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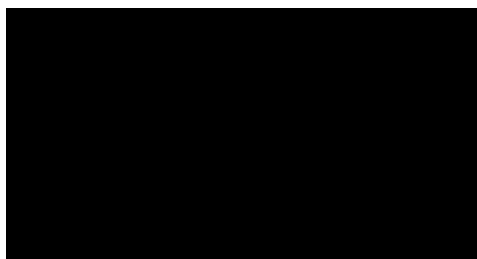
## **Clinical Protocol CA209140**

A Single-Arm, Open-Label Phase 2 Study of Nivolumab (BMS-936558) in Subjects with Relapsed or Refractory Follicular Lymphoma (FL)

(CheckMate 140: CHECKpoint pathway and nivoluMab clinical Trial Evaluation 140)

**Revised Protocol Number: 03**  
**Incorporates amendment(s) 04**

Medical Monitor



**24-hr Emergency Telephone Number**



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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 04 and Administrative Letter 02.
Amendment 04	21-Jul-2016	Safety management algorithms were updated in the Investigator Brochure, requiring revision of the <a href="#">Appendix 1</a> algorithms. This revision applies to all subjects receiving study drug, or who have discontinued study drug and are being treated for suspected pulmonary toxicity, skin toxicity and nephrotoxicity.
Administrative Letter 02	06-Oct-2014	Updates Medical Monitor contact information
Revised Protocol 02	23-Jul-2014	Incorporates Amendment(s) 03
Amendment 03	23-Jul-2014	<p>Removes the interim analyses and extends the duration of follow-up required for all subjects prior to performing the final analysis of the primary endpoint.</p> <p>Modifies a few eligibility criteria to facilitate subject enrollment.</p> <p>Allows for continued treatment of subjects in certain instances where protocol-defined progression criteria have been met.</p> <p>The amendment also serves to clarify various protocol requirements to ensure consistency in the execution of the study including secondary and exploratory objectives, submission of bone marrow aspirate and tumor biopsy samples for biomarker analyses, and assessments to be performed on subjects that discontinue study treatment to receive an allogeneic SCT or ASCT.</p>
Revised Protocol 01	06-Dec-2013	Incorporates Amendment(s) 02 and Administrative Letter 01
Amendment 02	06-Dec-2013	<p>The main objective of this amendment is to implement a mandatory recommendation received from the U.S. Food and Drug Administration (FDA) as follows:</p> <ul style="list-style-type: none"> <li>• The exclusion criterion has been added to exclude the subjects who received chest radiation <math>\leq</math> 24 weeks prior to first dose of the study drug.</li> </ul> <p>Justification for this exclusion criterion is that pneumonitis has been noted in the current Investigator Brochure as a treatment-related serious adverse event (SAE). The FDA notes that “Radiation pneumonitis can occur in patients who have received chest radiation up to 24 weeks after radiation therapy.” Chest radiation is not commonly used in the subjects eligible for this protocol, and this amendment will comply with the FDA recommendation without altering the basic study population or trial design.</p> <p>Additional updates were also made to the protocol including items such as clarifying the schedule of tumor assessment, correcting typographical and formatting errors, [REDACTED].</p>
Administrative	15-Nov-2013	Bullet “Admission for administration of anti-cancer therapy in the absence of any other SAEs” related to the hospitalizations was

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<b>Document</b>	<b>Date of Issue</b>	<b>Summary of Change</b>
Letter 01		erroneously added to the list of Serious Adverse Events (SAE) definitions.
Original Protocol	04-Oct-2013	Not applicable

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## SYNOPSIS

### Clinical Protocol CA209140

**Protocol Title:** A Single-Arm, Open-Label Phase 2 Study of Nivolumab (BMS-936558) in Subjects with Relapsed or Refractory Follicular Lymphoma (FL)

**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

**Study Phase:** 2b

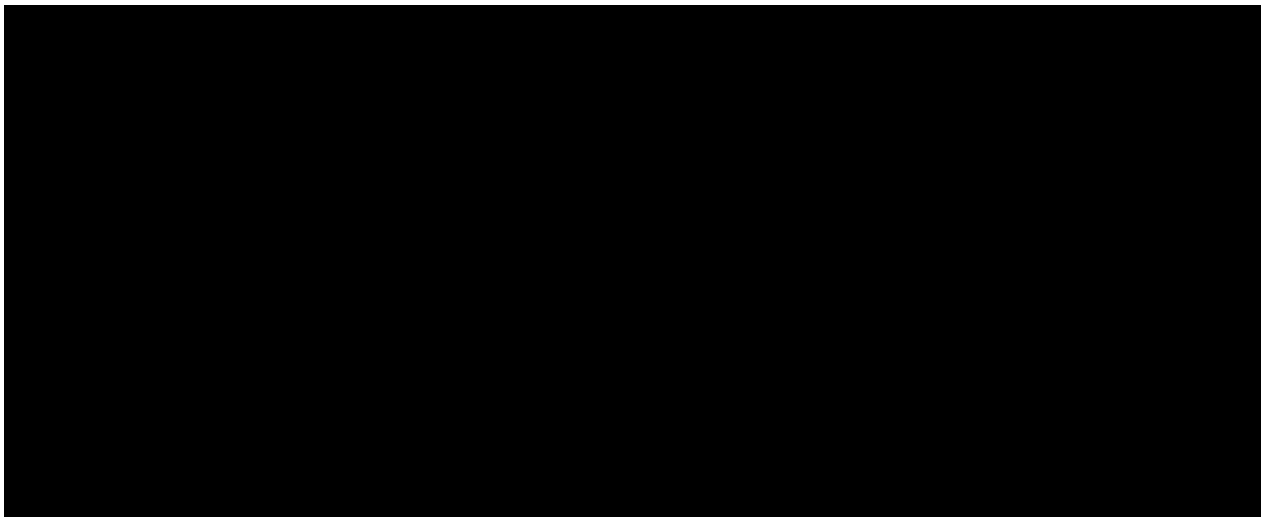
**Research Hypothesis:** Treatment with nivolumab will lead to clinical benefit, as demonstrated by an improved clinically meaningful objective response rate, including durable responses with substantial magnitude of tumor reduction in subjects with refractory FL who have failed therapy with both rituximab and an alkylating agent.

**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 FL who have failed therapy with both rituximab and an alkylating agent.

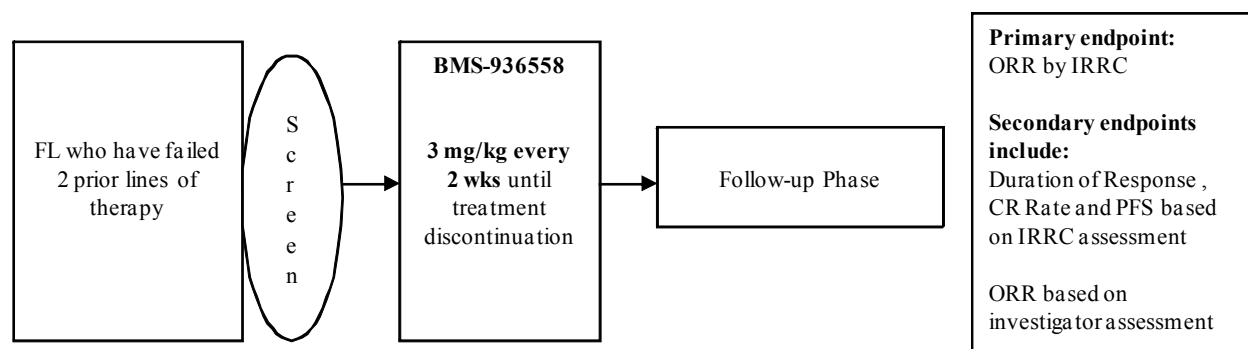
**Secondary Objectives:**

- 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 the progression free survival (PFS) based on IRRC assessment
- To assess the ORR, based on investigator assessments.

**Exploratory Objectives:**



**Study Design:** This is a single arm phase 2 study in subjects  $\geq 18$  years old with relapsed or refractory follicular lymphoma after failure of at least two prior lines of therapy. Approximately 90 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 2007 International Working Group (IWG) Response Criteria for Malignant Lymphoma. 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.



It is anticipated that accrual will last 18 months, with approximately 115 subjects enrolled.

**Study Population:** Male and female, ages 18 and above, with relapsed or refractory follicular lymphoma after failure of at least two prior lines of therapies (each containing CD20 antibody and/or an alkylating agent) will be eligible to participate in the study. Other key inclusion criteria include ECOG PS 0-1, at least one measurable lesion  $> 15$  mm (1.5 cm) in the longest diameter. (See protocol Sections 3.3.1 and 3.3.2 for full list of criteria.)

**Study Assessments:** The primary endpoint is ORR as determined by an IRRC according to the 2007 IWG criteria. 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 90 treated subjects.

The sample size was determined based on two considerations: the ability to produce a CI which would exclude an ORR of 20%, which is not considered clinically relevant and provide sufficient information for a reliable understanding of the safety profile.

Assuming the true ORR is 35%, the study has approximately 87% power to reject the null hypothesis that the true ORR is  $\leq 20\%$ , considering a 2-sided alpha of 5%. In addition, Table xx summarizes the 95% exact CI for the target ORRs ranging from 30% to 44% with sample size of 90. At observed ORR  $\geq 30\%$ , the lower bound of the 95% CI excludes 20%.


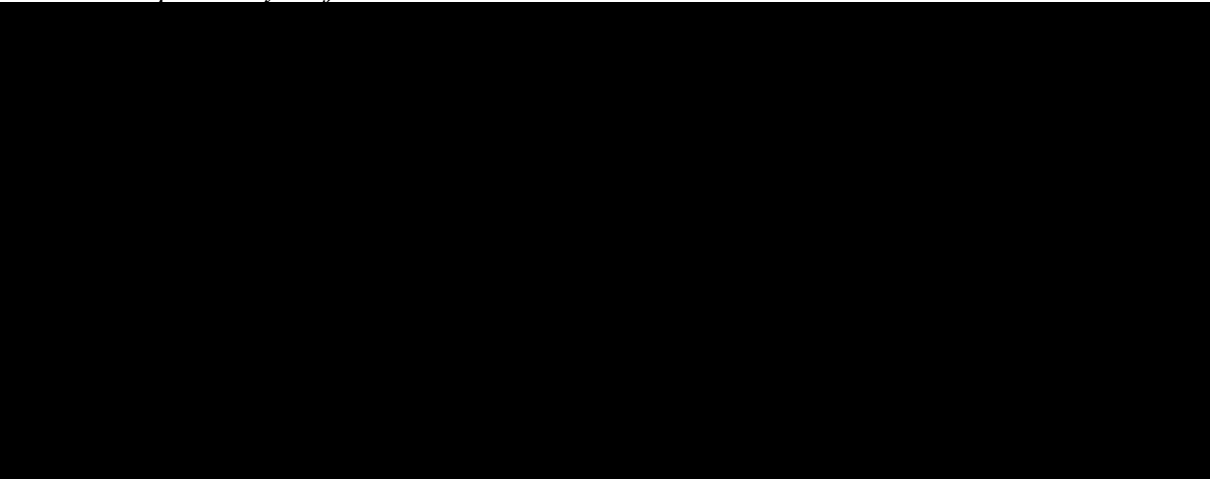
**Endpoints:** The primary endpoint is IRRC-assessed ORR. The secondary endpoints are duration of ORR (DOR) based on IRRC assessments, IRRC-assessed complete remission rate and duration of CR, IRRC-assessed PR rate and duration of PR, IRRC-assessed progression free survival (PFS), and investigator-assessed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

**Analyses:** The IRRC-assessed ORR will be summarized by binomial response rates and their corresponding two-sided 95% exact CIs using the Clopper-Pearson method. The null hypothesis will be rejected if the 2-sided 95% CI lower bound is greater than 20%.

The IRRC-assessed DOR will be summarized 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 CR and PR rates 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 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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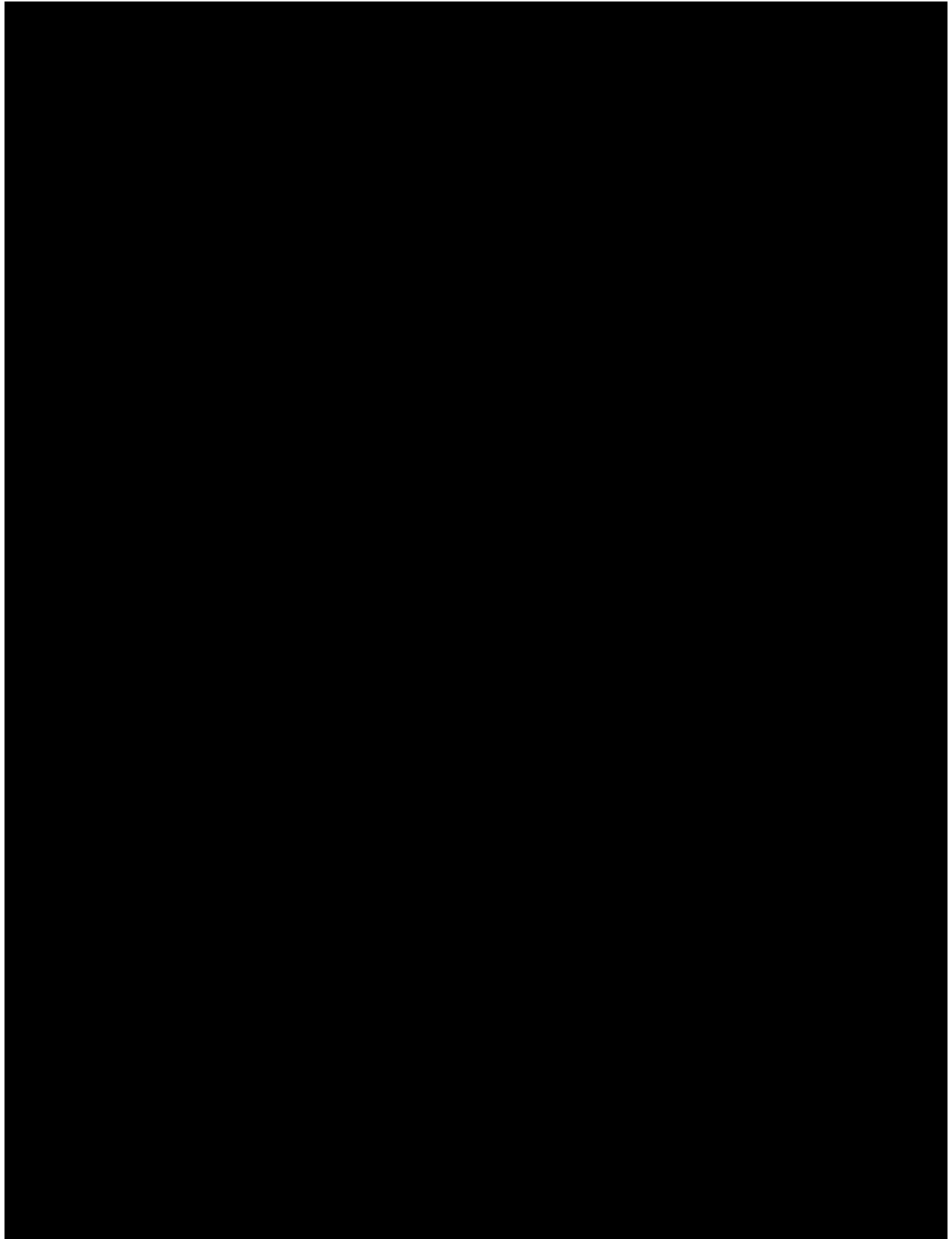
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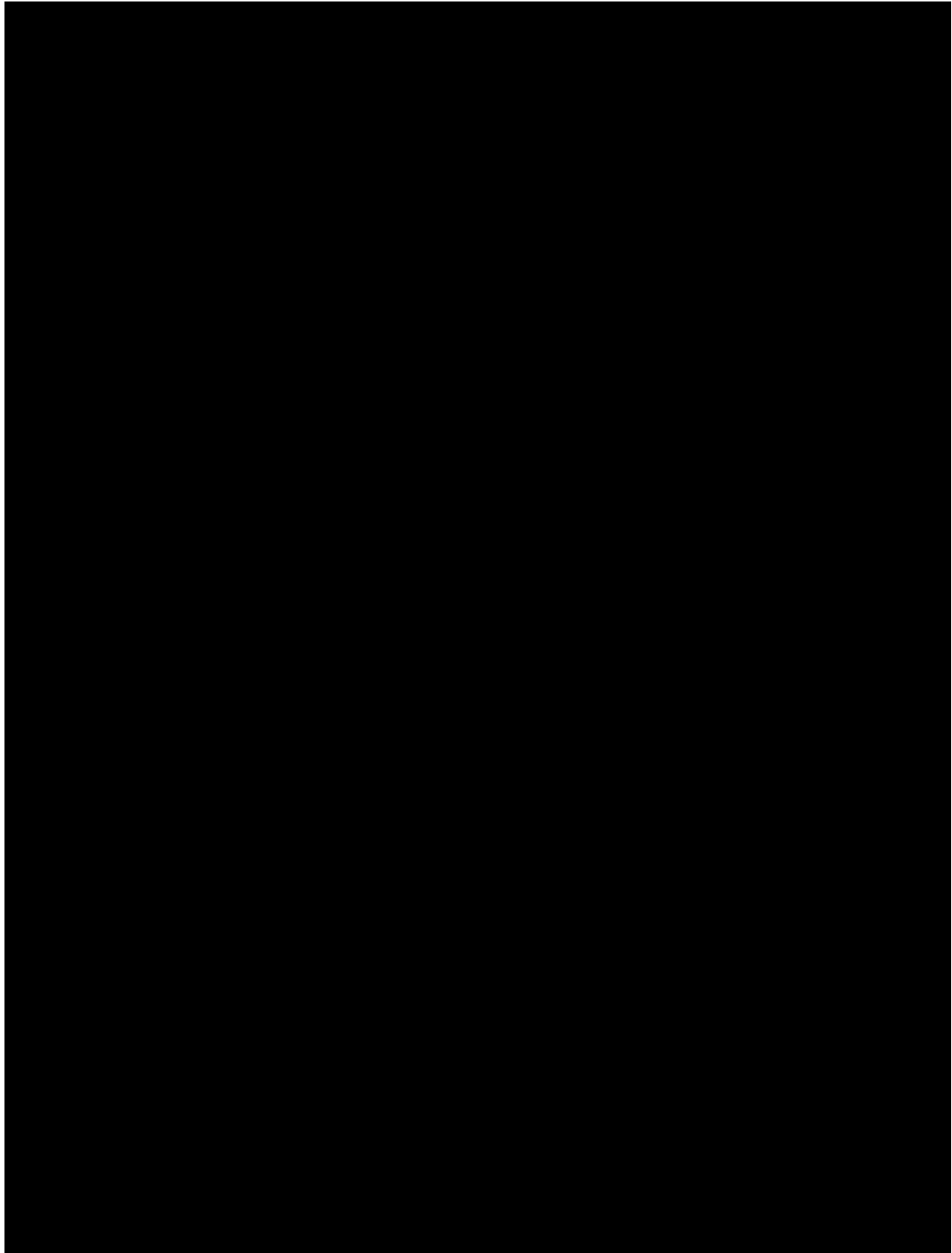
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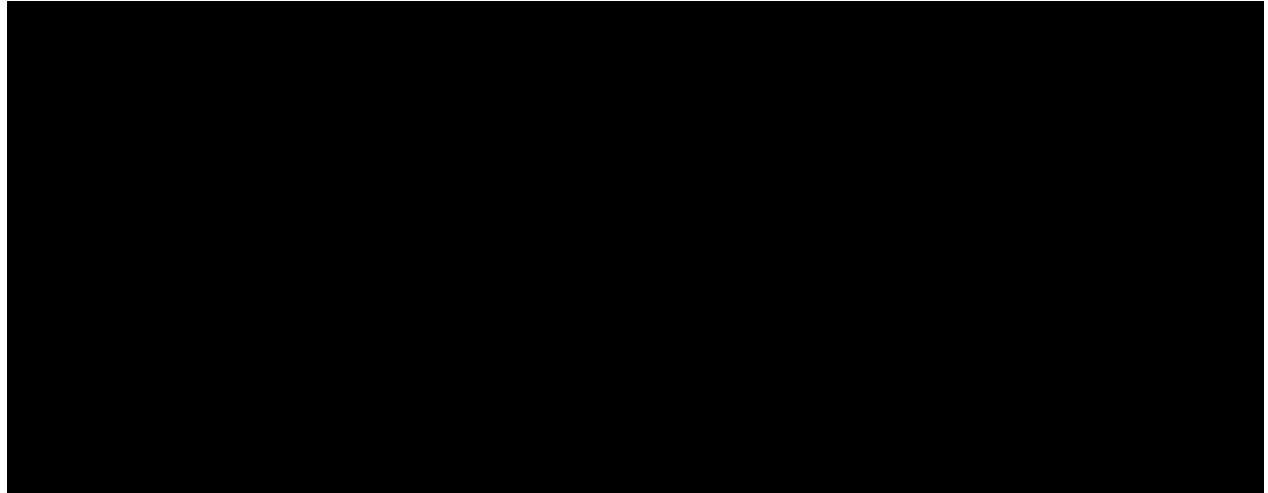
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**1 INTRODUCTION**







## **1.2 Research Hypothesis**

Treatment with nivolumab will lead to clinical benefit, as demonstrated by an improved clinically meaningful objective response rate, including durable responses with substantial magnitude of tumor reduction in subjects with refractory FL who have failed therapy with both rituximab and an alkylating agent.

