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Clinical Protocol CA209139

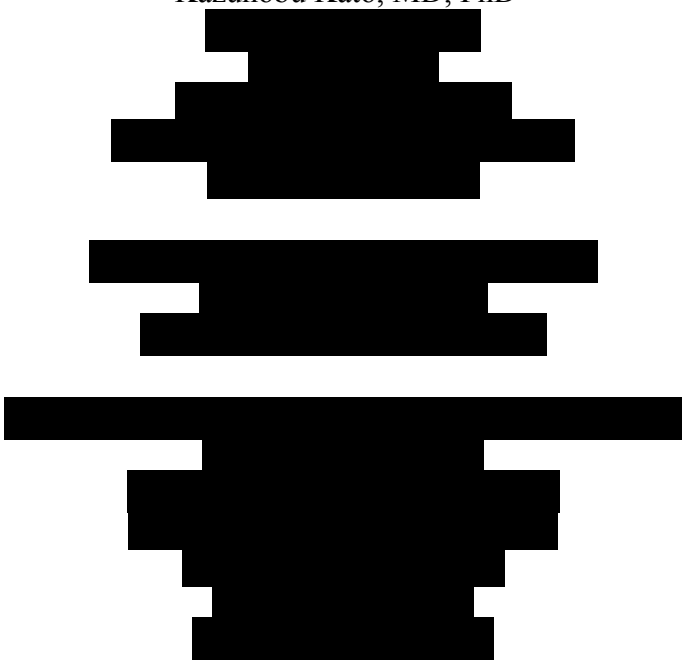
A Single-Arm, Open-Label, Phase 2 Study of Nivolumab (BMS-936558) in Subjects with Relapsed or Refractory Diffuse Large B-Cell Lymphoma (DLBCL) After Failure of Autologous Stem Cell Transplant (ASCT) or After Failure of At Least Two Prior Multi-Agent Chemotherapy Regimens in Subjects Who Are Not Candidates for ASCT

(CheckMate 139: CHECKpoint pathway and nivoluMAb clinical Trial Evaluation 139)

Revised Protocol No.:03
Incorporates Amendment(s):05

Medical Monitor/Study Director

Kazunobu Kato, MD, PhD



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

DOCUMENT HISTORY

Document	Date of Issue	Summary of Change
Revised Protocol 03	21-Jul-2016	Incorporates Amendment 05
Amendment 05	21-Jul-2016	[redacted]
Revised Protocol 02	23-Jul-2014	Incorporates Amendment 03
Amendment 03	23-Jul-2014	Allows for continued treatment of subjects in certain instances where protocol-defined progression criteria have been met. The amendment also serves to clarify various protocol requirements to ensure consistency in the execution of the study including secondary [redacted]
Revised Protocol 01	06-Dec-2013	Incorporates Amendment 01
Amendment 01	06-Dec-2013	Based on FDA feedback; the number of failed prior multi-agent chemotherapy regimens required for subjects that are ineligible for ASCT was changed from ≥ 1 to ≥ 2. Criteria were added to exclude subjects that had received chest radiation ≤ 24 weeks from first dose of study drug, and those that had received ≥ 1000 mg of carmustine (BCNU) as part of their pre-transplant conditioning regimen. Other minor corrections/clarifications were also made.
Original Protocol	30-Oct-2013	Not applicable

SYNOPSIS

Clinical Protocol CA209139

Protocol Title: **A Single-Arm**, Open-Label, Phase 2 Study of Nivolumab (BMS-936558) in Subjects with Relapsed or Refractory Diffuse Large B-Cell Lymphoma (DLBCL) After Failure of Autologous Stem Cell Transplant (ASCT) or After Failure of At Least Two Prior Multi-Agent Chemotherapy Regimens in Subjects Who Are Not Candidates for ASCT

Investigational Product(s), Dose and Mode of Administration, Duration of Treatment with Investigational Product(s): Nivolumab (BMS-936558) administered IV over 60 minutes at 3 mg/kg every 2 weeks until progression or unacceptable toxicity. Treatment beyond progression is allowed as specified in protocol section 4.3.8.

Study Phase: 2b

[redacted]

Primary Objective

To assess the clinical benefit of nivolumab, as measured by independent radiologic review committee (IRRC) assessed objective response rate (ORR) in subjects with DLBCL who are refractory or have relapsed following ASCT or after failure of at least two prior multi-agent chemotherapy regimens in ASCT ineligible patients.

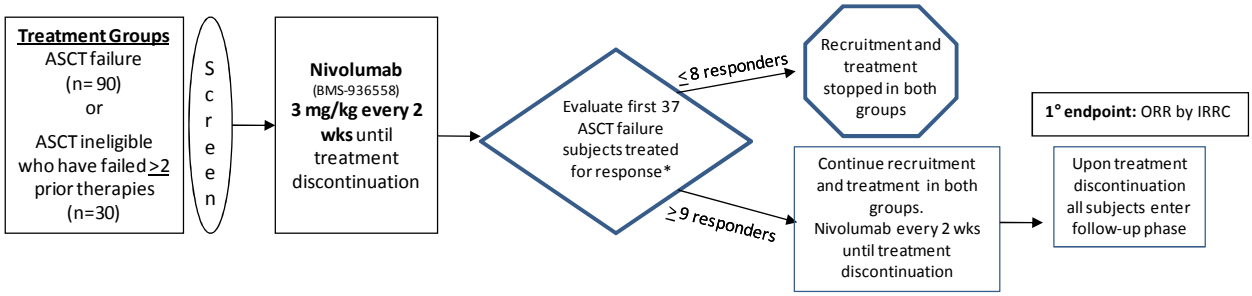
Secondary Objectives(s)

- To assess the duration of response (DOR) based on IRRC assessments
- To assess the complete remission rate (CRR) and the duration of CR based on IRRC assessment
- To assess the PR rate and the duration of PR based on IRRC assessment
- To assess the progression free survival (PFS) based on IRRC assessment
- To assess the ORR, based on investigator assessments

[redacted]

Study Design: This is a single-arm Phase 2 study in subjects ≥ 18 years old with relapsed or refractory DLBCL or transformed lymphoma (TL) after failure of ASCT or after failure of at least two prior multi-agent chemotherapy regimens in subjects who are not ASCT candidates. Approximately 120 subjects will be treated with nivolumab 3 mg/kg IV every 2 weeks. Subjects will undergo screening evaluations to determine eligibility within 28 days prior to first dose. Each 14-day dosing period will constitute a cycle. Tumor assessments will begin 8 weeks after the start of therapy and follow the schedule shown in Table 5.4.1-1. An independent radiology review committee (IRRC) will also be utilized. The primary endpoint of this study is IRRC-assessed ORR, using the 2007 revised International Working Group Criteria for Malignant Lymphoma criteria. Secondary endpoints include IRRC-assessed DOR, as well as CRR, duration of CR, PR rate, duration of PR, and PFS as determined by IRRC and ORR based on investigator assessment. Collection of fresh tumor tissue (FFPE tumor tissue block or 10 unstained slides from a biopsy performed during the screening phase or collected as a standard of care procedure within 90 days prior to

obtaining informed consent) for determination of PD-L1 expression status is mandatory. Archival tissue should be submitted for all subjects if available.



* Recruitment and treatment of subjects in both groups (ASCT failure and ASCT ineligible) will continue as described during the evaluation of the first 37 ASCT failure subjects treated.

It is anticipated that accrual will last 24 months, with approximately 150 subjects enrolled

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

Key Inclusion Criteria (see Protocol Section 3.3.1 for full list of criteria):

Inclusion Criteria:

1. Men and women ≥ 18 years of age.
2. Eastern Cooperative Oncology Group (ECOG) performance status (PS) 0 or 1.
3. Biopsy confirmation of relapsed, refractory DLBCL, or transformed lymphoma (TL) prior to the initiation of study drug. DLBCL or TL should be pathologically confirmed by standard immunohistochemical or flow cytometric techniques. Subjects with grade 3b follicular lymphoma are excluded.
4. Measurable disease on cross-sectional imaging that is > 1.5 cm in the longest diameter and measureable in two perpendicular dimensions per computed tomography (spiral CT) or MRI
5. Prior treatment as defined below:
    a. Subjects with relapsed or refractory DLBCL or TL after high-dose conditioning chemotherapy and ASCT, or
    b. Subjects with relapsed or refractory DLBCL or TL after at least 2 prior multi-agent chemotherapy regimens if ASCT ineligible. Ineligibility for ASCT will be determined using local institutional criteria.

Exclusion Criteria:

1) Prior chemotherapy within 2 weeks, nitrosureas within 6 weeks, therapeutic anticancer antibodies within 4 weeks, radio- or toxin immunoconjugates within 10 weeks, radiation therapy within 3 weeks, or major surgery within 2 weeks of first dose of the study drug
2) Prior therapy with 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
3) ASCT ≤ 12 weeks prior to first dose of the study drug.
4) Prior allogeneic SCT
5) Known central nervous system lymphoma
6) History of interstitial lung disease

7) Chest radiation ≤ 24 weeks prior to the first dose of study drug

8) Carmustine (BCNU) ≥ 1000 mg received as part of pre-transplant conditioning regimen

Study Assessments: The primary endpoint is objective response rate (ORR), as determined by an independent radiologic review committee (IRRC) according to the 2007 revised International Working Group Criteria for Malignant Lymphoma. Subjects will be assessed for response by imaging (spiral CT/MRI) beginning at week 8 and follow the schedule shown in Table 5.4.1-1. A PET scan is required to confirm CR.

Subjects that discontinue study treatment to receive an allogeneic SCT or ASCT will have tumor assessment and GVHD evaluations performed as described in sections 5.3 and 5.4.

Statistical Considerations:

Sample Size: The planned sample size for this study will be approximately 120 treated subjects, placed into two groups of subjects based on prior ASCT failure [n = 90] or ASCT ineligibility [n = 30].

For the ASCT-failed cohort, a modified Simon's two-stage design will be used to test the null hypothesis that the true ORR is ≤ 20% (not considered clinically compelling). In the first stage, 37 subjects will be accrued. If there are 8 or fewer responses in these 37 subjects, the study will be stopped. Otherwise, approximately 53 additional patients will be accrued to target a total of 90 treated subjects. The null hypothesis will be rejected if 25 or more responses are observed in 90 treated subjects. This design yields a one-sided type I error rate of 5% and power of 90% when the true response rate is 35%.

For the ASCT ineligible cohort, the sample size of 30 treated subjects is determined to achieve a confidence interval (CI) width around the ORR estimate with a sufficient level of precision. If the observed number of subjects with ORR is 10 (33%), the width of the exact 2-sided 95% CI is 36% with a lower bound of 17.3%.

Endpoints:

The primary endpoint is IRRC-assessed ORR. The secondary endpoints are duration of ORR (DOR) based on IRRC assessments, IRRC-assessed complete remission rate and duration of CR, IRRC-assessed PR rate and duration of PR, IRRC-assessed progression free survival (PFS), and investigator-assessed ORR.

Analyses:

The IRRC-assessed ORR will be summarized for each cohort by binomial response rates and their corresponding two-sided 90% and 95% exact CIs. The method proposed by Atkinson and Brown will be used to estimate the CI for the ASCT failed cohort. This confidence interval takes into account the group sequential nature of the two-stage design. The Clopper-Pearson method will be used to estimate the CI for the ASCT ineligible cohort.

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

IRRC-assessed CRR, PRR and investigator-assessed ORR will be summarized similarly to the primary endpoint. Duration of CR and PR will be summarized similarly to DOR. IRRC-assessed PFS will be summarized descriptively by cohort using the Kaplan-Meier (KM) product-limit method. Median values of PFS, along with the two-sided 95% CIs using a method based on the log-log transformation, will also be calculated.

