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Clinical Protocol CA209647

A Phase 2, Open-label, Single-arm, Two-cohort Study of Nivolumab in Relapsed/Refractory Primary Central Nervous System Lymphoma (PCNSL) or Relapsed/Refractory Primary Testicular Lymphoma (PTL)

(CheckMate 647: CHECKpoint pathway and nivoluMAB clinical Trial Evaluation 647)

Revised Protocol Number: 04

Study Director/Medical Monitor

Manish Sharma, MD

[redacted]

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 04	29-Nov-2017	To characterize nivolumab pharmacokinetic [redacted] in the cerebrospinal fluid (CSF), lumbar puncture(s) (optional) have been added and will be obtained from consenting patients with relapsed/refractory PCNSL or relapsed/refractory PTL with CNS involvement. [redacted].
Administrative Letter 06	04-Sep-2017	Corrected the appendix 6 of the protocol (Tumor Flare; Treatment strategies during TF) by removing the CTCAE classification of cerebral edema.
Revised Protocol 03	07-Apr-2017	Incorporates Amendment(s) 09
Amendment 09	07-Apr-2017	• Changes to eligibility – To allow enrollment of subjects with PTL who undergo orchiectomy – To allow enrollment of subjects with PTL with measurable nodule disease – To specify more precisely the first line of therapy in PCNSL and PTL – To exclude subjects with significantly increased risk for bleeding complications – To lower the dose of dexamethasone or equivalent allowed 14 days prior to first dose of nivolumab to less than or equal to 2 mg/day. • The use of CT Scans without PET scans will not be allowed for assessment for subjects with PTL. • Added the possibility for administrative interim analyses. • Recommendations for the management of Tumor Flare have been added as Appendix 6. • Incorporates changes per Administrative Letters 04, 03, and 02.
Administrative Letter 04	07-Feb-2017	Change Medical Monitor address.
Administrative Letter 03	17-Nov-2016	To further clarify protocol requirements for tumor tissue submission at screening and correct typographic errors in Table 5.1-2.
Administrative Letter 02	20-Oct-2016	Clarify the protocol requirements for tumor tissue submission at screening.
Revised Protocol 02	05-Oct-2016	Incorporates Amendment(s) 05
Amendment 05	05-Oct-2016	• To reflect update in the treatment management algorithms to be consistent with the updated nivolumab investigator brochure (IB) V15, updates to the acceptable methods of contraception in order to be consistent with the most recent version of BMS SOP and IB V15.

Document	Date of Issue	Summary of Change
		• To allow the enrollment of patients with PCNSL that cannot produce a minimum of 25 slides [redacted]. • [redacted] • Other changes were made to resolve minor inconsistencies or to provide clarifications.
Revised Protocol 01	22-Jun-2016	Incorporates Amendment(s) 01
Amendment 01	22-Jun-2016	• Subjects in the cohorts with PCNSL and PTL with brain and or spinal lesions are allowed to enroll if they are on 4 mg per day or less of dexamethasone. • Subjects who had undergone allogeneic stem cell transplant > 12 months prior to first dose of study drug, have no evidence of active graft versus host disease, and are not on systemic immunosuppressive therapy are allowed to participate in the study. • Neurologic Assessment in Neuro-Oncology (NANO) has been incorporated in the exploratory endpoints in the protocol. • If the dose of dexamethasone is increased during the screening period following the screening MRI, and if there is clinical worsening in neurological symptoms following the MRI, the MRI must be repeated. • Due to the rapidly progressing nature of CNS tumors, a brain MRI is to be performed within 14 days before the first dose of study treatment in both cohorts in order to accurately reflect the disease burden. • Language was added for the collection of prospective blood samples, and for BMS to retain residual blood and tissue samples, so that scientists can perform additional research. • Incorporation of other minor changes to correct and/or clarify protocol requirements.
Original Protocol	13-Apr-2016	Not applicable

OVERALL RATIONALE FOR THE REVISED PROTOCOL 04

Revised Protocol 04 incorporates changes that will allow for the characterization of nivolumab pharmacokinetics (PK) in paired cerebrospinal fluid (CSF) and blood samples, [redacted] in the CSF of patients with relapsed/refractory PCNSL or relapsed/refractory PTL with central nervous system (CNS) involvement, who consent for lumbar puncture. The collection of CSF is an optional assessment; consent for the lumbar puncture is required.

[redacted].

All revisions apply to future and currently enrolled patients.

SUMMARY OF KEY CHANGES OF REVISED PROTOCOL 04

Section Number & Title	Description of Change	Brief Rationale
[redacted]		
• Section 5.1, Flow Chart/Time and Events Schedule Table 5.1-2. CSF assessment note	• The note for the CSF on-treatment assessment was revised to include text for collection of CSF for nivolumab PK and select biomarkers, and paired blood samples for PK (optional consent required). •	[redacted]
• Section 5.1, Flow Chart/Time and Events Schedule Table 5.1-2. PK and	• Paired CSF and Blood PK and [redacted] added to procedures; • Table 5.5-2 (added) provides sampling details.	

SUMMARY OF KEY CHANGES OF REVISED PROTOCOL 04		
Section Number & Title	**Description of Change**	**Brief Rationale**
Immunogenicity Assessments		
• Section 5.5, Pharmacokinetic [redacted]	• Section 5.5 was revised and retitled to incorporate (optional) paired CSF collection and blood samples for PK, [redacted]. The previous title of this section was Pharmacokinetic Assessments • Table 5.5-1, Pharmacokinetic & Immunogenicity Sample Scheduling was revised to Pharmacokinetic & Immunogenicity Blood Sample Scheduling • Table 5.5-2, Paired Cerebrospinal Fluid & Blood Sampling Schedule has been added. This table provides the schedule for collection of paired CSF and blood samples for patients who consent to lumbar puncture. Footnotes provide additional guidance and instruction. • For patients who are on-study prior to Revised Protocol 04, paired sampling CSF and blood sampling should begin with the cycle the patients are on.	[redacted]

SUMMARY OF KEY CHANGES OF REVISED PROTOCOL 04		
Section Number & Title	**Description of Change**	**Brief Rationale**
• Section 5.5.1, Pharmacokinetic [redacted] Sample Analysis	Section 5.5.1 was revised and retitled to incorporate CSF collection (optional) for PK [redacted] characterization. The previous title of this section was Pharmacokinetic Sample Analysis.	

[redacted]

SUMMARY OF KEY CHANGES OF REVISED PROTOCOL 04		
Section Number & Title	**Description of Change**	**Brief Rationale**
	[redacted]	
Throughout the protocol	Minor editorial corrections or changes.	Minor, rationale not required.

SYNOPSIS

Clinical Protocol CA209647

Protocol Title: A Phase 2, Open-label, Single-arm, Two-cohort Study of Nivolumab in Relapsed/Refractory Primary Central Nervous System Lymphoma (PCNSL) or Relapsed/Refractory Primary Testicular Lymphoma (PTL)

(CheckMate 647: CHECKpoint pathway and nivoluMAB clinical Trial Evaluation 647)

Investigational Product(s), Dose and Mode of Administration, Duration of Treatment with Investigational Product(s): Nivolumab (BMS-936558) monotherapy administered intravenously (IV) 240 mg every 2 weeks (Q2W) for 8 cycles, followed by 480 mg every 4 weeks (Q4W) for a total treatment duration of 2 years, or until progressive disease (PD), unacceptable toxicity, or withdrawal of consent.

Study Phase: 2

Research Hypothesis: Treatment with nivolumab will demonstrate clinically meaningful efficacy in subjects with relapsed/refractory PCNSL or PTL.

Objectives:

Primary Objectives:

To assess the clinical benefit of nivolumab in subjects with relapsed/refractory PCNSL or relapsed/refractory PTL as measured by overall response rate (ORR) by blinded Independent Central Review (BICR).

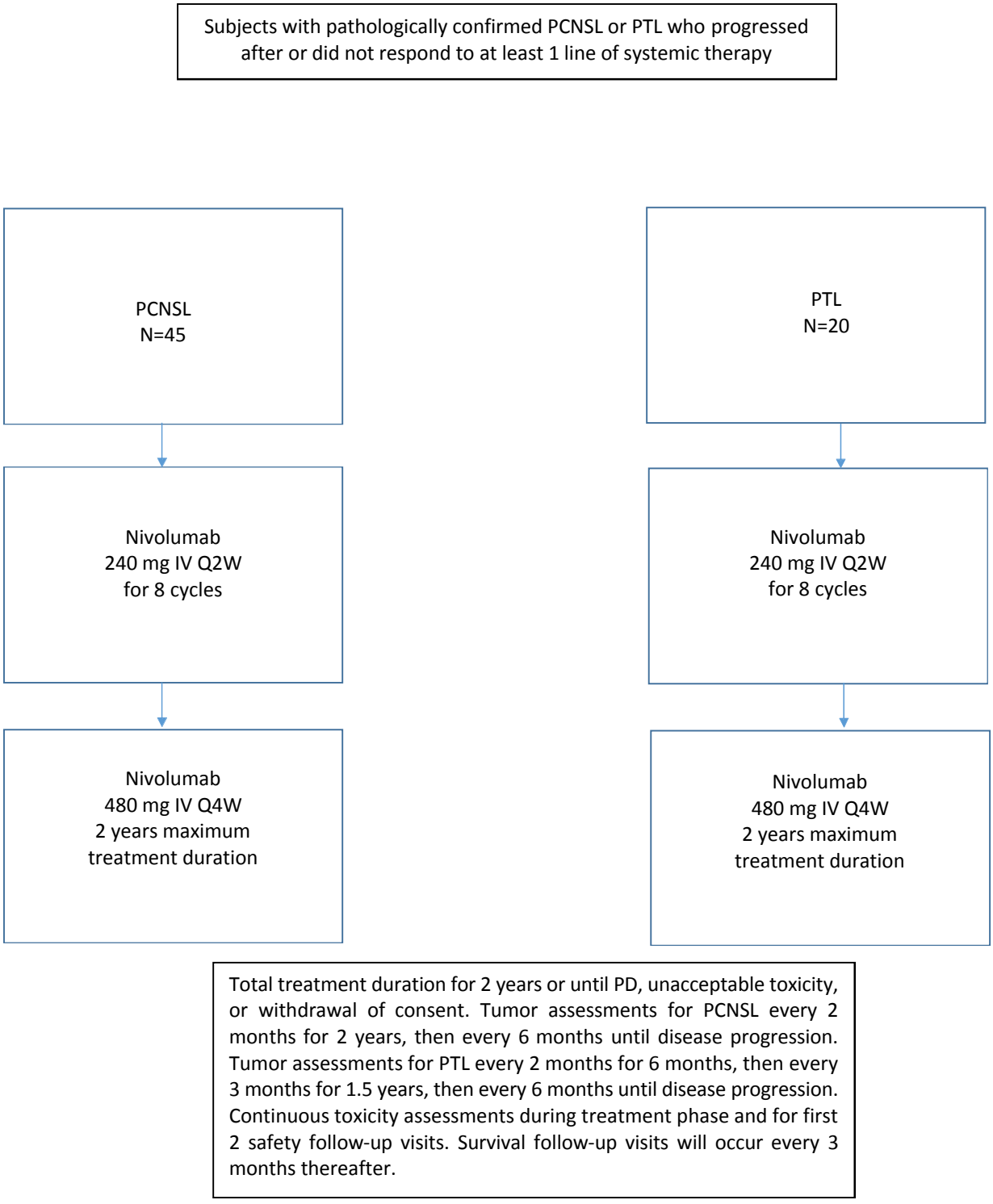
Secondary Objectives:

- To assess progression-free survival (PFS) based on BICR assessment for PCNSL or PTL, respectively
- To assess ORR and duration of response (DOR) based on investigator assessment for PCNSL or PTL, respectively
- To assess overall survival (OS) for PCNSL or PTL, respectively

[redacted].

Study Design: This is a Phase 2 open-label study to evaluate the safety and efficacy of nivolumab in subjects with relapsed/refractory PCNSL or PTL (Figure 1). Subjects should receive nivolumab at a dose of 240 mg as a 30-minute infusion on Day 1 of each treatment cycle for 8 cycle. Beginning with Cycle 9, subjects should receive nivolumab at a dose of 480 mg as a 30-minute infusion every 4 weeks (+/- 3 days), for a total of 2 years of treatment, or until progressive disease, unacceptable toxicity, or withdrawal of consent. Subjects should begin study treatment within 3 calendar days of treatment assignment.

Figure 1: **Study Design**



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

Inclusion criteria:

a) Men and women, age ≥ 18 years old at the time of screening
b) Subjects with pathologically confirmed PCNSL or PTL who progressed after or did not respond to at least 1 line of systemic therapy (PCNSL prior therapy may include: high-dose methotrexate [HD-MTX], HD-MTX based regimen, high dose cytarabine, radiation therapy alone as treatment or as part of consolidation therapy, high-dose therapy with autologous stem cell transplant as part of consolidation therapy, and/or intraocular MTX alone or as part of consolidation therapy; PTL prior therapy may include: chemoimmunotherapy such as CHOP-R or any other regimens, with/without prophylactic radiation to contralateral testis or orchiectomy or intrathecal chemotherapy)
c) Radiologically measurable disease within 28 days of first dose
d) Karnofsky performance status of 70 or higher

Exclusion criteria:

a) Intraocular PCNSL without evidence of brain disease. Patients with prior history of intraocular involvement treated only with intraocular methotrexate and no prior systemic therapy are excluded.
b) PCNSL with systemic disease
c) PCNSL patients who cannot undergo magnetic resonance imaging assessments
d) Patients with brain stem lesions
e) Active, known, or suspected autoimmune disease
f) Known history of positive test for human immunodeficiency virus or known acquired immunodeficiency syndrome
g) Prior treatment with an anti-programmed death ligand (PD)-1, anti-PD-L1, anti-PD-L2, anti-CD137, or anti-CTLA-4 antibody, or any other antibody or drug specifically targeting T-cell co-stimulation or checkpoint pathways

Study Drug: Includes both Investigational (Medicinal) Products (IP/IMP) and Non-investigational (Medicinal) Products (Non-IP/Non-IMP) as listed in Table 1.

Table 1: Study Drug for CA209647

Medication	Potency	IP/Non-IP
Nivolumab	100 mg (10 mg/mL) and 40 mg (10mg/mL)	IP

Study Assessments: The primary endpoint is BICR-assessed ORR, and will be analyzed 6 months after last patient first treatment in each cohort. All treated subjects will be evaluated. The BICR-assessed objective response will be further characterized by the DOR. DOR is defined as the time from first response (partial response [PR] or complete response [CR]) to the date of initial objectively documented progression as determined using the International Primary CNS Lymphoma Collaborative Group (IPCG) criteria for PCNSL and Lugano 2014 response evaluation for PTL, as determined by BICR, or death due to any cause, whichever occurs first. The secondary endpoints are PFS based on BICR assessment, ORR and DOR based on investigator assessment, and OS. Tumor assessments for PCNSL will occur every 2 months for 2 years, then every 6 months until disease progression. Tumor assessments for PTL will occur every 2 months for 6 months, then every 3 months for 1.5 years, then every 6 months until disease progression. Toxicity assessments will be continuous during the treatment phase as well as during the first 2 safety follow-up visits.