## **1.3 Objectives(s)**

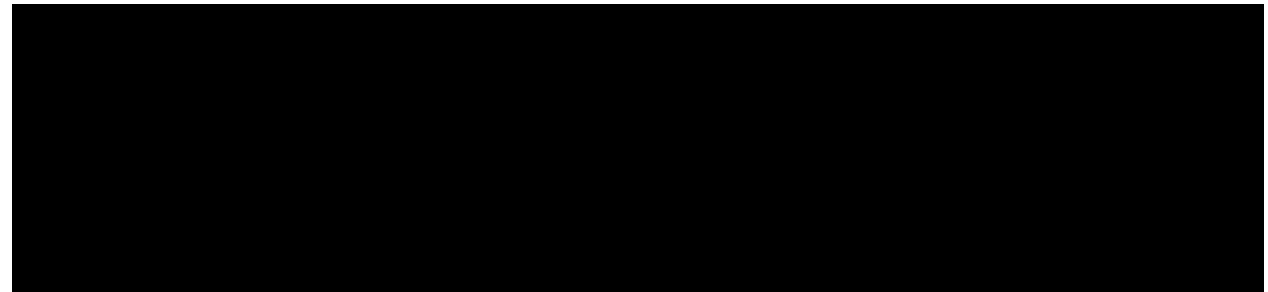
### **1.3.1 Primary Objectives**

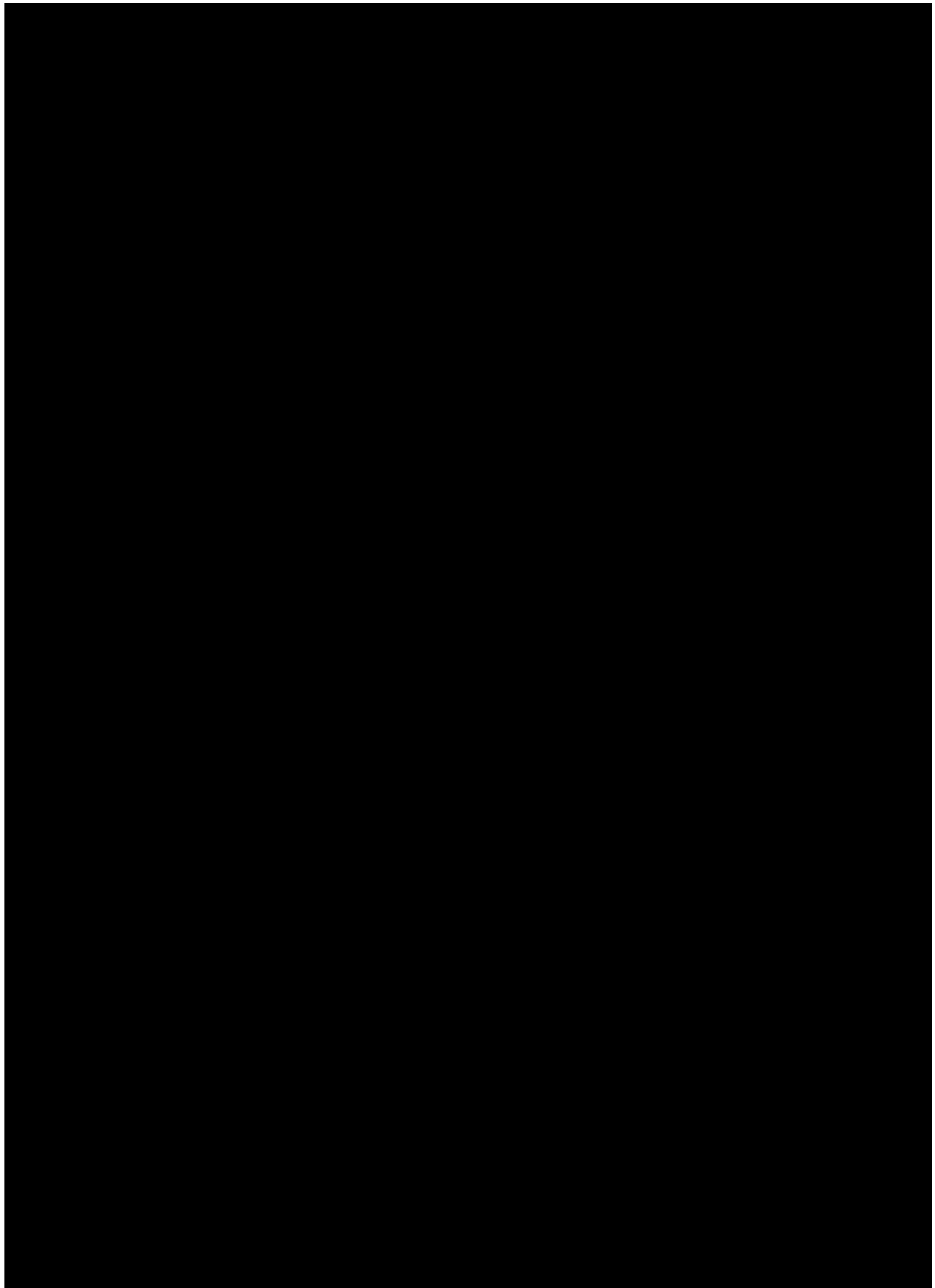
To assess the clinical benefit of nivolumab, as measured by independent radiologic review committee (IRRC) assessed objective response rate (ORR) in subjects with FL who have failed therapy with both rituximab and an alkylating agent.

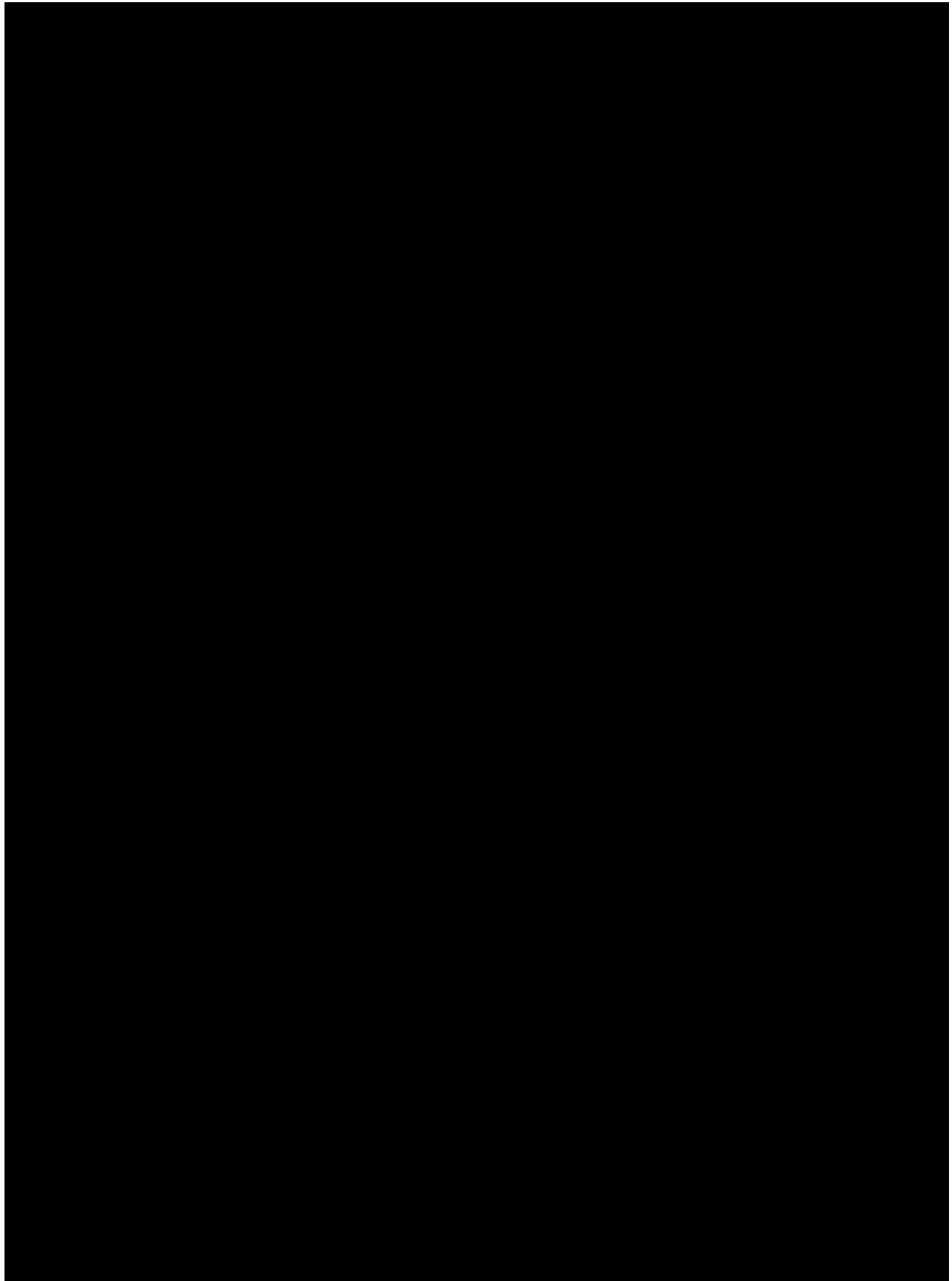
### **1.3.2 Secondary Objectives**

- 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 the PFS based on IRRC assessment
- To assess the ORR, based on investigator assessments

