of the screening MRI or CT scan and the start of treatment, a new baseline MRI or CT is required.

3.1.8 Ability to understand and the willingness to comply with scheduled visits, treatment schedule, laboratory testing, and other requirements of the study, including disease assessment by MRI (or CT), as confirmed by signing a written informed consent document.

3.1.9 For **Cohort 2**, patients must be a candidate for external beam radiotherapy including either conventional fractionated conformal dosing or stereotactic radiosurgical boost dosing (participants may enroll if they are receiving radiotherapy or have completed it within 12 weeks of starting immunotherapy);

3.1.9.1 For **Cohort 2** patients who are undergoing fractionated conformal re-irradiation to a tumor site that has been previously irradiated, an interval of at least 6 months must have passed since they completed their prior irradiation to be eligible unless the current course of radiation is targeting a new area of tumor growth outside the 80% isodose line of the original radiation field as determined by the treating investigator.

3.1.10 The effects of nivolumab on the developing human fetus are unknown. For this reason:

3.1.10.1 Women of childbearing potential (WOCPB; defined in Section 3.4) must have a negative serum or urine pregnancy test (minimum sensitivity 25 IU/L or equivalent units of HCG) within 24 hours of starting study therapy;

3.1.10.2 Women must not be breastfeeding;

3.1.10.3 WOCPB must agree to follow instructions for method(s) of contraception from the time of enrollment for the duration of treatment with study therapy plus 5 months after the last dose of Nivolumab.

3.1.10.4 Should a woman become pregnant or suspect she is pregnant while she or her partner is participating in this study, she should inform her treating physician immediately.

3.1.10.5 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 plus 7 months after the last dose of Nivolumab.

3.1.10.6 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.

3.1.10.7 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. Female partners of male subjects participating in the study may use hormone based contraceptives as one of the acceptable methods of contraception since they will not be receiving study drug
- Progestogen only hormonal contraception associated with inhibition of ovulation
- Intrauterine hormone-releasing system (IUS)
- 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*

UNACCEPTABLE METHODS OF CONTRACEPTION

- Periodic abstinence (calendar, symptothermal, post-ovulation methods)
- Withdrawal (coitus interruptus)
- Spermicide only
- Lactation amenorrhea method (LAM)

NOTE: *Azoospermic males and WOCBP who are continuously not heterosexually active are exempt from contraceptive requirements. However, WOCBP participants must still undergo pregnancy testing as described.*

3.2 Exclusion Criteria

The participant must be excluded from participating in the trial if s/he meets any of the following criteria:

3.2.1 Current or planned participation in a study of an investigational agent or using an investigational device.

3.2.2 Tumors that are primarily localized within the brainstem or spinal cord;

3.2.3 Evidence of intratumoral or peritumoral hemorrhage on baseline MRI scan other than those that are grade ≤ 1 and either post-operative or stable on at least 2 consecutive MRI scans;

3.2.4 Prior Therapy:

3.2.4.1 Prior treatment with systemic immunosuppressive treatments, aside from systemic dexamethasone therapy for cerebral edema, such as methotrexate, chloroquine, azathioprine, etc. within 3 months of start of study therapy;

3.2.4.2 Prior treatment with interstitial brachytherapy within 6 months of start of study therapy;

3.2.4.3 **All patients**: Previous treatment with PD-1 or PD-L1 directed therapy;

3.2.4.4 **Cohort 2** patients: Previous treatment with CTLA-4 directed therapy;

3.2.4.5 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;

3.2.4.6 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);

3.2.5 Other Meds:

3.2.5.1 Participants who are receiving any other investigational agents.

3.2.5.2 Immunosuppressive medications / steroids:

- Subject must not require high dose systemic corticosteroids defined as dexamethasone > 4 mg/day or bioequivalent for at least 3 consecutive days within 2 weeks prior to Day 1of study therapy;
- *Inhaled or topical steroids and adrenal replacement doses > 10 mg daily prednisone equivalents are permitted in the absence of active autoimmune disease.*
- *Subjects are permitted to use topical, ocular, intra-articular, intranasal, and inhalational corticosteroids (with minimal systemic absorption).*
- *Physiologic replacement doses of systemic corticosteroids are permitted, even if > 10 mg/day prednisone equivalents.*
- *A brief course of corticosteroids for prophylaxis (e.g., contrast dye allergy) or for treatment of non-autoimmune conditions (e.g., delayed-type hypersensitivity reaction caused by contact allergen) is permitted.*

3.2.5.3 Has received a live vaccine within 30 days prior to the first dose of study drug; seasonal influenza vaccination is permitted excluding the nasal spray formulation;

3.2.5.4 No concurrent treatment on another clinical trial. Supportive care trials or non-treatment trials, e.g. quality of life, are allowed;

3.2.6 Concomitant Medical Illnesses: Uncontrolled intercurrent illness, including - but not limited to:

3.2.6.1 Known additional malignancy that is progressing or requires active treatment within 3 years of start of study drug. Exceptions include basal cell carcinoma of the skin, squamous cell carcinoma of the skin, or in situ cervical cancer that has undergone potentially curative therapy;

3.2.6.2 Has evidence of interstitial lung disease or active, non-infectious pneumonitis;

3.2.6.3 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 examples include but are not limited to symptomatic congestive heart failure, unstable angina pectoris, cardiac arrhythmia or psychiatric illness/social situations that would limit compliance with study requirements;

3.2.6.4 Has an active autoimmune disease requiring systemic treatment within the past 3 months or a documented history of clinically severe autoimmune disease, or a syndrome that requires systemic steroids or immunosuppressive agents. Subjects with vitiligo, type 1 diabetes mellitus, residual hypothyroidism due to autoimmune condition requiring hormone replacement, psoriasis not requiring systemic treatment, conditions not expected to recur in the absence of an external trigger or resolved childhood asthma/atopy would be exceptions to this rule. Subjects that require intermittent use of bronchodilators or local steroid injections would not be excluded from the study. Subjects with hypothyroidism stable on hormone replacement or Sjogren's syndrome will not be excluded from the study;

3.2.6.5 Has an active infection requiring intravenous therapy;

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

3.2.7 Medical History:

3.2.7.1 History of intracranial abscess within 6 months prior to start of study therapy;

3.2.7.2 Known history of testing positive for human immunodeficiency virus (HIV) or known acquired immunodeficiency syndrome (AIDS);
NOTE: HIV-positive participants on combination antiretroviral therapy are ineligible because of the potential for pharmacokinetic interactions with Nivolumab. Appropriate studies will be undertaken in participants receiving combination antiretroviral therapy when indicated.

3.2.7.3 History of allergy to study drug components

3.2.7.4 History of severe hypersensitivity reaction to any monoclonal antibody;

3.2.8 Prisoners or participants who are involuntarily incarcerated;

3.2.9 Pregnant women are excluded from this study because Nivolumab is an agent with the potential for teratogenic or abortifacient effects. Because there is an unknown but potential risk for adverse events in nursing infants secondary to treatment of the mother with Nivolumab, breastfeeding should be discontinued if the mother is treated Nivolumab.

3.3 Inclusion of Women and Minorities

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

3.4 Women of Childbearing Potential

A woman 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.

4. REGISTRATION PROCEDURES

All sites should e-mail the Study Coordinator at NeuroOnc_Coor@dfci.harvard.edu to verify slot availability.

4.1 General Guidelines for DF/HCC Institutions

Institutions will register eligible participants in the Clinical Trials Management System (CTMS) OnCore. Registrations must occur prior to the initiation of protocol-specific therapy or intervention. Any participant not registered to the protocol before protocol-specific therapy or intervention begins will be considered ineligible and registration will be denied.

An investigator will confirm eligibility criteria and a member of the study team will complete the protocol-specific eligibility checklist.

Following registration, participants may begin protocol therapy. Issues that would cause treatment delays should be discussed with the Overall Principal Investigator (PI). If a participant does not receive protocol therapy following registration, the subject must be taken off study in the CTMS (OnCore) with an appropriate date and reason entered.

4.2 Registration Process for DF/HCC Institutions

Applicable DF/HCC policy (REGIST-101) must be followed.

5. TREATMENT PLAN

5.1 Cohort 1: Nivolumab Monotherapy Treatment Regimen

Nivolumab will be administered every 2 weeks*, with 14 consecutive days defined as a treatment cycle.

Dosing window*: There is an administration window of -2/+5 days for Nivolumab administrations; however, participants may be dosed no less than 12 days (11 non-dosing days) between doses.

Labs/assessments window: Labs/assessments may be performed up to 3 days prior to Nivolumab doses.

* NOTE: Participants who have received active study therapy for >/= 6 months will be allowed the option to adjust their Nivolumab dosing schedule from 240 mg once every 2 weeks (-2/+5 days) to 480 mg once every 4 weeks (+/- 1 week).

Counting of days will not be continuous on study. In the event of a treatment delay due to a toxicity, the current cycle will be extended until the criteria to resume treatment are met. The day of treatment restart will be the participant's subsequent cycle's Day 1.

If treatment with study medication is delayed > 6 weeks, the participant must be permanently discontinued from study therapy, except as specified in Section 6.4.

Treatment will be administered on an outpatient basis. Reported adverse events and potential risks are described in Section 7. Appropriate dose modifications are described in Section 6. No investigational or commercial agents or therapies other than those described below may be administered with the intent to treat the participant's malignancy.

For details regarding drug storage, preparation, administration, and use time please refer to Section 8 of the protocol and the current BMS-936558 (nivolumab) Investigator Brochure.

Nivolumab is to be administered as an IV infusion over 30 minutes (window of -10 / + 30 min). At the end of the infusion, flush the line with a sufficient quantity of normal saline.

Selection and Timing of Dose for Each Participant

The dosing regimen and schedule of nivolumab are detailed in Table 5.1-1.

Table 5.1-1 Dosing Schedule for Cohort 1

Cycles = 2 weeks (Nivolumab dosing every 2 weeks) *					
	Cycle 1 Day 1	**Cycle 2 Day 1**	**Cycle 3 Day 1**	**Cycle 4 Day 1**	**Cycle 5 Day 1**
Nivolumab Dose	240 mg	240 mg	240 mg	240 mg	240 mg

* NOTE: Participants who have received active study therapy for >/= 6 months will be allowed the option to adjust their Nivolumab dosing schedule from 240 mg once every 2 weeks (-2/+5 days) to 480 mg once every 4 weeks (+/- 1 week).

5.2 Cohort 2: Nivolumab plus Ipilimumab Treatment Regimen

The dosing regimen and schedule of nivolumab and ipilimumab are detailed in Table 5.2-1. Nivolumab and ipilimumab therapy will start no sooner than 1 week and no later than 12 weeks after completion of radiation therapy. Radiation therapy includes either initial radiation therapy or re-irradiation and can incorporate either conventional conformal dosing or stereotactic radiosurgical dosing based on established, institutional standard of care guidelines. An initial safety lead-in will be performed to determine the maximum tolerated dose (MTD)/recommended phase 2 dose (RP2D) of nivolumab plus ipilimumab following radiation therapy for patients with recurrent/progressive meningioma.

Table 5.2 Dosing Schedule for Cohort 2

Treatment Period	Agent	Dose	Frequency	# Planned Doses
Initial combination	Nivolumab	3 mg/kg	Every 3 weeks	4
	Ipilimumab	1 mg/kg	Every 3 weeks	4
Maintenance	Nivolumab	480 mg	Every 4 weeks	Indefinite

5.2.1 Safety Lead-In

The safety lead-in will utilize a 3+3 design to determine the MTD/RP2D of ipilimumab when administered with nivolumab following radiation therapy for patients with recurrent/progressive meningioma. Nivolumab will be administered at 3 mg/kg every three weeks with ipilimumab. The initial dose level of ipilimumab will be 1 mg/kg every three weeks and will be administered on the same day as nivolumab. There is extensive existing safety data confirming adequate tolerability of nivolumab administered with ipilimumab at these dose levels. However, since there is no safety data administering these two agents following radiation therapy for recurrent/progressive meningioma patients, the first six patients will be considered a safety lead-in and observed in groups of three for dose limiting toxicities (DLT) for an evaluation period of 42 days (see DLT definitions in Section 5.2.1.1) as follows:

- If at Dose Level 0, ≤1 of the first 3 patients develop DLT, 3 more patients will be enrolled to Dose Level 0.
- If at Dose Level 0, >1 of the first 3 patients or >1 of the first 6 patients develop DLT, cohort enrollment will be stopped immediately, and re-started from the beginning with 3+3 patients enrolled at a dosing interval of 4 weeks (Dose Level -1).
- If at Dose Level -1, >1 of the first 3 patients or >1 of 6 patients develop DLT, cohort enrollment will be stopped immediately, and re-started from the beginning with 3+3 patients enrolled at a dosing interval of 6 weeks (Dose Level -2).
- If at Dose Level -2, >1 of the first 6 patients develops DLT, the safety lead-in will be discontinued. In this case, a single-arm phase II study of nivolumab monotherapy will be performed.

Dose-limiting toxicities (DLT) will be determined by toxicities related to ipilimumab during or beginning over the first 42 days of treatment as defined below in Section 5.2.2.

Table 5.2.1. Dose levels and doses to be evaluated in safety lead-in.

Dose level	Nivolumab		Ipilimumab	
	Dose (mg/kg)	Frequency	Dose (mg/kg)	Frequency
Zero (0)	3	Every 3 weeks	1	Every 3 weeks
Minus one (-1)	3	Every 4 weeks	1	Every 4 weeks
Minus two (-2)	3	Every 6 weeks	1	Every 6 weeks

5.2.2 Definition of Dose-Limiting Toxicity

A DLT is defined as any grade ≥ 3 adverse event that is at least possibly, probably or definitely related to ipilimumab during the DLT period, unless judged by the treating Investigator to be more likely related to underlying tumor, concurrent medication or co-morbid event. The DLT period is considered the first 42 days of study therapy and will include labs and other evaluations taken at the end of six weeks of study therapy. Events that are considered unlikely related to ipilimumab, but at least probably related to radiation therapy will not be considered a DLT.

The following exceptions will not be classified as DLT:

- Grade 3 Immune-related adverse events (irAEs – see definition below) that downgrade to Grade ≤ 2 within 5 days, or to Grade ≤ 1 or baseline within 14 days after onset of the event, whereby maximal supportive care, including systemic corticosteroids, is permitted.
- Grade 3 asymptomatic endocrinopathy, managed with or without systemic corticosteroid therapy and/or hormone replacement therapy.
- Grade 3 inflammatory reaction attributed to a local antitumor response (e.g., inflammatory reaction at sites of metastatic disease, lymph nodes, etc).
- Grade 2 pneumonitis, neurological event, or uveitis that downgrades to Grade ≤ 1 within 3 days, whereby maximal supportive care is permitted.
- Liver transaminase elevation ≤ 8 times ULN.
- Total bilirubin ≤ 5 times ULN.
- Any pre-existing lab abnormality that deteriorates to Grade 3/4, but where the increment of deterioration is considered not clinically significant by Investigator, overall study Principal Investigator and sponsor.

DLT will also include grade 2 immune-related adverse events that occur during the DLT period defined above that require interruption of ipilimumab and do not improve to grade ≤ 1 with appropriate supportive care and symptomatic treatment with 7 days.

Immune-related adverse events (irAEs) are defined as AEs of immune nature (i.e., inflammatory) in the absence of a clear alternative etiology. In the absence of clinical abnormality, repeat laboratory testing will be conducted to confirm significant laboratory findings prior to designation as a DLT.

While rules for adjudicating DLTs are specified above, an AE of Grade < 3 (except if listed as exempt above), may also be defined as a DLT after a consultation with the Sponsor and the overall study Principal Investigator, based on the emerging safety profile of ipilimumab.

Patients who experience DLT may be discontinued from study therapy and will enter the post-study follow-up phase of the study (see Section 5.7) or participants who have fully recovered from

the DLT may proceed with nivolumab monotherapy dosing every 4 weeks if considered appropriate by the treating physician.

Adverse events that meet DLT criteria but occur outside the DLT window will be classified as unacceptable AEs and study treatment will be discontinued per Section 5.6.

For the safety lead-in portion of this study, patients are evaluable for DLTs if: 1) they experience a DLT at any time during the DLT evaluation period; or 2) in the absence of DLT have received at least one dose of ipilimumab and one dose of nivolumab, and have completed respective safety assessments without major violations over the entire DLT evaluation period. Patients who are not fully evaluable for DLTs during the DLT evaluation period of 6 weeks following Day 1, will be replaced.

5.2.3 Nivolumab Therapy

Nivolumab will initially be administered every 3 weeks at a dose of 3 mg/kg for four doses in combination with ipilimumab, and then will be administered at a flat dose of 480 mg every four weeks until study therapy discontinuation.

Dosing window: There is an administration window of -2/+5 days for Nivolumab administrations.

Labs/assessments window: Labs/assessments may be performed up to 7 days prior to Nivolumab doses.

Counting of days will not be continuous on study. In the event of a treatment delay due to a toxicity, the current cycle will be extended until the criteria to resume treatment are met. The day of treatment restart will be the participant's subsequent cycle's Day 1.

If treatment with study medication is delayed > 12 weeks, the participant must be permanently discontinued from study therapy, except as specified in Section 6.4.

Treatment will be administered on an outpatient basis. Reported adverse events and potential risks are described in Section 7. Appropriate dose modifications are described in Section 6. No investigational or commercial agents or therapies other than those described below may be administered with the intent to treat the participant's malignancy.

For details regarding drug storage, preparation, administration, and use time please refer to Section 8 of the protocol and the current BMS-936558 (nivolumab) Investigator Brochure.

Nivolumab is to be administered as an IV infusion over 30 minutes (window of -10 / + 30 min). At the end of the infusion, flush the line with a sufficient quantity of normal saline. On treatment days when both nivolumab and ipilimumab are administered, nivolumab will be administered first with a 30 minute observation window before starting ipilimumab.

5.2.4 Ipilimumab Therapy

Ipilimumab will be administered every 3 weeks at a dose of 1 mg/kg for 4 consecutive doses, with nivolumab.

Dosing window: There is an administration window of -2/+5 days for Ipilimumab administrations; however, participants may be dosed no less than 24 days (23 non-dosing days) between doses.

Labs/assessments window: Labs/assessments may be performed up to 7 days prior to Ipilimumab doses.

Counting of days will not be continuous on study. In the event of a treatment delay due to a toxicity, the current cycle will be extended until the criteria to resume treatment are met. The day of treatment restart will be the participant's subsequent cycle's Day 1.

If treatment with study medication is delayed > 12 weeks, the participant must be permanently discontinued from study therapy, except as specified in Section 6.4.

Treatment will be administered on an outpatient basis. Reported adverse events and potential risks are described in Section 7. Appropriate dose modifications are described in Section 6. No investigational or commercial agents or therapies other than those described below may be administered with the intent to treat the participant's malignancy.

For details regarding drug storage, preparation, administration, and use time please refer to Section 8 of the protocol and the current BMS-734016 (Ipilimumab) Investigator Brochure.

Ipilimumab is to be administered as an IV infusion over 30 minutes (window of -10 / + 30 min). At the end of the infusion, flush the line with a sufficient quantity of normal saline.

On treatment days when both nivolumab and ipilimumab are administered, nivolumab will be administered first with a 30-minute observation window before starting ipilimumab.

5.2.5 Radiation Therapy

The following applies to patients on cohort 2:

What: On-study Radiation Therapy will be administered according to established, institutional standard-of-care guidelines utilizing one of the following techniques for reirradiation and best clinician judgment:

- fractionated intensity-modulated radiation therapy (IMRT)
- 3-dimensional conformal radiation therapy (3D-CRT)
- or proton beam radiation therapy
- stereotactic radiosurgery
- or fractionated stereotactic radiotherapy

When: To occur prior to initiation of Cycle 1 of Nivolumab + Ipilimumab. Day 1 Cycle 1 of study immunotherapy will be no sooner than 1 week from the completion of XRT, and no later than 12 weeks after completion of XRT.

