Protocol Number: CA209908
IND Number: 119,590
EUDRACT Number 2016-004441-82
Date 12-Dec-2016
Revised Date: 11-Sep-2017

Clinical Protocol CA209908

Phase Ib /II Clinical Trial of Nivolumab Monotherapy and Nivolumab in Combination with Ipilimumab in Pediatric Subjects with High Grade Primary CNS Malignancies

CheckMate908: CHECKpoint pathway and nivoluMAb clinical Trial Evaluation 908

Revised Protocol 01

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

DOCUMENT HISTORY

Document	Date of Issue	Summary of Change
Revised Protocol 01	11-Sep-2017	To clarify protocol text based on local reviews and investigator feedback.
Original Protocol	12-Dec-2016	Not Applicable

OVERALL RATIONALE FOR THE REVISED PROTOCOL 01

The purpose of this amendment is to clarify protocol text based on local reviews and investigator feedback.

These changes affect all participants and should be implemented after IRB approval.

SUMMARY OF KEY CHANGES OF REVISED PROTOCOL 01

Section & Title	Description of Change
Section 1, Synopsis, Study Population; Section 6.1, Inclusion Criteria, Criterion 2.a; Section 5.1.1, Overall Design	Added that patients must have received Standard of Care therapy and that no potentially-curative therapy is available.
Section 1, Synopsis, Study Population; Section 6.1, Inclusion Criteria, Criterion 2.a.	Indicated for Cohort 1 "but no chemotherapy" and changed "thalamic" to "midline"; for Cohort 2, changed "supratentorial" to "non-brainstem"; for Cohort 3, added "and chemotherapy (regardless of age)"; for Cohort 4, added "(regardless of age)
Section 2, Schedule of Activities, Table 2.-1, Screening Procedural Outline	Removed pregnancy test at screening because a pregnancy test prior to the first dose is already required.
Section 2, Schedule of Activities, Table 2.-1, Screening Procedural Outline; Table 2.-2, Nivolumab Monotherapy [Module A] Procedural Outline (CA209908); Table 2.-3, Nivolumab + Ipilimumab combination [Module B] Procedural Outline (CA209908); Table 2.-4, Follow-up Procedural Outline (CA209908); [redacted]	Guidance on whether Spine MRI and CSF cytopathology are expected at baseline or on-study.

SUMMARY OF KEY CHANGES OF REVISED PROTOCOL 01

Section & Title	Description of Change
Section 2, Schedule of Activities, Table 2.-2, Nivolumab Monotherapy [Module A] Procedural Outline (CA209908); Table 2.-3, Nivolumab + Ipilimumab combination [Module B] Procedural Outline (CA209908); Table 2.-4, Follow-up Procedural Outline (CA209908	Increased interval of MRI scans from Q8 week to Q12 week after 1 year on study.
Section 3.1.2, Checkpoint Inhibitors for CNS Tumors; Section 3.1.3, Checkpoint Inhibitors in Pediatric Participants	Updated information on trials of nivolumab or nivolumab plus ipilimumab in adults with GBM and in children with non-CNS tumors
Section 3.2.1, Indications to be Studied	Included rationale for eligibility of Cohort 1 after initial RT rather than at progression
Section 3.2.4, Nivolumab Combined with Ipilimumab	Updated to focus text specifically on CNS tumors
[redacted]	
Synopsis, Overall Design; Section 5.1, Overall Design; Section 10.1 Sample Size Determination	Indicated that target number of participants is approximate, subject to recommendation of Study Steering Committee
[redacted]	

SUMMARY OF KEY CHANGES OF REVISED PROTOCOL 01

Section & Title	Description of Change
Section 5.1.2, Safety Lead In	Indicated that SSC may recommend to proceed with Expansion phase if 0 DLT is observed in the first 5 (of 6) in Cohort 1 or the first 7 (of 10) participants in Cohort 2
Section 5.1.3, Definition of Dose-limiting Toxicity	Clarified definition of "DLT-evaluable" to include subjects who delay or discontinue treatment due to related AE.
Section 5.1.5, Follow-up Phase; Section 5.3, End of Study Definition	Added a sentence regarding the length of follow-up.
Section 5.1.6.1, Data Monitoring Committee; Section 5.1.6.2 ,Study Steering Committee	Indicated that any major recommendation of one committee would be communicated to the other
Section 5.1.6.2, Study Steering Committee	Added a condition that accrual may be kept open to study a sub-population
[redacted]	
Section 5.5.1, Nivolumab	Expanded the justification for dose of nivolumab
[redacted]	
Section 6.1, Inclusion Criteria, Criterion 2.f.	Criterion has been modified minimum intervals from last prior therapy and added cautions for selected prior therapy and moved to criterion 2.j

SUMMARY OF KEY CHANGES OF REVISED PROTOCOL 01	
Section & Title	**Description of Change**
Table 6.2-1	Added maximum permitted creatinine values in SI (umol/L) units
Section 6.2, Exclusion Criteria, criterion 4.e; Section 7.4.1, Dose Delay Criteria; Section 8.1.1, Discontinuation of Nivolumab due to Toxicity [Module A or B]; Section 9.2.7, Potential Drug Induced Liver Injury (DILI)	Defined "fixed" ULN for AST and ALT.
Section 8.1.1, Discontinuation of Nivolumab Due to Toxicity [Module A or B]	Grade 3 Neurologic toxicity has been added as a discontinuation criteria.
Section 8.1.2, Discontinuation of Combination treatment due to Toxicity [Module B]	Added a criterion regarding select Grade 2 drug-related events; Restart of nivolumab after ipilimumab discontinuation for AE may be permitted
Section 9.1, Efficacy Assessments	Added additional guidance for investigators regarding imaging, including reference to RAPNO proposal. Clarified that lumbar puncture for CSF is done only if clinically indicated.
Section 9.1.1, Imaging Assessment for the Study	Provided extensive additional details on MRI assessments, including related to potential leptomeningeal dissemination
Section 9.2.2, Method of Detecting AEs and SAEs	Deleted prohibition against staff asking participant or family questions about specific AEs.

SUMMARY OF KEY CHANGES OF REVISED PROTOCOL 01	
Section & Title	**Description of Change**
Section 9.4.1, Physical Examinations	Defined neurologic examination as part of physical exam.
Section 9.5, Pharmacokinetics, Table 9.5-1, Pharmacokinetics and Anti-Drug Antibody Sampling Schedule for Nivolumab; Table 9.5-2, Pharmacokinetic and Anti-Drug Antibody Sampling Schedule for Nivolumab in Combination with Ipilimumab	Clarified that lumbar puncture for CSF is done only if clinically indicated.
[redacted]	
Section 10.1, Sample Size Determination	Provided additional detail on the formula used to calculate the sample size.
Section 10.3.5, Interim Analyses	Provided additional details regarding the interim analyses.
All	Minor formatting corrections, cross-references, and edits to improve clarity.

TABLE OF CONTENTS

1. SYNOPSIS

Protocol Title: Phase Ib /II Clinical Trial of Nivolumab Monotherapy and Nivolumab in Combination with Ipilimumab in Pediatric Subjects with High Grade Primary CNS Malignancies

Study Phase:

1b/2

[redacted]

Study Population:

Male and female, age ≥ 6 months and < 22 years old at the time of enrollment, and meeting one of the following CNS tumor type criteria:

Participants must have received standard of care therapy, and there must not be potentially-curative treatment available, in one of the following:

1) A newly diagnosed DIPG that has been treated with radiation therapy (RT) but no chemotherapy. Diagnosis of DIPG must be confirmed either based on MRI criteria or histology. (Cohort 1)
   a) Eligibility includes diffuse midline glioma with demonstrated H3K27M mutation
   b) Biopsy is not required for DIPG
   c) Enrollment can occur during radiation therapy or up to 4 weeks after end of RT
2) A histologically confirmed recurrent or progressive non-brainstem HGG previously treated with surgical resection and RT (with or without chemotherapy). (Cohort 2)
3) A histologically confirmed medulloblastoma that has relapsed or is resistant to at least one line of prior therapy including surgery, RT, and chemotherapy (regardless of age) (Cohort 3)
4) A histologically confirmed ependymoma that has relapsed or is resistant to at least one line of prior therapy including surgical resection and RT (regardless of age). (Cohort 4)
5) A histologically-confirmed high grade CNS malignancy "other than above" which is recurrent or progressive after at least one line of prior therapy, including for example: choroid plexus carcinoma, germ cell tumor, anaplastic pleomorphic xanthoastrocytoma, pineoblastoma, AT/RT, embryonal tumor with multilayered rosettes (ETMR; C19MC-altered) that has relapsed or is resistant to at least one line of prior therapy. (Cohort 5)

   Note: Participants with any of the above subtypes of high grade CNS tumors are eligible for the safety lead in phase, See Study Design (Section 5.1).

Objectives and Endpoints:

Objectives	Endpoints
PRIMARY	
Safety Lead In	
• To estimate the safety and tolerability of study treatment in pediatric participants with primary high- grade CNS tumors.	Incidence of DLTs, SAEs, and AEs leading to discontinuation.
Expansion	
• To estimate the OS in pediatric participants with newly diagnosed DIPG. (Cohort 1)	OS
• To estimate the PFS in pediatric participants with recurrent or progressive HGG. (Cohort 2)	PFS
• To estimate the PFS in pediatric participants with relapsed or resistant medulloblastoma. (Cohort 3)	PFS
• To estimate the PFS in pediatric participants with relapsed or resistant ependymoma. (Cohort 4)	PFS
• To estimate the PFS in pediatric participants with recurrent or progressive other rare CNS tumors (including pineoblastoma, AT/RT, embryonic CNS tumors) (Cohort 5)	PFS
SECONDARY	
Safety Lead In	
• To describe any observed anti-tumor activity of study treatment in pediatric primary high grade CNS tumors.	Secondary endpoints are the same as in the expansion phase.
Expansion	
• To estimate the safety of study therapy in pediatric participants with newly diagnosed DIPG, recurrent or progressive HGG, recurrent or progressive medulloblastoma, recurrent or progressive ependymoma and recurrent or progressive other primary rare CNS tumors.	Incidence of AEs, SAEs, drug-related AEs, AEs leading to discontinuation, and death. Incidence of laboratory abnormalities.
• To estimate the PFS and OSr in pediatric participants with newly diagnosed DIPG. (Cohort 1)	PFS, OS(12)
• To estimate the PFSr, OS, and OSr and in pediatric participants with recurrent or progressive HGG. (Cohort 2)	PFS(6), OS, OS(12)
• To estimate the PFSr, OS, and OSr in pediatric participants with recurrent or progressive medulloblastoma. (Cohort 3)	PFS(6), OS, OS(12)
• To estimate the PFSr, OS, and OSr in pediatric participants with recurrent or progressive ependymoma. (Cohort 4)	PFS(6), OS, OS(12)
• To estimate the PFSr and OS and in pediatric participants with recurrent or progressive other rare CNS tumors (including pineoblastoma, AT/RT, other embryonic CNS tumors). (Cohort 5)	PFS(6), OS
[redacted]	
[redacted]	[redacted]

Objectives	Endpoints
[redacted]	[redacted]

AE = adverse event; AT/RT = atypical teratoid rhabdoid tumor; CNS = central nervous system; DIPG = diffuse intrinsic pontine glioma; DLT = dose limiting toxicity; DOR = duration of response; HGG = high grade glioma; ORR = objective response rate; OS = overall survival; OSr = overall survival rate; PD = pharmacodynamic; PFS = progression free survival; PFSr = progression free survival rate; PK = pharmacokinetics; SAE = serious adverse event.

Overall Design:

CA209908 is an open-label, sequential-arm Phase 1b/2 clinical trial of nivolumab monotherapy and of nivolumab plus ipilimumab in pediatric participants with high grade primary CNS malignancies.

Cohorts are defined by tumor type (histology):

Cohort 1: N = 22 participants with newly-diagnosed DIPG, including midline glioma with H3K27M

Cohort 2: N = 15 participants with recurrent or progressive non-brainstem HGG, regardless of mutation status, including glioblastoma

Cohort 3: N = 15 participants with relapsed or resistant medulloblastoma

Cohort 4: N = 10 participants with relapsed or resistant ependymoma

Cohort 5: N = 18 participants with other recurrent subtypes of high-grade CNS malignancy (eg, pineoblastoma, AT/RT, germ cell tumor, and others)

The above intended target numbers for each Module are approximate.

Treatments are defined by Module:

Module A: nivolumab 3 mg/kg every 2 weeks, as monotherapy, and

Module B: nivolumab 3 mg/kg plus ipilimumab 1 mg/kg, every 3 weeks for 4 doses followed by nivolumab 3 mg/kg every 2 weeks.

Enrollment to Module A will open in parallel for all cohorts. The first 6 participants in Cohort 1 who are treated and DLT evaluable will be evaluated for safety before additional participants are treated in that cohort. Separately, the first 10 participants treated and DLT evaluable in the recurrent disease Cohorts 2-5 (combined) will be evaluated for safety before additional participants are treated (see Schema in Figure 5.1-1) in those Cohorts. At regularly-scheduled teleconferences, the Study Steering Committee (SSC) will review safety, assess potential DLTs, and make recommendations regarding reopening of enrollment.

Based on determination of adequate safety, enrollment will re-open for evaluation of efficacy to complete the planned number of participants for each cohort in Module A expansion. Participants evaluated in the safety lead-in will be included for evaluation of efficacy (ie, the 6 participants with DIPG evaluated for safety in Cohort 1 are included in the 22 planned participants).

Enrollment will begin in Module B, by cohort, based on completion of planned accrual in Module A or a decision of the SSC (see Section 5.1.6.2); therefore, accrual will not open in parallel for Module B. Investigators will be informed when Module B is open. For Module B, the first 10 participants treated and DLT evaluable in all cohorts combined will be evaluated for safety by the SSC before additional participants are enrolled (see Schema in Figure 5.1-1) after which cohorts will be re-opened for full accrual in the expansion.

Participants will be closely monitored for AEs throughout the study using clinical and laboratory evaluations (see Sections 2 and 9 for details). The SSC (see Section 5.1.6.2) will meet regularly during the study to ensure that participant safety is carefully monitored.

Tumor progression or response endpoints will be assessed using Radiologic Assessment in Neuro-Oncology criteria (RANO) 2010 described in Section 9.1.3, as assessed by Investigator.

Blood samples will be obtained prior to and post drug administration for PK and biomarkers. The PK sampling schedule for monotherapy and combination therapy are provided in Table 9.5-1 and Table 9.5-2, respectively.

After discontinuation of study treatment, all participants will be followed for safety, tumor progression, and OS (see Section 5.1.4).

Number of Participants:

Enrolled 176-200 (88-100 for nivolumab monotherapy; 88-100 for nivolumab + ipilimumab combination)

Treated 160 (80 for nivolumab monotherapy; 80 for nivolumab + ipilimumab combination)

Screen Failure Rate 10-25%

Cohorts A1 and B1: Sample sizes of 22 participants for each of the Cohorts A1 and B1 in DIPG is based on comparison of OS against an historical control of median OS 9 months, assuming 80% power, 1-sided alpha of 10%, target median OS of 15 months, and a one-sample log rank test. All distributions are assumed to be exponential; assume 12 months for accrual and 24 months for follow-up.

Cohorts A2 and B2: Sample sizes of 15 participants for each of the Cohorts A2 and B2 in HGG is based on an historical PFS(6) of 18%, one-year accrual, one year follow-up, a target PFS(6) of 38% providing 80% power using a one-sided Type 1 error of 10%, assuming an exponential distribution.

Cohort A3 and B3: Sample sizes of 15 participants for each of the cohorts is based on comparison of PFS against an historical control of PFS rate at 4 months of .18, assuming 80% power, 1-sided alpha of 10%, target PFS rate at 4 months of .38, and a one-sample log rank test. All distributions are assumed to be exponential; assume 12 months for accrual and 12 months follow-up.

Cohort A4 and B4: Sample sizes of 10 participants for each of the cohorts is based on comparison of PFS against an historical control of median PFS of 2.1 months, assuming 80% power, 1-sided alpha of 10%, target median PFS of 4.4 months, and a one-sample log rank test. All distributions are assumed to be exponential; assume 12 months for accrual and 12 months follow-up.

Cohort A5 and B5: Sample sizes of 18 participants for each of the Cohorts A5 and B5 is not based on statistical considerations as these cohorts contain various tumor types. However, if the disease control rate at 12 months is 30%, 18 patients provide 21% precision for the estimate.