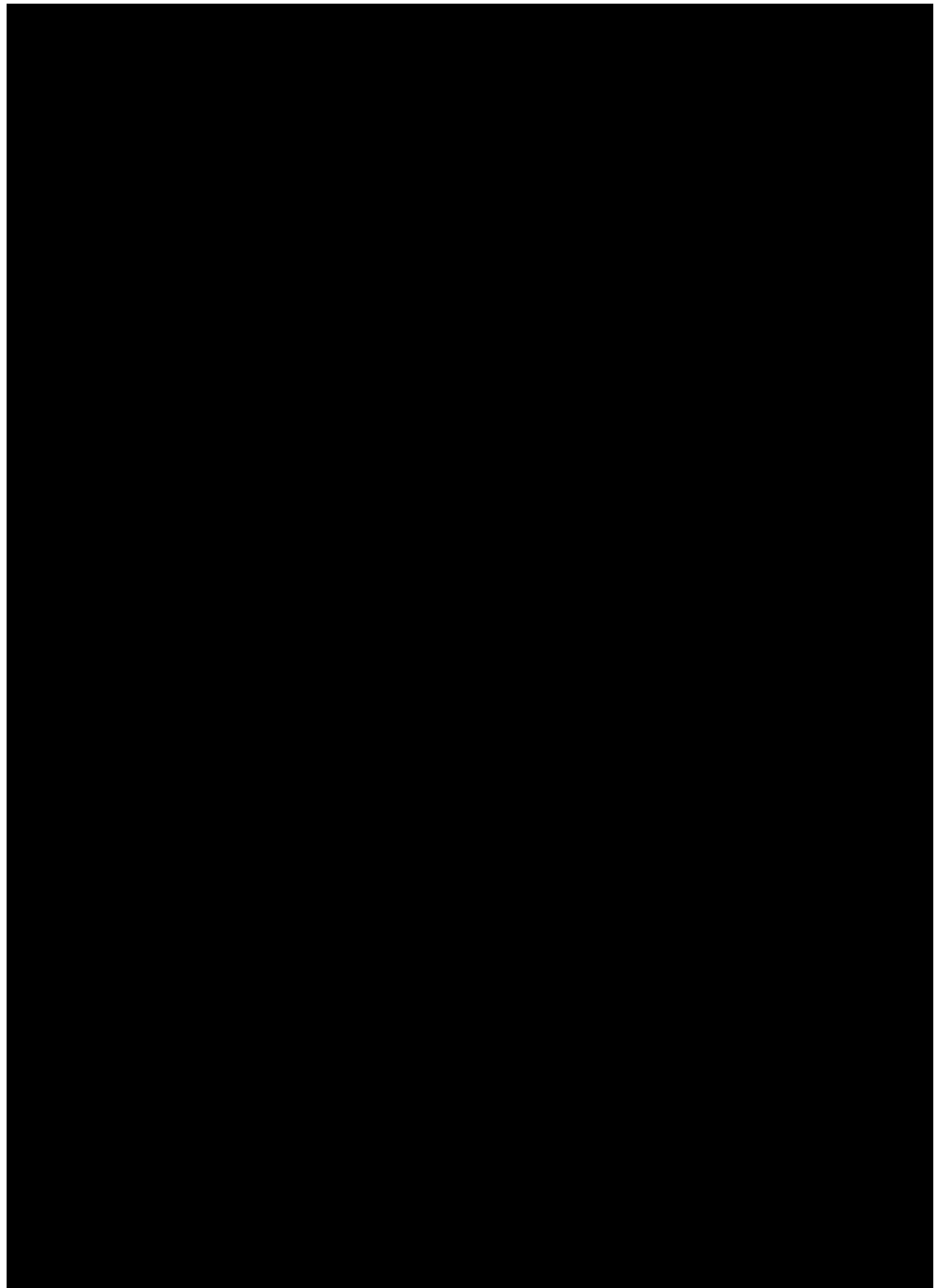
### **1.3.3 Exploratory Objectives**

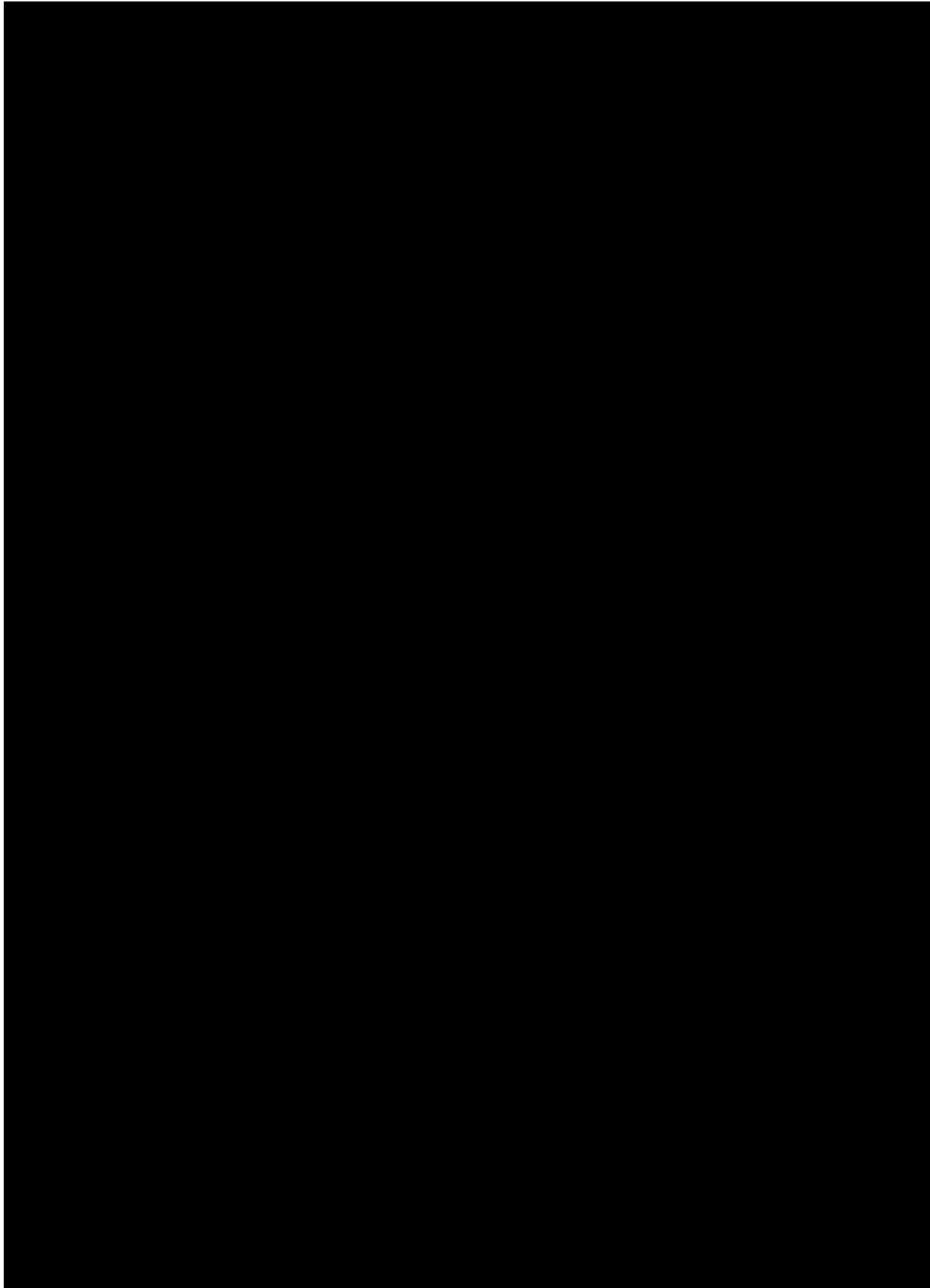


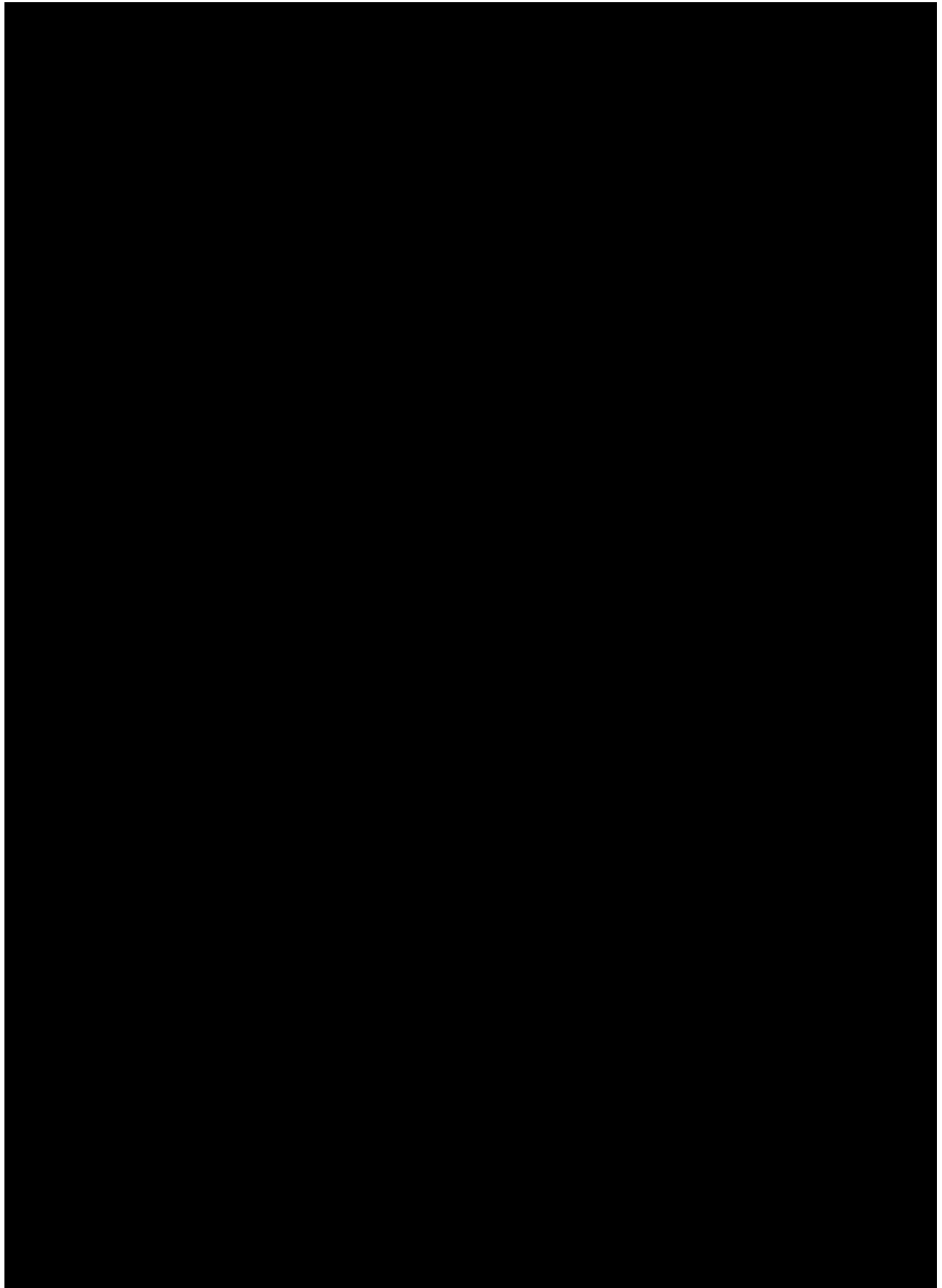


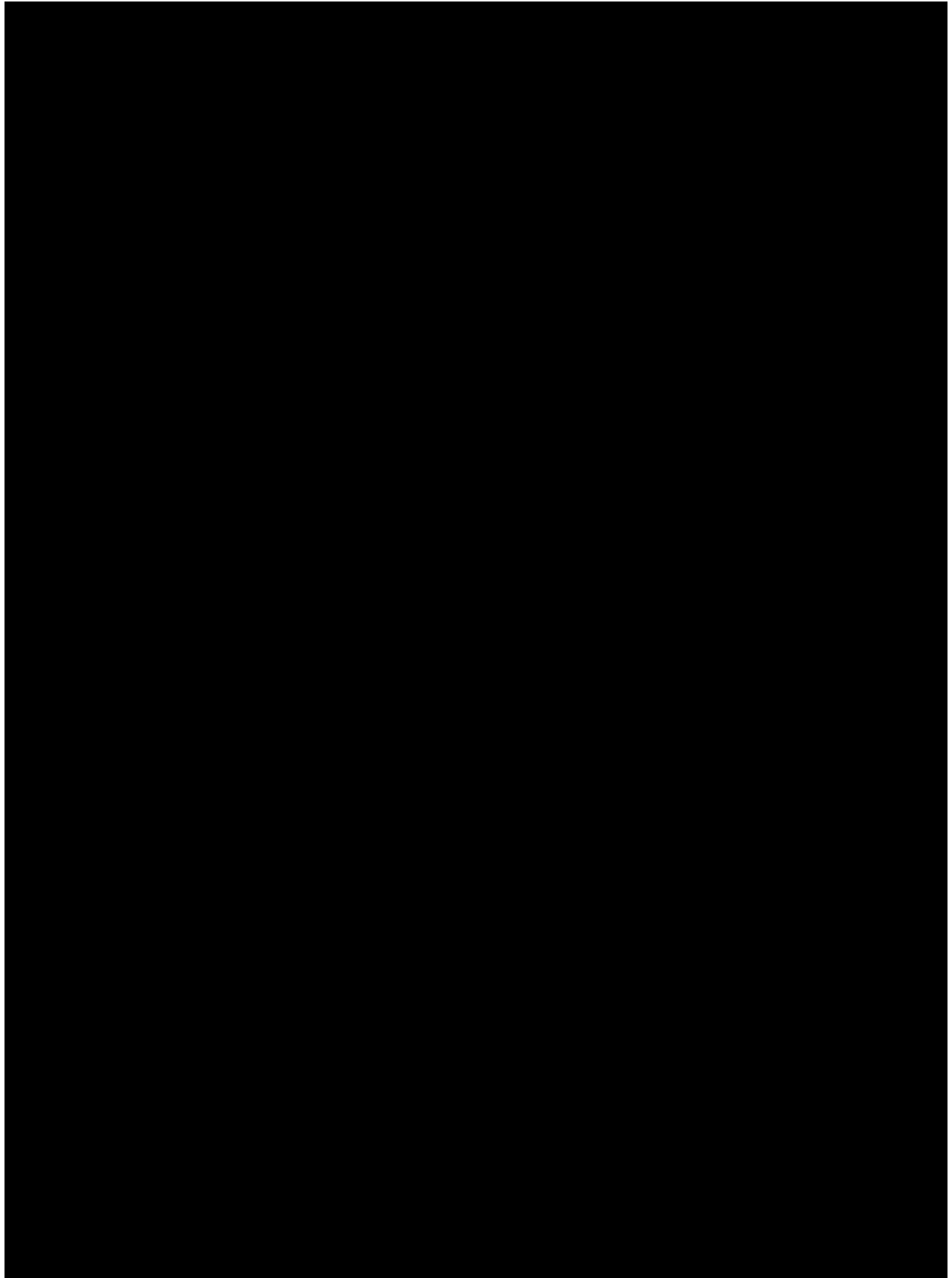


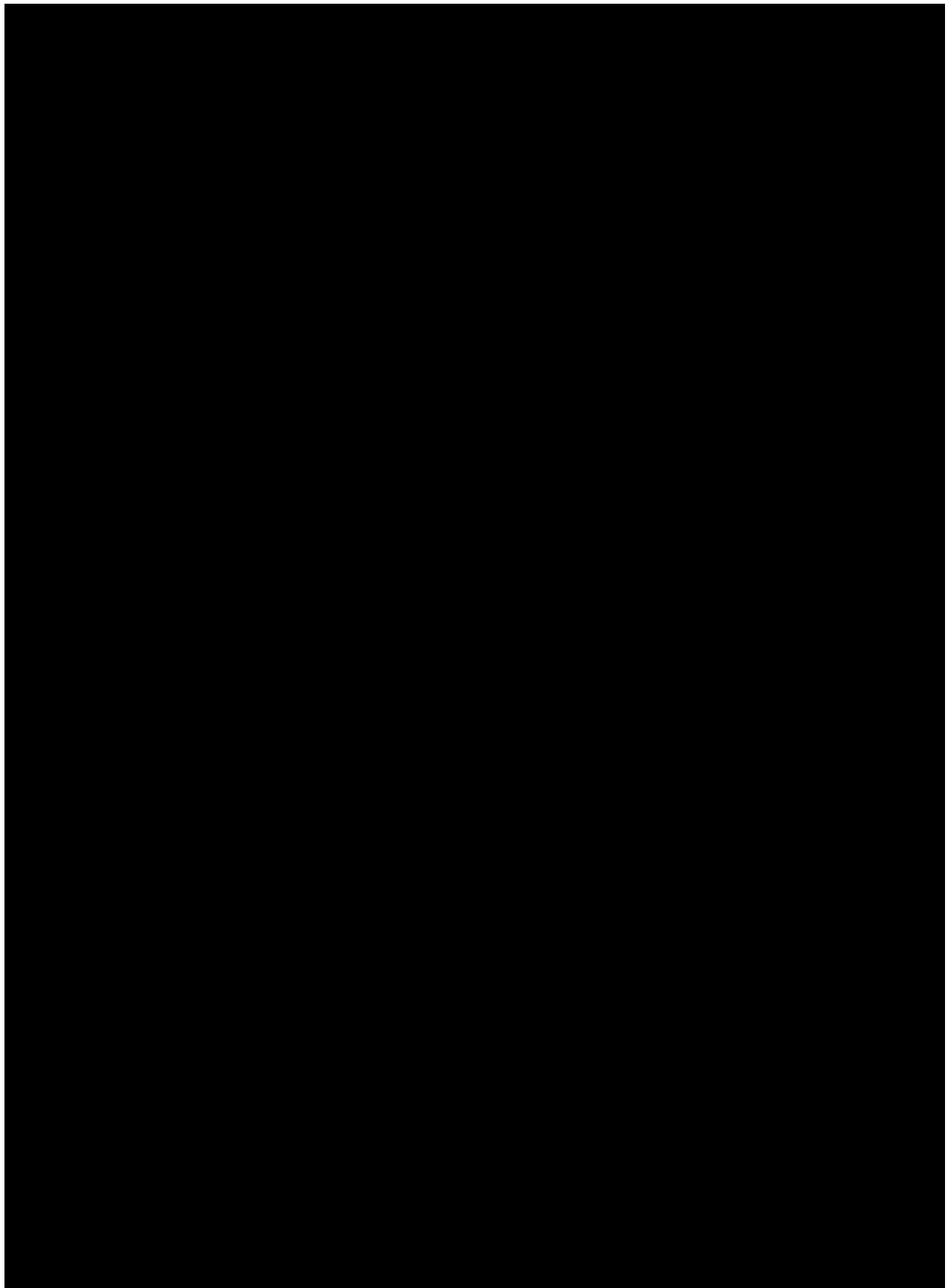


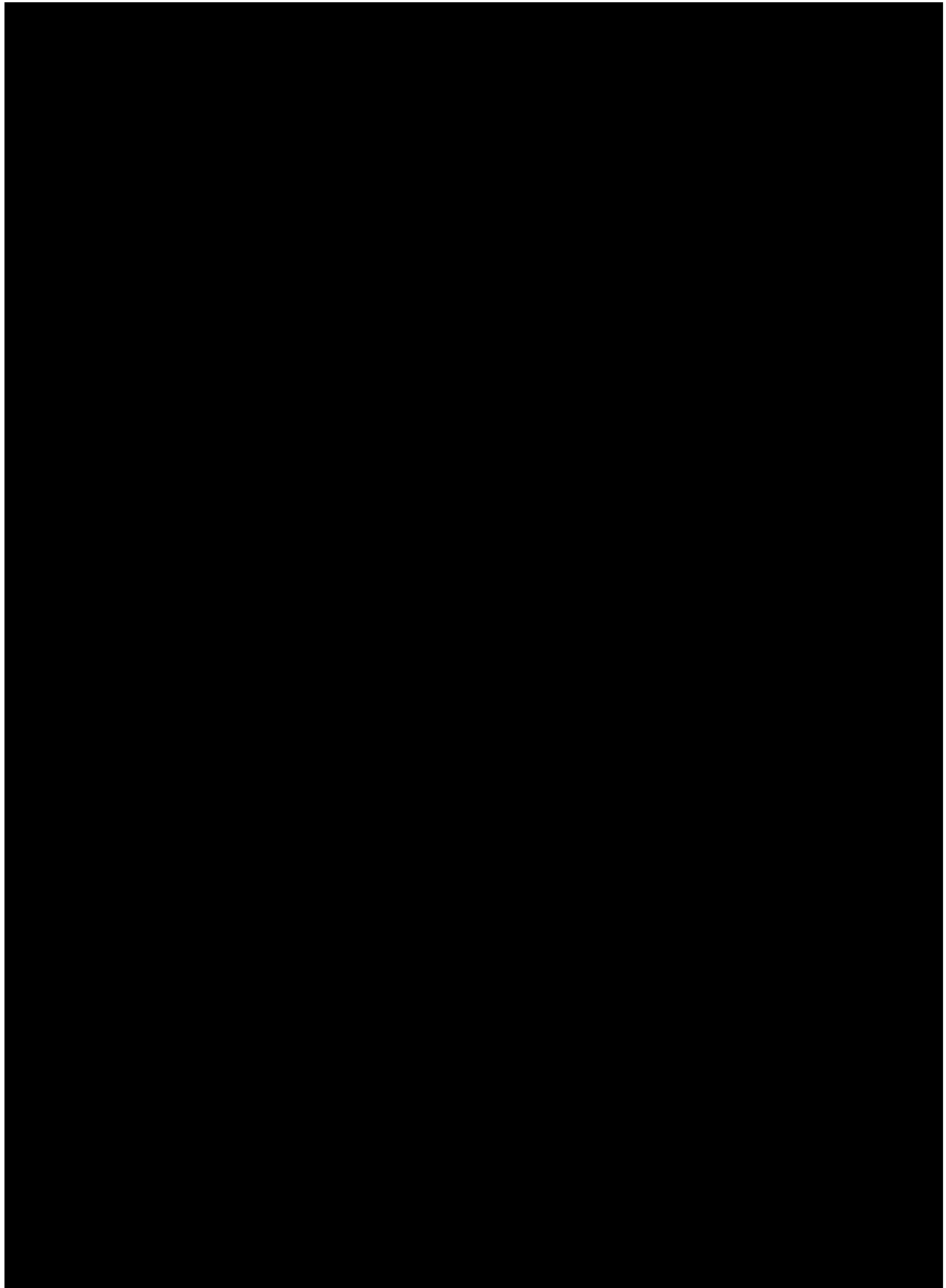


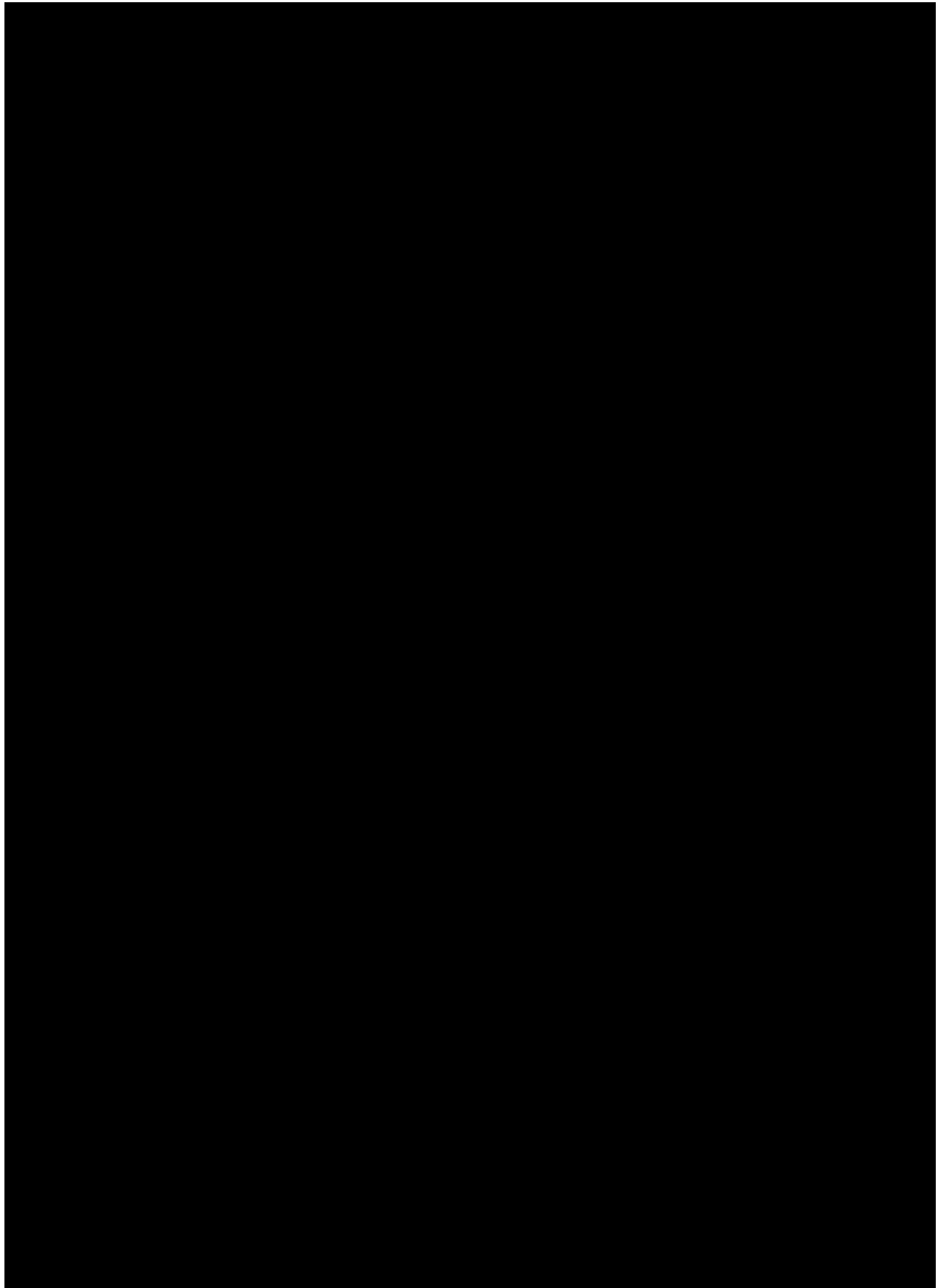












## **2 ETHICAL CONSIDERATIONS**

### **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

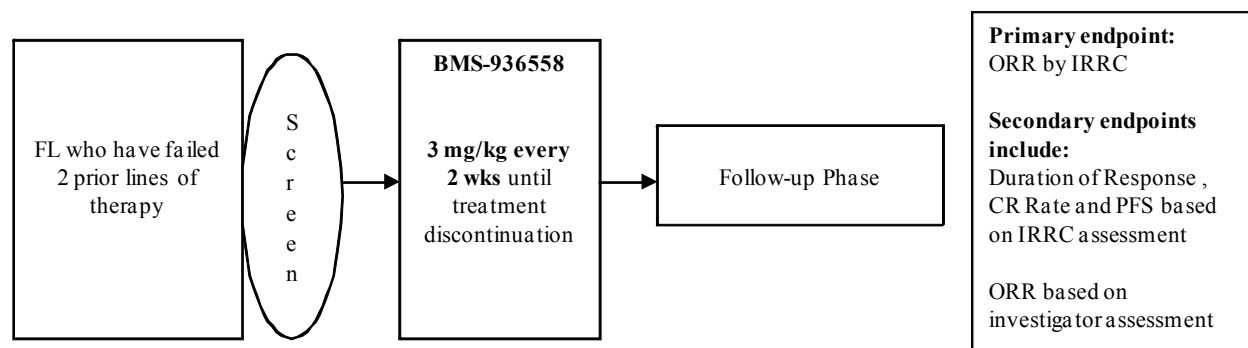
#### 3.1 Study Design and Duration

This is a single-arm Phase 2 study in subjects  $\geq 18$  years old with relapsed FL after failure of at least two prior lines of therapy, (each containing rituximab and/or an alkylating agent). Approximately 90 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 by spiral CT/MRI will begin 8 weeks after the start of therapy and will continue every 8 weeks through the first 8 months, every 12 weeks Months 9 - 24, and then every 6 months thereafter until disease progression. An IRRC will also be utilized. The primary endpoint of this study is IRRC-assessed objective response rate, using 2007 International Working Group (IWG) Response Criteria for Malignant Lymphoma criteria ([Appendix 2](#)). Secondary endpoints include IRRC-assessed duration of objective response, as well as complete remission rate, duration of CR, PR rate, duration of PR and 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**



#### Study Duration

It is anticipated that accrual will last 18 months, with approximately 115 subjects enrolled. It is anticipated that the analysis of the primary endpoint will take place approximately 30 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 3 phases: screening, treatment, and follow-up.

### **Screening:**

- Begins by establishing 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 FL 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 the study drug before the outcome of PD-L1 expression status become available.

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 can start the study drug before bone marrow biopsy results become available; results need to be documented in the subject's medical record later
- The Follicular Lymphoma International Prognostic Index (FLIPI) 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:**

- 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 ( $\pm$  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.
- All of the vital signs starting after Cycle 1 will be collected within 72 hours prior to dosing.
- Adverse event assessments should be documented at each clinic visit.
- Biomarker, PK and immunogenicity samples will be done according to the schedules in [Sections 5.5, 5.6, and 5.8.1](#).
- 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 [Section 4.3.2](#).
- Subjects will be evaluated for response according to revised International Working Group Criteria beginning at Week 9 and continuing every 8 weeks ( $\pm$  1 week) for the first eight months of treatment, then every 12 weeks ( $\pm$  2 weeks) up to 2 years of treatment, continuing every 6 months ( $\pm$  3 weeks) beyond 2 years of treatment, 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](#) and [Table 5.1-3](#).
- This phase ends when the subject is discontinued from study therapy. For a complete list of reasons for treatment discontinuation, refer to [Sections 3.5](#) and [4.3.5](#).

### **Follow-up:**

- 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 ( $\pm$  7 days) from the last dose of study therapy and Follow-up visit 2 (X02), 80 days ( $\pm$  7 days) from X01. After X02, subjects will be followed every 3 months for ongoing drug-related AEs until resolved, return to baseline or deemed irreversible, or until lost to follow-up or withdrawal of study consent.

- PK and immunogenicity samples will be collected at the first two follow-up visits.
- Subjects who discontinue study therapy for reasons other than disease progression or allogeneic SCT or ASCT 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 Graft-Versus-Host Disease (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 5.1-2](#) and [Table 5.1-3](#).

### **3.2 Post Study Access to Therapy**

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

### **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 FL must be obtained prior to the initiation of study drug.
  - i. Grade 1, 2, or 3a FL without pathologic evidence of transformation.
  - ii. FL 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 0 or 1 ([Appendix 4](#)).
- c) Measurable Disease: Subjects must have at least one lesion that is > 15 mm (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) Treatment of FL consisting of  $\geq 2$  prior treatment lines; each of the two prior treatment lines must include CD20 antibody and/or an alkylating agent (eg, bendamustine, cyclophosphamide, ifosfamide, chlorambucil, melphalan, busulfan, nitrosoureas). At least one of the prior treatment lines must include rituximab.

NOTE: Separate lines of therapy are defined as two regimens separated by disease progression, relapsed disease, or refractory disease.
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### Definition of Relapsed FL

- The appearance of new lesions > 6 months after obtaining a CR
- An increase  $\geq 50\%$  in the size of previously involved sites > 6 months after completing planned therapy.

### Definition of Refractory FL

- < 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  $\geq 50\%$  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 treated). If re-enrolled, the subject must be re-consented.

## 3. Physical and Laboratory Test Finding

- a) Screening laboratory values must meet the following criteria and should be obtained within 14 days prior to first dose:
  - i) Absolute neutrophil Count  $\geq 750/\mu\text{L}$  (no WBC growth factors for prior 14 days)
  - ii) Platelets  $\geq 50 \times 10^3/\mu\text{L}$  (no platelet transfusions for prior 14 days)

- iii) Hemoglobin  $\geq$  8.5 g/dL (no RBC transfusions for prior 7 days)
- iv) Serum creatinine  $\leq$  1.5 x ULN or creatinine clearance (CrCl)  $\geq$  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  $\leq$  3 x ULN
- vi) Total Bilirubin  $\leq$  1.5 x ULN (except subjects with Gilbert Syndrome, who can have total bilirubin  $<$  3.0 mg/dL).

#### 4. Age and Reproductive Status

- a) Men and women  $\geq$  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 study drug plus 5 half-lives of study drug 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 study drug plus 5 half-lives of study drug 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 or 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) 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 study drug
- b) 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
- c) Prior allogeneic SCT
- d) Autologous SCT  $\leq$  12 weeks prior to first dose of study drug
- e) Chest radiation  $\leq$  24 weeks prior to first dose of the study drug
- f) Carmustine (BCNU)  $\geq$  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.

## **3.4 Concomitant Treatments**

### **3.4.1 Prohibited and/or Restricted Treatments**

The following medications are prohibited during the study:

- Immunosuppressive agents (except to treat a drug-related adverse event)
- Systemic corticosteroids > 10 mg daily prednisone equivalent (except as stated in [Section 3.3.2](#) or to treat a drug-related adverse event).
- Any concurrent antineoplastic therapy (ie, chemotherapy, hormonal therapy, immunotherapy, radiation therapy except for palliative radiation therapy, or standard or investigational agents for treatment of cancer).

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

### **3.4.2 Other Restrictions and Precautions**

#### **3.4.2.1 Permitted Therapy**

Subjects are permitted to use topical, ocular, intra-articular, intranasal, and inhalational corticosteroids (with minimal systemic absorption). Physiologic replacement doses of systemic corticosteroids are permitted, even if > 10 mg/day prednisone equivalents. A brief course of

corticosteroids for prophylaxis (eg, contrast dye allergy) or for treatment of non-autoimmune conditions (eg, delayed-type hypersensitivity reaction caused by contact allergen) is permitted.

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

### **3.5 Discontinuation of Subjects from Treatment**

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

- 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-specific 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 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**

<b>Product Description and Dosage Form</b>	<b>Potency</b>	<b>Primary Packaging (Volume)/ Label Type</b>	<b>Secondary Packaging (Qty) /Label Type</b>	<b>Appearance</b>	<b>Storage Conditions (per label)</b>
BMS-936558-01 Solution for Injection <sup>a</sup>	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.

<sup>a</sup> 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 for this study.

#### **4.1.3 Handling and Dispensing**

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

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

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

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

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 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 of informed consent
- 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. Subjects must be treated within one day after study drug vial assignment. 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 drugs.

### **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  $\geq 2$  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  $\geq 2$  toxicity
  - If a subject has baseline AST, ALT, or total bilirubin within the Grade 1 toxicity range, delay dosing for drug-related Grade  $\geq 3$  toxicity
- Any adverse event, laboratory abnormality, or intercurrent illness which, in the judgment of the investigator, warrants delaying the dose of study medication.

#### **4.3.2.1 Management Algorithms for Immuno-Oncology Agents**

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

Gastrointestinal

Renal

Pulmonary

Hepatic

Endocrinopathies

Skin

Neurological

For subjects expected to require more than 4 weeks of corticosteroids or other immunosuppressants to manage an adverse event, consider recommendations provided in the algorithms. These algorithms are found in the Nivolumab IB and in [Appendix 1](#) of this protocol. Discussions with the BMS Medical Monitor on how to apply these algorithms are strongly encouraged. The guidance provided in these algorithms should not replace the Investigator's medical judgment but should complement it.

#### **4.3.3 Doses Reductions and Escalations**

Doses reductions and escalations of nivolumab are not permitted.

#### **4.3.4 Criteria to Resume Nivolumab Dosing**

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

- Subjects may resume treatment in the presence of Grade 2 fatigue
- Subjects who have not experienced a Grade 3 drug-related skin AE may resume treatment in the presence of Grade 2 skin toxicity
- Subjects with baseline 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, or colitis 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 timepoint per protocol.

If treatment is delayed  $>$  6 weeks, 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 drug-related 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 > 5 x ULN
    - Concurrent AST or ALT > 3 x ULN and total bilirubin > 2 x ULN
- Any Grade 4 drug-related adverse event or laboratory abnormality, except for the following events which do not require discontinuation:
  - Grade 4 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, the BMS medical monitor must be consulted. Tumor assessments should continue as per protocol even if dosing is interrupted.
  - Dosing interruptions > 6 weeks that occur for non-drug-related reasons may be allowed if approved by the BMS medical monitor. Prior to re-initiating treatment in a subject with a dosing interruption lasting > 6 weeks, the BMS medical monitor must be consulted. Tumor assessments should continue as per protocol even if dosing is interrupted.
- Any adverse event, laboratory abnormality, or intercurrent illness which, in the judgment of the Investigator, presents a substantial clinical risk to the subject with continued nivolumab 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 Nivolumab Related Infusion Reactions**

Since nivolumab contains only human immunoglobulin protein sequences, it is unlikely to be immunogenic and induce an infusion or hypersensitivity reaction. However, if such a reaction were to occur, it might manifest with fever, chills, rigors, headache, rash, pruritis, arthralgias, hypo- or hypertension, bronchospasm, or other symptoms. All Grade 3 or 4 infusion reactions should be reported within 24 hours to the BMS Medical Monitor and reported as an SAE if criteria are met. Infusion reactions should be graded according to National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) (Version 4.0) guidelines.

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

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

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

**For Grade 2 symptoms:** (Moderate reaction requires therapy or infusion interruption but responds promptly to symptomatic treatment [eg, antihistamines, non-steroidal anti-inflammatory drugs, narcotics, corticosteroids, bronchodilators, IV fluids]; prophylactic medications indicated for  $\leq 24$  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 Grade 4 symptoms:** (Severe reaction, Grade 3: prolonged [ie, not rapidly responsive to symptomatic medication and/or brief interruption of infusion]; recurrence of symptoms following initial improvement; hospitalization indicated for other clinical sequelae [eg, renal impairment, pulmonary infiltrates]). Grade 4: (life-threatening; pressor or ventilatory support indicated).