Once subjects reach the survival follow-up phase, either in-person visits or documented telephone calls to assess the subject's status are acceptable.

Statistical Considerations:

Sample Size:

The planned sample size for this study will be approximately 65 treated subjects, placed into 2 cohorts of subjects: PCNSL (N = 45), and PTL (N = 20).

In addition, Table 2 summarizes the 95% exact confidence interval (CI) for the target ORRs ranging from 28.9% to 60% with sample size of 20 and 45. At observed ORR ≥ 28.9% with 45 PCNSL subjects, the lower bound of the 95% CI excludes the historical response rates in of 14% in recurrent primary central nervous system lymphoma. At observed ORR ≥ 40% with 20 PTL subjects, the lower bound of the 95% CI excludes the response rate of 14%.

The sample size for the PCNSL cohort was empirically determined to support expanded assessment of the benefit-risk profile of nivolumab in PCNSL through observation of less common safety events. In particular, administration of nivolumab to 45 subjects provides 90% probability of observing at least 1 occurrence of any adverse event that would occur with 5% incidence in the population from which the sample is drawn.

Table 2: Observed ORR with Exact 95 % CI

N	ORR	95% Exact CI
20	30%	[11.9% - 54.3%]
	35%	[15.4% - 59.2%]
	40%	[19.1% - 63.9%]
	50%	[27.2% - 72.8%]
	60%	[36.1% - 80.9%]
45	28.9%	[16.4% - 44.3%]
	40.0%	[25.7% - 55.7%]
	51.1%	[35.8% - 66.3%]
	60%	[44.3% - 74.3%]

Endpoints:

The primary objective will be measured by the primary endpoint of BICR-assessed ORR. It is defined as the number of subjects with a BOR of CR or PR, based on the IPCG criteria for PCNSL, and Lugano Classification 2014 response evaluation for PTL, divided by the number of treated subjects within each cohort.

The BICR-assessed BOR is defined as the best response designation recorded between the date of first dose and the date of initial objectively documented progression per criteria or the date of subsequent therapy, whichever occurs first.

The BICR-assessed PFS is defined as the time from first dosing date to the date of the first documented progression per criteria, as determined by BICR, or death due to any cause, whichever occurs first.

Investigator-assessed ORR and DOR are defined similarly as described for ORR and DOR per BICR assessment above, but will be assessed per investigator.

Analyses:

All analyses will be performed separately for each cohort.

The analysis of the primary endpoint in each cohort will occur at least 6 months after last patient first treatment of each cohort.

The ORR based on BICR assessment will be summarized by binomial response rates and their corresponding two-sided 95% exact CIs using the Clopper-Pearson method. The analysis of ORR per investigator is similar as ORR analysis per BICR, but based on investigator assessment.

DOR based on BICR assessment will be summarized for subjects who achieve PR or CR using the Kaplan-Meier product-limit method. Median values of DOR along with 2-sided 95% CIs and range will also be calculated. The same analysis will be performed for the duration of CR.

PFS based on BICR assessment and OS will be summarized by the Kaplan-Meier product-limit method. Median values along with two-sided 95% CIs based on the log-log transformation, will be calculated. The PFS rate at 6, 12, and 24 months will also be calculated.

The analysis of ORR and DOR per investigator is similar as ORR and DOR analysis per BICR, but based on investigator assessment.

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[redacted]

1.2 Research Hypothesis

Treatment with nivolumab will demonstrate clinically meaningful efficacy in subjects with relapsed/refractory PCNSL or PTL.

1.3 Objectives(s)

1.3.1 Primary Objective

To assess the clinical benefit of nivolumab in subjects with relapsed/refractory PCNSL or relapsed/refractory PTL as measured by ORR by blinded Independent Central Review (BICR).

1.3.2 Secondary Objectives

- To assess PFS based on BICR assessment for PCNSL or PTL, respectively
- To assess ORR and DOR based on investigator assessment for PCNSL or PTL, respectively
- To assess overall survival (OS) for PCNSL or PTL, respectively

[redacted]

[redacted]

2 ETHICAL CONSIDERATIONS

2.1 Good Clinical Practice

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

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

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

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

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

2.2 Institutional Review Board/Independent Ethics Committee

Before study initiation, the investigator must have written and dated approval/favorable opinion from the IRB/IEC for the protocol, consent form, subject recruitment materials (eg, advertisements), and any other written information to be provided to subjects. The investigator or BMS should also provide the IRB/IEC with a copy of the Investigator Brochure[64] or product labeling information to be provided to subjects and any updates.

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

2.3 Informed Consent

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

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

BMS will provide the investigator with an appropriate (ie, Global or Local) sample informed consent form (ICF) which will include all elements required by ICH, GCP, and applicable

regulatory requirements. The sample ICF will adhere to the ethical principles that have their origin in the Declaration of Helsinki.

Investigators must ensure the following:

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

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

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

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

3 INVESTIGATIONAL PLAN

3.1 Study Design and Duration

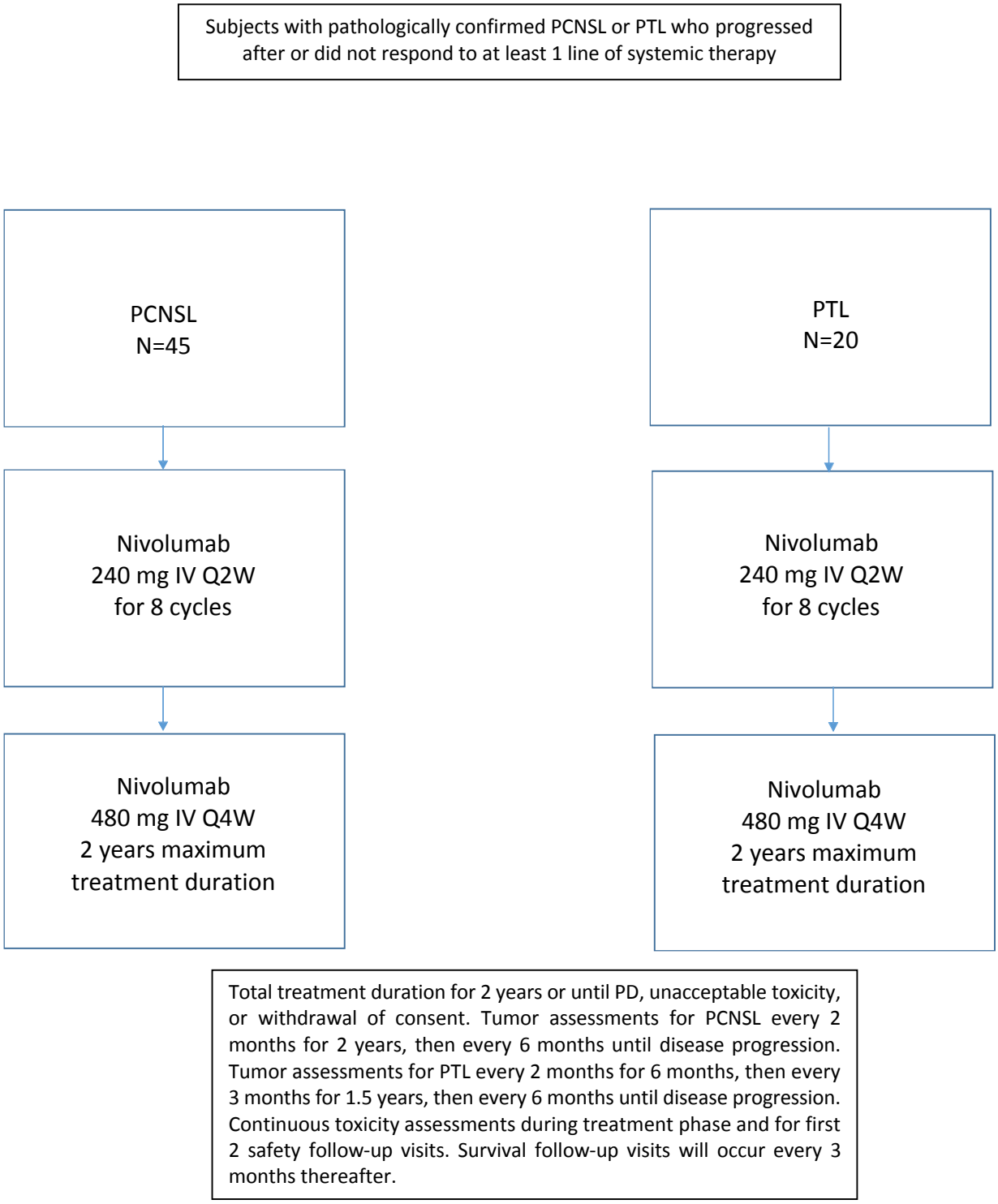
CA209647 is a Phase 2, open-label, single-arm, 2-cohort study to estimate the safety and efficacy of nivolumab in subjects with relapsed/refractory PCNSL or PTL. Nivolumab 240 mg will be given every 2 weeks for 8 cycles. Beginning with Cycle 9, nivolumab 480 mg will be given every 4 weeks for a total therapy duration of 2 years, or until progressive disease, unacceptable toxicity, or withdrawal of consent. Nivolumab will be administered as a 30-minute infusion. A finite treatment duration with immune therapies in this patient population remains an area of ongoing research; therefore the treatment duration chosen was 2 years.

The study will further characterize safety and evaluate the antitumor activity of nivolumab in subjects with relapsed/refractory PCNSL or PTL who progressed after or did not respond to at least 1 line of systemic therapy.

The primary endpoint is BICR-assessed ORR, and will be analyzed 6 months after last patient first treatment in each cohort.

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

Figure 3.1-1: Study Design Schematic



3.2 Post Study Access to Therapy

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

through another mechanism at the discretion of BMS. BMS reserves the right to terminate access to BMS-supplied study drug if any of the following occur: a) the marketing application is rejected by a responsible health authority; b) the study is terminated due to safety concerns; c) the subject can obtain medication from a government-sponsored or private health program; or d) therapeutic alternatives become available in the local market.

3.3 Study Population

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

3.3.1 Inclusion Criteria

1. Signed Written Informed Consent

a) Subjects must have signed and dated an IRB/IEC approved written informed consent form in accordance with regulatory and institutional guidelines. This must be obtained before the performance of any protocol-related procedures that are not part of normal subject care.

b) Subject must be willing and able to comply with scheduled visits, treatment schedule, laboratory tests, and other requirements of the study.

2. Target Population

a) Subject must be 18 years of age or older

b) Subjects with pathologically confirmed PCNSL or PTL who progressed after or did not respond to at least 1 line of systemic therapy

i) PCNSL prior therapy may include HD-MTX, HD-MTX-based regimen, high-dose cytarabine, radiation therapy alone as treatment or as part of consolidation therapy, high-dose therapy with autologous stem cell transplant as part of consolidation therapy, and/or intraocular MTX alone or as part of consolidation therapy

ii) PTL prior therapy may include chemo-immunotherapy (eg, CHOP-R or any other regimens), with/without prophylactic RT to contralateral testis or orchiectomy or intrathecal chemotherapy

c) Measurable disease requirements on scans done within 28 days of first dose (14 days for MRI of the brain):

i) PCNSL subjects should have at least 1 measurable extranodal brain lesion with the longest diameter > 1.0 cm on Gd-enhanced MRI

ii) PTL subjects should have either at least 1 measurable extranodal lesion with the longest diameter > 1.0 cm or at least 1 measurable nodal lesion with the longest diameter > 1.5 cm on fluorodeoxyglucose (FDG) PET/CT scan

d) Archived tumor block or unstained slides from biopsy. Histologically confirmed tissue will be required from the time of relapse or at the time of initial surgery.

e) Subjects must have a Karnofsky performance status of 70-100 (Appendix 2)

f) Subject re-enrollment: This study permits the re-enrollment of a subject that has discontinued the study as a pre-treatment failure (ie, subject has not been treated). If

re-enrolled, the subject must be re-consented and assigned a new subject number by the IVRS.

g) Subjects with prior history of allogeneic transplant can participate if the transplant was performed at least 6 or more months before screening. If there is no prior history of Grade 2 + acute graft versus host disease (GVHD), no history of extensive or Grade 4 chronic GVHD, or no immunosuppressive therapy for a minimum of 4 weeks with no clinically apparent GVHD.

3. Physical and Laboratory Test Findings

Screening laboratory values must meet the following criteria (using Common Terminology Criteria for Adverse Events [CTCAE] v4.03):

a) White blood count (WBC) ≥ 2000/uL

b) Neutrophils ≥ 1500/uL

c) Platelets ≥ $100x10^3$/uL

d) Hemoglobin ≥ 9.0 g/dL

e) Serum creatinine ≤ 1.5x upper limit of normal (ULN) or calculated creatinine clearance > 50 mL/min (using the Cockcroft-Gault formula)

$$\text{Female CrCl} = \frac{(140 - \text{age in years}) \times \text{weight in kg} \times 0.85}{72 \times \text{serum creatinine in mg/dL}}$$

$$\text{Male CrCl} = \frac{(140 - \text{age in years}) \times \text{weight in kg} \times 1.00}{72 \times \text{serum creatinine in mg/dL}}$$

f) Aspartate aminotransferase (AST) and alanine aminotransferase (ALT) ≤ 3.0 x ULN

g) Total bilirubin (TBILI) ≤ 1.5 x ULN (except subjects with Gilbert Syndrome who must have a total bilirubin level of < 3.0xULN)

4. Age and Reproductive Status

a) 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) within 24 hours prior to the start of study drug

b) Women must not be pregnant or breastfeeding

c) 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 {i.e., 30 days (duration of ovulatory cycle) plus the time required for the investigational drug to undergo approximately five half-lives.}

d) 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 {i.e., 90 days (duration of sperm turnover) plus the time required for the investigational drug to undergo approximately five half-lives.}

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

At a minimum, subjects must agree to use 1 highly effective method of contraception as listed in Appendix 1.

3.3.2 Exclusion Criteria

1. Target Disease Exceptions

a) Intraocular PCNSL without evidence of brain disease. Patients with prior history of intraocular involvement treated only with intraocular methotrexate and no prior systemic therapy are excluded.

b) PCNSL patients who cannot undergo MRI with contrast assessments

c) PCNSL patients with systemic disease

d) Patients with brain stem lesions

2. Medical History and Concurrent Diseases

a) Subjects with an active, known, or suspected autoimmune disease. Subjects 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) Subjects with a condition requiring systemic treatment with either corticosteroids (> 10 mg daily prednisone equivalent) or other immunosuppressive medications within 14 days of start of study treatment. Inhaled or topical steroids, and adrenal replacement steroid doses > 10 mg daily prednisone equivalent, are permitted in the absence of active autoimmune disease.[65,66]

For subjects with PCNSL and PTL with brain or spinal cord lesion: Subjects who have received 2 mg/day or less of dexamethasone equivalent in the 14 days prior to the first nivolumab dose are eligible for the study. Documentation that the dose has been stable or decreased for at least 14 days prior to the first dose of nivolumab is required. Subjects who have received doses of more than 2 mg/day of dexamethasone or equivalent within the 14 days period prior to the first dose of nivolumab are excluded.