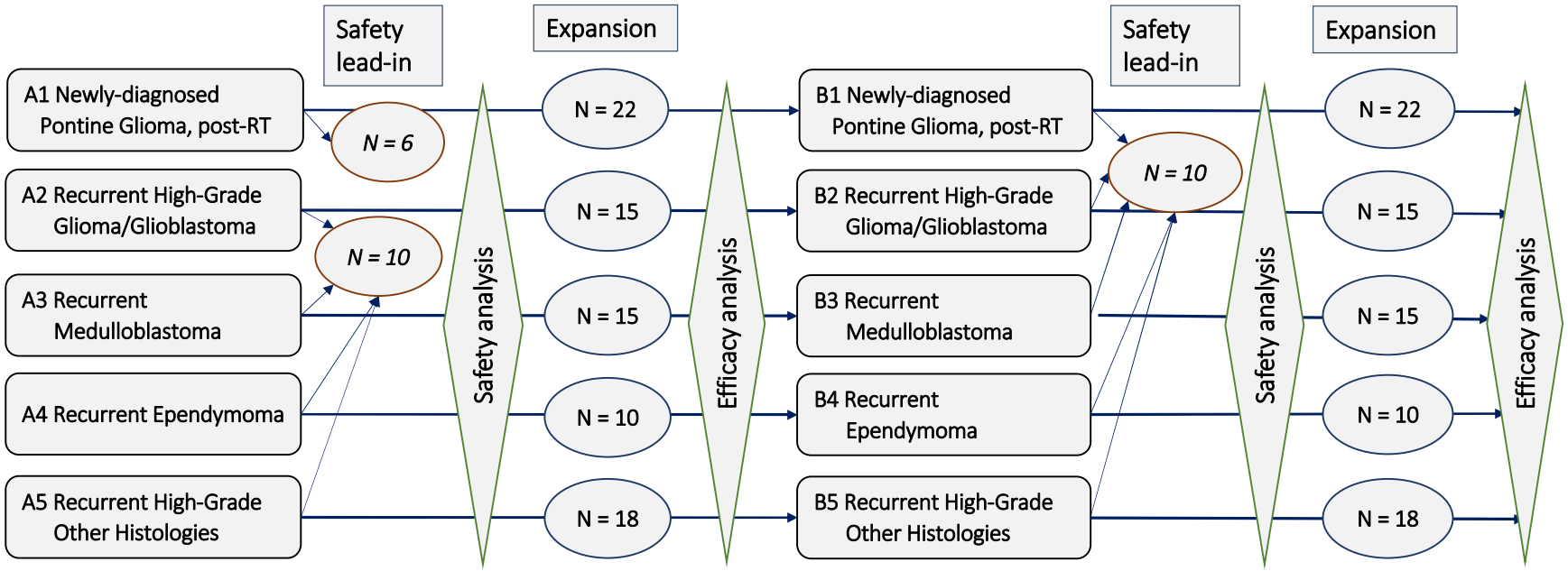
Treatment Arms and Duration:

Study treatment:

Study Drug for CA209908		
Medication	**Potency**	**IP/Non-IP**
Nivolumab (BMS-936558-01) Solution for Injection[a]	100 mg (10 mg/mL)	IP
Ipilimumab (BMS-734016) Solution for Injection	200 mg (5 mg/mL)	IP

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

Figure 1-1: Overall Study Design Schematic



Notes:

- Cohorts are indicated by tumor type; Study Treatments are indicated as A = nivolumab and B = nivolumab + ipilimumab
- Safety is evaluated *across* cohorts (indicated as "lead-in"), prior to expansion
- Efficacy is evaluated *by* cohort (indicated as Expansion), including lead-in population
- Module B opens, by cohort, when corresponding Module A is completed or upon decision of Steering Committee

2. SCHEDULE OF ACTIVITIES

Screening assessments for this study are summarized in Table 2.-1, On-treatment procedures for Module A in Table 2.-2 and for Module B in Table 2.-3, and Follow-Up procedures for both Modules A and B in Table 2.-4. Schematics for Treatment and Key Assessments are provided in Figure 2.-1 and Figure 2.-2 for Modules A and B, respectively. Detailed schedules for pharmacokinetic (PK) and immunogenicity sampling are provided (Modules A and B, respectively) in Table 9.5-1 and Table 9.5-2 and for biomarker sampling in Table 9.8-2 and Table 9.8-3.

Additional diagnostic procedures and laboratory tests not required by protocol should be performed as clinically-indicated; these results may be included in study data. Any clinically-appropriate intervention should be done, regardless of protocol requirement, for optimal management of each study participant.

Table 2.-1: Screening Procedural Outline (CA209908)

Procedure[a]	Screening Visit	Notes
Informed Consent	X	Register in Interactive Response System to obtain participant number; then again prior to treatment start if fully eligible (see instructions provided in manual)
Inclusion/Exclusion Criteria	X	Must be confirmed prior to treatment
Medical History	X	
Tumor Sample Submission	X	Tumor tissue, either FFPE block or a minimum of 20 slides from recent surgery if performed; archival tissue is required if no recent surgery done. (See Section 6.1; not required for DIPG) Sample should be sent with an institutional pathology report. Additional molecular information will be collected.
Physical Examination (including vital signs & performance status)	X	Include BP, HR, RR, temperature, and neurological exam at screening and within 72 hours prior to treatment Within 14 days prior to treatment: Height, weight, and Lansky play score (LPS) for ≤16 years or Karnofsky performance scale (KPS) for > 16 years of age.
Assessment of Signs and Symptoms	X	Within 14 days prior to treatment assignment.
[redacted]	[redacted]	[redacted]
Steroid Dose Documentation	X	Within 14 days prior to treatment assignment.
Serious Adverse Events Assessment	X	See Appendix 3.
Laboratory Tests	X	Within 14 days prior to treatment: CBC w/differential; Chemistry panel (see Section 9.4.4). Within 28 days prior to treatment: Thyroid panel and Hepatitis B/C serology (see Section 9.4.4).
Screening/Baseline Tumor Assessment	X	Contrast-enhanced MRI must be performed within 21 days prior to study treatment (see Imaging Manual). Complete MRI of the spine performed per clinical indication. See Section 9.1.1. CSF cytopathology per clinical indication up to 7 days before treatment start. See Section 9.8.1. In Cohort 1, MRI must be performed after RT and prior to study treatment; prior diagnostic MRI scan also will be collected.

[a] Some of the assessments referred to in this section may not be captured as data in the eCRF. They are intended to be used as safety monitoring by the treating physician. Additional testing or assessments may be performed as clinically necessary or where required by institutional or local regulations. If a participant is referred from another institution, assessments that were completed at the referring institution can be used as the screening assessments.

Table 2.-2: Nivolumab Monotherapy [Module-A] Procedural Outline (CA209908)

Procedure	Cycle 1 and subsequent cycles[a]	Notes[b] (Cycle duration = 2 weeks unless treatment is delayed)
Targeted Physical Examination, Vital Signs, Weight and Performance Status	X	To be performed within 72 hours of dosing. Physical and neurologic exam at C1D1 and as clinically indicated. See Section 9.4.1. VS (BP, HR, RR and temperature, weight) within 72 hours prior to dose. Lansky play score (LPS) for ≤16 years or Karnofsky performance scale (KPS) for > 16 years.
Adverse Event assessment	Continuously	Record at each visit. Assessed using NCI CTCAE v. 4.
[redacted]	[redacted]	[redacted]
Laboratory Tests	X	Within 72 hours prior to each dose. Include CBC w/differential, ALT, AST, T-Bili, BUN or serum urea, creatinine, Na, K, Cl, glucose. TSH every 6 weeks with reflexive Free T4 and Free T3 if TSH abnormal. Laboratory tests do not need to be repeated on C1D1 if done within 14 days prior to dose.
Pregnancy Test (WOCBP only)	X	Serum or urine (minimum sensitivity 25 IU/L or equivalent units of HCG) within 24 hours prior to first dose then at least once every 4 weeks (± 1 week) regardless of delays.
Tumor Assessment	X (See note)	Contrast enhanced MRI **after 6 & 12 wks** (± 1 week) **then Q 8 wk**s (± 1 week) **X 4, then Q 12 wks** (± 1 week), or earlier if clinically indicated. NOTE: Post-RT MRI required in Cohort 1. MRI of the spine also performed per clinical indication. See Section 9.1.1.
Tumor Tissue, on-study sample	X (See note)	If biopsy or resection is performed at suspected progression, tumor sample (block or slides) should be submitted to central laboratory. (See Section 9.8.5)
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
Dispense Study Drug	X	First dose within 3 calendar days of treatment assignment.

[a] If dose is delayed, the procedures scheduled for that same time point (except tumor assessments which should follow the specified schedule) should also be delayed to coincide with when that time point's dosing actually occurs.

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

Figure 2.-1: Module A Treatment and Key Assessments

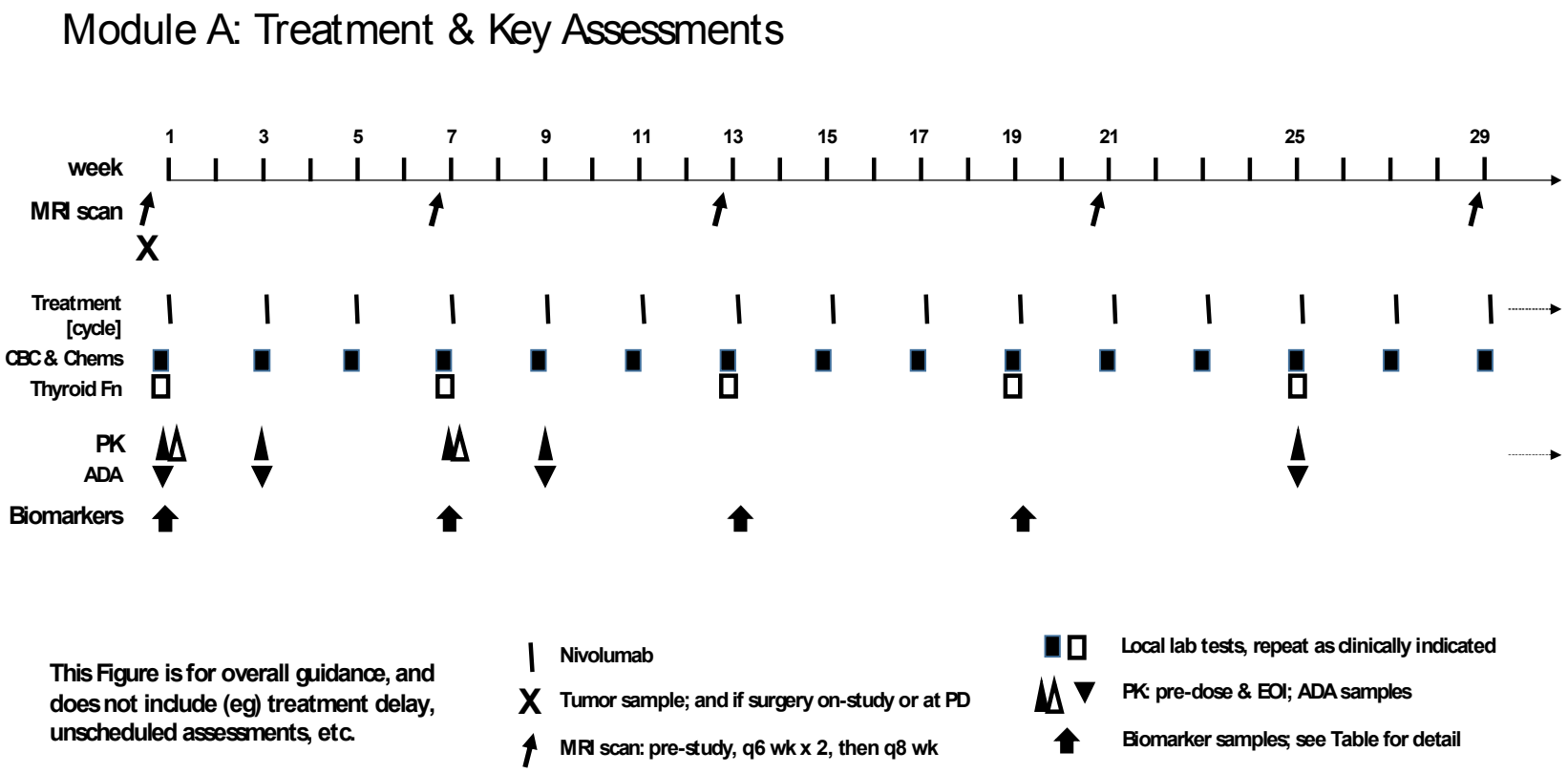


Table 2.-3: Nivolumab + Ipilimumab combination [Module B] Procedural Outline (CA209908)

Procedure	Cycles 1-4[a] (Cycle = 3 weeks)	Cycle 5 and beyond[a] (Cycle = 2 weeks)	Notes[b]
Targeted Physical Examination, Vital Signs, Weight and Performance Status	X	X	To be performed within 72 hours of dosing. Physical and neurologic exam at C1D1 and as clinically indicated. See Section 9.4.1, VS (BP, HR, RR and temperature, weight) within 72 hours prior to dose. Lansky play score (LPS) for ≤16 years or Karnofsky performance scale (KPS) for > 16 years.
Adverse Events Assessment	Continuously		Record at each visit using NCI CTCAE v. 4.
[redacted]	[redacted]		[redacted]
Laboratory Tests	X	X	Within 72 hours prior to each dose. Include CBC w/differential, ALT, AST, T-Bili, BUN or serum urea, creatinine, Na, K, Cl, glucose, amylase, and lipase. TSH every 6 weeks with reflexive Free T4 and Free T3 if TSH is abnormal. Laboratory tests do not need to be repeated on C1D1 if done within 14 days prior to dose.
Pregnancy Test (WOCBP only)	X	X	Serum or urine pregnancy test (minimum sensitivity 25 IU/L or equivalent units of HCG) within 24 hours prior to first dose then at least once every 4 weeks (± 1 week) regardless of dose delays.
12-Lead ECG	X	X	Only as clinically indicated.
Tumor Assessment	X (See note)		Contrast enhanced MRI **after 6 & 12 weeks** (± 1 week) **then Q 8 week**s (± 1 week) **X 4, then Q 12 weeks**, (± 1 week) or earlier if clinically indicated. Post-RT MRI required in Cohort 1. MRI of the spine also performed per clinical indication. See Section 9.1.1.
[redacted]	[redacted]		[redacted]
[redacted]	[redacted]		[redacted]
[redacted]	[redacted]		[redacted]
[redacted]	[redacted]		[redacted]
Dispense Study Drug	X (combination)	X (monotherapy)	First dose within 3 calendar days of treatment assignment.

[a] If a dose is delayed, the procedures for that same time point should also be delayed to coincide with when that time point's dosing actually occurs, except tumor assessments which should follow the specified schedule. Cycle 5 begins 3 weeks after Cycle 4

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

Figure 2.-2: Module B Treatment and Key Assessments

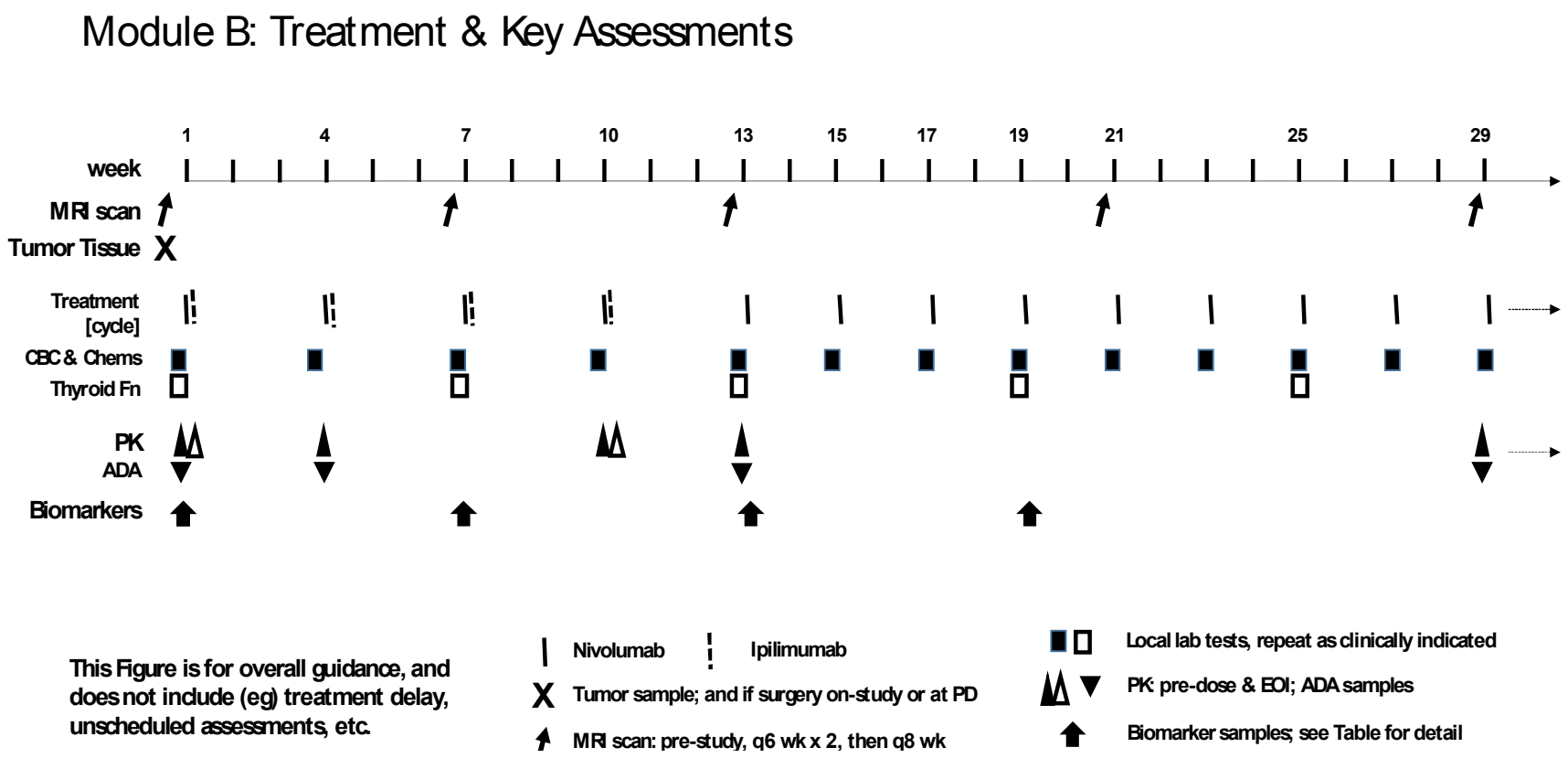


Table 2.-4: Follow-up Procedural Outline (CA209908)

Procedure	Follow-up Visits 1 & 2[a]	Survival Visits[b]	Notes[c]
Targeted Physical Examination	X		
Adverse Events Assessment	X	X	Drug-related adverse events will be followed until resolved or returned to baseline. See Section 9.2.3.
Serious Adverse Events Assessment	X		
Laboratory Tests	X		CBC w/differential, LFTs, T. Bili, BUN, creatinine, Na, K, Cl, glucose and TSH for follow-up #1, repeat labs at follow-up #2 if study drug-related toxicity persists.
Pregnancy Test WOCBP only	X		Serum or Urine.
[redacted]	[redacted]		
[redacted]	[redacted]		[redacted]
Survival Status	X	X	Every 3 months (clinic visit or telephone contact), during Survival phase, include documentation of subsequent chemotherapy.
Tumor Assessment	X	X	Participants who did not progress while on study treatment should continue MRI follow-up according to the schedule in Table 2.-2 and Table 2.-3, or earlier if clinically indicated, regardless of subsequent therapy. MRI of the spine and CSF cytopathology also performed per clinical indication.
Tumor tissue, on-study sample	X	X	If biopsy or surgical resection is performed at suspected progression, a tumor sample (block or slides) should be submitted to central laboratory.