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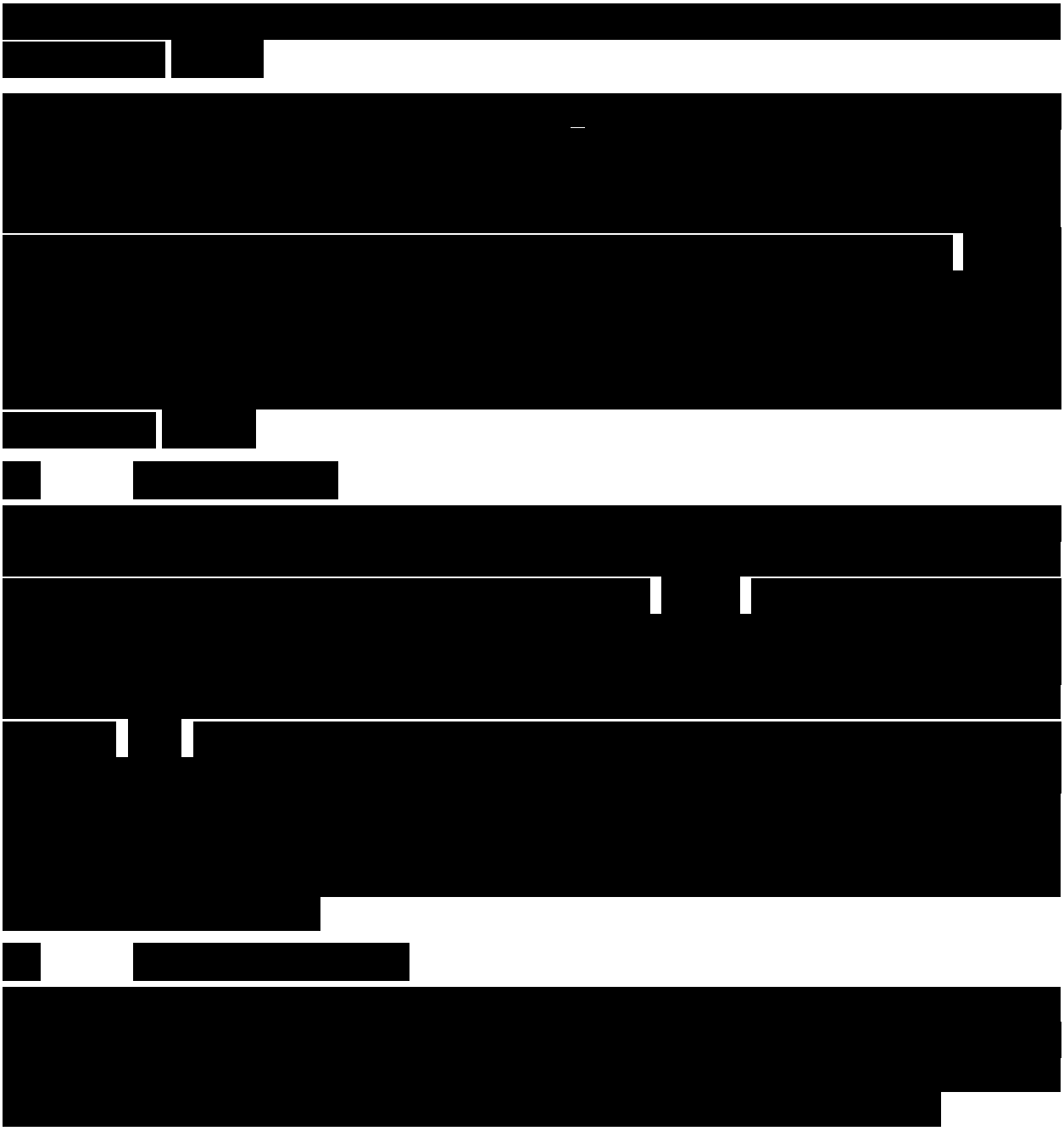


1.3 Objectives(s)

1.3.1 Primary Objectives

To assess the clinical benefit of nivolumab, as measured by independent radiologic review committee (IRRC) assessed objective response rate (ORR) in subjects with DLBCL or TL who are refractory or have relapsed following ASCT or after failure of at least two prior multi-agent chemotherapy regimens in ASCT ineligible patients.

1.3.2 Secondary Objectives

- To assess the duration of response (DOR) based on IRRC assessments

- To assess the complete remission rate (CRR) and the duration of CR based on IRRC assessment
- To assess the PR rate and the duration of PR based on IRRC assessment
- To assess progression free survival (PFS) based on IRRC assessment
- To assess the ORR, based on investigator assessments

[redacted]

[redacted]

[redacted]

[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 Harmonisation (ICH) and in accordance with the ethical principles underlying European Union Directive 2001/20/EC and the United States Code of Federal Regulations, Title 21, Part 50 (21CFR50).

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

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

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

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

2.2 Institutional Review Board/Independent Ethics Committee

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

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

2.3 Informed Consent

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

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

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

Investigators must:

1. Provide a copy of the consent form and written information about the study in the language in which the subject is most proficient prior to clinical study participation. The language must be non-technical and easily understood.
2. Allow time necessary for subject or subject's legally acceptable representative to inquire about the details of the study.

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

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

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

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

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

3 INVESTIGATIONAL PLAN

3.1 Study Design and Duration

This is a single-arm Phase 2 study in subjects ≥ 18 years old with relapsed or refractory DLBCL, or transformed lymphoma (TL), after failure of ASCT or after failure of at least two prior multi-agent chemotherapy regimens in subjects who are not ASCT candidates. Approximately 120 subjects will be treated with nivolumab 3 mg/kg IV every 2 weeks. Subjects will be placed into treatment groups based on prior ASCT failure [n = 90] or ASCT ineligibility [n = 30].

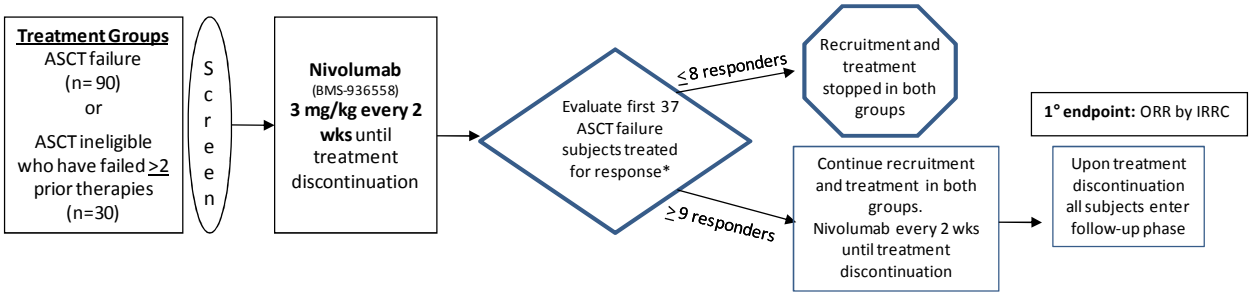
For the ASCT-failed cohort, a two-stage design will be used to test whether nivolumab yields a clinically compelling objective response rate. In the first stage, responses will be evaluated by the IRRC on the first 37 subjects treated. If there are 8 or fewer responses in these 37 subjects, the study will be stopped. In this case, the study will be terminated in both the ASCT-failed cohort as well as the ASCT ineligible cohort. Otherwise, approximately 53 additional subjects will be accrued into the ASCT-failed cohort to target a total of 90 treated subjects. The tolerability of the regimen will continue to be evaluated by the sponsor with the investigators to ensure that it is acceptable for continued enrollment. For the ASCT ineligible cohort a single-stage design will be used to estimate the objective response rate using approximately 30 treated subjects.

NOTE: During the evaluation of response in the first 37 ASCT-failed subjects treated, recruitment and treatment of subjects will continue for both the ASCT-failed and ASCT ineligible cohorts.

Subjects will undergo screening evaluations to determine eligibility within 28 days prior to first dose. Each 14-day dosing period will constitute a cycle. Tumor assessments will begin 8 weeks after the start of therapy and will continue every 8 weeks through the first 8 months of treatment, every 12 weeks from months 9 to year 2, and then every 6 months until disease progression (Table 5.4.1-1). An independent radiology review committee (IRRC) will also be utilized. The primary endpoint of this study is IRRC-assessed objective response rate (ORR), using the 2007 revised International Working Group Criteria for Malignant Lymphoma criteria (Appendix 2). Secondary endpoints include IRRC-assessed duration of objective response (DOR), as well as complete remission rate (CRR), duration of CR, PR rate, duration of PR, and progression free survival (PFS) as determined by IRRC assessment and ORR based on investigator assessment.

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

Figure 3.1-1: Study Design Schematic



* Recruitment and treatment of subjects in both groups (ASCT failure and ASCT ineligible) will continue as described during the evaluation of the first 37 ASCT failure subjects treated.

Study Duration

It is anticipated that accrual will last 18 months, with approximately 150 subjects enrolled. It is anticipated that the analysis of the primary endpoint will take place approximately 24 months from FPFV.

Additional survival analysis will be conducted for up to 5 years beyond analysis of the primary endpoint.

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

Screening (see Table 5.1-1)

- Begins by establishing the subject's initial eligibility and signing of the informed consent form (ICF).
- Subject is enrolled using the Interactive Voice Response System (IVRS) to obtain a subject ID.
- Confirm that documentation of relapsed or refractory DLBCL, or TL is present in the subject's medical record;
  - Submission of tumor tissue (FFPE tumor tissue block or 10 unstained slides) from a biopsy performed within 90 days prior to obtaining informed consent is mandatory for determination of PD-L1 expression status. If tissue taken as part of a standard of care procedure within 90 days prior to obtaining informed consent is not available, then a biopsy must be performed during the screening period and submitted accordingly.
  - Biopsy samples should be excisional, incisional or core needle
  - Subjects may initiate study drug therapy prior to the determination of PD-L1 expression status.

NOTE: In rare cases where tumor tissue, obtained during screening or within 90 days prior to obtaining informed consent, cannot be provided, the reason must be clearly documented in the medical record AND the BMS Medical Monitor must be contacted. Archival tissue, if available, should be submitted for these subjects. Submission of archival tissue is also encouraged for all subjects, irrespective of whether tumor biopsy tissue is available as specified.

- Confirm that a bone marrow biopsy/aspirate was performed within 90 days prior to obtaining informed consent-in the subject's medical record;
  - If a bone marrow biopsy/aspirate was not performed within 90 days prior to obtaining informed consent, a bone marrow biopsy/aspirate must be performed during the screening period.
    - ♦ If a bone marrow biopsy/aspirate needs to be performed during the screening period, submission of an aspirate sample for biomarker analyses is optional as per Table 5.1-1
    - ♦ Subjects may begin study drug treatment before bone marrow biopsy results become available; results need to be documented in the subject's medical record later
- The Revised International Prognostic Index (IPI) as determined at the time of initial disease diagnosis must be reported in the eCRF (See Appendix 3)
- Baseline disease or tumor assessments should be performed within 28 days of first dose of study drug, according to Table 5.1-1

- Subject is assessed for study eligibility within the required timeframe found in Table 5.1-1.
- The screening phase either ends with confirmation of full eligibility and treatment of the subject or with the confirmation that the subject is a screen failure.

