Official Title of Study:

# AN OPEN-LABEL, SINGLE-ARM PHASE II SAFETY STUDY OF NIVOLUMAB IN PARTICIPANTS WITH ADVANCED OR METASTATIC NON-SMALL CELL LUNG CANCER WHO HAVE PROGRESSED DURING OR AFTER RECEIVING AT LEAST ONE PRIOR SYSTEMIC REGIMEN

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# Clinical Protocol CA209907

An Open-label, Single-arm Phase II Safety Study of Nivolumab in Participants with Advanced or Metastatic Non-small Cell Lung Cancer Who Have Progressed During or After Receiving at Least One Prior Systemic Regimen

**(CheckMate 907: CHECKpoint pathway and nivoluMAb clinical Trial Evaluation 907)**

**Revised Protocol Number: 02**
**Incorporates Administrative Letters 03, 05, 06, and 07**

[redacted]

**24-hr Emergency Telephone Number**
[redacted]

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**protocol may apply to partners to which BMS has transferred obligations, e.g., a Contract Research Organization (CRO).**

## DOCUMENT HISTORY

| Document | Date of Issue | Summary of Change |
|---|---|---|
| Revised Protocol 02 | 10-Jul-2020 | • Extended follow-up radiographic tumor assessment collection and survival follow-up to a maximum duration of 5 years after first dose.<br>• Updated Appendix 4 and Appendix 6 to bring in line with current nivolumab and BMS protocol standards. |
| Administrative Letter 07 | 23-Oct-2018 | • Nivolumab dosing information updated to be consistent with IB v17.<br>• Study personnel information updated. |
| Administrative Letter 06 | 16-Jul-2018 | Study personnel information updated. |
| Administrative Letter 05 | 09-Jul-2018 | Nivolumab dosing information updated to be consistent with IB v16. |
| Administrative Letter 03 | 26-Feb-2018 | Study personnel information updated. |
| Revised Protocol 01 | 26-Jan-2018 | • Increased number of participants in study and sample size determination in statistical section<br>[redacted]<br>• Included additional language for nivolumab program level updates<br>• Incorporated Administrative Letters 01 and 02. |
| Administrative Letter 02 | 26-Oct-2017 | Added the IND Number to Protocol Title Page |
| Administrative Letter 01 | 17-Jul-2017 | Updated information for Study Director and Medical Monitor |
| Original Protocol | 10-Nov-2016 | Not Applicable |

## OVERALL RATIONALE FOR REVISED PROTOCOL 02:

The study was revised to allow for collection of efficacy data beyond 2 years for analyses.

| SUMMARY OF KEY CHANGES FOR REVISED PROTOCOL 02 | | |
|---|---|---|
| **Section Number & Title** | **Description of Change** | **Brief Rationale** |
| 2, Schedule of Activities<br><br>Table 2-3: Follow up and survival procedures (All Participants) | Modified follow-up radiographic tumor assessment collection and survival follow-up to a maximum duration of 5 years after first dose | To collect efficacy data beyond 2 years for analyses |
| 5.1, Overall Design | Modified follow-up radiographic tumor assessment collection and survival follow-up to a maximum duration of 5 years after first dose and specified that participants who discontinue treatment for reasons other than disease progression or completed 2 years of treatment will continue to have tumor assessments and be followed for survival. | To collect efficacy data beyond 2 years for analyses |
| Figure 5.1-1 Study Design Schematic | Modified footnote for survival follow-up to a maximum duration of 5 years after first dose and specified that participants who discontinue treatment for reasons other than disease progression or completed 2 years of treatment will continue to be followed for survival. | To collect efficacy data beyond 2 years for analyses |
| 5.3, End of Study Definition | Extension of study to a maximum of 5 years | To collect efficacy data beyond 2 years for analyses |

| SUMMARY OF KEY CHANGES FOR REVISED PROTOCOL 02 | | |
|---|---|---|
| **Section Number & Title** | **Description of Change** | **Brief Rationale** |
| 9.1.1: Imaging Assessment for the study | Added text: Participants who discontinue earlier than 2 years or completed 2 years of treatment but achieve SD/PR/CR at the end of Follow-up Visit 2 will have imaging scans every 3 months (12 weeks ± 7 days) until documented radiographic disease progression or up to a maximum duration of 5 years after first dose. | To collect efficacy data beyond 2 years for analyses |
| 10.3.1, Efficacy Analyses | Extended the PFS/OS rate timing intervals out to the maximum duration of 60 months (5 years) | To collect efficacy data beyond 2 years for analyses |
| Appendix 4, Management Algorithms | Algorithms updated | Bring in line with nivolumab and BMS protocol standards |
| Appendix 6, Study Governance Considerations | Updates to potential serious breach language<br><br>Addition of the word participants.<br><br>Update to drug traceability language under Study Treatment Records.<br><br>Additional of information about Scientific Publications | Bring in line with nivolumab and BMS protocol standards |

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# 1. SYNOPSIS

**Protocol Title: An Open-label, Single-arm Phase II Safety Study of Nivolumab in Participants with Advanced or Metastatic Non-small Cell Lung Cancer Who Have Progressed During or After Receiving at Least One Prior Systemic Regimen**

**Study Phase:**

Phase 2

**Rationale:**

A less frequent administration of nivolumab has the potential for improved convenience for patients and reduce administrative burden. A flat dosing is expected to reduce prescription dosing errors, shorten pharmacy preparation time, and improve ease of administration. Extending the dosing interval to 4 weeks would provide increased flexibility between clinical visits, as compared to Q2W dosing schedule.

A dose of 480 mg Q4W was selected based on equivalence to the approved 3 mg/kg every 2 weeks at the median body weight of ~80 kg in nivolumab-treated participants. A PPK model predicted overall nivolumab average exposures across participants with a wide range of body weight from 480 mg Q4W to be similar to that from 3 mg/kg Q2W. Although the flat dose is expected to lead to higher exposure in lighter patients, relative to the exposure in heavier patients given the relationship between nivolumab PK and body weight, the predicted median and 95th percentile of exposures are maintained below those in 10 mg/kg every 2 weeks, which was established as a safe and well-tolerable dose across multiple tumor types. There was no clinical meaningful relationship between nivolumab exposure or body weight and frequency or severity of AEs. Therefore, a 480 mg Q4W is expected to be safe and tolerable in those patients.

**Research Hypothesis**

There is no formal hypothesis. The safety profile of less frequent dosing regimen of 480 mg of nivolumab every 4 weeks is expected to be similar to that of 3 mg/kg of nivolumab every 2 weeks in participants with advanced or metastatic NSCLC. The analyses to summarize incidence of treatment-related select adverse events will be descriptive.

**Study Population:**

Participants ≥ 18 years old with advanced or metastatic non-small cell lung cancer who have progressed during, or after, receiving at least 1 prior systemic regimen.