NOTE: During study treatment, subjects may be treated with steroids including bolus doses for IMAEs or tumor flare detailed in Appendix 5 and Appendix 6, respectively, and in Sections 3.4.1 and 3.4.2.

c) Subjects who have received chemotherapy within 3 weeks of study treatment (except: HD-MTX within 2 weeks of treatment permitted if serum MTX levels < 1 μM and meets other

lab criteria for inclusion), nitrosoureas within 6 weeks of treatment, therapeutic anti-cancer antibodies (such as rituximab) within 4 weeks, radio- or toxin immune-conjugates within 10 weeks of treatment.

d) Received any investigational agent within 28 days or 5 half-lives (whichever is longer) prior to initiation of study treatment
e) Major surgery and/or radiotherapy within 14 days prior to initiation of study treatment
f) 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
g) Prior malignancy active within the previous 3 years except for locally curable cancers that have been apparently cured, such as basal or squamous cell skin cancer, superficial bladder cancer, or carcinoma in situ of the prostate, cervix, or breast
h) Patients with serious or uncontrolled medical disorders
i) Prior treatment with an anti-PD-1, anti-PD-L1, anti-PD-L2, anti-CD137, or anti-CTLA-4 antibody, or any other antibody or drug specifically targeting T-cell co-stimulation or checkpoint pathways
j) PCNSL patients only: prior therapy with Bruton's tyrosine kinase (BTK) inhibitor (eg, ibrutinib)
k) Patients on active anticoagulation therapy are excluded from this study. If a patient develops a thromboembolic event during the treatment period, treatment with anticoagulation is permitted.

3. Physical and Laboratory Test Findings

a) Any positive test for hepatitis B virus or hepatitis C virus indicating acute or chronic infection, and/or detectable virus

4. Allergies and Adverse Drug Reaction

a) History of severe allergy or hypersensitivity to study drug components

5. Other Exclusion Criteria

a) Prisoners or subjects who are involuntarily incarcerated. (Note: under certain specific circumstances a person who has been imprisoned may be included or permitted to continue as a subject. Strict conditions apply and BMS approval is required.)
b) Subjects who are compulsorily detained for treatment of either a psychiatric or physical (eg, infectious disease) illness.

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

3.3.3 Women of Childbearing Potential

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

Females treated with hormone replacement therapy (HRT) are likely to have artificially suppressed FSH levels and may require a washout period in order to obtain a physiologic FSH level. The duration of the washout period is a function of the type of HRT used. The duration of the washout period below are suggested guidelines and the investigators should use their judgement in checking serum FSH levels:

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

Other parenteral products may require washout periods as long as 6 months. If the serum FSH level is > 40 mIU/ml at any time during the washout period, the woman can be considered postmenopausal.

3.3.4 MRI Contraindication

Study-related MRI imaging of the brain will be performed per the frequency specified in the protocol. Investigators may obtain additional follow-up MRI scans as medically indicated. For other locally performed imaging, it is the local imaging facility's responsibility to determine, based on subject attributes (eg, allergy history, diabetic history, and renal status), the appropriate imaging modality, and contrast regimen for each subject. Imaging contraindications and contrast risks should be considered in this assessment. Subjects with renal insufficiency should be assessed as to whether or not they should receive contrast, and if so, what type and dose of contrast is appropriate. Specific to MRI, subjects with severe renal insufficiency (ie, estimated glomerular filtration rate < 30 mL/min/1.73 m^2) are at increased risk of nephrogenic systemic fibrosis. MRI contrast should not be given to this subject population, who should be excluded from the study. In addition, subjects with surgically implanted devices (pacemaker, deep brain stimulator, metallic implants, etc.) incompatible with MRI should not undergo such imaging techniques. The local imaging facility and investigator should determine the appropriate precautions or guidelines that should be instituted for subjects with tattoos, body piercings, or other body art.

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

[redacted]

[redacted]

3.5 Discontinuation of Subjects following any Treatment with Study Drug

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

- Subject's request to stop study treatment
- Disease progression, except as described in Section 4.5.6
- Unacceptable toxicity, see Section 4.5.5
- Any clinical AE, laboratory abnormality, or intercurrent illness which, in the opinion of the investigator, indicates that continued participation in the study is not in the best interest of the subject, see Section 4.5.5
- Pregnancy (as specified in Section 6.4)
- Termination of the study by 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.

This is a survival study; therefore subjects discontinuing study treatment will remain on study for documentation of progression and death.

In the case of pregnancy, the investigator must immediately notify Sponsor or designee of this event. In most cases, the study drug(s) will be permanently discontinued in an appropriate manner (eg, dose tapering if necessary for subject safety). Please contact the Sponsor or designee within 24 hours of awareness of 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.

All subjects who discontinue study drug should comply with protocol specified follow-up procedures as outlined in Section 5. The only exception to this requirement is when a subject withdraws consent for all study procedures including post-treatment study follow-up or loses the

ability to consent freely (ie, is imprisoned or involuntarily incarcerated for the treatment of either a psychiatric or physical illness).

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

3.6 Post Study Drug Study Follow-up

In this study, OS is a secondary endpoint. Post study follow-up is of critical importance and is essential to preserving subject safety and study integrity. Subjects who discontinue study drug must continue to be followed every 3 months after the second follow-up visit, for collection of outcome and/or survival follow-up data as required and in line with Section 5 until death or study conclusion. Survival follow-up may be accomplished by visit or phone contact.

BMS may request that survival data be collected on all treated subjects outside of the protocol-defined window (Table 5.1-1). At the time of this request, each subject will be contacted to determine their survival status unless the subject has withdrawn consent for all contacts or is lost to follow-up.

In addition, for subjects who discontinue study therapy by proceeding to allogeneic stem cell transplant, documentation of acute and chronic GVHD will be captured on Day 100, at 6 months, 1 year, and every year thereafter from the date of stem cell infusion until the first non-CR after stem cell transplant is documented.

3.6.1 Withdrawal of Consent

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

3.6.2 Lost to Follow-Up

All reasonable efforts must be made to locate subjects to determine and report their ongoing status. This includes follow-up with persons authorized by the subject as noted above. Lost to follow-up is defined as the inability to reach the subject after a minimum of 3 documented phone calls, faxes, or emails as well as lack of response by subject to 1 registered mail letter. All attempts should be documented in the subject's medical records. If it is determined that the subject has died, the site will use permissible local methods to obtain the date and cause of death.

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

4 STUDY DRUG

Study drug includes both Investigational (Medicinal) Product (IP/IMP) and Non-investigational (Medicinal) Product (Non-IP/Non-IMP) and can consist of the following (Table 4-1):

Table 4-1: Study Drugs for CA209647

Product Description / Class and Dosage Form	Potency	IP/Non-IMP	Blinded or Open Label	Packaging / Appearance	Storage Conditions (per label)
Nivolumab Solution for Injection	100 mg (10 mg/ml) and 40 mg (10 mg/mL)	IP	Open label	Clear to opalescent colorless to pale yellow liquid. May contain particles. 240 mg kit contains: 2 x 100-mg vials (10 mg/vial) and 1 x 40-mg vial (4 mL/vial) or carton containing 5 vials of 100 mg	2-8° C. Protect from light and freezing.

4.1 Investigational Product

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

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

In this protocol, the investigational product is nivolumab (BMS-936558).

4.2 Non-investigational Product

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

4.3 Storage and Dispensing

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

Study drug 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).

Nivolumab vials must be stored at a temperature of 2°C to 8°C and should be protected from light and freezing. If stored in a glass front refrigerator, vials should be stored in the carton. Recommended safety measures for preparation and handling of nivolumab include laboratory coats and gloves.

For details on prepared drug storage and use time of nivolumab under room temperature/light and refrigeration, please refer to the nivolumab Investigator Brochure[64] section for “Recommended Storage and Use Conditions” and/or Pharmacy Manual.

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

4.4 Method of Assigning Subject Identification

After the subject’s initial eligibility is established and informed consent has been obtained, the subject must be enrolled into the study by calling an interactive voice response system (IVRS) to

obtain the subject number in IVRS. Specific instruction for using IVRS will be provided to the investigational site in a separate document.

4.5 Selection and Timing of Dose for Each Subject

4.5.1 Nivolumab Dose and Schedule

Subjects should receive nivolumab at a dose of 240 mg as a 30-minute infusion on Day 1 of each treatment cycle for the first 8 cycles until progression, unacceptable toxicity, withdrawal of consent, or the study ends, whichever occurs first. Subjects should begin study treatment within 3 calendar days of treatment assignment. Beginning with Cycle 9, subjects should receive nivolumab at a dose of 480 mg as a 30-minute infusion until progression, unacceptable toxicity, withdrawal of consent, or the study ends, whichever occurs first.

There will be no dose escalations or reductions of nivolumab allowed. Subjects may be dosed no less than 12 days from the previous dose. For Q4W dosing cycles, subjects may be dosed within a +/- 3-day window. Premedications are not recommended for the first dose of nivolumab.

Subjects should be carefully monitored for infusion reactions during nivolumab administration. If an acute infusion reaction is noted, subjects should be managed according to Section 4.5.8.

Doses of nivolumab may be interrupted, delayed, or discontinued depending on how well the subject tolerates the treatment. Dosing visits are not skipped, only delayed.

Information regarding infusion details for nivolumab can be found in the Investigator Brochure.[64]

4.5.2 Dose Modifications for Nivolumab

Dose modifications are not allowed for nivolumab; for dose delay, see Section 4.5.3.

4.5.3 Dose Delay Criteria for Nivolumab

Tumor assessments should continue per protocol schedule, even if dosing is delayed.

Nivolumab administration should be delayed for the following:

- Any Grade ≥ 2 non-skin, drug-related AE, with the following exception:
  - Grade 2 drug-related fatigue or laboratory abnormalities do not require a treatment delay
- Grade 2 drug-related creatinine, AST, ALT, or TBILI abnormalities
- Any Grade 3 skin, drug-related AE
- Any Grade 3 drug-related laboratory abnormality (excluding AST, ALT, or TBILI), with the following exceptions for lymphopenia, AST, ALT, or TBILI or asymptomatic amylase or lipase:
  - Grade 3 lymphopenia does not require dose delay
  - Any Grade ≥ 3 drug-related amylase or lipase abnormality that is not associated with symptoms or clinical manifestations of pancreatitis does not require dose delay
- Any AE, laboratory abnormality, or intercurrent illness which, in the judgment of the investigator, warrants delaying the dose of study medication

Subjects 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.

4.5.4 Criteria to Resume Dosing for Nivolumab

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

- Subjects may resume treatment in the presence of Grade 2 fatigue
- Subjects who have not experienced a Grade 3 drug-related skin AE may resume treatment in the presence of Grade 2 skin toxicity
- For subjects 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
- Subjects with combined Grade 2 AST/ALT AND TBILI values meeting discontinuation parameters (Section 4.5.5) should have treatment permanently discontinued
- Drug-related pulmonary toxicity, diarrhea, or colitis must have resolved to baseline before treatment is resumed. Subjects 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
- Subjects with drug-related endocrinopathies adequately controlled with only physiologic hormone replacement may resume treatment after consultation with the BMS Medical Monitor

4.5.5 Treatment Discontinuation Criteria for Nivolumab

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 OR requires systemic treatment
- Any Grade 3 non-skin, drug-related AE lasting > 7 days, with the following exceptions for laboratory abnormalities, drug-related uveitis, pneumonitis, bronchospasm, hypersensitivity reactions, infusion reactions, and endocrinopathies:
  - Grade 3 drug-related uveitis, pneumonitis, bronchospasm, hypersensitivity reaction, or infusion reaction of any duration requires discontinuation
  - Grade 3 drug-related endocrinopathies adequately controlled with only physiologic hormone replacement do not require discontinuation
  - Grade 3 drug-related laboratory abnormalities do not require treatment discontinuation except:
    - Grade 3 drug-related thrombocytopenia > 7 days or associated with bleeding requires discontinuation
    - Grade ≥ 3 drug-related AST, ALT, or TBILI requires discontinuation*
    - Concurrent AST or ALT > 3xULN and TBILI > 2xULN

* 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 AE or laboratory abnormality, except for the following events which do not require discontinuation:
  - Grade 4 neutropenia ≤ 7 days
  - Grade 4 lymphopenia or leukopenia
  - Isolated Grade 4 amylase or lipase abnormalities that are not associated with symptoms or clinical manifestations of pancreatitis
  - 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 AEs, such as adrenal insufficiency, ACTH deficiency, hyper- or hypothyroidism, or glucose intolerance, which resolve or are adequately controlled with physiologic hormone replacement (corticosteroids, thyroid hormones) or glucose-controlling agents, respectively, may not require discontinuation after discussion with and approval from the BMS Medical Monitor
- Any event that leads to delay in dosing lasting > 6 weeks from the previous dose requires discontinuation, with the following exceptions:
  - Dosing delays to allow for prolonged steroid tapers to manage drug-related AEs are allowed. Prior to re-initiating treatment in a subject with a dosing delay lasting > 6 weeks from the previous dose, the BMS Medical Monitor must be consulted. Tumor assessments should continue as per protocol even if dosing is delayed. Periodic study visits to assess safety and laboratory studies should also continue every 6 weeks or more frequently if clinically indicated during such dosing delays.
  - 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 subject with a dosing delay lasting > 6 weeks, the BMS Medical Monitor must be consulted. Tumor assessments should continue as per protocol even if dosing is delayed. Periodic study visits to assess safety and laboratory studies should also continue every 6 weeks or more frequently if clinically indicated during such dosing delays.
- Any AE, laboratory abnormality, or intercurrent illness which, in the judgment of the investigator, presents a substantial clinical risk to the subject with continued nivolumab dosing

4.5.6 Nivolumab Treatment Beyond Progression

Evidence indicates a minority of subjects treated with immunotherapy may derive clinical benefit despite initial evidence of PD,[61] eg, due to inflammatory reaction simulating progression ("tumor flare" or pseudoprogression). Pseudoprogression is well described in neuro-oncology, and refers to radiographic enlargement of tumor lesions that would be interpreted as disease progression by conventional response criteria, but upon histologic examination reveals necrosis and/or

inflammation (treatment effect) and not disease progression.[61] A similar phenomenon has been observed in various tumors when treated with immunotherapeutic agents, in which transient enlargement of lesions or appearance of new lesions is attributable to the influx of immune cells. These potential immune treatment effects complicate the evaluation of response and may lead to premature discontinuation of therapy. Furthermore, the time period to pseudoprogression or tumor flare with different immune therapies varies in different malignancies. See Appendix 6 for the management of tumor flare for subjects enrolled in this study.

Subjects treated with nivolumab will be permitted to continue nivolumab treatment beyond initial progressive disease, assessed by the investigator, as long as they meet the following criteria:

- Investigator-assessed clinical benefit
- Tolerance of study drug
- Treatment beyond progression will not delay an imminent intervention to prevent serious complications of disease progression (eg, CNS metastases or from mass effect)
- Subject provides written informed consent prior to receiving additional nivolumab treatment

All other elements of the main consent including description of reasonably foreseeable risks or discomforts, or other alternative treatment options will still apply.