Immediately discontinue infusion of nivolumab. Begin an IV infusion of normal saline, and treat the subject as follows. Recommend bronchodilators, epinephrine 0.2 to 1 mg of a 1:1,000 solution for subcutaneous administration or 0.1 to 0.25 mg of a 1:10,000 solution injected slowly for IV administration, and/or diphenhydramine 50 mg IV with methylprednisolone 100 mg IV (or equivalent), as needed. Subject should be monitored until the investigator is comfortable that the symptoms will not recur. Nivolumab will be permanently discontinued. Investigators should follow their institutional guidelines for the treatment of anaphylaxis. Remain at bedside and monitor subject until recovery from symptoms. In the case of late-occurring hypersensitivity symptoms (eg, appearance of a localized or generalized 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 CRF.

## **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 Procedural Outline (CA209140)**

Procedure	Screening Visit <sup>a</sup>	Notes
<b><u>Eligibility Assessments</u></b>		
Informed Consent	X	
Inclusion/Exclusion Criteria	X	All inclusion/exclusion criteria should be assessed at screening and confirmed prior to first dose
Medical History	X	
Prior Systemic Therapy	X	
<b><u>Safety Assessments</u></b>		
Physical Examination	X	
Physical Measurements	X	Include Height, Weight, and ECOG performance Status
Follicular Lymphoma International Prognostic Index (FLIPI) at time of initial diagnosis	X	Refer to <a href="#">Appendix 3</a>
Vital Signs and Oxygen saturation	X	Temperature, BP, HR, and O <sub>2</sub> saturation by pulse oximetry (at rest and after exertion).
Assessment of Signs and Symptoms	X	After obtaining Informed Consent, assess all signs and symptoms within 14 days prior to first dose.
Concomitant Medication Collection	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.



**Table 5.1-1: Screening Procedural Outline (CA209140)**


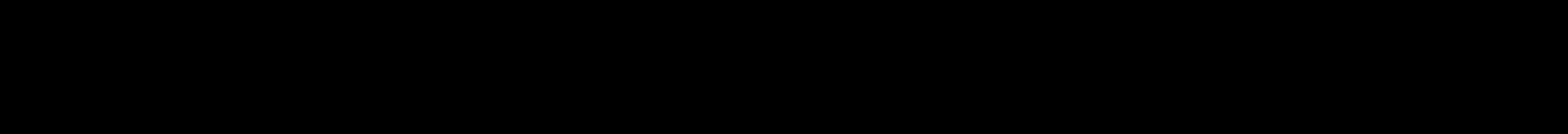
Procedure	Screening Visit <sup>a</sup>	Notes
Urinalysis	X	Total protein, glucose, blood, leukocyte esterase, specific gravity, and pH, within 14 days prior to first dose.
Pregnancy Test	X	For WOCBP only (serum or urine - local/site)
<b><u>Efficacy/Biomarker Assessments</u></b>		
Radiographic Tumor Assessment <ul style="list-style-type: none"> <li>Spiral CT/MRI of Chest, Abdomen, Pelvis, and any other known sites of disease</li> <li>PET scan</li> </ul>	X	Should be performed within 28 days prior to first dose. Additional sites of known or suspected disease (including CNS) should be imaged at the screening visit and at subsequent on-study assessments. PET scan required at screening.
Bone Marrow Biopsy/Aspirate	See Note	If results of a bone marrow biopsy/aspirate performed within 90days prior to obtaining consent are not in the subject's medical record then one must be performed during screening. If a biopsy/aspirate is performed, submission of aspirate for biomarker analyses is optional [REDACTED].
Collection of tumor tissue	X	Collection of tumor tissue (FFPE tumor tissue block or 10 unstained slides) for determination of PD-L1 expression status: Submission of tumor tissue (obtained during the screening phase or collected as a standard of care procedure within 90 days prior to obtaining informed consent) is mandatory. Tumor biopsies in formalin for IHC of tumor and TIL. Biopsy samples should be excisional, incisional or core needle.
<b><u>IVRS/Clinical Drug Supplies</u></b>		
Phone calls to IVRS		Phone calls must be made to IVRS as follows: <ul style="list-style-type: none"> <li>For subject number assignment at the time informed consent is obtained.</li> <li>Prior to dosing for study drug vial assignment (call should be made within 1 day prior to dosing).</li> </ul>

<sup>a</sup> Within 28 days prior to first dose

**Table 5.1-2: Short-term Procedural Outline (CA209140)**

Procedure	Cycle 1 Day 1	Cycle 1 Day 8	Each Cycle within 3 Days prior to Dosing	Notes
<b><u>Safety Assessments</u></b>				
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, 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
Physical Measurements	X	X	X	Includes Weight and ECOG performance status
Adverse Events Assessment	----- Continuously -----			Assessed using NCI CTCAE v. 4.0.
Review of Concomitant Medications	X	X	X	
Laboratory Tests	X	X	X	<u>Extended</u> on-study local laboratory assessments should be done within 72 hours prior to dosing for Cycle 1 through Cycle 5 and every alternate dose thereafter (Cycles 7, 9, 11, 13, etc) and include: CBC with differential, uric acid, serum urea level, serum creatinine, sodium, potassium, calcium, magnesium, phosphorus, chloride, amylase, lipase, glucose, AST, ALT, total bilirubin, alkaline phosphatase, LDH. <u>Limited</u> on-study local laboratory assessment should be done within 72 hours prior to dosing (beginning at Cycle 6 and every alternate dose thereafter (Cycles 8, 10, 12, 14, etc) and include: CBC with differential, LFTs (ALT, AST, total bilirubin, alkaline phosphatase) and creatinine.
Thyroid Function Testing			See Note	TSH (reflex to free T3 and free T4 if abnormal result) to be performed every 6 weeks ( $\pm$ 7 days) regardless of dosing schedule.

**Table 5.1-2: Short-term Procedural Outline (CA209140)**

Procedure	Cycle 1 Day 1	Cycle 1 Day 8	Each Cycle within 3 Days prior to Dosing	Notes
Pregnancy Test for WOCBP	X		See Note	Serum or urine - local/site test to be performed within 24 hours prior to first dose and then at least once every 4 weeks ( $\pm$ 7 days) regardless of dosing schedule
<b><u>Efficacy Assessments</u></b>				
Radiographic Tumor Assessment <ul style="list-style-type: none"> <li>• Spiral CT/MRI of Chest, Abdomen, Pelvis, and any other known sites of disease</li> <li>• PET Scan</li> </ul>			See Note	See <a href="#">Section 5.4.1</a> and <a href="#">Table 5.4.1-1</a> for spiral CT/MRI assessment schedule PET scan <u>required to confirm CR</u> .
Bone Marrow Aspirate and Biopsy	See Note		See Note	Required to confirm any CR in subjects with bone marrow disease at screening 
<b><u>Additional Exploratory Biomarker Testing</u></b>				
				
<b><u>PK and Immunogenicity Assessments</u></b>				
PK samples			See Note	See separate <a href="#">Table 5.5-1</a> for sampling details
Immunogenicity samples			See Note	See separate <a href="#">Table 5.5-1</a> for sampling details
<b><u>Outcomes Research Assessments</u></b>				
EORTC QLQ-C30	X		See Note	Assessments to be collected every 8 weeks for the first 8 months;

**Table 5.1-2: Short-term Procedural Outline (CA209140)**

Procedure	Cycle 1 Day 1	Cycle 1 Day 8	Each Cycle within 3 Days prior to Dosing	Notes
EQ-5D	X		See Note	<ul style="list-style-type: none"> <li>• Day 1 (prior to dosing) of Cycles 5, 9, 13, 17 every 12 weeks thereafter;</li> <li>• Day 1 (prior to dosing) of Cycles 23, 29, 35+.</li> </ul>
<b><u>Clinical Drug Supplies</u></b>				
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 (CA209140)**

Procedure	X, Follow Up, <sup>a</sup> Visits 1 and 2	S, Survival Follow-Up <sup>b</sup> Visits	Notes
<b><u>Safety Assessments</u></b>			
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	In survival follow-up period, only to include toxicities from study therapy
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
Thyroid Function Testing	X		TSH (reflex to free T3 and free T4 if abnormal 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 <a href="#">Section 5.3</a> .
<b><u>Efficacy Assessments</u></b>			
Radiographic Tumor Assessment <ul style="list-style-type: none"> <li>• Spiral CT/MRI</li> <li>• PET Scan</li> </ul>	X (See Note)	X	Only for subjects without progression on study therapy. <ul style="list-style-type: none"> <li>• 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.</li> <li>• Spiral CT/MRI of chest, abdomen, pelvis and all known sites of disease. Use same imaging method as was used at screening/baseline.</li> </ul> PET scan <u>required to confirm CR</u> .

**Table 5.1-3: Follow-Up Assessments (CA209140)**

Procedure	X, Follow Up, <sup>a</sup> Visits 1 and 2	S, Survival Follow-Up <sup>b</sup> Visits	Notes
Tumor Assessment by the Investigator (CR or non-CR)	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 <a href="#">Section 5.4</a> .
<b><u>Outcomes Research Assessments</u></b>			
EORTC QLQ-C30	X		
EQ-5D	X	X	EQ-5D during the survival follow-up will be assessed during a clinic visit or via a phone contact
<b><u>Pharmacokinetic/Immunogenicity Assessments</u></b>			
PK Samples	X		See separate <a href="#">Table 5.5-1</a> for Sampling Schedule details
Immunogenicity samples	X		See separate <a href="#">Table 5.5-1</a> for Sampling Schedule details
<b><u>Exploratory Biomarker Testing</u></b>			
<b><u>Subject Status</u></b>			
Survival Status	X	X	Every 3 months after X02; may be accomplished by visit or phone contact , to update survival information and assess subsequent anti-cancer therapy

<sup>a</sup> X visits occur as follows: X01 = 35 days ± 7 days from last dose, X02 = 80 days ± 7 days from X01

<sup>b</sup> S, Survival visits continue every 3 months after X visits

## 5.2 Study Materials

The following materials will be provided at study start:

- NCI CTCAE version 4.0
- Nivolumab Investigator Brochure
- Pharmacy Binder
- Laboratory manuals for collection and handling of blood (including PKs, biomarker and immunogenicity) and tissue specimens
- Site manual for operation of IVRS, including enrollment worksheet
- Manual for entry of local laboratory data
- Serious Adverse Events (or eSAE) case report forms
- EORTC QLQ-C30 and EQ-5D 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 and should be performed within 28 days prior to first dose as described in [Table 5.1-1](#) Notes. 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 first dose through the study treatment period.

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, 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 ( $\pm 7$  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 or documented telephone calls/emails to assess the subject's status are acceptable.

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

Performance status and body weight should be assessed at each on study visit prior to nivolumab dosing and at 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 treatments local laboratory assessments should be done within 72 hours prior to dosing;

- **Extended on-treatment local laboratory assessments:** 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, phosphorus, chloride, amylase, lipase, glucose, AST, ALT, total bilirubin, alkaline phosphatase, LDH.
- **Limited on-study treatment laboratory assessment:** beginning at Cycle 6 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 Free T4 and Free T3) should be performed every 6 weeks ( $\pm$  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 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 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 CA209140 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 ORR, defined as a subject achieving either a PR or CR according to the 2007 IWG criteria ([Appendix 2](#)). The primary efficacy assessment, along with the secondary endpoints of DOR, CRR, CR duration, PRR, PR duration and PFS will be based on IRRC assessments. 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 Section 5.4.1. 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, and 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 ( $\pm 1$  week) through the first 8 months, every 12 weeks ( $\pm 2$  weeks) Months 9 - 24, and then every 6 months ( $\pm 3$  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 2007 IWG 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 as per the frequency 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 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.<sup>95</sup> **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 metric notation (cm). 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

#### **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 CT/MRI slice thickness is 5 mm or less. When CT scans have slice thickness greater than 5 mm, the minimum size for a measurable lesion should be twice the slice thickness.

NOTE: 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  $\geq 10$  mm 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’).

##### **5.4.5 Bone Marrow Assessments**

To determine the extent of disease involvement in the bone marrow, biopsy/aspirate performed within 90 days prior to obtaining informed consent must be documented at screening or a bone marrow biopsy/aspirate must be performed during the screening period. If a bone marrow biopsy/aspirate is performed during the screening period, consider submitting a bone marrow aspirate sample for biomarker analyses.

For subjects with marrow involvement at screening, a bone marrow biopsy and aspirate will be required to confirm a CR, [REDACTED].

##### **5.4.6 Disease Response Evaluation**

The determination of disease response to study treatment will be made using 2007 IWG criteria ([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).

#### **5.5 Pharmacokinetic Assessments**

Samples for pharmacokinetic and immunogenicity assessment will be collected for all subjects receiving nivolumab. [Table 5.5-1](#) lists the sampling schedule to be followed for

pharmacokinetics and immunogenicity. All timepoints are relative to the start of study drug administration. All on treatment PK timepoints are intended to align with days on which study drug is administered. If it is known that a dose is going to be delayed, then the predose sample should be collected just prior to the delayed dose. However, if a predose sample is collected, but the dose is subsequently delayed, an additional predose sample should not be collected. Further details of blood collection and processing will be provided in the procedure manual.

**Table 5.5-1: Sampling Schedule**

Study Day	Time (Relative to Dosing) Hour	Time (Relative to Dosing) Hour:Min	Nivolumab PK Sample	Nivolumab Immunogenicity Sample
Cycle 1 Day 1	predose <sup>a</sup>	00:00	X	X
Cycle 1 Day 1	EOI <sup>b</sup>	01:00	X	
Cycle 3 Day 1	predose <sup>a</sup>	00:00	X	X
Cycle 7 Day 1	predose <sup>a</sup>	00:00	X	X
Cycle 7 Day 1	EOI <sup>b</sup>	01:00	X	
Day 1 of every 8th cycle until discontinuation of study treatment	predose <sup>a</sup>	00:00	X	X
First 2 Follow-up visits- FU1 & FU2			X	X

<sup>a</sup> Predose samples should be taken just prior to the administration (preferably within 30 minutes, however predose collection up to 4 hours before study drug administration would be acceptable). If the infusion is delayed and a predose sample was already collected, there is no need to collect an additional predose sample.

<sup>b</sup> EOI = end of infusion. This sample should be taken immediately prior to stopping the infusion of nivolumab (preferably within 2 minutes prior to the end of infusion). If the end of infusion is delayed to beyond the nominal infusion duration, the collection of this sample should also be delayed accordingly. EOI samples may not be collected from the same IV access as drug was administered; refer to the lab manual for additional restrictions.

### 5.5.1 Pharmacokinetic Sample Analysis

Serum samples will be analyzed for nivolumab by a validated method. In addition, selected serum samples may be analyzed by an exploratory analytical method that measures nivolumab for technology exploration purposes; exploratory results will not be reported.

### 5.6 Biomarker Assessments



**Tumor Biopsy:**

Minimum of 1 FFPE tumor tissue block (preferred) OR minimum of 10 FFPE unstained sections are required for assessment of PD-L1 status and other biomarker evaluations.

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

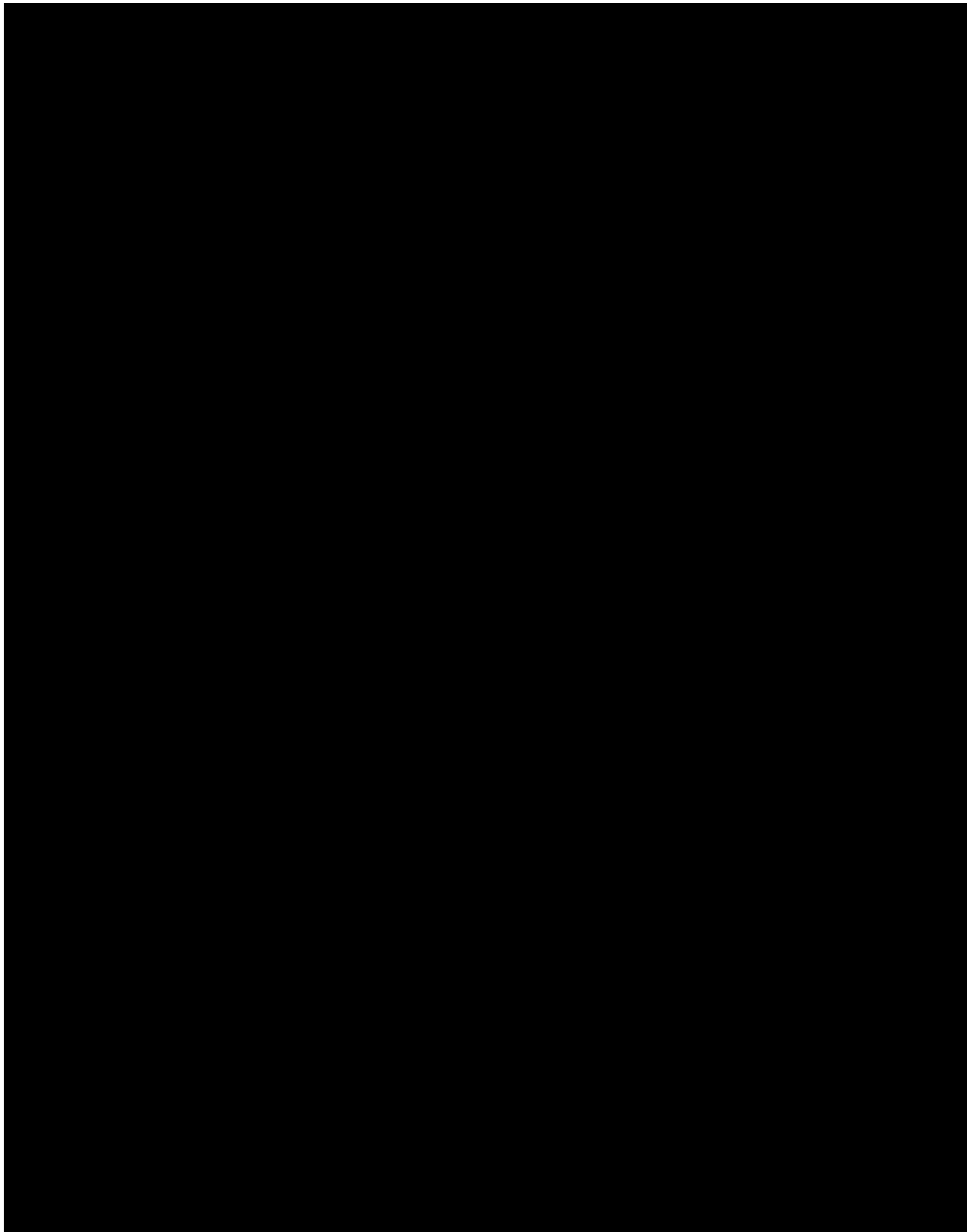
**Bone Marrow Aspirates**

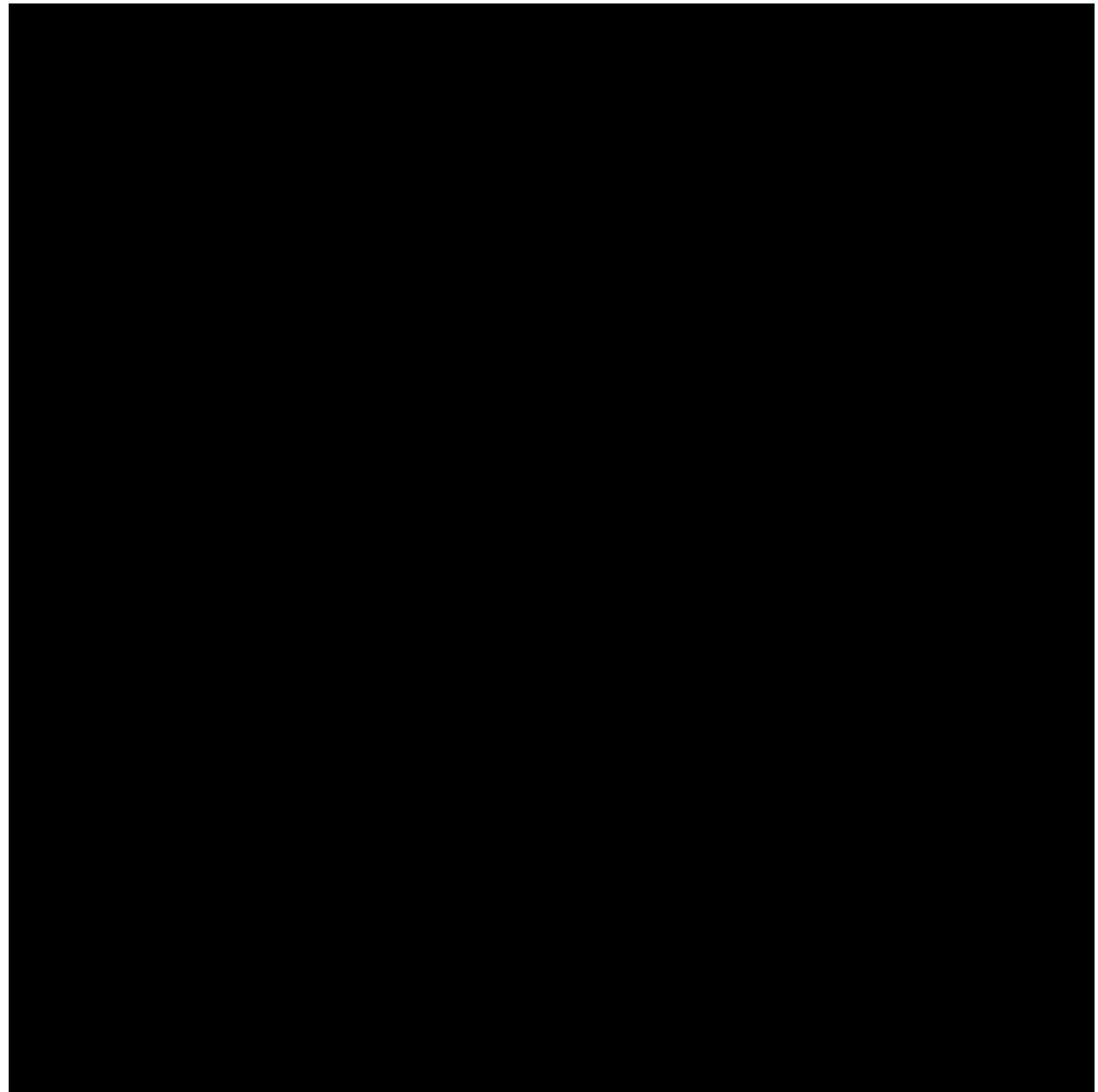
Submission of samples from bone marrow aspirates that may be performed at screening and during CR evaluation (only for subjects who had marrow involvement at study entry) is optional but strongly encouraged for biomarker assessment. These will be utilized to assess the phenotypic and functional status of immune cells and tumor cells.