**Key Inclusion:**

- ECOG Performance Status ≤ 1
- Participants with histologically documented NSCLC (SQ or NSQ) who present with Stage IIIB/Stage IV disease (according to version 7 of the International Association for the Study of Lung Cancer Staging Manual in Thoracic Oncology), or with recurrent or progressive disease following multimodal therapy (radiation therapy surgical resection, or definitive chemo radiotherapy for locally advanced disease).

- All participants with non-squamous histology must have been tested for EGFR mutation status; use of regulatory -approved test is strongly encouraged. ALK mutation testing is not required for this study. Participants with non-squamous histology must be tested for EGFR mutations (including, but not limited to, deletions in exon 19 and exon 21 [L858R] substitution). Participants who are positive on sensitizing EGFR mutations should have received EGFR inhibitors prior to study entry.
- Participants must be naïve to IO therapy.
- Participants must have at least 1 lesion with measurable disease as defined by RECIST v1.1 criteria for solid tumors response assessment. Participants with lesions in a previously irradiated field as the sole site of measurable disease will be permitted to enroll, provided the lesion(s) have demonstrated clear progression and can be measured accurately.

**1) Key Exclusion Criteria**

- Active brain metastases or leptomeningeal metastases. Participants with brain metastases are eligible if these have been treated there is no magnetic resonance imaging (MRI) - evidence of progression for at least 8 weeks after treatment is complete and within 28 days prior to first dose of study drug administration. When MRI is contraindicated, the results of the CT scan with IV contrast is acceptable.
- There must also be no requirement for immunosuppressive doses of systemic corticosteroids (> 10 mg/day prednisone equivalents) for at least 2 weeks prior to study drug administration.

**Objectives and Endpoints:**

**Table 1: Objectives and Endpoints**

| Objective | Endpoint |
|---|---|
| **Primary:** | |
| To characterize the safety of nivolumab 480 mg IV over 30 minutes every 4 weeks | • The number and percentage of participants who experience high-grade (Grades 3-4 and Grade 5), treatment-related select Adverse Events.<br>• The select Adverse Events (select AEs) consist of a list of preferred terms grouped by specific category (eg, pulmonary events, gastrointestinal events, hepatic events, renal events, skin events, endocrine events categories). These categories are defined by the Sponsor and the list that is most current at the time of analysis will be used. Also changes may be made to this list with each new version of MedDRA. |

| Table 1: Objectives and Endpoints | |
|---|---|
| **Objective** | **Endpoint** |
| **Secondary:** | |
| To estimate the efficacy of nivolumab 480 mg IV over 30 minutes every 4 weeks | • Progression-free survival (PFS) defined as the time from first dosing date to the date of the first documented tumor progression, as determined by investigators (per RECIST v1.1), or death due to any cause, whichever occurs first.<br>• Objective Response Rate (ORR) defined as the number and percentage of participants with a best overall response (BOR) of confirmed complete response (CR) or partial response (PR). Best overall response (BOR) is defined as the best response designation, recorded between the date of first dose and the date of the initial objectively documented tumor progression per RECIST v1.1 or the date of subsequent therapy, whichever occurs first.<br>• Overall survival (OS), defined as the time from first dosing date to the date of death.<br>• Duration of Response (DOR) defined as the time between the date of first confirmed response to the date of the first documented tumor progression (per RECIST 1.1), or death due to any cause, whichever occurs first. |
| [redacted] | |

## Overall Design:

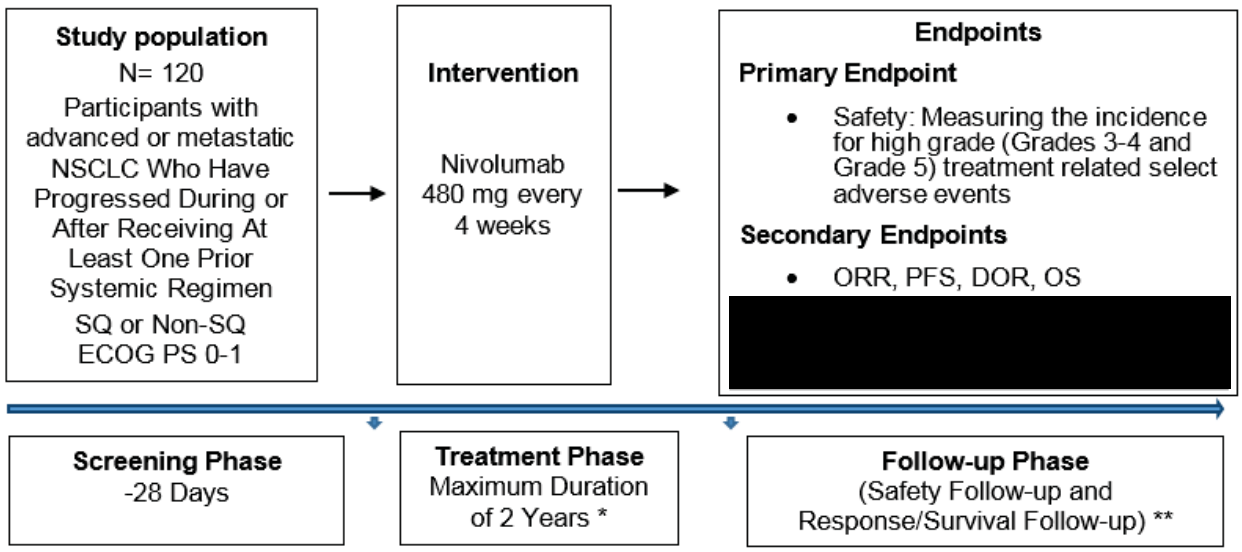
This will be an open-label, single arm Phase 2 safety study of less frequent flat dose administration of nivolumab in participants ≥ 18 years old with advanced or metastatic non-small cell lung cancer who have progressed during or after receiving at least 1 prior systemic regimen. Nivolumab 480 mg will be administered every 4 weeks. Each 28-day dosing period will constitute a cycle. Participants will receive treatment with nivolumab every 4 weeks until progression, unacceptable toxicity, withdrawal of consent, death or a maximum of 2 years, whichever occurs first. Treatment beyond initial investigator-assessed RECIST 1.1-defined progression will be considered in participants experiencing investigator assessed clinical benefit and tolerating study therapy. The post-treatment follow-up begins when the decision to discontinue a participant from treatment is made. Participants who discontinue treatment for reasons other than disease progression will continue to have tumor assessments (if clinically feasible) according to the schedule.

Participants will be followed for drug-related toxicities until these toxicities resolve, return to baseline or are deemed irreversible. All adverse events will be documented for a minimum of 100 days after the last dose of study medication.

BMS may request that survival data be collected on all treated participants outside of the Protocol defined window as detailed in the Section 2 (Schedule of Assessments: Follow-up Assessments). At the time of this request, each participant will be contacted to determine their survival status unless the participant has withdrawn consent for all contact. The study will end once survival follow-up has concluded.