Where: Participants are permitted to receive re-irradiation on study at the following locations:

a. the Radiation Oncology Department of the participating institution;
b. an IRB-approved satellite site of the participating institution;

c. any NRG Oncology-approved site;
d. or at another location, with **prior documented approval from the study's Overall PI**.

5.3 Study Phases

This study will consist of three phases: screening, treatment and follow-up.

Screening Phase:
- Begins by the signing of the informed consent form (ICF) and then establishing the subject's initial eligibility.
- Subject is enrolled.

Treatment Phase:
- Participants will begin study therapy within 14 days of completing screening.
- Adverse event assessments will be documented at each visit throughout the study.
- All of the laboratory tests and vital signs will be collected prior to study drug dosing at the time points specified in the Study Calendar (Table 10).
- All of a participant's study scans (screening scan(s), active-treatment scans, and off-treatment scan) will be reviewed for volumetric analysis *(as well as follow-up scans for participants in active follow-up)*. See Section 10.2.
- Study drug dosing may be delayed for toxicity. See Section 6.1.
- Treated subjects will be evaluated for response by the investigator according to the iRANO criteria (Section 11.2) every 8 weeks ± 1 week until disease progression or treatment discontinuation, whichever occurs later.
- Treated subjects will be evaluated for neurologic functioning by the investigator and according to the NANO scale (Section 11.6). Assessments will be performed at baseline scan and every 8 weeks (± 1 week) thereafter, at the time of imaging response assessment 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 taking a participant off protocol therapy, see Section 5.10.

Follow-Up Phase:
Begins when the decision to discontinue a participant from study therapy is made (no further treatment with study therapy).

AEs:
- Subjects will be followed for drug-related toxicities until these toxicities resolve, return to baseline or are deemed irreversible. All adverse events will be collected and documented for 30 days after the last dose, and serious adverse events that occur within 100 days after last dose or the start of new anti-cancer treatment, whichever comes first are to be reported per Section 5.10

Active Follow-Up:
- Participants who discontinue treatment for reasons other than tumor progression will continue to have tumor assessments at intervals determined by the treating investigator until unequivocal disease progression, initiation of a new therapy, or withdrawal of consent. All radiologically determined disease progression must be confirmed by an additional confirmatory MRI scan up to 12 weeks following the initial assessment of

radiological progression. Investigators may obtain additional follow-up MRI scans prior to 12 weeks as medically appropriate.

Long Term Follow-Up:

- After completion of the first follow-up visits, subjects will be followed every 3 months (+/- 1 month) for survival, post-study-therapy therapies, and future relapses.

5.4 Review of Safety

Safety of study participants will be monitored on an ongoing basis as described fully in Section 10.1.

5.5 Total Study Duration

Cohort 1: It is projected that accrual to this cohort will be completed within 24 months after the first participant is enrolled.

Cohort 2: It is projected that accrual to this cohort will be completed within 24 months after the first participant is enrolled.

The final analysis for the primary objective is expected 12 months after the last participant has initiated study therapy. Additional survival follow-up may continue after the primary analysis of survival.

5.6 Treatment Beyond Initial Radiologic Assessment of Disease Progression

Standard treatment for meningioma (including radiation therapy) may result in a transient increase in tumor enhancement (pseudoprogression) in a subset of participants 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. Accumulating evidence also indicates that some participants 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.(47) 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) 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. Second, 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 6.4) will be allowed to continue study therapy until a second radiologic confirmation of progression performed 12 weeks later as long as the following criteria are met: 1) the participant experiences investigator-assessed clinical benefit; 2) the participant is tolerating the study treatment; and 3) the participant is not experiencing significant neurologic decline that is felt to be attributable to underlying tumor progression.

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 participant is believed to demonstrate clinical benefit as determined by the investigator;
2) The participant is tolerating study medication;
3) The participant is not experiencing significant neurologic decline felt to be related to underlying tumor progression.

Participants 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 participant 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 participant's best interests, a surgical resection may be performed. Tumor biopsy samples (blocks or slides) must be submitted for review by a local neuropathologist for histopathologic assessment of progression versus treatment-related changes. If tumor pathology confirms progression, then the participant 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 participant may continue study medication. An MRI after the resection is required prior to treatment continuation. The participant will then continue all on-treatment tumor assessments as per the treatment schedule.

In addition, patients who develop progressive disease at an anatomical site that did not receive study radiation therapy, either as progression of existing lesion(s) or as a new site of disease, may be allowed to continue study therapy as long as site(s) of disease that received study radiation therapy are at least stable. Study radiation therapy will be administered to such sites of progressive disease utilizing a type and schedule of radiation therapy deemed to be best suited for the patient based on assessment by the treating investigator. The date of study therapy progression will correspond to the date of initial progressive disease, but the ability of study therapy including radiation therapy with immune checkpoint blockade to control such sites of tumor progression will be assessed.

5.7 Pre-Treatment Criteria

Cohort 1: Nivolumab dosing will continue every 2 weeks unless criteria for dose delay (Section 6.1) or study discontinuation criteria (Section 6.4) are met. In the event of a dose delay, dosing will be resumed when criteria to resume treatment (Section 6.3) are met.

NOTE: Participants who have received active study therapy for >/= 6 months will be allowed the option to adjust their Nivolumab dosing schedule from 240 mg once every 2 weeks (-2/+5 days) to 480 mg once every 4 weeks (+/- 1 week).

Cohort 2: Treatment with study therapy [External Beam RT followed by 4 cycles of Nivolumab + Ipilimumab (dosing every 3 weeks), followed by Nivolumab monotherapy (dosing every 4 weeks)] unless criteria for dose delay (Section 6.1) or study discontinuation criteria (Section 6.4) are met. In the event of a dose delay, dosing will be resumed when criteria to resume treatment (Section 6.3) are met.

5.8 Study Agents

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 (e.g., 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.

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 products are: BMS-936558 (nivolumab) and BMS-734016 (ipilimumab).

5.8.1 Nivolumab (BMS-936558)

Table 5.5-1 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 (Nivolumab) Solution for injection[a]	100 mg (10 mg/mL)	10 mL vial/ Open-label	5 vials per carton/ Open-label	Clear to opalescent colorless to pale yellow liquid. May contain particles.	2 to 8˚C. Protect from light and freezing.

[a]May be labeled as either "BMS-936558-01" or "Nivolumab"

5.8.1.1 Nivolumab (BMS-936558) Administration, Handling and Dispensing

Nivolumab is to be administered (flat dosing) on Day 1 of every cycle, as an IV infusion over 30 minutes (window of -10 / + 30 min). At the end of the infusion, flush the line with a sufficient quantity of normal saline.

Cohort 1: Nivolumab (240 mg) is to be administered every 2 weeks (on Day 1 of every 14-day cycle). There is an administration window of -2/+5 days for Nivolumab administrations; although a minimum 12-day interval (11 non-dosing days) is required between nivolumab doses.

NOTE: Participants who have received active study therapy for >/= 6 months will be allowed the option to adjust their Nivolumab dosing schedule from 240 mg once every 2 weeks (-2/+5 days) to 480 mg once every 4 weeks (+/- 1 week).

Cohort 2: During the initial combination phase of therapy for cohort 2, nivolumab is to be administered every 3 weeks at 3 mg/kg with ipilimumab for four doses. Thereafter, during the maintenance phase of nivolumab monotherapy, patients will receive flat dosing of 480 mg once every four weeks until discontinuation of protocol therapy (Section 5.10). There is an administration window of -2/+5 days for Nivolumab administrations; although the following minimum intervals are required between nivolumab doses: a minimum 14-day interval (13 non-dosing days) during combination therapy cycles (nivolumab every 3 weeks), and a minimum 21-day interval (20 non-dosing days) during nivolumab monotherapy therapy cycles (nivolumab every 4 weeks).

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 Section 8 of the protocol as well as the current version of the Investigator Brochure for complete storage, handling, dispensing, and infusion information for BMS-936558 (nivolumab).

5.8.2 Ipilimumab (BMS-734016)

5.8.2.1 Ipilimumab (BMS-734016) Administration, Handling and Dispensing

The ipilimumab injection, 200 mg/40 mL (5 mg/mL), is formulated as a clear to slightly opalescent, colorless to pale yellow, sterile, nonpyrogenic, single-use, isotonic aqueous solution that may contain particles. The ipilimumab injection, 200 mg/40 mL, is supplied in 10-cc or 50-cc Type I flint glass vials, respectively, stoppered with gray butyl stoppers and sealed with aluminum seals. The drug product is formulated at a concentration of 5 mg/mL at a pH of 7.0.

Ipilimumab injection (5 mg/mL) can be used for intravenous (IV) administration without dilution after transferring to a polyvinyl chloride (PVC), non PVC/non di (2 ethylhexyl)phthalate (DEHP), or glass container and is stable for 24 hours at 2°C to 8°C or room temperature/room light. Ipilimumab injection may be diluted in 0.9% Sodium Chloride Injection, United States Pharmacopeia (USP) or 5% Dextrose Injection, USP to concentrations between 1 mg/mL and 4 mg/mL and stored in PVC, non PVC/non DEHP, or glass containers for up to 24 hours at 2°C to 8°C or room temperature/room light. The product may be infused using a volumetric pump at the protocol-specific dose(s) and rate(s) through a PVC IV solution infusion set with an in-line, sterile, nonpyrogenic, low protein binding filter (pore size of 0.2 µm to 1.2 µm). Ipilimumab injection must not be administered as an IV push or bolus injection. Care must be taken to assure sterility of the prepared solutions since the drug product does not contain any antimicrobial preservatives or bacteriostatic agents.

Ipilimumab injection, 200 mg/40 mL (5 mg/mL), must be stored refrigerated (2°C to 8°C) and protected from light. Ipilimumab injection must not be frozen. Partially used vials or empty vials of ipilimumab injection should be discarded at the site according to appropriate drug disposal procedures. Ipilimumab injection may be stored undiluted (5 mg/mL) or following dilution in 0.9% Sodium Chloride Injection, USP or 5% Dextrose Injection, USP in PVC, non-PVC/non-DEHP, or glass containers for up to 24 hours at 2°C to 8°C or room temperature/room light. Recommended safety measures for preparation and handling include protective clothing, gloves, and safety cabinets.

5.9 General Concomitant Medication and Supportive Care Guidelines

5.9.1 Anti-emetic Premedications

Anti-emetic premedications should not be routinely required but are allowed as needed. See Section 5.8.3 for premedication recommendations following a nivolumab-related infusion reaction.

5.9.2 Prohibited and/or Restricted Treatments

The following medications are prohibited during the study:

- Any concurrent drug or radiotherapeutic (cohort 1 only) or investigational agent for the treatment of meningioma;
- Medications contraindicated with nivolumab treatment (refer to Investigator Drug Brochure).
    - Cohort 2 participants: Medications contraindicated with ipilimumab treatment (refer to Investigator Drug Brochure).

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

5.9.3 Treatment of Nivolumab or Ipilimumab Related Infusion Reactions

Since nivolumab and ipilimumab contain only human immunoglobulin protein sequences, they are 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 participant 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 participant 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 associated immune checkpoint inhibitor 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. Participant should be monitored until the investigator is comfortable that the symptoms will not recur. The associated immune checkpoint inhibitor (nivolumab or ipilimumab) will be permanently discontinued. Investigators should follow their institutional guidelines for the treatment of anaphylaxis. Remain at bedside and monitor participant 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 (e.g., oral antihistamine, or corticosteroids).

5.9.4 Permitted Therapy

Participants 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 meningioma 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.

Participants 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.

5.9.5 Other Restrictions and Precautions

Study related MRI (or CT) imaging of the brain will be performed per the frequency specified in the protocol. Investigators may obtain additional follow-up scans as medically indicated. For other locally performed imaging, it is the institutional imaging facility's responsibility to determine, based on subject attributes (e.g., 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 (i.e., 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 institutional 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.

5.10 Criteria for Taking a Participant Off Protocol Therapy

Duration of therapy will depend on individual response, evidence of disease progression and tolerance. In the absence of treatment delays due to adverse event(s), treatment may continue for indefinitely or until one of the following criteria applies:

- Confirmed radiological disease progression or investigator assessed clinical progression as described in Section 11.4;

- Unacceptable adverse event/toxicity as specified in Section 6.4;
- 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 participant;
- Participant demonstrates an inability or unwillingness to comply with the oral medication regimen and/or documentation requirements;
- Participant decides to withdraw from the protocol therapy;
- General or specific changes in the participant's condition render the participant unacceptable for further treatment in the judgment of the treating investigator
- Pregnancy;
- Loss of ability to freely provide consent through imprisonment or involuntarily incarceration for treatment of either a psychiatric or physical (eg, infectious disease) illness;
- Termination of the trial by the study's sponsor.

Participants will be removed from the protocol therapy when any of these criteria apply. The reason for removal from protocol therapy, and the date the participant was removed, must be documented in the in the subject's medical records and on the appropriate case report form (CRF). Alternative care options will be discussed with the participant.

All subjects who discontinue investigational product should comply with protocol specified follow-up procedures as outlined in Section 5.2. 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 (i.e. is imprisoned or involuntarily incarcerated for the treatment of either a psychiatric or physical illness).

When a participant is removed from protocol therapy and/or is off of the study, the relevant Off-Treatment/Off-Study information will be updated in OnCore.

In the event of unusual or life-threatening complications, treating investigators must immediately notify the Overall PI, David A. Reardon, M.D. at 617-632-2166 or 617-632-3352, pager 43339.

5.11 Duration of 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.

Participants who discontinue study treatment must continue to be followed for collection of outcome and/or survival follow-up data as described in Section 5.2 until death, withdrawal of consent to be followed, lost to follow-up, or the conclusion of the study, whichever occurs first.

Participants removed from protocol therapy for unacceptable adverse event(s) will be followed until resolution or stabilization of the adverse event.

5.12 Criteria for Taking a Participant Off Study

Participants will be removed from study when any of the following criteria apply:

- Lost to follow-up

- Withdrawal of consent for data submission
- Death
- Sponsor decides to terminate the study

The reason for taking a participant off study, and the date the participant was removed, must be documented in the case report form (CRF).

When a participant is removed from protocol therapy and/or is off of the study, the relevant Off-Treatment/Off-Study information will be updated in OnCore.

5.12.1 Withdrawal of Informed Consent

Participants 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 participant specifically withdraws consent for any further contact with him/her or persons previously authorized by subject to provide this information. Participants should notify the investigator of the decision to withdraw consent from future follow-up in writing, whenever possible. The withdrawal of consent should be explained in detail in the medical records by the investigator, as to whether the withdrawal is from further treatment with study drug only or also from study procedures and/or post treatment study follow-up, and entered on the appropriate CRF page. In the event that vital status (whether the participant 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.

5.12.2 Lost to Follow-Up

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

The site staff and representative will consult publicly available sources, such as public health registries and databases, in order to obtain updated contact information. If after all attempts, the participant remains lost to follow-up, then the last known alive date as determined by the investigator should be reported and documented in the participant's medical records.

6. DOSING DELAYS/DOSE MODIFICATIONS

Dose delays and modifications will be made as indicated in the following section. The descriptions and grading scales found in the revised NCI Common Terminology Criteria for Adverse Events (CTCAE) version 4.0 will be utilized for dose delays and dose modifications. A copy of the CTCAE version 4.0 can be downloaded from the CTEP website http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm.

Dosing Modifications/Reductions:

Dose reduction outside of the safety lead-in is not permitted on study for any reason; there will be no dose reductions allowed for the management of toxicities of individual participants. Dose

delays for the management of study treatment related adverse events are described in this section. Of note, given the overlapping toxicities associated with nivolumab and ipilimumab, dose delay criteria specified below should be applied to participants in Cohort 2 who develop a potential immune related adverse event while receiving combined nivolumab plus ipilimumab therapy. In addition, participants who require discontinuation of ipilimumab due to immune related adverse events as defined below, may be allowed to resume study nivolumab therapy if the treating clinician feels that the adverse event was more likely related to ipilimumab therapy than nivolumab therapy. Participants who discontinue ipilimumab and resume nivolumab therapy will follow the monotherapy nivolumab dosing schedule of 480 mg every 4 weeks.

Dosing window:

Participants may be dosed no more than 5 days after - and no more than 2 days before - the scheduled dosing date. Dose given after the 5-day window is considered a dose delay.

Cohort 1: Participants may be dosed no less than 12 days (11 non-dosing days) between doses.

Cohort 2: The following minimum intervals are required between nivolumab doses: a minimum 14-day interval (13 non-dosing days) during combination therapy cycles (nivolumab every 3 weeks), and a minimum 21-day interval (20 non-dosing days) during nivolumab monotherapy therapy cycles (nivolumab every 4 weeks).

A maximum delay of 42 days *between doses* is allowed.

6.1 Dose Delay Criteria for Nivolumab and/or Ipilimumab

Dose delay criteria specified below apply for all nivolumab and/or ipilimumab related adverse events. Nivolumab and ipilimumab must be delayed until treatment can resume (see Section 6.3).

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

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 lymphopenia or leukopenia does not require dose delay.
  - 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 study's Overall PI, David Reardon, MD, 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 participant has a baseline AST, ALT, or total bilirubin that is within normal limits, delay dosing for drug-related Grade ≥ 2 toxicity
  - If a participant 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.

6.1.1 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

The algorithms recommended for utilization in this protocol are included in Appendix B (Nivolumab) and Appendix C (Ipilimumab).

For participants expected to require more than 4 weeks of corticosteroids or other immunosuppressants to manage an adverse event, consider recommendations provided in Appendix B (Nivolumab) and Appendix C (Ipilimumab). The guidance provided in these algorithms should not replace the Investigator's medical judgment but should complement it.

6.2 Dose Modifications

Dose reductions or dose escalations are not permitted.

6.3 Criteria to Resume Treatment

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

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

- Participants may resume treatment in the presence of Grade 2 fatigue
- Participants who have not experienced a Grade 3 drug-related skin AE may resume treatment in the presence of Grade 2 skin toxicity
- Participants 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
- Participants with combined Grade 2 AST/ALT AND total bilirubin values meeting discontinuation parameters (Section 6.4) should have treatment permanently discontinued
- Drug-related pulmonary toxicity, diarrhea, or colitis, must have resolved to baseline before treatment is resumed
  - Participants with persistent Grade 1 pneumonitis after completion of a steroid taper over at least 1 month may be eligible for retreatment after prospective discussion with and approval from the study's Overall PI, David A. Reardon, MD, or selected designee.
- Drug-related endocrinopathies adequately controlled with only physiologic hormone replacement may resume treatment

If the criteria to resume treatment are met, the participant should restart treatment at the next scheduled time point per protocol. However, if the treatment is delayed past the next scheduled timepoint per protocol, the next scheduled timepoint will be delayed until dosing resumes.

If treatment with study medication is delayed > 6 weeks, the participant must be permanently discontinued from study therapy, except as specified in Section 6.4.

6.4 Discontinuation Criteria

Treatment with combination nivolumab and 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, infusion reactions, and endocrinopathies:
  - 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 endocrinopathies adequately controlled with only physiologic hormone replacement do not require discontinuation
  - Grade 3 drug-related laboratory abnormalities do not require treatment discontinuation except those noted below:
    - 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 requires 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:
  - Isolated Grade 4 amylase or lipase abnormalities that are not associated with symptoms or clinical manifestations of pancreatitis and decrease to < Grade 4 within 1 week of onset.
  - Isolated Grade 4 electrolyte imbalances/abnormalities that are not associated with clinical sequelae and are corrected with supplementation/appropriate management within 72 hours of their onset
  - Grade 4 lymphopenia or leukopenia
  - Grade 4 drug-related endocrinopathy adverse events, such as adrenal insufficiency, ACTH deficiency, hyper- or hypothyroidism, or glucose intolerance, which resolve or are adequately controlled with physiologic hormone replacement (corticosteroids, thyroid hormones) or glucose-controlling agents, respectively, may not require discontinuation after prospective discussion with and approval from the study's Overall PI, David A. Reardon, MD or designee.
- 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 participant with a dosing

interruption lasting > 6 weeks, the study's Overall PI, David A. Reardon, MD or designee must be consulted and approve of the plan. Tumor assessments should continue as per protocol even if dosing is interrupted.
  - If Treating Investigator wants to hold drug for > 6 weeks for non-drug-related reasons, the study's Overall PI, David A. Reardon, MD or designee must provide approval prior to re-initiating treatment. Tumor assessments should continue as per protocol even if dosing is interrupted.
- Any adverse event, laboratory abnormality, or intercurrent illness that, in the judgment of the Investigator, presents a substantial clinical risk to the subject with continued nivolumab or ipilimumab dosing.