All subjects may volunteer to undergo bone marrow biopsy and aspirate at any time during therapy if clinically indicated. When bone marrow biopsy is done, submission of bone marrow aspirate is strongly encouraged

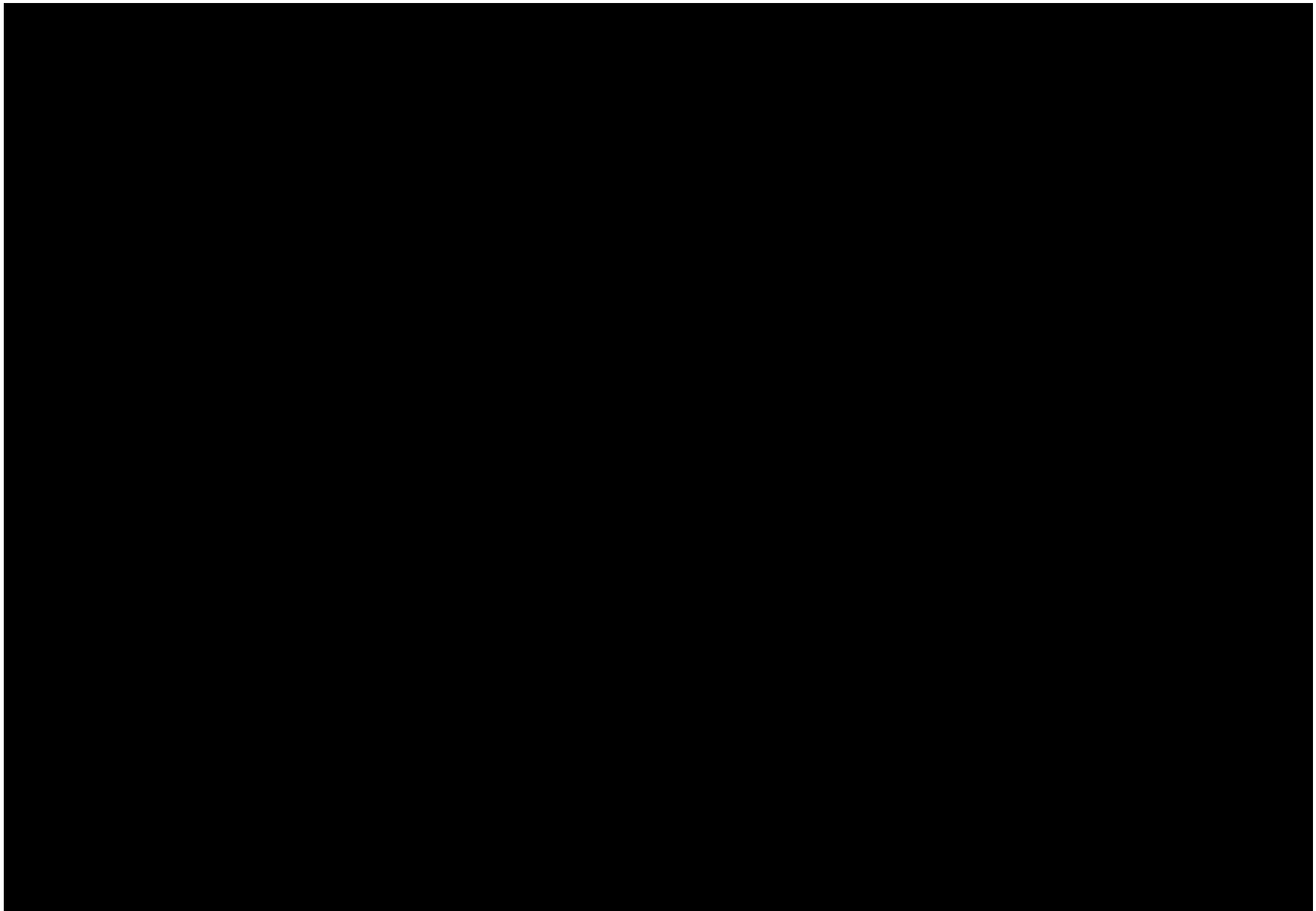
Bone marrow aspirates will be obtained using institutional standards for these procedures.











## 5.7 Outcomes Research Assessments

Outcomes research data including health related quality of life and patient reported symptom burden provide a more complete understanding of the impact of treatment by incorporating the patients' perspective. These data offer insights into the patient experience that may not be captured through physician reporting. Generic health related quality of life scales provide data necessary in calculating utility values for health economic models. The EQ-5D will be collected in order to assess the impact of nivolumab on generic health related quality of life and the data will be used for populating health economic models most notably, cost effectiveness analysis. The EORTC-QLQ C-30 will be collected in order to assess cancer specific health related quality of life. The combination of the generic scale for general health status and economic evaluation and the cancer specific scale will provide a robust outcomes research package.

The EORTC QLQ-C30 is one the most commonly used QoL instrument in oncology studies. The EORTC QLQ-C30 is a 30-item instrument comprising six functional scales (physical functioning, cognitive functioning, emotional functioning, role functioning, social functioning and global quality of life) as well as nine symptom scales (fatigue, pain, nausea/vomiting, dyspnea, insomnia, appetite loss, constipation, diarrhea, and financial difficulties). Except for the overall health status and global quality of life items, responses for all items are 4-point categorical scales ranging from 1 (Not at all) to 4 (Very much). The overall health status/quality of life responses are 7-point Likert scales.

General health status will be measured using the EQ-5D. The EQ-5D is a standardized instrument for use as a measure of self-reported general health status. The EQ-5D comprises 5 dimensions (mobility, self-care, usual activities, pain/discomfort, and anxiety) and a visual analog rating scale (VAS). The utility data generated from the EQ-5D is recommended for and commonly used in cost effectiveness analysis.

All QoL assessments will be administered as outlined in [Table 5.1-2](#) and [Table 5.1-3](#).

## 5.8 Other Assessments

### 5.8.1 Immunogenicity Assessments

Serum samples collected at timepoints identified in [Table 5.5-1](#) will be analyzed by a validated immunogenicity assay. All on-treatment timepoints are intended to align with days on which study drug is administered, if dosing occurs on a different day, the immunogenicity sampling should be adjusted accordingly. [REDACTED]

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

## 5.9 Results of Central Assessments

The primary endpoint is ORR, as determined by the IRRC.

Site will be informed of quality issues or needs for repeat scanning via queries from the corelab. Results of central Imaging analysis will not be returned to the site.

## 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 causal relationship can be one of the following:

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

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

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

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 *Serious Adverse Event (SAE)* is any untoward medical occurrence that at any dose:

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

Examples of such events include, but are not limited to, intensive treatment in an emergency room or at home for allergic bronchospasm; blood dyscrasias or convulsions that do not result in hospitalization.) Potential drug induced liver injury (DILI) is also considered an important medical event. (See [Section 6.6](#) for the definition of potential DILI.)

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

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

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

**NOTE:**

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

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

### **6.1.1 Serious Adverse Event Collection and Reporting**

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

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

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

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

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

**SAE Email Address:** Refer to Contact Information list.

**SAE Facsimile Number:** Refer to Contact Information list.

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

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

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

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

All SAEs should be followed to resolution or stabilization.

## **6.2 Nonserious Adverse Events**

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

### **6.2.1 Nonserious Adverse Event Collection and Reporting**

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

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

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

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

### **6.3 Laboratory Test Result Abnormalities**

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

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

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

### **6.4 Pregnancy**

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

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

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

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

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

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

### **6.5 Overdose**

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

## 6.6 Potential Drug Induced Liver Injury (DILI)

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

Potential drug induced liver injury is defined as:

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

## 6.7 Other Safety Considerations

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

## 7 DATA MONITORING COMMITTEE AND OTHER EXTERNAL COMMITTEES

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 90 treated subjects.

The sample size was determined based on two considerations: the ability to produce a CI which would exclude an ORR of 20%, which is not considered clinically relevant and provide sufficient information for a reliable understanding of the safety profile.

Assuming the true ORR is 35%, the study has approximately 87% power to reject the null hypothesis that the true ORR is  $\leq 20\%$ , considering a 2-sided alpha of 5%. In addition, [Table 8.1-1](#) summarizes the 95% exact CI for the target ORRs ranging from 30% to 44% with sample size of 90. At observed ORR  $\geq 30\%$ , the lower bound of the 95% CI excludes 20%.

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

True ORR	95% Exact CI
30%	[20.8%-40.6%]
34%	[24.7%-45.2%]
40%	[29.8%-50.9%]
44%	[34.0%-55.3%]

## 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
- PK subjects: All subjects with available serum time-concentration data from subjects dosed with nivolumab
- Immunogenicity evaluable subjects: all treated subjects with baseline and at least one post baseline immunogenicity assessment.
- All PD-L1 evaluable subjects: All treated PD-L1 subjects with quantifiable baseline PD-L1 expression
- Biomarker subjects: All treated subjects with available biomarker data
- Outcomes Research subjects: all treated subjects who have an assessment at baseline (Visit 1 assessment prior to administration of drug) and at least 1 subsequent assessment (for EORTC QLQ-C30 and EQ-5D separately).

## 8.3 Endpoints

### 8.3.1 Primary Endpoint(s)

The primary objective will be measured by the primary endpoint of IRRC-assessed ORR. It is defined as the number of subjects with a best overall response (BOR) of CR or PR, according to the 2007 IWG criteria, divided by the number of treated subjects. The final analysis of the primary endpoint will occur at least 12 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 IWG criteria 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 DOR based on IRRC assessment. DOR is defined as the time from first remission (CR or PR) to the date of initial objectively documented progression as determined using the 2007 IWG criteria 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.

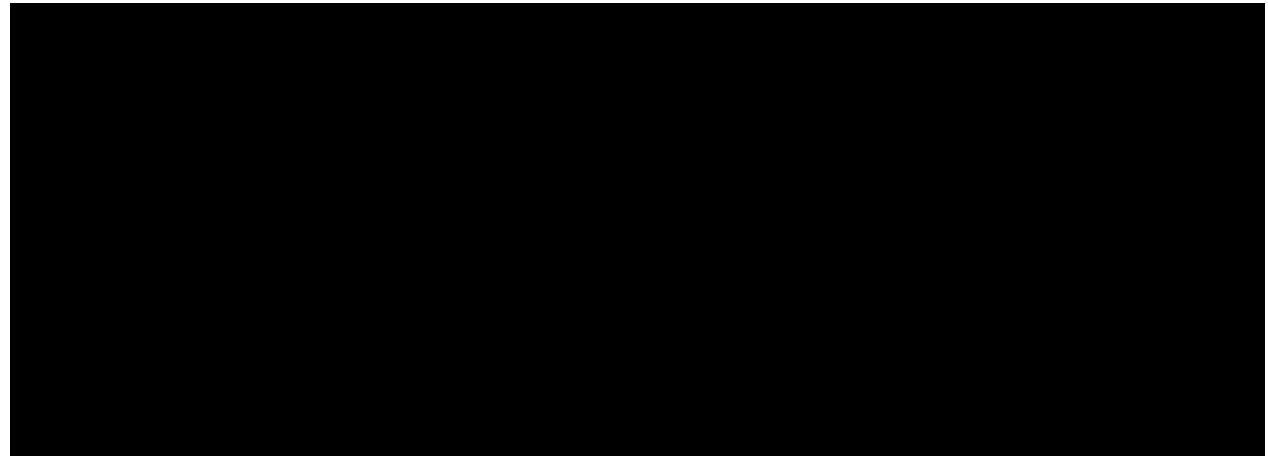
The second secondary objective will be measured by the CRR based on IRRC assessment. The CRR is defined as the number of subjects with a BOR of CR according to the 2007 IWG criteria, divided by the number of treated subjects. The BOR is defined similarly as above. The duration of CR will only be evaluated 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 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 IWG 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 IWG 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 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.

### **8.3.3 Exploratory Endpoint(s)**



## **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

### **8.4.2 Efficacy Analyses**

#### **8.4.2.1 Primary Endpoint Methods**

The IRRC-assessed ORR will be summarized by a binomial response rate and its corresponding two-sided 95% exact CI using the Clopper-Pearson method.<sup>97</sup> The null hypothesis will be rejected if the 2-sided 95% CI lower bound is greater than 20%. This translates in observing at least 27 responders out of 90 treated subjects.

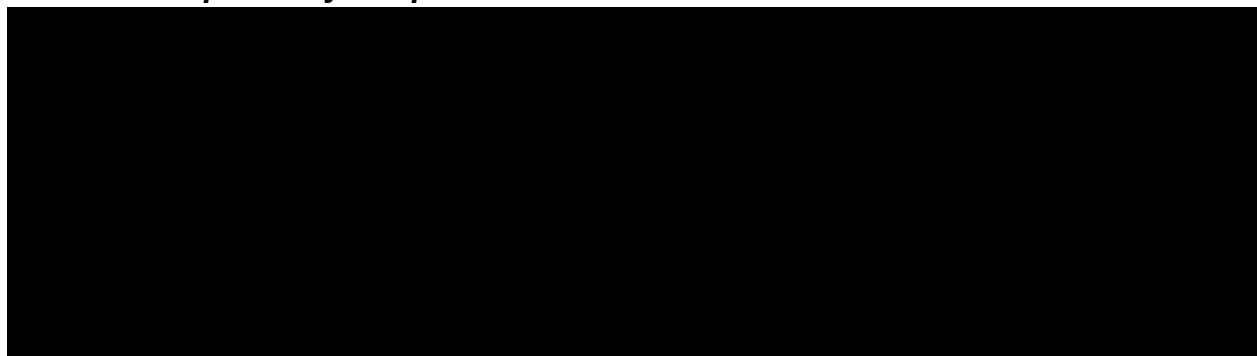
As sensitivity analysis, a summary of IRRC-assessed ORR based on response evaluable subjects instead of all treated subjects will also be presented.

#### **8.4.2.2 Secondary Endpoint Methods**

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

### **8.4.2.3 Exploratory Endpoint Methods**



### **8.4.3 Safety Analyses**

Safety analyses will be performed in all treated subjects. Descriptive statistics of safety will be presented using NCI 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.

### **8.4.4 Pharmacokinetic Analyses**

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

### **8.4.5 Biomarker Analyses**

Methodology for exploratory biomarker analyses is described in the statistical analysis plan.

### **8.4.6 Outcomes Research Analyses**

The analysis of EORTC QLQ-C30 will be performed in all treated subjects who have an assessment at baseline (Visit 1 assessment prior to administration of drug) and at least 1 subsequent assessment.

All scales and single items are scored on categorical scales and linearly transformed to 0-to-100 scales with higher scores for a functional scale representing higher levels of functioning, higher scores for the global health status/quality of life representing higher levels of global health status/quality of life and higher scores for a symptom scale representing higher level of symptoms. Data will be analyzed as change from baseline scores. Baseline and change from baseline in EORTC QLQ-C30 global health status/QoL composite scale data and the remaining EORTC QLQ-C30 scale data will be summarized using descriptive statistics (N, mean, standard deviation, median, first and third quartiles, minimum, maximum) at each of the assessment time points. In addition, the percentage of subjects demonstrating a clinically

meaningful deterioration (defined as a 10 point change from baseline) will be presented for each scale at each assessment timepoint. Percentages will be based on number subjects assessed at assessment time point.

As previously mentioned in [Section 5.1](#), the EQ-5D comprises 5 dimensions (mobility, self-care, usual activities, pain/discomfort, and anxiety) and a VAS. EQ-5D data will be described in the following three ways:

- Subject's overall health state on a visual analog scale (EQ-VAS) at each assessment time point will be summarized using descriptive statistics. (N, mean, standard deviation, median, first and third quartiles, minimum, maximum).
- Proportion of subjects reporting problems for the 5 EQ-5D dimensions at each assessment time point will be summarized by level of problem. Percentages will be based on number subjects assessed at assessment time point
- A by-subject listing of EQ-5D with the problem levels for each of the 5 dimensions (mobility, self-care, usual activities, pain/discomfort and anxiety/depression), health state (5 dimensions digits combined in a 5-digit number) and EQ-VAS will be provided.

#### **8.4.7 Other Analyses**

##### **8.4.7.1 Immunogenicity Analyses**

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

#### **8.5 Interim Analyses**

Not applicable.

### **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 subinvestigator and who is delegated this task on the Delegation of Authority Form. For electronic CRFs, review and approval/signature is completed electronically through the BMS electronic data capture tool. The investigator must retain a copy of the CRFs including records of the changes and corrections.

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

### **9.3 Clinical Study Report and Publications**

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

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

- 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

<b>Term</b>	<b>Definition</b>
ACTH	Adrenocorticotropic Hormone
AE	adverse event
ADA	Anti-Drug Antibody
ADL	Activities of daily living
Ag	Antigen
AIDS	Acquired ImmunoDeficiency Syndrome
ALP	alkaline phosphatase
ALT	alanine aminotransferase
ANC	absolute neutrophil count
ANOVA	analysis of variance
ASCT	Autologous Stem Cell Transplant
AST	aspartate aminotransferase
AT	aminotransaminases
AUC(INF)	area under the concentration-time curve from time zero extrapolated to infinite time
BCL	B-cell lymphoma
BMS	Bristol-Myers Squibb
BOR	best overall response
BP	blood pressure
BUN	blood urea nitrogen
C	Celsius
Ca <sup>++</sup>	calcium
CBC	complete blood count
CFR	Code of Federal Regulations
CI	confidence interval
Cl <sup>-</sup>	chloride
cm	centimeter
C <sub>max</sub> , C <sub>MAX</sub>	maximum observed concentration
CMV	cytomegalovirus

<b>Term</b>	<b>Definition</b>
CNS	Central nervous system
CR	Complete remission
CRF	Case Report Form, paper or electronic
CRR	complete remission rate
CRO	Contract Research Organisation
CT	computed tomography
CTA	Clinical Trial Agreement
CTCAE	Common Terminology Criteria for Adverse Events
DLBCL	Diffuse large B-cell lymphoma
dL	deciliter
DILI	Drug Induced Liver Injury
DNA	Deoxyribonucleic acid
DOR	Duration of Response
EBV	Epstein-Barr Virus
ECG	electrocardiogram
eCRF	Electronic Case Report Form
ECOG	Eastern Cooperative Oncology Group
EDC	Electronic Data Capture
eg	exempli gratia (for example)
ELISA	enzyme-linked immunosorbent assay
EOI	End of Infusion
EORTC	European Organisation for Research and Treatment of Cancer
FFPE	formalin-fixed, paraffin-embedded
FL	Follicular Lymphoma
FLIPI	Follicular Lymphoma International Prognostic Index
FSH	follicle stimulating hormone
FU	Follow-up
g	gram
GCB	germinal center B cells
GCP	Good Clinical Practice

<b>Term</b>	<b>Definition</b>
GVHD	Graft-Versus-Host Disease
h	hour
HBV	hepatitis B virus
HCV	hepatitis C virus
HCG	human chorionic gonadotropin
HD-ASCT	high-dose therapy and autologous stem cell transplantation
HIPAA	Health Insurance Portability and Accountability Act
HIV	Human Immunodeficiency Virus
HR	heart rate
HRT	hormone replacement therapy
IB	Investigator brochure
IFN- $\gamma$	interferon-gamma
ICF	Informed Consent Form
ICH	International Conference on Harmonisation
ie	id est (that is)
IEC	Independent Ethics Committee
Ig	Immunoglobulin
IHC	Immunohistochemistry
IL	Interleukine
IMP	investigational medicinal products
IND	Investigational New Drug
I-O	Immuno-oncology
IRB	Institutional Review Board
IRRC	independent radiology review committee
ITIM	Immunoreceptor Tyrosine Inhibitory Motif
IU	International Unit
IV	intravenous
IVRS	Interactive voice response system
K+	potassium
kg	kilogram

<b>Term</b>	<b>Definition</b>
KM	Kaplan-Meier
L	liter
LDH	lactate dehydrogenase
LFT	liver function test
mg	milligram
Mg <sup>++</sup>	magnesium
min	minute
mL	milliliter
MLR	Mixed Lymphocyte Reaction
MRI	Magnetic resonance imaging
MTD	maximum tolerated dose
µg	microgram
N	number of subjects or observations
Na <sup>+</sup>	sodium
NCI	National Cancer Institute
NHL	Non-Hodgkin Lymphoma
NIMP	non-investigational medicinal products
ORR	Overall response rate
P	Phosphorus
PBMC	peripheral blood mononuclear cell
PET	Positron emission tomography
PFS	progression free survival
PK	pharmacokinetics
QLQ	Quality of life questionnaire
QoL	Quality of life
qPCR	quantitative real-time polymerase chain reaction
RCC	Renal Cancer Carcinoma
R-CHOP	Chemotherapy regimen: cyclophosphamide, hydroxydaunorubicin, oncovir, prednisone
RECIST	Response Evaluation Criteria In Solid Tumors

<b>Term</b>	<b>Definition</b>
RIT	Radio Immunotherapy
RNA	Ribonucleic acid
RT-PCR	reverse transcription polymerase chain reaction
SAE	serious adverse event
SAP	Statistical Analysis Plan
SCT	Stem Cell Transplant
SNP	single nucleotide polymorphisms
SOP	Standard Operating Procedures
SPD	Sum of the Product of the Diameters
t	temperature
T. bili	Total bilirubin
T-HALF	Half life
TILs	tumor infiltrating lymphocytes
TSH	Thyroid stimulating hormone
TTP	Time To Progression
ULN	Upper limit of normal
VAS	visual analog rating scale
Vz	Volume of distribution of terminal phase (if IV and if multi-exponential decline)
WOCBP	women of childbearing potential

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## **APPENDIX 1            MANAGEMENT ALGORITHMS FOR IMMUNO-ONCOLOGY AGENTS**

These general guidelines constitute guidance to the Investigator and may be supplemented by discussions with the Medical Monitor representing the Sponsor. The guidance applies to all immuno-oncology agents and regimens.

A general principle is that differential diagnoses should be diligently evaluated according to standard medical practice. Non-inflammatory etiologies should be considered and appropriately treated.