The study design schematic is presented in Figure 1.

**Figure 1: Study Design Schematic**




* Nivolumab to be administered as a flat dose, 480 mg every 4 weeks, until progression, unacceptable toxicity, withdrawal of consent, or a maximum treatment duration of 2 years, whichever comes first.

** Participants discontinuing treatment earlier than 2 years or completed 2 years of treatment will continue to be followed for survival follow up every **3 months** until death, lost to follow-up, withdrawal of study consent, or up to a maximum duration of 5 years after the first dose.

### Number of Participants:

The present study will treat approximately 120 participants.

### Treatment Arms and Duration:

Participants will receive treatment 480 mg nivolumab every 4 weeks until progression, unacceptable toxicity, withdrawal of consent, death, or a maximum of 2 years, whichever occurs first.

**Study treatment:**

| Study Drug for CA209907 | | |
|---|---|---|
| **Medication** | **Potency** | **IP/Non-IP** |
| BMS-936558-01<br>Solution for Injection/ Nivolumab[a] | 10 mg/mL | IP |

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

## STATISTICAL CONSIDERATIONS

### Sample Size Determination

Approximately 200 participants will be enrolled in order to treat up to 120 participants. This number of treated participants was chosen to provide descriptive analysis to estimate incidence rate of high-grade (Grades 3-4 or Grade 5), drug-related, select AE and rate of immune-mediated adverse events in all treated participants with nivolumab alternate dosing schedule. Overall, the safety profile of nivolumab monotherapy is manageable and generally consistent across completed and ongoing clinical trials with no MTD reached at any dose tested up to 10 mg/kg. Most AEs were low-grade (Grade 1 to 2) with relatively few related high-grade (Grades 3 to 4) AEs. Rates of high-grade (Grades 3-4 or Grade 5), drug-related, select AE and rate of immune-mediated adverse events by category observed in 2L NSCLC CheckMate 063, 017 and 057 were low and <7%. Nivolumab monotherapy has been extensively studied in multiple tumor types, including melanoma, NSCLC, RCC, cHL, Head and Neck and UC with body weight normalized dosing (mg/kg). PPK modelling predicted median and 95th percentile of exposures are maintained below those in 10 mg/kg every 2 weeks, which was established as a safe and well-tolerable dose across multiple tumor types. There was no clinical meaningful relationship between nivolumab exposure or body weight and frequency or severity of AEs. Therefore, a 480 mg Q4W is expected to be safe and tolerable in those patients.

The table below shows the 95% Confidence Intervals for different AE rates for a sample size of 120 participants.

**Table 2: 95% Confidence Intervals for different AE rates for a sample size of 120**

| Number of participants with AE (%) | Exact 95% CI around proportion |
|---|---|
| 0/120 (0%) | 0%-3.0% |
| 1/120 (0.8%) | 0.8%-4.6% |
| 2/120 (1.7%) | 0.2%-5.9% |
| 3/120 (2.5%) | 0.5%-7.1% |
| 4/120 (3.3%) | 0.9%-8.3% |

| **Table 2:** | **95% Confidence Intervals for different AE rates for a sample size of 120** |
|---|---|
| **Number of participants with AE (%)** | **Exact 95% CI around proportion** |
| 5/120 (4.2%) | 1.4%-9.5% |
| 6/120 (5.0%) | 1.9%-10.6% |

With a sample size of 120, the chance of observing at least one participant with the event is greater than 80% for true probabilities of events higher than 1.3%.

- If true probability of event is 1%, the chance of observing at least 1 participant with event among 120 treated participant s is 70%.
- If true probability of event is 2%, the chance of observing at least 1 participant with event among 120 treated participant s is 91%.

## 2. SCHEDULE OF ACTIVITIES

**Table 2-1: Screening Assessments (All Participants)**

| Procedure | Screening Visit (≤ 28 days) | Notes: To occur within 28 days of first dose, unless otherwise specified. |
|---|---|---|
| **Eligibility Assessments** | | |
| Informed Consent | X | Register in Interactive Response system to obtain participant numbers |
| Inclusion/Exclusion Criteria | X | All inclusion/exclusion criteria should be reassessed prior to first dose |
| Medical History | X | Medical history will include smoking history. In addition, mutational status EGFR, ALK, ROS, MET, KRAS and BRAF should be collected, if available. If mutational status is not available in the medical history of participants with non-squamous histology, EGFR mutational status must be determined. Includes risk factors (eg, pleural effusion and pneumonitis). Include any toxicities or allergy to previous treatment. |
| Prior Systemic Cancer Therapies | X | |
| **SAFETY ASSESSMENTS** | | |
| Physical Measurements/Physical Examination, Vital Signs, and Performance Status | X | Include height and weight, Performance Status (Appendix 2), BP, HR, RR, temperature within 72 hours prior to first dose. Complete physical examination within 14 days prior to first dose. |
| Assessment of Baseline Signs and Symptoms | X | Assess within 14 days prior to first dose. |
| Serious Adverse Event Assessments | X | SAEs present from time of consent. See Section 9.2. |
| Concomitant Medication Collection | X | Collect within 14 days prior to first dose through the study treatment period. |
| Pregnancy Test (WOCBP only) | X | Serum or urine pregnancy test (minimum sensitivity 25 IU/L or equivalent units of HCG) to be done at screening visit and within 24 hours of first dose of study therapy on Day 1. |
| Laboratory Tests | X | Must be performed within 14 days prior to first dose of study therapy:<br>• CBC w/differential and platelets<br>• Chemistry panel including AST, ALT, ALP, T Bili, BUN or serum urea level, creatinine, phosphate, Ca, Na, K, Cl, LDH, Glucose, albumin<br>• Thyroid panel including TSH, free T3 and free T4 |

| **Table 2-1: Screening Assessments (All Participants)** | | |
|---|---|---|
| **Procedure** | **Screening Visit (≤ 28 days)** | **Notes: To occur within 28 days of first dose, unless otherwise specified.** |
| | | • Serology: Hep B surface antigen and Hep C antibody (if Hep C antibody is positive reflex Hep C RNA) or Hep C RNA.<br>• Follicle stimulating hormone (FSH)-only required to confirm menopause in women < age 55<br>Note: Testing for HIV-1 and HIV-2 must be performed at sites where mandated by local requirements. |
| ECG (12-lead) | X | Obtained only for participants who have met all eligibility criteria. |
| **EFFICACY ASSESSMENTS** | | |
| Radiographic Tumor Assessments(chest, abdomen, pelvis, brain) | X | Performed within 28 days prior to first dose.<br>CT of Chest, Abdomen, Pelvis and all known or suspected sites of disease should be imaged at the screening visit. MRI of brain without and with gadolinium is required for those with known or suspected brain metastases.<br>Tumor assessments will be according to RECIST 1.1 (Appendix 3) |
| **BIOMARKER ASSESSMENTS** | | |
| Mandatory Archived Tumor Tissue or Recent Tumor Biopsy | X | Fresh or archival sample from the primary site of the disease, obtained preferably within 6 months prior to enrollment. If the tissue from the primary site is unobtainable or unsuitable, tissue from a metastasis site is acceptable if its pathology report matches a pathology report from the primary tumor. Submission of archival tissue from time of diagnosis may be acceptable in some circumstances following a discussion with the BMS Study Director (or Medical Monitor). If archived slides are to be submitted, they must not have been cut > 6 months prior to submission, as the sample may have degraded. One formalin-fixed paraffin embedded tumor tissue block or a minimum of 10 unstained tumor slides are required. Submission of fewer than 10 unstained slides may be acceptable in some circumstances following discussion with the BMS Study Director (or Medical Monitor).<br>Tissue samples are to be submitted with each matching pathology report and biopsy date. If there is inadequate tissue, BMS will contact the site for additional tissue. Criterion 2m in Section 6.1 discusses acceptable and unacceptable methods of collection. |