A radiographic assessment/scan should be performed within 8 weeks of initial investigator-assessed progression to determine whether there has been a decrease in the tumor size or continued PD. The assessment of clinical benefit should be balanced by clinical judgment as to whether the subject is clinically deteriorating and unlikely to receive any benefit from continued treatment with nivolumab.

If the investigator considers that the nivolumab subject continues to achieve clinical benefit by continuing treatment, the subject should remain on the trial and continue to receive monitoring according to the time and events schedule in Section 5.1.

If at the radiographic assessment/scan at 8 weeks of initial investigator-assessed progression (based on IPCG for brain in PCNSL, or Lugano for systemic disease and potential brain/spine lesions in PTL) the assessment determines continued PD but all the above criteria are met and the investigator considers the subject continues to achieve clinical benefit by continuing treatment, the subject may remain on the trial and continue to receive treatment and monitoring according to the time and events schedule in Section 5.1. Potential for clinical benefit should be balanced by clinical judgment as to whether the subject is clinically deteriorating and unlikely to receive benefit from continued treatment with nivolumab.

A second radiographic assessment/scan should be performed within 8 weeks of second investigator-assessed progression to determine whether there has been a decrease in the tumor size or continued PD (based on IPCG for brain in PCNSL, or Lugano for systemic disease and potential brain/spine lesions in PTL). If this second 8-week radiographic assessment/scan determines continued PD, then the patient should discontinue therapy and enter the follow-up period.

4.5.7 Management Algorithms for Immuno-Oncology Agents

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

- Gastrointestinal
- Renal
- Pulmonary
- Hepatic
- Endocrinopathy
- Skin
- Neurological

The above algorithms are found in the nivolumab Investigator Brochure[64] and Appendix 5 of this protocol.

4.5.8 Treatment of Nivolumab-Related Infusion Reactions

Since nivolumab contains only human immunoglobulin protein sequences, it is unlikely to be immunogenic and induce infusion or hypersensitivity reactions. However, if such a reaction were to occur, it might manifest with fever, chills, rigors, headache, rash, pruritus, arthralgia, hypotension, hypertension, bronchospasm, or other allergic-like reactions. All Grade 3 or 4 infusion reactions should be reported within 24 hours to the study medical monitor and reported as an SAE if it meets the criteria. Infusion reactions should be graded according to National Cancer Institute (NCI) CTCAE v4.03 guidelines.

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

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

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

For Grade 2 symptoms (moderate reaction required therapy or infusion interruption but responded promptly to symptomatic treatment [eg, antihistamines, non-steroidal anti-inflammatory drugs, narcotics, corticosteroids, bronchodilators, IV fluids]; prophylactic medications indicated for ≤ 24 hours):

- Stop the nivolumab infusion, begin an IV infusion of normal saline, and treat the subject with diphenhydramine 50 mg IV (or equivalent) and/or acetaminophen/paracetamol 325 to 1000 mg; remain at bedside and monitor subject 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 subject closely. If symptoms recur, then no further nivolumab will be administered at that visit.
- For future infusions, the following prophylactic premedications are recommended: diphenhydramine 50 mg (or equivalent) and/or acetaminophen/paracetamol 325 to 1000 mg 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 (Grade 3: severe reaction, 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. Begin an IV infusion of normal saline and treat the subject as follows: Recommend bronchodilators, epinephrine 0.2 to 1 mg of a 1:1000 solution for subcutaneous administration or 0.1 to 0.25 mg of a 1:10,000 solution injected slowly for IV administration, and/or diphenhydramine 50 mg IV with methylprednisolone 100 mg IV (or equivalent), as needed. Subject should be monitored until the investigator is comfortable that the symptoms will not recur. Nivolumab will be permanently discontinued. Investigators should follow their institutional guidelines for the treatment of anaphylaxis. Remain at bedside and monitor subject 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).

4.6 Blinding/Unblinding

Not applicable.

4.7 Treatment Compliance

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

4.8 Destruction of Study Drug

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

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

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

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

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

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

4.9 Return of Study Drug

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

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

[redacted]

5 STUDY ASSESSMENTS AND PROCEDURES

5.1 Flow Chart/Time and Events Schedule

Table 5.1-1: Screening Assessments (CA209647)

Procedure	Screening Visit	Notes (Screening procedures are to occur within 28 days prior to first dose unless otherwise specified)
Eligibility Assessment		
Informed Consent	X	This study permits the re-enrollment of a subject that has discontinued the study as a pre-treatment failure (ie, subject has not been treated). If re-enrolled, the subject must be re-consented and assigned a new subject number by the IVRS.
Inclusion/Exclusion Criteria	X	All inclusion/exclusion criteria should be assessed at screening
Medical History	X	
Prior Systemic Therapy	X	
Prior Radiation Therapy	X	
Prior Surgery	X	
Safety Assessments		
Complete Physical Examination	X	Include assessment of lymph node areas (eg, submandibular, cervical, supraclavicular, axillary, or inguinal lymph node), abdominal organs (eg, spleen) and neurological examination
Performance Status	X	Karnofsky Performance Status
Vital Signs	X	Temperature, BP, HR.
Assessment of Signs and Symptoms	X	Required for the 28 days prior to first dose
Concomitant Medication Collection	X	Required for the 28 days prior to first dose
Laboratory Tests	X	CBC with differential, chemistry panel including LDH, AST, ALT, ALP, albumin, TBILI, BUN or serum urea level, uric acid, creatinine, phosphate, Ca, Mg, Na, K, Cl, glucose, amylase, lipase, TSH, Free T3, Free T4 within 14 days prior to first dose. HIV, Hepatitis B surface antigen (HBV sAg), and hepatitis C antibody (HCV Ab) or HCV ribonucleic acid (RNA) within 28 days prior to first dose.
Pregnancy Test	X	For WOCBP (Refer to Section 3.3.3) only and must be done within 24 hours of first dose

Table 5.1-1: Screening Assessments (CA209647)		
Procedure	**Screening Visit**	**Notes (Screening procedures are to occur within 28 days prior to first dose unless otherwise specified)**
[redacted]		

Table 5.1-1: Screening Assessments (CA209647)		
Procedure	**Screening Visit**	**Notes (Screening procedures are to occur within 28 days prior to first dose unless otherwise specified)**
[redacted]		[redacted]
[redacted]	[redacted]	[redacted]
[redacted]		
[redacted]		[redacted]

Table 5.1-2: On Treatment Procedures (CA209647)			
Procedure	**Cycle 1 Day 1**	**Cycle 2 & Beyond, Day 1**	**Notes** **All windows proposed are calendar days. Procedures must be done within 72h prior to dosing unless otherwise specified. Cycle duration is 2 weeks until 8 doses have been completed; subsequent cycles are 4 weeks in duration.**
Safety Assessments			
Targeted Physical Examination	X	X	Include assessment of lymph node areas (eg, submandibular, cervical, supraclavicular, axillary, or inguinal lymph node), abdominal organs (eg, spleen) and neurological examination
Vital Signs	X	X	Temperature, BP, HR
Adverse Events Assessment	----------Continuously----------		Assessed using NCI CTCAE v. 4.03
Review of Concomitant Medications	X	X	
Physical Measurements	X	X	Includes weight
Karnofsky Status	X	X	
Laboratory Tests		X	To be done within 72 hours prior to dosing and include: CBC with differential, uric acid, BUN or serum urea level, creatinine, Ca, Mg, K, Cl, Na, amylase, lipase, glucose, phosphate, AST, ALT, TBILI, ALP, albumin, LDH. Cycle 1 Day 1: Laboratory tests do not need to be repeated if performed within 14 days prior to first dose.
Thyroid Function Testing		See Note	Thyroid function testing (TSH with reflexive fT3 and fT4) is to be done every 6 weeks (every 3 infusions) for subjects receiving nivolumab at 240 mg Q2W, then every 8 weeks for subjects receiving nivolumab at 480 mg qw4 (every other infusion)
Pregnancy Test (WOCBP only)	X	See Note	Serum or urine within 24 hours prior to first dose and then at least once every 4 weeks (± 1 week) regardless of dosing schedule.

Table 5.1-2: On Treatment Procedures (CA209647)			
Procedure	**Cycle 1 Day 1**	**Cycle 2 & Beyond, Day 1**	**Notes** **All windows proposed are calendar days. Procedures must be done within 72h prior to dosing unless otherwise specified. Cycle duration is 2 weeks until 8 doses have been completed; subsequent cycles are 4 weeks in duration.**
[redacted]			

Table 5.1-2: On Treatment Procedures (CA209647)			
Procedure	**Cycle 1 Day 1**	**Cycle 2 & Beyond, Day 1**	**Notes** **All windows proposed are calendar days. Procedures must be done within 72h prior to dosing unless otherwise specified. Cycle duration is 2 weeks until 8 doses have been completed; subsequent cycles are 4 weeks in duration.**
[redacted]			
Outcomes Research Questionnaire			
EQ-5D 3L (PCNSL and PTL cohorts) EORTC QLQ C30 (PCNSL and PTL cohorts) EORTC QLQ-BN20 (PCNSL only)	X	X	Subjects will be asked to complete the questionnaires prior to dosing Day 1 Week 1 and then prior to each radiographic tumor assessment. Refer to Section 5.6.6 for more information.

Table 5.1-2: On Treatment Procedures (CA209647)			
Procedure	**Cycle 1 Day 1**	**Cycle 2 & Beyond, Day 1**	**Notes** **All windows proposed are calendar days. Procedures must be done within 72h prior to dosing unless otherwise specified. Cycle duration is 2 weeks until 8 doses have been completed; subsequent cycles are 4 weeks in duration.**
PK and Immunogenicity Assessments			
PK and Immunogenicity Samples			See Table 5.5-1 for sampling details.
Paired CSF and Blood PK and [redacted] Samples	See Table 5.5.2 for sampling details.		
Clinical Drug Supplies			
Administer nivolumab	X	X	Subjects should receive nivolumab at a dose of 240 mg as a 30-minute infusion on Day 1 of each treatment cycle for 8 cycles until Q4W dosing begins. Subjects may be dosed no less than 12 days from the previous dose. For Q2W dosing cycles, subjects may be dosed within a ± 2-day window. Beginning with Cycle 9, subjects should receive nivolumab at a dose of 480 mg as a 30-minute infusion every 4 weeks (± 3 days) for a maximum 2 years of total treatment, or until PD, unacceptable toxicity, or withdrawal of consent.
IVRS			IVRS must be called up to 3 days prior to each dosing visit

Table 5.1-3: Follow-up Assessments (CA209647)

Procedure	Follow Up, Visits 1 and 2[a] (X01 & X02)	Survival Follow-Up Visits[b]	Notes
Safety Assessments			
Targeted Physical Examination	X		Lymph node areas (eg, submandibular, cervical, supraclavicular, axillary, or inguinal lymph node), abdominal organs (eg, spleen) and neurological examination
Adverse Events Assessment	X		
Laboratory Tests	X		Required for X01: CBC with differential, uric acid, serum urea level, serum creatinine, sodium, potassium, calcium, magnesium, chloride, glucose, AST, ALT, total bilirubin, alkaline phosphatase, LDH, TSH (reflex to free T3, free T4 for abnormal TSH result). Panel should also be performed at X02 if X01 results were abnormal.
Pregnancy Test (WOCBP only)	X		Serum or urine
GVHD Assessments	See Note	See Note	Only for subjects who discontinued study therapy by proceeding to allogeneic stem cell transplant: To be assessed on Day 100, at 6 months, at 1 year, and every year thereafter from the date of transplant until the first non-CR after SCT is documented. See Section 5.3.
Efficacy Assessments			
Radiographic Tumor Assessment Gadolinium-enhanced MRI of the brain Gadolinium-enhanced MRI of the spine FDG PET-CT	X	X	**Only for subjects without documented progression at the end of treatment:** Tumor assessments in both PCNSL and PTL cohorts will occur every 6 months until disease progression or subsequent treatment
Subsequent Anticancer Therapy	X	X	
Other Primary Malignancies	X	X	

Table 5.1-3: Follow-up Assessments (CA209647)

Procedure	Follow Up, Visits 1 and 2[a] (X01 & X02)	Survival Follow-Up Visits[b]	Notes
Eye Examination (PCNSL and PTL with brain involvement)	X		Detailed ophthalmological examination with dilated fundus examination, slit lamp examination, and color photography of the exterior pole (only if positive findings at screening and for confirmation of response)
[redacted]			
[redacted]	[redacted]		[redacted]
[redacted]			
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]		
[redacted]			
[redacted]		[redacted]	[redacted]

[a] Follow-up visit 1 (FU1) = 35 days from the last dose ± 7 days. Follow-up visit 2 (FU2) = 84 days (± 7 days) from follow-up visit 1.

[b] Survival follow-up visits to occur every 3 months (± 14 days) from FU2. BMS may request that survival data be collected on all treated subjects outside of the 3-month specified window. At the time of this request, each subject will be contacted to determine their survival status unless the subject has withdrawn consent for all contact.

5.1.1 Retesting During Screening or Lead-in Period

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

Any new result will override the previous result and is the value by which study inclusion will be assessed, as it represents the subject's most current, clinical state.

Laboratory parameters and/or assessments that are included in Table 5.1-1 may be repeated in an effort to find all possible well-qualified subjects. Consultation with the Medical Monitor may be needed to identify whether repeat testing of any particular parameter is clinically relevant.

5.2 Study Materials

- NCI CTCAE version 4.03
- Nivolumab Investigator Brochure[64]
- Pharmacy Binder
- Laboratory manuals for collection and handling of blood (including PKs, biomarker and immunogenicity) and tissue specimens
- Site manual for operation of IVRS, including enrollment worksheet
- Manual for submission of local laboratory results
- QoL questionnaires
- Pregnancy Surveillance Forms
- Imaging Manual
- Patient Alert Card

5.3 Safety Assessments

At screening, a medical history will be obtained to capture relevant underlying conditions. The screening examinations should include weight, height, Karnofsky status, blood pressure (BP), heart rate (HR), and temperature.

Screening local laboratory assessments should be done within 14 days prior to treatment assignment and are to include: CBC with differential, chemistry panel including LFTs (ALT, AST, TBILI, ALP), amylase, lipase, uric acid, BUN or serum urea level, creatinine, Ca, Na, K, Cl, Mg, albumin, phosphate, LDH, glucose, and thyroid panel including TSH, free T3, and free T4.

Pregnancy tests for WOCBP must be performed within 24 hours prior to the initial administration of study drug.

The following screening local laboratory assessments should be done within 28 days prior to treatment: Hepatitis B and C testing (HBV sAg and HCV Ab or HCV RNA), and HIV testing.

While on-study the following local laboratory assessments are to be done within 3 calendar days prior to each dose: CBC with differential, LFTs (ALT, AST, TBILI, ALP), BUN or serum urea level, creatinine, Ca, Mg, Na, K, Cl, phosphate, LDH, uric acid, amylase, lipase, albumin, glucose.