[a] Participants must be followed for at least 100 days after last dose of study treatment. Follow-up visit #1 should occur 30 days from the last dose (±7 days) or can be performed on the date of discontinuation if that date is greater than 42 days from the last dose. Follow-up #2 occurs approximately 100 days (± 7 days) after the last dose of study treatment. Both follow-up visits should be conducted in person.

[b] Survival visits to occur every 3 months (±14 days) from Follow-up visit 2. May be conducted in person or by telephone. BMS may request that survival data be collected on all treated participant s outside of the 3 month specified window. At the time of this request each participant will be contacted to determine their survival status unless the participant has withdrawn consent for all contact.

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

4. OBJECTIVES AND ENDPOINTS

Table 4.-1: Objectives and Endpoints

Objectives	Endpoints
PRIMARY	
Safety Lead In	
• To estimate the safety and tolerability of study treatment in pediatric participants with primary high-grade CNS tumors.	Incidence of DLTs, SAEs, and AEs leading to discontinuation.
Expansion	
• To estimate the OS in pediatric participants with newly diagnosed DIPG. (Cohort 1)	OS
• To estimate the PFS in pediatric participants with recurrent or progressive HGG. (Cohort 2)	PFS
• To estimate the PFS in pediatric participants with relapsed or resistant medulloblastoma. (Cohort 3)	PFS
• To estimate the PFS in pediatric participants with relapsed or resistant ependymoma. (Cohort 4)	PFS
• To estimate the PFS in pediatric participants with recurrent or progressive other rare CNS tumors (including pineoblastoma, AT/RT, embryonic CNS tumors) (Cohort 5)	PFS
SECONDARY	
Safety Lead In	
• To describe any observed anti-tumor activity of study treatment in pediatric primary high-grade CNS tumors.	Secondary endpoints are the same as in the expansion phase.
Expansion	
• To estimate the safety of study therapy in pediatric participants with newly diagnosed primary DIPG, recurrent or progressive HGG, recurrent or progressive primary medulloblastoma, recurrent or progressive primary ependymoma and recurrent or progressive other primary rare CNS tumors.	Incidence of AEs, SAEs, drug-related AEs, AEs leading to discontinuation, and death. Incidence of laboratory abnormalities.
• To estimate the PFS and OSr in pediatric participants with newly diagnosed DIPG. (Cohort 1)	PFS, OS(12)
• To estimate the PFSr, OS, and OSr and in pediatric participants with recurrent or progressive HGG. (Cohort 2)	PFS(6), OS, OS(12)
• To estimate the PFSr, OS, and OSr in pediatric participants with recurrent or progressive medulloblastoma. (Cohort 3)	PFS(6), OS, OS(12)
• To estimate the PFSr, OS, and OSr in pediatric participants with recurrent or progressive ependymoma. (Cohort 4)	PFS(6), OS, OS(12)
• To estimate the PFSr and OS and in pediatric participants with recurrent or progressive other rare CNS tumors (including pineoblastoma, AT/RT, other embryonic CNS tumors). (Cohort 5)	PFS(6), OS

Table 4.-1: Objectives and Endpoints

Objectives	Endpoints
EXPLORATORY	
[redacted]	[redacted]

AE = adverse event; AT/RT = atypical teratoid rhabdoid tumor; CNS = central nervous system; DIPG = diffuse intrinsic pontine glioma; DLT = dose limited toxicity; DOR = duration of response; HGG = high grade glioma; ORR = objective response rate; OS = overall survival; OSr = overall survival rate; PD = pharmacodynamic; PFS = progression-free survival; PFSr = progression-free survival rate; PK = pharmacokinetics; SAE = serious adverse event.

5. STUDY DESIGN

5.1 Overall Designs

CA209908 is an open-label, sequential-arm Phase 1b/2 clinical trial of nivolumab monotherapy and of nivolumab plus ipilimumab in pediatric participants with high-grade primary CNS malignancies.

Cohorts are defined by tumor type (histology):

Cohort 1: N = 22 participants with newly-diagnosed DIPG, including midline glioma with H3K27M mutation

Cohort 2: N = 15 participants with recurrent or progressive non-brainstem HGG, regardless of mutation status, including glioblastoma

Cohort 3: N = 15 participants with relapsed or resistant medulloblastoma

Cohort 4: N = 10 participants with relapsed or resistant ependymoma

Cohort 5: N = 18 participants with other recurrent subtypes of high-grade CNS malignancy (eg, pineoblastoma, AT/RT, germ cell tumor, and others)

The above intended target numbers for each Module are approximate.

Molecular phenotype analyses will be performed according to institutional standard. Details on the molecular subtype of the individual tumors will be reported when they become available.

Treatments are defined by Module:

Module A: nivolumab 3 mg/kg every 2 weeks, as monotherapy, and

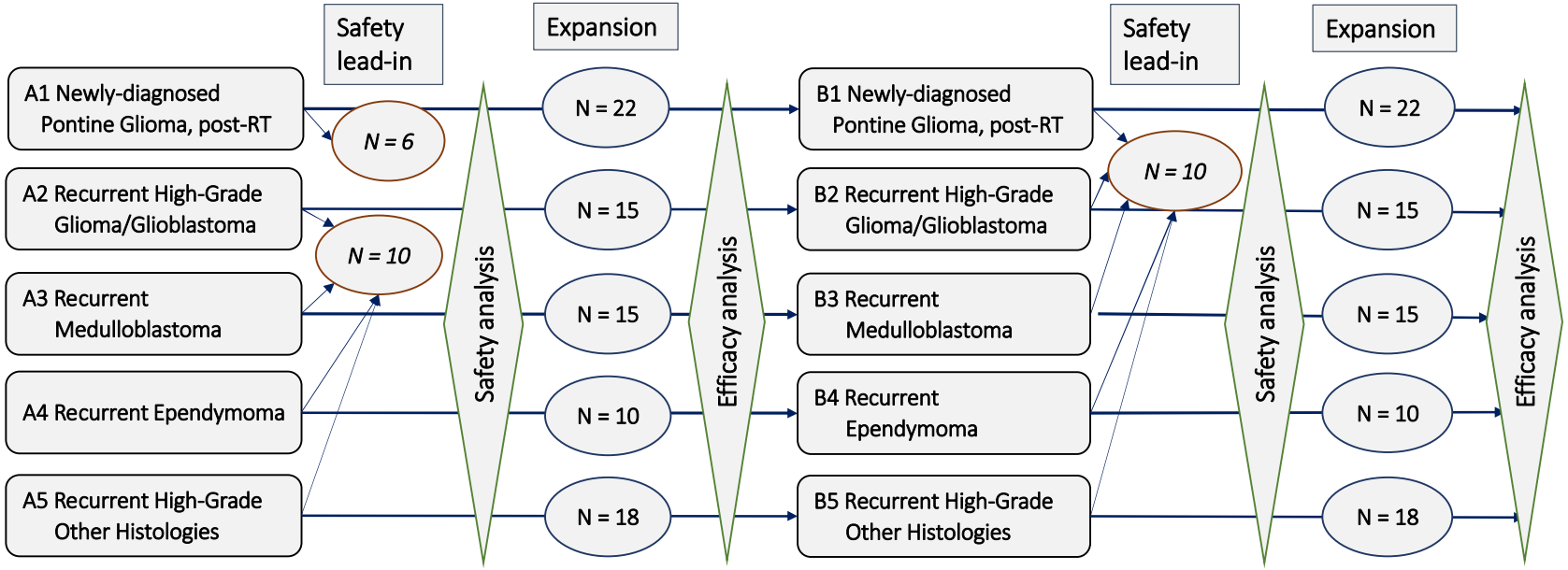
Module B: nivolumab 3 mg/kg plus ipilimumab 1 mg/kg, every 3 weeks for 4 doses followed by nivolumab 3 mg/kg every 2 weeks.

Enrollment to Module A will open in parallel for all cohorts. The first 6 participants in Cohort 1 who are treated and DLT evaluable will be evaluated for safety before additional participants are treated in that Cohort. Separately, the first 10 participants treated and DLT evaluable in the recurrent disease Cohorts 2-5 (combined) will be evaluated for safety before additional participants are treated (see Schema in Figure 5.1-1) in those Cohorts. At regularly-scheduled teleconferences, the Study Steering Committee (SSC) will review safety, assess potential DLTs, and make recommendations regarding reopening of enrollment. See additional details in Section 5.1.2.

Based on determination of adequate safety, enrollment will re-open for evaluation of efficacy to complete the planned number of participants for each cohort in Module A expansion. Participants evaluated in the safety lead-in will be included for evaluation of efficacy (ie, the 6 participants with DIPG evaluated for safety in Cohort 1 are included in the 22 planned participants).

Enrollment will begin in Module B, by cohort, based on completion of planned accrual in Module A or a decision of the SSC (see Section 5.1.6.2); therefore, accrual will not open in parallel for all cohorts into Module B. Investigators will be informed when Module B is open. For Module B, the first 10 participants treated and DLT evaluable in all cohorts combined will be evaluated for safety by the SCC before additional participants are enrolled in all cohorts combined will be evaluated for safety by the SSC before additional participants are enrolled (see Schema in Figure 5.1-1) after which cohorts will be re-opened for full accrual in the expansion. (NOTE: An individual participant may not enroll in more than one Module.)

Figure 5.1-1: Overall Study Design Schematic



Notes:

- Cohorts are indicated by tumor type; Study Treatments are indicated as A = nivolumab and B = nivolumab + ipilimumab
- Safety is evaluated *across* cohorts (indicated as "lead-in"), prior to expansion
- Efficacy is evaluated *by* cohort (indicated as Expansion), including lead-in population
- Module B opens, by cohort, when corresponding Module A is completed or upon decision of Steering Committee

Participants will be closely monitored for AEs throughout the study using clinical and laboratory evaluations (see Sections 2 and 9 for details). The SSC (see Section 5.1.6.2) will meet regularly during the study to ensure that participant safety is carefully monitored.

Tumor progression or response endpoints will be assessed using Radiologic Assessment in Neuro-Oncology criteria (RANO) 2010 described in Section 9.1.3, as assessed by Investigator.

Blood samples will be obtained prior to and post drug administration for PK and biomarkers. The PK sampling schedule for monotherapy and combination therapy are provided in Table 9.5-1 and Table 9.5-2, respectively.

After discontinuation of study treatment, all participants will be followed for safety, tumor progression, and survival (see Section 5.1.5).

5.1.1 Screening Period

Screening procedures are provided in Table 2.-1. Procedures which are standard of care may be performed prior to Informed Consent. See Section 7.2 for Treatment Assignment.

Participants in Cohort 1 may be enrolled at any time from diagnosis until 4 weeks after completion of RT. (RT is not specified by protocol, but is considered standard of care.) For participants in Cohort 1, study treatment must be initiated within a maximum of 6 weeks post-RT. The screening period for participants in Cohorts 2-5 may be up to 4 weeks as needed.

For all Cohorts, study treatment should begin within 3 days after assignment of study treatment.

All molecular information about the tumor will be entered on the case report form when it becomes available (not required for treatment start). Testing for genetic or molecular features (eg, H3K27M mutation, BRAF mutation, RELA-fusion, etc) is not performed centrally but will be performed according to institutional procedures.

5.1.2 Safety Lead-in

A safety lead-in will be implemented because nivolumab, as monotherapy or immediately after RT or in combination with ipilimumab, has not been studied in pediatric participants with CNS tumors.

In Module A, 6 participants with newly-diagnosed DIPG (Cohort 1) will be evaluated for safety of nivolumab administered following RT and 10 participants with recurrent CNS tumors will be evaluated for safety of nivolumab monotherapy. Tolerability and safety of the treatment will be determined after these participants have completed 3 doses and a minimum of 6 weeks on study or discontinued due to dose-limiting toxicity (DLT; see Section 5.1.3). Safety evaluation will be conducted based on criteria described in Sections 9.2 and 9.4. Enrollment will proceed to expansion for Module A only if not more than 2 DLTs are observed in Cohort 1, and separately only if not more than 3 DLTs are observed among the 10 participants in Cohorts 2-5. If no DLTs are observed in the first 5 (of 6) participants in Cohort 1 or in the first 8 (of 10) participants in Cohorts 2-5, then after review by the SSC, enrollment to corresponding Expansion phase may proceed. Participants who discontinue study treatment prior to 3 doses for reasons other than drug-related toxicities are not evaluable for DLT and will be replaced.

If exactly 2 DLTs are observed in Cohort 1 or exactly 3 DLTs are observed in Cohorts 2-5, the SSC will make a determination as to continuation of enrollment based on the nature, severity, and reversibility of the AEs observed. In this circumstance, enrollment will be stopped until the DMC has agreed.

In Module B, 10 participants from any Cohort (ie, those for which Module A has closed) will be evaluated for safety of nivolumab in combination with ipilimumab. Tolerability and safety of the treatment will be determined after these participants have completed 2 doses and observed for a minimum of 6 weeks or discontinued due to DLT. Safety evaluation will be conducted based on criteria described in Sections 9.2 and 9.4. If not more than 3 DLTs are observed among the 10 participants in Cohorts 1-5, enrollment will proceed into expansion for Module B. Participants who are not evaluable for DLT will be replaced. The same condition as noted above will be implemented if exactly 3 DLTs are observed in this safety population.

The SSC will review safety information in order to determine closure and re-opening of enrollment by Cohort. Safety and tolerability beyond initial dosing may also be taken into consideration.

5.1.3 Definition of Dose-Limiting Toxicity

A dose limiting toxicity (DLT) is defined as a drug-related AE occurring in the first 6 weeks of study treatment. A participant will be considered evaluable for a DLT if study treatment was delayed > 2 weeks or was discontinued due to a related AE, or if planned study treatment (3 doses of nivolumab in Module A, 2 doses of nivolumab plus ipilimumab in Module B) was administered and safety evaluation after 6 weeks on study is available to the SSC. Participants who discontinue treatment for a reason other than toxicity (ie, without DLT) are not evaluable for DLT and will be replaced in enrollment.

The Sponsor and SSC will determine whether a toxicity qualifies as DLT. In addition, the SSC may consider AEs occurring after 6 weeks of study in assessment of overall tolerability.

DLTs will be assessed separately for Cohort 1 because the anatomic location of DIPG and the administration of study treatment shortly after RT may create additional risks of immune-treatment effect. The frequency of DLTs will be assessed as a group for participants with recurrent or progressive CNS tumors (Cohorts 2-5).

The following drug-related AEs will be considered DLT:

- Any Grade ≥ 3 clinical toxicity including:
  - Grade ≥ 3 non-neurologic AE of any duration
  - Grade ≥ 3 neurologic AE consistent with immune-treatment effect (ie, associated with tumor location, but not consistent with progressive disease) and not resolved to Grade 0-1 within 14 days despite appropriate treatment
  - Grade ≥ 2 uveitis (eg, with eye pain or blurred vision) that does not respond to topical therapy (ie, improved to Grade 0-1 within 14 days) or requires systemic treatment
  - Exception: fever or vomiting lasting < 72 hours is not a DLT

- Any Grade ≥ 3 laboratory value not resolved to Grade 0-1 within 14 days, except
  - Elevation of AST, ALT or total bilirubin of any duration
  - DILI (AST or ALT >3 x ULN with total bilirubin >2 x ULN) of any duration
- Any Grade 4 laboratory value, except the following are not DLT
  - lipase or amylase without associated symptoms
  - lymphocytopenia
  - electrolyte abnormality lasting < 72 hours
- Any IMAE, regardless of Grade, which requires discontinuation of study treatment (eg, pneumonitis, hypersensitivity reaction, acute kidney injury) will be a DLT.

5.1.4 Expansion

After acceptable safety has been established in the safety lead-in, enrollment will continue in the expansion.

In Modules A and B, study therapy (see Section 7.1) will be administered to the total numbers of participants per Cohort given in Section 5.1. Participants evaluable for efficacy who were treated in the safety lead-in will be included in the total number planned for expansion.

5.1.5 Follow-Up Phase

The follow-up phase begins when the decision is made to discontinue a participant from study treatment (see Section 8.1), including for AEs, for maximum clinical benefit (investigator decision), for participant request, disease progression, or another reason.

Participants will be evaluated for AEs with visits at 30 days (± 7 days) from the last dose of study drug or can be performed on the date of discontinuation if that date is greater than 42 days from the last dose. Follow-up visit #2 occurs approximately 100 days (± 7 days) after last dose of drug; for details, see Table 2.-4 and Section 9.2. All AEs must be documented for a minimum of 100 days after discontinuation, but drug-related toxicities should continue be followed until they resolve, return to baseline, or are deemed irreversible.

Participants who discontinue treatment for a reason other than disease progression will continue to undergo tumor assessments according to the schedule in Table 2.-2 and Table 2.-3, or earlier if clinically indicated, regardless of subsequent therapy. Introduction of anti-tumor therapy in the absence of progression is strongly discouraged.

Regardless of subsequent therapy, a minimum observation time of 3 years is planned for long-term survivors.

5.1.6 Data Monitoring Committee and Other External Committees

Three independent committees will be utilized: a SSC, a data monitoring committee (DMC) and a Blinded Independent Central Review Committee (BICR).

5.1.6.1 Data Monitoring Committee

A Data Monitoring Committee will be established to provide oversight of safety and to provide advice to the sponsor regarding actions the committee deems necessary for the continuing

protection of participants. The DMC will be charged with assessing such actions in light of an acceptable benefit/risk profile for nivolumab. The DMC will act in an advisory capacity to BMS and will monitor participant safety and evaluate the available efficacy data for the study. The oncology therapeutic area of BMS has primary responsibility for design and conduct of the study. The DMC will meet at least every 6 months or more frequently as needed on an ad hoc basis. Information regarding DMC membership, responsibilities, and procedures are detailed in the DMC charter. The DMC will be informed should a safety signal emerge and may convene an ad-hoc meeting on its own initiative. Any major recommendation of the SSC will be communicated to the DMC. When required, adjudicated events will be submitted to the DMC and Health Authorities for review. The DMC will review all available data (safety and efficacy) data at each meeting. At the conclusion of each DMC meeting, the committee will provide the sponsor with a recommendation to continue, modify or terminate the study protocol based upon their review. Ultimately, decisions regarding the study protocol will be made by the sponsor in conjunction with advice from the SSC and the DMC.