For Cohort 2 – Patients who experience AEs while receiving nivolumab plus ipilimumab combination therapy that meet criteria for discontinuation of nivolumab/ipilimumab combination therapy may resume study therapy with nivolumab monotherapy once they fully recover as long as they are benefiting from study therapy and it is felt to be medically appropriate by the treating physician. However, if a patient experiences a clinically significant recurrence in any of the aforementioned toxicities, nivolumab monotherapy will be permanently discontinued.

Study treatment must be discontinued upon confirmed radiologic progression or clinical progression (whichever comes first) as described in Section 11.2.

7. ADVERSE EVENTS: LIST AND REPORTING REQUIREMENTS

Adverse event (AE) monitoring and reporting is a routine part of every clinical trial. The following list of reported and/or potential AEs (Section 7.1) and the characteristics of an observed AE (Section 7.2) will determine whether the event requires expedited reporting **in addition** to routine reporting.

All adverse events experienced by participants will be collected from the time of the first dose of study treatment (first nivolumab or ipilimumab administration), through the study and until the final study visit. Participants continuing to experience toxicity at the end of treatment visit may be contacted for additional assessments until the toxicity has resolved or is deemed irreversible.

7.1 Expected Toxicities

7.1.1 Adverse Events List

7.1.1.1 **Adverse Event List for Nivolumab**

A list of the more common adverse events and potential risks associated with nivolumab appear below and a comprehensive listing is available in the Investigator Drug Brochure for nivolumab.

- Blood and lymphatic disorders: anemia; lymphopenia; thrombocytopenia
- Cardiac disorders: arrhythmia; myocarditis; pericarditis; tachycardia
- Endocrine disorders: adrenal insufficiency; hypothyroidism; hyperthyroidism
  - Endocrine disorders – Other, specify:
    - diabetes mellitus
    - hypophysitis

        - hypopituitarism
- Eye disorders: blurred vision; uveitis
    - Eye disorders – Other, specify: Iritis
- Gastrointestinal disorders: abdominal pain; constipation; diarrhea; duodenal ulcer; dry mouth; enterocolitis; nausea; perforation (colonic, duodenal, esophageal, gastric, ileal, jejunal, rectal, small intestinal); vomiting; pancreatitis
- General disorders and administration site conditions: chills; edema (face, limbs); fever; fatigue; infusion related reaction
- Immune system disorders: allergic reaction
- Infection and infestations: encephalitis infection; lymphadenitis; meningitis
    - Infections and infestations – Other, specify: Pneumonia
- Investigations: alanine aminotransferase increased; alkaline phosphatase increased aspartate aminotransferase increased; blood bilirubin increased; lipase increased; serum amylase increased; weight loss
- Metabolism and nutrition disorders: anorexia; dehydration; hyperglycemia; hyponatremia; hypercalcemia; hypocalcemia; hypokalemia; hyperkalemia; hypomagnesemia; tumor lysis syndrome
- Musculoskeletal and connective tissue disorders: arthralgia; myositis; pain (back, bone, buttock, chest wall, extremity, flank, neck)
    - Musculoskeletal and connective tissue disorders – Other, specify:
        - Rhabdomyolysis
        - Rejection of solid organ or tissue transplants;
        - Graft versus host disease (GVHD), including fatal cases, in patients who have previously undergone allogeneic hematopoietic stem cell transplant (HSCT);
        - Increased risk of transplant-related complications, including GVHD, in patients who receive allogeneic hematopoietic stem cell transplant (HSCT) after Nivolumab
- Nervous system disorders: dizziness; headache; myelitis; peripheral motor neuropathy; peripheral sensory neuropathy
    - Nervous system disorders – Other, specify:
        - Demyelination
        - Guillain-Barre syndrome
        - Myasthenic syndrome
- Respiratory, thoracic and mediastinal disorders: cough; dyspnea; pneumonitis
- Renal and urinary: increased creatinine
    - Renal and urinary – Other, specify: Nephritis
- Skin and subcutaneous tissue disorders: alopecia
    - All CTCAE v. 4 rashes are considered expected: bullous dermatitis, erythema multiforme, erythroderma, palmar-plantar erythrodysesthesia syndrome, pruritus, rash acneiform, rash maculo-papular, skin hyperpigmentation, skin hypopigmentation, skin induration, skin ulceration, Stevens-Johnson syndrome, toxic epidermal necrolysis (TEN)
- Vascular disorders: hypertension; hypotension; vasculitis

In addition, nivolumab and other immune checkpoint inhibitors have been associated

with immune mediated adverse events as detailed in Section 6.1.1 and Appendix B.

7.1.1.2 Adverse Event List for Ipilimumab

A list of the more common adverse events and potential risks associated with ipilimumab appear below and a comprehensive listing is available in the package insert for ipilimumab.

- Blood and lymphatic disorders: anemia; lymphopenia; thrombocytopenia
- Cardiac: myocarditis; pericarditis
- Endocrine disorders: adrenal insufficiency; hypothyroidism; hyperthyroidism
  - Endocrine disorders – Other, specify:
    - diabetes mellitus
    - hypopituitarism
- Eye disorders: blurred vision; eye pain; uveitis
  - Eye disorders – Other, specify: Iritis
- Gastrointestinal disorders: abdominal pain; constipation; diarrhea; duodenal ulcer; enterocolitis; nausea; perforation (colonic, duodenal, esophageal, gastric, ileal, jejunal, rectal, small intestinal); vomiting; pancreatitis
- General disorders and administration site conditions: chills; fatigue; fever; infusion related reaction; injection site reaction
- Infection and infestations: encephalitis infection; meningitis
- Investigations: alanine aminotransferase increased; aspartate aminotransferase increased; alkaline phosphatase increased; blood bilirubin increased; lipase increased; serum amylase increased; weight loss
- Metabolism and nutrition disorders: anorexia; dehydration; hyponatremia; hypocalcemia; hyperkalemia; hypokalemia; hypomagnesemia
- Musculoskeletal and connective tissue disorders: arthralgia; myositis; pain (back, bone, buttock, chest wall, extremity, flank, neck)
  - Musculoskeletal and connective tissue disorders – Other, specify: Rhabdomyolysis
- Nervous system disorders: dizziness; headache; peripheral motor neuropathy; peripheral sensory neuropathy
  - Nervous system disorders – Other, specify:
    - Demyelination
    - Guillain-Barre syndrome
    - Myasthenic syndrome
- Respiratory, thoracic and mediastinal disorders: cough; dyspnea; pneumonitis
- Renal and urinary: increased creatinine
  - Renal and urinary – Other, specify: Nephritis
- Skin and subcutaneous tissue disorders: alopecia; dry skin
  - All CTCAE v. 4 rashes are considered expected: bullous dermatitis, erythema multiforme, erythroderma, palmar-plantar erythrodysesthesia syndrome, pruritus, rash acneiform, rash maculo-papular, skin hyperpigmentation, skin hypopigmentation, skin induration, skin ulceration, Stevens-Johnson syndrome, toxic epidermal necrolysis (TEN)

- Vascular disorders: hypotension, flushing, hot flashes

In addition, ipilimumab and other immune checkpoint inhibitors have been associated with immune mediated adverse events as detailed in Section 6.1.1 and Appendix C.

7.2 Adverse Event Characteristics and Definitions

7.2.1 Adverse Event (AE) Definition:

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.

Abnormal laboratory values or diagnostic test results constitute adverse events only if they induce clinical signs or symptoms or require treatment or further diagnostic tests.

7.2.2 CTCAE term (AE description) and grade:

The descriptions and grading scales found in the revised NCI Common Terminology Criteria for Adverse Events (CTCAE) version 4.0 will be utilized for AE reporting. All appropriate treatment areas should have access to a copy of the CTCAE version 4.0. A copy of the CTCAE version 4.0 can be downloaded from the CTEP web site http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm.

7.2.3 General Considerations:

- Information on all adverse events, whether reported by the participant, directly observed, or detected by physical examination, laboratory test or other means, will be collected, recorded, followed and reported as described in the following sections.
- The occurrence of adverse events should be sought by non-directive questioning of the participant at each visit during the study. Adverse events also may be detected when the participant volunteers them during or between visits or through physical examination, laboratory test, or other assessments. As far as possible, each adverse event should be evaluated to determine:
    - the severity grade (using CTCAE v. 4.0)
    - its attribution to the study drug
    - its duration (start and end dates or if continuing at final exam)
    - action taken (no action taken; study drug dosage adjusted/temporarily interrupted; study drug permanently discontinued due to this adverse event; concomitant medication taken; non-drug therapy given; hospitalization/prolonged hospitalization)
    - whether it constitutes a serious adverse event (SAE)
- Adverse events experienced by participants will be collected and reported from **initiation of study medication**, throughout the study, and within 30 days of the last dose of study medication. Participants who experience an ongoing adverse event related to a study procedure and/or study medication beyond 30 days will continue to be contacted by a member of the study team until the event is resolved, stabilized, or determined to be

irreversible by the participating investigator.

- All adverse events should be treated appropriately. Such treatment may include changes in study drug treatment including possible interruption or discontinuation, starting or stopping concomitant treatments, changes in the frequency or nature of assessments, hospitalization, or any other medically required intervention. Once an adverse event is detected, it should be followed until its resolution, and assessment should be made at each visit (or more frequently, if necessary) of any changes in severity, the suspected relationship to the study drug, the interventions required to treat it, and the outcome.
- Participants should be instructed to report any serious post-study-treatment event(s) that might reasonably be related to participation in this study. The investigator should notify the IRB and any other applicable regulatory agency of any unanticipated death or adverse event occurring after a participant has discontinued or terminated study participation that may reasonably be related to the study.

7.2.4 For expedited reporting purposes only:

- AEs for the agent(s) that are listed above should be reported only if the adverse event varies in nature, intensity or frequency from the expected toxicity information that is provided.
- Other AEs for the protocol that do not require expedited reporting are outlined in the next section (Expedited Adverse Event Reporting) under the sub-heading of Protocol-Specific Expedited Adverse Event Reporting Exclusions.

7.2.5 Expectedness of the AE:

Adverse events can be 'Expected' or 'Unexpected.'

- Expected adverse event
  "Expected" adverse events are those that have been previously identified as resulting from administration of the agent. For recording and reporting purposes on this trial, an adverse event is considered expected when it appears in the current nivolumab or ipilimumab IB.
- Unexpected adverse event
  For recording and reporting purposes on this trial, an adverse event is considered "unexpected" when it varies in nature, intensity or frequency from information provided in the nivolumab or ipilimumab IB.

7.2.6 Attribution of the AE:

The causal relationship will be made for each of the agents of study therapy: nivolumab, ipilimumab (when applicable), and radiation (when applicable). Attribution is determined by an appropriately trained and delegated clinician and should be used to assess all adverse events (AE). The casual relationship can be one of the following:

- Definite – The AE *is clearly related* to the study treatment.
- Probable – The AE *is likely related* to the study treatment.
- Possible – The AE *may be related* to the study treatment.
- Unlikely – The AE *is doubtfully related* to the study treatment.
- Unrelated – The AE *is clearly NOT related* to the study treatment.

7.2.7 Serious Adverse Event (SAE) Definition:

A serious adverse event (SAE) is any adverse event, occurring at any dose and regardless

of causality that:

- Results in death
- Is life-threatening. Life-threatening means that the person was at immediate risk of death from the reaction as it occurred, i.e., it does not include a reaction which hypothetically might have caused death had it occurred in a more severe form.
- Requires or prolongs inpatient hospitalization (i.e., the event required at least a 24-hour hospitalization or prolonged a hospitalization beyond the expected length of stay). Hospitalization admissions and/or surgical operations scheduled to occur during the study period, but planned prior to study entry are not considered SAEs if the illness or disease existed before the person was enrolled in the trial, provided that it did not deteriorate in an unexpected manner during the trial (e.g., surgery performed earlier than planned).
- Results in persistent or significant disability/incapacity. Disability is defined as a substantial disruption of a person's ability to conduct normal life functions.
- Is a congenital anomaly or birth defect; or
- 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 [e.g., medical, surgical] to prevent one of the other serious outcomes listed in the definition above.). Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home; blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse.
  - For the purpose of this trial, potential drug induced liver injury (DILI) is also considered an important medical event.
- Suspected transmission of an infectious agent (e.g., pathogenic or nonpathogenic) via the study drug

NOTE: Although pregnancy, overdose, and cancer are not always serious by regulatory definition, these events must be reported to sponsor and BMS as SAEs.

7.2.7.1 Protocol-Specific Expedited Adverse Event Reporting Exclusions:

Events **not** considered to be serious adverse events in this trial are:

- Lymphopenia (grades 2-4)
- 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)
- Emergency outpatient treatment for an event not fulfilling the serious criteria outlined above and not resulting in inpatient admission
- Elective surgery, planned prior to signing consent
- Routine health assessment requiring admission for baseline/trending of health status (e.g., routine colonoscopy)
- Hospitalization for routine treatment or monitoring of the studied indication, not associated with any deterioration in condition, or for elective procedures
- Hospitalization for scheduled debulking surgery
- Hospitalization for seizure, if felt related to patient's underlying disease
- Hospitalization for elective or pre-planned treatment for a pre-existing condition that did not worsen

- Hospitalization for respite care not associated with an adverse event attributed to the study drug
- Hospitalization for treatment of patient's underlying disease (e.g. admission after patient is removed from active study treatment for craniotomy)
- 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).

7.2.8 Potential Drug Induced Liver Injury (DILI) Definition:

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.

Potential drug induced liver injury is defined as:

1. 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 AST/ALT 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.

7.3 Procedures for AE and SAE Recording and Reporting

Participating investigators will assess the occurrence of AEs and SAEs at all participant evaluation time points during the study.

All AEs and SAEs whether reported by the participant, discovered during questioning, directly observed, or detected by physical examination, laboratory test or other means, will be recorded in the participant's medical record and on the appropriate study-specific case report forms (eCRFs).

7.4 Expedited Adverse Event Reporting

7.4.1 Investigators **must** report to the Overall PI and BMS any serious adverse event (SAE) that occurs after a subject's consent, during treatment, or within 100 days of the last dose of treatment (or until the start of new anti-cancer treatment, whichever comes first) via the appropriate applicable reporting form (MedWatch 3500A and/or local institutional IRB submission form).

7.4.2 <u>DF/HCC Expedited Reporting Guidelines</u>

Investigative sites within DF/HCC will report AEs directly to the DFCI Office for

Human Research Studies (OHRS) per the DFCI IRB reporting policy.

7.4.3 Expedited Adverse Event Reporting Requirements (By Site to Overall PI and BMS)

The study must be conducted in compliance with local safety reporting requirements, and reporting requirements of the principal investigator.

Each adverse event will be assessed to determine if it meets the criteria for reporting. Adverse event reporting is to occur according to the site's specific IRB guidelines, and as outlined in this Section. Any serious adverse event occurring after the participant has initiated study treatment and until 100 days after the participant has stopped the study drug or the start of new anti-cancer treatment (whichever comes first) must be reported. Serious adverse events must be followed until resolution.

Investigators **must** report to the Overall PI any serious adverse event (SAE) that occurs after the participant has signed consent to participate in the study, during treatment, and until 100 days after the last dose of treatment or the start of new anti-cancer treatment (whichever comes first) on the local institutional SAE form.

It is the responsibility of each participating investigator to report adverse events to the Overall PI, BMS, DF/HCC IRB, and/or others as described below. The Overall PI or representative Coordinating Center personnel will ensure the report is forwarded to the proper parties, as appropriate.

Adverse event reporting by each site is detailed in Table 7.4.3-1.

For trials where a DF/HCC investigator is serving as the Overall Principal Investigator, each participating institution **must** abide by the reporting requirements set by the DF/HCC. This applies to any medical event equivalent to an unexpected grade 2 or 3 with a possible, probable or definite attribution, any grade 4 unexpected toxicities, and grade 5 (death) regardless of attribution.

Whenever feasible, the participating investigator should provide follow-up information on the serious adverse event within the following 24-48 hours. Follow-up information should describe whether the event has resolved or continues, if and how the event was treated, and whether the participant will continue or discontinue study participation.

Note: If the participant is in long term follow up, report the death at the time of continuing review.

Table 7.4.3-1: Reporting to Study's Overall PI, BMS, and IRB:

Adverse Event Characteristics				**Notification Requirement**		
Serious-ness	**Toxicity**	**Known correlation**	**Attribution to study drug(s)**	**Bristol-Myers Squibb Company (BMS) - Via Fax Use Facsimile Coversheet [b] and Medwatch 3500A [c]**	**David A. Reardon, MD: Overall PI - Via Email [a] Use Facsimile Coversheet [b] and Medwatch 3500A [c]**	**DF/HCC IRB**
Serious	Any	Any (Expected or Unexpected)	Any	Within 24 hours from notification [d]	Within 24 hours from notification [d]	As needed if required per local IRB To be submitted within IRB established reporting timelines. Please ensure that Dr. Reardon prospectively approves all submissions.
Any	Potential Drug Induced Liver Injury (DILI)[e], Any Grade, Overdose, or Pregnancy	Any (Expected or Unexpected)	Any	Within 2 working days from notification [d]	Within 2 working days from notification [d]	

a. Email the Medwatch 3500A form, facsimile coversheet, and the IRB SAE report to the DFCI Coordinating Site with the subject title as "Nivolumab SAE" to NeuroOnc_SAE@dfci.harvard.edu. All SAE reports received at this account are forwarded immediately to study's Overall PI, David A. Reardon, MD, and to the DFCI Coordinating Center personnel.

b. Facsimile Coversheet is found in Appendix D. Adverse Event Reporting Facsimile Coversheet contains all FAX numbers/e-mails and destinations.

c. Medwatch 3500A downloadable form at http://www.fda.gov/medwatch/getforms.htm

d. In the event that the participating investigator does not become aware of the serious adverse event immediately (e.g., participant sought treatment elsewhere), the participating investigator is to report the event within 24 hours after learning of it and document the time of his or her first awareness of the adverse event.

e. See section 7.2.8 of the protocol for definition of Potential Drug Induced Liver Injury (DILI)

7.5 Reporting of 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 investigational product exposure (including at least 5 months after the last dose of Nivolumab and/or Ipilimumab for women), the investigational product will be permanently discontinued in an appropriate manner (e.g., dose tapering if necessary for subject safety).

The investigator must immediately notify Worldwide Safety @ BMS of this event via the Pregnancy Surveillance Form in accordance with SAE reporting procedures.

In addition, 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 (also in accordance with SAE reporting procedures).

- This will include any pregnancy that occurs within 7 months post-treatment in male participants.
- In order for Sponsor or designee to collect any pregnancy surveillance information from the female partner, the partner must sign an informed consent form for disclosure of this information.

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 [provided upon request from BMS]. Details on the pregnancy will be collected for safety analysis throughout the pregnancy and for up to one year following the birth of the infant. The Pregnancy Surveillance Form provided by BMS will be completed and submitted to study sponsor and BMS Worldwide Safety at a frequency dependent upon the pregnancy; updates provided when new information is available. Initial pregnancy notifications as well as any complications identified will be submitted in accordance with SAE reporting procedures (within 24 hours of notification).

7.6 Overdose

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

7.7 Other Safety Considerations

Any significant worsening noted during interim or final physical examinations, scans, and any other potential safety assessments, whether or not these procedures are required by the protocol, should also be recorded as a non-serious or serious AE, as appropriate, and reported accordingly.

7.8 Expedited Reporting to Hospital Risk Management

Participating investigators will report to their local Risk Management office any participant safety reports or sentinel events that require reporting according to institutional policy.