Thyroid function testing (TSH with reflexive fT3 and fT4) is to be done every 6 weeks (every 3 infusions) for subjects receiving nivolumab at 240 mg Q2W, then every 8 weeks for subjects receiving nivolumab at 480 mg Q4W (every other infusion).

On treatment pregnancy tests should be performed as per the schedule in the time and events table (Table 5.1-2).

Subjects will be evaluated for safety if they have received any study drug. Toxicity assessments will be continuous during the treatment phase as well as during the first 2 safety follow-up visits. Once subjects reach the survival follow-up phase, either in-person visits or documented telephone calls to assess the subject's status are acceptable.

For subjects who discontinue study therapy by proceeding to allogeneic stem cell transplant, documentation of acute and chronic GVHD will be captured on Day 100, at 6 months, 1 year, and every year thereafter from the date of stem cell infusion until the first non-CR after transplant is documented. Investigators will make telephone contact with the subject's hematologist/oncologist/transplant physician to obtain this information if the subject is being followed by another physician.

Adverse events and laboratory values will be graded according to the NCI CTCAE version 4.03.

The start and stop time of the study therapy infusions and any interruptions or infusion rate reductions should be documented.

Physical examinations are to be performed as clinically indicated. If there are any new or worsening clinically significant changes since the last exam, report changes on the appropriate non-serious or SAE page.

On treatment local laboratory assessments are to be completed within 3 calendar days prior to dosing.

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 subject shows pulmonary-related signs (hypoxia, fever) or symptoms (eg, dyspnea, cough, fever) consistent with possible pulmonary AEs, the subject should be immediately evaluated to rule out pulmonary toxicity, according to the suspected pulmonary toxicity management algorithm (Appendix 5) and in the nivolumab Investigator Brochure.[64]

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.

5.3.1 Imaging Assessment for the Study

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. Additional details are provided in the study Imaging Manual.

Radiographic tumor assessments for PCNSL or PTL will be performed (Section 5.1).

5.4 Efficacy Assessments

Radiographic images will be collected for BICR.

5.4.1 Assessment of Overall Tumor Burden and Disease

Efficacy assessment will be conducted and reported on the eCRF using the appropriate efficacy assessment based on tumor type. Subjects with PCNSL will be evaluated using the modified International PCNSL Collaborative Group (IPCG) Criteria for PCNSL (Appendix 3), while subjects with PTL will be evaluated using the Lugano 2014 Classification (Appendix 4).

The primary efficacy endpoint is ORR based on BICR assessment. BICR will also be used for the assessment of the secondary endpoint PFS. Investigator assessments will be also be used for the ORR and DOR secondary endpoints and the PFS exploratory endpoint.

Efficacy assessments will be required as follows (Section 5.1):

- PCNSL (Appendix 3)
- PTL (Appendix 4)

Baseline Staging

PCNSL

All PCNSL subjects will undergo gadolinium-enhanced MRI of the brain (and of the spine for subjects with spinal symptoms) at the timepoints specified in Table 5.1-1and Table 5.1-2 for baseline assessment and on study response assessment purposes. Investigators may obtain more frequent follow-up MRI scans as medically indicated. Local radiologic assessment of tumor measurements will be used for clinical management and investigator-assessed clinical endpoints.

Subjects who are unable (due to existent medical condition, ie, pacemaker or implantable cardioverter-defibrillator device) or unwilling to have a brain MRI at baseline are excluded from the study (Section 3.3.4). Subjects who become unable to undergo MRI imaging after enrollment may continue in the study for assessment of OS as long as there is no safety issue which would require monitoring by MRI.

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 below in Section 6.

At baseline, for staging purposes all PCNSL subjects will undergo the following procedures:

- Gadolinium-enhanced MRI of the brain
- Gadolinium-enhanced MRI of the spine (for subjects with spinal symptoms)
- Whole-body FDG-PET or CT scan of the neck, chest, abdomen, pelvis, and other relevant body parts with suspected or known disease (to exclude patients with systemic disease)
- Lumbar puncture for CSF cytology (before/1 week after surgical biopsy, when applicable)
- Detailed ophthalmological examination, with dilated fundus examination, slit-lamp examination, and color photography of the posterior pole
- Bone marrow biopsy with aspirate, only if clinically indicated.

If MRI of the spine, ophthalmological examination, CSF cytology, or bone marrow biopsy are positive for lymphoma involvement at baseline, these tests must be repeated for confirmation of objective response.

PTL

All PTL subjects will undergo fluorodeoxyglucose (FDG) PET-CT scans at the timepoints specified in Table 5.1-3 for baseline assessment and on study response assessment purposes. Investigators may obtain more frequent follow-up FDG PET-CT scans as medically indicated. Local radiologic assessment of tumor measurements will be used for clinical management and investigator-assessed clinical endpoints.

Study sites will retain local access to the imaging results for safety and efficacy reading purposes. The study investigator will review the local FDG PET-CT 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 below in Section 6.

At baseline, for staging purposes all PTL subjects will undergo the following procedures:

- FDG PET/CT scan
- Gadolinium-enhanced MRI of the brain
- Gadolinium-enhanced MRI of the spine (in subjects with spinal symptoms)
- Bone marrow biopsy with aspirate, if clinically indicated
- Lumbar puncture for CSF cytology, if clinically indicated
- Eye examination for PTL patients with CNS involvement

If brain and/or spine MRI, bone marrow biopsy, or CSF cytology are positive for lymphoma involvement at baseline, these tests must be repeated for confirmation of objective response.

On-study Assessment of Response

PCNSL

Assessment of treatment response in subjects with PCNSL while on study requires the following assessments:

- Gadolinium-enhanced MRI scan of the brain
- Gadolinium-enhanced MRI scan of the spine, if positive at baseline or if clinically indicated
- Detailed ophthalmological examination with dilated fundus examination, slit-lamp examination, and color photography of the posterior pole, if clinically indicated and for confirmation of objective response
- Whole-body CT scan, if clinically indicated
- Lumbar puncture for CSF cytology, if clinically indicated
- Bone marrow biopsy with aspirate, if clinically indicated

The criteria for response assessment are illustrated in Appendix 3. Additionally, objective response requires confirmation by repeat brain MRI at 8 weeks from the initially documented response. If MRI of the spine, ophthalmological examination, CSF cytology, or bone marrow biopsy are positive for lymphoma involvement at baseline or on-study when warranted by symptoms, these tests should be also repeated at 8 weeks for confirmation of objective response.

PTL

Assessment of treatment response in subjects with PTL while on study requires the following assessments:

- FDG PET-CT scan
- Bone marrow biopsy with aspirate, if clinically indicated
- Gadolinium-enhanced MRI scan of the brain and/or of the spine, if clinically indicated
- Lumbar puncture for CSF cytology, if clinically indicated
- Eye examination for PTL patients with CNS involvement

The criteria for response evaluation in PTL patients are described in Appendix 4. Additionally, objective response requires confirmation by repeat brain MRI at 8 weeks from the initially documented response (only for patients with CNS involvement per IPCG criteria). If bone marrow biopsy, brain and/or spine MRI, or CSF cytology are positive for lymphoma involvement at baseline or on-study when warranted by symptoms, these tests should be also repeated at 8 weeks for confirmation of objective response.

Radiographic Assessments

Radiographic study evaluations will take place as outlined in Section 5.1.

Baseline assessments should be performed within 28 days prior to the first dose (14 days for MRI of the brain). A whole-body PET/CT is required at baseline for all subjects.

On-study assessments should include chest, abdomen, and pelvis, and all known sites of disease (including CNS and/or spine) and should use the same imaging method that was used at baseline.

PCNSL subjects will be evaluated for tumor response by MRI at Week 8 from the first dose and continuing for every 8 weeks for the first 2 years (104 weeks). PTL subjects will be evaluated for tumor response by FDG-PET/CT or PET/MRI at Week 8 from the first dose and continuing for every 8 weeks for the first 6 months (26 weeks), then every 12 weeks for 18 months. After the first 2 years, tumor assessments are to occur every 24 weeks until disease progression is documented.

Assessment of Overall Tumor Burden and Measurable Disease

To serially evaluate tumor response to therapy, it is necessary to estimate the overall tumor burden at baseline and use this as a comparator for subsequent measurements. Measurable disease is defined by the presence of at least one measurable tumor lesion. At baseline, tumor lesions/lymph nodes will be categorized as measurable or non-measurable.

Measurable Lesions

- Focal uptake in nodal and extranodal sites that is in keeping with lymphoma, according to the distribution and/or CT characteristics, is considered involvement with lymphoma, including spleen, liver, bone, thyroid, and so on.
- Measured dominant lesions: Up to 6 of the largest dominant nodes, nodal masses, and extranodal lesions selected to be clearly measurable in 2 diameters.
  - Nodes should preferably be from disparate regions of the body and should include, where applicable, mediastinal and retroperitoneal areas. A measurable node must have a longest diameter (LDi) > 1.5 cm.
  - Non-nodal lesions include those in solid organs (eg, liver, spleen, kidneys, lungs), GI involvement, cutaneous lesions, or those noted on palpation. A measurable extranodal lesion must have a LDi > 1.0 cm and may be included in the 6 representative, measured lesions (eg, hepatic nodules).
- A sum of the product of the diameters (SPD) will be calculated for all target lesions (CNS and non-CNS) and recorded as the baseline SPD. The baseline SPD will be used as reference to further characterize any objective tumor regression in the measurable dimension of the disease.

<u>CT Measurements</u>

For subjects staged with CT, up to 6 of the largest target nodes, nodal masses, or other lymphomatous lesions that are measurable in 2 diameters (LDi and shortest diameter) should be identified from different body regions representative of the patient's overall disease burden and include mediastinal and retroperitoneal disease, if involved. A measurable node must have a LDi greater than 1.5 cm. Measurable extranodal disease (eg, hepatic nodules) may be included in the 6 representative, measured lesions. For extranodal measurable lesion the LDi must be greater than 1.0 cm. All other lesions (including nodal, extranodal, and assessable disease) should be followed as non-measured disease (eg, cutaneous, GI, bone, spleen, liver, kidneys, pleural or pericardial effusions, ascites).

Non-Measurable Lesions

Besides small lymph nodes (longest diameter < 10 mm), truly non-measurable lesions include: leptomeningeal disease, ascites, pleural or pericardial effusion, inflammatory breast disease, lymphangitic involvement of skin or lung, or abdominal masses/abdominal organomegaly identified by physical exam that are not measurable by reproducible imaging techniques.

Any disease not selected as measured, dominant disease and truly assessable disease should be considered not measured. These sites include any nodes, nodal masses, and extranodal sites not selected as dominant or measurable or that do not meet the requirements for measurability but are still considered abnormal, as well as truly assessable disease, which is any site of suspected disease that would be difficult to follow quantitatively with measurement, including pleural effusions, ascites, bone lesions, leptomeningeal disease, abdominal masses, and other lesions that cannot be confirmed and followed by imaging. In Waldeyer's ring or in extranodal sites (eg, GI tract, liver, bone marrow), FDG uptake may be greater than in the mediastinum with complete metabolic response, but should be no higher than surrounding normal physiologic uptake (eg, with marrow activation as a result of chemotherapy or myeloid growth factors).

All other lesions (or sites of disease) including non-measurable lymph nodes should be identified as non-target lesions and should also be recorded at baseline. Measurements are not required and these lesions should be followed as 'present', 'absent', or in rare cases 'unequivocal progression'. In addition, it is possible to record multiple non-target lesions involving the same organ as a single item on the CRF (eg, 'multiple enlarged pelvic lymph nodes' or multiple liver nodules').

Bone Marrow Assessments

Bone marrow assessments should be done only if clinically indicated in both subjects with PCNSL or PTL. The biopsy/aspirate performed within 90 days prior to obtaining informed consent must be documented at screening or a bone marrow biopsy/aspirate must be performed during the screening period if clinically indicated. For PCNSL or PTL subjects with bone marrow involvement at screening, a bone marrow biopsy and aspirate will be required to confirm an objective response.

In addition to efficacy assessments, additional, optional, bone marrow biopsy and aspirate samples may be collected and submitted for biomarker studies.

CSF Assessments

CSF cytology should be done if clinically indicated. If performed within 90 days prior to obtaining informed consent they must be documented at screening or a lumbar puncture must be performed during the screening period. For PCNSL or PTL subjects with CSF involvement at screening, a lumbar puncture with CSF collection will be required to confirm an objective response.

[redacted]

is an objective, quick, user-friendly and quantifiable evaluation of nine major domains for subjects with brain tumors. The domains include: gait, strength, ataxia, sensation, visual field, facial strength, language, level of consciousness, behavior and overall. Each domain is rated on a scale of 0 to 3 where 0 represents normal and 3 represents the worst severity. A given domain should be scored non-evaluable if it cannot be accurately assessed due to preexisting conditions, co-morbid events and/or concurrent medications. The evaluation is based on direct observation/testing performed during routine office visits.

The NANO scale will be completed by the investigator or designated study physician prior to dosing on Day 1 Week 1 and then with each MRI (but must be completed before MRI scan results are reviewed with the subject).

5.5 Pharmacokinetic and CSF Biomarker Assessments

Blood samples for PK and immunogenicity assessments will be collected in all subjects. Paired [redacted] blood samples for PK [redacted] will also be collected in patients who consent to having lumbar punctures performed. Table 5.5-1 lists the sampling schedule to be followed for routine PK and immunogenicity samples. Blood samples should be drawn from a site other than the infusion site (ie, contralateral arm) on days of the infusion. All samples collected predose should be taken just prior to nivolumab administration, and end-of-infusion (EOI) samples should be taken as close to EOI as possible (preferably 2 minutes prior to EOI) on the contralateral arm (ie, the arm not for the infusion). All on-treatment PK time points are intended to align with days on which nivolumab is administered. If it is known that a dose is going to be delayed, then the predose sample should be collected just prior to the delayed dose. However, if a predose sample is collected but the dose is subsequently delayed, an additional predose sample should not be collected. Table 5.5-2 lists the sampling schedule to be followed for paired [redacted] blood samples. For those patients who are on-study prior to Revised Protocol 04, sampling should begin with the cycle the patients are on, according to Table 5.5-2. Further details of blood collection, [redacted] collection, processing, labeling, handling, storage, and shipment of samples will be provided in the Procedure Manual.