Treatment: (see Table 5.1-2)

- Treatment begins with the call to the IVRS to obtain vial assignments. A negative pregnancy test should be documented within 24 hours prior to the start of investigational product. Subsequently, women of childbearing potential (WOCBP) must have a pregnancy test every 4 weeks (± 7 days) regardless of dosing schedule.
- The subject should receive the dose of study medication within 1 day of vial assignment.
- Subjects may be dosed no less than 12 days between doses and no more than 3 days after the scheduled dosing date. Dose given after the 3-day window is considered a dose delay. A maximum delay of 42 days between doses is allowed.
- On-study laboratory assessments should be drawn within 72 hours prior to dosing.
- Adverse event assessments should be documented at each clinic visit.
- [redacted]
- Study drug is administered as an IV infusion over 60 minutes on Treatment Day 1 of each cycle until disease progression or discontinuation due to toxicity, withdrawal of study consent, or the study ends. Treatment beyond progression is allowed in certain instances as described in Section 4.3.8.
- Study drug dosing may be delayed for toxicity. See Sections 4.3.2 and 4.3.4.
- Subjects will be evaluated for tumor response according to the 2007 revised International Working Group Criteria for Malignant Lymphoma (Appendix 2) by spiral CT/MRI beginning at week 9 and continuing every 8 weeks (+/- 1 week) through the first 8 months, every 12 weeks (+/- 2 weeks) months 9-24, and then every 6 months (+/-3 weeks) thereafter until disease progression is documented or until the subject initiates a preparative regimen for allogeneic SCT or ASCT, whichever occurs earlier. If the subject discontinues treatment prior to disease progression, tumor assessment will continue in the follow-up phase.
- Screening/Baseline and all subsequent scans will be submitted to an IRRC, once the subject has been enrolled and throughout the study period.
- Quality of Life (QoL) tools must be completed at Treatment Day 1 prior to the first dose of study drug. Following that, QoL tools will be completed according to the schedule in Table 5.1-2.
- This phase ends when the subject is discontinued from study therapy. For a complete list of reasons for treatment discontinuation, see Section 3.5 and 4.3.5.

Follow-Up Phase (See Table 5.1-3):

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

- Subjects will have two follow-up visits for safety. Follow-up visit 1 (X01), 35 days from the last dose (+/- 7d) and follow-up visit 2 (X02) 80 days (+/- 7d) later. After X02, subjects will be followed every 3 months for ongoing drug-related adverse events until resolved, return to baseline or deemed irreversible, or until lost to follow-up, or withdrawal of study consent.
- [redacted]
- Subjects who discontinue study therapy for reasons other than disease progression or to receive an allogeneic or autologous stem cell transplant, will continue to have radiographic assessments at the intervals described in the Treatment Phase until disease progression, lost to follow-up, or withdrawal of study consent.
- For subjects who discontinue study therapy by proceeding to allogeneic SCT or ASCT, tumor assessment by the investigator will be required after allogeneic SCT or ASCT (see Section 3.6). For the subjects who discontinue study therapy by proceeding to allogeneic SCT, acute and chronic GVHD documentation will also be simultaneously collected (see Section 5.3).
- After completion of the two follow-up visits for safety, subjects will be followed every 3 months for survival, until death, lost to follow-up or withdrawal of study consent.
- QoL tools will be completed according to the schedule in Table 5.1-3

3.2 Post Study Access to Therapy

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

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

2. Target Population

a) Tumor Biopsy confirmation of relapsed or refractory DLBCL, or transformed lymphoma (TL), prior to the initiation of study drug.

   i) TL is limited to DLBCL. Subjects with Grade 3b follicular lymphoma are excluded.

   ii) DLBCL or TL should be pathologically confirmed by standard immunohistochemical or flow cytometric techniques.

   iii) Documentation of the above should be present in the subject's medical record.

b) Eastern Cooperative Oncology Group (ECOG) performance status of 0-1 (Appendix 4).

c) Measurable disease: Subjects must have at least one lesion that is > 15mm (1.5 cm) in the longest diameter on cross-sectional imaging and measureable in two perpendicular dimensions per computed tomography (spiral CT) or MRI.

d) Prior treatment as defined below;

   i) Subjects with relapsed DLBCL or TL after high-dose conditioning chemotherapy and ASCT, or

   ii) Subjects with relapsed or refractory DLBCL or TL after at least 2 prior multi-agent chemotherapy regimens if ASCT ineligible. Ineligibility for ASCT will be determined using local institutional criteria.

   For subjects with TL, chemotherapy regimens used for the treatment of follicular lymphoma can be considered as prior therapy provided these regimens utilized multi-agents in combination (excluding rituximab-based regimens without any cytotoxic drug)

   Definition of Relapsed DLBCL

   - the appearance of new lesions > 6 months after obtaining a CR
   - an increase ≥50% in the size of previously involved sites > 6 months after completing planned therapy.

   Definition of Refractory DLBCL

   - < 50% decrease in lesion size after planned therapy,
   - the appearance of new lesions during therapy or < 6 months after completion of planned therapy
   - an increase of ≥50% in the size of previously involved sites during therapy or < 6 months after completion of planned therapy.

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

3. Physical and Laboratory Test Finding

Screening laboratory values must meet the following criteria and should be obtained within 14 days prior to first dose:

i) Absolute Neutrophil Count ≥ 750/μL (no WBC growth factors for prior 14 days)

ii) Platelets ≥50 x10^3/μL (no platelet transfusions for prior 14 days)

iii) Hemoglobin ≥ 8.5 g/dL (no RBC transfusions for prior 7 days)

iv) Serum creatinine ≤ 1.5 x ULN or creatinine clearance (CrCl) ≥ 40 ml/min (measured using the Cockcroft-Gault formula below):

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

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

v) AST/ALT ≤ 3 x ULN

vi) Total Bilirubin ≤ 1.5 x ULN (except subjects with Gilbert's Syndrome, who can have total bilirubin < 3.0 mg/dL).

4. Age and Reproductive Status

a) Men and women ≥ 18 years of age.

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

c) Women must not be breastfeeding

d) WOCBP must agree to follow instructions for method(s) of contraception from the time of enrollment for the duration of treatment with nivolumab plus 5 half-lives of nivolumab plus 30 days (duration of ovulatory cycle) for a total of 23 weeks post treatment completion.

e) Men who are sexually active with WOCBP must agree to follow instructions for method(s) of contraception for the duration of treatment with nivolumab plus 5 half-lives of nivolumab plus 90 days (duration of sperm turnover) for a total of 31 weeks post-treatment completion.

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

Investigators shall counsel WOCBP and male subjects who are sexually active with WOCBP on the importance of pregnancy prevention and the implications of an unexpected pregnancy Investigators shall advise WOCBP and male subjects who are sexually active with WOCBP on

the use of highly effective methods of contraception. Highly effective methods of contraception have a failure rate of < 1% per year when used consistently and correctly.

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

HIGHLY EFFECTIVE METHODS OF CONTRACEPTION

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

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

LESS EFFECTIVE METHODS OF CONTRACEPTION

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

*A male and female condom must not be used together

3.3.2 Exclusion Criteria

1. Target Disease Exceptions

a) Known central nervous system lymphoma.

2. Medical History and Concurrent Diseases

a) History of interstitial lung disease.

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

c) 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.

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

e) Subjects with a condition requiring systemic treatment with either corticosteroids (> 10 mg daily prednisone equivalents) or other immunosuppressive medications within 14 days of study drug administration. Inhaled or topical steroids, and adrenal replacement doses > 10 mg daily prednisone equivalents are permitted in the absence of active autoimmune disease.

3. Physical and Laboratory Test Findings

a) Any positive test for hepatitis B virus or hepatitis C virus indicating acute or chronic infection.

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

4. Allergies and Adverse Drug Reaction

a) History of allergy to study drug components.

b) History of severe hypersensitivity reaction to any monoclonal antibody with the following exception.

Subjects who experienced grade 3-4 infusion-related reaction with the first dose of rituximab, but who were able to receive subsequent rituximab without recurrence of grade 3 or 4 infusion-related reaction are eligible

5. Prohibited Treatments and or Therapies

a) Autologous Stem Cell Transplant (ASCT) ≤ 12 weeks prior to first dose of the study drug.

b) Prior chemotherapy within 2 weeks, nitrosureas within 6 weeks, therapeutic anticancer antibodies within 4 weeks, radio- or toxin immunoconjugates within 10 weeks, radiation therapy within 3 weeks, or major surgery within 2 weeks of first dose of the study drug.

c) Prior treatment with an anti-PD-1, anti-PD-L1, anti-PD-L2, anti-CTLA-4 antibody, or any other antibody or drug specifically targeting T-cell costimulation or immune checkpoint pathways

d) Prior allogeneic SCT.

e) Chest radiation ≤ 24 weeks prior to the first dose of study drug

f) Carmustine (BCNU) ≥ 1000 mg received as part of pre-transplant conditioning regimen

6. Other Exclusion Criteria

a) Prisoners or subjects who are involuntarily incarcerated

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

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

3.3.3 Women of Childbearing Potential

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

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

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

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

[redacted]

[redacted]

3.5 Discontinuation of Subjects from Treatment

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

- Disease progression as determined by investigator assessment following the guidelines given in section 5.4 except as outlined in section 4.3.8 Treatment Beyond Disease Progression.
- Subject's request to stop study treatment
- Any clinical adverse event (AE), laboratory abnormality or intercurrent illness which, in the opinion of the investigator, indicates that continued participation in the study is not in the best interest of the subject
- Termination of the study by Bristol-Myers Squibb (BMS)
- Loss of ability to freely provide consent through imprisonment or involuntarily incarceration for treatment of either a psychiatric or physical (eg, infectious disease) illness
- Additional protocol-specified reasons for discontinuation (see Section 4.3.5)

In the case of pregnancy, the investigator must immediately notify the BMS Medical Monitor/designee of this event. In most cases, the study drug will be permanently discontinued in an appropriate manner. If the investigator determines a possible favorable benefit/risk ratio that warrants continuation of study drug, a discussion between the investigator and the BMS Medical Monitor/designee must occur.

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

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

3.6 Post Treatment Study Follow up

In this study, ORR and DOR are key endpoints of the study. Post treatment study follow-up is of critical importance and is essential to preserving subject safety and the integrity of the study. Subjects who discontinue study treatment must continue to be followed for collection of outcome and/or survival follow-up data as required and in line with Section 5 until death or the conclusion of the study.

In addition, subjects who discontinue study therapy by proceeding to allogeneic SCT or ASCT will require tumor assessment (CR or non-CR) by the investigators according to the 2007 IWG criteria 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 SCT is documented (see Section 5.4). For the subjects who discontinue study therapy by proceeding to allogeneic SCT, documentation of acute and chronic GVHD will be simultaneously collected (see Section 5.3).

3.6.1 Withdrawal of Consent

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

3.6.2 Lost to Follow-Up

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

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

attempts, the subject remains lost to follow-up, then the last known alive date as determined by the investigator should be reported and documented in the subject's medical records.

4 TREATMENTS

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

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

4.1 Study Treatments

Table 4.1-1: Product Description - Treatment Period

Product Description and Dosage Form	Potency	Primary Packaging (Volume)/ Label Type	Secondary Packaging (Qty) /Label Type	Appearance	Storage Conditions (per label)
BMS-936558-01 Solution for Injection[a]	100 mg (10 mg/mL)	10 mL per vial (Open label)	10 vials per carton/Open label	Clear to opalescent colorless to pale yellow liquid. May contain particles	2 to 8 °C. Protect from light and freezing

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

Premedications or medications used to treat infusion-related reactions should be sourced by the investigative sites if available and permitted by local regulations.

4.1.1 Investigational Product

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

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

BMS-936558 100 mg (10 mg/mL) will be packaged in an open-label fashion.

Ten BMS-936558, 10 mL vials will be packaged within a carton (see Table 4.1-1), and are not subject or treatment arm specific. Vial assignments by subjects will be made through the IVRS to track usage and resupply.

4.1.2 Non-investigational Product

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

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

4.1.3 Handling and Dispensing

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

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

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

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

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

Nivolumab is to be administered as a 60-minute IV infusion, using a volumetric pump with a 0.2/0.22 micron in-line filter at the protocol-specified dose. The drug can be diluted with 0.9% normal saline for delivery but the total drug concentration of the solution cannot be below 0.35 mg/mL. It is not to be administered as an IV push or bolus injection. At the end of the infusion, flush the line with a sufficient quantity of normal saline.

4.2 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. Every subject that signs the informed consent form must be assigned a subject number in IVRS. Specific instructions for using IVRS will be provided to the investigational site in a separate document.