5.1.6.2 Study Steering Committee

A SSC will be utilized. The SSC will be comprised of subject matter experts, with chairman representation from each of the Cooperative Groups (eg, COG and ITCC). They will provide guidance for study design and input as needed throughout the course of the study including oversight of safety and efficacy considerations, study conduct, and risk-benefit ratio in protocol CA209-908 (See Section 10.3.5). Any major recommendation of the DMC will be communicated to the SSC.

The Steering committee may recommend to:

1) Terminate or continue accrual to any cohort for safety or efficacy reasons, and overall clinical risk/benefit considerations.
   a) a test for futility, as defined in Section 10.3.5
   b) any of Cohorts 2-5 may be stopped at discretion of Steering Committee; for example, a cohort would be considered for closure if 0/9 evaluable participants experience an objective response
   c) keep accrual open beyond the stated target number of participants in any Cohort, for example, in order to study a sub-population with preliminary evidence of benefit (requires Amendment)
   d) proceed to Expansion phase based on safety criteria (Section 5.1.2)
2) Open a newly-diagnosed HGG cohort, contingent on safety and preliminary efficacy in recurrent HGG, or another cohort based on new information (requires Amendment)
3) Implement any clinically-indicated safety modifications (eg, prolonging infusion duration) to be effective immediately, pending distribution of an Amendment.

Following review, the SSC will recommend continuation, modification, or discontinuation of this study based on reported safety and efficacy data.

5.1.6.3 Blinded Independent Central Review Committee

The clinical management of participants during the study protocol will be based upon local radiologic tumor measurements and the investigator-assessed RANO response criteria described in Section 9.1.3. Radiologic imaging from this study will also be transmitted to a centralized imaging core lab for storage and sponsor access. Imaging will be analyzed for PFS and response by a BICR as determined by the sponsor. Details of the BICR responsibilities and procedures will be specified in the Blinded Independent Central Review charter.

5.2 Number of Participants

A complete description of the sample size is provided in Section 10.1. Up to 200 participants are planned to be enrolled and screened, with up to 100 in Module A and 100 in Module B to include up to 80 participants treated per module.

5.3 End of Study Definition

This study will consist of safety lead in and expansion; and 3 periods: screening, treatment, and follow-up. The start of the trial is defined as the first visit for the first screened participant. The end of the trial is defined as the last scheduled procedure shown in the Schedule of Activities in Section 2 for the last participant. Study completion is defined as the final date on which data for the primary endpoint is expected to be collected. Follow-up for a minimum of 3 years (from study entry) is planned, if applicable.

[redacted]

[redacted]

6. STUDY POPULATION

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

6.1 Inclusion Criteria

1) Signed Written Informed Consent

a) Prior to study participation, written informed consent from participants, or in the case of minors, written permission (informed consent) from parents (both, if required by local law), guardians, or legally acceptable representatives must be obtained according to local laws and regulations.

b) Assent from minor participants should be obtained per local laws and regulations and should be documented in accordance with local requirements.

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

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

2) Type of Participant and Target Disease Characteristics

a) Participants must have received standard of care therapy, and there must be no potentially-curative treatment available, in one of the following Cohorts:

i) A newly diagnosed DIPG that has been treated with radiation therapy (RT) but no chemotherapy. Diagnosis of DIPG must be confirmed either based on MRI criteria or histology. (Cohort 1)

(1). Eligibility includes diffuse midline glioma with demonstrated H3K27M mutation

(2). Biopsy is not required for DIPG

(3). Enrollment can occur during radiation therapy or up to 4 weeks after end of RT

ii) A histologically confirmed recurrent or progressive non-brainstem HGG previously treated with surgical resection and RT (with or without chemotherapy). (Cohort 2)

iii) A histologically confirmed medulloblastoma that has relapsed or is resistant to at least one line of prior therapy including surgery, RT, and chemotherapy (regardless of age). (Cohort 3)

iv) A histologically confirmed ependymoma that has relapsed or is resistant to at least one line of prior therapy including surgical resection and RT (regardless of age). (Cohort 4)

v) A histologically-confirmed high grade CNS malignancy “other than above” which is recurrent or progressive after at least one line of prior therapy, including for example: choroid plexus carcinoma, germ cell tumor, anaplastic pleomorphic xanthoastrocytoma, pineoblastoma, AT/RT, embryonal tumor with multilayered rosettes (ETMR; C19MC-altered) that has relapsed or is resistant to at least one line of prior therapy. (Cohort 5)

b) An interval of at least 12 weeks after the end of prior radiation therapy is required unless there is either: i) histopathologic confirmation of recurrent tumor, or ii) new enhancement on MRI outside of the radiotherapy treatment field (applies only to Cohorts 2-5).

c) Lansky play score (LPS) for ≤ 16 years of age or Karnofsky performance scale (KPS) for > 16 years of age assessed within two weeks of enrollment must be ≥ 60. Participants who are unable to walk because of neurologic deficits, but who are up in a wheelchair, will be considered ambulatory for the purpose of assessing the performance score (Appendix 6)

d) A tumor sample must be available for submission to central laboratory [not required for DIPG (Cohort 1)].

   i) If surgery was performed at time of recurrence, prior to study entry, a tumor sample from this resection should be submitted.

   ii) If no re-operation was performed, archival tumor from the most recent previous resection should be submitted.

   iii) Tumor sample must be submitted within 30 days after treatment assignment

   iv) Either a formalin-fixed, paraffin-embedded (FFPE) tissue block or unstained tumor tissue sections (recent: cut within 3 months), with an associated pathology report, must be submitted for inclusion.

e) Substantial recovery (ie, no ongoing safety issues) from surgical resection prior to first dose of study therapy.

f) **Revised as per Revised Protocol 02. Please refer to criterion 2j**: *An interval of 4 weeks (or 5 half-lives of a targeted therapies with short half-life) after the last administration of any other treatment for CNS malignancies (6 weeks for nitrosoureas). The interval from most recent bevacizumab must be 5 weeks. The interval from most recent biological agent must be 7 days or 5 half-lives, whichever is longer.*

g) Able to taper steroids, preferably discontinue. Participants must be receiving not more than 0.05 mg/kg dexamethasone per day (or equivalent) for intracranial mass effect at study entry.

h) Participants who have received high-dose chemotherapy with autologous hematopoietic cell transplantation must be at least 6 months post-hematopoietic cell transplantation and they must have a CD4 count of at least 200.

i) Participant re-enrollment: This study permits the re-enrollment of a participant that has discontinued the study as a pre-treatment failure (ie, participant has not been treated). If re-enrolled, the participant must be re-consented.

j) A minimum interval of 21 days after any prior therapy, including chemotherapy or biologic agents, and at least 48 hours after any intrathecal therapy. Caution should be used for blood counts recovery after prior alkylating agent and for possible rebound edema after prior bevacizumab; in such cases, a longer interval may be needed.

3) Age and Reproductive Status

a) Males and Females, ages ≥ 6 months to < 22 years old at the time of enrollment

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

c) Women must not be breastfeeding

d) WOCBP must agree to follow instructions for method(s) of contraception for the duration of study treatment with nivolumab and 5 months after the last dose of study treatment [ie, 30 days (duration of ovulatory cycle) plus the time required for the investigational drug to undergo approximately five half-lives.]

e) Males who are sexually active with WOCBP must agree to follow instructions for method(s) of contraception for the duration of study treatment with nivolumab and 7 months after the last dose of study treatment [ie, 90 days (duration of sperm turnover) plus the time required for the investigational drug to undergo approximately 5 half-lives.]

f) Azoospermic males are exempt from contraceptive requirements. WOCBP who are continuously not heterosexually active are also exempt from contraceptive requirements, but still must undergo pregnancy testing as described in this section.

Investigators shall counsel WOCBP, and male participants who are sexually active with WOCBP, on the importance of pregnancy prevention and the implications of an unexpected pregnancy. At a minimum, contraceptive counseling should be provided at the time of assent or consent. Investigators shall advise on the use of highly effective methods of contraception, (Appendix 4) which have a failure rate of < 1% when used consistently and correctly.

6.2 Exclusion Criteria

1) Medical Conditions

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

b) Participants with a concurrent condition requiring systemic treatment with either corticosteroids (> 0.25 mg/kg daily prednisone equivalent) or other immunosuppressive medications within 14 days of start of study treatment. Inhaled or topical steroids, and adrenal replacement steroid doses > 0.25 mg/kg daily prednisone equivalent, are permitted in the absence of active autoimmune disease.

c) Known history of positive test for human immunodeficiency virus (HIV) or known acquired immunodeficiency syndrome (AIDS). NOTE: Testing for HIV must be performed at sites where mandated locally.

d) 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 participant to receive protocol therapy, or interfere with the interpretation of study results.

e) Participants who cannot undergo magnetic resonance imaging (MRI) with contrast enhancement.

2) Target Disease Exclusions

a) Unable to taper steroids due to ongoing mass effect; a maximum dexamethasone dose of 0.05 mg/kg/day is allowed, but preferably have been discontinued.

b) Participants with low-grade gliomas or tumors of unknown malignant potential are not eligible

c) Evidence of > Grade 1 recent CNS hemorrhage on the baseline MRI scan.

d) Participants with bulky tumor on imaging are ineligible; bulky tumor is defined as:

i) Tumor with any evidence of uncal herniation or severe midline shift

ii) Tumor with diameter of > 6 cm in one dimension on T1 contrast-enhanced MRI

iii) Tumor that in the opinion of the investigator, shows significant mass effect. (Contact BMS medical monitor for questions.)

3) Prior/Concomitant Therapy

a) Prior treatment with an anti-PD-1, anti-PD-L1, anti-PD-L2, or anti-CTLA-4 antibody, or any other antibody or drug specifically targeting T-cell co-stimulation or checkpoint pathways.

b) Prior allogeneic hematopoietic cell transplantation unless MM approval in advance.

c) Participants who are receiving any other anti-cancer or investigational drug therapy or non-palliative radiation therapy are ineligible.

4) Physical and Laboratory Test Findings

a) WBC < 2000/μL

b) Neutrophils < 1000/μL

c) Platelets < 75 x 10^3/μL (or transfusion-dependent)

d) Hemoglobin < 9.0 g/dL (can be transfused)

e) Serum creatinine > 1.5 x upper limit of normal based on age/gender as follows:

Table 6.2-1: Age/Gender Serum Creatinine Limits

Age	Maximum Serum Creatinine (mg/dL)			
	Male		Female	
	mg/dL	umol/L (SI)	mg/dL	umol/L (SI)
1 to < 2 years	0.6	53	0.6	53
2 to < 6 years	0.8	71	0.8	71
6 to < 10 years	1	88	1	88
10 to < 13 years	1.2	106	1.2	106
13 to < 16 years	1.5	133	1.4	124
≥ 16 years	1.7	150	1.4	124

Note: the threshold values in this table were derived from the Schwartz formula for estimating GFR,[60] utilizing child length and stature data published by the US Centers for Disease Control and Prevention.

f) AST/ALT: > 3.0 x ULN. For the purposes of this trial, a fixed ULN = 45 will be used for AST and ALT.

g) Total bilirubin > 1.5 x ULN (except participants with Gilbert Syndrome who must have a total bilirubin level of < 3.0 x ULN).

h) Any positive test result for hepatitis B virus or hepatitis C virus indicating presence of virus, eg, Hepatitis B surface antigen (HBsAg, Australia antigen) positive, or Hepatitis C antibody (anti-HCV) positive (except if HCV-RNA negative).

5) Allergies and Adverse Drug Reaction

a) History of allergy or hypersensitivity to study drug components

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

6) Other Exclusion Criteria

a) Prisoners or participants who are involuntarily incarcerated. (Note: under certain specific circumstances a person who has been imprisoned may be included or permitted to continue as a participant. Strict conditions apply and Bristol-Myers Squibb approval is required.

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

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

6.3 Lifestyle Restrictions

Not applicable. No restrictions are required.

6.4 Screen Failures

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

6.4.1 Retesting During Screening or Lead-In Period

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

Retesting of laboratory parameters and/or other assessments within any single Screening or Lead-in period will be permitted (in addition to any parameters that require a confirmatory value).

The most current result prior to first dose of study treatment is the value by which study inclusion will be assessed, as it represents the participant's most current, clinical state.

Laboratory parameters and/or assessments that are included in Table 2.-1, Screening Procedural Outline may be repeated in an effort to find all possible well-qualified participants. Consultation with the Medical Monitor may be needed to identify whether repeat testing of any particular parameter is clinically relevant.

7. TREATMENT

Study treatment is defined as any investigational treatment(s), marketed product(s), placebo or medical device intended to be administered to a study participant according to the study treatment allocation.

Study treatment includes both Investigational [Medicinal] Product (IP/IMP) and Non-investigational [Medicinal] Product (Non-IP/Non-IMP) and can consist of the following:

- Nivolumab
- Ipilimumab

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.

In this protocol, nivolumab and ipilimumab are investigational products. Radiotherapy (prior to treatment start in Cohort 1) is not an investigational product, even if given after enrollment.

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

Table 7.-1: Study treatments for CA209908					
Product Description / Class and Dosage Form	**Potency**	**IP/Non-IMP**	**Blinded or Open Label**	**Packaging / Appearance**	**Storage Conditions (per label)**
Nivolumab Solution for Injection[a]	100 mg (10 mg/mL)	IP	Open label	10 mL Vial (5 or 10 vials /carton) Clear to opalescent colorless to pale yellow liquid. May contain particles.	Store at 2 to 8°C. Protect from light and freezing
Ipilimumab Solution for Injection	200 mg (5 mg/mL)	IP	Open-label	40 mL vial (4 vials per carton) Clear to opalescent colorless to pale yellow liquid. May contain particles	Store at 2 to 8°C. Protect from light and freezing.

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

7.1 Treatments Administered

Dosing calculations should be based on the actual body weight assessed at baseline. It is not necessary to recalculate subsequent doses if the participant weight is within 10% of the weight used to calculate the previous dose. All doses should be rounded up to the nearest milligram per institutional standard.

Participants should be carefully monitored for infusion reactions during nivolumab administration. If an acute infusion reaction is noted, participants should be managed according to Section 7.4.3.

Doses of nivolumab may be interrupted during infusion (see Section 7.4.3), delayed (see Section 7.4.1), or discontinued (see Section 8.1) depending on how the participant tolerates treatment. Dosing visits (cycles) are not skipped or omitted, but they may be delayed. There will be no dose escalations or reductions of nivolumab allowed. Premedications are not recommended for the first dose of nivolumab. Nivolumab and ipilimumab may be administered within 3 days before or after the scheduled dose.

Nivolumab Injection, 100 mg/10 mL (10 mg/mL) and 40 mg/4 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 in-line filter at the protocol-specified doses. It is not to be administered as an IV push or bolus injection; any programmable infusion pump may be used. 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. Instructions for dilution and infusion of nivolumab injection may be provided in the clinical protocol, or

pharmacy binder. Care must be taken to assure sterility of the prepared solution as the product does not contain any antimicrobial preservative or bacteriostatic agent.

Nivolumab infusions are compatible with polyvinyl chloride (PVC) or polyolefin containers and infusion sets, and glass bottles.

Ipilimumab injection can be used for IV administration with or without dilution after transferring to a PVC, non-PVC/non-DEHP or glass container and is stable for 24 hours at 2-8°C or room temperature/room light (RT/RL). For ipilimumab preparation and storage instructions, refer to ipilimumab IB and Section 7.1.2.

When study drugs (nivolumab and ipilimumab) are to be administered on the same day, nivolumab is to be administered first. Nivolumab infusion must be promptly followed by a saline flush or D5W flush to clear the line of nivolumab before starting the ipilimumab infusion. The second infusion will always be the ipilimumab study drug and will start after the infusion line has been flushed, filters changed, and participant has been observed to ensure no infusion reaction has occurred. The time in between infusions is expected to be approximately 30 minutes but may be more or less depending on the situation.

Separate infusion bags and filters should be used when administering nivolumab and ipilimumab on the same day.

Care must be taken to assure sterility of the prepared solutions, since the drug product does not contain any antimicrobial preservatives or bacteriostatic agents. At the end of the infusion, flush the line with a sufficient quantity of normal saline or 5% dextrose solution.

This study consists of 2 modules:

7.1.1 Module A (Nivolumab Monotherapy):

Participants in Module A will receive nivolumab at a dose of 3 mg/kg as a 30-minute IV infusion, on Day 1 of each treatment cycle every 2 weeks. Participants should begin study treatment within 3 calendar days of treatment assignment (ie, second IRT visit entry). Participants in Cohort 1 will begin treatment within 6 weeks after the end of RT.

The selection and timing of dose for each participant is as follows:

Table 7.1.1-1: Selection and Timing of Dose for Module A (Nivolumab Monotherapy)

Study Treatment	Unit dose strength(s)/Dosage level(s)	Dosage formulation Frequency of Administration	Route of Administration
Nivolumab	3 mg/kg	Every 2 weeks	IV

7.1.2 Module B (Nivolumab 3 mg/kg + Ipilimumab 1 mg/kg Combination):

First 4 Cycles:

Participants should receive nivolumab at a dose of 3 mg/kg as a 30-minute IV infusion, followed 30 minutes after by ipilimumab at a dose of 1 mg/kg as a 30 minutes IV infusion on Day 1 of each treatment cycle every 3 weeks, for 4 doses, until progression, unacceptable toxicity, withdrawal of consent, or the study ends, whichever occurs first. Participants should begin study treatment within 3 calendar days of treatment assignment (ie, second IRT visit entry). Participants in Cohort 1 will begin treatment within 6 weeks after the end of RT.

When study drugs (nivolumab and ipilimumab) are to be administered on the same day, nivolumab is to be administered first. Nivolumab infusion must be promptly followed by a normal saline or D5W flush to clear the line of nivolumab before starting the ipilimumab infusion. The second infusion will always be the ipilimumab study drug and will start after the infusion line has been flushed, filters changed and participant has been observed to ensure no infusion reaction has occurred. The time in between infusions is expected to be approximately 30 minutes but may be more or less depending on the situation.