Table 5.5-1: Pharmacokinetic & Immunogenicity Blood Sampling Schedule

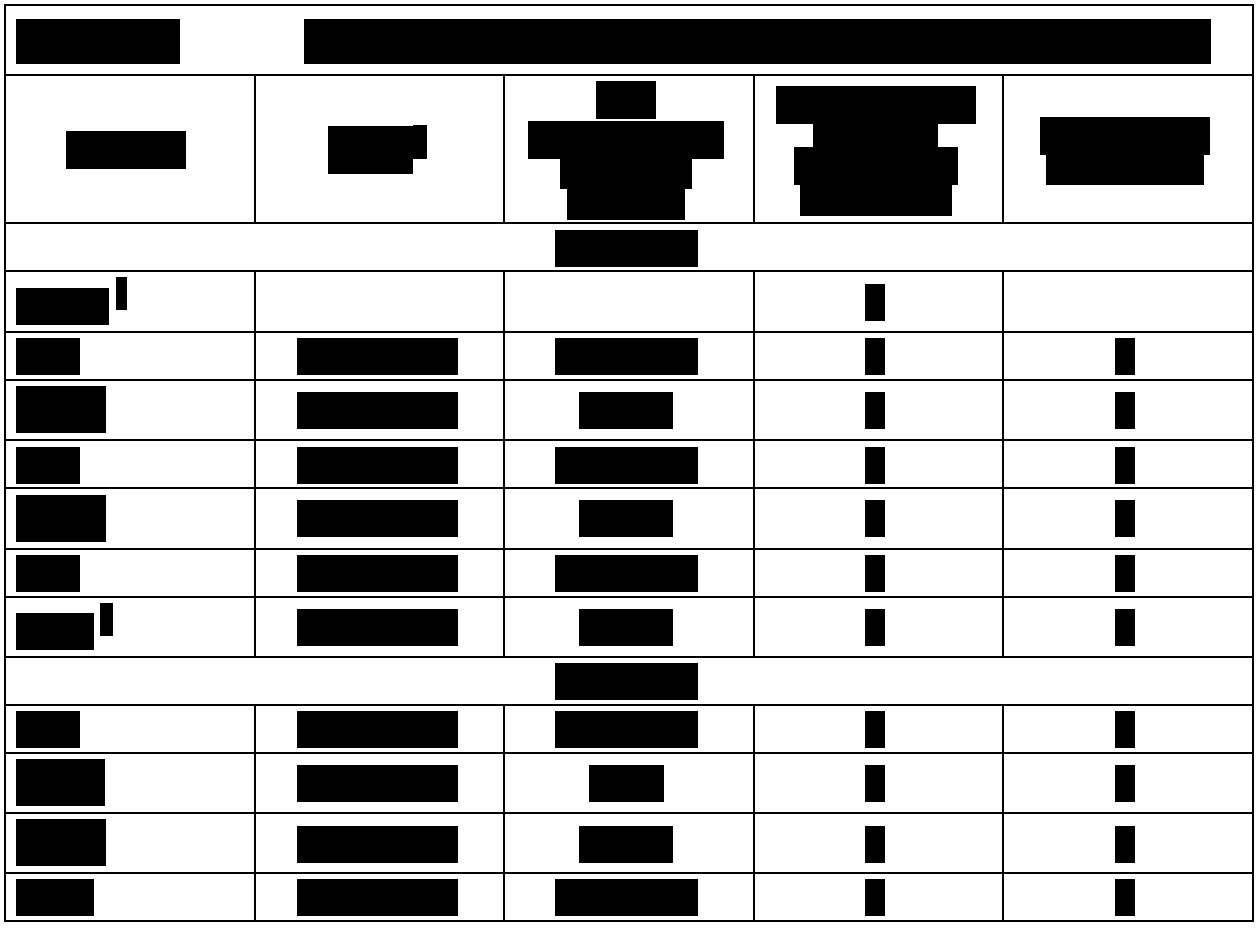
Study Day C1 – C8: 2-week cycles C9 and beyond: 4-week cycles	Event	Time (Relative to Start of Infusion) Hour: Min	Nivolumab PK Blood Sample	Nivolumab Immunogenicity Sample
C1D1	predose[a]	00:00	X	X
C3D1	predose[a]	00:00	X	X
C7D1	predose[a]	00:00	X	X
C9D1	predose[a]	00:00	X	X
C9D1	EOI[b]	00:30	X	

Table 5.5-1: Pharmacokinetic & Immunogenicity Blood Sampling Schedule

Study Day C1 – C8: 2-week cycles C9 and beyond: 4-week cycles	Event	Time (Relative to Start of Infusion) Hour: Min	Nivolumab PK Blood Sample	Nivolumab Immunogenicity Sample
C10D1	predose[a]	00:00	X	
C13D1	predose[a]	00:00	X	X
C17D1	predose[a]	00:00	X	X
C21D1	predose[a]	00:00	X	X
D1 of every 6th cycle (24 weeks) after C21	predose[a]	00:00	X	X

[a] All predose samples should be taken just prior to the start of nivolumab infusion (preferably within 30 minutes)

[b] EOI samples should be taken as close to the end of infusion as possible (preferably two minutes prior to EOI) on the contralateral arm (ie, the arm not for the infusion). Study sites should ensure accurate collection of the time and date for PK and immunogenicity assessment are obtained.



[redacted]				
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
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5.7 Outcomes Research Assessments

Outcomes research data including health-related quality of life (QoL) and patient-reported symptom burden provide a more complete understanding of the impact of treatment by incorporating the patients' perspective. Treatment-related toxicities have been identified as a significant problem in both PCNSL, where neurotoxicity has been attributed to cognitive dysfunction, and in PTL, where patient age has reduced tolerance to aggressive chemotherapies. The importance of capturing patient-reported outcomes data has become critically important as

symptom management and maintaining QoL are key metrics for assessing overall treatment benefit.

5.7.1 EORTC QLQ-C30 and BN20

The EORTC QLQ-C30[68] is the most commonly used quality of life instrument in oncology trials. The instrument's 30 items are divided among 5 functional scales (physical, role, cognitive, emotional, and social), 9 symptom scales (fatigue, pain, nausea/vomiting, dyspnea, insomnia, appetite loss, constipation, diarrhea, and financial difficulties), and a global health/quality of life scale. With the exception of 2 items included in the global health/quality of life scale, for which responses range from 1 (Very poor) to 7 (Excellent), item responses range from 1 (Not at all) to 4 (Very much). Reduced cognitive function has been recognized as a significant problem in patients treated for PCNSL, and previous research has supported the validity of the cognitive functioning scale of the QLQ-C30 in a variety of populations. The EORTC QLQ-BN20[69] is a validated measure of concerns and symptoms specific to brain neoplasms. The questionnaire's 20 items are divided among multi-item scales measuring future uncertainty (4 items), visual disorders (3 items), motor dysfunction (3 items), and communication deficits (3 items), as well as single-item measures of problems with headaches, seizures, drowsiness, itchy skin, hair loss, lower extremity weakness, and bladder control. Each of the questionnaire's items uses a 4-point response scale ranging from 1 (Not at all) to 4 (Very much). Raw scores for the QLQ-C30 and QLQ-BN20 are transformed to a 0-100 metric such that higher values indicate better functioning or QoL or a higher level of symptoms. The QLQ-C30 will be administered to all treated subjects in both the PCNSL and PTL cohorts, while the QLQ-BN20 will be administered to all treated subjects in the PCNSL cohort, during the on-study and follow-up phases as outlined in Section 5.1.

5.7.2 EQ-5D 3L

The EQ-5D-3L[70] is a generic multi-attribute health-state classification system by which health is described in 5 dimensions: mobility, self-care, usual activities, pain/discomfort, and anxiety/depression. Each dimension is evaluated using 3 levels: no problems, some problems, and severe problems. Responses to these 5 dimensions are converted into 1 of 243 unique EQ-5D health state descriptions, which range between no problems on all 5 dimensions (11111) to severe/extreme problems on all 5 dimensions (33333). Using appropriate country-specific value weighting algorithms, a respondent's self-described health state can be converted into a utility representing the societal desirability of his/her own health. In addition, the EQ-5D includes a visual analogue scale (VAS) allowing a respondent to rate his/her health on a scale ranging from 0–100 with 0 being the worst health state imaginable and 100 being the best health state imaginable. The EQ-5D-3L will be administered to all treated subjects in both the PCNSL and PTL cohorts during the on-study, follow-up, and survival follow-up phases as outlined in Section 5.1.

5.8 Other Assessments

5.8.1 Immunogenicity Assessments

Serum samples collected at timepoints identified in Section 5.1 will be analyzed by a validated immunogenicity assay. Additional characterization (ie, neutralizing antibodies) for any detected

anti-drug antibodies (ADA) response to nivolumab may also be performed using a validated functional cell-based assay. All on-treatment timepoints are intended to align with days on which study drug is administered, if dosing occurs on a different day, the immunogenicity sampling should be adjusted accordingly. Selected serum samples may be analyzed by an exploratory method that measures anti-nivolumab for technology exploration purposes; exploratory data will not be reported.

In addition, serum samples designated for PK or biomarker assessments may also be used for immunogenicity analysis if required (eg, insufficient volume for complete immunogenicity assessment or to follow up on suspected immunogenicity related AE).

6 ADVERSE EVENTS

An ***Adverse Event (AE)*** is defined as any new untoward medical occurrence or worsening of a preexisting medical condition in a clinical investigation subject administered 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.

The causal relationship to study drug is determined by a physician and should be used to assess all AEs. The causal relationship can be 1 of the following:

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

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

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

Immune-mediated adverse events (IMAEs) 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 subject's CRF.

BMS will be reporting AEs 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.

6.1 Serious Adverse Events

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

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

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

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

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

NOTE:

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

- A visit to the emergency room or other hospital department < 24 hours, that does not result in admission (unless considered an important medical or life-threatening event)
- Elective surgery, planned prior to signing consent
- Admissions as per protocol for a planned medical/surgical procedure
- Routine health assessment requiring admission for baseline/trending of health status (eg, routine colonoscopy)
- Medical/surgical admission other than to remedy ill health and planned prior to entry into the study. Appropriate documentation is required in these cases.

- Admission encountered for another life circumstance that carries no bearing on health status and requires no medical/surgical intervention (eg, lack of housing, economic inadequacy, caregiver respite, family circumstances, administrative reason)
- Admission for administration of anticancer therapy in the absence of any other SAEs (applies to oncology protocols)

6.1.1 Serious Adverse Event Collection and Reporting

Sections 5.6.1 and 5.6.2 in the Investigator Brochure[64] represent the Reference Safety Information to determine expectedness of SAEs for expedited reporting. Following the subject's written consent to participate in the study, all SAEs, whether related or not related to study drug, must be collected, including those thought to be associated with protocol-specified procedures. All SAEs must be collected that occur during the screening period and within 100 days of the last dose of nivolumab. For subjects assigned to treatment and never treated with study drug, SAEs should be collected for 30 days from the date of treatment assignment. If applicable, SAEs must be collected that relate to any later protocol-specified procedure (eg, a follow-up biopsy).

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

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

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

SAEs, whether related or not related to study drug, and pregnancies must be reported to BMS (or designee) within 24 hours 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, 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.

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.

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.

6.2 Nonserious Adverse Events

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

6.2.1 Nonserious Adverse Event Collection and Reporting

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

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

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

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

Every AE must be assessed by the investigator with regard to whether it is considered immune-mediated. For events which are potentially immune-mediated, additional information will be collected on the subject's CRF.

6.3 Laboratory Test Result Abnormalities

The following laboratory test result abnormalities should be captured on the nonserious AE CRF page or SAE Report Form 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 subject to have study drug discontinued or interrupted
- Any laboratory test result abnormality that required the subject to receive specific corrective therapy

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

6.4 Pregnancy

If, following initiation of the study drug, it is subsequently discovered that a study subject is pregnant or may have been pregnant at the time of study exposure, including during at approximately 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 Section 6.1.1.

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

The investigator must immediately notify the BMS (or designee) Medical Monitor of this event and complete and forward a Pregnancy Surveillance Form to BMS (or designee) within 24 hours of awareness of the event and in accordance with SAE reporting procedures described in Section 6.1.1.

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

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

6.5 Overdose

An overdose is defined as the accidental or intentional administration of any dose of a product that is considered both excessive and medically important. All occurrences of overdose must be reported as an SAE (see Section 6.1.1 for reporting details).

6.6 Potential Drug Induced Liver Injury (DILI)

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

Potential drug induced liver injury is defined as:

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

6.7 Other Safety Considerations

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

7 BLINDED INDEPENDENT CENTRAL REVIEW

A blinded independent central review will be conducted of the images and relevant clinical data in this study. The activities and processes regarding the independent read will be outlined in the CA209-647 Imaging Review Charter.

8 STATISTICAL CONSIDERATIONS

8.1 Sample Size Determination

The planned sample size for this study will be approximately 65 treated subjects, placed into 2 cohorts of subjects: PCNSL (N = 45), and PTL (N = 20).

In addition, Table 8.1-1 summarizes the 95% exact confidence interval (CI) for the target ORRs ranging from 28.9% to 60% with sample size of 20 and 45. At observed ORR ≥ 28.9% with 45 PCNSL subjects, the lower bound of the 95% CI excludes the historical response rates in of 14% in recurrent primary central nervous system lymphoma [41]. At observed ORR ≥ 40% with 20 PTL subjects, the lower bound of the 95% CI excludes the response rate of 14%.

The sample size for the PCNSL cohort was empirically determined to support expanded assessment of the benefit-risk profile of nivolumab in PCNSL through observation of less common safety events. In particular, administration of nivolumab to 45 subjects provides 90% probability of observing at least 1 occurrence of any AE that would occur with 5% incidence in the population from which the sample is drawn.

Table 8.1-1: Observed ORR with Exact 95 % CI

N	ORR	95% Exact CI
20	30%	[11.9% - 54.3%]
	35%	[15.4% - 59.2%]
	40%	[19.1% - 63.9%]
	50%	[27.2% - 72.8%]
	60%	[36.1% - 80.9%]
45	28.9%	[16.4% - 44.3%]
	40.0%	[25.7% - 55.7%]
	51.1%	[35.8% - 66.3%]
	60%	[44.3% - 74.3%]

8.2 Populations for Analyses

Within each cohort the following populations will be defined:

- All Enrolled Subjects: All subjects who signed an ICF and were registered into the IVRS
- All Treated Subjects: All subjects who received at least 1 dose of nivolumab. This is the primary population for safety and efficacy analyses

- PK Subjects: All subjects with available serum time-concentration data from subjects dosed with nivolumab
- Immunogenicity Evaluable Subjects: All treated subjects with baseline and at least 1 postbaseline immunogenicity assessment

8.3 Endpoints

8.3.1 Primary Endpoint(s)

The primary objective will be measured by the primary endpoint of BICR-assessed ORR. It is defined as the number of subjects with a best overall response (BOR) of CR or PR, based on the IPCG Criteria for PCNSL[21] and Lugano 2014 response evaluation for PTL,[22] divided by the number of treated subjects within each cohort.

The BICR-assessed BOR is defined as the best response designation recorded between the date of first study drug dose and the date of initial objectively documented progression per criteria or the date of subsequent therapy, whichever occurs first. For purposes of analysis, if a subject receives one dose and discontinues the study without assessment or receives subsequent therapy prior to assessment, this subject will be counted in the denominator (as non-responder).

The BICR-assessed objective response will be further characterized by the DOR, defined as the time from first response (CR or PR) to the date of initial objectively documented progression as determined using the IPCG Criteria for PCNSL and Lugano 2014 response evaluation for PTL, as determined by BICR, or death due to any cause, whichever occurs first. For subjects who neither progress nor die, the DOR will be censored on the date of their last tumor assessment. Subjects who start subsequent anticancer therapy without a prior reported progression will be censored at the last tumor assessments prior to initiation of the subsequent anticancer therapy. This endpoint will only be evaluated in subjects with objective response of CR or PR.