| **Table 2-1: Screening Assessments (All Participants)** | | |
|---|---|---|
| **Procedure** | **Screening Visit (≤ 28 days)** | **Notes: To occur within 28 days of first dose, unless otherwise specified.** |
| | | [redacted] |

| **Table 2-2: On Treatment Assessments (All Participants)[a]** | | | | |
|---|---|---|---|---|
| **Procedure** | **Cycle 1 Day 1[b]** | **Each Subsequent Cycle Day 1[b]** | **EOT[c]** | **Notes**<br>**For purposes of this table, a cycle refers to 4 weeks (28 days) of treatment.**<br>**If a dose is delayed, the procedures scheduled for that same time point (with the exception of tumor assessments) should also be delayed to coincide with when that time point's dosing actually occurs.** |
| **SAFETY ASSESSMENTS** | | | | |
| Targeted Physical Examination, Vital Signs, Performance Status | X (see note) | X | X | Weight, BP, HR, RR, temperature within 72 hours prior to dosing, and Performance Status.<br>Note: C1D1 Targeted Physical Examination, Vital Signs, and Performance Status do not need to be repeated if Screening Physical Measurements/Physical Examination, Vital Signs, and Performance Status were performed within 72 hours of first dose. |
| Adverse Event Assessments | Continuously during the study | | | SAEs should be approved within 5 days from entry. For AE reporting, see Section 9.2 and Appendix 7. |
| Review of Concomitant Medications | Continuously during the study | | | |
| Laboratory Tests | X | X | X | • CBC w/ differential and platelets<br>• Chemistry panel including AST, ALT, ALP, T. Bili, BUN or serum urea level, creatinine, phosphate, Ca, Na, K, Cl, LDH, glucose, albumin<br>• TSH panel including reflex Free T4 and Free T3<br>• Within 72 hours prior to dosing.<br>Note: C1D1 labs do not need to be repeated if they were performed within 14 days of dosing. |
| Pregnancy Test (WOCBP only) | X | X | X | To be evaluated at least every 4 weeks. |
| **EFFICACY ASSESSMENTS** | | | | |
| Radiographic Tumor Assessment<br>Repeat CT/MRI of chest/ abdomen with or without pelvis is required for participants | See notes | | | First assessment to occur at Week 8 (± 7 days) and then every 8 weeks (± 7 days) until documented radiographic disease progression for a maximum of 2 years from the first dose. |

| Table 2-2: On Treatment Assessments (All Participants)[a] | | | | |
|---|---|---|---|---|
| **Procedure** | **Cycle 1 Day 1[b]** | **Each Subsequent Cycle Day 1[b]** | **EOT[c]** | **Notes**<br>**For purposes of this table, a cycle refers to 4 weeks (28 days) of treatment.**<br>**If a dose is delayed, the procedures scheduled for that same time point (with the exception of tumor assessments) should also be delayed to coincide with when that time point's dosing actually occurs.** |
| with metastases in those areas at baseline, or if clinically indicated.) | | | | *Participants with a history of brain metastasis must have surveillance MRI approximately every 12 weeks from the date of first dose, or sooner if clinically indicated.<br>Participants being treated beyond progression tumor assessment continues per protocol specified schedule until the participant comes off study or for a maximum duration of 2 years from first dose. |
| [redacted] | | | | |
| **CLINICAL DRUG SUPPLIES** | | | | |
| IRT Vial Assignment | X | X | | Within 3 calendar days prior to first dosing |
| Nivolumab 480 mg | X | X | | |

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

[b] If a dose is delayed, the procedures scheduled for that same timepoint should also be delayed to coincide with when that timepoint's dosing actually occurs.

[c] EOT (end of treatment) is defined as the visit where the decision is made to discontinue the participants from treatment. For participants who complete all the scheduled cycles of therapy for a maximum of 2 years duration from first dose, the EOT will be the most recent on-treatment visit. For participants who discontinue from the study earlier than the maximum duration of 2 years from first dose , the EOT will be the most recent on-treatment visit (with all available safety and response data) and does not need to be repeated and will be considered the start of the week 1 safety follow up visit.

| **Table 2-3: Follow-up and Survival Procedures (All Participants)[a]** | | | |
|---|---|---|---|
| **Procedure** | **Follow-Up[b] Visits 1 & 2** | **Survival[c] Follow-up Visits** | **Notes** |
| **SAFETY ASSESSMENTS** | | | |
| Physical Examination | X | | To assess for potential late emergent study drug related issues. |
| Vital Signs | X | | Including BP, HR, RR and temperature. |
| Adverse Event Assessment | X | | SAEs should be approved within 5 days from entry. Beyond 100 days from the last dose of study drug, participants will be followed for ongoing drug-related adverse events until resolved, return to baseline or deemed irreversible, or until lost to follow-up, withdrawal of study consent, or start of subsequent therapy. |
| Review of Concomitant Medications | X | | |
| Laboratory Tests | X | | Required at Visit 1. Repeat at Visit 2 only if study drug related toxicity persists. |
| Pregnancy Test (WOCBP only) | X | | |
| **EFFICACY ASSESSMENTS** | | | |
| Radiographic Tumor Assessment (CT chest and known sites of disease. Repeat CT/MRI of abdomen with or without pelvis is required for participants with metastases in those areas at baseline, or if clinically indicated.) | X* | X** | An unconfirmed PR or unconfirmed CR must be confirmed at least 4 weeks after initial assessment<br>*Radiographic assessments for participants who have not experienced PD must be obtained every 8 weeks (± 7 days) and not delayed until Follow-up Visits 1 & 2.<br>**Participants who discontinue earlier than 2 years or completed 2 years of treatment but achieve SD/PR/CR at the end of Follow-up Visit 2 will have imaging scans every 3 months (12 weeks ± 7 days) until documented radiographic disease progression or up to maximum duration of 5 years after first dose |
| Collection of Survival Status and Subsequent Therapy Information | X | X | Collect **every 3 months** in Survival Visits until death, lost to follow-up, withdrawal of study consent, or up to a maximum duration of 5 years after the first dose. May be performed by phone contact or office visit. |

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

[b]Participants must be followed for at least 100 days after last dose of study treatment. Follow-up Visit 1 (FU1) should occur 30 days from the last dose (± 7) days or can be performed on the date of discontinuation if that date is greater than 42 days from last dose. Follow-up Visit 2 (FU2) occurs approximately 100 days (± 7 days) from last dose of study drug. Both Follow-up Visits should be conducted in person.