Ipilimumab is to be administered as a 30 minute IV infusion, using a volumetric pump with a 0.2 to 1.2 micron in-line filter at the protocol-specified dose. The drug can be diluted with 0.9% normal saline or 5% Dextrose Injection to concentrations between 1 mg/mL and 4 mg/mL. It is not to be administered as an IV push or bolus injections. Care must be taken to assure sterility of the prepared solutions, since the drug product does not contain any antimicrobial preservatives or bacteriostatic agents. At the end of the infusion, flush the line with a sufficient quantity of normal saline or 5% dextrose solution.

The selection and timing of dose for each participant is as follows:

Table 7.1.2-1: Selection and Timing of Dose for Module B (Nivolumab and Ipilimumab Combination) - First 4 cycles

Study Treatment	Unit dose strength(s)/Dosage level(s)	Dosage formulation Frequency of Administration	Route of Administration
Nivolumab	3 mg/kg	Every 3 weeks	IV
Ipilimumab	1 mg/kg	Every 3 weeks	IV

Cycle 5 and beyond:

Participants should receive nivolumab at a dose of 3 mg/kg as a 30-minute IV infusion, on Day 1 of each treatment cycle every 2 weeks, starting 3 weeks after the fourth dose of the combination.

The selection and timing of dose for each participant is as follows:

Table 7.1.2-2: Selection and Timing of Dose for Module B (Nivolumab and Ipilimumab Combination) - Cycle 5 and Beyond

Study Treatment	Unit dose strength(s)/Dosage level(s)	Dosage formulation Frequency of Administration	Route of Administration
Nivolumab	3 mg/kg	Every 2 weeks	IV

7.2 Method of Treatment Assignment

This is an open-label study. All participants will be assigned to treatment using an Interactive Response Technology (IRT). Before the study is initiated, each user will receive log in information and directions on how to access the IRT.

The first call to IRT will be made in order to enroll a participant and should be made as soon as possible after informed consent has been obtained. An identification number will be assigned and should be used in all subsequent communications.

The second call to IRT will be made when eligibility has been established and the participant is ready to begin study treatment. Subsequent assignments of study drug are also managed via IRT.

7.3 Blinding

This is an open-label study; blinding procedures are not applicable.

7.4 Dosage Modification

Dose modifications related to management of specific AEs are described further in Appendix 5.

7.4.1 Dose Delay Criteria

Premedications are not recommended for the first dose of nivolumab.

Participants should be carefully monitored for infusion reactions during nivolumab administration. If an acute infusion reaction is noted, participants should be managed according to Section 9.2.9.

Doses of nivolumab and ipilimumab may be interrupted, delayed, or discontinued depending on how well the participant tolerates the treatment. Dosing visits are not skipped, only delayed. Tumor assessments for all participants should continue as per protocol even if dosing is delayed. During Module B (nivolumab and ipilimumab combination), both nivolumab and ipilimumab should be delayed at the same time. There will be no dose escalations or reductions of nivolumab allowed.

For the purposes of this trial, a fixed ULN = 45 will be used for AST and ALT.

Nivolumab administration should be delayed for the following:

- Grade 2 non-skin, drug-related adverse event, with the exception of fatigue
- Grade 2 drug-related creatinine, AST, ALT and/or Total Bilirubin abnormalities
- Grade 3 skin, drug-related adverse event

- Grade 3 drug-related laboratory abnormality, with the following exceptions:
  - Grade 3 lymphopenia or asymptomatic amylase or lipase does not require dose delay
  - Grade ≥ 3 AST, ALT, Total Bilirubin will require dose discontinuation (see Section 9.2.7)
- Any AE, laboratory abnormality, or intercurrent illness which, in the judgment of the investigator, warrants delaying the dose of study medication.

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

7.4.2 Criteria to Resume Treatment

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

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

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

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

If nivolumab treatment is delayed for any reason, ipilimumab must also be delayed until the participant has appropriately recovered and is able to resume the combination treatment on the first day of the subsequent cycle.

7.4.3 Treatment of Related Infusion Reactions

Since nivolumab and ipilimumab contain only human immunoglobulin protein sequences, each is unlikely to be immunogenic and induce infusion or hypersensitivity reactions. However, if such a reaction were to occur, it might manifest with fever, chills, rigors, headache, rash, pruritus, arthralgias, hypotension, hypertension, bronchospasm, or other allergic-like reactions. All Grade 3 or 4 infusion reactions should be reported within 24 hours to the BMS Study

Medical Monitor and reported as an SAE if it meets the criteria. Infusion reactions should be graded according to NCI CTCAE (Version 4) 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 (as pediatric equivalent per kg or weight based pediatric equivalent, at investigator discretion) and/or acetaminophen/paracetamol appropriate for age/weight at least 30 minutes before additional nivolumab administrations.

For Grade 2 symptoms: (moderate reaction required 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 (as pediatric equivalent per kg or weight based pediatric equivalent, at investigator discretion) and/or acetaminophen/paracetamol appropriate for age/weight; remain at bedside and monitor participant until resolution of symptoms. Corticosteroid and/or bronchodilator therapy may also be administered as appropriate. If the infusion is interrupted, then restart the infusion at 50% of the original infusion rate when symptoms resolve; if no further complications ensue after 30 minutes, the rate may be increased to 100% of the original infusion rate. Monitor participant closely. If symptoms recur, then no further nivolumab or ipilimumab will be administered at that visit.
- For future infusions, the following prophylactic premedications are recommended: diphenhydramine 50 mg (or pediatric equivalent per kg, at investigator's discretion) and/or acetaminophen/paracetamol appropriate for age/weight should be administered at least 30 minutes before nivolumab infusions. If necessary, corticosteroids (up to 25 mg of hydrocortisone or equivalent) may be used.

For Grade 3 or 4 symptoms: (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 participant as follows: Recommend bronchodilators, epinephrine 0.2 to 1 mg of a 1:1000 solution for subcutaneous administration or 0.1 to 0.25 mg of a 1:10,000 solution injected slowly for IV administration, and/or diphenhydramine 50 mg IV (or pediatric equivalent per kg, at investigator's discretion) with methylprednisolone 100 mg

IV (or weight-based equivalent), as needed. Participant should be monitored until the Investigator is comfortable that the symptoms will not recur. Study drug will be permanently discontinued. Investigators should follow their institutional guidelines for the treatment of anaphylaxis. Remain at bedside and monitor participant until recovery of the symptoms.

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

7.5 Preparation/Handling/Storage/Accountability

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 participants. The investigational product must be dispensed only from official study sites by authorized personnel according to local regulations.

The product storage manager should ensure that the study treatment 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 treatment arise, the study treatment should not be dispensed and contact BMS immediately.

Study treatment not supplied by BMS will be stored in accordance with the package insert.

Investigational product documentation (whether supplied by BMS or not) 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).

For details on prepared drug storage and use time of nivolumab and ipilimumab under room temperature/light and refrigeration, please refer to the nivolumab IB[47] section for "Recommended Storage and Use Conditions" and/or pharmacy manual.

- Further guidance and information for final disposition of unused study treatment are provided in Appendix 2 and Study Pharmacy Manual.

7.5.1 Retained Samples for Bioavailability / Bioequivalence

Not Applicable.

7.6 Treatment Compliance

Treatment compliance will be monitored by drug accountability as well as by the participant's medical record and Case Report Form (CRF).

[redacted]

[redacted]

7.8 Treatment After the End of the Study

At the conclusion of the study, participants who continue to demonstrate clinical benefit will be eligible to receive BMS supplied study treatment. Study treatment will be provided via an extension of the study, a rollover study requiring approval by responsible health authority and ethics committee or through another mechanism at the discretion of BMS.

BMS reserves the right to terminate access to BMS supplied study treatment if any of the following occur: a) the study is terminated due to safety concerns; b) the development of the nivolumab is terminated for other reasons, including but not limited to lack of efficacy and/or not meeting the study objectives; c) the participant can obtain medication from a government sponsored or private health program. In all cases BMS will follow local regulations.

8. DISCONTINUATION CRITERIA

Tumor assessments should continue as per protocol even if dosing is delayed. Periodic study visits to assess safety and laboratory studies should also continue every 6 weeks or more frequently if clinically indicated during such dosing delays.

8.1 Discontinuation from Study Treatment

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

- Confirmed radiologic disease progression or investigator-assessed clinical progression as described in Section 9.1.2
- Toxicity as specified below and in Section 9.2
- Participant's request to stop study treatment. 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 participant to provide this information (See Section 8.2)

- 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.
- Maximum clinical benefit as assessed by Investigator
- Pregnancy (as specified in Section 9.2.5)
- Termination of the study by Bristol-Myers Squibb (BMS)
- Loss of ability to freely provide consent through imprisonment or involuntarily incarceration for treatment of either a psychiatric or physical (eg, infectious disease) illness

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

Discontinuation of the study treatment for abnormal liver tests should be considered by the investigator when a participant meets one of the conditions outlined (in the algorithm below) OR (in Appendix 5) or if the investigator believes that it is in best interest of the participant.

Refer to the Schedule of Activities for data to be collected at the time of treatment discontinuation and follow-up and for any further evaluations that can be completed

All participants who discontinue study treatment should comply with protocol specified follow-up procedures as outlined in Section 2. The only exception to this requirement is when a participant withdraws consent for all study procedures including post-treatment study follow-up or loses the ability to consent freely (ie, is imprisoned or involuntarily incarcerated for the treatment of either a psychiatric or physical illness).

If study treatment is discontinued prior to the participant's completion of the study, the reason for the discontinuation must be documented in the participant's medical records and reported page.

8.1.1 Discontinuation of Nivolumab Due to Toxicity [Module A or B]

For the purposes of this trial, a fixed ULN = 45 will be used for AST and ALT.

Nivolumab treatment should be permanently discontinued for the following:

- Any Grade 2 drug-related uveitis, eye pain or blurred vision that does not respond to topical therapy and does not improve to Grade 1 severity within the re-treatment period OR requires systemic treatment

- Any Grade 3 non-skin, drug-related adverse event lasting > 7 days or recurs, with the following exceptions for laboratory abnormalities, drug-related uveitis, pneumonitis, bronchospasm, neurologic toxicity, hypersensitivity reactions, infusion reactions, and endocrinopathies:
  - Grade 3 drug-related uveitis, pneumonitis, bronchospasm, neurologic toxicity, hypersensitivity reaction, myocarditis or infusion reaction of any duration requires discontinuation
  - Grade 3 drug-related endocrinopathies, adequately controlled with only physiologic hormone replacement do not require discontinuation. Adrenal insufficiency requires discontinuation regardless of control with hormone replacement.
  - Grade 3 drug-related laboratory abnormalities do not require treatment discontinuation except:
    - Grade 3 drug-related thrombocytopenia > 7 days or associated with bleeding requires discontinuation
    - Grade ≥ 3 drug-related AST, ALT or Total Bilirubin requires discontinuation*
    - Concurrent AST or ALT > 3 x ULN and total bilirubin > 2x ULN (see Section 9.2.7)
- Any Grade 4 drug-related adverse event or laboratory abnormality (including but not limited to creatinine, AST, ALT, or Total Bilirubin), except for the following events which do not require discontinuation:
  - Grade 4 neutropenia ≤ 7 days
  - Grade 4 lymphopenia or leukopenia or asymptomatic amylase or lipase
  - Isolated Grade 4 electrolyte imbalances/abnormalities that are not associated with clinical sequelae and are corrected with supplementation/appropriate management within 72 hours of their onset
  - Grade 4 drug-related endocrinopathy adverse events, such as, hyper- or hypothyroidism, or glucose intolerance, which resolve or are adequately controlled with physiologic hormone replacement (corticosteroids, thyroid hormones) or glucose-controlling agents, respectively, may not require discontinuation after discussion with and approval from the BMS Medical Monitor.
- Any event that leads to delay in dosing lasting > 6 weeks for nivolumab monotherapy from the previous dose requires discontinuation, with the following exceptions:
  - Dosing delays to allow for prolonged steroid tapers to manage drug-related adverse events are allowed.
  - Dosing delays lasting > 6 weeks from the previous dose that occur for non-drug-related reasons may be allowed if approved by the BMS medical monitor.

Prior to re-initiating treatment in a participant with a dosing delay lasting > 6 weeks, the BMS medical monitor must be consulted.

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

8.1.2 Discontinuation of Combination treatment due to Toxicity [Module B]

Additional criteria apply to participants in Module B; the criteria above for nivolumab apply to both Modules. To the extent possible, assessment for discontinuation of nivolumab should be made separately from the assessment made for discontinuation of ipilimumab. Although there is overlap among the discontinuation criteria, if discontinuation criteria are met for ipilimumab but not for nivolumab, treatment with nivolumab may continue if ipilimumab is discontinued. After discussion with the Medical Monitor, nivolumab monotherapy may continue if ipilimumab is discontinued. If a participant in Module B meets criteria for discontinuation and investigator is unable to determine whether the event is related to both or one study drug, the participant should discontinue both nivolumab and ipilimumab, and be taken off the treatment phase of the study. At investigator discretion, with approval of BMS medical monitor, participant may discontinue ipilimumab and (after recovery of AEs) may restart nivolumab monotherapy.

Nivolumab and Ipilimumab treatment should be **permanently discontinued** for the following:

- Any Grade 2 drug-related uveitis, eye pain or blurred vision that does not respond to topical therapy and does not improve to Grade 1 severity within the re-treatment period OR requires systemic treatment
- Any Grade 3 non-skin, drug-related adverse event lasting > 7 days, or recurs with the following exceptions for laboratory abnormalities, diarrhea, colitis, neurologic toxicity, drug-related uveitis, pneumonitis, bronchospasm, hypersensitivity reactions, infusion reactions, and endocrinopathies:
  - Grade 3 drug-related diarrhea, colitis, neurologic toxicity, uveitis, pneumonitis, bronchospasm, hypersensitivity reaction, myocarditis, or infusion reaction of any duration requires discontinuation
  - Grade 3 drug-related endocrinopathies, adequately controlled with only physiologic hormone replacement do not require discontinuation. Adrenal insufficiency requires discontinuation regardless of control with hormone replacement.
  - Grade 3 drug-related laboratory abnormalities do not require treatment discontinuation except:
    - Grade 3 drug-related thrombocytopenia > 7 days or associated with bleeding requires discontinuation
    - Any drug-related liver function test (LFT) abnormality that meets the following criteria require discontinuation:
      - Grade ≥ 3 drug-related AST, ALT or Total Bilirubin requires discontinuation*
      - Concurrent AST or ALT > 3 x ULN and total bilirubin > 2x ULN

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

- Any Grade 4 drug-related adverse event or laboratory abnormality (including but not limited to creatinine, AST, ALT, or Total Bilirubin), except for the following events which do not require discontinuation:
  - Grade 4 neutropenia ≤ 7 days
  - Grade 4 lymphopenia or leukopenia or asymptomatic amylase or lipase
  - Isolated Grade 4 electrolyte imbalances/abnormalities that are not associated with clinical sequelae and are corrected with supplementation/appropriate management within 72 hours of their onset
  - Grade 4 drug-related endocrinopathy: adverse events, such as, hyper- or hypothyroidism, or glucose intolerance, which resolve or are adequately controlled with physiologic hormone replacement (corticosteroids, thyroid hormones) or glucose-controlling agents, respectively, may not require discontinuation after discussion with and approval from the BMS Medical Monitor.
- Any event that leads to delay in dosing during combination therapy lasting > 8 weeks (Module B) from the previous dose requires discontinuation, with the following exceptions:
  - Dosing delays to allow for prolonged steroid tapers to manage drug-related adverse events are allowed.
  - Dosing delays lasting > 8 weeks for combination therapy from the previous dose that occur for non-drug-related reasons may be allowed if approved by the BMS medical monitor.

Prior to re-initiating treatment in a participant with a dosing delay lasting > 6 weeks, the BMS medical monitor must be consulted.

8.1.3 Post Study Drug Study Follow-up

For follow-up of AEs and SAEs after discontinuation of study treatment, see Section 9.2.

OS and PFS are key endpoints of this study. Post study follow-up is of critical importance and is essential to preserving participant safety and the integrity of the study. Participants who discontinue study treatment must continue to be followed for collection of progression and/or survival information according to Section 5.1.5, ie, until disease progression and at least 3 years for survival (as applicable).

BMS may request that survival data be collected on all treated participants outside of the protocol defined window (Table 2.-1, Table 2.-2, Table 2.-3, and Table 2.-4). At the time of this request, each participant will be contacted to determine their survival status unless the participant has withdrawn consent for all contacts or is lost to follow-up.

8.2 Discontinuation from the Study

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 participant to provide this information.

- Participants should notify the investigator of the decision to withdraw consent from future follow-up **in writing**, whenever possible.

- The withdrawal of consent should be explained in detail in the medical records by the investigator, as to whether the withdrawal is from further treatment with study treatment 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.
- If the participant withdraws consent for disclosure of future information, the sponsor may retain and continue to use any data collected before such a withdrawal of consent.
- Withdrawal of consent may be requested by participants, parents, guardians, or legally acceptable representatives, in accordance with local regulations. The wishes of minor participants to withdraw their assent should also be respected.

8.3 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.
- 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 date and cause of death.
- If investigator's use of third-party representative to assist in the follow-up portion of the study has been included in the participant's informed consent, then the investigator may use a Sponsor retained third-party representative to assist site staff with obtaining participant's contact information or other public vital status data necessary to complete the follow-up portion of the study.
- The site staff and representative will consult publicly available sources, such as public health registries and databases, in order to obtain updated contact information.
- If after all attempts, the participant remains lost to follow-up, then the last known alive date as determined by the investigator should be reported and documented in the participant's medical records.

9. STUDY ASSESSMENTS AND PROCEDURES

- Study procedures and timing are summarized in the Schedule of Activities.
- Protocol waivers or exemptions are not allowed.
- All immediate safety concerns must be discussed with the Sponsor immediately upon occurrence or awareness to determine if the participant should continue or discontinue treatment.
- Adherence to the study design requirements, including those specified in the Schedule of Activities, is essential and required for study conduct.
- All screening evaluations must be completed and reviewed to confirm that potential participants meet all eligibility criteria before treatment start. The investigator will maintain a

screening log to record details of all participants screened and to confirm eligibility or record reasons for screening failure, as applicable.