7.9 Monitoring of Adverse Events and Period of Observation

All adverse events, both serious and non-serious, and deaths that are encountered from initiation of study intervention, throughout the study, and within 30 days of the last study intervention should be followed to their resolution, or until the participating investigator assesses them as stable, or the participating investigator determines the event to be irreversible, or the participant is lost to follow-up. Serious adverse events will be reported from time of consent through 100 days after last dose or the start of new anti-cancer treatment, whichever comes first. The presence and resolution of AEs and SAEs (with dates) should be documented on the appropriate case report form and recorded in the participant's medical record to facilitate source data verification.

For some SAEs, the Overall PI or designee may follow-up by telephone, fax, and/or monitoring visit to obtain additional case details deemed necessary to appropriately evaluate the SAE report (e.g., hospital discharge summary, consultant report, or autopsy report).

Participants should be instructed to report any serious post-study event(s) that might reasonably be related to participation in this study. Participating investigators should notify the DF/HCC Overall Principal Investigator and their respective IRB of any unanticipated death or adverse event occurring after a participant has discontinued or terminated study participation that may reasonably be related to the study.

7.10 Routine Adverse Event Reporting

All Adverse Events **must** be reported in routine study data submissions to the Overall PI on the toxicity case report forms. **AEs reported through expedited processes (e.g., reported to the IRB, FDA, etc.) must <u>also</u> be reported in routine study data submissions.**

7.11 Reporting by the Study Sponsor / Overall Principal Investigator

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

As this PI-Initiated Trial does not include external sites, the Study Sponsor / Overall Principal Investigator (also the DF/HCC Overall PI) will not be circulating either of the following to participating Investigator Teams:

- Reportable AEs occurring on this study protocol.
- IND safety reports received on study.

7.11.1 Expedited Reporting to the Food and Drug Administration (FDA)

The Overall PI, as study sponsor, will be responsible for all communications with the FDA. The Overall PI will report to the FDA, regardless of the site of occurrence, any serious adverse event that meets the FDA's criteria for expedited reporting following the reporting requirements and timelines set by the FDA.

8. PHARMACEUTICAL INFORMATION

A list of the adverse events and potential risks associated with the investigational agent administered in this study can be found in Section 7.1.

8.1 Nivolumab

8.1.1 Description

Nivolumab (BMS-936558-01) Injection drug product is a sterile, non-pyrogenic, single-use, isotonic aqueous solution formulated at 10 mg/mL. Other names = MDX-1106, ONO-4538, and anti-PD-1. Nivolumab may be labeled as 'BMS-936558-01 Solution for Injection'.

8.1.2 Form

Nivolumab is a clear to opalescent, colorless to pale yellow liquid that may contain particles, and is provided at a concentration of 10mg/mL in 10mL vials (100 mg/vial). Vials are 10-cc Type 1 flint glass vials stoppered with butyl stoppers and sealed with aluminum seals, and cartons contain 5 or 10 vials.

8.1.3 Storage, Handling, and Stability

Please refer to the Nivolumab Pharmacy Reference Sheet for full details on storage, handling and stability information.

BMS-936558-01 Injection must be stored at 2 to 8 degrees C (36 to 46 degrees F) and protected from light and freezing

If stored in a glass front refrigerator, vials should be stored in the carton. Recommended safety measures for preparation and handling of nivolumab include laboratory coats and gloves.

For additional details on prepared drug storage and use time of nivolumab under room temperature/light and refrigeration, please refer to the BMS-936558 (nivolumab) Investigator Brochure section for "Recommended Storage and Use Conditions"

Storage Conditions & Handling:

- Store at 2-8°C (36-46°F), protect from light, freezing, and shaking.
- If any temperature excursions are encountered during storage, please report these to BMS for assessment via the Temperature Excursion Response Form.
- As with all injectable drugs, care should be taken when handling and preparing nivolumab. Whenever possible, nivolumab should be prepared in a laminar flow hood or safety cabinet using standard precautions for the safe handling of intravenous agents applying aseptic

technique.
- Partially used vials should be disposed at the site following procedures for the disposal of anticancer drugs.

Qualified personnel, familiar with procedures that minimize undue exposure to themselves and the environment, should undertake the preparation, handling, and safe disposal of the chemotherapeutic agent in a self-contained and protective environment.
After final drug reconciliation, unused nivolumab vials should be disposed at the site following procedures for the disposal of anticancer drugs. (For sites where Institutional policy does not allow Teams to keep and store used vials for reconciliation, please ensure utilization of the NCI DAR form or equivalent.) For further information, please either discuss with your BMS CSR&O protocol manager or refer to your site IP Destruction policies and procedures.

Use Time/Stability: Please refer to section 3.2.3 of the current Investigator Brochure. Due to parameters surrounding the use time of Nivolumab, the time of preparation should be noted in the Pharmacy Source documents [accountability logs] or in study files as required for investigator sponsored research [FDA and GCP]

The administration of BMS-936558-01 injection prepared for dosing nivolumab infusion must be completed within 24 hours of preparation. If not used immediately, the infusion solution may be stored up to 20 hours in a refrigerator at under refrigeration conditions (2°-°-8°C (, 36°-46°F) and used within 4for up to 24 hours, and a maximum of 4 hours of the total 24 hours can be at room temperature (20°-25°C, 68°-77°F) and under room light. The maximum 4-hour period under room temperature and room light conditions for undiluted and diluted solutions of BMS-936558-01 injection in the IV bag should be inclusive of the includes the product administration period.

8.1.4 Compatibility

No incompatibilities between nivolumab and polyvinyl chloride (PCV) and non-PCV/non-DEHP (di(2-ethylhexyl)phthalate) containers/IV components or glass bottles have been observed. Please refer to the Nivolumab (BMS-936558-01) IB for any potential compatibility issues.

8.1.5 Preparation and Administration

Dose administration

Participants should initiate drug within 14 days of screening assessments, unless otherwise noted.

Nivolumab is to be administered on Day 1 of every cycle, as an IV infusion over 30 minutes (window of -10 / + 30 min). At the end of the infusion, flush the line with a sufficient quantity of normal saline.

Cohort 1: Nivolumab (240 mg) is to be administered every 2 weeks (on Day 1 of every 14-day cycle). There is an administration window of -2/+5 days for Nivolumab administrations; although a minimum 12-day interval (11 non-dosing days) is required between nivolumab doses.

NOTE: Participants who have received active study therapy for >/= 12 months will be allowed the option to adjust their Nivolumab dosing schedule from once every 2 weeks (-2/+5 days) to once every 4 weeks (+/- 1 week).

Cohort 2: During the initial combination phase of therapy for cohort 2, nivolumab is to be administered every 3 weeks at 3 mg/kg with ipilimumab for four doses. Thereafter, during the maintenance phase of nivolumab monotherapy, patients will receive flat dosing of 480 mg once every four weeks until discontinuation of protocol therapy (Section 5.10). There is an administration window of -2/+5 days for Nivolumab administrations

There are no premedications recommended for nivolumab on the first cycle.

There will be no dose modifications allowed.

Subjects should be carefully monitored for infusion reactions during nivolumab administration. If an acute infusion reaction is noted, subjects should be managed according to Protocol Section 5.8.3.

Doses of nivolumab may be interrupted, delayed, or discontinued depending on how well the subject tolerates the treatment.

Nivolumab Injection, 100 mg/10 mL (10 mg/mL). Nivolumab injection is to be administered as an IV infusion through a 0.2-micron to 1.2-micron pore size, low-protein binding polyethersulfone membrane in-line filter at the protocol-specified doses. It is not to be administered as an IV push or bolus injection. Nivolumab injection can be infused undiluted (10 mg/mL) or diluted with 0.9% Sodium Chloride Injection, USP or 5% Dextrose Injection, USP to protein concentrations as low as 0.35 mg/mL. Care must be taken to assure sterility of the prepared solution as the product does not contain any antimicrobial preservative or bacteriostatic agent.

Administration

1. Visually inspect the drug product solution for particulate matter and discoloration prior to administration. Discard if solution is cloudy, if there is pronounced discoloration (solution may have a pale-yellow color), or if there is foreign particulate matter other than a few translucent-to-white, amorphous particles.

   *Note: Mix by **gently** inverting several times. **Do not** shake.*
2. Aseptically withdraw the required volume of nivolumab solution into a syringe, and dispense into an IV. bag. If multiple vials are needed for a subject, it is important to use a separate sterile syringe and needle for each vial to prevent problems such as dulling of needle tip, stopper coring, repeated friction of plunger against syringe barrel wall. **Do not** enter into each vial more than once. **Do not** administer study drug as an IV push or bolus injection

3. Add the appropriate volume of 0.9% Sodium Chloride Injection solution or 5% Dextrose Injection solution. *It is acceptable to add nivolumab solution from the vials into an appropriate pre-filled bag of diluent.*

   Note: Nivolumab infusion concentration must be at or above the minimum allowable

concentration of 0.35 mg/mL [IBV13 Addendum Section 3.2.2]

Note: It is not recommended that so-called "channel" or tube systems are used to transport prepared infusions of nivolumab.

4. Attach the IV bag containing the nivolumab solution to the infusion set and filter.
5. At the end of the infusion period, flush the line with a sufficient quantity of approved diluents.

8.1.6 Availability/Ordering

Initial Orders

- Following submission and approval of the required regulatory documents, a supply of nivolumab may be ordered from by completing a Drug Request Form provided by BMS for this specific trial.
- The initial order should be limited to 20 vials. Allow 5 business days for shipment of drug from BMS receipt of the Drug Request Form. Drug is protocol specific, but not patient specific. All drug product will be shipped by courier in a temperature-controlled container. It is possible that sites may have more than one nivolumab clinical study ongoing at the same time. It is imperative that only drug product designated for this protocol number be used for this study.
- Pharmacy supplies not provided by BMS: Empty IV bags/containers, approved diluents, In-line filters and infusion tubing

Re-Supply

- Drug re-supply request form should be submitted electronically business days before the expected delivery date. Deliveries will be made Tuesday through Friday.
- When assessing need for resupply, institutions should keep in mind the number of vials used per treatment dose, and that shipments may take 14 business days from receipt of request. Drug is not patient-specific. Be sure to check with your pharmacy regarding existing investigational stock to assure optimal use of drug on hand.

Drug Excursions

- Drug excursions should be reported immediately to BMS on the form provided with the study-specific drug order form

8.1.7 Accountability

The investigator, or a responsible party designated by the investigator, should maintain a careful record of the inventory and disposition of the agent using the NCI Drug Accountability Record Form (DARF) or another comparable drug accountability form. (See the NCI Investigator's Handbook for Procedures for Drug Accountability and Storage.)

8.1.8 Destruction and Return

8.1.8.1 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.

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.

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

8.1.8.2 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.

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

8.2 Ipilimumab

8.2.1 Description

Ipilimumab is a recombinant, human monoclonal antibody that binds to the cytotoxic T-lymphocyte-associated antigen 4 (CTLA-4). Ipilimumab is an IgG1 kappa immunoglobulin with an approximate molecular weight of 148 kDa. Ipilimumab is produced in mammalian (Chinese hamster ovary) cell culture.

8.2.2 Form

Ipilimumab is a sterile, preservative-free, clear to slightly opalescent, colorless to pale yellow solution for intravenous infusion, which may contain a small amount of visible translucent-to-white, amorphous ipilimumab particulates. It is supplied in single-use vials of 50 mg/10 mL and 200 mg/40 mL. Each milliliter contains 5 mg of ipilimumab and the following inactive ingredients: diethylene triamine pentaacetic acid (DTPA) (0.04 mg), mannitol (10 mg), polysorbate 80 (vegetable origin) (0.1 mg), sodium chloride (5.85 mg), tris hydrochloride (3.15 mg), and Water for Injection, USP at a pH of 7.

8.2.3 Storage, Handling, Stability

Ipilimumab injection, 50 mg/10 mL (5 mg/mL) or 200 mg/40 mL (5 mg/mL), must be stored

refrigerated (2°C to 8°C) and protected from light. Ipilimumab injection must not be frozen. Partially used vials or empty vials of ipilimumab injection should be discarded at the site according to appropriate drug disposal procedures.

Ipilimumab injection may be stored undiluted (5 mg/mL) or following dilution in 0.9% Sodium Chloride Injection, USP or 5% Dextrose Injection, USP in PVC, non-PVC/non-DEHP, or glass containers for up to 24 hours at 2°C to 8°C or room temperature/room light.

Recommended safety measures for preparation and handling include protective clothing, gloves, and safety cabinets.

8.2.4 Compatibility

No incompatibilities between ipilimumab and polyvinyl chloride (PCV) and non-PCV/non-DEHP (di(2-ethylhexyl)phthalate) containers/IV components or glass bottles have been observed.

8.2.5 Preparation and Administration

Ipilimumab injection (5 mg/mL) can be used for intravenous (IV) administration without dilution after transferring to a polyvinyl chloride (PVC), non PVC/non di (2 ethylhexyl)phthalate (DEHP), or glass container and is stable for 24 hours at 2°C to 8°C or room temperature/room light. Ipilimumab injection may be diluted in 0.9% Sodium Chloride Injection, United States Pharmacopeia (USP) or 5% Dextrose Injection, USP to concentrations between 1 mg/mL and 4 mg/mL and stored in PVC, non PVC/non DEHP, or glass containers for up to 24 hours at 2°C to 8°C or room temperature/room light. The product may be infused using a volumetric pump at the protocol-specific dose(s) and rate(s) through a PVC IV solution infusion set with an in-line, sterile, nonpyrogenic, low protein binding filter (pore size of 0.2 µm to 1.2 µm). Ipilimumab injection must not be administered as an IV push or bolus injection. Care must be taken to assure sterility of the prepared solutions since the drug product does not contain any antimicrobial preservatives or bacteriostatic agents.

<u>Preparation of Solution</u>

- Do not shake product.
- Inspect parenteral drug products visually for particulate matter and discoloration prior to administration. Discard vial if solution is cloudy, there is pronounced discoloration (solution may have pale-yellow color), or there is foreign particulate matter other than translucent-to-white, amorphous particles.
- Allow the vials to stand at room temperature for approximately 5 minutes prior to preparation of infusion.
- Withdraw the required volume of YERVOY and transfer into an intravenous bag.
- Dilute with 0.9% Sodium Chloride Injection, USP or 5% Dextrose Injection, USP to prepare a diluted solution with a final concentration ranging from 1 mg/mL to 2 mg/mL. Mix diluted solution by gentle inversion.
- Store the diluted solution for no more than 24 hours under refrigeration (2°C to 8°C, 36°F to 46°F) or at room temperature (20°C to 25°C, 68°F to 77°F).
- Discard partially used vials or empty vials of YERVOY.

Administration Instructions

- Do not mix YERVOY with, or administer as an infusion with, other medicinal products.
- Flush the intravenous line with 0.9% Sodium Chloride Injection, USP or 5% Dextrose Injection, USP after each dose.
- Administer diluted solution over 30 minutes (window of -10 / + 30 min) through an intravenous line containing a sterile, non-pyrogenic, low-protein-binding in-line filter.

When administered in combination with nivolumab, infuse nivolumab first followed by ipilimumab on the same day. Use separate infusion bags and filters for each infusion.

8.2.6 Availability/Ordering

Initial Orders

- Following submission and approval of the required regulatory documents, a supply of ipilimumab may be ordered from by completing a Drug Request Form provided by BMS for this specific trial. The first request may take place upon screening of the first patient
- The initial order should be limited to 20 vials. Allow 5 business days for shipment of drug from BMS receipt of the Drug Request Form. Drug is protocol specific, but not patient specific. All drug product will be shipped by courier in a temperature-controlled container. It is possible that sites may have more than one ipilimumab clinical study ongoing at the same time. It is imperative that only drug product designated for this protocol number be used for this study.
- Pharmacy supplies not provided by BMS: Empty IV bags/containers, approved diluents, in-line filters and infusion tubing

Re-Supply

- Drug re-supply request form should be submitted electronically business days before the expected delivery date. Deliveries will be made Tuesday through Friday.
- When assessing need for resupply, institutions should keep in mind the number of vials used per treatment dose, and that shipments may take 14 business days from receipt of request. Drug is not patient-specific. Be sure to check with your pharmacy regarding existing investigational stock to assure optimal use of drug on hand.

Drug Excursions

- Drug excursions should be reported immediately to BMS on the form provided with the study-specific drug order form

8.2.7 Accountability

The investigator, or a responsible party designated by the investigator, should maintain a careful record of the inventory and disposition of the agent using the NCI Drug Accountability Record Form (DARF) or another comparable drug accountability form. (See the NCI Investigator's Handbook for Procedures for Drug Accountability and Storage.)

8.2.8 Destruction and Return

8.2.8.1 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.

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.
- 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.

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

8.2.8.2 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.

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.

9. EXPLORATORY ANALYSES

9.1 Biomarker Studies

The precise mechanisms by which nivolumab and ipilimumab exert their anti-tumor activity is unclear, however, particular cell types, such as effector T cells and regulatory T cells are critical for the anti-tumor response. The current study will explore tumor expression of PD-L1 as well as expression of an interferon- gene expression signature, which has been associated with a heightened likelihood of therapeutic benefit following anti-PD-1 therapy in other cancer indications,[65] as potential biomarkers of therapeutic benefit. Tumor material will consist of the most recently available archival sample prior to study enrollment. Archival tumor material is not required for study eligibility. In addition, if a biopsy or surgical resection is performed at the time of potential progression, a tumor sample (block or slides) should also be submitted if sufficient tumor material is available.

9.1.1 Archival Tumor PD-L1 Expression

If available, a minimum of 1 formalin-fixed paraffin-embedded (FFPE) archival tumor tissue block (preferred) or a minimum of 10 FFPE unstained sections from most recent pre-registration biopsy/surgery are to be submitted within 60 days of registration. An immunohistochemistry stain to characterize tumor PD-L1 expression will be performed at the Center for Immuno-Oncology Core Laboratory, Dana-Farber Cancer Institute.
Guidelines for submission of archival tumor tissue:

- A memorandum indicating the study, the date of submission, name of study site submitting the tissue, and a list of contents. The DFCI Coordinating Center will supply a template memorandum to sites at the time of the SIV or upon request.
- A copy of the pathology and surgical report for the sample being submitted should be included in the shipment.
- Slides should be shipped in a plastic slide holder/slide box. Place a small wad of padding in top of the container in order to avoid slides breaking during shipping and handling process.
- An email is to be sent before or at the time of each shipment to the Coordinating Center (NeuroOnc_Coor@dfci.harvard.edu) indicating what is being shipped and when.
- Please note that the submitting institution is responsible for the costs of shipping and handling.
- Ship samples to:

  David A. Reardon, MD c/o Kristen Fisher
  DFCI Center for Neuro-Oncology Coordinating Center (Tissue Inbox)
  Dana-Farber Cancer Institute
  450 Brookline Avenue, LG-GC12D
  Boston, MA 02215
  Telephone: 617-632-4341

Archival tumor samples will be submitted to be initially shipped to the DFCI Coordinating Center and subsequently batch shipped to a central lab for determination of PD-L1 expression at the end of the study.

9.1.2 Archival Tumor Immune Gene Expression Signature

Material needed
If available, a minimum of 2 scrolls, each of 20-25 micron thickness, will be submitted from a formalin-fixed paraffin-embedded (FFPE) archival tumor tissue block, in an RNAase free procedure.

Guidance for storage of FFPE scrolls
The scrolls need to be stored in RNAse free Eppendorf tubes, and can be kept at **-80C** for a maximum of **2 weeks.**

Guidance for submission of FFPE scrolls
The scrolls need to be shipped on dry-ice, **overnight** using FedEx to:

Ana Lako
Brigham and Women's Hospital
20 Shattuck Street
Thorn bldg., Room 603B

Boston, MA 02115

RNA Isolation from FFPE
RNA from FFPE scrolls will be isolated using the RNeasy FFPE Kit (QIAGEN), following manufacturer's protocol.

Nanostring Assay
The RNA isolated from these biopsies will be analyzed using the newly nCounter XT Gene Expression assay from NanoString Technologies using the Pancancer Immune Profiling gene expression panel from Nanostring.