The investigator (or designee) will register the subject for enrollment by following the enrollment procedures established by BMS. The following information is required for enrollment:

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

4.3 Selection and Timing of Dose for Each Subject

Eligible subjects will receive treatment with nivolumab at a dose of 3 mg/kg as a 60-minute IV infusion, on Day 1 of a treatment cycle every 2 weeks. Dosing calculations should be based on the body weight assessed as per Table 5.1-2. If the subject's weight on the day of dosing differs by > 10% from the weight used to calculate the dose, the dose must be recalculated. All doses should be rounded to the nearest milligram. There will be no dose escalations or reductions of nivolumab allowed. Subjects may be dosed no less than 12 days between doses and no more than 3 days after the scheduled dosing date. There are no premedications recommended for nivolumab on the first cycle. If an acute infusion reaction is noted, subjects should be managed according to Section 4.3.6.

Treatment may be delayed for up to a maximum of 6 weeks from the previous dose (See Sections 4.3.2 and 4.3.4).

Tumor assessments by spiral CT/MRI for all subjects should continue as per protocol even if dosing is delayed.

Subjects will be monitored continuously for AEs while on study. Treatment modifications (eg, dose delay or discontinuation) will be based on specific laboratory and adverse event criteria.

4.3.1 Antiemetic Premedications

Antiemetic premedications should not be routinely administered prior to dosing of study drug.

4.3.2 Dose Delay Criteria

Dose delay criteria apply for all drug-related adverse events. Nivolumab must be delayed until treatment can resume (see Section 4.3.4).

Nivolumab administration should be delayed for the following:

- Any Grade ≥ 2 non-skin, drug-related adverse event, with the following exceptions:
    - Grade 2 drug-related fatigue or laboratory abnormalities do not require a treatment delay.
- Any Grade 3 skin, drug-related adverse event.
- Any Grade 3 drug-related laboratory abnormality, with the following exceptions for lymphopenia, leukopenia, AST, ALT, or total bilirubin:
    - Grade 3 lymphopenia or leukopenia does not require dose delay.

      If a subject has a baseline AST, ALT or total bilirubin that is within normal limits, delay dosing for drug-related Grade ≥ 2 toxicity.

      If a subject has baseline AST, ALT, or total bilirubin within the Grade 1 toxicity range, delay dosing for drug-related Grade ≥ 3 toxicity.
- Any adverse event, laboratory abnormality, or intercurrent illness which, in the judgment of the investigator, warrants delaying the dose of study medication.

[redacted]

[redacted]

4.3.3 Dose Modifications

Dose reductions and escalations of nivolumab are not permitted.

4.3.4 Criteria to Resume Nivolumab Dosing

Subjects may resume treatment with nivolumab (BMS-936558) when the drug-related AE(s) resolve(s) to Grade ≤ 1 or baseline, with the following exceptions:

- Subjects may resume treatment in the presence of Grade 2 fatigue.
- Subjects who have not experienced a Grade 3 drug-related skin AE may resume treatment in the presence of Grade 2 skin toxicity.
- Subjects with baseline AST/ALT or total bilirubin in the Grade 1 toxicity range who require dose delays for reasons other than a 2-grade shift in AST/ALT or total bilirubin may resume treatment in the presence of Grade 2 AST/ALT OR total bilirubin.
- Subjects with combined Grade 2 AST/ALT AND total bilirubin values meeting discontinuation parameters (Section 4.3.5) should have treatment permanently discontinued.
- Drug-related pulmonary toxicity, diarrhea, colitis or nephritis must have resolved to baseline before treatment is resumed.
- Drug-related endocrinopathies adequately controlled with only physiologic hormone replacement may resume treatment.

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

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

4.3.5 Treatment Discontinuation Criteria

Nivolumab treatment should be permanently discontinued for the following:

- Any Grade 2 drug-related uveitis or eye pain or blurred vision that does not respond to topical therapy and does not improve to Grade 1 severity within the re-treatment period OR requires systemic treatment.
- Any Grade 3 non-skin, drug-related adverse event lasting > 7 days, with the following exceptions for 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
- Any drug-related liver function test (LFT) abnormality that meets the following criteria require discontinuation:
  - AST or ALT > 5 - 10 x ULN for > 2 weeks
  - AST or ALT > 10 x ULN
  - Total bilirubin > 5x ULN
  - Concurrent AST or ALT > 3x ULN and total bilirubin > 2x ULN

- Any Grade 4 drug-related adverse event 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 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 amylase or lipase abnormalities that are not associated with symptoms or clinical manifestations, or radiographic signs of pancreatitis. It is recommended to consult with the BMS Medical Monitor for Grade 4 amylase or lipase abnormalities
  - Grade 3 or 4 drug-related endocrinopathy AEs such as adrenal insufficiency, ACTH (Adrenocorticotropic Hormone) deficiency, hyper- or hypothyroidosis, or glucose intolerance, which resolve or are adequately controlled with physiologic hormone replacement (steroids, thyroid hormones) or glucose controlling agents, respectively, may not require discontinuation after discussion with and approval from the BMS Medical Monitor
- Any dosing interruption lasting > 6 weeks from the previous dose, with the following exceptions:
  - Dosing interruptions to allow for prolonged steroid tapers to manage drug-related adverse events are allowed. Prior to re-initiating treatment in a subject with a dosing interruption lasting > 6 weeks from the previous dose, the BMS medical monitor must be consulted. Tumor assessments should continue as per protocol even if dosing is interrupted
  - Dosing interruptions > 6 weeks from the 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 interruption 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 interrupted
- Any adverse event, laboratory abnormality, or intercurrent illness which, in the judgment of the Investigator, presents a substantial clinical risk to the subject with continued nivolumab (BMS-936558) dosing.

- Disease progression (as determined by investigator assessment following the guidelines given in section 5.4). Treatment beyond progression is allowed in certain instances as described in Section 4.3.8.
- Subject who initiated the preparative regimen for allogeneic SCT or ASCT after the first dose of nivolumab treatment.

4.3.6 Treatment of BMS-936558-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, arthalgias, 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 NCI CTCAE (Version 4.0) guidelines.

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

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

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

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

Stop the nivolumab infusion, begin an IV infusion of normal saline, and treat the subject with diphenhydramine 50 mg IV (or equivalent) and/or paracetamol 325 to 1000 mg (acetaminophen); remain at bedside and monitor subject until resolution of symptoms. Corticosteroid or bronchodilator therapy may also be administered as appropriate. If the infusion is interrupted, 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. Administer diphenhydramine 50 mg IV, and remain at bedside and monitor the subject until resolution of symptoms. The amount of study drug infused must be recorded on the electronic case report form (eCRF). The following prophylactic premedications are recommended for future infusions: diphenhydramine 50 mg (or equivalent) and/or paracetamol 325 to 1000 mg (acetaminophen) should be administered at least 30 minutes before additional

nivolumab administrations. If necessary, corticosteroids (recommended dose: up to 25 mg of IV hydrocortisone or equivalent) may be used.

For Grade 3 or 4 symptoms: (Severe reaction, Grade 3: prolonged [ie, not rapidly responsive to symptomatic medication and/or brief interruption of infusion]; recurrence of symptoms following initial improvement; hospitalization indicated for other clinical sequelae [eg, renal impairment, pulmonary infiltrates]. Grade 4: Life-threatening; pressor or ventilatory support indicated).

- Immediately discontinue infusion of nivolumab. 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 the case of late-occurring hypersensitivity symptoms (eg, appearance of a localized or generalized pruritis within 1 week after treatment), symptomatic treatment may be given (eg, oral antihistamine, or corticosteroids).

4.3.7 Guidelines for Assessment and Management of Tumor Lysis Syndrome

The possibility of tumor lysis syndrome cannot be ruled out for the subjects with lymphoma. Therefore, adequate management such as hydration and/or the use of allopurinol is recommended in the subjects who have risk factor of potential tumor lysis syndrome, for example the subjects with high tumor burden, reflected by high serum LDH levels, or bulky disease, or those with preexisting renal failure.

4.3.8 Treatment Beyond Disease Progression

4.3.8.1 Circumstances in which post-progression treatment is permitted

Subjects meeting progression defined by relapsed disease (after CR) or progressive disease (after PR, SD) per 2007 IWG criteria may continue receiving study medication beyond investigator-assessed progression as long as they meet the following criteria:

- Continue to meet all other study protocol eligibility criteria
- Investigator-assessed clinical benefit, and do not have rapid disease progression
- Stable performance status
- Treatment beyond progression will not delay an imminent intervention to prevent serious complications of disease progression
- Patients will be re-consented with an informed consent document describing any reasonably foreseeable risks or discomfort and other alternative treatment options
- Tolerance of study drug

The decision to continue treatment beyond investigator-assessed progression should be discussed with the BMS Medical Monitor and documented in the study records. The assessment of clinical benefit should take into account whether the subject is clinically deteriorating and unlikely to receive further benefit from continued treatment.

4.3.8.2 Assessment schedule for the subjects with post-progression treatment

The subject should continue to receive monitoring according to the On-Treatment Assessments on Table 5.1-2 except for FDG-PET scans. Radiographic assessment by CT (preferred) or MRI described in the section 5.4.1 and Table 5.4.1-1 are required when subjects continue post-progression treatment. FDG-PET scans are not mandated after investigator-assessed progression.

4.3.8.3 Discontinuation due to further progression

Subjects should discontinue study therapy upon evidence of further progression, defined as an additional 10% or greater increase in tumor burden volume from time of initial progression (including all target lesions and new measurable lesions).

- Further progression is evaluated by a subsequent CT or MRI which is performed at least 8 weeks from previous CT or MRI.
- The tumor burden volume from time of initial progression should be used as the reference baseline for comparison with the post-progression assessment.
- New lesions are considered measurable at the time of initial progression if the long axis is more than 15 mm regardless of the short axis. If a lymph node has a long axis of 11 to 15 mm, it should only be considered measurable if its short axis is more than 10 mm.
- Any new lesion considered non-measurable at the time of or after initial progression may become measurable and therefore included in the tumor burden determination.

4.3.8.4 Radiographic assessment for subjects who discontinue study drug during post-progression treatment

For subjects that discontinue post-progression treatment, no additional radiographic assessments will be required. Upon treatment discontinuation, these subjects will continue in the follow-up phase of the study (see section 5.1). Subjects who proceed to allogeneic SCT or ASCT will be followed as described in Section 5.4.

4.4 Blinding/Unblinding

Not applicable.

4.5 Treatment Compliance

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

4.6 Destruction and Return of Study Drug

4.6.1 Destruction of Study Drug

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

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

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

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

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

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

4.6.2 Return of Study Drug

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

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

5 STUDY ASSESSMENTS AND PROCEDURES

5.1 Flow Chart/Time and Events Schedule

Table 5.1-1: Screening Assessments (CA209139)

Procedure	Screening Visit	Notes
Eligibility Assessments		
Informed Consent	X	
Inclusion/Exclusion Criteria	X	All inclusion/exclusion criteria should be assessed at screening, with confirmation of eligibility documented prior to first dose
Medical History	X	
Prior Systemic Therapy	X	
Safety Assessments		
Physical Examination	X	
Physical Measurements	X	Include Height, Weight, and ECOG Performance Status
Revised International Prognostic Index (IPI) at time of initial disease diagnosis	X	Refer to Appendix 3
Vital Signs and oxygen saturation	X	Temperature, BP, HR, O_2 saturation by pulse oximetry (at rest and after exertion).
Assessment of Signs and Symptoms	X	Within 14 days prior to first dose
[redacted]	X	Within 14 days prior to first dose
Laboratory Tests	X	CBC with differential, Chemistry panel including LDH, AST, ALT, ALP, T.Bili, BUN or serum urea level, uric acid, creatinine, Ca, Mg, Na, K, Cl, P, glucose, amylase, lipase TSH (reflex to free T3, free T4 for abnormal TSH result), hepatitis B surface antigen (HBV sAg), and hepatitis C antibody (HCV Ab) or HCV ribonucleic acid (RNA) within 14 days prior to first dose.
Urinalysis	X	Total protein, glucose, blood, leukocyte esterase, specific gravity, and pH, within 14 days prior to first dose
Pregnancy Test	X	

Table 5.1-1: Screening Assessments (CA209139)		
Procedure	**Screening Visit**	**Notes**
Efficacy [redacted] Assessments		
Radiographic Tumor Assessment • Spiral CT/MRI of Chest, Abdomen, Pelvis, and any other known sites of disease, • PET scan	X	Should be performed within 28 days prior to first dose. Additional sites of known or suspected disease (including CNS) should be imaged by spiral CT/MRI at the screening visit and at subsequent on-study assessments. PET scan required at screening.
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
IVRS/Clinical Drug Supplies		
Phone calls to IVRS		Phone calls must be made to IVRS as follows; • For subject number assignment at the time informed consent is obtained. • Prior to dosing for study drug vial assignment (call should be made within 1 day prior to dosing).