- Procedures conducted as part of the participant's routine clinical management (eg, blood count) and obtained before signing of informed consent may be utilized for screening or baseline purposes provided the procedure meets the protocol-defined criteria and has been performed within the timeframe defined in the Schedule of Activities.

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

If a participant shows pulmonary-related signs (hypoxia, tachypnea) or symptoms (eg. dyspnea, cough, fever) consistent with possible pulmonary adverse events, the participant should be immediately evaluated to rule out pulmonary toxicity, according to the suspected pulmonary toxicity management algorithm Appendix 5.[47]

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

9.1 Efficacy Assessments

Efficacy will be based on imaging assessments (Section 9.1.1) supplemented by clinical neurologic examination and performance status as well as additional considerations as applicable eg, steroid requirement, CSF cytopathology. Consensus Recommendations for imaging of brain tumors[61] should be followed. Additional sequences, based on the clinical setting, should be included at the discretion of the neuroradiologist.

Study endpoints of response or progression will be based on widely-accepted RANO criteria (See Section 9.1.3); in pediatric tumors, however, interpretation by an experienced neuroradiologist is essential. For tumors with a propensity to disseminate in the leptomeninges, guidance contained in paper entitled Response Assessment in Medulloblastoma and Leptomeningeal Seeding Tumors: Recommendations from the Response Assessment in Pediatric Neuro-Oncology Committee by Warren et al[54] should be considered, particularly with respect to imaging and cytopathologic parameters. The expectations stated in Schedule of Activities and Section 9.1.1 are generally applicable, but investigators have discretion to modify the frequency of spine MRI and CSF cytopathology based on individual circumstances.

In addition, consideration may be given to the recent iRANO proposal.[62] As these proposed criteria have not yet been widely applied, they may be considered as an exploratory endpoint.

9.1.1 Imaging Assessment for the Study

All participants will undergo contrast enhanced brain MRI at the time points specified in Table 2.-1, Table 2.-2, Table 2.-3, and Table 2.-4. An Imaging Manual will be provided. Screening MRI may be performed prior to informed consent, as part of standard care. Adequate quality of the baseline evaluation must be assured by the PI prior to treatment start and repeat imaging performed if not adequate. However, it is not necessary that the MRI machine be "qualified" (by imaging CRO) for the screening evaluation.

For Inclusion of Cohorts 2-5, if first recurrence of the CNS tumor is documented by MRI, an interval of at least 12 weeks after the end of prior radiation therapy is required unless there is either: i) histopathologic confirmation of recurrent tumor, or ii) new enhancing mass on MRI outside of the radiotherapy treatment field.

Evaluation of the leptomeninges is standard in many pediatric CNS malignancies and should be performed as clinically indicated. In Cohorts 3 and 5, a baseline MRI spine and CSF cytopathology are expected, unless clinically contraindicated. In Cohorts 2 and 4, baseline MRI spine and CSF cytopathology may be obtained based on clinical judgment; these are not expected in Cohort 1.

On treatment and follow up MRIs should occur on the following schedule: Q6W x 2 assessments, then Q8W x 4, and then Q12W (± 1 week). The expected timing of tumor assessments is therefore at Weeks 7, 13, 21, 29, 37, 45, and subsequently every 12 weeks. Investigators may obtain more frequent follow-up MRI scans as medically indicated. Local radiologic assessment of tumor measurements will be used during the study for clinical management and investigator-assessed disease progression. MRI scans should continue on the indicated schedule regardless of treatment delay.

If baseline MRI spine showed metastatic deposits, then it should be repeated at the same intervals as the MRI of brain, ie regular tumor assessments indicated in Table 2.-2, Table 2.-3, and Table 2.-4, ordinarily at the same imaging session. Frequency of MRI spine is at the investigator's discretion. If the baseline is negative, then less frequent re-assessment may be appropriate depending on the individual circumstances. All imaging assessments of sites of disease should be submitted (Section 5.1.6.3) to the central imaging laboratory.

If baseline CSF cytopathology is positive, then it should be repeated approximately every 8 weeks during study, as clinically indicated.

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

Study-related MRI imaging of the brain will be performed per the frequency specified above. Investigators may obtain additional MRI scans as medically indicated. For other locally performed imaging, it is the local imaging facility's responsibility to determine, based on

participant attributes (eg, allergy history, diabetic history, and renal status), the appropriate imaging modality, and contrast regimen for each participant. Imaging contraindications and contrast risks should be considered in this assessment. Participants with severe renal insufficiency (ie, estimated glomerular filtration rate < 30 mL/min/1.73 m^2) are at increased risk of nephrogenic systemic fibrosis. MRI contrast should not be given to this participant population, who should be excluded from the study. In addition, participants with surgically implanted devices (pacemaker, deep brain stimulator, metallic implants, etc) incompatible with MRI should not undergo such imaging techniques. The local imaging facility and investigator should determine the appropriate precautions or guidelines that should be instituted for participants with tattoos, body piercings, or other body art.

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

Study sites will retain local access to the imaging results for safety and efficacy reading purposes. The study investigator will review the local MRI results as clinically appropriate to ensure that any potentially emergent clinical situations are addressed in a timely fashion. Clinically significant radiologic findings or changes from baseline scans will be coded as AEs or SAEs according to the criteria described in Section 9.2. Any additional or incidental radiographic findings of potential clinical relevance that are not directly associated with the objectives of the protocol should be evaluated and handled by the Study Investigator as per standard medical/clinical judgment.

Sites will be trained in image acquisition parameters, the submission process, and application of RANO criteria[63] prior to scanning the first study participant. These guidelines will be outlined in a separate Site Imaging Manual provided by the imaging core lab. Investigators will assess PFS, ORR and DOR based on RANO criteria.

All radiologic imaging from this study will be transmitted to a centralized imaging core lab for storage and sponsor access. At Sponsor request, BICR will assess PFS in all Cohorts and ORR in participants with measurable disease.

9.1.2 Suspected Progression

In order to distinguish potential treatment effects (or "pseudo-progression"), from progressive disease and thus to minimize premature discontinuation of treatment, participants who initially meet radiologic criteria for disease progression, but are tolerating study drug, may continue receiving study drug until confirmation of progression. If the follow-up assessment confirms that progression has occurred, the date of progression will be the date at which progression was first determined. If the follow-up assessment does not confirm progression, then the original time point response will be assessed as SD. If possible, MRI perfusion images should also be obtained.

If a determination cannot be made after a 6 to 8 week interval, then treatment may continue until either progression is confirmed or regression is observed, consistent with either

pseudoprogression (in Cohort 1) or immune-treatment effect. There is no time limit for confirmation of progression. The BMS Medical Monitor should be consulted.

Suspected disease progression within 12 weeks after the end of RT must be confirmed (per RANO) by subsequent MRI performed approximately 6-8 weeks after the initial radiological assessment of progression. Prior to 12 weeks after RT, progression can only be defined using diagnostic imaging if there is new enhancement outside of the radiation field (beyond the high-dose region or 80% isodose line) or if there is unequivocal evidence of viable tumor on histopathologic sampling.[63] Note: in the absence of radiographic or histologic confirmation of progression, clinical decline alone is not sufficient for definition of progressive disease.

9.1.3 Assessment of Response

Response will be assessed using RANO 2010 criteria.[63] Table 9.1.3-1 describes the radiological and clinical criteria that will be used for determining tumor response. Table 9.1.3-2 describes the criteria used for assessing eligibility (for Cohorts 2-5), based on time from prior RT (See Section 6.1). Table 9.1.3-3 describes the criteria will be used for assessing BOR. All measurable and non-measurable lesions must be assessed using the same techniques as at baseline.

Participants who have no lesion measuring ≥ 1 cm on 2 perpendicular diameters on baseline MRI cannot have a complete or partial response and will be followed only for recurrence. Similarly, participants with DIPG in Cohort 1 (ie, in the post-RT period) will be considered to have non-measureable disease. These participants will be considered non-evaluable for BOR analysis, but their disease status will be assessed (SD or PD) at each tumor assessment, and they will be included in analysis of PFS and OS. If no signs of progression are observed by MRI, the radiologic assessment will be categorized as SD. The appearance of any new lesion consistent with tumor will be categorized as PD.

The assessments that will contribute to evaluation of PD include response assessments recorded between the date of first dose of study therapy and the first to occur of the following:

1) The date of objectively documented progression per RANO criteria
2) The date of subsequent therapy, or
3) The date of pathology results from diagnostic surgical resection
4) The date of clinical progression

The minimum duration between baseline scan and first on-study scan in order to determine BOR of SD is at least 5 weeks on study. If the minimum time is not met when SD is otherwise the best time point response, the participant's best response will depend on the subsequent assessments. For example, a participant who has SD at a time point < 6 weeks and PD at a second assessment, will have a best response of PD.

Table 9.1.3-1: RANO Criteria for Time-point Response Assessment Incorporating MRI and Clinical Factors

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

Table 9.1.3-2: Criteria for Determining First Progression Depending on Time after Radiotherapy

First Progression	Definition[a]
Progressive disease < 12 weeks after completion of radiotherapy	Progression can only be defined using diagnostic imaging if there is new enhancement outside of the radiation field (beyond the high-dose region or 80% isodose line) or if there is unequivocal evidence of viable tumor or histopathologic sampling (eg, solid tumor areas [ie, > 70% tumor cell nuclei in areas], high or progressive increase in MIB-1 proliferation index compared with prior biopsy, or evidence for histologic progression or increased anaplasia in tumor). Note: Given the difficulty of differentiating true progression from pseudoprogression, clinical decline alone, in the absence of radiographic or histologic confirmation of progression, will not be sufficient for definition of progressive disease in the first 12 weeks after completion of radiotherapy.
Progressive disease ≥ 12 weeks after completion of radiotherapy	1. New contrast-enhancing lesion outside of radiation field on decreasing, stable, or increasing doses of corticosteroids. 2. Increase by ≥ 25% in the sum of the products of perpendicular diameters between the first post radiotherapy scan, or a subsequent scan with smaller tumor size, and the scan at 12 weeks or later on stable or increasing doses of corticosteroids. 3. Clinical deterioration not attributable to concurrent medication or comorbid conditions is sufficient to declare progression on current treatment but not for entry onto a clinical trial for recurrence. 4. For participants receiving antiangiogenic therapy, significant increase in T2/FLAIR non-enhancing lesion may also be considered progressive disease. The increased T2/FLAIR must have occurred with the participant on stable or increasing doses of corticosteroids compared with baseline scan or best response after initiation of therapy and not be a result of comorbid events (eg, effects of radiation therapy, demyelination, ischemic injury, infection, seizures, postoperative changes, or other treatment effects).

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

Table 9.1.3-3: Assessment of Best Overall Response

Best Overall Response	Criteria[a]
CR	CR observed in assessments ≥ 4 weeks apart per RANO
PR	PR observed in assessments ≥ 4 weeks apart per RANO
SD Note: To qualify for SD there must be a minimum on-treatment period of 6 weeks.)	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
PD	No CR, PR, or SD prior to PD

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

9.1.4 Results of Central Radiology Assessments

The clinical management of participants during the study protocol and secondary outcomes (PFS) will be based upon local radiologic tumor measurements and the investigator-assessed RANO response criteria described in Section 9.1.3. Radiologic imaging from this study will be also be transmitted to a centralized imaging core lab for storage and for analysis by blinded independent central review as determined by the Sponsor. The site will be informed of quality issues or need for repeat scanning via queries from the core lab.

9.2 Adverse Events

The definitions of an AE or SAE can be found in Appendix 3.

AEs will be reported by the participant (or, when appropriate, by a caregiver, surrogate, or the participant's legally authorized representative).

The investigator and any designees are responsible for detecting, documenting, and reporting events that meet the definition of an AE or SAE and remain responsible for following up AEs that are serious, considered related to the study treatment or the study, or that caused the participant to discontinue before completing the study.

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

Contacts for SAE reporting specified in Appendix 3

9.2.1 Time Period and Frequency for Collecting AE and SAE Information

The collection of nonserious AE information should begin at initiation of study treatment until [the follow-up contact], at the timepoints specified in the Schedule of Activities (Section 2). Nonserious AE information should also be collected from the start of a placebo lead-in period or other observational period intended to establish a baseline status for the participants.

Sections 5.6.1 and 5.6.2 in the IB represent the Reference Safety Information to determine expectedness of serious adverse events for expedited reporting.[47] Following the participant’s written consent (or the parent/guardian/LAR’s permission) to participate in the study, all SAEs, whether related or not related to study drug, must be collected, including those thought to be associated with protocol-specified procedures.

All SAEs must be collected that occur during the screening period and within 100 days of last dose of study treatment. For participants who are assigned treatment but never treated, SAEs should be collected for 30 days from the date of treatment assignment.

- Medical occurrences that begin before the start of study treatment but after obtaining informed consent will be recorded on the appropriate section of the eCRF section.

- All SAEs will be recorded and reported to Sponsor or designee within 24 hours, as indicated in Appendix 3.
- The investigator will submit any updated SAE data to the sponsor within 24 hours of this being available.

Investigators are not obligated to actively seek AEs or SAEs in former study participants. However, if the investigator learns of any SAE, including a death, at any time after a participant has been discharged from the study, and he/she considers the event reasonably related to the study treatment or study participation, the investigator must promptly notify the sponsor.

The method of evaluating, and assessing causality of AEs and SAEs and the procedures for completing and reporting/transmitting SAE reports are provided in Appendix 3.

9.2.2 Method of Detecting AEs and SAEs

Adverse events can be spontaneously reported or elicited during open-ended questioning, examination, or evaluation of a participant. Care should be taken not to introduce bias when collecting AEs or/or SAEs. Inquiry about specific AEs should be guided by clinical judgment in the context of known adverse reactions, when appropriate for the next program or protocol.

9.2.3 Follow-up of AEs and SAEs

- Nonserious AEs should be followed to resolution or stabilization, or reported as SAEs if they become serious (see Appendix 3).
- Follow-up is also required for nonserious AEs that cause interruption or discontinuation of study treatment and for those present at the end of study treatment as appropriate.
- All identified nonserious AEs must be recorded and described on the nonserious AE page of the CRF (paper or electronic). Completion of supplemental CRFs may be requested for AEs and/or laboratory abnormalities that are reported/identified during the course of the study.

After the initial AE/SAE report, the investigator is required to proactively follow each participant at subsequent visits/contacts. All SAEs, and non-serious AEs of special interest (as defined in Section 9.2 will be followed until resolution, until the condition stabilizes, until the event is otherwise explained, or until the participant is lost to follow-up (as defined in Section 8.3).

Further information on follow-up procedures is given in Appendix 3.

9.2.4 Regulatory Reporting Requirements for SAEs

- Prompt notification by the investigator to the Sponsor of SAEs is essential so that legal obligations and ethical responsibilities towards the safety of participants and the safety of a product under clinical investigation are met.
- An investigator who receives an investigator safety report describing SAEs or other specific safety information (eg, summary or listing of SAEs) from the Sponsor will file it along with the Investigator's Brochure and will notify the IRB/IEC, if appropriate according to local requirements.

Sponsor or designee will be reporting adverse events to regulatory authorities and ethics committees according to local applicable laws including European Directive 2001/20/EC and FDA Code of Federal Regulations 21 CFR Parts 312 and 320. A SUSAR (Suspected, Unexpected Serious Adverse Reaction) is a subset of SAEs and will be reported to the appropriate regulatory authorities and investigators following local and global guidelines and requirements.

All SAEs must be collected that occur during the screening period and within 100 days of the last dose of study treatment. For participants randomized/assigned to treatment and never treated with study drug, SAEs should be collected for 30 days from the date of treatment assignment.

9.2.5 Pregnancy

If, following initiation of the study treatment, it is subsequently discovered that a participant is pregnant or may have been pregnant at the time of study exposure, including during at least 5 half-lives after product administration, the investigator must immediately notify the BMS Medical Monitor/designee of this event and complete and forward a Pregnancy Surveillance Form to BMS Designee within 24 hours of awareness of the event and in accordance with SAE reporting procedures described in Appendix 3.

In most cases, the study treatment will be permanently discontinued in an appropriate manner (eg, dose tapering if necessary for participant safety). Please call the BMS Medical Monitor within 24 hours of awareness of the pregnancy.

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

Any pregnancy that occurs in a female partner of a male study participant should be reported to Sponsor or designee. In order for Sponsor or designee to collect any pregnancy surveillance information from the female partner, the female partner must sign an informed consent form for disclosure of this information. Information on this pregnancy will be collected on the Pregnancy Surveillance Form if permissible by local regulations.

9.2.6 Laboratory Test Result Abnormalities

The following laboratory test result abnormalities should be captured on the nonserious AE CRF page or SAE Report Form electronic, as appropriate. Paper forms are only intended as a back-up option when the electronic system is not functioning.

- Any laboratory test result that is clinically significant or meets the definition of an SAE
- Any laboratory test result abnormality that required the participant to have study treatment discontinued or interrupted
- Any laboratory test result abnormality that required the participant to receive specific corrective therapy

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

9.2.7 Potential Drug Induced Liver Injury (DILI)

Wherever possible, timely confirmation of initial liver-related laboratory abnormalities should occur prior to the reporting of a potential DILI event. All occurrences of potential DILIs, meeting the defined criteria, must be reported as SAEs (see Section 9.2 and Appendix 3 for reporting details). For the purposes of this trial, a fixed ULN = 45 will be used for AST and ALT.

Potential drug induced liver injury is defined as:

1) AT (ALT or AST) elevation > 3 x ULN, AND
2) Total bilirubin > 2 x ULN, without initial findings of cholestasis (elevated serum alkaline phosphatase), AND
3) No other immediately apparent possible causes of AT elevation and hyperbilirubinemia, including, but not limited to, viral hepatitis, pre-existing chronic or acute liver disease, or the administration of other drug(s) known to be hepatotoxic.

9.2.8 Other Safety Considerations

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

[redacted]

9.3 Overdose

An overdose is defined as the accidental or intentional administration of any dose of a product that is considered both excessive and medically important. All occurrences of overdose must be reported as an SAE (see Section 9.2).

In the event of an overdose the [investigator/treating physician] should:

1) Contact the Medical Monitor immediately
2) Closely monitor the participant for AEs/SAEs and laboratory abnormalities.
3) Document the quantity of the excess dose as well as the duration of the overdosing in the CRF.