[c] After completion of Follow-up Visit 1 and 2, all participants will enter Survival/ Response Follow-Up phase to occur approximately every 3 months from Follow-Up Visit 2 until death, lost to follow up, withdrawal of consent, or up to maximum duration of 5 years after the first dose, whichever comes first.

# 3. INTRODUCTION

Nivolumab (OPDIVO®) was approved in the United States (US) to treat patients with metastatic squamous cell NSCLC with progression on or after platinum-based chemotherapy. The approval was based on the results of Study CA209017, a randomized trial of nivolumab versus docetaxel. The median overall survival (OS) for participants in the nivolumab arm was 9.2 months versus 6 months for those in the docetaxel arm (hazard ratio [HR] = 0.59). Improvement in survival was observed for nivolumab regardless of PD-L1 expression; however, there was a trend for better efficacy for those with PD-L1-positive tumors. A single-arm trial (Study CA209063) of 117 participants with metastatic squamous cell NSCLC, with progression after platinum-based chemotherapy and at least 1 additional systemic regimen, showed a 15% overall response rate (ORR); 59% of these participants had response durations of 6 months or longer. A second Phase 3 study, Study CA209057 demonstrating superior OS of nivolumab versus docetaxel in participants with previously-treated non squamous NSCLC with a 27% reduction in risk of death (HR = 0.73; P = 0.0015). Interaction P-values reported for PD-L1 expression subgroups by each of the predefined expression levels suggested a clinically important signal of a predictive association. Nivolumab also significantly improved ORR versus docetaxel (P = 0.0246), with ORR as high as 36% in participants with PD-L1-expressing tumors. OS approximately doubled with nivolumab versus docetaxel across the PD-L1 expression continuum. In contrast, no difference in OS was seen between nivolumab and docetaxel when PD-L1 was not expressed in the tumor.

In general, nivolumab has been well tolerated to date, with a favorable safety profile consistent with anticipated toxicities based on an immunostimulatory mechanism of action. Nivolumab has been studied and is widely approved in multiple indications. Extensive details on the safety profile of nivolumab are available in the Investigator Brochure.

Overall, the safety profile of nivolumab monotherapy is manageable and generally consistent across completed and ongoing clinical trials with no maximum tolerated dose (MTD) reached at any dose tested up to 10 mg/kg. Most AEs were low-grade (Grade 1 to 2) with relatively few related high-grade (Grade 3 to 4) AEs. There was no pattern in the incidence, severity, or causality of AEs with respect to nivolumab dose level. Additional details on the safety profile of nivolumab, including results from other clinical studies, are also available in the nivolumab IB.

Decreasing the frequency of administration of nivolumab has the potential for improved convenience for patients and to reduce administrative burden. A flat dosing is expected to reduce prescription dosing errors, shorten pharmacy preparation time, and improve ease of administration. Extending the dosing interval to 4 weeks would provide increased flexibility between clinical visits, as compared to Q2W dosing schedule. The development of nivolumab is ongoing to provide additional data on the optimal dose and frequency of nivolumab administration that balances quality of life and compliance for patients in addition to efficacy and safety. This study will evaluate the safety profile of a less frequent dose administration.

## 3.1 Study Rationale

Nivolumab has been studied and is widely approved in multiple indications and has been well tolerated to date, with a favorable safety profile. An unmet need was identified to characterize the

safety of less frequent dosing regimen 480 mg flat dose dosing regimen of nivolumab monotherapy.

A less frequent administration of nivolumab has the potential for improved convenience for patients and reduce administrative burden. A flat dosing is expected to reduce prescription dosing errors, shorten pharmacy preparation time, and improve ease of administration. Extending the dosing interval to 4 weeks would provide increased flexibility between clinical visits as compared to Q2W dosing schedule

### *3.1.1 Research Hypothesis*

There is no formal hypothesis. The safety profile of less frequent dosing regimen of 480 mg of nivolumab every 4 weeks is expected to be similar to that of 3 mg/kg of nivolumab every 2 weeks in participants with advanced or metastatic NSCLC. The analyses to summarize incidence of drug related select adverse events will be descriptive.

## 3.2 Background

### *3.2.1 Non-Small Cell Lung Cancer (NSCLC) Background*

Lung cancer is the leading cause of cancer and cancer-related deaths globally, accounting for 1.8 million new cases and 1.6 million deaths worldwide in 2012.[1] Between 2004 and 2010, according to the SEER database, the overall 5-year survival rate was 21.4%.[2] The majority of patients were diagnosed with advanced or metastatic disease. Prognosis for these patients remains dismal, with 5-year survival rates of < 5%. Approximately 85% of lung cancer is NSCLC, and of these, approximately 80% are non-squamous, and 20% are squamous histology. The use of platinum-based chemotherapy doublets, given for up to 6 cycles, is standard-of-care for patients with newly diagnosed advanced or metastatic NSCLC who do not have EGFR mutation or ALK translocation.[3] Current first-line chemotherapy doublets include cisplatin or carboplatin in combination with antimicrotubule agents, gemcitabine, or pemetrexed. Overall response rates with these platinum doublets is approximately 30-35%. Progression-free survival (PFS) has remained about 4 to 5.5 months, with an overall survival (OS) of about 9 to 11 months.[4]

In early clinical trials, the immunotherapeutic agent, nivolumab, has demonstrated activity in several tumor types, including melanoma, renal cell cancer, and NSCLC.[5] Tumors may modulate and evade the host immune response through a number of mechanisms, including down regulation of tumor-specific antigen expression and presentation, secretion of anti-inflammatory cytokines, and upregulation of inhibitory ligands. T cell checkpoint regulators such as CTLA-4 and programmed death-1 (PD-1, CD279) are cell surface molecules that, when engaged by their cognate ligands, induce signaling cascades down-regulating T cell activation and proliferation. One proposed model by which therapeutic T cell checkpoint inhibitors derive antitumor activity is through breaking of immune tolerance to tumor cell antigens.

Nivolumab (BMS-936558) is a fully human, IgG4 (kappa) isotype mAb that binds PD-1 on activated immune cells and disrupts engagement of the receptor with its ligands PD-L1 (B7-H1/CD274) and PD-L2 (B7-DC/CD273), thereby abrogating inhibitory signals and augmenting the host antitumor response.