9.2 Volumetric Analysis

All of a participant's scans until progression may be collected and centrally reviewed for volumetric analysis; this includes patient's baseline/screening scan, all active-treatment scans, off-treatment scan, and all active follow-up scans for any participant who comes off active study treatment for any reason other than PD (e.g. toxicity, withdrawal of consent to continue active study treatment, etc.). These images will be downloaded through Partners' Research Patient Data Registry (RPDR). One dimensional, 2-dimensional and volumetric measurement of contrast enhancing will be determined. Descriptive statistics will be performed for calculation of the percentage of patients who progress or demonstrate response at 6 months at varying threshold values for 1D, 2D and volumetric measurements. The tumor volume measurements during the pre-treatment and post-treatment time periods will be fitted to a linear model and the calculated slope, indicating tumor volume growth rates during pre- and post-treatment period will be compared using paired t-test.

Pre-treatment MRI will also be evaluated by radiomic feature extraction technique to identify predictors of treatment response.

Confidentiality of Data: MRI data will be stored within secure network server and all data analysis will be performed in Partner's high performance computing cluster. Only study team member has access to imaging data. All data will be deleted once analysis is complete.

10. STUDY CALENDARS

10.1 Cohort 1

Baseline evaluations are to be conducted within 14 days of start of protocol therapy unless indicated otherwise. Pre-treatment baseline brain MRI must be done ≤ 14 days prior to the start of therapy. Cycles are 14-days. Study assessments may be performed up to 3 days prior to dosing and must be performed and reviewed prior to administration of any study agent at any treatment visit. Nivolumab should be administered within -2/+5 days of the protocol-specified date.

Assessments	Screen-ing [a]	Cycle 1 D1[b]	D1[b] Treatment Cycles 2-10	D1[b] Subsequent Tx Cycles	End of Tx Visit [d]	30-Day Post Drug [e]	Active Follow-Up Visit [f]	Long Term Follow-Up [g]
Informed consent [h]	X							
Background information/history [i]	X							
Inclusion/exclusion criteria [j]	X							
Vital signs and Oxygen Saturation [k]	X	X	X	X	X			
Full Physical Exam [l]	X	X	X	X	X			
Neurologic Exam [m]	X	X	X	X	X			
Physical Measurements (including KPS) [o]	X	X	X	X	X	X[hh]		
Concomitant medications [p]	X	----------	----------	X[p]	----------	----------		
Adverse event assessment & Recording [q]		----------	----------	X[q]	----------	----------		
Recording/Reporting of Serious Adverse Events [q]	----------	----------	----------	X[q]	----------	----------		
Pregnancy Test – Urine or Serum β-HCG [r]	X	X						
12-lead ECG [s]	X							
Hematology [t]	X	X	X	X[c]	X	X		
Serum Chemistry [u]	X	X	X	X	X	X		
Urinalysis [v]	X							
FT3, FT4 & TSH [w]	X	X	X	X	X	X		
Imaging – MRI (or CT) [x]	X		X	X	X		X	
Response Assessment [y]			X	X	X		X	
NANO Scale[z]	X		X	X	X		X	
Nivolumab Administration [aa]		X	X	X				
Blood (serum) for soluble biomarkers [bb]		X	X					
Peripheral Blood Mononuclear Cells (PBMCs) [cc]		X	X					
Submission of archival tumor tissue [dd]		X						
Submission of tumor sample at the time of progression or suspected progression [ee]					X			
Post-end-of-treatment oncology therapies [ff]							X	X
Survival [gg]							X	X

10.2 Cohort 2

Baseline evaluations are to be conducted within 14 days of start of protocol therapy unless indicated otherwise. Pre-treatment baseline brain MRI must be done ≤ 14 days prior to the start of therapy. Cycles are 21-days during Combination Therapy and 28-days during Nivolumab Monotherapy. Study assessments may be performed up to 3 days prior to dosing and must be performed and reviewed prior to administration of any study agent at any treatment visit. Nivolumab and ipilimumab should be administered within -2/+5 days of the protocol-specified date.

		RT	**Combination Therapy** (Nivolumab + Ipilimumab)		**Maintenance Monotherapy** (Nivolumab)				
Assessments	**Screen-ing** [a]	**Prior to Cycle 1 D1** [b]	**Cycle 1 D1** [b]	**D1** [b] **Treatment Cycles 2-4**	**D1** [b] **Subsequent Tx Cycles**	**End of Tx Visit** [d]	**30-Day Post Drug** [e]	**Active Follow-Up Visit** [f]	**Long Term Follow-Up** [g]
Informed consent [h]	X								
Background information/history [i]	X								
Inclusion/exclusion criteria [j]	X								
Vital signs and Oxygen Saturation [k]	X		X	X	X	X			
Full Physical Exam [l]	X		X	X	X	X			
Neurologic Exam [m]	X		X	X	X	X			
Physical Measurements (including KPS) [o]	X		X	X	X	X	X[hh]		
Concomitant medications [p]	X	----------		X[p]		----------			
Adverse event assessment & Recording [q]		----------		X[q]		----------			
Recording/Reporting of Serious Adverse Events [q]		----------			X[q]			----------	
Pregnancy Test – Urine or Serum β-HCG [r]	X		X						
12-lead ECG [s]	X								
Hematology [t] and Serum Chemistry [u]	X		X	X	X	X	X		
Urinalysis [v]	X								
FT3, FT4 & TSH [w]	X		X	X	X	X	X		
Imaging – MRI (or CT) [x] and NANO Scale [z]	X			X	X	X		X	
Response Assessment [y]				X	X	X		X	
Nivolumab Administration [ii]			X	X	X				
Ipilimumab Administration [jj]			X	X					
Radiation Therapy [kk]		X							
Submission of archival tumor tissue [dd]		X							
Submission of tumor sample at the time of progression or suspected progression [ee]						X			
Post-end-of-treatment oncology therapies [ff]								X	X
Survival [gg]								X	X

a. All screening procedures to be performed within 14 days prior to start of study treatment, except informed consent (which may occur up to 28 days prior to start of study treatment).
b. C1D1 and Day 1 of subsequent cycles:
   - For C1D1 only, screening assessments may serve as day 1 assessments, except pregnancy test (within 72 hrs of drug) and vital signs & oxygen saturation (within 3 days prior to drug), except in the event that there are any indications that the participant's condition is deteriorating for which laboratory evaluations should be repeated within 48 hrs prior to initiation
   - For all subsequent cycles, required assessments should be performed within 3 days prior to dose.

c. Intentionally blank
d. End of Tx: End of treatment assessments to be performed within 7 days after last day drug administration or within 7 days after decision to end treatment. Assessments may continue for ongoing reportable adverse events.
e. 30-Day Post Drug: A contact/visit is to be performed at 30 days (+/-7 days) after date of last study drug administration. This may be performed via documented phone conversation with a study nurse or clinician or a clinic visit. All participants will be followed until resolution or stabilization of any serious or reportable adverse events occurring during treatment or starting within 30 days of last study drug.
f. Active Follow-Up: Applies only to those pts who did not progress while on study therapy (including pts who start subsequent anti-cancer therapy), until documented disease progression or pt comes off study for some other reason. Participants will be followed every 3 months (+/- 1 month). See footnote x for scan schedule during Active Follow-Up. Once progression is confirmed, participants will enter long-term follow-up.
g. Participants enter Long-Term Follow-Up after coming off active treatment for disease progression or after completion of Active Follow-Up: Participants will be followed every 3 months (+/- 1 month) via contact or medical record review until death for post-treatment therapies, reason for stopping those therapies, and survival.
h. Informed Consent: Performed by MD attending only. Informed consent process to be fully documented: e.g. prospective participant had sufficient time for deliberation, all questions were answered, treatment options provided by MD, full study reviewed including risks, and a copy of signed consent given to the participant. No study specific screening procedures may occur until after the informed consent process is complete. Informed Consent may be obtained within 28 days of start of study treatment.
i. Background information/history: to include review of treatment history for meningioma, any ongoing medical conditions and medical history pertaining to eligibility on study and involvement during study.
j. Inclusion/exclusion criteria: source documentation providing investigator's confirmation that the participant had met all eligibility criteria must be available prior to registration.
k. Vital signs: blood pressure, respiratory rate, heart rate, and temperature:
   - At screening, within 3 days prior to first dose, and prior to administration of treatment on treatment days

   Oxygen saturation:
   - Pulse oximetry at rest and after exertion. If screening pulse oximetry at rest and after exertion performed within 3 days prior to first dose, does not need to be repeated prior to C1D1 dose.
   - Oxygen Saturation at Rest must be performed prior to administration of treatment on treatment days (also monitor amount of supplemental oxygen if applicable)
   - Oxygen saturation to also be obtained any time a participant has any new or worsening respiratory symptoms
     - NOTE: If a pt shows changes on pulse oximetry or other pulmonary related signs (e.g., hypoxia, fever) or symptoms (e.g., dyspnea, cough) consistent with possible pulmonary AEs, the participant should be immediately evaluated to rule out pulmonary toxicity (an algorithm for the management of suspected pulmonary toxicity can be found in Appendix B).

l. Full Physical Exam: to be completed by the investigator or qualified designee at screening, C1D1 and start of all subsequent cycles.
m. Neurologic Exam: to be completed by the investigator or qualified designee at screening, C1D1 and start of all subsequent cycles.
n. *Intentionally blank*
o. Weight and KPS prior to each dose; height required only at screening and may be obtained within 1 year prior to registration. See Appendix A for KPS scale.
p. Concomitant medications: concomitant medications (including steroid dose) and reason for administration should be documented in the case history from within 28 days before starting study treatment up to the 30-Day Post Drug Visit.

q. Adverse event assessment: Adverse events experienced by participants will be collected and recorded from the first dose of study treatment up to the 30-Day Post Drug Visit of the last dose of study medication (+/- 7 days depending on when 30-Day Post Drug visit/contact occurs) and all SAEs (related and unrelated to trial treatment) up to 100 days after the last dose of trial treatment or the start of new anti-cancer treatment, whichever comes first. Afterwards, report only SAEs that are considered related to trial treatment.
r. Pregnancy Test: For women of child bearing potential, a urine pregnancy test should be performed within 72 hours of first dose of study treatment. If urine pregnancy results cannot be confirmed as negative, a serum pregnancy test will be required.
s. 12-Lead ECG at screening and as clinically indicated.
t. Hematology: CBC w/differential, ANC, platelets, Hgb
u. Serum Chemistry: alkaline phosphatase (ALP), amylase, BUN (or serum urea level), calcium, chloride, creatinine, glucose, LDH, lipase, magnesium, potassium, SGOT (AST), SGPT (ALT), sodium, total bilirubin
   - Hep B/C (HBV sAg and HCV antibody or HCV RNA) will also be performed @ screening only
   - Where required by local regulations, an HIV test must also be performed
v. Urinalysis via dipstick at screening and to be repeated as clinically indicated.
w. T3, T4, & TSH: Free T3, Free T4 & TSH @ screening and every 3 cycles (C4D1, C7D1, etc) while on study. NOTE: Thyroid tests do not need to be resulted and reviewed prior to treating but must be reviewed prior to subsequent cycle's dosing (e.g. C4D1 thyroid tests must be reviewed prior to C5D1 dose).
x. CT alternative, if MRI contraindicated. The same imaging technique should be used in a participant throughout the trial, if feasible. Local reading (investigator assessment) will be used to determine eligibility and for participant management.
   - Baseline scan should be performed within 14 days prior to first dose of study treatment (ideally as close as possible to the date of study therapy initiation).
   - On-study imaging should be performed every 8 weeks (+/- 1 week) and should follow calendar days (i.e. should not be adjusted for delays in cycle starts or extension of Nivolumab cycles).
   - Active Follow-Up: Applies only to those pts who did not progress while on study therapy (including pts who start subsequent anti-cancer therapy), until documented disease progression or pt comes off study for some other reason. MRI schedule & response assessments will be determined by treating investigator.
y. Response Assessment – Per iRANO criteria (section 11);
z. The NANO scale (Section 11.6) will be completed by study physician prior to Cycle 1 Day 1 dose, and then with each MRI (but must be completed before MRI scan results are reviewed with the subject) using the scorecard provided in Appendix F.
aa. 240 mg Nivolumab administered every 2 weeks (-2/+5 days)
   - There must be a minimum of 12 days (11 non-dosing days) between administrations
   - The start and stop time of the nivolumab infusion administration should be documented.
   - Participants who have received active study therapy for >/= 6 months will be allowed the option to adjust their Nivolumab dosing schedule from 240 mg once every 2 weeks (-2/+5 days) to 480 mg once every 4 weeks (+/- 1 week).
bb. Blood (serum) for soluble biomarkers: to be collected & submitted per section 9.1 and Appendix E, prior to C1D1 study treatment and prior to C5D1 study treatment (or at off-treatment for any participant who comes off-treatment prior to C5D1).
cc. Peripheral Blood Mononuclear Cells (PBMCs): to be collected & submitted per section 9.1 and Appendix E, prior to C1D1 study treatment and prior to C5D1 study treatment.
dd. Submission of archival tumor tissue: submission of available tissue from most recent pre-registration biopsy/surgery (per section 9.1 and Appendix E) to be submitted within 60 days of registration, if feasible.
ee. Submission of tumor sample at the time of progression or suspected progression: submission of available tissue from tumor sample at the time of progression or suspected progression (per section 9 and Appendix E) within 60 days of resection, biopsy, if feasible. This is an optional submission.
ff. Post-end-of-treatment oncology therapies: start/stop dates, names of treatment regimens and reason for stopping should be collected.
gg. Survival: date of death and reason should be collected for overall survival purposes, when applicable.
hh. KPS only required at 30-Day Post-Drug time point.

ii. There is an administration window for nivolumab of -2/+5 days
- There must be a minimum of 14-days (13 non-dosing days) during combination therapy cycles (nivolumab every 3 weeks), and a minimum 21-day interval (20 non-dosing days) during nivolumab monotherapy therapy cycles (nivolumab every 4 weeks)
- The start and stop time of the nivolumab infusion administration should be documented.

jj. There is an administration window for ipilimumab of -2/+5 days
- The start and stop time of the ipilimumab infusion administration should be documented.
- There must be a minimum of 24 days (23 non-dosing days) between administrations
- On treatment days when both nivolumab and ipilimumab are administered, nivolumab will be administered first with a 30 minute observation window before starting ipilimumab.

kk. On-study Radiation Therapy will be administered according to established, institutional standard-of-care guidelines for reirradiation and best clinician judgment. See section 5.2.3 for techniques and locations. On-study RT to occur prior to initiation of Cycle 1 of Nivolumab + Ipilimumab. Day 1 Cycle 1 of study immunotherapy will be no sooner than 1 week from the completion of XRT, and no later than 12 weeks after completion of XRT.

10.3 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 the Study Calendars. Baseline signs and symptoms are those that are assessed within 14 days prior to registration. Concomitant medications will be collected from within 28 days prior to registration through the study treatment period.

Baseline local laboratory assessments should be done within 14 days prior to registration 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, total T4, and Hep B and C testing (HBV sAg, HCV Ab or HCV RNA) (see Table 6.1-1). Serum pregnancy testing for WOCBP (done locally) must be performed within 72 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 on-study phase, toxicity assessments should be done in person. Once participants reach the survival follow-up phase, either in person or documented telephone calls to assess the participant's status are acceptable.

Adverse events and laboratory values will be graded according to the NCI-CTCAE version 4.0. Adverse events experienced by participants will be collected and recorded from the first dose of study treatment up to the 30-Day Post Drug Visit of the last dose of study medication (+/- 7 days depending on when 30-Day Post Drug visit/contact occurs) and all SAEs (related and unrelated to trial treatment) up to 100 days after the last dose of trial treatment or the start of new anti-cancer treatment, whichever comes first. Afterwards, report only SAEs that are considered related to trial treatment.

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. The start and stop time of the nivolumab infusion 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 (e.g., 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 participant has any new or worsening respiratory symptoms. (If screening pulse oximetry at rest and after exertion performed within 3 days prior to first dose, does not need to be repeated prior to C1D1 dose). A reading at rest should be obtained at each time point. If a participant shows changes on pulse oximetry or other pulmonary related signs (e.g., hypoxia, fever) or symptoms (e.g., dyspnea, cough) consistent with possible pulmonary adverse events, the participant should be immediately evaluated to rule out pulmonary toxicity. An algorithm for the management of suspected pulmonary toxicity can be found in the Appendix B.

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.

11. MEASUREMENT OF EFFECT

Tumor response will be assessed by MRI (or CT, if MRI contraindicated) every 8 weeks (+/- 1 week) for patients treated on this study using iRANO criteria as outlined below. Clinicians may repeat response assessment more frequently as clinically indicated.

Local radiologic assessment of tumor measurements will be used during the study for clinical management and investigator-assessed disease progression. Cases of suspected radiologic disease progression will be confirmed by an MRI (or CT, as applicable) performed approximately 12 weeks after the initial radiological assessment of progression.

11.1 Antitumor Effect – Definitions

11.1.1 Evaluable for toxicity. All participants who receive at least one dose of study treatment will be evaluable for toxicity from the time of their first treatment.

11.1.2 Evaluable for objective response. Only those participants who have measurable disease present at baseline (obtained within 14 days of cycle 1, day 1) scan and have received at least one dose of therapy will be considered evaluable for response. These participants will have their response classified according to the definitions stated below. (Note: Participants who exhibit objective disease progression or die prior to the end of cycle 1 will also be considered evaluable.)

11.1.3 Measurable disease. Bi-dimensionally, contrast-enhancing, measurable lesions with clearly defined margins by CT or MRI scan, with a minimal diameter of 1 cm, and visible on 2 axial slices which are at least 5 mm apart with 0 mm skip. Measurement of tumor around a cyst or surgical cavity, if necessary, requires a minimum thickness of 3 mm. If there are too many measurable lesions to measure at each evaluation, the investigator must choose the largest two to be followed before a participant is entered on study. The remaining lesions will be considered non-measurable for the purpose of objective response determination. Unless progression is observed, objective response can only be determined when all measurable and non-measurable lesions are assessed.

11.1.4 Non-measurable evaluable disease. Unidimensionally measurable lesions, masses with margins not clearly defined, lesions with maximal diameter < 1cm.

11.2 Efficacy Assessments (Response/Progression Categories)

The primary efficacy measure of the study is progression-free survival at 6 months (PFS-6). PFS-6 is defined as the proportion of participants in the analysis population who remain progression-free for at least six months following initiation of study therapy. 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 5.2).

Investigator-assessed tumor response will be based upon iRANO criteria. Tumor assessments will be performed at baseline 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 11.2-1 describes the radiologic and clinical criteria that will be used for determining tumor response.

Table 11.2-1 iRANO Criteria for Response Assessment Incorporating MRI and Clinical Factors

Response	Criteria
Complete Response	Requires all of the following: • Complete disappearance of all enhancing measurable and non-measurable disease sustained for at least 4 weeks; • No new lesions; • Stable or improved non-enhancing (T2/FLAIR) lesions; • Patients must be off corticosteroids (or on physiologic replacement doses only); • And stable or improved clinically. *Note: Patients with non-measurable 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 non-measurable disease; • No new lesions; • Stable or improved non-enhancing (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 non-measurable disease only cannot have a partial response; the best response possible is stable disease.*

Response	Criteria
Stable Disease	Requires all of the following: • Does not qualify for complete response, partial response, or progression; • Stable non-enhancing (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.*
Progressive Disease	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 non-enhancing lesions on stable or increasing doses of corticosteroids compared with baseline scan or best response after initiation of therapy* not cause by co-morbid 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 non-measurable disease. *Confirmation of radiographic progression should be performed on follow-up imaging for participants who are not developing significant neurologic decline felt to be attributable to underlying tumor growth as detailed in Section 11.4.*
* Stable doses of corticosteroids include subjects not on corticosteroids Abbreviations: MRI, magnetic resonance imaging; FLAIR, fluid-attenuated inversion recovery	

For purposes of this study, the minimum time from baseline for determination of SD will be 4 weeks.