The analysis of the primary endpoint in each cohort will occur at least 6 months after last patient first treatment in each cohort.

8.3.2 Secondary Endpoint(s)

Secondary endpoints will be analyzed at the same time as the primary endpoint.

8.3.2.1 Progression Free Survival Based on BICR Assessment

PFS is defined as the time from first dosing date to the date of the first documented progression using the IPCG Criteria for PCNSL and Lugano 2014 response evaluation for PTL, as determined by BICR, or death due to any cause, whichever occurs first. Subjects who die without a reported progression will be considered to have progressed on the date of their death. Subjects who did not progress or die will be censored on the date of their last tumor assessment. Subjects who did not have any on study assessments and did not die will be censored on the first dosing date. Subjects who started any subsequent anti-cancer therapy without a prior reported progression will be censored at the last tumor assessment prior to initiation of the subsequent anti-cancer therapy.

8.3.2.2 Objective Response Rate and Duration of Response Based on Investigator Assessment

Investigator-assessed ORR and DOR are defined similarly as described for ORR and DOR per BICR assessment above, but will be assessed per investigator.

8.3.2.3 Overall Survival

OS is defined as the time from first dosing date to the date of death. For subjects without documentation of death, OS will be censored on the last date the subject was known to be alive.

8.4 Analyses

All analyses will be performed separately for each cohort.

8.4.1 Demographics and Baseline Characteristics

Demographic and baseline laboratory results will be summarized using descriptive statistics for all treated subjects.

8.4.2 Efficacy Analyses

8.4.2.1 Primary Endpoint Methods

The BICR-assessed ORR will be summarized by binomial response rates and their corresponding two-sided 95% exact CI using the Clopper-Pearson method.

The BICR-assessed DOR will be summarized by cohort for subjects who achieve PR or CR using the Kaplan-Meier product-limit method. Median values of DOR, along with two-sided 95% CIs (based on the log-log transformation) and range, will also be calculated.

8.4.2.2 Secondary Endpoint Methods

The BICR-assessed PFS will be summarized by the Kaplan-Meier product-limit method. Median values along with two-sided 95% CIs based on the log-log transformation, will be calculated.

BICR-assessed PFS will be evaluated in all treated subjects. The BICR-assessed PFS rate at 6, 12, and 24 months will also be calculated.

The analysis of ORR per investigator is similar as ORR analysis per BICR, but based on investigator assessment.

The analysis of DOR per investigator is similar as DOR analysis per BICR, but based on investigator assessment.

OS will be summarized by the Kaplan-Meier product-limit method. Median values along with two-sided 95% CIs based on the log-log transformation, will be calculated. OS will be evaluated in all treated subjects. OS rate at 6, 12, and 24 months will also be calculated.

[redacted]

8.4.3 Safety Analyses

The safety analysis will be performed in all treated subjects. Descriptive statistics of safety will be presented using NCI CTCAE version 4.03 by treatment group. AEs, drug-related AEs, SAEs, and drug-related SAEs will be tabulated using worst grade per NCI CTCAE v.4.03 criteria by system organ class and preferred term. On-study lab parameters including hematology, chemistry, liver function, and renal function will be summarized using worst grade per NCI CTCAE v.4.03 criteria.

8.4.4 Pharmacokinetic Analyses

The nivolumab concentration-time data obtained in this study may be analyzed separately or combined with data from other studies in the clinical development programs to develop or refine population PK models. These models may be used to evaluate the effects of intrinsic and extrinsic covariates on the PK of nivolumab and to determine measures of individual exposure (such as steady-state peak, trough, and time-averaged concentration). In addition, model-determined exposures may be used for exposure-response analyses. Results of population PK and exposure-response analyses would be reported separately.

[redacted]

8.4.6 Outcomes Research Analyses

Analyses will be done by cohort.

8.4.6.1 EORTC QLQ-C30 and QLQ-BN-20

All randomized subjects who have an assessment at baseline and at least 1 subsequent assessment while on treatment will be analyzed. Questionnaire completion rates at each assessment at each timepoint will be estimated for both the QLQ-C30 and the QLQ-BN20. Scores and post-baseline changes in scales of the EORTC QLQ-C30 and the QLQ-BN20 will be summarized at each assessment timepoint using appropriate descriptive statistics (ie, N, mean with standard deviation and 95% CI, median, first and third quartiles, minimum, maximum).

8.4.6.2 EQ-5D -3L

All randomized subjects who have an assessment at baseline and at least 1 subsequent assessment while on treatment will be analyzed. Questionnaire completion rates at each assessment at each timepoint will be estimated for both the EQ-5D-3L VAS, and EQ-5D-3L utility index. Scores and post-baseline changes in scores for the EQ-5D-3L VAS and EQ-5D-3L utility index will be summarized at each assessment timepoint using appropriate descriptive statistics (ie, N, mean with SD and 95% CI, median, first and third quartiles, minimum, maximum). UK preference-weighting algorithm will be used to derive EQ-5D-3L VAS and EQ-5D-3L utility index in base case.

8.4.7 Other Analyses

Methodology for exploratory analyses including NANO assessment will be described in the statistical analysis plan.

Immunogenicity will be reported for ADA positive status (such as persistent positive, neutralizing positive, only last sample positive, baseline positive, and other positive) and ADA negative status, relative to baseline. Effect of immunogenicity on safety, efficacy, biomarkers, and PK may be explored. Additional details will be described in the Statistical Analysis Plan.

8.5 Interim Analyses

Administrative interim analyses of the data may be performed at several times prior to completion of the study in order to facilitate program decisions.

9 STUDY MANAGEMENT

9.1 Compliance

9.1.1 Compliance with the Protocol and Protocol Revisions

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

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

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

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

If an amendment substantially alters the study design or increases the potential risk to the subject: (1) the consent form must be revised and submitted to the IRB(s)/IEC(s) for review and

approval/favorable opinion; (2) the revised form must be used to obtain consent from subjects currently enrolled in the study if they are affected by the amendment; and (3) the new form must be used to obtain consent from new subjects prior to enrollment.

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

9.1.2 Monitoring

BMS 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.

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

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

9.1.2.1 Source Documentation

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), AE 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.

9.1.3 Investigational Site Training

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

9.2 Records

9.2.1 Records Retention

The investigator must retain all study records and source documents for the maximum period required by applicable regulations and guidelines, or institution procedures, or for the period

specified by BMS, whichever is longer. The investigator must contact BMS prior to destroying any records associated with the study.

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

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

9.2.2 Study Drug Records

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

- Amount received and placed in storage area
- Amount currently in storage area
- Label identification number or batch number
- Amount dispensed to and returned by each subject, including unique subject identifiers
- Amount transferred to another area/site for dispensing or storage
- Nonstudy disposition (eg, lost, wasted)
- Amount destroyed at study site, if applicable
- Amount returned to BMS
- Retain samples for bioavailability/bioequivalence, if applicable
- Dates and initials of person responsible for IP dispensing/accountability, as per the Delegation of Authority Form.

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

9.2.3 Case Report Forms

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

For sites using the BMS electronic data capture tool, electronic CRFs will be prepared for all data collection fields except for fields specific to SAEs and pregnancy, which will be reported on the 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 BMS.

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

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

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

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

9.3 Clinical Study Report and Publications

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

For this protocol, the Signatory Investigator will be the External Principal Investigator designated at protocol development.

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

10 GLOSSARY OF TERMS

Term	Definition
Complete Abstinence	Complete Abstinence is defined as complete avoidance of heterosexual intercourse and is an acceptable form of contraception for all study drugs. This also means that abstinence is the preferred and usual lifestyle of the patient. This does not mean periodic abstinence (eg, calendar, ovulation, symptothermal, profession of abstinence for entry into a clinical trial, post-ovulation methods) and withdrawal, which are not acceptable methods of contraception. Women must continue to have pregnancy tests. Acceptable alternate methods of highly effective contraception's must be discussed in the event that the subject chooses to forego complete abstinence.

11 LIST OF ABBREVIATIONS

Term	Definition
ADA	anti-drug antibody
AE	adverse event
AIDS	acquired immunodeficiency syndrome
ALT	alanine aminotransferase
AST	aspartate aminotransferase
AT	aminotransaminases
BBB	blood-brain barrier
BICR	blinded independent central review
BMS	Bristol-Myers Squibb
BP	blood pressure
BUN	blood urea nitrogen
CHOP	cyclophosphamide, doxorubicin, vincristine, and prednisone
CI	confidence interval
CL	geometric mean clearance
CMV	cytomegalovirus
CNS	central nervous system
CR	complete response
CrCl	creatinine clearance
CRF	Case Report Form, paper or electronic
CSF	cerebrospinal fluid
CTA	clinical trial agreement
CTCAE	Common Terminology Criteria for Adverse Events
CV	coefficient of variation
DFS	disease-free survival
DILI	drug-induced liver injury
DLBCL	diffuse large B-cell lymphoma
DNA	deoxyribonucleic acid
DOR	duration of response
EBV	Epstein-Barr virus

Term	Definition
EFS	event-free survival
EOI	end of infusion
EORTC	European Organization for Research and Treatment of Care
EU	European Union
FDG	fluorodeoxyglucose
FSH	follicle stimulating hormone
GCP	Good Clinical Practice
GVHD	Graft versus host disease
HD-ASCT	high-dose chemotherapy followed by hematopoietic stem-cell rescue
HD-MTX	high-dose methotrexate
HIV	Human Immunodeficiency Virus
HL	Hodgkin's Lymphoma
HR	heart rate
HRT	hormone replacement therapy
ICF	Informed Consent Form
ICH	International Conference on Harmonisation
IEC	Independent Ethics Committee
IFN	interferon
IMAE	immune-mediated adverse events
IMP	investigational medicinal products
I-O	immuno-oncology
IP	investigational product
IPCG	International PCNSL Collaborative Group
IRB	Institutional Review Board
IV	intravenous
IVRS	interactive voice response system
LDi	longest diameter
MRI	magnetic resonance imaging
MTX	methotrexate
NANO	Neurologic Assessment in Neuro-Oncology

Term	Definition
NHL	non-Hodgkin's lymphoma
NSCLC	non-small cell lung cancer
ORR	overall response rate
OS	overall survival
PBMC	peripheral blood mononuclear cells
PCNSL	primary central nervous system lymphoma
PD	pharmacodynamics
PD	programmed death
PFS	progression-free survival
PK	pharmacokinetics
PMBCL	primary mediastinal B-cell lymphoma
PPK	population pharmacokinetics
PTL	primary testicular lymphoma
Q2W	every 2 weeks
Q4W	every 4 weeks
QLQ-BN20	European Organization for Research and Treatment of Care Brain Cancer Module
QLQ-C30	European Organization for Research and Treatment of Care General Cancer Module
QoL	quality of life
RCC	renal cell carcinoma
R-CHOP	rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone
RT	radiation therapy
SAE	serious adverse event
SEER	Surveillance, Epidemiology, and End Results
SPD	sum of the product of the diameters
SUSAR	suspected, unexpected serious adverse reaction
TBILI	total bilirubin
TIL	tumor infiltrating lymphocyte
ULN	upper limit of normal
US	United States

Term	Definition
VAS	visual analog rating scale
WBC	white blood cell
WOCBP	women of childbearing potential

APPENDIX 1 METHODS OF CONTRACEPTION

At a minimum, subjects must agree to use one highly effective method of contraception as listed below:

HIGHLY EFFECTIVE METHODS OF CONTRACEPTION

Highly effective methods of contraception have a failure rate of < 1% when used consistently and correctly. WOCBP and female partners of male subjects, who are WOCBP, are expected to use one of the highly effective methods of contraception listed below. Male subjects must inform their female partners who are WOCBP of the contraceptive requirements of the protocol and are expected to adhere to using contraception with their partner. Contraception methods are as follows:

1) Progestogen only hormonal contraception associated with inhibition of ovulation.
2) Hormonal methods of contraception including oral contraceptive pills containing combined estrogen + progesterone, vaginal ring, injectables, implants and intrauterine devices (IUDs) such as Mirena®
3) Nonhormonal IUDs, such as ParaGard®
4) Bilateral tubal occlusion
5) Vasectomised partner with documented azoospermia 90 days after procedure
    - Vasectomised partner is a highly effective birth control method provided that partner is the sole sexual partner of the WOCBP trial participant and that the vasectomised partner has received medical assessment of the surgical success.
6) Intrauterine hormone-releasing system (IUS).
7) Complete abstinence
    - Complete abstinence is defined as the complete avoidance of heterosexual intercourse (refer to Glossary of Terms)
    - Complete abstinence is an acceptable form of contraception for all study drugs and must be used throughout the duration of the study treatment (plus approximately 5 half-lives of the investigational drug plus 30 days).
    - It is not necessary to use any other method of contraception when complete abstinence is elected.
    - Subjects who choose complete abstinence must continue to have pregnancy tests, as specified in Section 5.1.
    - Acceptable alternate methods of highly effective contraception must be discussed in the event that the subject chooses to forego complete abstinence.
    - The reliability of sexual abstinence needs to be evaluated in relation to the duration of the clinical trial and the preferred and usual lifestyle of the subject.

UNACCEPTABLE METHODS OF CONTRACEPTION

1) Periodic abstinence (calendar, symptothermal, post-ovulation methods)
2) Withdrawal (coitus interruptus)

3) Spermicide only
4) Lactation amenorrhea method (LAM)

APPENDIX 2 KARNOFSKY PERFORMANCE SCALES

100	Normal; no complaints; no evidence of disease
90	Able to carry on normal activity; minor signs or symptoms of disease
80	Normal activity with effort, some sign or symptoms of disease
70	Cares for self; unable to carry on normal activity or do active work
60	Requires occasional assistance, but is able to care for most personal needs
50	Requires considerable assistance and frequent medical care
40	Disabled; requires special care and assistance
30	Severely disabled; hospitalization is indicated, although death nor imminent
20	Very sick; hospitalization necessary; active support treatment is necessary
10	Moribund; fatal processes progressing rapidly
0	Dead

APPENDIX 3 RESPONSE CRITERIA FOR PCNSL

Subjects with PCNSL will be evaluated using the International Primary CNS Lymphoma Collaborative Group (IPCG) Criteria for PCNSL[14].