Nivolumab (Opdivo®) has recently been approved in the United States (US) to treat patients with advanced (metastatic) squamous cell and nonsquamous cell lung cancer whose disease has progressed during or after platinum-based chemotherapy. Approval of nivolumab in advanced NSCLC was based on 2 Phase 3 trials (CheckMate 017 and CheckMate 057) which demonstrated survival benefit over docetaxel across histologies. The approval in squamous NSCLC was based on the results of CA209017, a randomized trial of nivolumab versus docetaxel. The median OS for patients in the nivolumab arm was 9.2 months versus 6 months for those in the docetaxel arm (HR = 0.59). Improvement in survival was observed for nivolumab regardless of PD-L1 expression, though there was a trend toward better efficacy for those with PD-L1 expressing tumors. A single-arm trial (CA209063) of 117 patients with metastatic squamous NSCLC with progression after platinum-based chemotherapy and at least 1 additional systemic regimen showed a 15% objective response rate (ORR); 59% of participants with an ORR had response durations of 6 months or longer.

The approval of nivolumab for the treatment of non-squamous NSCLC is based on a second Phase 3 study, CA209057, which met its primary endpoint of superior OS of nivolumab versus docetaxel in patients with previously treated non-squamous NSCLC at a preplanned interim analysis. Patients in the nivolumab arm had a 27% reduction in risk of death (HR = 0.73; P = 0.0015). Interaction P values, reported for PD L1 expression subgroups by each of the predefined expression levels, suggested a clinically important signal of a predictive association. Nivolumab also significantly improved ORR vs docetaxel (P=0.0246), with ORR as high as 36% in patients with PD-L1 expressing tumors. OS approximately doubled with nivolumab vs docetaxel at 1%, 5% and 10% PD-L1 expression level. In contrast, no statistically significant difference in OS was seen between nivolumab and docetaxel when PD-L1 was not expressed in the tumor, although these patients also experienced durable responses, and the safety profile was more favorable for nivolumab vs docetaxel.[6]

In general, nivolumab is well tolerated, with a favorable safety profile relative to anticipated toxicities based on an immunostimulatory mechanism of action. Nivolumab is currently in Phase 3 development in the first-line metastatic and the early stage NSCLC settings. A detailed description of the chemistry, pharmacology, efficacy, and safety of nivolumab is provided in the Investigator's Brochure and local package insert.

### 3.2.2 Nivolumab Mechanism of Action

Cancer immunotherapy rests on the premise that tumors can be recognized as foreign rather than as self and can be effectively attacked by an activated immune system. An effective immune response in this setting is thought to rely on immune surveillance of tumor antigens expressed on cancer cells that ultimately results in an adaptive immune response and cancer cell death. Meanwhile, tumor progression may depend upon acquisition of traits that allow cancer cells to evade immunosurveillance and escape effective innate and adaptive immune responses.[7,8,9] Current immunotherapy efforts attempt to break the apparent tolerance of the immune system to tumor cells and antigens by either introducing cancer antigens by therapeutic vaccination or by modulating regulatory checkpoints of the immune system. T-cell stimulation is a complex process

involving the integration of numerous positive as well as negative co-stimulatory signals in addition to antigen recognition by the T-cell receptor (TCR).[10] Collectively, these signals govern the balance between T-cell activation and tolerance.

PD-1 is a member of the CD28 family of T-cell co-stimulatory receptors that also includes CD28, CTLA-4, ICOS, and BTLA.[11] PD-1 signaling has been shown to inhibit CD-28-mediated upregulation of IL-2, IL-10, IL-13, interferon-γ (IFN-γ) and Bcl-xL. PD-1 expression also been noted to inhibit T cell activation and expansion of previously activated cells. Evidence for a negative regulatory role of PD-1 comes from studies of PD-1 deficient mice, which develop a variety of autoimmune phenotypes.[12] These results suggest that PD-1 blockade has the potential to activate anti-self T-cell responses, but these responses are variable and dependent upon various host genetic factors. Thus, PD-1 deficiency or inhibition is not accompanied by a universal loss of tolerance to self-antigens.

In vitro, nivolumab (BMS-936558) binds to PD-1 with high affinity (EC50 0.39-2.62 nM), and inhibits the binding of PD-1 to its ligands PD-L1 and PD-L2 (IC50 ≤ 1 nM). Nivolumab binds specifically to PD-1 and not to related members of the CD28 family such as CD28, ICOS, CTLA-4 and BTLA. Blockade of the PD-1 pathway by nivolumab results in a reproducible enhancement of both proliferation and IFN-γ release in the mixed lymphocyte reaction (MLR). Using a CMV restimulation assay with human PBMC, the effect of nivolumab on antigen specific recall response indicates that nivolumab augmented IFN-γ secretion from CMV specific memory T cells in a dose-dependent manner versus isotype-matched control. In vivo blockade of PD-1 by a murine analog of nivolumab enhances the anti-tumor immune response and results in tumor rejection in several immunocompetent mouse tumor models (MC38, SA1/N, and PAN02).[13]

### 3.2.3 Nivolumab in NSCLC

PD-1 is a 55 kD type I transmembrane protein primarily expressed on activated T cells, B cells, myeloid cells, and antigen presenting cells (APC).[14] Binding of PD-1 to PD-L1 and PD-L2 has been shown to down-regulate T-cell activation in both murine and human systems.[15,16,17,18] In particular, PD-L1 has been shown to be upregulated on several cancers types including NSCLC and, in some cases, correlated to negative prognosis.[19,20,21,22,23] PD-1/PD-L interactions may also indirectly modulate the response to tumor antigens through T-cell/APC interactions. Therefore, PD-1 engagement may represent one means by which tumors evade immunosurveillance and clearance.[24] Blockade of the PD-1 pathway by nivolumab has been studied in a variety of preclinical in vitro assays, and antitumor activity using a murine analog of nivolumab has been shown in a number of immunocompetent mouse cancer models. Based on these and other preclinical data, PD-1 blockade by nivolumab has been pursued as a promising therapeutic strategy to reverse immune tolerance and enhance T-cell effector function in several tumor types including NSCLC.[11]

### 3.2.4 Rationale for Nivolumab Dose and Schedule

Nivolumab monotherapy has been extensively studied in multiple tumor types, including melanoma, NSCLC, RCC, cHL, Head and Neck, and UC with body weight normalized dosing

(mg/kg). Nivolumab PK was determined to be linear, with dose proportional exposures over a dose range of 0.1 to 10 mg/kg. Nivolumab clearance and volume of distribution was found to increase with increasing body weight, but the increase was less than proportional, indicating that mg/kg dose represents an over-adjustment for the effect of body weight on nivolumab PK. A flat dosing is expected to reduce prescription dosing errors, shorten pharmacy preparation time, and improve ease of administration. Extending the dosing interval to 4 weeks provided numerous benefits to patients as they would have increased flexibility between clinical visits, as compared to Q2W dosing schedule.