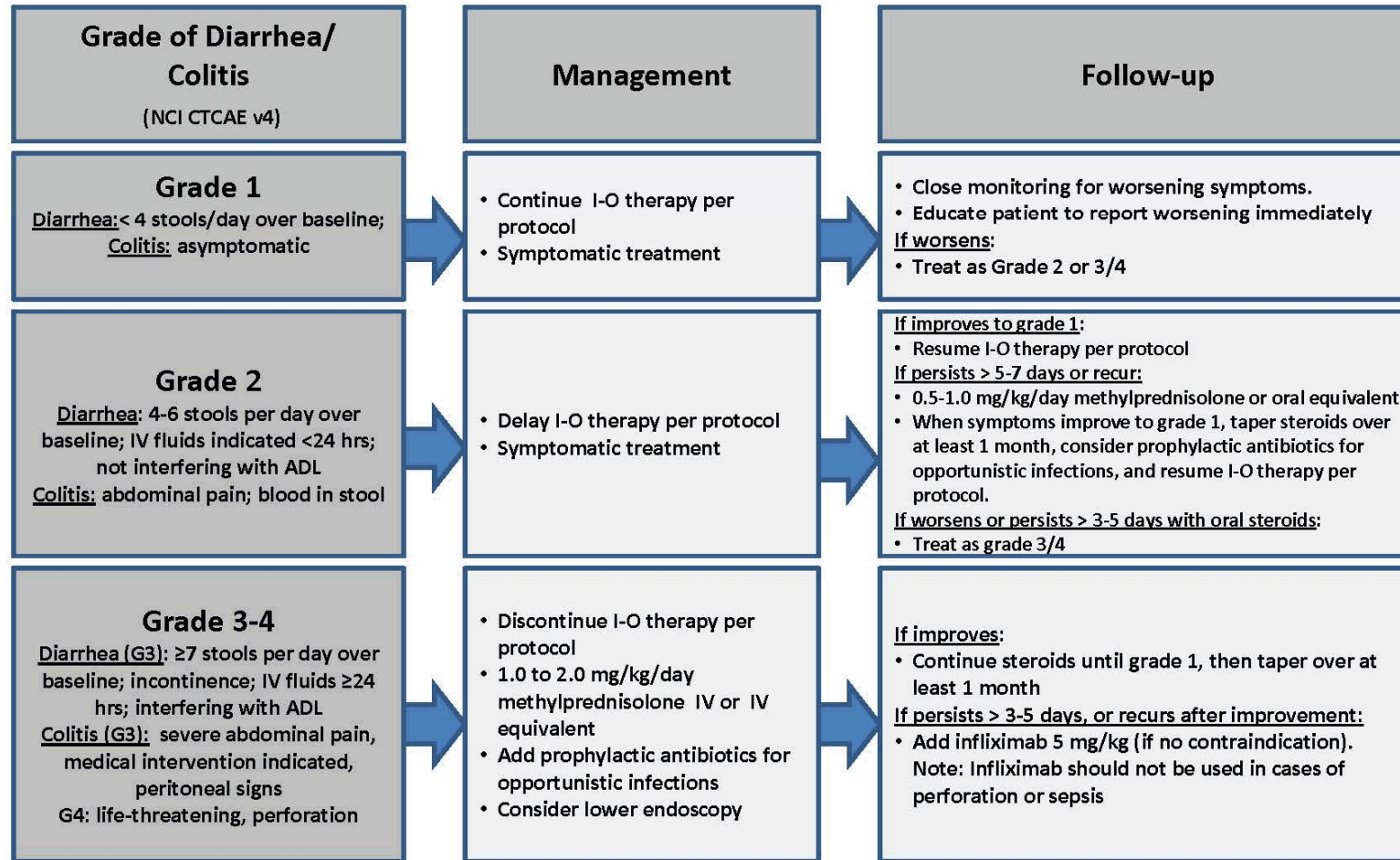
Corticosteroids are a primary therapy for immuno-oncology drug-related adverse events. The oral equivalent of the recommended IV doses may be considered for ambulatory patients with low-grade toxicity. The lower bioavailability of oral corticosteroids should be taken into account when switching to the equivalent dose of oral corticosteroids.

Consultation with a medical or surgical specialist, especially prior to an invasive diagnostic or therapeutic procedure, is recommended.

The frequency and severity of the related adverse events covered by these algorithms will depend on the immuno-oncology agent or regimen being used.

## GI Adverse Event Management Algorithm

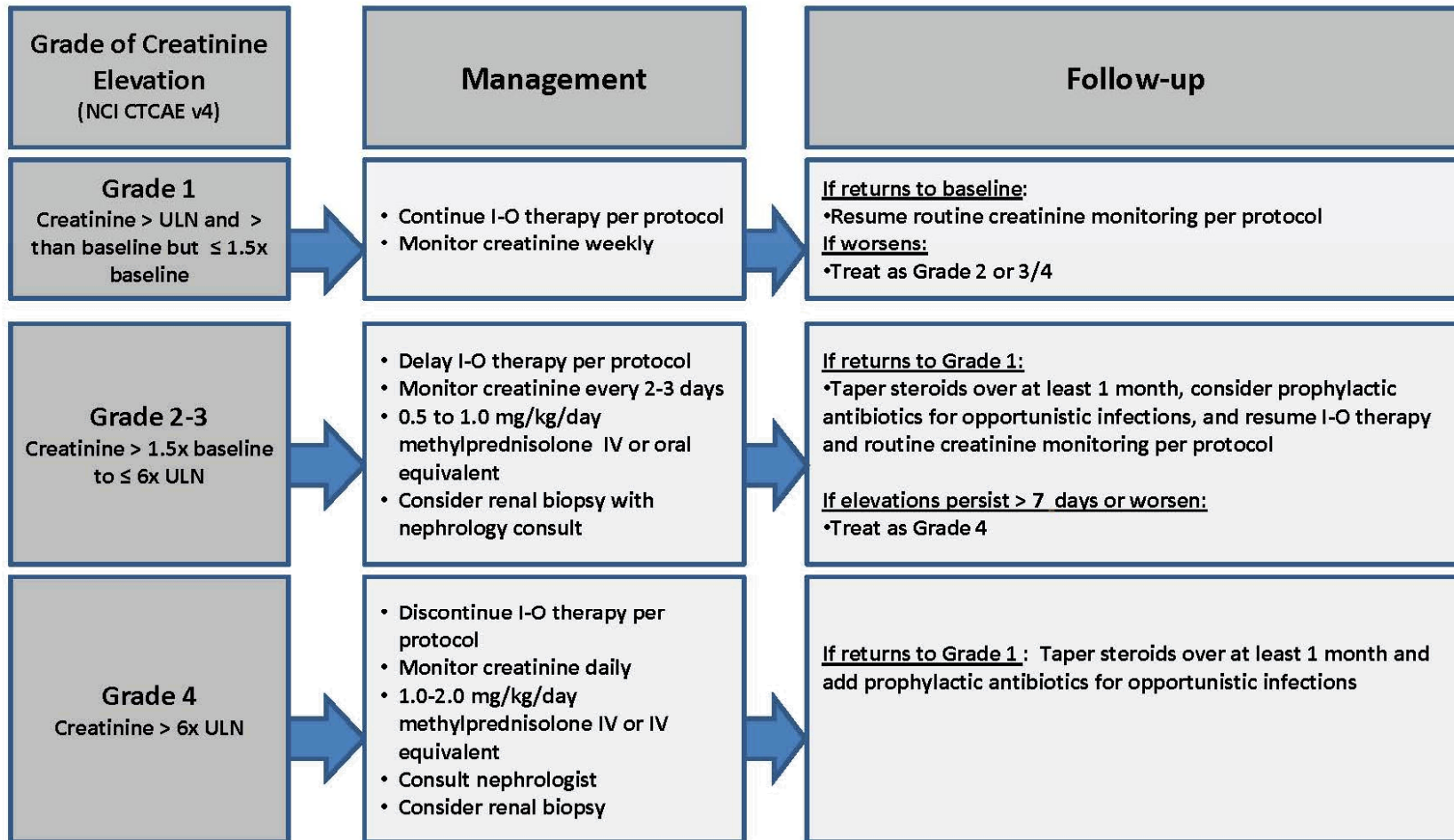
Rule out non-inflammatory causes. If non-inflammatory cause is identified, treat accordingly and continue I-O therapy. Opiates/narcotics may mask symptoms of perforation. Infliximab should not be used in cases of perforation or sepsis.



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

## Renal Adverse Event Management Algorithm

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

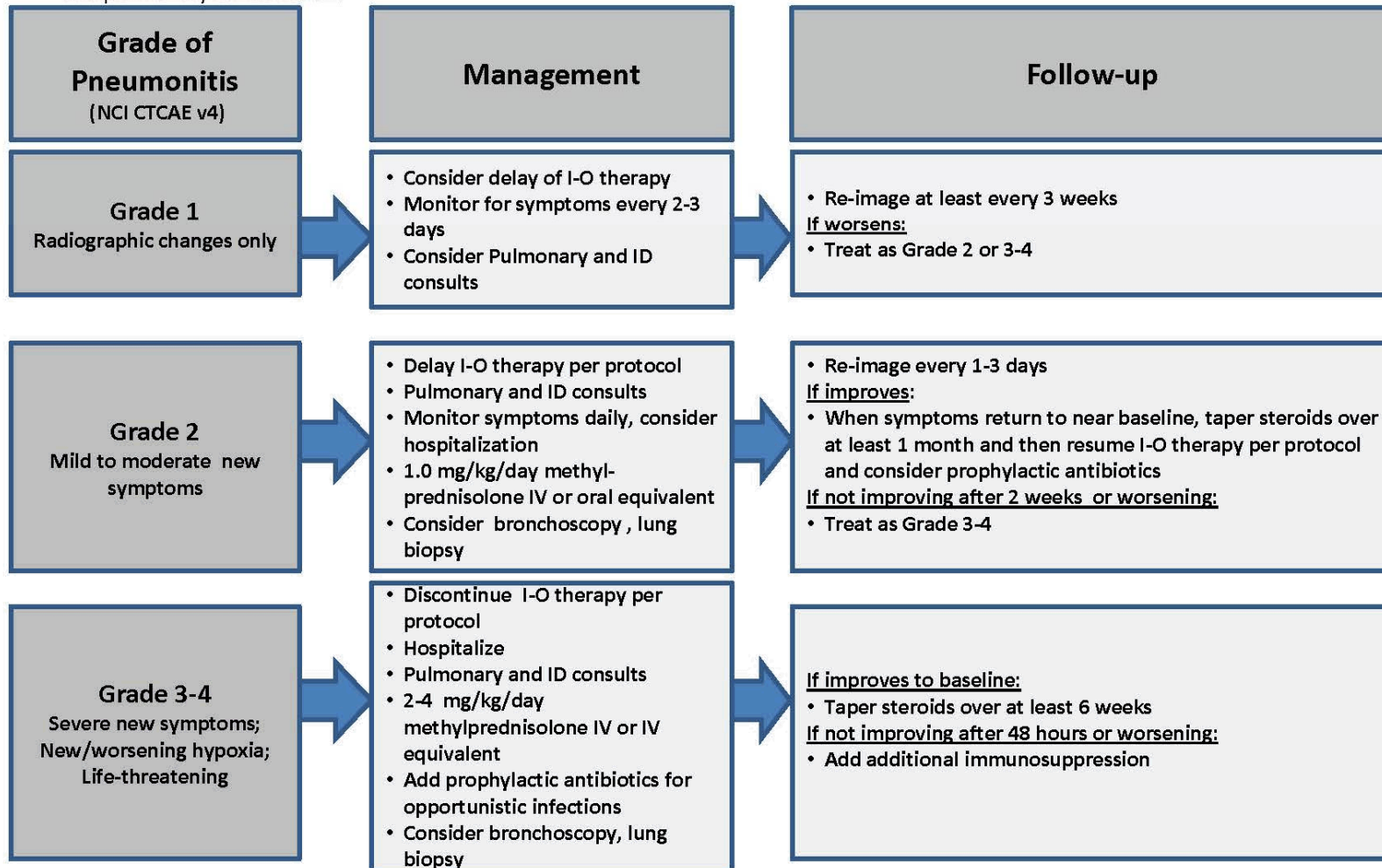


Patients on IV steroids may be switched to an equivalent dose of oral corticosteroids (e.g. prednisone) at start of tapering or earlier, once sustained clinical improvement is observed. Lower bioavailability of oral corticosteroids should be taken into account when switching to the equivalent dose of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



## Pulmonary Adverse Event Management Algorithm

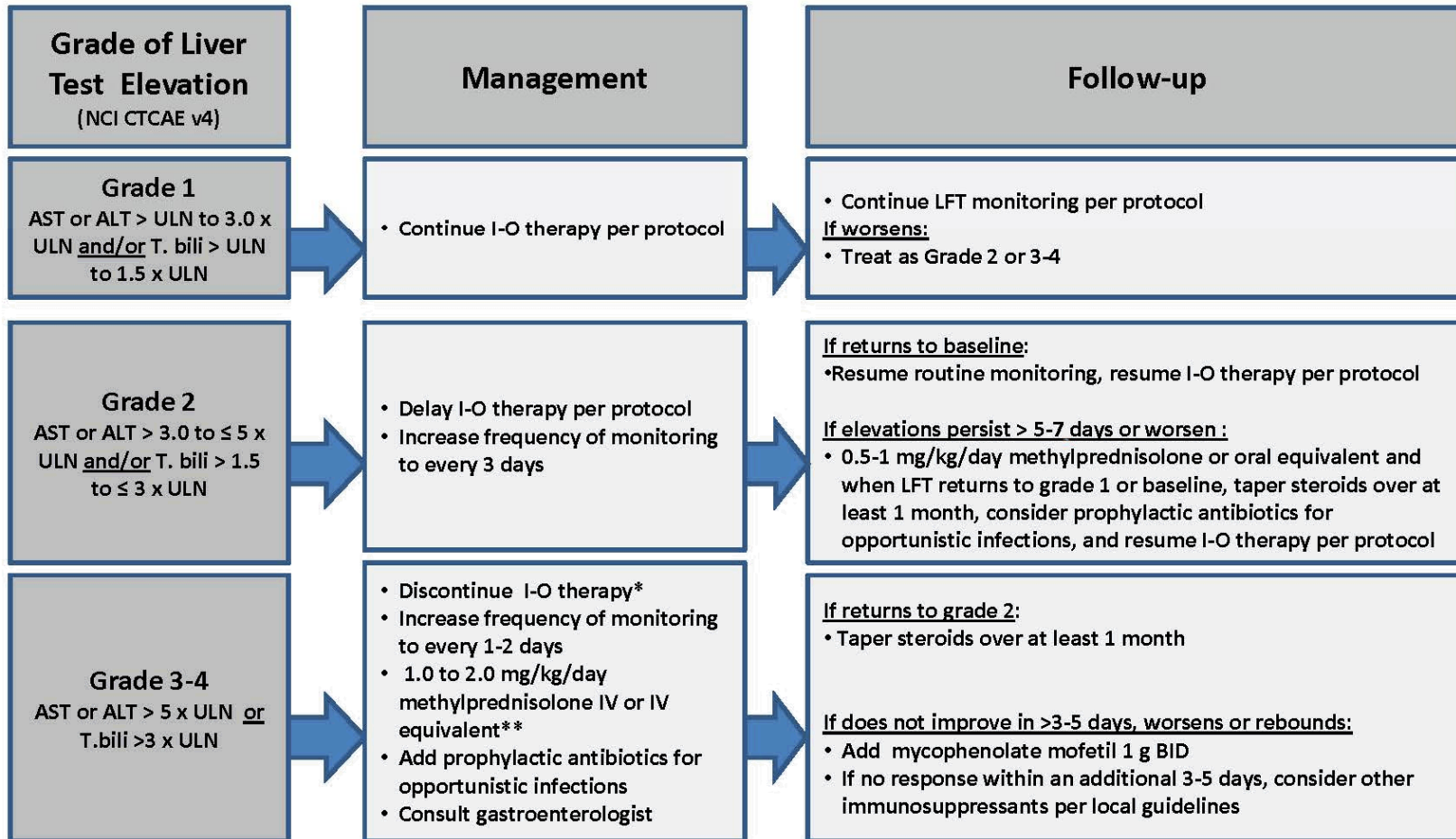
Rule out non-inflammatory causes. If non-inflammatory cause, treat accordingly and continue I-O therapy. Evaluate with imaging and pulmonary consultation.



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

## Hepatic Adverse Event Management Algorithm

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



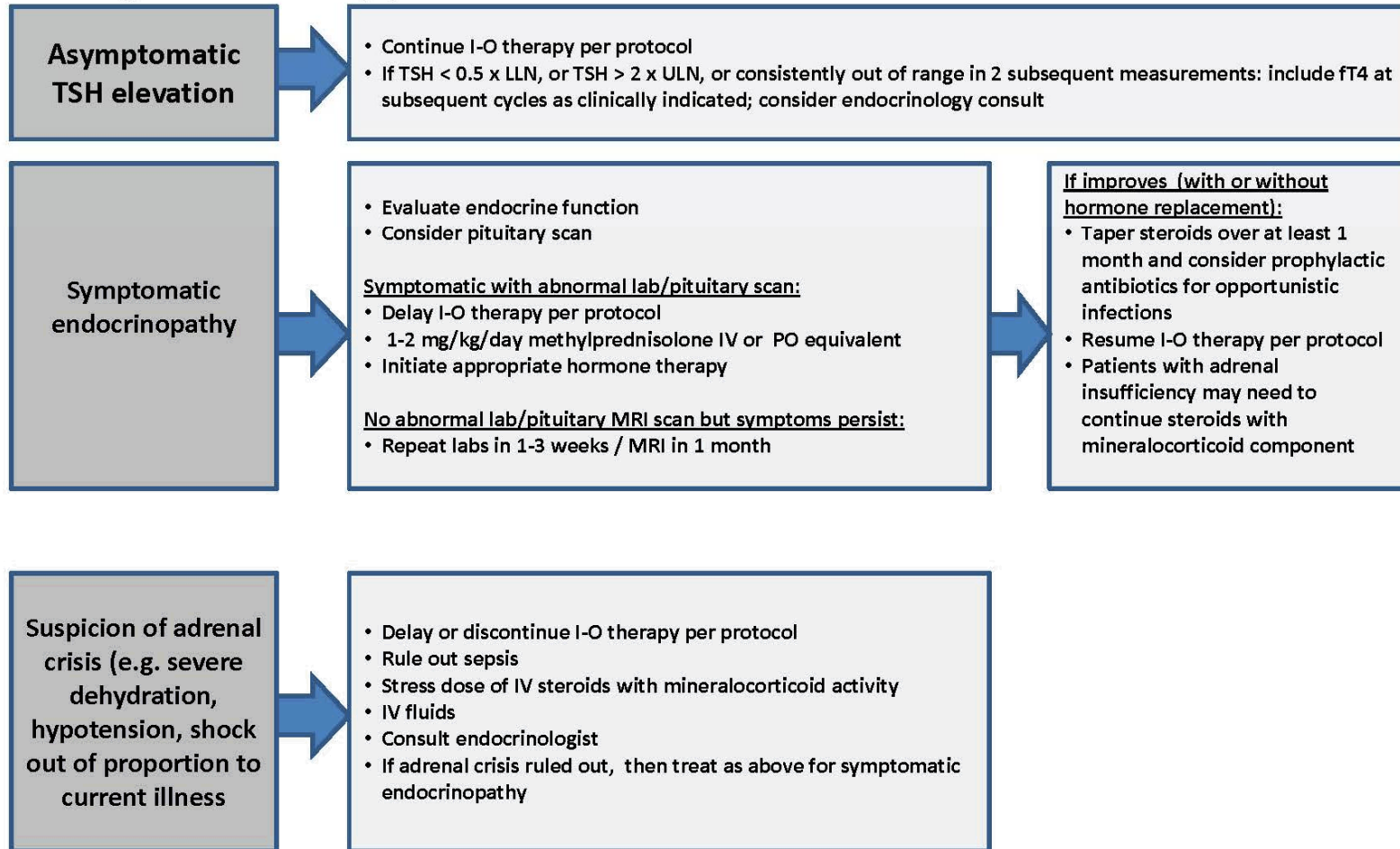
Patients on IV steroids may be switched to an equivalent dose of oral corticosteroids (e.g. prednisone) at start of tapering or earlier, once sustained clinical improvement is observed. Lower bioavailability of oral corticosteroids should be taken into account when switching to the equivalent dose of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

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

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

## Endocrinopathy Management Algorithm

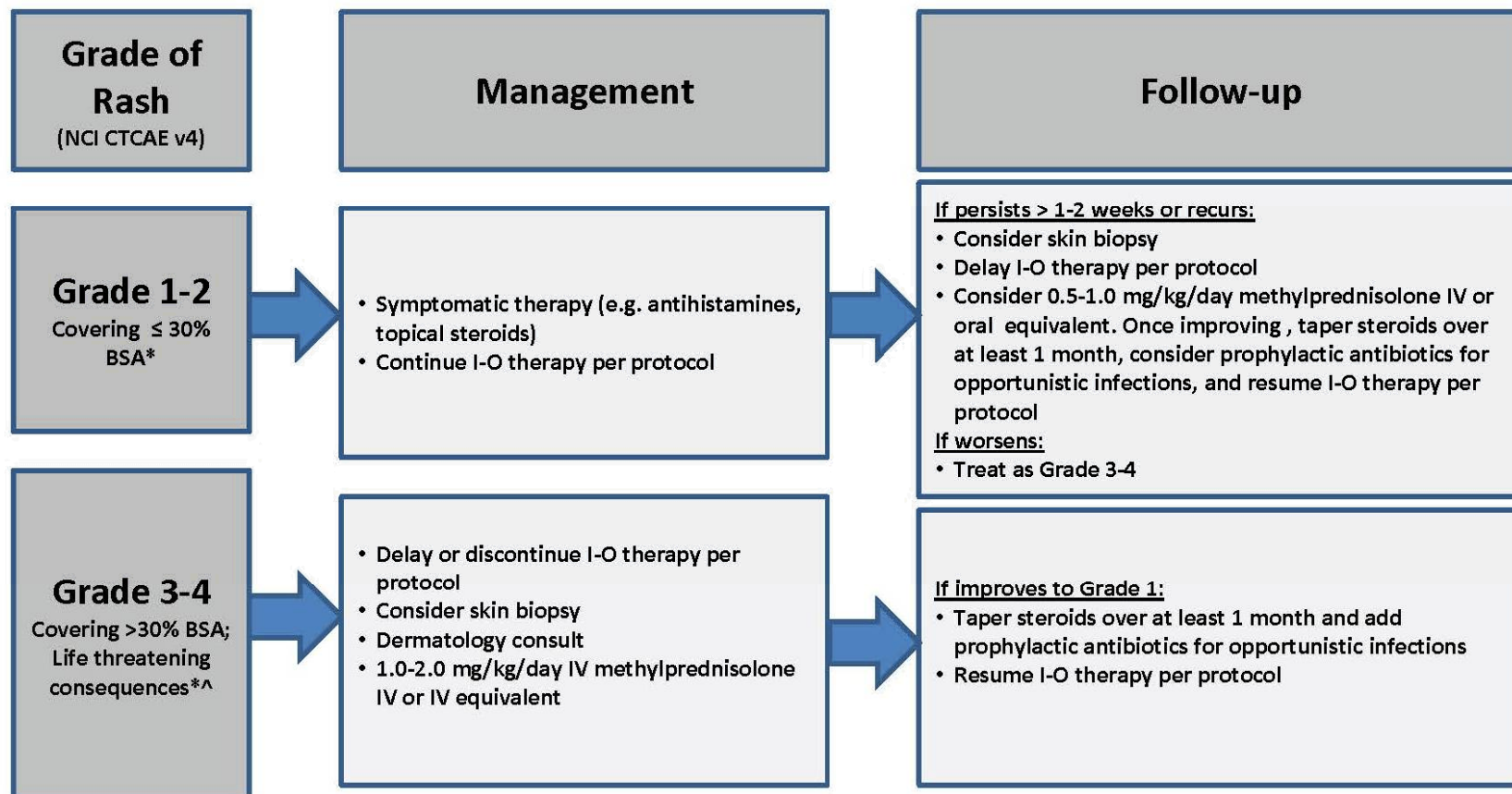
Rule out non-inflammatory causes. If non-inflammatory cause, treat accordingly and continue I-O therapy. Consider visual field testing, endocrinology consultation, and imaging.