The iRANO Response Criteria to be used in this study are summarized in Table 11.2-2.

Table 11.2-2 Summary of the RANO Response Criteria

	CR	PR	SD	PD#
T1-Gd +	None	≥50% decrease	<50% decrease- <25% increase	≥25% increase*
T2/FLAIR	Stable or decrease	Stable or decrease	NA	NA
New Lesion	None	None	None	Present*
Corticosteroids	None	Stable or decrease	Stable or decrease	Stable or increasing
Clinical Status	Stable or increase	Stable or increase	Stable or increase	Decrease*
Requirement for Response	All	All	All	Any*

CR=complete response; PR=partial response; SD=stable disease; PD=progressive disease; NA= not applicable

#: Progression occurs when any of the criteria with * is present

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

Of note, patients who require increased corticosteroids within two weeks of MRI assessment (relative to the dose taken at the time of the prior assessment) cannot be classified as CR, PR or SD and should be classified as non-evaluable at that time point. Conversely, patients who decrease corticosteroids within two weeks of MRI assessment (relative to the dose taken at the time of the prior assessment) cannot be classified as PD and should be classified as non-evaluable.

11.3 Methods for Evaluation of Measurable Disease

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

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

11.4 Confirmation of Progression

In order to distinguish potential treatment-associated pseudoprogression from progressive disease and minimize premature discontinuation of study medication, participants who initially meet radiologic criteria for disease progression within six months of starting study therapy should remain on study until confirmation of progression with an MRI performed 12 weeks later (see Section 11.2) as long as the following criteria are met:

- They are felt to be deriving clinical benefit from study therapy;
- They are tolerating study therapy without significant adverse events;
- They are not experiencing significant neurologic decline felt to be related to underlying progressive tumor and not due to co-morbid event (seizures, stroke, infection, etc) or change in concomitant medication (i.e. decrease in corticosteroid medication).

If the follow-up imaging assessment confirms that progression has occurred, the date of progression will be the date at which progression was first determined. Participants who develop significant new or worsened neurologic deficits not due to co-morbid event or change in co-administered medication at any time within the three months follow-up window will be designated as a treatment failure and should discontinue study therapy. For these participants, the date of actual tumor progression should also be back-dated to the date radiographic PD was initially identified.

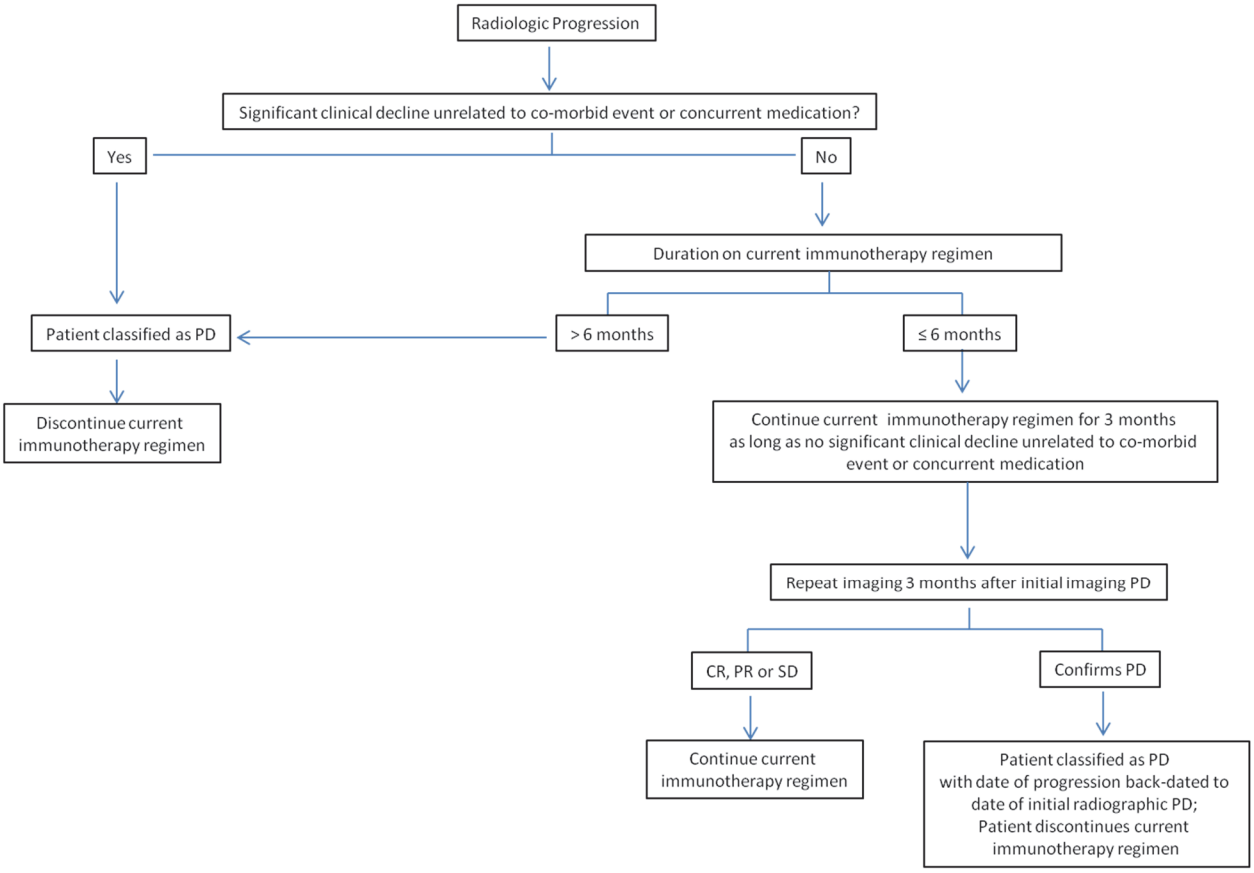
If radiographic findings during the three months follow-up window meet criteria for SD, PR or CR according to RANO and there are no new or worsened neurologic deficits, such participants will be considered as deriving clinical benefit from therapy and allowed to continue treatment.

Participants who develop radiographic findings greater than six months from study therapy initiation are expected to have a low likelihood of ultimately deriving clinical benefit and should be considered a treatment failure with a recommendation to discontinue their current therapy. Confirmation of radiographic progression on follow-up imaging 12 weeks later will not be required for such patients.

Participants who satisfy criteria to confirm radiographic progression outlined above may continue to receive study therapy pending evaluation of the potential benefits and risks of study therapy by the treating investigator in consultation with the study Principal Investigator or designee. Continuation of study therapy may be considered pending follow-up imaging as long as patients are deriving apparent clinical benefit with minimal and acceptable toxicity. In contrast, clinicians may consider interrupting study therapy for participants who require a significant increase in corticosteroids (i.e. > 4 mg of dexamethasone or equivalent per day) for significant evolving symptoms associated with cerebral edema or who are experiencing more than mild treatment-related toxicity such as immune related adverse events grade ≥ 2. If interrupted, study therapy may be resumed when deemed to be safe and in the best medical interest of the participant by the treating investigator in consultation with the study Principal Investigator or designee. Factors for consideration in the decision of when to resume study therapy include but are not limited to: decrease in systemic dexamethasone to ≤ 4 mg/day; enhancing tumor burden is classified as SD, PR or CR on follow-up scan; or when relevant treatment-related toxicity has resolved to grade ≤ 1 or pre-treatment baseline.

An algorithm highlighting treatment decision making for radiographic progression is provided in Figure 11.4-1.

Figure 11.4-1 iRANO Algorithm for Treatment Decision Making for Radiographic Progression



11.5 Best Objective Response (BOR)

Best objective response (BOR) should be determined based on response designations recorded per iRANO defined criteria. The participant'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 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 11.5-1 will be used to determine BOR.

Table 11.5-1 Assessment of Best Overall Response (BOR)	
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 4 weeks.

For purposes of this study, the minimum duration between baseline (start of treatment) and first on-study scan in order to determine best objective response (BOR) of SD is 4 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 time point < 4 weeks and PD at a second assessment, will have a best response of PD.

Participants with non-measurable disease at baseline only cannot have a complete or partial response, 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. Participants who have undergone surgical resection or biopsy at the time of their recurrence of meningioma and have as a result of that procedure non-measurable disease at their baseline MRI (lesions < 10 mm x 10 mm on contrast enhancing MRI) will be followed for progression. If upon subsequent contrast-enhancing MRI, there are no significant signs of progression and the participant 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.

11.6 Neurologic Assessment in Neuro-Oncology (NANO)

Neurologic functioning will be evaluated using the overall score of The Neurologic Assessment in Neuro-Oncology (NANO) scale (Appendix F) which will be administered by the investigator at the study.

The NANO scale is an objective, quick, user-friendly and quantifiable evaluation of nine major domains for subjects with brain tumors. The domains include: gait, strength, ataxia, sensation, visual field, facial strength, language, level of consciousness, behavior and overall. Each domain is rated on a scale of 0 to 3 where 0 represents normal and 3 represents the worst severity. A given domain should be scored non-evaluable if it cannot be accurately assessed due to pre-existing conditions, co-morbid events and/or concurrent medications. The evaluation is based on direct observation/testing performed during routine office visits. The NANO scale will be completed by the investigator or designated study physician prior to dosing Day 1 Week 1 (baseline) and then with each MRI (but must be completed prior to the review of the MRI scan results).

12. DATA REPORTING / REGULATORY REQUIREMENTS

Adverse event lists, guidelines, and instructions for AE reporting can be found in Section 7.0 (Adverse Events: List and Reporting Requirements).

12.1 Data Reporting

12.1.1 Method

The Office of Data Quality (ODQ) will collect, manage, and perform quality checks on the data for this study.

12.1.2 Responsibility for Data Submission

Investigative sites are responsible for submitting data and/or data forms to the ODQ in accordance with DF/HCC policies.

12.2 Data Safety Monitoring

The DF/HCC Data and Safety Monitoring Committee (DSMC) will review and monitor toxicity and accrual data from this study. The committee is composed of medical oncologists, research nurses, pharmacists and biostatisticians with direct experience in cancer clinical research. Information that raises any questions about participant safety will be addressed with the Overall PI and study team.

The DSMC will review each protocol up to four times a year with the frequency determined by the outcome of previous reviews. Information to be provided to the committee may include: up-to-date participant accrual; current dose level information; DLT information; all grade 2 or higher unexpected adverse events that have been reported across all sites; summary of all deaths occurring with 30 days of intervention for Phase I or II protocols; for gene therapy protocols, summary of all deaths while being treated and during active follow-up; any response information; audit results, and a summary provided by the study team. Other information (e.g. scans, laboratory values) will be provided upon request.

12.3 Monitoring

The quality control process for a clinical trial requires verification of protocol compliance and data

accuracy. The Coordinating Center, with the aid of the ODQ, provides quality control oversight for the protocol.

Involvement in this study as a participating investigator implies acceptance of planned study monitoring, as well as potential audits or inspections, including both on-site and remote source data verification, by representatives designated by the DF/HCC Overall Principal Investigator (or Protocol Chair). The purpose of these reviews is to examine study-related activities and documents to determine whether these activities were conducted and data were recorded, analyzed, and accurately reported in accordance with the protocol, institutional policy, Good Clinical Practice (GCP), the Code of Federal Regulations (CFR), and any additional applicable regulatory requirements.

The Participating Institutions may be required to submit participant source documents to the Coordinating Center for monitoring. Participating Institution may also be subject to on-site monitoring conducted by the Coordinating Center.

Data will be monitored for timeliness of submission, completeness, and adherence to protocol requirements. Monitoring will begin at the time of participant registration and will continue during protocol performance and completion.

13. REGULATORY CONSIDERATIONS

13.1 Protocol Review and Amendments

This protocol, the proposed informed consent and all forms of participant information related to the study (e.g., advertisements used to recruit patients) and any other necessary documents must be submitted, reviewed and approved by a properly constituted IRB governing each study location.

Any changes made to the protocol must be submitted as amendments and must be approved by the IRB prior to implementation. Any changes in study conduct must be reported to the IRB. The DF/HCC Overall Principal Investigator (or a representative) will disseminate protocol amendment information to all participating investigator teams.

All decisions of the IRB concerning the conduct of the study must be made in writing.

13.2 Informed Consent

All patients must be provided a consent form describing this study and providing sufficient information for patients to make an informed decision about their participation in this study. The formal consent of a participant, using the IRB approved consent form, must be obtained before the participant is involved in any study-related procedure. The consent form must be signed and dated by the participant or the participant's legally authorized representative, and by the person obtaining the consent. The participant must be given a copy of the signed and dated consent document. The original signed copy of the consent document must be retained in the medical record or research file.

This study is to be conducted according to the following considerations, which represent good and sound research practice:

- US Code of Federal Regulations (CFR) governing clinical study conduct and ethical principles that have their origin in the Declaration of Helsinki
- Title 21 Part 50 – Protection of Human Subjects
  www.access.gpo.gov/nara/cfr/waisidx_02/21cfr50_02.html
- Title 21 Part 54 – Financial Disclosure by Clinical Investigators
  www.access.gpo.gov/nara/cfr/waisidx_02/21cfr54_02.html
- Title 21 Part 56 – Institutional Review Boards
  www.access.gpo.gov/nara/cfr/waisidx_02/21cfr56_02.html
- Title 21 Part 312 – Investigational New Drug Application
  www.access.gpo.gov/nara/cfr/waisidx_02/21cfr312_02.html
- State laws
- DF/HCC research policies and procedures
  http://www.dfhcc.harvard.edu/clinical-research-support/clinical-research-unit-cru/policies-and-procedures/

It is understood that deviations from the protocol should be avoided, except when necessary to eliminate an immediate hazard to a research participant. In such case, the deviation must be reported to the IRB according to the local reporting policy.

13.3 Study Documentation

The investigator (or a representative) must prepare and maintain adequate and accurate case histories designed to record all observations and other data pertinent to the study for each research participant. This information enables the study to be fully documented and the study data to be subsequently verified.

Original source documents supporting entries in the case report forms include but are not limited to hospital records, clinical charts, laboratory and pharmacy records, recorded data from automated instruments, microfiches, photographic negatives, microfilm or magnetic media, and/or x-rays.

13.4 Records Retention

All study-related documents must be retained for the maximum period required by applicable federal regulations and guidelines or institutional policies.

14. STATISTICAL CONSIDERATIONS

This section outlines the statistical analysis strategy and procedures for the study. If, after the study has begun, changes are made to primary and/or key secondary hypotheses, or the statistical methods related to those hypotheses, then the protocol will be amended (consistent with ICH Guideline E-9). Changes to exploratory or other non-confirmatory analyses made after the protocol has been finalized, along with an explanation as to when and why they occurred, will be listed in the Clinical Study Report (CSR) for the study. Post hoc exploratory analyses will be clearly identified in the CSR. No separate Statistical Analysis Plan (SAP) for the primary, secondary and exploratory endpoints will be issued for this study.

14.1 Statistical Analysis Plan

This section contains a brief summary of the statistical analyses for this trial. This trial includes allocation of accrual to two experimental treatment arms (nivolumab monotherapy or nivolumab plus ipilimumab). The outcome of each treatment arm will be assessed relative to appropriate historical controls.

14.1.1 Responsibility for Analysis

The statistical analysis of the data obtained from this study will be the responsibility of the biostatistics department of the Dana-Farber/Harvard Comprehensive Cancer Center.

This trial is being conducted as an open-label study, i.e., subjects and investigators will be aware of subject treatment assignments after each subject is enrolled and treatment is assigned.

14.1.2 Endpoints

14.1.2.1 Primary Endpoint

The primary endpoint of this study is progression-free survival at six months (PFS-6). PFS-6 is defined as the proportion of participants in the analysis population who remain progression-free for at least six months following initiation of study therapy. Response for the primary analysis will be determined by the investigator assessment.

14.1.2.2 Secondary Endpoints

Secondary endpoints for this study include median PFS, median overall survival (OS), objective radiologic response rate (ORR) and assessment of safety/toxicity.

PFS is defined as the time from initiation of study therapy to the date of the first documented tumor progression or death due to any cause. Participants who die without a reported prior progression will be considered to have progressed on the date of death. Participants who did not have disease progression or die will be censored at the date of last tumor assessment. Participants who did not have any on study tumor assessment and did not die will be censored at date of last follow-up. Participants who started any subsequent anti-cancer therapy without a prior reported progression will be censored at the last tumor assessment prior to initiation of the subsequent anti-cancer therapy, which excludes the surgical resection for differentiating radiology progression from pseudoprogression. Participants who had surgical resection for differentiating radiologic progression from pseudoprogression and tumor pathology confirms disease progression will defined as progressive as of the date of radiographic progression that led to surgery. PFS will be determined by investigator reported response based on iRANO criteria (Section6.4). Tumor assessment will occur every 8 weeks (+/- 1 week) until disease progression is documented. Subjects with non-measurable 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.

ORR is defined as the number of subjects whose best overall response (BOR) is confirmed CR or PR divided by response evaluable subjects (Section 11.1.2). 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 study therapy initiation and the date of objectively documented progression per iRANO criteria (Section 11.5), 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 iRANO criteria.

Tumor assessments will occur 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 8-week tumor assessment, this subject will be counted in the denominator as a non-responder.

14.1.2.3 Exploratory Endpoints

Exploratory endpoints will include: 1) evaluation of correlative biomarkers of systemic immune response as described below and the evaluation of these data with progression-free and overall survival; 2) evaluation of archival tumor expression of PD-L1 and PD-1 expressing tumor infiltrating lymphocytes; 3) evaluation of archival tumor expression of immune gene expression signature; 4) evaluation of neurologic function as measured by the NANO scale' and 5) evaluation of change in tumor growth rate as measured by volumetric analysis.

14.1.3 Hypotheses/Estimation

Objectives and hypotheses of the study are stated in Section 1.0.

14.1.4 Power and Sample Size

This study will determine whether nivolumab monotherapy and/or nivolumab plus ipilimumab significantly delays progression among patients with recurrent meningioma based on a primary endpoint of PFS-6 with a planned sample size of 25 patients per cohort. Effective therapy for patients with atypical or anaplastic meningioma who progress after surgery and radiotherapy does not exist. A recent meta-analysis of salvage medical therapies for recurrent WHO grade II/III meningiomas refractory to surgery or radiation therapy revealed a weighted PFS-6 of 26% (95% CI: 19.3-32.7%) and 29% (95% CI: 20.3%, 37.7%) among those with grade I meningiomas that progressed after prior radiation therapy.(20) With a sample size of 25 patients per cohort, our study will have 90% power to detect a PFS-6 increase of 25% (26% vs. 51%) using a one-sided significance level of 0.10 (exact alpha=0.089). At the final stage of analysis, the null hypothesis will be rejected and nivolumab monotherapy or nivolumab plus ipilimumab therapy will be considered worthy of further investigation for patients with atypical/anaplastic meningioma if at least 10 patients are progression-free at the six months timepoint.

14.1.5 Interim Analysis

14.1.5.1 Monitoring of Efficacy

One interim analysis will be conducted on each cohort. Each Interim Analysis will occur once 10 patients have been followed for at least six months on that cohort. Accrual will not stop for this interim analysis. If at least 3 out of the first 10 evaluable patients are alive and progression free at 6 months, that cohort will proceed to full accrual. If 2 or fewer of the

first 10 evaluable patients have remained progression free at six months, further accrual will to that cohort will be stopped and that cohort will be discontinued. Under this stopping criterion, the chances of stopping a cohort early is 0.5 and 0.048 under the null and alternative respectively. The stopping rule for the interim analysis was designed to optimize for a low type II error.

14.1.5.2 Monitoring of Toxicity (Stopping Rule for Unexpected Toxicity)

A futility monitoring boundary of toxicity will be assessed separately for this study. Unacceptable toxicity rates of 20% or less are considered desirable. Patients will be monitored for adverse events and if, at any time during the course of the study, 2 out of the first 10 patients in a cohort - or more than 20% after the first 10 patients in that cohort - experience a grade 4 or higher non-hematologic adverse event considered related to study treatment, accrual for that cohort will be temporarily suspended to allow for full investigation of all adverse events by the study team.