A 480 mg Q4W regimen was selected based on equivalence to the approved 3 mg/kg every 2 weeks at the median body weight of ~80 kg in nivolumab-treated participants. A PPK model predicted overall nivolumab average exposures across participants with a wide range of body weight from 480 mg Q4W to be similar to that from 3 mg/kg Q2W. Although the flat dose is expected to lead to higher exposure in lighter patients, relative to the exposure in heavier patients given the relationship between nivolumab PK and body weight, the predicted median and 95th percentile of exposures are maintained below those in 10 mg/kg every 2 weeks, which was established as a safe and well-tolerable dose across multiple tumor types. The simulated median and 95th prediction interval of nivolumab summary exposures across body weight range (35 to 160 kg) are predicted to be maintained below the corresponding observed highest exposure experienced in nivolumab, ie, 95th percentile following nivolumab 10 mg/kg Q2W from clinical study CA209003. Thus, while participants in the lower body weight ranges would have greater exposures than 80 kg participants, the exposures are predicted to be within the range of observed exposures at doses (up to 10 mg/kg Q2W) used in the nivolumab clinical program, and are not considered to put participants at increased risk. There was no clinical meaningful relationship between nivolumab exposure or BW and frequency or severity of AEs. Therefore, a 480 mg Q4W is expected to be safe and tolerable in those patients. In terms of efficacy, 480 mg Q4W is expected to result in similar efficacy given a flat exposure-response relationship and same dose intensity. Overall, the benefit-risk profile of nivolumab 480 mg Q4W is expected to be similar to approved regimen 3 mg/kg Q2W, and it is recommended for further investigation in this study.

## 3.3 Benefit/Risk Assessment

Participants with advanced or metastatic NSCLC who progress with first-line therapy represent a great unmet need. The clinical activity of nivolumab observed to date in NSCLC suggests the potential for improved clinical outcomes as monotherapy. A flat dosing is expected to reduce prescription dosing errors, shorten pharmacy preparation time, and improve ease of administration. Extending the dosing interval to 4 weeks provided numerous benefits to patients as they would have increased flexibility between clinical visits, as compared to Q2W dosing schedule.

Overall, the safety profile of nivolumab monotherapy is manageable and generally consistent across completed and ongoing clinical trials with no MTD reached at any dose tested up to 10 mg/kg. Most AEs were low-grade (Grade 1 to 2) with relatively few related high-grade (Grade 3 to 4) AEs. There was no pattern in the incidence, severity, or causality of AEs with respect to nivolumab dose level.

A pattern of immune-related adverse events has been defined, for which management algorithms have been developed; these are provided in Appendix 4. Most high-grade events were manageable with the use of corticosteroids or hormone replacement therapy (endocrinopathies) as instructed in these algorithms.

Additional details on the safety profile of nivolumab, including results from other clinical studies, are also available in the nivolumab IB.

## 4. OBJECTIVES AND ENDPOINTS

**Table 4.-1: Objectives and Endpoints**

| Objective | Endpoint |
|---|---|
| **Primary:** | |
| To characterize the safety of nivolumab 480 mg IV over 30 minutes every 4 weeks | • The number and percentage of participants who experience high-grade (Grades 3-4 and Grade 5), treatment-related select Adverse Events<br>The select Adverse Events (select AEs) consist of a list of preferred terms grouped by specific category (eg, pulmonary events, gastrointestinal events, hepatic events, renal events, skin events, endocrine events categories). These categories are defined by the Sponsor and the list that is most current at the time of analysis will be used. Also changes may be made to this list with each new version of MedDRA. |
| **Secondary:** | |
| To estimate the efficacy of nivolumab 480 mg IV over 30 minutes every 4 weeks | • Progression-free survival (PFS) defined as the time from first dosing date to the date of the first documented tumor progression, as determined by investigators (per RECIST v1.1), or death due to any cause, whichever occurs first.<br>• Objective Response Rate (ORR) defined as the number and percentage of participants with a best overall response (BOR) of confirmed complete response (CR) or partial response (PR). Best overall response (BOR) is defined as the best response designation, recorded between the date of first dose and the date of the initial objectively documented tumor progression per RECIST v1.1 or the date of subsequent therapy, whichever occurs first.<br>• Overall survival (OS) defined as the time from first dosing date to the date of death.<br>• Duration of Response (DOR) defined as the time between the date of first confirmed response to the date of the first documented tumor progression (per RECIST 1.1), or death due to any cause, whichever occurs first. |
| [redacted] | |

# 5. STUDY DESIGN

## 5.1 Overall Design

This will be an open-label, single arm Phase 2 safety study of less frequent flat dose administration of nivolumab in participants ≥ 18 years old with advanced or metastatic non-small cell lung cancer who have progressed during or after receiving at least 1 prior systemic regimen.

The study will consist of 3 phases: screening, treatment, and follow-up.

Screening Phase

Begins by establishing the participant's initial eligibility and signing of the informed consent (ICF). The participant will be enrolled using an interactive response technology (IRT). The screening period will last for 28 days. All screening assessments and procedures must be performed within 28 days prior to treatment.

[redacted]

Treatment Phase

Eligible participants will be assigned by IRT. Participants will receive treatment with nivolumab every 4 weeks until progression, unacceptable toxicity, withdrawal of consent, or a maximum treatment duration 2 years.

Tumor assessment will be performed every 8 weeks (± 7 days). Assessment of partial assessment response (PR) and complete response (CR) must be confirmed at least 4 weeks following initial assessment. Tumor response assessment will be assessed using RECIST 1.1 (Appendix 3).

- Treatment beyond initial investigator-assessed RECIST 1.1-defined progression will be considered in participants experiencing investigator assessed clinical benefit and tolerating study therapy as per Section 7.4.4. Such participants must discontinue therapy when further progression is documented. Study assessments are to be collected as outlined in Table 2-2. Upon end of treatment participants will enter the Follow-up Phase. The post-treatment follow-up begins when the decision to discontinue a participant from all treatment is made.

Follow-up Phase

Upon completion of the study, participants will enter the Follow-up Phase including in Safety Follow-up and Response/Survival Follow-up.