Table 5.1-2: On Treatment Assessments (CA209139)				
Procedure	**Cycle 1 Day 1**	**Cycle 1 Day 8**	**Each cycle within 3 days prior to dosing**	**Notes**
Safety Assessments				
Targeted Physical Examination	X		X	Lymph node areas (eg, submandibular, cervical, supraclavicular, axillary, or inguinal lymph node), and abdominal organs (eg, spleen)
Vital Signs and Oxygen Saturation	X	X	X	Temperature, BP, HR, RR, O2 saturation by pulse oximetry at rest and after exertion (also monitor amount of supplemental oxygen if applicable) prior to dosing and at any time a subject has any new or worsening respiratory symptoms
Adverse Events Assessment	X	X	X	Assessed using NCI CTCAE v. 4.0
[redacted]	X	X	X	
Physical Measurements	X	X	X	Includes Weight and ECOG status
Laboratory Tests	X	X	X	extended on-treatment local laboratory assessments should be done within 72 hours prior to dosing for Cycle 1 through Cycle 5, and every alternate dose thereafter (Cycle 7, 9, 11, 13 etc) and include: CBC with differential, uric acid, serum urea level, serum creatinine, sodium, potassium, calcium, magnesium, phosphate, chloride, amylase, lipase, glucose, AST, ALT, total bilirubin, alkaline phosphatase, LDH. limited on-treatment local laboratory assessments should be done within 72 hours prior to dosing (beginning at Cycle 6 and every alternate dose thereafter (Cycle 8, 10, 12, 14 etc) and include: CBC with differential, LFTs (ALT, AST, total bilirubin, alkaline phosphatase) and creatinine.

Table 5.1-2: On Treatment Assessments (CA209139)				
Procedure	**Cycle 1 Day 1**	**Cycle 1 Day 8**	**Each cycle within 3 days prior to dosing**	**Notes**
Thyroid Function Testing			See Note	TSH (reflex to free T3 and free T4 if abnormal result) to be performed every 6 weeks (± 7 days) regardless of dosing schedule.
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 (± 7 days) regardless of dosing schedule.
Efficacy [redacted] Assessments				
Radiographic Tumor Assessment • Spiral CT/MRI of Chest Abdomen, Pelvis, and any other known sites of disease • PET scan			See Note	See Section 5.4.1 and Table 5.4.1-1 for spiral CT/MRI assessment schedule PET scan required to confirm CR
[redacted]			[redacted]	[redacted]
[redacted]			[redacted]	[redacted]
[redacted]				
[redacted]			[redacted]	[redacted]
[redacted]				
[redacted]	[redacted]		[redacted]	[redacted]

Table 5.1-2: On Treatment Assessments (CA209139)				
Procedure	**Cycle 1 Day 1**	**Cycle 1 Day 8**	**Each cycle within 3 days prior to dosing**	**Notes**
				[redacted]
Clinical Drug Supplies				
Administer Study Drug	X		X	IVRS should be called within 1 day prior to study drug administration to receive vial assignment

Table 5.1-3: Follow-up Assessments (CA209139)			
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), and abdominal organs (eg,spleen) To assess for potential late emergent study drug related issues
Adverse Events Assessment	X	X	
Laboratory Tests	X		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)
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 SCT. To be assessed on Day 100, at 6 months, at 1 year and every one year thereafter from the date of stem cell infusion until the first non-CR after SCT is documented. See Section 5.3

Table 5.1-3: Follow-up Assessments (CA209139)			
Procedure	**Follow Up, Visits 1 and 2[a] (X01 & X02)**	**Survival Follow-Up Visits[b]**	**Notes**
Efficacy Assessments			
Spiral CT/MRI PET scan	X	X	Only for subjects without progression on study therapy. • Tumor assessments should occur at the same intervals described in the Treatment Phase until disease progression, lost to follow-up, or withdrawal of study consent. • Spiral CT or MRI chest, abdomen, pelvis and all known sites of disease. Use same imaging method as was used at screening/baseline. PET scan required to confirm CR.
Investigator tumor assessment for subjects receiving subsequent allogeneic SCT or ASCT	See note	See note	Only for subjects who discontinued study therapy by proceeding to allogeneic SCT or ASCT. To be assessed on Day 100, at 6 months, at 1 year and every one year thereafter from the date of stem cell infusion until the first non-CR after SCT is documented. See Section 5.4
[redacted]			
[redacted]	[redacted]		
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]			
[redacted]	[redacted]		[redacted]

Table 5.1-3: Follow-up Assessments (CA209139)			
Procedure	**Follow Up, Visits 1 and 2[a] (X01 & X02)**	**Survival Follow-Up Visits[b]**	**Notes**
[redacted]			
[redacted]	[redacted]		[redacted]
Subject Status			
Survival Status	X	X	Every 3 months after X02; may be accomplished by visit, phone contact or email, to update survival information and assess subsequent anti-cancer therapy

[a] Follow-up visit 1 (X01) = 35 days from the last dose +/- 7 days. Follow-up visit 2 (X02) = 80 days (+/- 7 days) from follow-up visit X01.

[b] Survival Follow-up visits to occur every 3 months from X02

5.2 Study Materials

The following materials will be provided at study start:

- NCI CTCAE version 4.0
- BMS-936558 (nivolumab) Investigational Brochure
- Pharmacy Binder
- Laboratory manuals for collection and handling of blood (including PKs, biomarker and immunogenicity) and tissue specimens
- Site manual for operation of interactive voice response system (IVRS)
- Manual for entry of local laboratory data
- Serious Adverse Event (or eSAE) case report forms
- EQ-5D and EORTC QLQ-C30 questionnaires
- Pregnancy Surveillance Forms
- IRRC manual

5.3 Safety Assessments

At baseline, a medical history will be obtained to capture relevant underlying conditions. The baseline examinations should include weight, height, ECOG Performance Status, BP, HR, temperature, and oxygen saturation by pulse oximetry at rest and after exertion should be performed within 28 days prior to first dose. Baseline signs and symptoms are those that are assessed within 14 days prior to first dose. Concomitant medications will be collected from within 14 days prior to the first dose through the study treatment period (see Table 5.1-1).

Baseline local laboratory assessments should be done within 14 days prior to first dose to include: CBC w/differential, LFTs (ALT, AST, total bilirubin, alkaline phosphatase), uric acid, BUN or serum urea level, creatinine, Ca, Mg, Na, K, Cl, P, LDH, amylase, lipase glucose, urinalysis, TSH, and Hep B and C testing (HBV sAg, HCV Ab, or HCV RNA) (see Table 5.1-1). Pregnancy testing for WOCBP (done locally) must be performed at baseline (within 28 days prior to first dose) and repeated within 24 hours prior to the initial administration of study drug, then every 4 weeks (± 7 days) regardless of dosing schedule.

Subjects will be evaluated for safety if they have received any study drug. Toxicity assessments will be continuous during the treatment phase. During the safety follow-up phase (Follow-up visits X01 and X02, Table 5.1-3) toxicity assessments should be done in person. Once subjects reach the survival follow-up phase, either in-person visits or documented telephone calls/email correspondence to assess the subject's status are acceptable.

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

On-study weight, ECOG performance status, and vital signs should be assessed at each on-study visit prior to nivolumab dosing and ay Cycle 1 Day 8. Vital signs should also be taken as per institutional standard of care prior to, during and after dosing. Oxygen saturation by pulse oximetry at rest and after exertion should be assessed at each on-study visit prior to nivolumab

dosing. The start and stop time of the nivolumab infusion should be documented. Physical examinations are to be performed as clinically indicated. If there are any new or worsening clinically significant changes since the last exam, report changes on the appropriate non-serious or serious adverse event page.

On treatment local laboratory assessments should be done within 72 hours prior to dosing;

- **Extended on-treatment local laboratory assessments**: Cycle 1 (including day 1 and day 8) through Cycle 5 and every alternate dose thereafter (Cycle 7, 9, 11, 13 etc) and include: CBC with differential, uric acid, serum urea level, serum creatinine, sodium, potassium, calcium, magnesium, phosphate, chloride, amylase, lipase, glucose, AST, ALT, total bilirubin, alkaline phosphatase, LDH.
- **Limited on-treatment laboratory assessments**: beginning at Cycle 6 (week 11) and every alternate dose thereafter (Cycle 8, 10, 12, 14 etc) and include: CBC, LFTs (ALT, AST, total bilirubin, alkaline phosphatase) and creatinine.

In addition, TSH (with reflexive testing to free T3, free T4 for abnormal TSH result) should be performed every 6 weeks (± 7 days) regardless of dosing schedule.

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 elevations) will be monitored during the follow-up phase via on site/local labs until all study drug related toxicities resolve, return to baseline or are deemed irreversible.

Oxygen saturation by pulse oximetry should be obtained prior to each dose of nivolumab and at any time a subject has any new or worsening respiratory symptoms. A reading at rest and on exertion should be obtained at each time point. The extent of the exertion should be based on the judgment of the investigator, but should remain consistent for each individual subject throughout the study. If the patient's subject's status changes, the investigator can alter the extent of exertion based on their medical judgment. If a subject shows changes on pulse oximetry or other pulmonary-related signs (eg, hypoxia, fever) or symptoms (eg, dyspnea, cough) consistent with possible pulmonary adverse events, the patient subject should be immediately evaluated to rule out pulmonary toxicity. An algorithm for the management of suspected pulmonary toxicity can be found in Appendix 1 and the BMS-936558 (nivolumab) Investigator Brochure.

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

For subjects who discontinue study therapy by proceeding to allogeneic SCT, 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 SCT is documented [Appendix 5]. 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.

5.3.1 Imaging Assessment for the Study

Images will be submitted to an imaging corelab for central review. Sites will be trained prior to scanning the first study subject. Image acquisition guidelines and submission process will be outlined in the CA209139 Imaging Manual to be provided by the corelab.

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.

5.4 Efficacy Assessments

The primary efficacy assessment is objective response rate (ORR), defined as a subject achieving either a partial remission (PR) or complete remission (CR) according to the 2007 revised International Working Group Criteria for Malignant Lymphoma (Appendix 2) The primary efficacy assessment, along with the secondary endpoints of DOR, CRR, CR duration, PRR, PRR duration, and PFS will be performed by an independent radiologic review committee (IRRC). Assessment of ORR, based on investigator assessments, will be examined as a secondary endpoint. Sites are required to send all on-study disease assessments to the IRRC for review.

Once subjects discontinue study therapy by proceeding to allogeneic SCT or ASCT, they will not undergo IRRC- radiographic assessments as described in Table 5.4.1-1. Instead, they will be evaluated using the following schedule. Tumor assessment (CR or non-CR) will be assessed by the investigator according to the 2007 IWG criteria and will be required 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 SCT is documented. Investigators will make telephone contacts with the subject's referring hematologist/oncologist/transplant physician to obtain CR or non-CR status and document the status if subject is being followed by another physician.

5.4.1 Radiographic Assessments

Radiographic study evaluations will take place in accordance with the flow charts in Section 5.1 and Table 5.4.1-1. Baseline assessments should be performed within 28 days prior to the first dose, utilizing spiral CT or MRI. In addition to chest, abdomen, pelvis, all known sites of disease (including CNS) should be assessed at baseline. A PET scan is required at baseline for all subjects, and to confirm a complete response (CR).