14.1.6 Analysis Endpoints

Efficacy and safety endpoints that will be evaluated for within- and/or between-treatment differences are listed below, followed by the descriptions of the derivations of selected endpoints.

14.1.6.1 Efficacy Endpoints

Efficacy endpoints that will be evaluated for are listed below, followed by the descriptions of the derivations of selected endpoints.

The primary efficacy endpoint for this study is PFS-6, defined as the proportion of subjects in the analysis population who remain progression-free for at least six months following initiation of study therapy. Response for the primary analysis will be determined by the investigator assessment, and a confirmation assessment is required per iRANO.

Secondary efficacy endpoints include: (1) ORR defined as the proportion of subjects in the analysis population who have complete response (CR) or partial response (PR) using iRANO criteria as well as duration of response, defined as time from first iRANO response to disease progression in subjects who achieve a PR or better; (2) progression-free survival (PFS), defined as the time from allocation to the first documented disease progression according to iRANO or death due to any cause, whichever occurs first; and (3) overall survival (OS). Secondary endpoints will be assessed using standard descriptive statistics and the Kaplan Meier method to estimate median OS and PFS and rates at times of interest. Duration of response (DOR), defined as the time from first documented disease response to progression or death, whichever comes first.

Additional supportive analyses of best overall response rate, duration of response, and PFS will be conducted using iRANO criteria, in which a confirmation assessment of disease progression must be obtained at least 4 weeks after the initial disease assessment indicating progressive disease.

Nominal p –values may be computed for efficacy analyses as a measure of strength of association between the endpoint and the treatment effect rather than formal tests of hypotheses. Unless otherwise stated, all statistical tests will be conducted at the α=0.05 (2-sided) level.

14.1.6.2 Safety Endpoints

The primary safety endpoints are AEs graded using CTCAE (Version 4.0) criteria. Safety will be assessed by quantifying the toxicities and grades experienced by subjects who have received nivolumab, including serious adverse events (SAEs). Other safety endpoints include laboratory safety assessments, KPS status, vital signs and physical examinations.

Adverse experiences (specific terms as well as system organ class terms) and predefined limits of change in laboratory, and vital sign parameters that are not pre-specified as events of interest will be summarized with descriptive statistics (counts, percentage, mean, standard deviation, etc.).

Continuous measures such as changes from baseline in laboratory, and vital signs parameters that are not pre-specified as events of interest will be summarized using descriptive statistics (mean, standard deviation, etc.) for baseline, on-treatment, and change from baseline values.

14.1.6.3 Summary of Demographic and Baseline Characteristics

Baseline characteristics will be assessed by the use of tables and/or graphs for this study. No statistical hypothesis tests will be performed on these characteristics. The number and percentage of subjects screened, allocated to treatment, the primary reasons for screening failure, and the primary reason for discontinuation will be displayed. Demographic variables (e.g., age, gender), baseline characteristics, primary and secondary diagnoses, and prior and concomitant therapies will be summarized by treatment either by descriptive statistics or categorical tables.

14.1.6.4 Analysis of Immunocorrelative Data

Descriptive statistics (mean, SD, CV% or median [range]) will be performed on correlative immune biomarker data. Specific statistical analyses on these data will depend on the amount and quality of the data obtained as well as the overall success of the treatment. In addition, longitudinal analyses of PBMC immune response kinetics and circulating cytokines to nivolumab therapy will be presented graphically and descriptively at each time point. Changes in the magnitude of the response relative to pre-treatment after nivolumab therapy will be summarized descriptively. Changes in response between pre-treatment and prior to initiation of cycle 5 of nivolumab therapy will be assessed using the Wilcoxon signed-rank test.

14.1.6.5 Neurologic Assessment in Neuro-Oncology (NANO) Scale

The evaluation of neurologic function as defined by the NANO scale will be assessed as an exploratory objective in this study and evaluated by assessing mean changes from baseline in the level of function score for each domain.

14.1.6.6 Compliance (Medication Adherence)

A day within the study will be considered an On-Therapy day if the subject receives the study medication infusion. The number of Days Should be on Therapy is the total number of days from the first day of study medication to the date of the last dose of study medication. For each subject, percent compliance will then be calculated using the following formula:

Percent Compliance =

(Number of Days Should be on Therapy/Number of Days on Therapy) x 100

Summary statistics will be provided on percent compliance by treatment group for the FAS population.

14.1.6.7 Extent of Exposure

Extent of exposure for a subject is defined as number of cycles in which the subject receives the study medication infusion. Summary statistics will be provided on Extent of Exposure for treated participant study population.

14.2 Populations for Analyses

- Enrolled participants: All participants who signed an informed consent form and were registered into the study. This is the dataset for disposition.
- Treated participants: All participants who received at least one dose of study drug. This is the dataset for baseline demographics, efficacy, and safety evaluation.
- Response-Evaluable participants: All treated participants with measurable disease at a baseline tumor assessment.
- Biomarker participants: All treated participants with available biomarker data.
- NANO participants: All treated participants with available NANO data (Cohorts 1c, 1d, and 2)

15. PUBLICATION PLAN

This trial is intended for publication, even if terminated prematurely. Publication may include any or all of the following: posting of a synopsis online, abstract and/or presentation at a scientific conference, or publication of a full manuscript. The Principal Investigator and/or designee will work to submit a manuscript describing trial results within 12 months after the last data become available, which may take up to several months after the last participant visit in some cases such as vaccine trials. However, manuscript submission timelines may be extended.

Authorship credit should be based on 1) substantial contributions to conception and design, or acquisition of data, or analysis and interpretation of data; 2) drafting the article or revising it critically for important intellectual content; and 3) final approval of the version to be published. Authors must meet conditions 1, 2 and 3. Significant contributions to trial execution may also be taken into account to determine authorship, provided that contributions have also been made to all three of the preceding authorship criteria. Although publication planning may begin before conducting the trial, final decisions on authorship and the order of authors' names will be made based on participation and actual contributions to the trial and writing, as discussed above. The first author is responsible for defending the integrity of the data, method(s) of data analysis and the scientific content of the manuscript.

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APPENDIX A PERFORMANCE STATUS CRITERIA: KARNOFSKY PERFORMANCE SCALE (KPS)

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

APPENDIX B MANAGEMENT ALGORITHMS - NIVOLUMAB

- These general guidelines constitute guidance to the Investigator and may be supplemented by discussions with the Overall PI. The guidance was designed for all immuno-oncology (I-O) agents and regimens, and – for the purpose of this trial – will be utilized for nivolumab.

- Where applicable the Approved Label should be used for guidance around dose modifications and discontinuation

- 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.

- Investigators should refer to the most current version of the IB or Approved Label for current recommendations for management of a specific Adverse Event of interest.

- On the next 7 pages, find Nivolumab Management Algorithms for the following AEs:
    - GI AEs
    - Renal AEs
    - Pulmonary AEs
    - Hepatic AEs
    - Endocrinopathy
    - Skin AEs
    - Neurological AEs

GI Adverse Event Management Algorithm

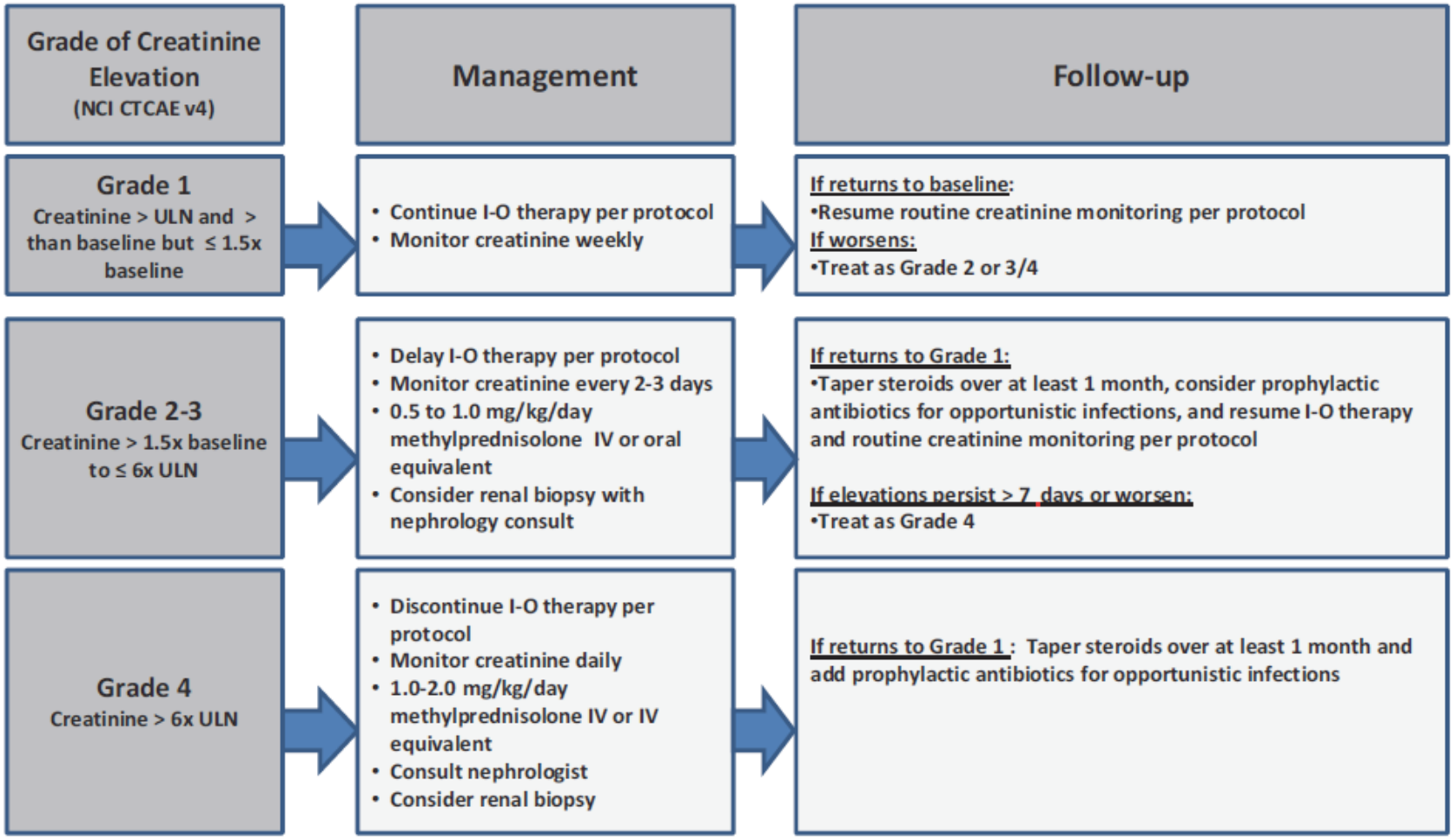
Rule out non-inflammatory causes. If non-inflammatory cause is identified, treat accordingly and continue I-O therapy. Opiates/narcotics may mask symptoms of perforation. Infliximab should not be used in cases of perforation or sepsis.

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.

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.

Pulmonary Adverse Event Management Algorithm

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

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

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

Hepatic Adverse Event Management Algorithm

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

Grade of Liver Test Elevation (NCI CTCAE v4)	Management	Follow-up
Grade 1 AST or ALT > ULN to 3.0 x ULN and/or T. bili > ULN to 1.5 x ULN	• Continue I-O therapy per protocol	• Continue LFT monitoring per protocol If worsens: • Treat as Grade 2 or 3-4
Grade 2 AST or ALT > 3.0 to ≤ 5 x ULN and/or T. bili > 1.5 to ≤ 3 x ULN	• Delay I-O therapy per protocol • Increase frequency of monitoring to every 3 days	If returns to baseline: •Resume routine monitoring, resume I-O therapy per protocol If elevations persist > 5-7 days or worsen : • 0.5-1 mg/kg/day methylprednisolone or oral equivalent and when LFT returns to grade 1 or baseline, taper steroids over at least 1 month, consider prophylactic antibiotics for opportunistic infections, and resume I-O therapy per protocol
Grade 3-4 AST or ALT > 5 x ULN or T.bili >3 x ULN	• Discontinue I-O therapy* • Increase frequency of monitoring to every 1-2 days • 1.0 to 2.0 mg/kg/day methylprednisolone IV or IV equivalent** • Add prophylactic antibiotics for opportunistic infections • Consult gastroenterologist	If returns to grade 2: • Taper steroids over at least 1 month If does not improve in >3-5 days, worsens or rebounds: • Add mycophenolate mofetil 1 g BID • If no response within an additional 3-5 days, consider other immunosuppressants per local guidelines

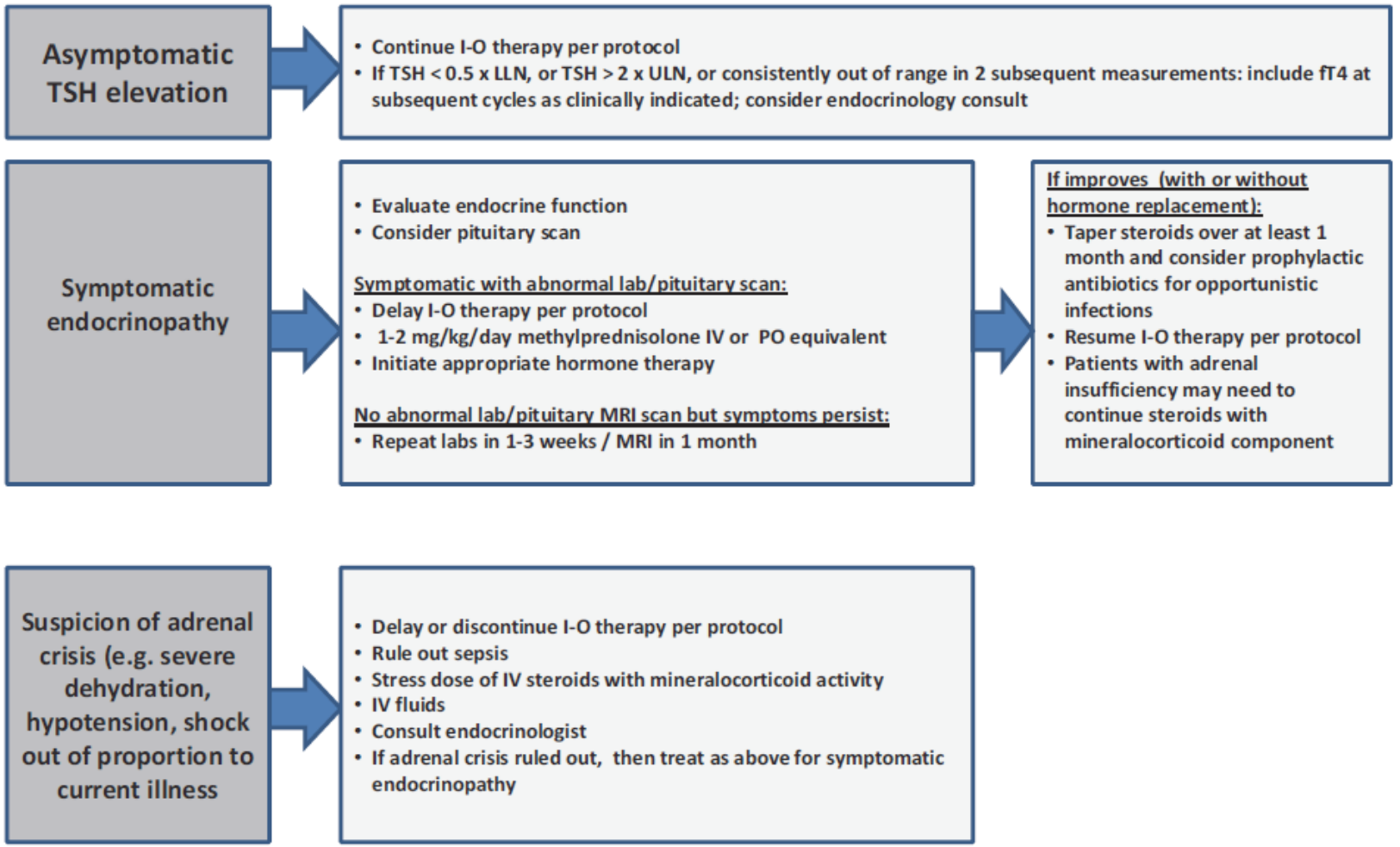
Patients on IV steroids may be switched to an equivalent dose of oral corticosteroids (e.g. prednisone) at start of tapering or earlier, once sustained clinical improvement is observed. Lower bioavailability of oral corticosteroids should be taken into account when switching to the equivalent dose of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

Endocrinopathy Management Algorithm

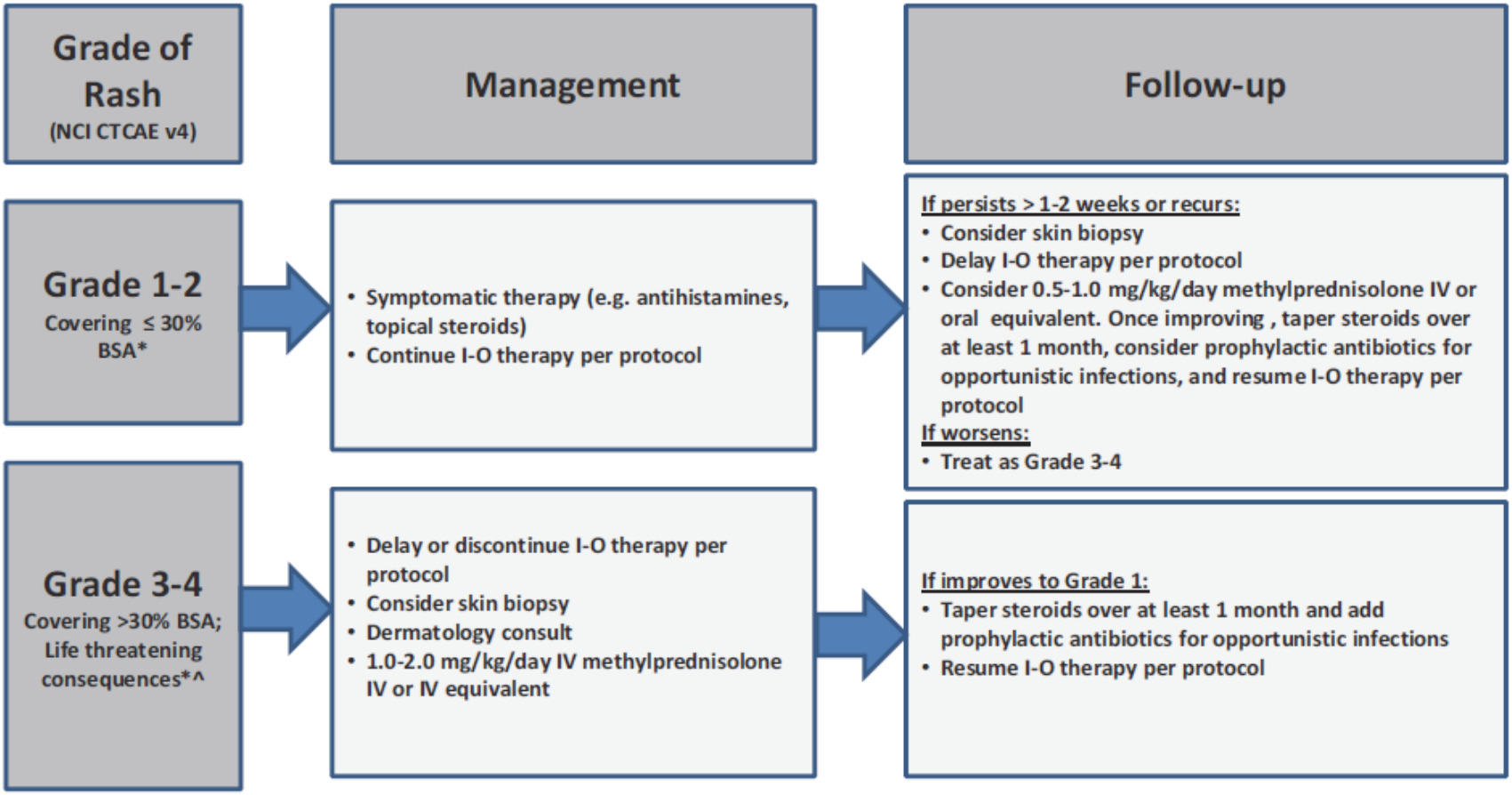
Rule out non-inflammatory causes. If non-inflammatory cause, treat accordingly and continue I-O therapy. Consider visual field testing, endocrinology consultation, and imaging.