Decisions regarding dose interruptions or modifications will be made by the investigator in consultation with the Medical Monitor based on the clinical evaluation of the participant.

9.4 Safety

Planned timepoints for all safety assessments are listed in the Schedule of Activities (Section 2). Safety assessments include AEs, physical examinations, vital signs, performance status, assessment of signs and symptoms, laboratory tests, and pregnancy tests as outlined in the Schedule of Activities.

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

If a participant shows pulmonary-related signs (hypoxia, fever) or symptoms (eg, dyspnea, cough, fever) consistent with possible pulmonary adverse events, the participant should be immediately evaluated to rule out pulmonary toxicity, according to the suspected pulmonary toxicity management algorithm Appendix 5.[47]

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

9.4.1 Physical Examinations

Refer to Schedule of Activities in Section 2.

In addition to the usual physical examination, a neurologic exam is performed routinely in a pediatric neuro-oncology clinic. Neurological exams are expected during Screening and at C1D1, and as clinically indicated. Normal institutional practice is expected. The exam includes observation of gait and coordination, cranial nerve function (including speech and visual fields), extremity strength and report of bladder/bowel function, with particular attention to any changes in previously-noted deficits.

9.4.2 Vital signs

Refer to Schedule of Activities in Section 2.

9.4.3 Electrocardiograms

Refer to Schedule of Activities, Table 2.-3, for electrocardiograms for Module B. A 12-lead ECG should be performed during the study period only as clinically indicated.

9.4.4 Clinical Safety Laboratory Assessments

- Investigators must document their review of each laboratory safety report.
- See Section 2 for additional details on the assessments to be conducted.

Laboratory tests evaluated are included in Table 9.4.4-1.

Table 9.4.4-1: Laboratory Tests

Hematology	
Hemoglobin	
Hematocrit	
Total leukocyte count, including differential	
Platelet count	
Serum Chemistry	
Aspartate aminotransferase (AST) Alanine aminotransferase (ALT) Total bilirubin Creatinine Blood Urea Nitrogen (BUN) Uric acid Glucose Total Protein - screening only Albumin - screening only	Sodium Potassium Chloride Calcium - screening only Phosphorus - screening only Lipase (Module B only) Amylase (Module B only)
Serology (screening only)	
Serum for hepatitis C antibody, hepatitis B surface antigen, (HIV-1 and -2 antibody where mandated locally)	
Other Analyses	
TSH (reflex to free T3 and Free T4 only if abnormal) Pregnancy test (WOCBP only: predose, discharge).	

9.4.5 Imaging Safety Assessment

Any incidental findings of potential clinical relevance that are not directly associated with the objectives of the protocol should be evaluated and handled by the Study Investigator as per standard medical/clinical judgment.

[redacted]

[redacted]

[redacted]

9.9 Health Economics OR Medical Resource Utilization and Health Economics

Health Economics/Medical Resource Utilization and Health Economics parameters will not be evaluated in this study.

10. STATISTICAL CONSIDERATIONS

10.1 Sample Size Determination

[redacted]

By applying the above methodology, the intended target number of participants (N) for cohort 1-4 are obtained as follows:

Cohort 1: 22 participants are required (17 events) for each cohort. This assumes 80% power with a one sided Type 1 error of 10%, a historical median OS of 9 months ([redacted]), 1-year accrual, 2-year follow-up, and a target effect size of median OS 15 months.

Cohort 2: 15 participants are required for each cohort. This assumes 80% power with a one-sided Type 1 error of 10%, a historical PFS(6) of 18% [redacted]), one-year accrual, one-year follow-up, a target PFS(6) of 38%. An interim analysis based on PFS(6) for futility only will be conducted after at least 8 of the planned number of participants are enrolled with 6 months follow-up. In addition, all other available efficacy data will be evaluated in the futility analysis. The method is adapted according to [redacted] Details of the futility criteria and simulations will be contained in the Statistical Analysis Plan (SAP).

Cohort 3: 15 participants are required for each cohort. This assumes 80% power with a one-sided Type 1 error of 10%, 1-year accrual and 1-year follow-up, a historical median PFS(4) of 18% and a target PFS(4) of 38% (see [redacted], equivalent to PFS(6) of 23%). An interim analysis based on PFS(6) for futility only will be conducted after at least 8 of the planned number of participants are enrolled with 6 months follow-up. In addition all other available efficacy data will be evaluated in the futility analysis.

Cohort 4: 10 participants are required for each cohort. This assumes at least 80% power with a one-sided Type 1 error of 10%, a historical median PFS of 2.1 months (see etoposide arm of [redacted]), 1-year accrual, 1-year follow-up, and a target median PFS of 4.4 months.

Cohort 5: 18 participants are required for each cohort. Sample sizes each of the expansion Cohorts A5 and B5 is not based on statistical considerations as these cohorts contain various tumor types. However, if the disease control rate at 12 months is 30%, 18 participants provide 21% precision for the estimate.

10.2 Populations for Analyses

For purposes of analysis, the following populations are defined:

Population	Description
Enrolled	All participants who sign informed consent. This is the dataset for disposition.
Treated	All enrolled participants who received at least one dose of study drug. This is the dataset for safety evaluation.
Safety Lead-in participants	In Module A, the first 6 DLT-evaluable participants in Cohort 1 and the first 10 DLT-evaluable participants in Cohorts 2-5; in Module B, the first 10 DLT-evaluable participants.
Response-evaluable participants	All treated participants with measurable disease at a baseline tumor assessment (Source: CRF).
[redacted]	[redacted]
[redacted]	[redacted]

10.3 Statistical Analyses

The statistical analysis plan will be developed and finalized before database lock and will describe the selection of participants to be included in the analyses, and procedures for accounting for missing, unused, and spurious data. Below is a summary of planned statistical analyses of the primary and secondary endpoints.

10.3.1 Efficacy Analyses

The primary efficacy analyses will be performed on treated population for the final analysis. Details on censoring scheme on time-to-event endpoints such as OS, PFS, and DOR will be described in the SAP. Efficacy analysis will be performed by each cohort separately; however, treated participants in the safety lead-in period who meet the inclusion criteria for the corresponding cohort will also be included in the cohort analysis.

OS is defined as the time between the date of diagnosis and the date of death in Cohort 1 and the time between date of first dose and the date of death for Cohorts 2-5. A participant who has not died will be censored at the last known alive date. OS will be followed continuously while

participants are on study drug and every 3 months via in-person or phone contact during the survival follow-up phase of the study drug.

PFS is defined as the time from first dose 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 evaluable tumor assessment. Participants who did not have any on study tumor assessment and did not die will be censored at the first dose date. PFS will be determined by investigators based on RANO criteria. First tumor assessments will occur at week 6 and 12, and will be at every 8 weeks for the first year and then every 12 weeks thereafter until disease progression is documented.

ORR is defined as the number of participants whose BOR is confirmed CR or PR divided by all participants who are evaluable for response, ie have measurable disease at baseline. BOR is defined as the best response designation, as determined by investigators, recorded between the date of first dose and the date of objectively documented progression per RANO criteria or the date of subsequent therapy, whichever occurs first. All available response designations will contribute to the BOR assessment. For participants without documented progression or subsequent therapy, all available response designations will contribute to the BOR assessments.

DOR for a participant with a BOR of CR or PR, is defined as the time between the date of first response and the date of the first objectively documented tumor progression per RANO or death, whichever occurs first.

Endpoint	Statistical Analysis Methods
Primary	
Cohort A1 and B1: OS	For each cohort separately, OS curve will be estimated using the Kaplan-Meier (KM) method. The distribution of OS in all treated participants will be compared against the historical control of an exponential distribution with median OS 9 months (Cohen, Heideman, et al) using a one-sided one-sample log rank test when approximately 17 events have occurred or after each participant has been followed for at least 24 months. Median OS and the corresponding two-sided 80% confidence intervals using the log-log transformation will be computed.
Cohort A2 and B2: PFS	For each cohort separately, PFS curve will be estimated using the Kaplan-Meier (KM) method. The distribution of PFS in all treated participants will be compared against the historical control of an exponential distribution with median PFS 2.25 months (Hwang, et al) using a one-sided one-sample log rank test when each participant has been followed for at least 12 months. Median PFS and the corresponding two-sided 80% confidence intervals using the log-log transformation will be computed.
Cohort A3 and B3: PFS	For each cohort separately, PFS curve will be estimated using the Kaplan-Meier (KM) method. The distribution of PFS in all treated

Endpoint	Statistical Analysis Methods
	participants will be compared against the historical control of an exponential distribution with PFS(4) equal to .18 using a one-sided one-sample log rank test when either 15 events have occurred or each participant has been followed for at least 12 months. Median PFS and the corresponding two-sided 80% confidence intervals using the log-log transformation will be computed.
Cohort A4 and B4: PFS	For each cohort separately the distribution of PFS in all treated participants will be compared against the historical control of an exponential distribution with median PFS equal to 2.1 months using a one-sided one-sample log rank test when either 10 events have occurred or each participant has been followed for at least 12 months.
Cohort A5 and B5: PFS	For each cohort separately individual PFS will be listed by tumor type after each participant reaches 12 months follow-up. PFS curve will be estimated using the Kaplan-Meier (KM) method for all tumor types (pooled) and selected individual tumor types, if there is enough data.
Secondary	
Cohort A1 and B1: PFS, OS(12)	**Cohorts A1 and B1:** PFS is estimated by Kaplan-Meier method and the corresponding 95% CI for median OS will be calculated via Brookmeyer and Crowley methodology using log-log transformation. OS(12) will be estimated using the Kaplan-Meier (KM) method. The corresponding 95% confidence interval for median OS will be calculated via Brookmeyer and Crowley methodology using log-log transformation and corresponding 95% confidence interval for OS(12) will be derived based on Greenwood formula. All secondary endpoints will be analyzed at the time of the primary analysis.
Cohort A2 and B2: PFS(6), OS, OS(12) **Cohort A3 and B3:** PFS(6), OS, OS(12) **Cohort A4 and B4:** PFS(6), OS, OS(12)	**Cohorts A2, A3, A4, B2, B3, B4** Secondary statistics analysis for other cohorts A2, A3, and A4, B2, B3, and B4 is the same as for Cohort A1 and B1 (except timepoint for OS(r) and PFS(r) may differ.
Cohort A5 and B5: PFS(12), OS	**Cohorts A5, B5:** OS will be listed. OS curve will be computed using Kaplan-Meier method for pooled indications and selected individual indications. The corresponding 95% confidence interval for median OS will be calculated via Brookmeyer and Crowley methodology using log-log transformation and corresponding 95% confidence interval for PFS(12) will be derived

Endpoint	Statistical Analysis Methods
	based on Greenwood formula.
[redacted]	[redacted]
[redacted]	[redacted]

10.3.2 Safety Analyses

All safety analyses will be performed on the treated population.

Endpoint	Statistical Analysis Methods
Primary **<u>Module A and B Safety Lead-in:</u>** Incidence of AEs, SAEs, drug-related AEs, AEs leading to discontinuation, and death. AEs will be graded according to CTCAE v4.03. Incidence of laboratory abnormalities Laboratory values will be graded according to CTCAE v4.03.	**<u>Module A and B Safety Lead-in:</u>** Frequency distribution of treated participants with AE using the worst CTC grade. Participants will only be counted (1) once at the preferred term (PT) level, (2) once at the system organ class (SOC) level, and (3) once in the 'Total participant' row at their worst CTC grade, regardless of SOC or PT. By Cohort. Lab shift table using the worst CTC grade per participant by Cohort.

Endpoint	Statistical Analysis Methods
Secondary **<u>All Cohorts A1-A5, B1-B5:</u>** Incidence of AEs, SAEs, drug-related AEs, AEs leading to discontinuation, and death. AEs will be graded according to CTCAE v4.03. Incidence of laboratory abnormalities Laboratory values will be graded according to CTCAE v4.03.	**<u>All Cohorts A1-A5, B1-B5:</u>** Frequency distribution of treated participants with AE using the worst CTC grade. Participants will only be counted (1) once at the preferred term (PT) level, (2) once at the system organ class (SOC) level, and (3) once in the 'Total participant' row at their worst CTC grade, regardless of SOC or PT. By Cohort. Lab shift table using the worst CTC grade per participant by Cohort.
[redacted]	[redacted]

[redacted]

10.3.5 Interim Analyses

Cohorts A1 and B1: No interim analysis for futility is planned, as the Cohorts are expected to be fully enrolled when the OS endpoint becomes available. However, in Module A if other indications are stopped for futility, enrollment in Module B may be initiated based on recommendations of the Steering Committee.

Cohorts A2 and B2: The interim futility analysis for Cohorts A2 and B2 (HGG) will be conducted using PFS(6) and after at least 8 participants have been followed for 6 months. In addition, all other available efficacy data will be evaluated in the futility analysis.

Cohorts A3 and B3: An interim analysis based on PFS(6) for futility only will be conducted after at least 8 of the planned number of participants are enrolled with 6 months follow-up. In addition all other available efficacy data will be evaluated in the futility analysis.

Cohorts A4 and B4: No interim analysis for futility is planned as the sample size is too small.

Cohorts A5 and B5: No interim analysis for futility is planned as it is comprised of many diverse histologies. However, in Module A if other indications are stopped for futility enrollment in Module B may be initiated based on the recommendation of the Steering Committee.

For Cohorts 2 and 3: the Bayesian statistical methodology is described in Bayesian Adaptive Methods for Clinical Trial by Berry et al published in Chapman and Hall (2011) and is outlined here with adaptations from Lee and Liu A predictive probability design for phase II cancer clinical trials.

Cohort 4 has a smaller sample size than the other cohorts (n=10) so it is not appropriate to add an interim analysis for futility. For Cohorts 2 and 3: The Bayesian statistical methodology is described in Bayesian Adaptive Methods for Clinical Trial by Berry et al published in Chapman and Hall (2011) and is outlined here with adaptations from Lee and Liu REF A predictive probability design for phase II cancer clinical trials. Clinical Trials. 2008 5(2):93-106.

1) Once 8 subjects have been followed for at least 6 months a Cox proportional hazards model will be fit to interim data and estimate of hazard rate obtained.
2) Based on memoryless property of exponential survival times will be generated for each subject conditional on the observed data using the estimated hazard rate and one-sample log rank test applied to the fully enrolled cohort. The simulated trial will be declared success if log rank is significant.
3) Simulations will be repeated 1000 times. The predictive probability of success is defined as the proportion of simulated trials that are declared success based on observed interim data.
4) If predictive probability of success is <20%, futility may be declared. The totality of data will be considered in any decision to stop the cohort.

Detailed simulations will be described in the Statistical Analysis Plan.

12. APPENDICES

APPENDIX 1 ABBREVIATIONS AND TRADEMARKS

Term	Definition
AA	anaplastic astrocytoma
ADA	anti-drug antibodies
AE	adverse event
AIDS	acquired immunodeficiency syndrome
ALT	alanine aminotransferase
AST	aspartate aminotransferase
AT/RT	atypical teratoid/rhabdoid tumor
AUC	area under the concentration-time curve
BICR	blinded independent central review committee
BMS	Bristol-Myers Squibb
BOR	best overall response
BP	blood pressure
BUN	blood urea nitrogen
C	Celsius
CBC	complete blood count
CFR	Code of Federal Regulations
cHL	classic Hodgkins lymphoma
CI	confidence interval
$C1^-$	chloride
CLcr	creatinine clearance
cm	centimeter
Cmax, CMAX	maximum observed concentration
CNS	Central nervous system
CR	complete response
CRC	colorectal cancer
CRF	Case Report Form, paper or electronic
CSF	cerebrospinal fluid
CV	coefficient of variation
DILI	Drug induced liver injury

Term	Definition
DIPG	diffuse intrinsic pontine glioma
dL	deciliter
DLT	dose limiting toxicity
DMC	Data monitoring committee
DNA	deoxyribonucleaic acid
DOR	duration of response
ECG	electrocardiogram
eCRF	electronic Case Report Form
EFS	event free survival
eg	exempli gratia (for example)
EOI	end of infusion
EOMES	eomesodermin
ESR	Expedited Safety Report
ETMR	embryonal tumor with multilayered rosettes
FDA	Food and Drug Administration
FFPE	formalin-fixed paraffin-embedded
FLAIR	fast fluid-attenuated inversion recovery
FSH	follicle stimulating hormone
GBM	glioblastoma
GCP	Good Clinical Practice
GFR	glomerular filtration rate
HBsAg	hepatitis B surface antigen
HBV	hepatitis B virus
HCC	hepatocellular carcinoma
HCG	human chorionic gonadotropin
HCV	hepatitis C virus
HCV-RNA	hepatitis C virus-ribonucleic acid
HGG	high grade glioma
HIV	Human Immunodeficiency Virus
HLA	human leukocyte antigen

Term	Definition
HR	heart rate; hazard ratio
IB	Investigator Brochure
ICD	implantable cardioverter defibrillator
ICF	informed consent form
ICH	International Conference on Harmonisation
ICOS	inducible T cell co-stimulator
ie	id est (that is)
IEC	Independent Ethics Committee
IHC	immunohistochemistry
IMAE	Immune-mediated adverse event
IMG	immunogenicity
IMP	investigational medicinal products
IND	Investigational New Drug Exemption
IP	investigational product
ir	immune-related
IRB	Institutional Review Board
IRT	Interactive Response Technology
IU	International Unit
IV	intravenous
K^+	potassium
KPS	Karnofsky Performance Score
kg	kilogram
L	liter
LAM	Lactation amenorrhea method
LDH	lactate dehydrogenase
LFT(s)	liver function test(s)
LPS	Lansky Play Score
mg	milligram
MGMT	O^6-methylguanylmethyltransferase
min	minute

Term	Definition
mL	milliliter
MLR	mixed lymphocyte reaction
MRI	magnetic resonance imaging
MS	mass spectrometry
MTD	maximum tolerated dose
µg	microgram
N	number of subjects or observations
N	Nivolumab (BMS-936558)
Na^+	sodium
NE	not evaluable
NSCLC	non-small cell lung carcinoma
OR	objective response
ORR	objective response rate
OS	overall survival
PBMC	peripheral blood mononuclear cell
PD	progressive disease
PD	pharmacodynamics
PD-1	Programmed cell death protein 1
PD-L1	Programmed cell death ligand 1
PFS	progression free survival
PK	pharmacokinetics
PO	per os (by mouth route of administration)
PR	partial response
QC	quality control
QD, qd	quaque die, once daily
R^2	coefficient of determination
RANO	Radiologic Assessment in Neuro-Oncology
RBC	red blood cell
RCC	Renal cell carcinoma
RT	radiotherapy

Term	Definition
SAE	serious adverse event
SCLC	squamous cell lung carcinoma
SD	standard deviation; stable disease
SmPC	Summary of Product Characteristics
SOP	Standard Operating Procedures
SSC	study steering committee
t	temperature
T	time
TAO	Trial Access Online, the BMS implementation of an EDC capability
TCR	T cell receptor
TILs	Tumor infiltrating lymphocytes
WBC	white blood cell
WHO	World Health Organization
WOCBP	women of childbearing potential

APPENDIX 2 STUDY GOVERNANCE CONSIDERATIONS

The term 'Participant' is used in the protocol to refer to a person who has consented to participate in the clinical research study. The term 'Subject' used in the eCRF is intended to refer to a person (Participant) who has consented to participate in the clinical research study.