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

## Skin Adverse Event Management Algorithm

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



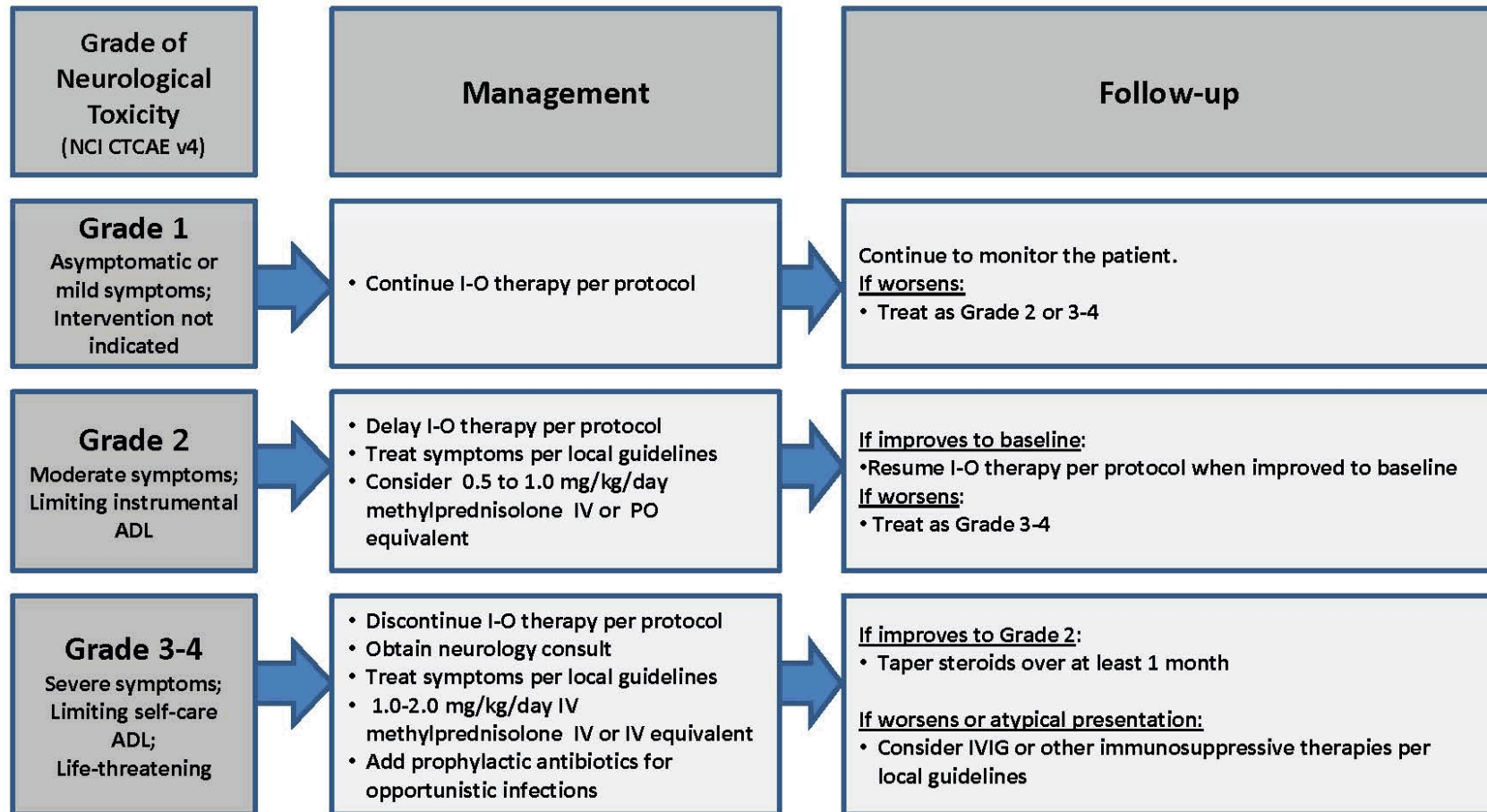
Patients on IV steroids may be switched to an equivalent dose of oral corticosteroids (e.g. prednisone) at start of tapering or earlier, once sustained clinical improvement is observed. Lower bioavailability of oral corticosteroids should be taken into account when switching to the equivalent dose of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

\*Refer to NCI CTCAE v4 for term-specific grading criteria.

^If SJS/TEN is suspected, withhold I-O therapy and refer patient for specialized care for assessment and treatment. If SJS or TEN is diagnosed, permanently discontinue I-O therapy.

# Neurological Adverse Event Management Algorithm

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



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

**APPENDIX 2 2007 INTERNATIONAL WORKING GROUP RESPONSE  
CRITERIA FOR MALIGNANT LYMPHOMA**

<b>2007 IWG Response Criteria for Malignant Lymphoma</b>				
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.
2. a. Typically [<sup>18</sup>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.
3. 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 ( $\leq 1.5$  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  $\leq 1.0$  cm in their short axis after treatment.
4. 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.
5. 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  $\geq 50\%$  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:

1. 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]).
2. 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.
3. 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  $\leq 1.0 \times \leq 1.0$  cm will not be considered abnormal for relapse or progressive disease.

1. 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.



2. 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  $\geq 50\%$  and to a size of 1.5 x 1.5 cm or > 1.5 cm in the long axis.
3. At least a 50% increase in the longest diameter of any single previously identified node > 1 cm in its short axis.
4. 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.

Reference: Cheson BD, Pfisner B, Juweid ME, et al. Revised Response Criteria for Malignant Lymphoma. *Journal of Clinical Oncology* 2007;25:579-586.

### **APPENDIX 3      FLIPI SCALE**

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

- Age ( $> 60$  years vs  $\leq 60$  years)
- Serum LDH level (above normal vs normal or below)
- Number of involved nodal areas ( $> 4$  vs  $\leq 4$ )
- Ann Arbor stage (III-IV vs I-II)
- Hemoglobin level ( $< 120$  g/L vs  $\geq 120$  g/L)

#### Reference:

Solal-Celigny P, Roy P, Colombat P, et al. Follicular lymphoma international prognostic index. *Blood* 2004 Sep 1;104(5):1258-65. Epub 2004 May 4. PubMed PMID: 15126323.

**APPENDIX 4 ECOG PERFORMANCE STATUS**

<b>ECOG PERFORMANCE STATUS<sup>a</sup></b>	
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

<sup>a</sup> Oken MM, Creech RH, Tormey DC, Horton J, Davis TE, McFadden ET, and Carbone PP. Toxicity and Response Criteria of the Eastern Cooperative Oncology Group. Am J Clin Oncol 1982; 5: 649-655..

## APPENDIX 5 ACUTE GVHD GRADING AND STAGING

**Table 1: Extent of Organ Involvement**

Stage	Skin	Liver	Gut
1	Rash on < 25% of skin <sup>a</sup>	Bilirubin 2 - 3 mg/dL <sup>b</sup>	Diarrhea > 500 mL/day <sup>c</sup> or persistent nausea <sup>d</sup>
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
<b>Grade<sup>e</sup></b>			
<b>I</b>	Stage 1 - 2	None	None
<b>II</b>	Stage 3 or	Stage 1 or	Stage 1
<b>III</b>	--	Stage 2 - 3 or	Stages 2 - 4
<b>IV<sup>f</sup></b>	Stage 4	Stage 4	--

<sup>a</sup> Use “Rules of Nines” (Table 2) or burn chart to determine extent of rash.

<sup>b</sup> Range given as total bilirubin. Downgrade one stage if an additional cause of elevated bilirubin has been documented.

<sup>c</sup> 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.

<sup>d</sup> Persistent nausea with histologic evidence of GVHD in the stomach or duodenum.

<sup>e</sup> Criteria for grading given as minimum degree of organ involvement required to confer that grade.

<sup>f</sup> 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%

Ref.: Przepiorcka et al. Bone Marrow Transplant 1995;15(6):825.

### 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.

Ref. Sullivan KM, Blood 1981;57:267.

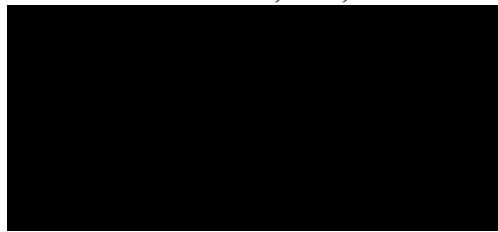
Page: 1  
Protocol Number: CA209140  
IND Number: 119,380  
Ex-US Non-IND  
EUDRACT Number 2013-003645-42  
Date: 06-Dec-2013

**Protocol CA209140:** A Single-Arm, Open-Label Phase 2 Study of Nivolumab (BMS-936558) in Subjects with Relapsed or Refractory Follicular Lymphoma (FL)

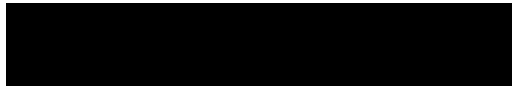
(CheckMate 140: CHECKpoint pathway and nivoluMab clinical Trial Evaluation 140)

**Amendment Number 02**  
**Site Number: All**

**Medical Monitor**  
Kazunobu Kato, MD, PhD



**24-hr Emergency Telephone Number:**



**Bristol-Myers Squibb Research and Development**  
Oncology Clinical Research and Development  
Avenue de Finlande 4  
B-1420 Braine-l'Alleud, Belgium  
Route 206 & Province Line Road  
Lawrenceville, NJ 08543  
5 Research Parkway  
Wallingford, CT 06492

**This protocol amendment contains information that is confidential and proprietary to Bristol-Myers Squibb (BMS).**

*This amendment must be maintained with the referenced protocol.*

### **Amendment Rationale:**

The main objective of this amendment is to implement a mandatory recommendation received from the U.S. Food and Drug Administration (FDA) as follows:

- The exclusion criterion has been added to exclude the subjects who received chest radiation  $\leq 24$  weeks prior to first dose of the study drug.

Justification for this exclusion criterion is that pneumonitis has been noted in the current Investigator Brochure as a treatment-related serious adverse event (SAE). The FDA notes that “Radiation pneumonitis can occur in patients who have received chest radiation up to 24 weeks after radiation therapy.” Chest radiation is not commonly used in the subjects eligible for this protocol, and this amendment will comply with the FDA recommendation without altering the basic study population or trial design.

Additional updates were also made to the protocol including items such as clarifying the schedule of tumor assessment, correcting typographical and formatting errors, [REDACTED].

### **Changes to the Protocol:**

#### 1. Section 3.1, Study Design and Duration, Treatment

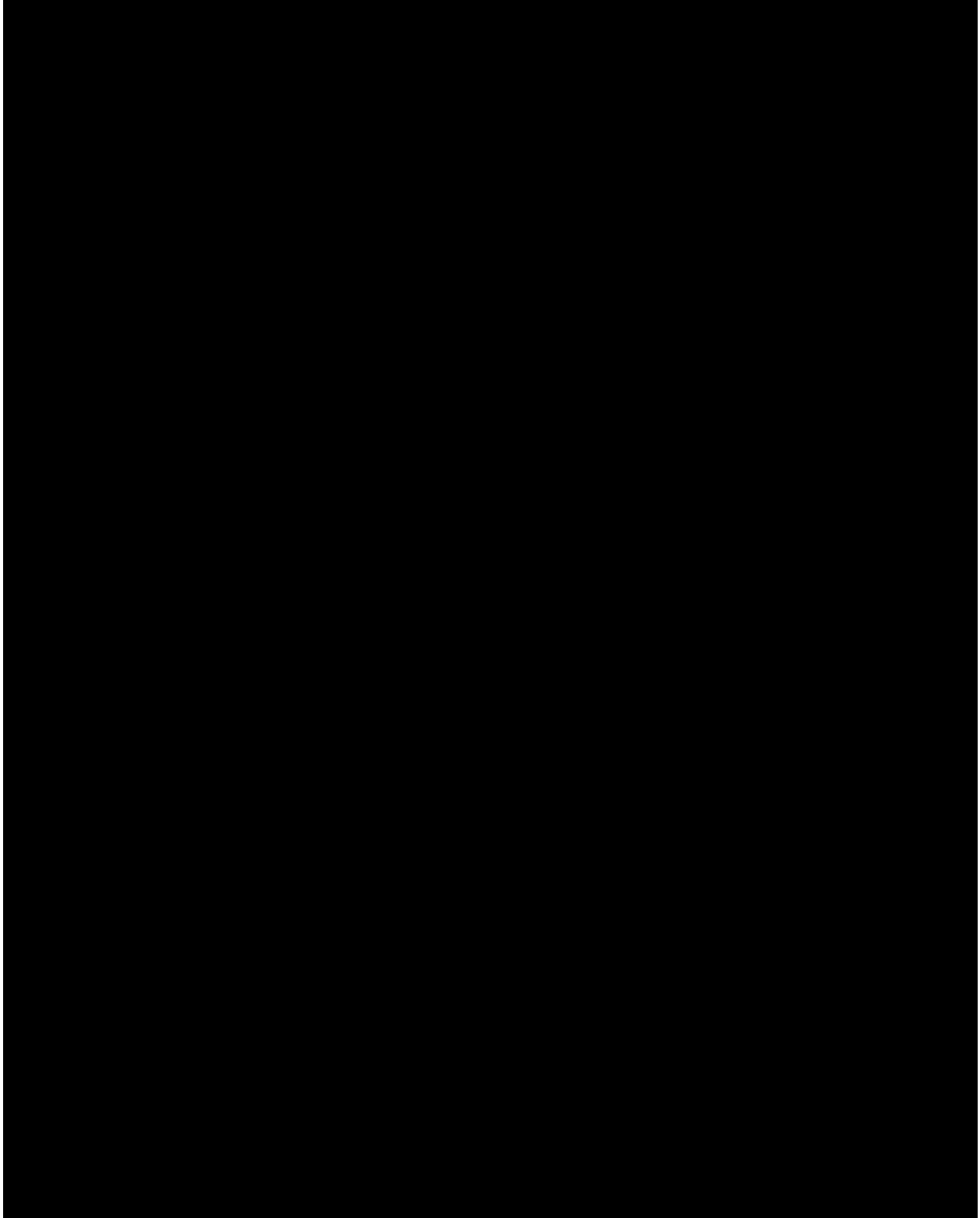
- a) Bullet point 8: Corrected “Subjects will be evaluated for response according to revised International Working Group Criteria beginning at Week 9 (Day 1 of Cycle 5) and continuing every 8 weeks ( $\pm 7$  days) for the first eight months of treatment, then every 12 weeks up to 2 years of treatment, continuing every 6 months beyond 2 years of treatment, until disease progression. If the subject discontinues treatment prior to disease progression, tumor assessment will continue in the follow-up phase

#### 2. Section 3.3.2 Exclusion Criteria:

- a) Added Criterion 5 e): Chest radiation  $\leq 24$  weeks prior to first dose of the study drug.
- [REDACTED]

4. Section 5.3.1, Imaging Assessment for the Study: Corrected typo in “Image acquisition guidelines and submission process will be outlined in the CA209140 Imaging Manual to be provided by the corelab.

**Please maintain a copy of this amendment with your protocol. Please provide a copy to your Investigational Review Board / Ethics Committee, unless agreed otherwise with BMS.**





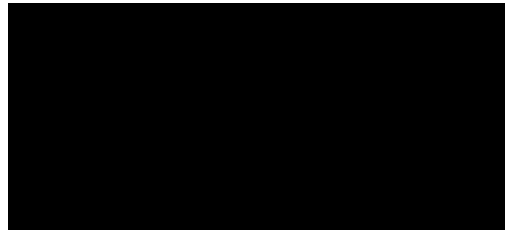
Page: 1  
Protocol Number: CA209140  
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Date: 23-Jul-2014

**Protocol CA209140:** A Single-Arm, Open-Label Phase 2 Study of Nivolumab (BMS-936558) in Subjects with Relapsed or Refractory Follicular Lymphoma (FL).

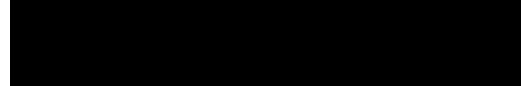
(CheckMate 140: CHECKpoint pathway and nivoluMab clinical Trial Evaluation 140)

**Amendment Number 03**  
**Site Number: All**

**Medical Monitor**  
Kazunobu Kato, MD, PhD



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**This protocol amendment contains information that is confidential and proprietary to Bristol-Myers Squibb (BMS).**

*This amendment must be maintained with the referenced protocol.*

### Amendment Rationale:

- One of the main purposes of this global amendment is to modify a few eligibility criteria to facilitate subject enrollment:

- Rationale to authorize subject population with prior autologous SCT outside a window of 12 weeks prior to first dose of study therapy.

Recent evidence indicates that Autologous Stem Cell Transplant (ASCT) may provide clinical benefits for patients with relapsed follicular lymphoma (FL).<sup>1,2</sup> A European randomized study has confirmed the superiority of the ASCT arm over the standard therapy arm in relapsed FL.<sup>3</sup> Additional retrospective studies provide further evidence supporting the clinical benefits of using ASCT for relapsed FL patients.<sup>1,4</sup> The optimal timing for ASCT remains uncertain, however, as the clinical benefits from ASCT have been limited to a large extent to patients with relapsed FL. A similar benefit, however, has not been observed in the front-line setting.<sup>2</sup> Therefore, the current use of ASCT in relapsed FL can vary depending on each country or on each transplant center.<sup>5</sup> Nevertheless, the current ESMO Clinical Practice Guidelines recognizes that high-dose chemotherapy with ASCT prolongs PFS and OS and should be specifically considered in patients with short-lived first remissions after failure of rituximab-containing regimens.<sup>6</sup> The present NCCN guideline for NHL also lists high-dose therapy with ASCT as one of the second-line consolidation or extended dosing options. Thus, based on these data, it is appropriate to enroll patients who have had previous ASCT for BMS-sponsored CA209140 study.

- Rationale to modify exclusion criterion 4b

A randomized study testing R-CHOP (n = 202) vs CHOP (n = 197) shows that Grade 3 or 4 adverse events related to the infusion of rituximab were observed in 19 patients in the CHOP-plus-rituximab group (9%); the most frequent of these were respiratory symptoms (with or without bronchospasm), chills, fever, and hypotension. In all cases, the symptoms disappeared after the infusion was slowed or stopped, and no patient died as a result of such an adverse event. All patients were able to receive further cycles of CHOP plus rituximab without recurrence of Grade 3 or 4 infusion-related reactions.

Exclusion criteria of history of severe hypersensitivity reaction to any monoclonal antibody is reworded to allow for 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 to be eligible.

- Another objective of this amendment is to remove the interim analysis and extend the duration of follow-up required for all subjects prior to performing the final analysis of the primary endpoint:

- Rationale to remove the Interim Analyses

In the original protocol, an interim analysis of independent radiologic review (IRRC)-assessed ORR is planned to be performed after the first 37 subjects have been treated and those subjects who remain on treatment have completed a minimum of 8 weeks follow-up. Updated results from the FL cohort (n = 10) in the ongoing Phase 1 study (CA209039) indicate that the time to response may be longer than the protocol assumptions for both the interim and final analyses with late responses observed 10 months after the administration of the first dose of nivolumab. In particular, two out of four responders with FL achieved the first OR at Week 39. Consequently, the estimated cumulative response rate at 8, 16, 24 and 48 weeks are 10, 20, 20, 40%, respectively. Thus, the planned interim analysis at 8 weeks after the first dose date of the subjects who remain on treatment in the original protocol is not expected to adequately evaluate the clinical efficacy of nivolumab. Furthermore, since the observed response rate for nivolumab from the updated Phase 1 data shows a higher response rate (40%) than the preliminary data (25%) supporting the original protocol assumptions, an interim analysis for futility should be removed from the study.

- Rationale for extending the timing of the final analysis of the primary endpoint from 6 months to 1 year after the last enrolled subject's first dose of study therapy

Late responses, occurring up to 39 weeks from the initial dose, were observed in the FL cohort of the Phase 1 study (CA209039) in recently updated results. In the original protocol, the primary endpoint analysis is planned to be performed after six months follow-up for the last patient enrolled in this study. Thus, subjects enrolled late in the study and experiencing late response will have insufficient follow-up time after the first response to adequately characterize the duration of response. Taking the late responses observed in the CA209039 study into consideration, extending the evaluation of DOR with longer follow-up, until 1 year after the last enrolled subject's first dose of study therapy, is likely to provide more scientifically meaningful clinical outcome.

- This global amendment will also clarify that subject may start study drug before Bone Marrow biopsy results become available:

The purpose of a bone marrow biopsy/aspirate is to determine the extent of disease (lymphoma) involvement in the bone marrow before starting study drug treatment.

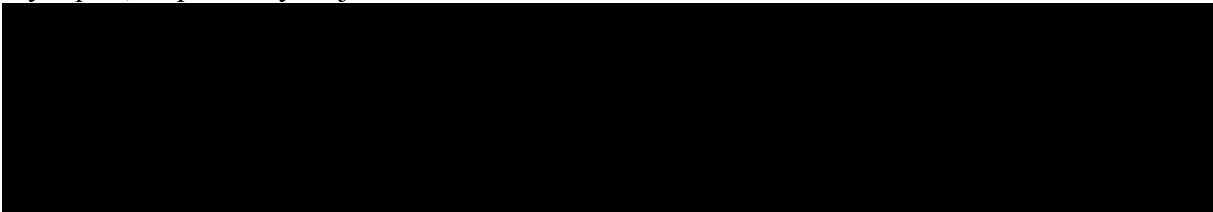
Results of a bone marrow biopsy (pathological reports) may not be able to be confirmed before the first dose of study drug. Because bone marrow biopsy results will not change eligibility, it is acceptable that sites cannot confirm the results of a bone marrow biopsy as long as sites can verify the documentation that a bone marrow biopsy was performed. The results of a bone marrow biopsy can be confirmed later.