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

Subjects will be evaluated for tumor response by spiral CT/MRI beginning at week 9 and continuing every 8 weeks (+/- 1 week) through the first 8 months, every 12 weeks (+/- 2 weeks) months 9-24, and then every 6 months (+/-3 weeks) thereafter until disease progression is documented or until the subject initiates a preparative regimen for allogeneic SCT or ASCT, whichever occurs earlier.

Tumor assessments for ongoing study treatment decisions will be completed by the investigator using the 2007 revised International Working Group Criteria for Malignant Lymphoma criteria. (Appendix 2)

Table 5.4.1-1: Schedule of Spiral CT-MRI Tumor Assessments

Time On Study	Assessment Frequency	Assessment Week (day 1 of week shown)	Assessment Window
Dose 1 to 8 Months	Every 8 weeks	9, 17, 25, 33	+/- 1 week
Month 9 to 2 Years	Every 12 weeks	45, 57, 69, 81, 93	+/- 2 weeks
> 2 Years	Every 6 months	119, 145, 171+	+/- 3 weeks

Note: Once subjects discontinue study therapy by proceeding to allogeneic SCT or ASCT, they will not undergo radiographic assessments described here, but will be followed with specific schedule (see Section 5.4)

5.4.2 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. When spiral CT scans have slice thickness greater than 5 mm, the minimum size for a measurable lesion should be twice the slice thickness.

At baseline, tumor lesions/lymph nodes will be categorized as measurable or nonmeasurable as follows in Sections 5.4.2.1 and 5.4.2.2.

5.4.2.1 Measurable Lesions

Measurable lesions must be accurately measured in at least two perpendicular dimensions based on Cheson 2007 criteria[48]. **In order to meet eligibility criteria, subjects must have at least one lymph node or extra-nodal node with long axis measurement > 15 mm**, **regardless of the short axis measurement**. Additional lymph nodes are considered to be measurable for purposes of efficacy assessments if the longest axis is 11 to 15 mm AND the short axis is > 10 mm. Lymph nodes ≤ 10 mm x ≤ 10 mm will not be considered as measurable.

If possible, nodes or masses should be from disparate regions of the body and they should include mediastinal and retroperitoneal areas of disease whenever these sites are involved.

5.4.2.2 Non-Measurable Lesions

- All other lesions, including small lymph nodes (longest diameter ≤ 10 mm) as well as truly non-measurable lesions.
- Lesions considered truly non-measurable include: leptomeningeal disease, ascites, pleural or pericardial effusion, inflammatory breast disease, lymphangitic involvement of skin or lung, abdominal masses/abdominal organomegaly identified by physical exam that is not measurable by reproducible imaging techniques.

5.4.3 Specifications by Method of Assessment

5.4.3.1 Measurement of Lesions

All measurements should be recorded in the eCRF in metric notation (mm). All baseline evaluations should be performed as close as possible to the treatment start and never more than 28 days before the beginning of treatment.

5.4.3.2 Method of Assessment

The same method of assessment and the same technique should be used to characterize each identified and reported lesion at baseline and during follow-up. Imaging based evaluation should always be done rather than clinical examination unless the lesion(s) being followed cannot be imaged but are assessable by clinical exam.

5.4.3.3 Spiral CT/MRI Scan

Spiral CT/MRI is the best currently available and reproducible method to measure lesions selected for response assessment. Measurability of lesions on spiral CT/MRI scan is based on the assumption that spiral CT/MRI slice thickness is 5 mm or less. When spiral CT scans have slice thickness greater than 5 mm, the minimum size for a measurable lesion should be twice the slice thickness.

PET/CT hybrid scanners may be used for the acquisition of required CT images only if the CT is of diagnostic quality and adheres to protocol-specified scan parameters. Also, the CT images must be separated from the PET data prior to submitting the data, and cannot be transmitted as fused CT/PET images.

Note on PET/CT scans: Combined modality scanning such as with PET/CT is increasingly used in clinical care. Low dose or attenuation correction CT portions of a combined PET/CT are of limited use in anatomically based efficacy assessments and it is therefore suggested that they should not be substituted for dedicated diagnostic contrast enhanced CT scans for anatomically based measurements. However, if a site can document that the CT performed as part of a PET/CT is of identical diagnostic quality to a diagnostic CT (with IV and oral contrast) then the CT portion of the PET/CT can be used for measurements.

5.4.3.4 Clinical Lesions

Clinical lesions will only be considered measurable when they are superficial and ≥ 1 cm diameter as assessed using calipers. As previously noted, when lesions can be evaluated both by

clinical exam and imaging, imaging evaluation should be undertaken since it is more objective and may also be reviewed by the IRRC

5.4.3.5 PET scan

A baseline PET scan is required for each treated subject. An additional PET scan is required to confirm a CR.

5.4.4 Baseline Documentation of "Target" and "Non-Target Lesions

5.4.4.1 Target Lesions

At baseline, up to 6 of the largest dominant nodes or nodal masses meeting the criteria for measurable lesions given in Section 5.4.2.1 should be identified as target lesions and their measurements recorded. Other measurable lesions will be designated as non-target lesions.

A sum of the product of the diameters (SPD) will be calculated for all target lesions 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.

5.4.4.2 Non-Target Lesions

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 case report form (eg, 'multiple enlarged pelvic lymph nodes' or multiple liver nodules').

[redacted]

5.4.6 Disease Response Evaluation

The determination of disease response to study treatment will be made using 2007 revised International Working Group Response Criteria for Malignant Lymphoma (Appendix 2).

Note: 2007 IWG criteria define relapsed disease or progressive disease based largely on the evaluation of nodal masses, spleen/liver, and bone marrow (Appendix 2). The criteria also stipulate that disease that is only assessable but not measureable (eg, pleural effusion or bone lesion) will be recorded as "present" or "absent", unless such an assessable abnormality, noted

by imaging studies or physical examination, is confirmed to be histologically negative. For purposes of protocol-defined disease progression, the appearance of new sites of assessable but not measureable disease while on treatment meets protocol criteria for progression if histological results are documented (eg, the presence of lymphoma cells in a pleural effusion or spinal fluid).

[redacted]

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[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
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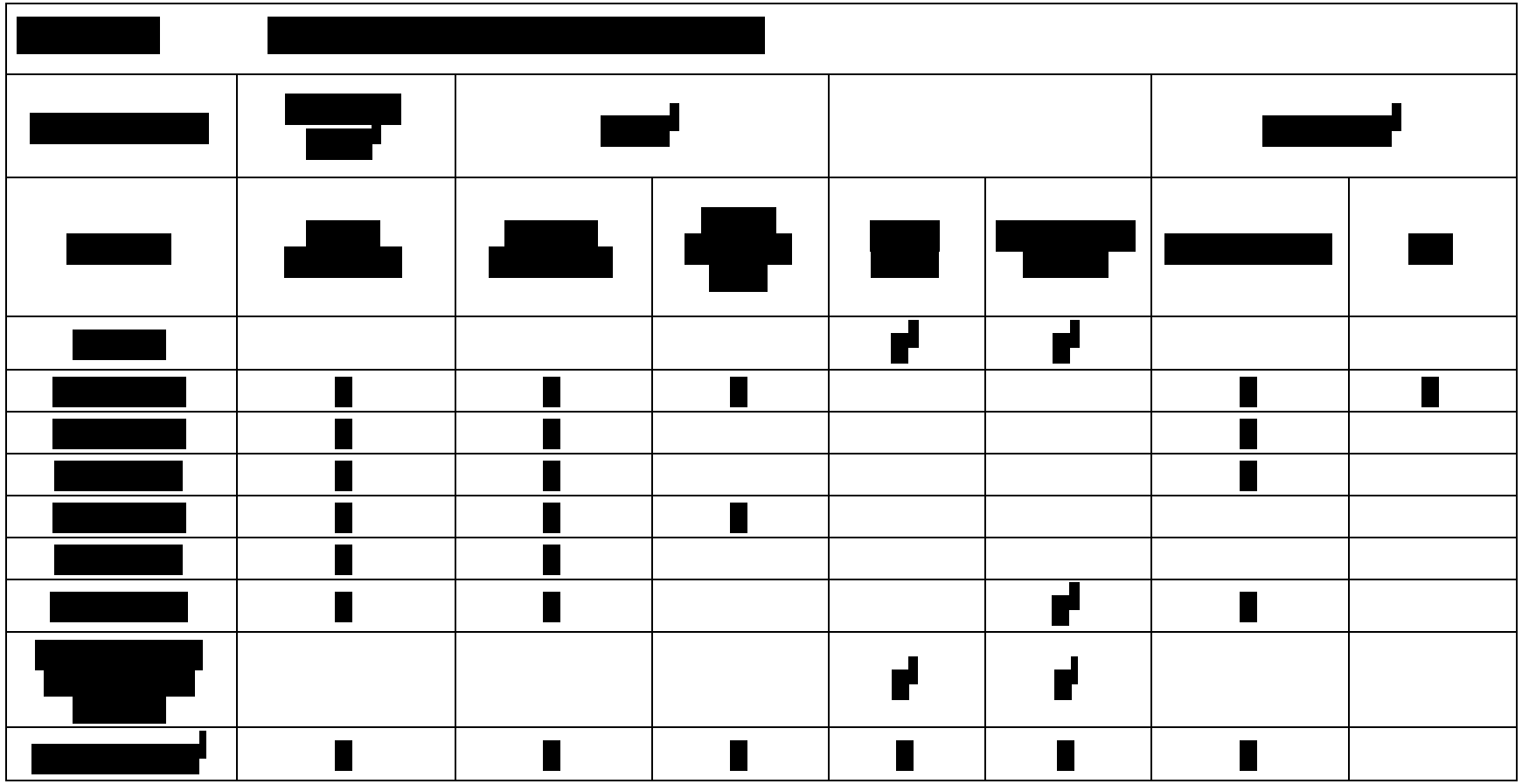

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6 ADVERSE EVENTS

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

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

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

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

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

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

6.1 Serious Adverse Events

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

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

result in hospitalization.) Potential drug induced liver injury (DILI) is also considered an important medical event. (See Section 6.6 for the definition of potential DILI.)

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

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

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

NOTE:

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

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

6.1.1 Serious Adverse Event Collection and Reporting

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

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

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

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

SAEs, whether related or not related to study drug, and pregnancies must be reported to BMS (or designee) within 24 hours. SAEs must be recorded on the SAE Report Form; pregnancies on a Pregnancy Surveillance Form (electronic or paper forms). When using paper forms, the reports are to be transmitted via email or confirmed facsimile (fax) transmission to:

SAE Email Address: Refer to Contact Information list.

SAE Facsimile Number: Refer to Contact Information list.

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

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

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

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

All SAEs should be followed to resolution or stabilization.

6.2 Nonserious Adverse Events

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

6.2.1 Nonserious Adverse Event Collection and Reporting

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

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

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

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

6.3 Laboratory Test Result Abnormalities

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

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

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

6.4 Pregnancy

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

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

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

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

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

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

6.5 Overdose

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

6.6 Potential Drug Induced Liver Injury (DILI)

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

Potential drug induced liver injury is defined as:

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

AND

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

AND

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

6.7 Other Safety Considerations

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

7 DATA MONITORING COMMITTEE AND OTHER EXTERNAL COMMITTEES

7.1 Independent Radiology Review Committee (IRRC)

An IRRC will be utilized in this study for determination of IRRC-assessed primary (ORR) and secondary (DOR, CRR, PFS) endpoints. The IRRC will review all available tumor assessment scans for all treated subjects. Details of IRRC responsibilities and procedures will be specified in the IRRC charter.

8 STATISTICAL CONSIDERATIONS

8.1 Sample Size Determination

The planned sample size for this study will be approximately 120 treated subjects, separated into two treatment groups based on prior ASCT failure [n=90] or ASCT ineligibility [n=30].