REGULATORY AND ETHICAL CONSIDERATIONS

GOOD CLINICAL PRACTICE

This study will be conducted in accordance with:

- Good Clinical Practice (GCP),
- as defined by the International Council on Harmonisation (ICH)
- in accordance with the ethical principles underlying European Union Directive 2001/20/EC
- United States Code of Federal Regulations, Title 21, Part 50 (21CFR50)
- Consensus ethical principles derived from international guidelines including the Declaration of Helsinki and Council for International Organizations of Medical Sciences (CIOMS) International Ethical Guidelines
- applicable local requirements.

The study will be conducted in compliance with the protocol. The protocol and any amendments and the participant informed consent will receive approval/favorable opinion by Institutional Review Board/Independent Ethics Committee (IRB/IEC), and regulatory authorities according to applicable local regulations prior to initiation of the study.

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

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

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

INSTITUTIONAL REVIEW BOARD/INDEPENDENT ETHICS COMMITTEE

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

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

COMPLIANCE WITH THE PROTOCOL AND PROTOCOL REVISIONS

The investigator should not implement any deviation or change to the protocol without prior review and documented approval/favorable opinion of an amendment from the IRB/IEC (and if applicable, also by local health authority) except where necessary to eliminate an immediate hazard(s) to study subjects.

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

- IRB/IEC for
- Regulatory Authority(ies), if applicable by local regulations (per national requirements)

Documentation of approval/favorable opinion signed by the chairperson or designee of the IRB(s)/IEC(s) and if applicable, also by local health authority must be sent to BMS.

If an amendment substantially alters the study design or increases the potential risk to the participant: (1) the consent form must be revised and submitted to the IRB(s)/IEC(s) for review and approval/favorable opinion; (2) the revised form must be used to obtain consent from subjects currently enrolled in the study if they are affected by the amendment; and (3) the new form must be used to obtain consent from new subjects prior to enrollment.

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

FINANCIAL DISCLOSURE

Investigators and sub-Investigators will provide the Sponsor with sufficient, accurate financial information in accordance with local regulations to allow the Sponsor to submit complete and accurate financial certification or disclosure statements to the appropriate health authorities. Investigators are responsible for providing information on financial interests during the course of the study and for 1 year after completion of the study.

INFORMED CONSENT PROCESS

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

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

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

Investigators must:

- Provide a copy of the consent form and written information about the study in the language in which the participant is most proficient prior to clinical study participation. The language must be non-technical and easily understood.
- Allow time necessary for participant or participant's legally acceptable representative to inquire about the details of the study.
- Obtain an informed consent signed and personally dated by the participant or the participant's legally acceptable representative and by the person who conducted the informed consent discussion.
- Obtain the IRB/IEC's written approval/favorable opinion of the written informed consent form and any other information to be provided to the subjects, prior to the beginning of the study, and after any revisions are completed for new information.

If informed consent is initially given by a participant's legally acceptable representative or legal guardian, and the participant subsequently becomes capable of making and communicating his or her informed consent during the study, consent must additionally be obtained from the participant.

Revise the informed consent whenever important new information becomes available that is relevant to the participant's consent. The investigator, or a person designated by the investigator, should fully inform the participant or the participant's legally acceptable representative or legal guardian, of all pertinent aspects of the study and of any new information relevant to the participant's willingness to continue participation in the study. This communication should be documented.

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

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

For minors, according to local legislation, one or both parents or a legally acceptable representative must be informed of the study procedures and must sign the informed consent form approved for the study prior to clinical study participation. The explicit wish of a minor, who is capable of forming an opinion and assessing this information to refuse participation in, or to be withdrawn from, the clinical study at any time should be considered by the investigator.

Minors who are judged to be of an age of reason must also give their written assent.

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

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

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

SOURCE DOCUMENTS

The Investigator is responsible for ensuring that the source data are accurate, legible, contemporaneous, original and attributable, whether the data are hand-written on paper or entered electronically. If source data are created (first entered), modified, maintained, archived, retrieved, or transmitted electronically via computerized systems (and/or any other kind of electronic devices) as part of regulated clinical trial activities, such systems must be compliant with all applicable laws and regulations governing use of electronic records and/or electronic signatures. Such systems may include, but are not limited to, electronic medical/health records (EMRs/EHRs), adverse event tracking/reporting, protocol required assessments, and/or drug accountability records).

When paper records from such systems are used in place of electronic format to perform regulated activities, such paper records should be certified copies. A certified copy consists of a copy of original information that has been verified, as indicated by a dated signature, as an exact copy having all of the same attributes and information as the original.

STUDY TREATMENT RECORDS

Records for study treatments nivolumab and ipilimumab (whether supplied by BMS, its vendors, or the site) must substantiate study treatment integrity and traceability from receipt, preparation, administration, and through destruction or return. Records must be made available for review at the request of BMS/designee or a Health Authority.

If	Then
Supplied by BMS (or its vendors):	Records or logs must comply with applicable regulations and guidelines and should include: • amount received and placed in storage area • amount currently in storage area • label identification number or batch number • amount dispensed to and returned by each participant, including unique participant identifiers • amount transferred to another area/site for dispensing or storage • nonstudy disposition (e.g., lost, wasted) • amount destroyed at study site, if applicable • amount returned to BMS • retain samples for bioavailability/bioequivalence, if applicable • dates and initials of person responsible for Investigational Product dispensing/accountability, as per the Delegation of Authority Form.
Sourced by site, and not supplied by BMS or its vendors (examples include IP sourced from the sites stock or commercial supply, or a specialty pharmacy)	The investigator or designee accepts responsibility for documenting traceability and study drug integrity in accordance with requirements applicable under law and the SOPs/standards of the sourcing pharmacy. These records should include: • label identification number or batch number • amount dispensed to and returned by each participant, including unique participant identifiers • dates and initials of person responsible for Investigational Product dispensing/accountability, as per the Delegation of Authority Form.

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

CASE REPORT FORMS

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

For sites using the Sponsor or designee electronic data capture tool, electronic CRFs will be prepared for all data collection fields except for fields specific to SAEs and pregnancy, which will be reported on the electronic SAE form and Pregnancy Surveillance form, respectively. If electronic SAE form is not available, a paper SAE form can be used. Spaces may be left blank only in those circumstances permitted by study-specific CRF completion guidelines provided by Sponsor or designee.

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

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

The completed CRF, SAE/pregnancy CRFs, must be promptly reviewed, signed, and dated by the investigator or qualified physician who is a subinvestigator and who is delegated this task on the Delegation of Authority Form. Subinvestigators in Japan may not be delegated the CRF approval task. For electronic CRFs, review and approval/signature is completed electronically through the BMS electronic data capture tool. The investigator must retain a copy of the CRFs including records of the changes and corrections.

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

MONITORING

Sponsor or designee representatives will review data centrally to identify potential issues to determine a schedule of on-site visits for targeted review of study records.

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

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

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

RECORDS RETENTION

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

BMS or designee will notify the investigator (or head of the study site in Japan) when the study records are no longer needed.

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

RETURN OF STUDY TREATMENT

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

If..	Then
Study treatments supplied by BMS (including its vendors	Any unused study treatments supplied by BMS can only be destroyed after being inspected and reconciled by the responsible Study Monitor unless study treatments containers must be immediately destroyed as required for safety, or to meet local regulations (eg, cytotoxics or biologics). If study treatments will be returned, the return will be arranged by the responsible Study Monitor.
Study treatments sourced by site, not supplied by BMS (or its vendors) (examples include study treatments sourced from the sites stock or commercial supply, or a specialty pharmacy)	It is the investigator's or designee's responsibility to dispose of all containers according to the institutional guidelines and procedures.

It is the investigator's or designee's responsibility to arrange for disposal, 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. The following minimal standards must be met:

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

It is the investigator's or designee's responsibility to arrange for disposal of all empty containers.

If conditions for destruction cannot be met the responsible Study Monitor will make arrangements for return of study treatments provided by BMS (or its vendors). Destruction of non- study treatments sourced by the site, not supplied by BMS, is solely the responsibility of the investigator or designee.

For this study, study treatments (those supplied by BMS or its vendors) such as full or partially used study treatment containers, vials, syringes cannot be destroyed on-site.

It is however, the investigator's or designee's responsibility to arrange for disposal of all empty study treatment 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. The return of full or partially used study treatments supplied by BMS or its vendors will be arranged by the responsible Study Monitor.

CLINICAL STUDY REPORT AND PUBLICATIONS

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

For this protocol, the Signatory Investigator will be selected as appropriate based on the following criteria:

- External Principal Investigator designated at protocol development
- National Coordinating Investigator
- Study Steering Committee chair or their designee
- Participant recruitment (eg, among the top quartile of enrollers)
- Involvement in trial design
- Regional representation (eg, among top quartile of enrollers from a specified region or country)
- Other criteria (as determined by the study team)

The data collected during this study are confidential and proprietary to Sponsor or designee. Any publications or abstracts arising from this study must adhere to the publication requirements set forth in the clinical trial agreement (CTA) governing [Study site or Investigator] participation in the study. These requirements include, but are not limited to, submitting proposed publications to Sponsor or designee at the earliest practicable time prior to submission or presentation and otherwise within the time period set forth in the CTA.

APPENDIX 3 ADVERSE EVENTS AND SERIOUS ADVERSE EVENTS: DEFINITIONS AND PROCEDURES FOR RECORDING, EVALUATING, FOLLOW UP AND REPORTING

ADVERSE EVENTS

Adverse Event Definition:
An Adverse Event (AE) is defined as any new untoward medical occurrence or worsening of a preexisting medical condition in a clinical investigation participant administered study drug 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 study drug, whether or not considered related to the study drug.

SERIOUS ADVERSE EVENTS

Serious Adverse Event (SAE) is defined as any untoward medical occurrence that, at any dose:
Results in death
Is life-threatening (defined as an event in which the participant was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe)
Requires inpatient hospitalization or causes prolongation of existing hospitalization (see NOTE below) NOTE: The following hospitalizations are not considered SAEs in BMS clinical studies: o 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) o elective surgery, planned prior to signing consent o admissions as per protocol for a planned medical/surgical procedure o routine health assessment requiring admission for baseline/trending of health status (eg, routine colonoscopy) o medical/surgical admission other than to remedy ill health and planned prior to entry into the study. Appropriate documentation is required in these cases o 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) o admission for administration of anticancer therapy in the absence of any other SAEs (applies to oncology protocols)
Results in persistent or significant disability/incapacity
Is a congenital anomaly/birth defect
is an important medical event (defined as a medical event(s) that may not be immediately life-threatening or result in death or hospitalization but, based upon appropriate medical and scientific judgment, may jeopardize the participant or may require intervention [eg, medical, surgical] to prevent one of the other serious outcomes listed in the definition above.) Examples of such events include, but are not limited to, intensive treatment in an emergency room or at home for allergic bronchospasm; blood dyscrasias or convulsions that do not result in hospitalization.) Potential drug induced liver injury (DILI) is also considered an important medical event. (See Section 8.1.1 for the definition of potential DILI.)

Suspected transmission of an infectious agent (e.g., pathogenic or nonpathogenic) via the study treatment is an SAE.

Although pregnancy, overdose, cancer, and potential drug induced liver injury (DILI) are not always serious by regulatory definition, these events must be handled as SAEs. (See Section 9.2.5 for reporting pregnancies).

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

EVALUATING AES AND SAES

Assessment of Causality
The causal relationship to study drug is determined by a physician and should be used to assess all adverse events (AE). The causal relationship can be one of the following: Related: There is a reasonable causal relationship between study drug administration and the AE. Not related: There is not a reasonable causal relationship between study drug administration and the AE. The term "reasonable causal relationship" means there is evidence to suggest a causal relationship.

Follow-up of AEs and SAEs
If only limited information is initially available, follow-up reports are required. (Note: Follow-up SAE reports must include the same investigator term(s) initially reported.) If an ongoing SAE changes in its intensity or relationship to study drug or if new information becomes available, the SAE report must be updated and submitted within 24 hours to BMS (or designee) using the same procedure used for transmitting the initial SAE report. All SAEs must be followed to resolution or stabilization.

REPORTING OF SAES TO SPONSOR OR DESIGNEE

- SAEs, whether related or not related to study drug, and pregnancies must be reported to BMS (or designee) within 24 hours of awareness of the event.
- SAEs must be recorded on the SAE Report Form; pregnancies on a Pregnancy Surveillance Form (electronic or paper forms).
- The preferred method for SAE data reporting collection is through the eCRF.
- The paper SAE/pregnancy surveillance forms are only intended as a back-up option when the eCRF system is not functioning.
    - In this case, the paper forms are to be transmitted via email or confirmed facsimile (fax) transmission to:

SAE Email Address: Refer to Contact Information list.

SAE Facsimile Number: Refer to Contact Information list.

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

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

APPENDIX 4 WOMEN OF CHILDBEARING POTENTIAL DEFINITIONS AND METHODS OF CONTRACEPTION

DEFINITIONS

Woman of Childbearing Potential (WOCBP)

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

Women in the following categories are not considered WOCBP

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

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

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

CONTRACEPTION GUIDANCE FOR FEMALE PARTICIPANTS OF CHILD BEARING POTENTIAL

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

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

Highly Effective Contraceptive Methods That Are User Dependent *Failure rate of <1% per year when used consistently and correctly.*[a]
• Combined (estrogen- and progestogen-containing) hormonal contraception associated with inhibition of ovulation[b] – oral – intravaginal – transdermal

• Progestogen-only hormonal contraception associated with inhibition of ovulation[b] – oral – injectable
Highly Effective Methods That Are User Independent
• Implantable progestogen-only hormonal contraception associated with inhibition of ovulation [b] • Hormonal methods of contraception including oral contraceptive pills containing a combination of estrogen and progesterone, vaginal ring, injectables, implants and intrauterine hormone-releasing system (IUS)[c] • Intrauterine device (IUD)[c] • Bilateral tubal occlusion
• Vasectomized partner *A vasectomized partner is a highly effective contraception method provided that the partner is the sole male sexual partner of the WOCBP and the absence of sperm has been confirmed. If not, an additional highly effective method of contraception should be used.*
• Sexual abstinence *Sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the study drug. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the study and the preferred and usual lifestyle of the participant.* • It is not necessary to use any other method of contraception when complete abstinence is elected. • WOCBP participants who choose complete abstinence must continue to have pregnancy tests, as specified in Section 2. • Acceptable alternate methods of highly effective contraception must be discussed in the event that the WOCBP participants chooses to forego complete abstinence
NOTES: [a] Typical use failure rates may differ from those when used consistently and correctly. Use should be consistent with local regulations regarding the use of contraceptive methods for participants participating in clinical studies. [b] Hormonal contraception may be susceptible to interaction with the study drug, which may reduce the efficacy of the contraceptive method. Hormonal contraception is permissible only when there is sufficient evidence that the IMP and other study medications will not alter hormonal exposures such that contraception would be ineffective or result in increased exposures that could be potentially hazardous. In this case, alternative methods of contraception should be utilized. [c] Intrauterine devices and intrauterine hormone releasing systems are acceptable methods of contraception in the absence of definitive drug interaction studies when hormone exposures from intrauterine devices do not alter contraception effectiveness

Unacceptable Methods of Contraception
• Male or female condom with or without spermicide.[1, 2] Male and female condoms cannot be used simultaneously • Diaphragm with spermicide • Cervical cap with spermicide • Vaginal Sponge with spermicide • Progestogen-only oral hormonal contraception, where inhibition of ovulation is not the primary mechanism of action • Periodic abstinence (calendar, symptothermal, post-ovulation methods) • Withdrawal (coitus interruptus). • Spermicide only • Lactation amenorrhea method (LAM)

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

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

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

COLLECTION OF PREGNANCY INFORMATION

Guidance for collection of Pregnancy Information and outcome of pregnancy on the Pregnancy Surveillance Form is provided in Section 9.2.5 and the Appendix for Adverse Events and Serious Adverse Events Definitions and procedures for Evaluating, Follow-up and Reporting.

APPENDIX 6 KARNOFSKY AND LANSKY CRITERIA

STATUS		STATUS
KARNOFSKY	**LANSKY**	**KARNOFSKY or LANSKY**
Normal, no complaints	Fully active, normal	100
Able to carry on normal activities; minor signs or symptoms of disease	Minor restrictions in physically strenuous activity	90
Normal activity with effort; some signs or symptoms of disease	Active, but tires more quickly	80
Cares for self. Unable to carry on normal activity or to do active work	Substantial restriction of, and less time spent, in play activity	70
Requires occasional assistance, but able to care for most of his needs	Out of bed, but minimal active play; keeps busy with quiet activities	60
Requires considerable assistance and frequent medical care	Gets dressed, but inactive much of day; no active play, able to participate in quiet play	50
Disabled. Requires special care and assistance	Mostly in bed; participates in some quiet activities	40
Severely disabled. Hospitalization indicated though death non imminent	In bed; needs assistance even for quiet play	30
Very sick. Hospitalization necessary. Active supportive treatment necessary	Often sleeping; play limited to passive activities	20
Moribund	No play; does not get out of bed	10