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.

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.

Neurological Adverse Event Management Algorithm

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

Grade of Neurological Toxicity (NCI CTCAE v4)	Management	Follow-up
Grade 1 Asymptomatic or mild symptoms; Intervention not indicated	• Continue I-O therapy per protocol	Continue to monitor the patient. If worsens: • Treat as Grade 2 or 3-4
Grade 2 Moderate symptoms; Limiting instrumental ADL	• Delay I-O therapy per protocol • Treat symptoms per local guidelines • Consider 0.5 to 1.0 mg/kg/day methylprednisolone IV or PO equivalent	If improves to baseline: •Resume I-O therapy per protocol when improved to baseline If worsens: • Treat as Grade 3-4
Grade 3-4 Severe symptoms; Limiting self-care ADL; Life-threatening	• Discontinue I-O therapy per protocol • Obtain neurology consult • Treat symptoms per local guidelines • 1.0-2.0 mg/kg/day IV methylprednisolone IV or IV equivalent • Add prophylactic antibiotics for opportunistic infections	If improves to Grade 2: • Taper steroids over at least 1 month If worsens or atypical presentation: • Consider IVIG or other immunosuppressive therapies per local guidelines

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.

APPENDIX C MANAGEMENT ALGORITHMS - IPILIMUMAB

- These general guidelines constitute guidance to the Investigator and may be supplemented by discussions with the Overall PI. This guidance will be utilized for ipilimumab.

- Where applicable the Approved Label should be used for guidance around dose modifications and discontinuation

- 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.

- Investigators should refer to the most current version of the IB or Approved Label for current recommendations for management of a specific Adverse Event of interest.

- On the next 5 pages, find Ipilimumab Management Algorithms for the following AEs:
    - GI AEs
    - Hepatic AEs
    - Skin AEs
    - Endocrinopathy AEs
    - Neurological AEs

GI Toxicity Management Algorithm

Rule out non-inflammatory causes. If non-inflammatory cause, treat accordingly and continue ipilimumab.

Opiates/narcotics mask symptoms of perforation! Infliximab should not be used in case of perforation/sepsis!

Severity of diarrhea/ colitis	Management	Follow-up
Grade 1 Diarrhea: < 4 stools/day over baseline; Colitis: asymptomatic	• Continue ipilimumab • Symptomatic treatment	• Close monitoring for worsening symptoms • Educate patient to report any worsening immediately
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	• Withhold/delay ipilimumab • Symptomatic treatment	**Symptoms improve/resolve** (grade 0/1): Resume ipilimumab **Symptoms persist for > 5-7 days, worsen, or recur:** • Moderate to high dose steroids PO (e.g., prednisone 0.5 - 1 mg/kg/day) • Continue to hold/delay ipilimumab until grade 1 • When symptoms are grade 1 or less slowly taper steroids over at least 1 month and resume ipilimumab. **Symptoms worsen:** 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*): fever, ileus, peritoneal signs	• Permanently discontinue ipilimumab • High dose IV steroids (e.g., methylprednisolone 1-2 mg/kg/day) • Consider endoscopy	**Symptoms improve:** • Continue steroids (same dose) until grade 1 • Then taper over at least 1 month **Symptoms persist 3-5 days, or recur after improvement:** • 1 dose* of infliximab 5 mg/kg (if no contraindication)

*G4 = life-threatening, perforation

*Some patients have required a second dose of infliximab

Patients on IV steroids may be switched to oral corticosteroid (e.g., prednisone) at an equivalent dose 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 PO corticosteroids.

Hepatotoxicity Management Algorithm

Rule out non-inflammatory causes. If non-inflammatory cause, treat accordingly and continue ipilimumab.

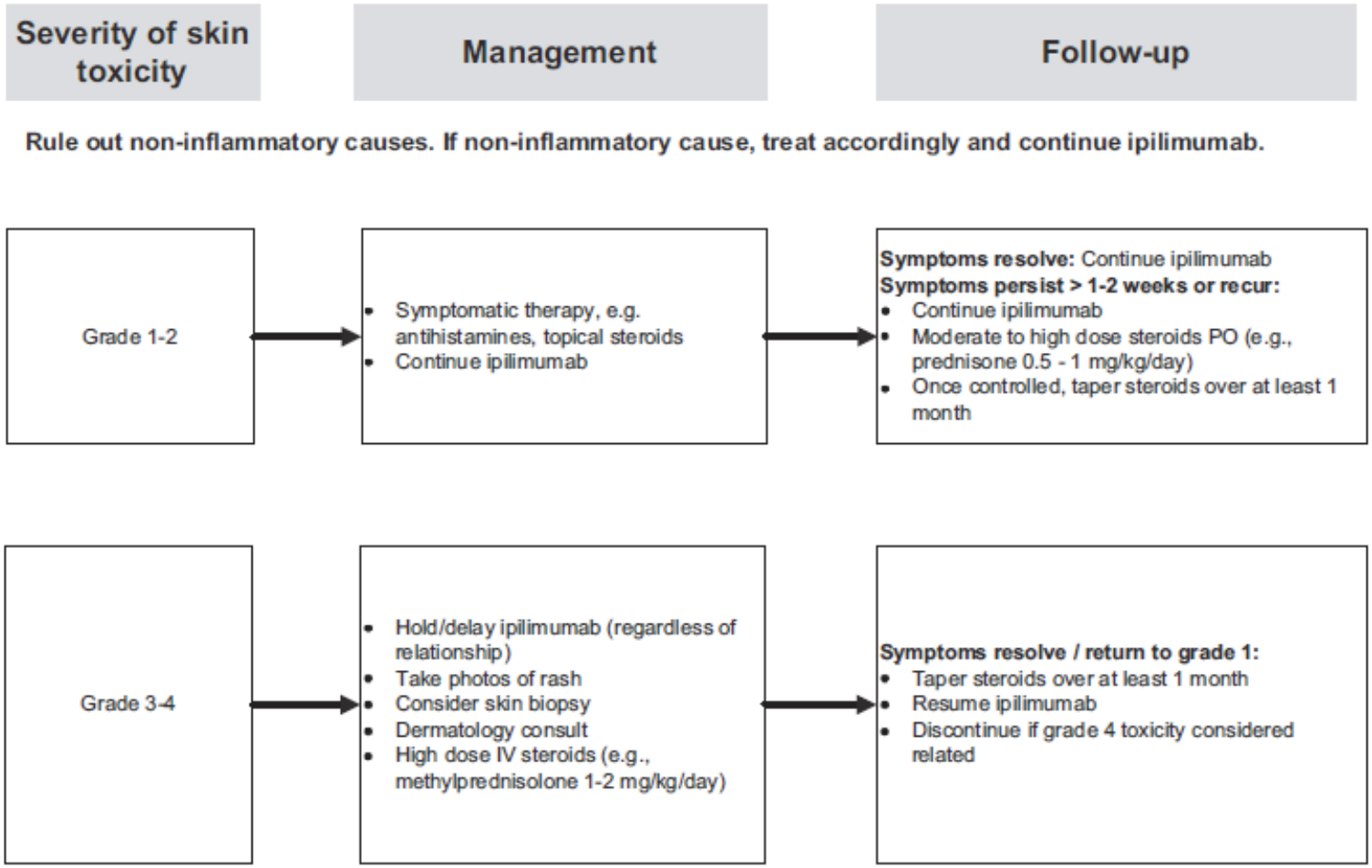
Caution: Infliximab is contraindicated in hepatic insufficiency!

Severity of hepatitis	Management	Follow-up
Grade 1 AST or ALT ≤ 2.5 x ULN or Total bilirubin ≤ 1.5 x ULN	• Continue ipilimumab	• Continue monitoring LFT prior to each dose
Grade 2 AST or ALT > 2.5 to ≤ 5.0 x ULN **or** Total bilirubin > 1.5 to ≤ 3.0 x ULN	• Increase frequency of monitoring (q3d) • Withhold/delay ipilimumab while investigating alternative etiology	**Return to baseline** • Resume q3w monitoring • Resume ipilimumab **Elevations persist for > 5-7 days or worsen, and no alternative etiologies are identified** • Consider moderate to high dose steroids PO (e.g., 0.5- 1 mg/kg/day prednisone or equivalent)
Grade 3-4 AST or ALT > 5.0 x ULN **or** Total bilirubin > 3.0 ULN	• Discontinue ipilimumab* • Increase frequency of monitoring (q1-3d) • High dose IV steroids (e.g., methylprednisolone 1-2 mg/kg/day**)	**AST/ALT/Tbili return to grade 2** • Taper steroids over at least 1 month **Labs do not decrease over 3-5 days, worsen or rebound:** • Add MMF*** 1 g BID • If no response within 3-5 days, consider other immunosuppressants per local guidelines

*Ipilimumab may be held/delayed rather than discontinued if AST/ALT ≤ 8 x ULN and Tbili ≤ 5 x ULN. Resume ipilimumab when AST/ALT/ Tbili return to grade 2 and meet protocol specific retreatment criteria.
**The recommended starting dose for grade 4 hepatitis is 2 mg/kg/day methylprednisolone IV.
*** MMF, mycophenolate mofetil

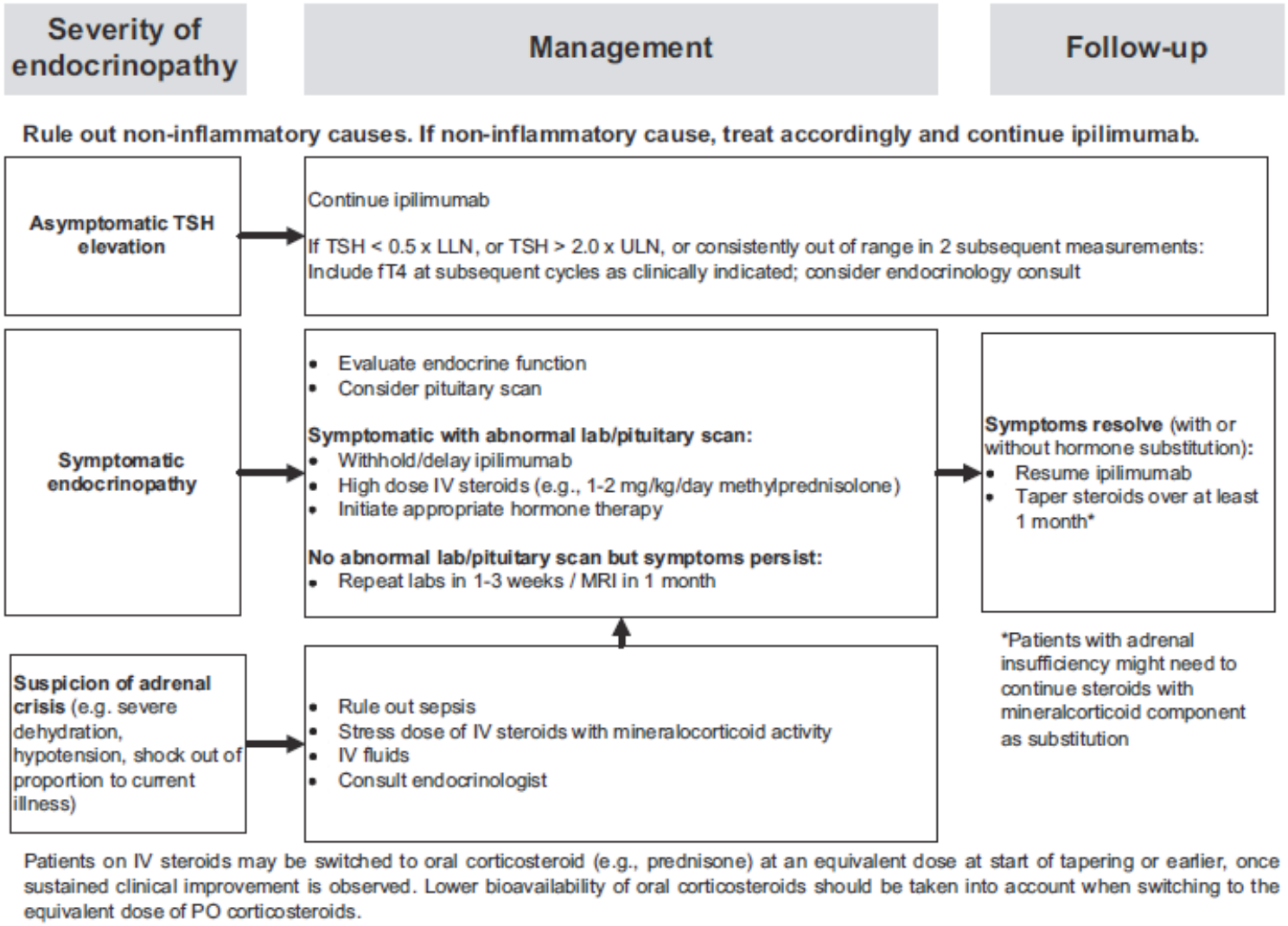
Patients on IV steroids may be switched to oral corticosteroid (e.g., prednisone) at an equivalent dose at start of tapering or earlier, once sustained clinical improvement is observed. Lower bioavailability of oral corticosteroids should be taken into account when switching to the equivalent dose of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

Skin Toxicity Management Algorithm



Patients on IV steroids may be switched to oral corticosteroid (e.g., prednisone) at an equivalent dose 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 PO corticosteroids.

Endocrinopathy Management Algorithm



Patients on IV steroids may be switched to oral corticosteroid (e.g., prednisone) at an equivalent dose 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 PO corticosteroids.

Neurological Toxicity Management Algorithm

Rule out non-inflammatory causes. If non-inflammatory cause, treat accordingly and continue ipilimumab.
Discontinue ipilimumab for any grade 3-4 motor neuropathy, regardless of relationship.

Severity of neurological toxicity	Management	Follow-up
Grade 1	• Continue ipilimumab	Continue monitoring the patient. If symptoms worsen, treat as below.
Grade 2	• Hold/delay ipilimumab • Treat symptoms per local guidelines	Resume ipilimumab when resolved / grade 1 If symptoms worsen, treat as below.
Grade 3-4 sensory	• Discontinue ipilmumab if considered related • Obtain neuro consult • Treat symptoms per local guidelines • High dose IV steroids (e.g., 1-2 mg/kg/ day methylprednisolone)	**Symptoms resolve / return to grade 2:** • Taper steroids over at least 1 month
Grade 3-4 motor	• Discontinue ipilimumab **regardless of relationship** • Obtain neuro consult • Treat symptoms per local guidelines • High dose IV steroids (e.g., 1-2 mg/kg/ day methylprednisolone)	**Symptoms resolve / return to grade 2:** • Taper steroids over at least 1 month **Symptoms do not resolve or progress; atypical presention:** • Consider IVIg or other immunosuppressive therapies per local guidelines

Patients on IV steroids may be switched to oral corticosteroid (e.g., prednisone) at an equivalent dose 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 PO corticosteroids.

APPENDIX D STUDY SAFETY REPORTING COVERSHEET

Updated Study Safety Reporting Coversheet – All Cohorts

DF/HCC Protocol No. 15-490 BMS Protocol No. CA209-324

Date:_____ Number of pages including cover sheet:_____

To *[check off recipient(s) of this submission]*:

☐ David Reardon, MD, MD (Overall PI) @ Dana Farber Cancer Institute: NeuroOnc_SAE@dfci.harvard.edu
Please e-mail coversheet and MedWatch with the words "15-490 Nivolumab SAE" in the subject line

☐ BMS Global Pharmacovigilance & Epidemiology; Fax: 609-818-3804; email: Worldwide.safety@bms.com

From:	Phone No:
Study Site:	Fax No.:
Participant # and Initials:	Participant Cohort:
Type of Report: ☐ Initial ☐ Follow-up	Was Patient Hospitalized? ☐ Yes ☐ No
Date Event 1st Met Reporting Criteria *(as defined in protocol)*:	Date Investigator Team Made Aware of Event:

(Please use another sheet if more than 2 events being reported at this time)

Event #1 Description *(CTCAE v. 4 term)*:	Event #2 *(if applicable)* Description *(CTCAE v. 4 term)*:
Meets Protocol Definition of Serious AE? ☐ Serious ☐ Non-serious	Meets Protocol Definition of Serious AE? ☐ Serious ☐ Non-serious
Toxicity Grade: ☐ G1/mild ☐ G2/moderate ☐ G3/severe ☐ G4/life threatening ☐ G5	Toxicity Grade: ☐ G1/mild ☐ G2/moderate ☐ G3/severe ☐ G4/life threatening ☐ G5
Attribution to **Nivolumab**: ☐ Unrelated ☐ Unlikely ☐ Possible ☐ Probable ☐ Definite	Attribution to **Nivolumab**: ☐ Unrelated ☐ Unlikely ☐ Possible ☐ Probable ☐ Definite
Historical/Known Correlation to **Nivolumab**: ☐Expected ☐Unexpected ☐N/A *(only if unrelated)*	Historical/Known Correlation to **Nivolumab**: ☐Expected ☐Unexpected ☐N/A *(only if unrelated)*
Attribution to **Ipilimumab**: ☐ Unrelated ☐ Unlikely ☐ Possible ☐ Probable ☐ Definite ☐N/A *(pt is NOT on Coh 2)*	Attribution to **Ipilimumab**: ☐ Unrelated ☐ Unlikely ☐ Possible ☐ Probable ☐ Definite ☐N/A *(pt is NOT on Coh 2)*
Historical/Known Correlation to **Ipilimumab**: ☐Expected ☐Unexpected ☐N/A *(only if unrelated or pt is NOT on Coh 2)*	Historical/Known Correlation to **Ipilimumab**: ☐Expected ☐Unexpected ☐N/A *(only if unrelated or pt is NOT on Coh 2)*
Attribution to **RT**: ☐ Unrelated ☐ Unlikely ☐ Possible ☐ Probable ☐ Definite ☐N/A *(pt is NOT on Coh 2)*	Attribution to **RT**: ☐ Unrelated ☐ Unlikely ☐ Possible ☐ Probable ☐ Definite ☐N/A *(pt is NOT on Coh 2)*
Historical/Known Correlation to **RT**: ☐Expected ☐Unexpected ☐N/A *(only if unrelated or pt is NOT on Coh 2)*	Historical/Known Correlation to **RT**: ☐Expected ☐Unexpected ☐N/A *(only if unrelated or pt is NOT on Coh 2)*
Reporting Investigator:	

Signature of Investigator:_____Date:_____

APPENDIX E IMMUNOCORRELATIVE BIOMARKER SPECIMEN GUIDANCE

NOTE: Blood is no longer being collected for Immunocorrelative Biomarkers on study, so the information previously contained within this appendix (sample processing, handling, and shipping instructions) has been removed. Please refer to a previous version of the protocol for this information.

APPENDIX F NEUROLOGIC ASSESSMENT IN NEURO-ONCOLOGY (NANO) SCALE

Scoring assessment is based on direct observation and testing performed during clinical evaluation and is not based on historical information or reported symptoms. Please check 1 answer per domain. Please check "Not assessed" if testing for that domain is not done. Please check "Not evaluable" if a given domain cannot be scored accurately due to pre-existing conditions, co-morbid events and/or concurrent medications.

Participant ID # and Initials: _____

Date Assessment Performed (day/month/year): _____

Study time point (i.e. cycle 1, day 1, etc): _____

Assessment performed by (please print name): _____

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

NANO SCALE (pg 2 of 2)

Participant ID # and Initials: _____

Date Assessment Performed (day/month/year): _____

Visual Fields

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

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

Facial Strength

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

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

Language

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

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

Level of Consciousness

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

- None

Behavior

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

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