For the ASCT-failed cohort, a modified Simon's two-stage design will be used to test the null hypothesis that the true ORR is ≤ 20% (not considered clinically compelling). In the first stage, 37 subjects will be accrued. If there are 8 or fewer responses in these 37 subjects, the study will be stopped. In this case, the study will be terminated in both the ASCT-failed cohort as well as the ASCT ineligible cohort. Otherwise, approximately 53 additional subjects will be accrued into the ASCT-failed cohort to target a total of 90 treated subjects. The null hypothesis will be rejected if 25 or more responses are observed in 90 treated subjects. This design yields a

one-sided type I error rate of 5% and power of 90% when the true response rate is 35%. The interim stopping rule for this design is identical to Simon's 'optimal' 2-stage design[50]. However, the sample size at the final analysis is larger than required by Simon's optimal design in order to provide additional subjects for safety evaluation. Table 8.1-1 provides the probabilities of stopping at different ORR using this rule.

Table 8.1-1: Operating Characteristics of Stopping Rule

True ORR	P(early stop)
15%	0.91
20%	0.69
25%	0.40
30%	0.18
35%	0.06
40%	0.01

For the ASCT ineligible cohort, the sample size of 30 treated subjects is determined to achieve a confidence interval (CI) width around the ORR estimate with a sufficient level of precision. If the observed number of subjects with ORR is 10 (33%), the width of the exact 2-sided 95% CI is 36% with a lower bound of 17.3%. Such an observation would provide evidence in support that the true ORR is greater than or equal to 17.3% with a Type I error rate of 5%.

8.2 Populations for Analyses

- All Enrolled Subjects: All subjects who signed an informed consent form and were registered into the IVRS.
- All Treated Subjects: All subjects who received at least one dose of nivolumab. This is the primary population for safety and efficacy analyses.
- All response evaluable subjects: All treated subjects who have baseline and at least one on-study evaluable tumor measurement.

[redacted]

8.3 Endpoints

8.3.1 Primary Endpoint(s)

The primary objective will be measured by the primary endpoint of IRRC-assessed objective response rate (ORR). It is defined as the number of subjects with a best overall response (BOR) of complete remission (CR) or partial remission (PR), according to the 2007 revised International Working Group Criteria for Malignant Lymphoma, divided by the number of treated subjects. The final analysis of the primary endpoint will occur at least 6 months after the last enrolled subject's first dose of study therapy. The BOR is defined as the best response designation recorded between the date of first dose and the date of initial objectively documented progression per the 2007 revised International Working group Criteria for Malignant Lymphoma or the date of subsequent therapy, whichever occurs first. Stem Cell Transplant will be considered as subsequent therapy. For subjects without documented progression or subsequent therapy, all available response designations will contribute to the BOR determination. 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).

8.3.2 Secondary Endpoint(s)

The first secondary objective will be measured by the duration of ORR (DOR) based on IRRC assessment. DOR is defined as the time from first response (CR or PR) to the date of initial objectively documented progression as determined using the 2007 revised International Working Group Criteria for Malignant Lymphoma 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 evaluable tumor assessment. Subjects who start subsequent therapy without a prior reported progression will be censored at the last evaluable 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 second secondary objective will be measured by the complete remission rate (CRR) based on IRRC assessment. The CRR is defined as the number of subjects with a BOR of CR according to the 2007 revised International Working Group Criteria for Malignant Lymphoma, divided by the number of treated subjects. The BOR is defined similarly as above. The duration of CR will only be evaluated in subjects with BOR of CR and is defined as the time from first documentation of CR (the date of first negative FDG-PET scan or the date of first documentation of no disease involvement in the bone marrow (if required), whichever occurs later) to the date of initial objectively documented progression as determined using the revised 2007 IWG response criteria for malignant lymphoma or death due to any cause, whichever occurs first. Censoring will be applied as per DOR definition.

The third secondary objective will be measured by PR rate based on IRRC assessment. It is defined as the number of subjects with a BOR of PR according to the 2007 revised IWG response criteria, based on IRRC assessment, divided by the number of treated subjects. The duration of PR will only be evaluated in subjects with BOR of PR and is defined as the time

from first documentation of PR to the date of initial objectively documented progression as determined using the 2007 revised IWG response criteria or death due to any cause, whichever occurs first. Censoring will be applied as per DOR definition.

The fourth secondary objective will be measured by IRRC-assessed progression free survival (PFS). It is defined as the time from first dosing date to the date of the first documented progression, as determined by an IRRC, 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 evaluable 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 evaluable assessment prior to initiation of the subsequent anti-cancer therapy.

The fifth secondary objective will be measured by investigator-assessed ORR. Investigator-assessed ORR is defined similarly as described for the primary endpoint above.

8.4 Analyses

8.4.1 Demographics and Baseline Characteristics

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

8.4.2 Efficacy Analyses

8.4.2.1 Primary Endpoint Methods

The IRRC-assessed ORR will be summarized for the ASCT failed and the ASCT ineligible cohorts separately by binomial response rates and their corresponding two-sided 95% exact CIs. In the ASCT failed cohort, the two-sided 90% CI will also be presented, corresponding to the 1-sided 5% alpha from the modified Simon design. The method proposed by Atkinson and Brown[51] will be used to estimate the CI for the ASCT failed cohort. This confidence interval

takes into account the group sequential nature of the two-stage design. The Clopper-Pearson method will be used to estimate the CI for the ASCT ineligible cohort.

In the ASCT failed cohort, the null hypothesis will be rejected if 25 or more responses are observed in 90 treated subjects. Success of the ASCT ineligible cohort will be determined by a 2-sided 95% CI lower bound greater than 17.3%. As sensitivity analysis, a summary of IRRC-assessed ORR based on response evaluable subjects instead of all treated subjects will also be presented.

8.4.2.2 Secondary Endpoint Methods

The IRRC-assessed DOR will be summarized by cohort for subjects who achieve PR or CR using the Kaplan-Meier (KM) 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.

IRRC-assessed CRR, PRR, and investigator-assessed ORR will be summarized by binomial response rates and their corresponding two-sided 95% CI using the Clopper-Pearson method. Duration of CR and PR will be summarized similarly to DOR. IRRC-assessed PFS will be summarized descriptively by cohort using the Kaplan-Meier (KM) product-limit method. Median values of PFS, along with two-sided 95% CIs (based on the log-log transformation), will also be calculated.

[redacted]

8.4.3 Safety Analyses

Safety analyses will be performed in all treated subjects. Descriptive statistics of safety will be presented using National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) version 4.0. All on-study AEs, drug-related, AEs, SAEs and drug-related SAEs will be tabulated using worst grade per NCI CTCAE v4.0 criteria by system organ class and MedDRA preferred term. On-study lab parameters including hematology, chemistry, liver function, thyroid function, and renal function will be summarized using worst grade per NCI CTCAE v4.0 criteria.

[redacted]

[redacted]

8.5 Interim Analyses

One interim analysis of IRRC-assessed ORR in the ASCT failure group will be performed when 37 ASCT-failed subjects have been treated and those subjects still on treatment have completed the first tumor assessment (week 9) . In case the last assessment of some subjects show CR that has not yet been confirmed by PET, the interim analysis will take place after availability of the confirmation. If there are 8 or fewer responses in these 37 subjects, the study will be stopped. Otherwise, approximately 53 additional subjects will be accrued to target a total of 90 treated subjects in the ASCT failure group. Accrual and treatment will continue during the time period that the interim analysis is being conducted. This may result in more than 37 treated subjects in the event that the study is terminated for lack of efficacy. The tolerability of the regimen will continue to be evaluated by the sponsor with the investigators to ensure that it is acceptable for continued enrollment. Additional specifications of analyses produced at interim analysis (eg, on biomarkers, safety) will be addressed in the statistical analysis plan.

9 STUDY MANAGEMENT

9.1 Compliance

9.1.1 Compliance with the Protocol and Protocol Revisions

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

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

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

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

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

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

9.1.2 Monitoring

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

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

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

9.1.3 Investigational Site Training

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

9.2 Records

9.2.1 Records Retention

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

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

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

9.2.2 Study Drug Records

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

- amount received and placed in storage area
- amount currently in storage area
- label identification number or batch number
- amount dispensed to and returned by each subject, including unique subject identifiers
- amount transferred to another area/site for dispensing or storage
- nonstudy disposition (eg, lost, wasted)
- amount destroyed at study site, if applicable

- amount returned to BMS
- retain samples for bioavailability/bioequivalence, if applicable
- dates and initials of person responsible for Investigational Product dispensing/accountability, as per the Delegation of Authority Form.

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

9.2.3 Case Report Forms

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

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

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

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

The completed CRF, including any paper or electronic SAE/pregnancy CRFs, must be promptly reviewed, signed, and dated by the investigator or qualified physician who is a 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 selected considering the following criteria:

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

10 GLOSSARY OF TERMS

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

11 LIST OF ABBREVIATIONS

Term	Definition
ACTH	Adrenocorticotropic Hormone
AE	adverse event
AIDS	Acquired immunodeficiency syndrome
ALT	alanine aminotransferase
ANC	absolute neutrophil count
ASCT	Autologous Stem Cell Transplant
AST	aspartate aminotransferase
AT	Aminotransferase (ALT or AST)
BID, bid	bis in die, twice daily
BMI	body mass index
BMS	Bristol-Myers Squibb
BOR	best overall response
BP	blood pressure
BUN	blood urea nitrogen
C	Celsius
Ca++	calcium
CBC	complete blood count
CFR	Code of Federal Regulations
CI	confidence interval
C1	chloride
CLcr	creatinine clearance
CLR	renal clearance
cm	centimeter
CNS	Central nervous system
CR	Complete remission
CRC	Clinical Research Center
CRF	Case Report Form, paper or electronic
CT	Computed tomograhpy
CTA	Clinical Trial Agreement
CTCAE	Common Terminology Criteria for Adverse Events
D/C	discontinue
DILI	drug induced liver injury
dL	deciliter

Term	Definition
DLBCL	Diffuse large B-Cell lymphoma
DOR	Duration of overall response rate (ORR)
ECG	electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	Electronic Case Report Form
EDC	Electronic Data Capture
eg	exempli gratia (for example)
ELISA	enzyme-linked immunosorbent assay
eSAE	Electronic Serious Adverse Event
ESR	Expedited Safety Report
FDA	Food and Drug Administration
FFPE	Formalin-Fixed Parafin-Embedded
FSH	follicle stimulating hormone
g	Gram
GCP	Good Clinical Practice
GGT	gamma-glutamyl transferase
GFR	glomerular filtration rate
GVHD	Graft versus host disease
h	Hour
HBsAg	hepatitis B surface antigen
HBV	hepatitis B virus
HCG	Human chorionic gonadotropin
HCV	hepatitis C virus
HCO3-	Bicarbonate
ASCT	High dose therapy and autologous stem cell transplantation
HIPAA	Health Insurance Portability and Accountability Act
HIV	Human Immunodeficiency Virus
HL	Hodgkin lymphoma
HR	heart rate
HRT	hormone replacement therapy
IB	Investigational Brochure
ICD	International Classification of Diseases
ICH	International Conference on Harmonisation
ie	id est (that is)

Term	Definition
IEC	Independent Ethics Committee
IHC	Immunohistochemistry
IMP	investigational medicinal products
IND	Investigational New Drug
IRB	Institutional Review Board
IRRC	Independent radiologic review committee
IU	International Unit
IV	intravenous
IVRS	Interactive voice response system
K+	potassium
kg	kilogram
L	liter
LDH	lactate dehydrogenase
LFT	Liver function test
mAbs	monoclonal antibodies
mg	milligram
Mg++	magnesium
min	minute
mL	milliliter
MLR	mixed lymphocyte reaction
mmHg	millimeters of mercury
MTD	maximum tolerated dose
µg	microgram
N	number of subjects or observations
Na+	sodium
N/A	not applicable
NCI-CTCAE	National Cancer Institute-Common Terminology Criteria for Adverse Events
ng	nanogram
NIMP	non-investigational medicinal products
NHL	Non-Hodgkin lymphoma
NSAID	nonsteroidal anti-inflammatory drug
ORR	Objective response rate
OS	Overall survival
PBMC	peripheral blood mononuclear cells