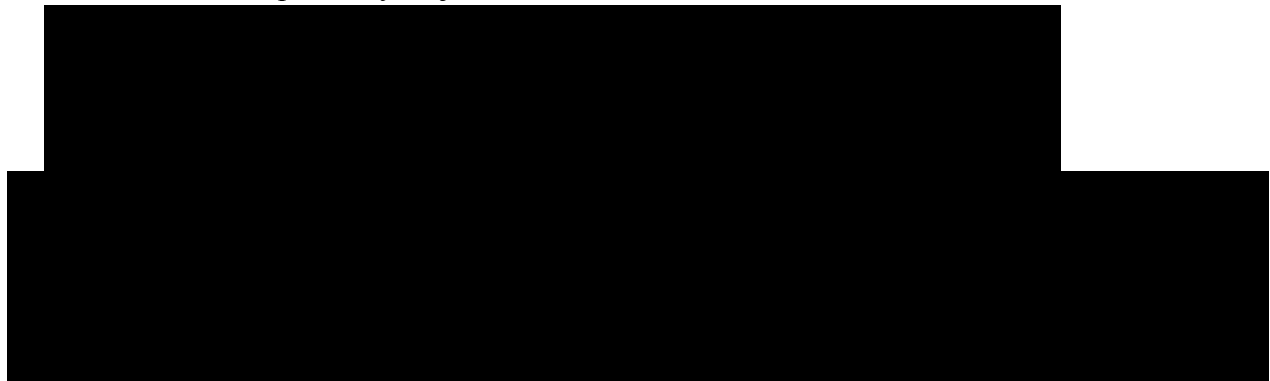
- The last main objective of this amendment is to authorize subject to continue study treatment beyond progression:  
Immunotherapeutic agents produce atypical clinical response patterns, which are not usually observed in conventional chemotherapy. Two distinct non-conventional patterns have been reported: 1) a reduction in total tumor burden despite of the appearance of new lesion(s), and 2) responses after a transit increase in total tumor burden in an initial phase, followed by subsequent tumor shrinkage. Therefore, it is important to avoid premature discontinuation of the study drug as nivolumab might induce non-conventional response patterns in some patients. Under the current discontinuation criteria (Section 3.5), subjects must stop the study drug when investigator assessment determines disease progression using the 2007 Revised IWG Response Criteria. The change in this amendment will permit the subjects to continue on the study drug beyond investigator-assessed disease progression in certain cases.
- Additional modifications are as described below:
  - Incorporate other minor changes to correct and/or clarify protocol requirements.

The revisions in this global amendment apply to all subjects.

This amendment will impact data analysis.

**Changes to the Protocol:**

1. Synopsis, Secondary objectives
  - a) 2nd bullet, assessment of duration of CR added.
  - b) New bullet added as 3rd bullet: “to assess the PR rate and the duration of PR based on IRRC assessment
2. Synopsis, Exploratory Objectives  

3. Synopsis, Study Design
  - a) 5th sentence corrected
  - b) 7th sentence corrected with revised secondary endpoints
  - c) Study design schematic corrected to reflect the removal of the interim analysis
  - d) 2nd paragraph, duration of accrual corrected

4. Synopsis, Study Population
  - a) First sentence: Corrected to “Male and female, age 18 and above, with relapsed or refractory follicular lymphoma after failure of at least two prior lines of therapy (each containing anti-CD 20 antibody and/or an alkylating agent) will be eligible to participate in the study.”
  - b) 2nd sentence: dimension in mm added
5. Synopsis, Study Assessments
  - a) 1st and 2nd sentences corrected
  - b) New paragraph added after last paragraph for documenting GVDH at different time points after study discontinuation for allogeneic SCT
6. Synopsis, Statistical Considerations, Sample Size: 2nd paragraph deleted and replaced by a new one
7. Synopsis, Statistical Considerations, Endpoints: 2nd sentence corrected with revised secondary endpoints
8. Synopsis, Statistical Considerations, Analysis
  - a) 1st paragraph modified to reflect the new method to analyze the primary endpoint
  - b) 3rd paragraph, 1st sentence modified to include PR rate
  - c) 3rd paragraph, new sentence added after 1st sentence
9. Section 1.3.2, Secondary Objectives
  - a) 2nd bullet, assessment of duration of CR added.
  - b) New bullet added as 3rd bullet: “To assess the PR rate and the duration of PR based on IRRC assessment”
10. Section 1.3.3, Exploratory Objectives  

13. Section 3.1, Study Design and Duration
  - a) 2nd and 3rd paragraphs deleted to reflect the removal of the interim analysis
  - b) 4th paragraph, 5th and 6th sentences corrected
  - c) Figure 3.1-1 corrected to reflect the removal of the interim analysis
14. Section 3.1, Study Design and Duration, Study Duration: 1st sentence corrected to reflect the timing extension of the analysis of the primary endpoint

15. Section 3.1, Study Design and Duration, Screening

- a) 3rd bullet, 2nd sub-bullet, 2nd sentence deleted
- b) 3rd bullet, new sub-bullet: “Subjects may initiate the study drug before the outcome of PD-L1 expression status becomes available.”
- c) 4th bullet corrected
- d) 4th bullet, 2nd sub-bullet corrected
- e) 4th bullet, new sub-bullet added as 3rd sub-bullet

16. Section 3.1, Study Design and Duration, Treatment

- a) 1st bullet, new sentence added: “Subsequently, women of childbearing potential (WOCBP) must have a pregnancy test every 4 weeks ( $\pm$  7 days) regardless of dosing schedule.”
- b) New bullet after 2nd bullet added: “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.”
- c) 3rd bullet: Corrected to: “All of the vital signs will be collected after Cycle 1 within 72 hours prior to dosing.”
- d) 4th bullet, 2nd sentence deleted
- e) 6th bullet, text added indicating that treatment beyond progression is allowed in certain instances as described in Section 4.3.8
- f) 8th bullet corrected
- g) 9th bullet corrected

17. Section 3.1, Study Design and Duration, Follow-up

- a) 4th bullet: Corrected to: “Subjects who discontinue study therapy for reasons other than disease progression or allogeneic SCT or ASCT 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.”
- b) New bullet after 4th bullet added: “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 Graft-Versus-Host Disease (GVHD) documentation will also be simultaneously collected (see Section 5.3).”

18. Section 3.3.1, Inclusion Criteria:

a) Criterion 2, Target Population

i) c): Modified with conversion in mm added and MRI added

ii) d):

(1) Corrected to “Treatment of FL consisting of  $\geq 2$  prior treatment lines; each of the two prior treatment lines must include anti-CD 20 antibody and/or an alkylating agent (eg, bendamustine, cyclophosphamide, ifosfamide, chlorambucil, melphalan, busulfan, nitrosoureas). At least one of the two prior treatment lines must include rituximab.”

(2) Definition of Refractory FL, 2nd and 3rd bullets corrected

b) Criterion 4, Age and Reproductive Status

i) Sub-bullet f) moved after sub-bullet e)

19. Section 3.3.2, Exclusion Criteria

a) Criterion 4, Allergies and Adverse Drug Reaction, b): Corrected to “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”

b) Criterion 5, Prohibited Treatments and/or Therapies,

i) d): Corrected to: “Autologous SCT  $\leq 12$  weeks prior to first dose of study drug”

ii) New criterion 5f) added: “Carmustine (BCNU)  $\geq 1000$  mg received as part of pre-transplant conditioning regimen”

20. Section 3.5, Discontinuation of Subjects from Treatment:

a) Corrections were made to the first bullet and text was added referencing Section 4.3.8 for guidance on continued treatment beyond disease progression

b) 4th bullet removed and new mandatory paragraph added after last bullet to comply with the revised wording of the protocol model document

21. Section 3.6, Post Treatment Study Follow up: Added new paragraph after 1st paragraph: “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 revised IWG Response Criteria for Malignant Lymphoma 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).”

22. Section 4.3, Selection and Timing of Dose for Each Subject, 1st paragraph, 7th sentence: Corrected to “Subjects may be dosed no less than 12 days between doses and no more than 3 days after the scheduled dosing date.”

23. Section 4.3.1, Antiemetic Premedications: The text “*See Section 4.3.6 for premedication recommendations following a nivolumab related infusion reaction.*” was removed.

24. Section 4.3.5, Treatment Discontinuation Criteria

- a) 2nd bullet corrected
- b) 2nd bullet, new sub-bullet added after 1st sub-bullet: «Grade 3 drug-related endocrinopathies adequately controlled with only physiologic hormone replacement do not require discontinuation»
- c) 3rd bullet: New 4th sub-bullet added: “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”
- d) New bullet added after 3rd bullet: “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.”
- e) Text was added to the “Disease Progression” bullet, referencing Section 4.3.8 for guidance on continued treatment beyond disease progression
- f) New bullet after last bullet: “Subject who initiated the preparative regimen for allogeneic SCT or ASCT after the first dose of nivolumab treatment.”

25. Section 4.3.7: New section created: “Guidelines for assessment and management of tumor lysis syndrome”

26. Section 4.3.7, Treatment Beyond Progression: Re-categorized as Section 4.3.8 and new sub-sections added authorizing the treatment beyond progression

27. Section 5.1, Flow chart/Time and Events Schedule, Table 5.1-1, Screening Procedural Outline (CA209140):

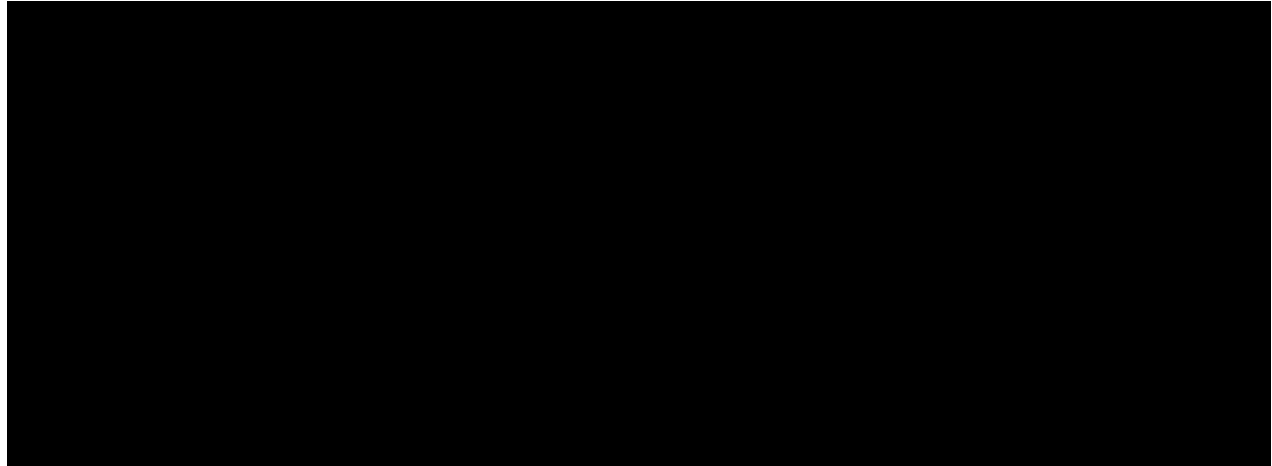
- a) Laboratory Tests: Clarified in the notes that either hepatitis C antibody (HCV Ab) or HCV RNA can be performed at screening, bicarbonates testing deleted, and amylase and lipase testing should be performed
- b) Pregnancy test, Notes corrected: “for WOCBP only (serum or urine - local/site)”
- c) Bone Marrow Aspirate: Text added to clarify the requirements for performing a bone marrow biopsy/aspirate at screening and the submission of optional bone marrow aspirate samples.


28. Section 5.1, Flow chart/Time and Events Schedule, Table 5.1-2, Short-term Procedural Outline (CA209140):

- a) Title of 4th column: Clarified that procedures can be performed every 2 weeks within 3 days prior to dosing
- b) Vital Signs and Oxygen Saturation: Clarified in the Notes that O2 saturation by pulse oximetry will also be performed after exertion.
- c) Laboratory Tests: Added in the notes that amylase and lipase testing are to be performed during the extended local laboratory assessment
- d) Thyroid Function Testing: Notes corrected
- e) Pregnancy test, Procedure: Corrected to “Pregnancy Test for WOCBP”, and Notes corrected to better describe that testing frequency is regardless of dosing schedule



29. Section 5.1, Flow chart/Time and Events Schedule, Table 5.1-3, Follow-Up Assessments (CA209140):
  - a) Adverse Events Assessment: Notes added
  - b) Laboratory Tests: Clarified in the Notes that phosphorus and bicarbonate testing are deleted
  - c) Pregnancy Test, Procedure corrected to “Pregnancy Test (for WOCBP only)”
  - d) New Safety Procedure added: GVHD assessment
  - e) New efficacy assessment added: Tumor Assessment by the Investigator (CR or non-CR)
  - f) EQ-5D procedure: Clarified in the Notes that EQ-5D during the survival follow-up will be assessed during a clinic visit or via a phone contact
30. Section 5.3, Safety Assessments:
  - a) 2nd paragraph:
    - i) Clarified that either hepatitis C antibody (HCV Ab) or Hepatitis C RNA (HCV RNA) test can be performed at screening
    - ii) Clarified that pregnancy test must be performed two times prior to first dose
  - b) 3rd paragraph, last sentence: Clarified that subject’s status in the survival follow-up phase can also be contacted by emails
  - c) 6th paragraph, 1st bullet: amylase and lipase added as local laboratory assessments, and bicarbonate deleted
  - d) 7th paragraph: Clarified that TSH testing is being performed regardless of dosing schedule
  - e) New paragraph added after last paragraph for documenting GVDH at different time points after study discontinuation for allogeneic SCT
31. Section 5.4, Efficacy Assessments:
  - a) 1st and 2nd sentences corrected
  - b) New paragraph added
32. Section 5.4.1, Radiographic Assessments: 3rd and 4th paragraphs corrected
33. Table 5.4.1-1, Schedule of Spiral CT/MRI Tumor Assessments: Note added to the table
34. Section 5.4.2.1, Measurable Lesions: Paragraph corrected with measurements reported in mm
35. Section 5.4.3.3, Spiral CT/MRI Scan: New paragraph added
36. Section 5.4.5, Bone Marrow Assessments: Paragraphs corrected
37. Section 5.4.6, Disease Response Evaluation:
  - a) Sentence corrected
  - b) New paragraph added after first sentence
38. Section 5.5, Pharmacokinetic Assessments: Clarified PK sampling when a dose is delayed
39. Table 5.5-1, Sampling Schedule: Footnote “a” corrected
40. Section 5.6, Biomarker Assessments, Bone Marrow Aspirates:
  - a) 1st paragraph corrected
  - b) New paragraph added after 1st paragraph



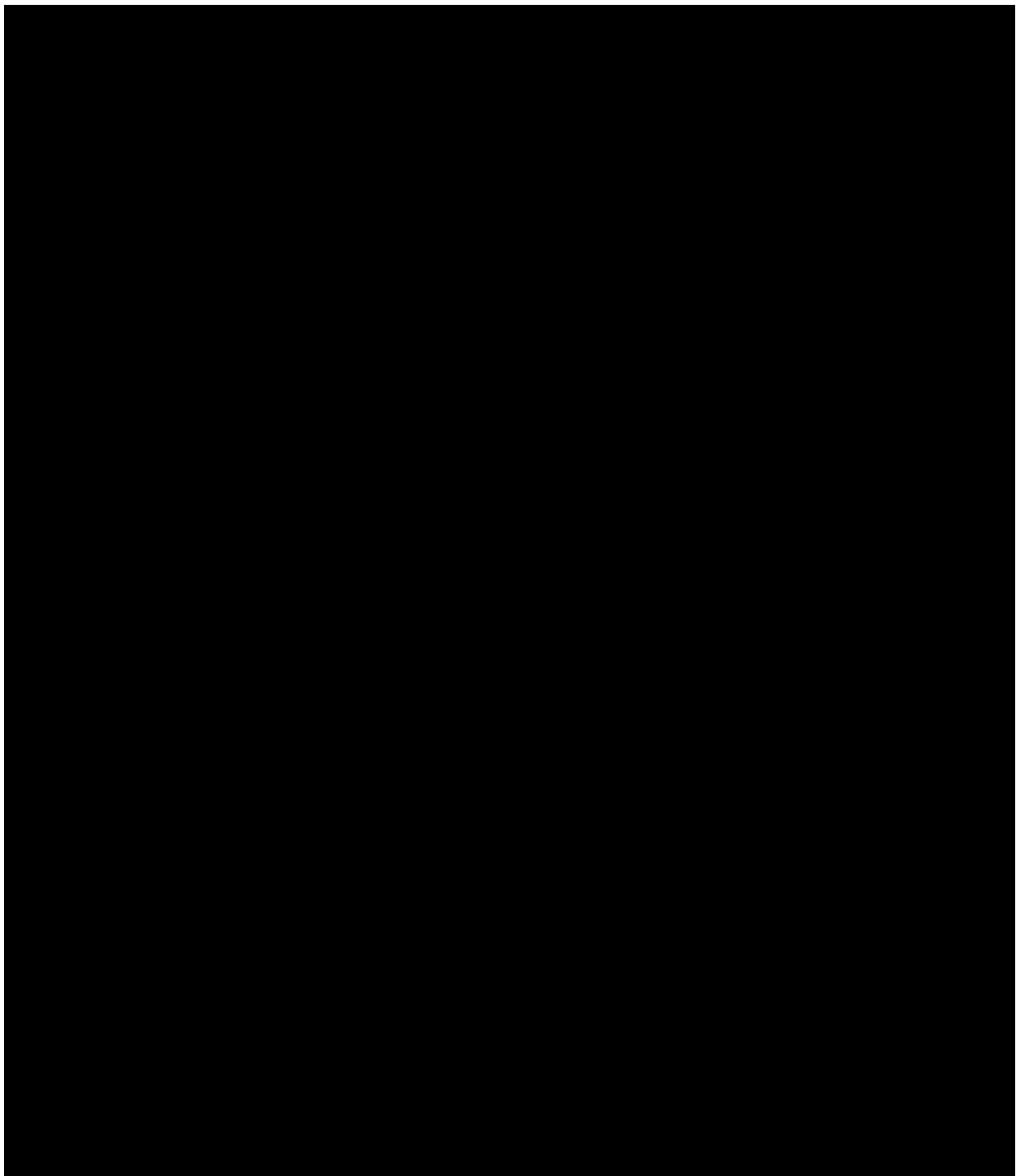
45. Section 5.9, Results of Central Assessments: 2nd sentence deleted
46. Section 6.4, Pregnancy: new paragraph added to the end of the section to comply with the revised wording of the protocol model document
47. Section 8.1, Sample Size Determination: Full section corrected
48. Section 8.2, Populations for Analyses: 5th and 6th bullets corrected.
49. Section 8.3.1, Primary Endpoint: 1st paragraph, 2nd, 3rd, 4th, 5th and last sentences corrected
50. Section 8.3.2, Secondary Endpoint:
  - a) 2nd sentence corrected
  - b) Added new sentence after 2nd sentence: “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.”
  - c) 2nd paragraph, 3rd and 4th paragraphs corrected
    - i) 2nd sentence corrected
    - ii) New sentences added after last sentence to clarify the evaluation of duration of CR
  - d) New paragraph added after 2nd paragraph to define PR rate.
  - e) 3rd paragraph, first sentence corrected
  - f) 4th paragraph, first sentence corrected
51. Section 8.3.3, Exploratory Endpoint: 1st sentence corrected
52. Section 8.4.2.1, Primary Endpoint Methods, 1st paragraph: Method used corrected
53. Section 8.4.2.2, Secondary Endpoint Methods: 1st and 2nd paragraphs corrected
54. Section 8.4.2.3, Exploratory Endpoint Methods: 
55. Section 8.4.7.1, Immunogenicity Analyses: 1st sentence corrected
56. Section 8.5, Interim Analyses: Section removed as not applicable anymore
57. Section 11, List of Abbreviations: Added ACTH and GVHD to the list.
58. Section 12, References: Deleted and added references to reflect the changes in the text.

59. Appendix 2, International Working Group Criteria for Nonhodgkin Lymphoma: Title corrected to “2007 International Working Group Response Criteria for Malignant Lymphoma”.
60. Appendix 5, Acute GVHD Grading and Staging added.

## AMENDMENT RATIONALE’S REFERENCES

- <sup>1</sup> Gouill S, De Guibert S, Planche L, et al.; GELA and GOELAMS. Impact of the use of autologous stem cell transplantation at first relapse both in naive and previously rituximab exposed follicular lymphoma patients treated in the GELA/GOELAMS FL2000 study. *Haematologica* 2011;96(8):1128-35.
- <sup>2</sup> Laport GG. Changing role of stem cell transplantation in follicular lymphoma. *Hematology Am Soc Hematol Educ Program* 2012;2012:417-25.
- <sup>3</sup> Schouten HC, Qian W, Kvaloy S, et al. High-dose therapy improves progression free survival and survival in relapsed follicular non-Hodgkin’s lymphoma: results from the randomized European CUP trial. *J Clin Oncol* 2003;21:3918-3927.
- <sup>4</sup> Montoto S, Canals C, Rohatiner AZ, et al.; EBMT Lymphoma Working Party. Long-term follow-up of high-dose treatment with autologous haematopoietic progenitor cell support in 693 patients with follicular lymphoma: an EBMT registry study. *Leukemia* 2007;21(11):2324-3.
- <sup>5</sup> Montoto S, Corradini P, Dreyling M, et al. Indications for hematopoietic stem cell transplantation in patients with follicular lymphoma: a consensus project of the EBMT-Lymphoma Working Party. *Haematologica*. 2013;98(7):1014-21.
- <sup>6</sup> Dreyling M, Ghilmini M, Marcus R, et al.; ESMO Guidelines Working Group. Newly diagnosed and relapsed follicular lymphoma: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. *Ann Oncol* 2011 Sep;22 Suppl 6:vi59-63.

**Please maintain a copy of this amendment with your protocol. Please provide a copy to your Investigational Review Board / Ethics Committee, unless agreed otherwise with BMS.**

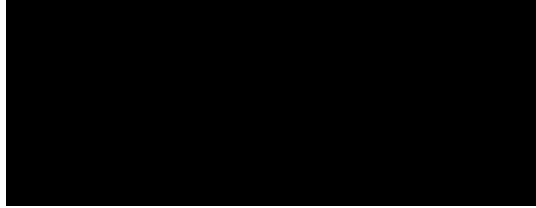


Page: 1  
Protocol Number: CA209140  
IND Number: 119,380  
EUDRACT Number 2013-003645-42  
Date: 21-Jul-2016

**Protocol CA209140:** An Open-Label Phase 2 Study of Nivolumab (BMS-936558) or Nivolumab plus Rituximab in Subjects with Relapsed or Refractory Follicular Lymphoma (FL)  
(CheckMate 140: CHECKpoint pathway and nivoluMAb clinical Trial Evaluation 140)

**Amendment Number 04**  
**Site Number: All**

**Study Director/Central Medical Monitor**



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**This protocol amendment contains information that is confidential and proprietary to Bristol-Myers Squibb (BMS).**

*This amendment must be maintained with the referenced protocol.*

**Amendment Rationale:**

Safety management algorithms were updated in the Investigator Brochure, requiring revision of the Appendix 1 algorithms. This revision applies to all subjects receiving study drug, or who have discontinued study drug and are being treated for suspected pulmonary toxicity, skin toxicity and nephrotoxicity.

**Changes to the Protocol:**

1. Updated Appendix 1 Algorithm for Renal, Pulmonary and Skin to match with updated Nivolumab IB v15 and Erratum 01 to Nivolumab IB v15.

**Please maintain a copy of this amendment with your protocol. Please provide a copy to your Investigational Review Board / Ethics Committee, unless agreed otherwise with BMS.**