Table 1: Response criteria for PCNSL

Response	Criteria			
	Brain imaging	**Corticosteroid dose**	**Eye examination**	**CSF cytology**
Complete response (CR)	No contrast enhancement	None	Normal	Negative
Unconfirmed complete response (CRu)	No contrast enhancement	Any	Normal	Negative
	Minimal abnormality	Any	Minor RPE abnormality	Negative
Partial response (PR)	50% decrease in enhancing tumor	Irrelevant	Minor RPE abnormality or normal	Negative
	No contrast enhancement	Irrelevant	Decrease in vitreous cells or retinal infiltrate	Persistent or suspicious
Progressive disease (PD)	25% increase in lesion	Irrelevant	Recurrent or new ocular disease	Recurrent or positive
	Any new site of disease: CNS or systemic			

Source: Abrey et al., 2005

Complete Response (CR):

- Complete disappearance of all enhancing abnormalities on gadolinium-enhanced MRI.
- No evidence of active ocular lymphoma as defined by absence of cells in the vitreous and resolution of any previously documented retinal or optic nerve infiltrates. Chronic changes of the retinal pigment epithelium in the setting of a prior retinal or optic nerve infiltrate does not preclude the definition of a CR. Detailed ophthalmologic examination with dilated fundus examination, slit-lamp examination and color photography of the posterior pole, and lumbar puncture for cytology are required only if these studies were initially positive or became positive during treatment and if clinically indicated by new symptoms or signs.
- Lumbar puncture for CSF cytology is necessary to confirm cytologic response observed in the ventricular CSF.
- At the time a CR is determined, the patient should have discontinued corticosteroids for at least 2 weeks.
- Residual lesions (other than lesions < 10 mm) if presumed to be non-malignant should be further investigated (eg, by PET scans) before CR can be accepted.
- If there was evidence of PET abnormality suspicious for systemic disease then PET has to be repeated to confirm CR (Radiology comment)

- All subjects who appear to achieve CR require the following:
  - Confirmation scan at 8 weeks
  - Repeat CSF cytology, bone marrow biopsy and aspirate, and ophthalmologic examination if involved at baseline

Unconfirmed CR (CRu): Any patient who fulfills all criteria for CR but continues to require corticosteroid therapy at any dose should be considered an unconfirmed CR. Subjects with a persistent minor abnormality on follow-up ophthalmologic examination (persistent non- malignant cells in the vitreous, alteration of the retina/optic nerve that is not consistent with tumor infiltration) may be considered a CRu if this abnormality is unlikely to represent ocular lymphoma.

Partial response (PR) requires all of the following:

- A ≥ 50% decrease in the contrast-enhancing lesion seen on MRI as compared with baseline imaging.
- Corticosteroid dose is irrelevant to the determination of PR.
- Ophthalmologic examination should show a decrease in the vitreous cell count or retinal/optic nerve cellular infiltrate but may continue to show persistent malignant or suspicious cells. Color photos of the posterior pole of the eye should be obtained to document improvement in retinal/optic nerve infiltrates.
- CSF cytologic examination may be negative or continue to show persistent malignant or suspicious cells in subjects with a ≥ 50% decrease in the primary brain lesion.
- No new sites of disease. In the setting of primary leptomeningeal lymphoma, PR is not recognized; all subjects should be categorized as CR, CRu, stable disease, or progressive disease.

Stable disease (SD) is defined as less than a PR but is not progressive disease (PD).

Progressive disease requires the following:

- A more than 25% increase in the contrast-enhancing lesion seen on MRI as compared with baseline or best response (comparison should be made to the smallest of multiple lesions).
- Progression of ocular disease as indicated by an increase in the vitreous cell count or progressive retinal or optic nerve infiltration.
- Appearance of any new lesion or site of disease (ocular, leptomeningeal or systemic) during or at the end of therapy.

Relapsed disease (only applicable to subjects with a prior CR, CRu) requires the following:

- Appearance of any new lesion.

APPENDIX 4 RESPONSE EVALUATION IN PTL

Subjects with PTL will be evaluated for response using a 2 compartment model, where the 2014 Lugano Classification will be used for systemic lesions and the IPCG criteria will be used for CNS lesions.

Table 1: Revised Criteria for Response Assessment: 2014 Lugano Classification

Response and Site	PET-CT–Based Response	CT-Based Response
Complete	Complete metabolic response	Complete radiologic response (all of the following)
Lymph nodes and extralymphatic sites	Score 1, 2, or 3* with or without a residual mass on 5PS†	Target nodes/nodal masses must regress to ≤ 1.5 cm in LDi
	It is recognized that in Waldeyer's ring or extranodal sites with high physiologic uptake or with activation within spleen or marrow (eg, with chemotherapy or myeloid colony-stimulating factors), uptake may be greater than normal mediastinum and/or liver. In this circumstance, complete metabolic response may be inferred if uptake at sites of initial involvement is no greater than surrounding normal tissue even if the tissue has high physiologic uptake	No extralymphatic sites of disease
Nonmeasured lesion	Not applicable	Absent
Organ enlargement	Not applicable	Regress to normal
New lesions	None	None
Bone marrow	No evidence of FDG-avid disease in marrow	Normal by morphology; if indeterminate, IHC negative
Partial	Partial metabolic response	Partial remission (all of the following)
Lymph nodes and extralymphatic sites	Score 4 or 5† with reduced uptake compared with baseline and residual mass(es) of any size	≥ 50% decrease in SPD of up to 6 target measurable nodes and extranodal sites
	At interim, these findings suggest responding disease	When a lesion is too small to measure on CT, assign 5 mm × 5 mm as the default value
	At end of treatment, these findings indicate residual disease	When no longer visible, 0 × 0 mm
		For a node > 5 mm × 5 mm, but smaller than normal, use actual measurement for calculation
Nonmeasured lesions	Not applicable	Absent/normal, regressed, but no increase
Organ enlargement	Not applicable	Spleen must have regressed by > 50% in length beyond normal
New lesions	None	None
Bone marrow	Residual uptake higher than uptake in normal marrow but reduced compared with baseline (diffuse uptake compatible with reactive changes from chemotherapy allowed). If there are persistent focal changes in the marrow in the context of a nodal response, consideration should be given to further evaluation with MRI or biopsy or an interval scan	Not applicable
No response or stable disease	No metabolic response	Stable disease
Target nodes/nodal masses, extranodal lesions	Score 4 or 5 with no significant change in FDG uptake from baseline at interim or end of treatment	< 50% decrease from baseline in SPD of up to 6 dominant, measurable nodes and extranodal sites; no criteria for progressive disease are met
Nonmeasured lesions	Not applicable	No increase consistent with progression
Organ enlargement	Not applicable	No increase consistent with progression
New lesions	None	None
Bone marrow	No change from baseline	Not applicable
Progressive disease	Progressive metabolic disease	Progressive disease requires at least 1 of the following
Individual target nodes/nodal masses	Score 4 or 5 with an increase in intensity of uptake from baseline and/or	PPD progression:
Extranodal lesions	New FDG-avid foci consistent with lymphoma at interim or end-of-treatment assessment	An individual node/lesion must be abnormal with: LDi > 1.5 cm and Increase by ≥ 50% from PPD nadir and An increase in LDi or SDi from nadir 0.5 cm for lesions ≤ 2 cm 1.0 cm for lesions > 2 cm In the setting of splenomegaly, the splenic length must increase by > 50% of the extent of its prior increase beyond baseline (eg, a 15-cm spleen must increase to > 16 cm). If no prior splenomegaly, must increase by at least 2 cm from baseline New or recurrent splenomegaly
Nonmeasured lesions	None	New or clear progression of preexisting nonmeasured lesions

(continued on following page)

Response and Site	PET-CT–Based Response	CT-Based Response
New lesions	New FDG-avid foci consistent with lymphoma rather than another etiology (eg, infection, inflammation). If uncertain regarding etiology of new lesions, biopsy or interval scan may be considered	Regrowth of previously resolved lesions A new node > 1.5 cm in any axis A new extranodal site > 1.0 cm in any axis; if < 1.0 cm in any axis, its presence must be unequivocal and must be attributable to lymphoma Assessable disease of any size unequivocally attributable to lymphoma
Bone marrow	New or recurrent FDG-avid foci	New or recurrent involvement

Abbreviations: 5PS, 5-point scale; CT, computed tomography; FDG, fluorodeoxyglucose; IHC, immunohistochemistry; LDi, longest transverse diameter of a lesion; MRI, magnetic resonance imaging; PET, positron emission tomography; PPD, cross product of the LDi and perpendicular diameter; SDi, shortest axis perpendicular to the LDi; SPD, sum of the product of the perpendicular diameters for multiple lesions.

*A score of 3 in many patients indicates a good prognosis with standard treatment, especially if at the time of an interim scan. However, in trials involving PET where de-escalation is investigated, it may be preferable to consider a score of 3 as inadequate response (to avoid undertreatment). Measured dominant lesions: Up to six of the largest dominant nodes, nodal masses, and extranodal lesions selected to be clearly measurable in two diameters. Nodes should preferably be from disparate regions of the body and should include, where applicable, mediastinal and retroperitoneal areas. Non-nodal lesions include those in solid organs (eg, liver, spleen, kidneys, lungs), GI involvement, cutaneous lesions, or those noted on palpation. Nonmeasured lesions: Any disease not selected as measured, dominant disease and truly assessable disease should be considered not measured. These sites include any nodes, nodal masses, and extranodal sites not selected as dominant or measurable or that do not meet the requirements for measurability but are still considered abnormal, as well as truly assessable disease, which is any site of suspected disease that would be difficult to follow quantitatively with measurement, including pleural effusions, ascites, bone lesions, leptomeningeal disease, abdominal masses, and other lesions that cannot be confirmed and followed by imaging. In Waldeyer's ring or in extranodal sites (eg, GI tract, liver, bone marrow), FDG uptake may be greater than in the mediastinum with complete metabolic response, but should be no higher than surrounding normal physiologic uptake (eg, with marrow activation as a result of chemotherapy or myeloid growth factors).

†PET 5PS: 1, no uptake above background; 2, uptake ≤ mediastinum; 3, uptake > mediastinum but ≤ liver; 4, uptake moderately > liver; 5, uptake markedly higher than liver and/or new lesions; X, new areas of uptake unlikely to be related to lymphoma.

*The recommendations from Lugano Classification is to use a 5 point scale to assess the metabolic response in PET-CT based response.

Response Evaluation for systemic lesions in PTL:

CR (Complete Remission)

The designation of CR requires all of the following be met:

1) Complete disappearance of all detectable clinical evidence of disease.
   a) PET-CT-based response: A score of ≤ 3 is considered to represent complete metabolic response.
   b) CT based response: Target node/nodal masses must regress to ≤ 1.5 cm in LDi, with no extralymphatic sites of disease
2) Organ involvement: Absence of organomegaly
3) Bone marrow: No evidence of FDG- avid disease in marrow. If there was evidence of involvement of bone marrow with lymphoma at screening/baseline and a biopsy was performed (PTCL), a bone marrow biopsy will be required to confirm CR.
4) The presence of residual symptoms in the absence of detectable disease by imaging does not preclude the designation of CR.

PR (Partial Remission)

The designation of PR requires all of the following:

1) PET-CT based response: Score of 4 or 5, provided reduced uptake compared with base line and absence of structural progression development on CT Scan.

2) CT based response: ≥ 50% regression in SPD of up to 6 measurable nodal and extranodal lesions
3) Splenic and hepatic nodules must regress by ≥ 50% in length beyond normal.
4) Bone marrow: reduced uptake compared with baseline. If there is evidence of nodal response but persistent focal changes in the marrow consider further evaluation

SD (Stable Disease)

SD is defined as the following:

1) PET-CT based response: no metabolic response, score of 4 or 5 with no significant changes from baseline.
2) CT based response: < 50% decrease from baseline, absence of new lesions
3) Bone marrow: no change from baseline.

PD: Relapsed Disease (after CR)/Progressive Disease (after PR, SD)

1) PET-CT based response: Score of 4 or 5 with increase in intensity from baseline or interim scan/ or any new FDG avid focus consistent with malignant lymphoma
2) CT based response: New node, new or recurrent splenomegaly, progression of existing lesions

Response Evaluation for CNS lesions in PTL:

The IPCG criteria as described in Appendix 3 will be used for PTL patients with CNS lesions.

APPENDIX 6 TUMOR FLARE

Tumor Flare in CNS tumors:

Tumor flare (TF): Immunomodulatory agents, such as immune checkpoint inhibitors, may be associated with clinical and imaging findings during treatment, suggestive of progressive disease (PD) despite evidence of clinical benefit (tumor flare or pseudo-progression).[1,2] This phenomenon has been well described with checkpoint blockade therapy in solid tumors, with an incidence of 10% in melanoma and 3% in lung cancer.[3] Furthermore, this has also been reported anecdotally in lymphomas.[4] Pseudoprogression appears as tumor progression or radiographic progression with target lesion size increase. Often it may be associated with mixed responses, which include good response (i.e., shrinkage) but increased tumor size or even new lesion appearance elsewhere. The patient may or may not present with deterioration in clinical symptoms. Considering this finding as PD could lead to patients being prematurely removed from a treatment from which they actually stand to benefit. Therefore it is important to remain cognizant of this effect during treatment.

Few important characteristics observed with TF are outlined below:

- Tumor inflammation is the intended effect of anti-tumor immune therapies, so tumor flare is consistent with eventual benefit. As it is important not to abandon immunotherapy prematurely, these observations have led to development of immune-related response criteria.[1,4]
- TF may be more clinically evident, i.e. lead to early development of symptoms, in CNS tumors than in tumors of other sites due to their intracranial location.
- TF is indistinguishable from disease progression (thus sometimes called 'pseudoprogression'), and thus presents a major clinical challenge.

It is ordinarily not possible to determine whether increased neurologic symptoms and/or radiographic findings represent tumor progression or transient TF. Observation, sometimes prolonged, is required to make this determination.

- In some settings, moreover, adverse effects of other concomitant treatment (such as RT) may be equally as likely.
- Less frequently adverse effects of immunotherapy on normal brain tissues may be possible.

In other Central Nervous System trials of nivolumab (alone or with ipilimumab), clinical findings of TF have been highly variable, based on the location of the lesion, including confusion, aphasia, hemiplegia, seizure, etc. Because of this neurologic heterogeneity, we have used the overall diagnostic term "Tumor Flare" in order to capture it systematically in our adverse event database.

Treatment strategies during TF:

- Corticosteroids (e.g. dexamethasone 4-8 mg/day) are generally fairly effective in reversing neurologic dysfunction, perhaps more effective than might be seen with disease progression. They may be tapered as quickly as tolerated (in contrast to systemic IMAEs such as pneumonitis, for which very slow tapering is advised). If acute or severe neurologic deterioration, dexamethasone bolus of 10-20 mg intravenously or corticosteroid equivalent, once, can be considered, followed by a smaller dose for maintenance such as 2-4mg daily, to be rapidly tapered off once neurologic deficits improve.
- If symptoms are moderate to severe, delay of immune treatment is appropriate.
- Generalized effects of increased pressure, including midline shift, hydrocephalus, obliteration of sulci, etc. have also been noted, but are non-specific.
- Imaging changes are sometimes more striking than clinical AEs; if radiographic findings are not associated with clinical deterioration, immune treatment need not be delayed. Cerebral edema on imaging by itself need not be a criteria for drug discontinuation.
- Investigations on potential radiographic features which could assist in discriminating TF from disease progression are in progress.

If surgically accessible, a diagnostic biopsy may be feasible.

- As always, there is concern that a representative sample be obtained.
- A predominance of necrosis, and inflammation is consistent with TF, and very helpful in allaying the concern generated by clinical and imaging changes. Unfortunately, of course, a biopsy may confirm tumor progression.
- In such cases, we would encourage that the immune treatment be resumed.

Every patient is different; consultation with the Medical Monitor and review of the imaging is often useful.