Term	Definition
PD	pharmacodynamics
PD-1	Programmed death-1 receptor
PET	Positron emission tomography
PFS	Progression free survival
PK	pharmacokinetics
PO	per os (by mouth route of administration)
PR	Partial response
qPCR	Quantitative real-time polymerase chain reaction
RBC	red blood cell
R-CHOP	Rituximab plus cyclophosphamide, doxorubicin, vincristine, prednisone/prednisolone
RT-PCR	Reverse transcription- polymerase chain reaction
SAE	serious adverse event
SCT	Stem cell transplant
SmPC	Summary of product characteristics
SNP	Single nucleotide polymorphisms
SOP	Standard Operating Procedures
t	temperature
T	time
TAO	Trial Access Online, the BMS implementation of an EDC capability
TCR	T-cell receptor
T-HALF	Half life
TIL	tumor infiltrating lymphocytes
ULN	upper limit of normal
WBC	white blood cell
WHO	World Health Organization
WOCBP	women of childbearing potential

[redacted]

APPENDIX 2 2007 REVISED INTERNATIONAL WORKING GROUP CRITERIA FOR MALIGNANT LYMPHOMA

2007 IWG Response Criteria for Malignant Lymphoma				
Response	Definition	Nodal masses	Spleen, Liver	Bone marrow
CR	Disappearance of all evidence of disease	(a) FDG-avid or PET positive prior to therapy; residual mass of any size permitted if PET negative (b) Variably FDG-avid or PET negative; regression to normal size on CT	Not palpable, nodules disappeared	Infiltrate cleared on repeat biopsy; if indeterminate by morphology, immunohistochemistry should be negative
PR	Regression of measurable disease and no new sites	≥ 50% decrease in SPD of up to 6 largest dominant masses (index lesions); no increase in size of other nodes (non-index lesions) (a) FDG-avid or PET positive prior to therapy; one or more PET positive at previously involved site (b) Variably FDG-avid or PET negative; regression on CT	≥ 50% decrease in SPD of nodules (for single nodule in greatest transverse diameter); no increase in size of liver or spleen	Irrelevant if positive prior to therapy; cell type should be specified
SD	Failure to attain CR/PR or PD	(a) FDG-avid or PET positive prior to therapy; PET positive at prior sites of disease and no new sites on CT or PET (b) Variably FDG-avid or PET negative; no change in size of previous lesions on CT	N/A	N/A
Relapsed disease or PD	Any new lesion or increase by ≥ 50% of previously involved sites from nadir	Appearance of a new lesion(s) > 1.5 cm in any axis, ≥ 50% increase in SPD of more than one node (index lesions), or ≥ 50% increase in longest diameter of a previously identified node > 1 cm in short axis. Lesions PET positive if FDG-avid lymphoma or PET positive prior to therapy	> 50% increase from nadir in the SPD of any previous lesions	New or recurrent involvement

Key: CR = complete remission CT = computed tomography; FDG = [18F] fluorodeoxyglucose; IWG = International Working Group; NA = Not applicable; PD = progressive disease; PET = positron-emission tomography; PR = partial remission; SD = stable disease; SPD = sum of the product of the diameters.

CR (Complete Remission)

The designation of CR requires the following:

1. Complete disappearance of all detectable clinical evidence of disease and disease-related symptoms, if present before therapy.
   a) Typically [^{18}F] fluorodeoxyglucose (FDG)-avid lymphoma: in patients with no pretreatment positron emission tomography (PET) scan or when the PET scan was positive before therapy, a post-treatment residual mass of any size is permitted as long as it is PET negative.
   b) Variably FDG-avid lymphomas/FDG avidity unknown: in patients without a pretreatment PET scan, or if a pretreatment PET scan was negative, all lymph nodes and nodal masses must have regressed on computed tomography (CT) scan to normal size (≤ 1.5 cm in their greatest transverse diameter for nodes > 1.5 cm before therapy). Previously involved nodes that were 1.1 to 1.5 cm in their long axis and > 1.0 cm in their short axis before treatment must have decreased to ≤ 1.0 cm in their short axis after treatment.
2. The spleen and/or liver, if considered enlarged before therapy on the basis of a physical examination or CT scan, should not be palpable on physical examination and should be considered normal size by imaging studies, and nodules related to lymphoma should disappear. However, determination of splenic involvement is not always reliable because a spleen considered normal in size may still contain lymphoma, whereas an enlarged spleen may reflect variations in anatomy, blood volume, the use of hematopoietic growth factors, or causes other than lymphoma.
3. If the bone marrow was involved by lymphoma before treatment, the infiltrate must have cleared on repeat bone marrow biopsy. The biopsy sample on which this determination is made must be adequate (with a goal of > 20 mm unilateral core). If the sample is indeterminate by morphology, it should be negative by immunohistochemistry. A sample that is negative by immunohistochemistry but demonstrates a small population of clonal lymphocytes by flow cytometry will be considered a CR until data become available demonstrating a clear difference in patient outcome.

PR (Partial Remission)

The designation of PR requires all of the following:

1. At least a 50% decrease in the sum of the product of the diameters (SPD) of up to 6 of the largest dominant nodes or nodal masses. These nodes or masses should be selected according to all of the following: they should be clearly measurable in at least 2 perpendicular dimensions; if possible they should be from disparate regions of the body; and they should include mediastinal and retroperitoneal areas of disease whenever these sites are involved.
2. No increase should be observed in the size of other nodes, liver, or spleen.
3. Splenic and hepatic nodules must regress by ≥ 50% in their SPD or, for single nodules, in the greatest transverse diameter.
4. With the exception of splenic and hepatic nodules, involvement of other organs is usually assessable and no measurable disease should be present.

5. Bone marrow assessment is irrelevant for determination of a PR, if the sample was positive before treatment. However, if positive, the cell type should be specified (eg, large-cell lymphoma or small neoplastic B cells). Patients who achieve a CR by the above criteria but have persistent morphologic bone marrow involvement will be considered partial responders. When the bone marrow was involved before therapy and a clinical CR was achieved but with no bone marrow assessment after treatment, patients should be considered partial responders.
6. No new sites of disease should be observed.
7. FDG:
   a) Typically FDG-avid lymphoma: for patients with no pretreatment PET scan or if the PET scan was positive before therapy, the post-treatment PET should be positive in at least 1 previously involved site.
   b) Variably FDG-avid lymphomas/FDG-avidity unknown: for patients without a pretreatment PET scan, or if a pretreatment PET scan was negative, CT criteria should be used. In patients with follicular lymphoma or mantle-cell lymphoma, a PET scan is only indicated with 1 or at most 2 residual masses that have regressed by > 50% on CT; those with more than 2 residual lesions are unlikely to be PET negative and should be considered partial responders.

SD (Stable Disease)

SD is defined as the following:

8. A patient is considered to have SD when he or she fails to attain the criteria needed for a CR or PR but does not fulfill those for progressive disease (see Relapsed Disease [after CR]/Progressive Disease [after PR, SD]).
9. Typically FGD-avid lymphomas: the PET should be positive at prior sites of disease with no new areas of involvement on the post-treatment CT or PET scan.
10. Variably FDG-avid lymphomas/FDG-avidity unknown: for patients without a pretreatment PET scan or if the pretreatment PET was negative, there must be no change in the size of the previous lesions on the post-treatment CT scan.

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

Lymph nodes should be considered abnormal if the long axis is > 1.5 cm regardless of the short axis. If a lymph node has a long axis of 1.1 to 1.5 cm, it should only be considered abnormal if its short axis is > 1.0. Lymph nodes ≤ 1.0 x ≤ 1.0 cm will not be considered abnormal for relapse or progressive disease.

11. Appearance of any new lesion > 1.5 cm in any axis during or at the end of therapy, even if other lesions are decreasing in size. Increased FDG uptake in a previously unaffected site should only be considered relapsed or PD after confirmation with other modalities. In patients with no prior history of pulmonary lymphoma, new lung nodules identified by CT are mostly benign. Thus, a therapeutic decision should not be made solely on the basis of the PET without histologic confirmation.

12. At least a 50% increase from nadir in the SPD of any previously involved nodes, or in a single involved node, or the size of other lesions (eg, splenic or hepatic nodules). To be considered PD, a lymph node with a diameter of the short axis of < 1.0 cm must increase by ≥ 50% and to a size of 1.5 x 1.5 cm or > 1.5 cm in the long axis.
13. At least a 50% increase in the longest diameter of any single previously identified node > 1 cm in its short axis.
14. Lesions should be PET positive if observed in a typical FDG-avid lymphoma or the lesion was PET positive before therapy unless the lesion is too small to be detected with current PET systems (< 1.5 cm in its long axis by CT).

Measurable extranodal disease should be assessed in a manner similar to that for nodal disease. For these recommendations, the spleen is considered nodal disease. Disease that is only assessable (eg, pleural effusions, bone lesions) will be recorded as present or absent only, unless, while an abnormality is still noted by imaging studies or physical examination, it is found to be histologically negative.

In clinical trials where PET is unavailable to the vast majority of participants, or where PET is not deemed necessary or appropriate for use (eg, a trial in patients with MALT lymphoma), response should be assessed as above, but only using CT scans. However, residual masses should not be assigned CRu status, but should be considered partial responses.

[redacted]

APPENDIX 3 REVISED INTERNATIONAL PROGNOSTIC INDEX (IPI) SCALE*

Composite score determined by assigning 1 point for each of the following factors;

- Age > 60 years
- ECOG PS > 2
- Elevated Serum LDH
- More than 1 extranodal site
- Stage III/IV disease (Ann Arbor staging)

APPENDIX 4 ECOG PERFORMANCE STATUS

ECOG PERFORMANCE STATUS[a]	
0	Fully active, able to carry on all pre-disease performance without restriction
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, eg, light house work, office work
2	Ambulatory and capable of all selfcare but unable to carry out any work activities. Up and about more than 50% of waking hours
3	Capable of only limited selfcare, confined to bed or chair more than 50% of waking hours
4	Completely disabled. Cannot carry on any selfcare. Totally confined to bed or chair
5	Dead

a [redacted]

APPENDIX 5 ACUTE GVHD GRADING AND STAGING

Table 1: Extent of Organ Involvement

Stage	Skin	Liver	Gut
1	Rash on < 25% of skin[a]	Bilirubin 2 - 3 mg/dL[b]	Diarrhea > 500 mL/day[c] or persistent nausea[d]
2	Rash on 25 - 50% of skin	Bilirubin 3 - 6 mg/dL	Diarrhea > 1000 mL/day
3	Rash on > 50% of skin	Bilirubin 6 - 15 mg/dL	Diarrhea > 1500 mL/day
4	Generalized erythroderma with bullous formation	Bilirubin >15 mg/dL	Severe abdominal pain with or without ileus
Grade[e]			
I	Stage 1 - 2	None	None
II	Stage 3 or	Stage 1 or	Stage 1
III	--	Stage 2 - 3 or	Stages 2 - 4
IV[f]	Stage 4	Stage 4	--

[a] Use "Rules of Nines" (Table 2) or burn chart to determine extent of rash.

[b] Range given as total bilirubin. Downgrade one stage if an additional cause of elevated bilirubin has been documented.

[c] Volume of diarrhea applies to adults. For pediatric patients, the volume of diarrhea should be based on body surface area. Downgrade one stage if an additional cause of diarrhea has been documented.

[d] Persistent nausea with histologic evidence of GVHD in the stomach or duodenum.

[e] Criteria for grading given as minimum degree of organ involvement required to confer that grade.

[f] Grade IV may also include lesser organ involvement with an extreme decrease in performance status.

Table 2: Percent Body Surfaces

Body Area	Percent	Total Percentage
Each Arm	9%	18%
Each Leg	18%	36%
Chest & Abdomen	18%	18%
Back	18%	18%
Head	9%	9%
Pubis	1%	1%

[redacted]

Stage of Chronic GVHD

Limited: Localized skin involvement resembling localized scleroderma with or without liver involvement; no other organ involvement.
Extensive: Generalized skin and/or multiple organ involvement.

[redacted]