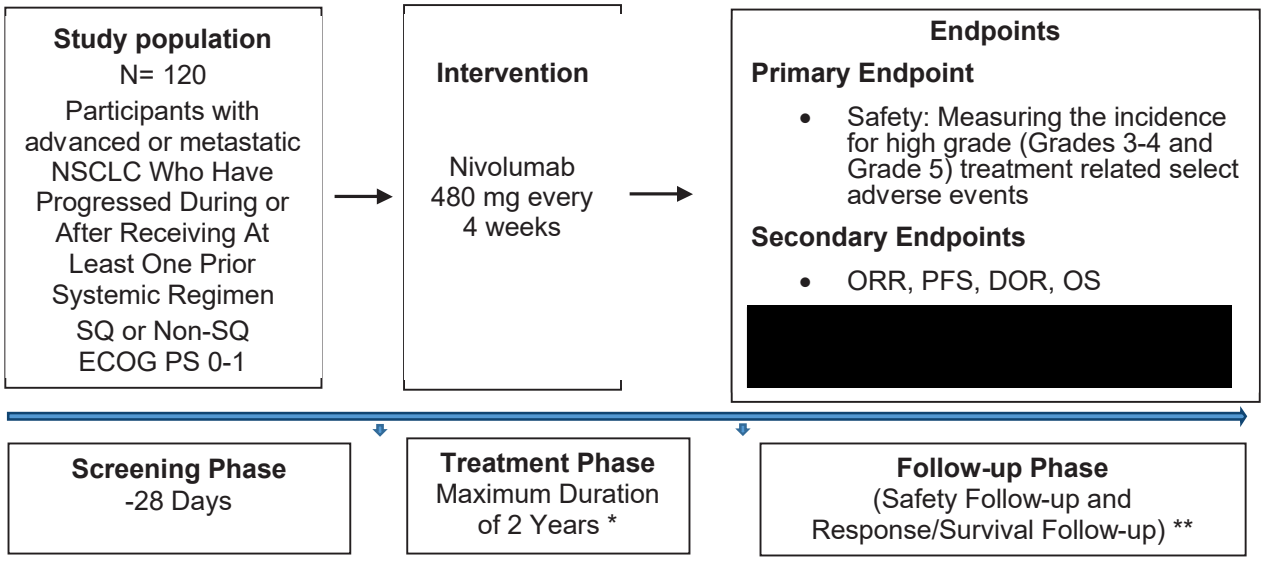
- Safety follow-up: Upon completion of the study, participants will enter the safety follow-up period lasting approximately 100 days from the last treatment. After the end of the treatment (EOT visit), participants will be followed for drug-related toxicities until these toxicities

resolve, return to baseline, or are deemed irreversible. All adverse events will be documented for a minimum of 100 days after the last dose of study medication. Participants must complete the 2 clinical safety follow-up visits regardless of whether they start new anticancer therapy.

- Response/Survival follow-up: Participants who discontinue treatment for reasons other than disease progression or completed 2 years of treatment will continue to have tumor assessments (if clinically feasible) according to the schedule. In follow-up period, participants with ongoing SD, PR or CR at the EOT visit will enter response follow-up period. These participants will continue to have radiological and clinical tumor assessment every 3 months (12 weeks) until disease progression, death, lost to follow-up, withdrawal of study consent, or up to a maximum duration of 5 years after the first dose.
- In addition, all participants who are discontinued from treatment earlier than 2 years or completed 2 years of treatment will be followed for survival every 3 months (12 weeks) until death, lost to follow up, withdrawal of consent, or up to a maximum duration of 5 years after the first dose.

The study design schematic is presented in Figure 5.1-1.

**Figure 5.1-1: Study Design Schematic**




* Nivolumab to be administered as a flat dose, 480 mg every 4 weeks, until progression, unacceptable toxicity, withdrawal of consent, or a maximum treatment duration of 2 years, whichever comes first.

** Participants discontinuing treatment earlier than 2 years or completed 2 years of treatment will continue to be followed for survival follow up every 3 months until death, lost to follow-up, withdrawal of study consent, or up to a maximum duration of 5 years after the first dose.

### *5.1.1 Data Monitoring Committee and Other External Committees*

The Sponsor of this study will not utilize an independent data safety monitoring board (DSMB). BMS will assign a physician responsible for reviewing, on a systematic and continuous basis, the safety of participants in this study. This includes a review of serious and non-serious adverse events

and all hematological and non-hematological events. In addition, BMS has a Medical Surveillance Team (MST), independent from the clinical medical monitor. The MST has the primary responsibility within Bristol-Myers Squibb for assessing emerging safety trends, identifying potential safety signals, notifying appropriate stakeholders of relevant findings, and implementing risk mitigation activities to ensure the safety of patients participating in BMS trials. The MST is also responsible for reviewing data from all sources including non-clinical studies and clinical trials, monitoring the progress of various nivolumab safety support activities, and recommending and implementing necessary changes to the safety plan and any other specific safety-related activities.

## 5.2 Number of Participants

The present study plans to treat approximately 120 participants.

## 5.3 End of Study Definition

The start of the trial is defined as the first screening visit for the first participant. End of trial is defined as last participant last follow-up visit, or up to a maximum of 5 years from last participant's first dosing.

## 5.4 Scientific Rationale for Study Design

This is an open-label, single-arm, Phase 2 safety study of nivolumab that will provide additional safety data to support the alternate less frequent dosing regimen for nivolumab monotherapy. An open-label design will ensure that immune-mediated AEs are promptly identified and managed.

The study will consist of 3 phases: screening, treatment, and follow-up.

## 5.5 Justification for Dose

### *5.5.1 Rationale for 480 mg Every 4 Week*

Details regarding dose rationale are provided in Section 3.2.4.

# 6. STUDY POPULATION

Males and female participants ≥ 18 years old with advanced or metastatic non-small cell lung cancer who have progressed during or after receiving at least 1 prior systemic regimen will be included in this population.

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

## 6.1 Inclusion Criteria

**1) Signed Written Informed Consent**

a) Participants must be able to give self-consent and then sign and date an IRB/IEC-approved written informed consent in accordance with regulatory and institutional guidelines. This must be obtained before the performance of any protocol-related procedures that are not considered part of normal patient care.

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

**2) Type of Participant and Target Disease Characteristics**

a) ECOG Performance Status ≤ 1

b) Participants with histologically documented NSCLC (SQ or NSQ) who present with Stage IIIB/Stage IV disease (according to version 7 of the International Association for the Study of Lung Cancer Staging Manual in Thoracic Oncology), or with recurrent or progressive disease following multimodal therapy (radiation therapy surgical resection, or definitive chemo radiotherapy for locally advanced disease).

   i) Participants must have experienced disease progression or recurrence during or after at least 1 systemic therapy for advanced or metastatic disease.

      (1) Each subsequent line of therapy must be preceded by disease progression. A switch of an agent within a regimen in order to manage toxicity does not define the start of a new line of therapy.

      (2) Maintenance therapy following platinum doublet-based chemotherapy is not considered as a separate regimen of therapy.

c) Participants who received platinum-containing adjuvant, neoadjuvant or definitive chemo-radiation therapy given for locally advanced disease, and developed recurrent (local or metastatic) disease within 6 months of completing therapy are eligible.

d) Participants with recurrent disease > 6 months after completing a platinum-containing adjuvant, neoadjuvant or definitive chemo-radiation therapy given for locally advanced disease, who also subsequently progressed during or after a systemic regimen given to treat the recurrence, are eligible.

e) All participants with non-squamous histology must have been tested for EGFR mutation status; use of regulatory-approved test is strongly encouraged. ALK mutation testing is not required for this study. Participants with non-squamous histology must be tested for EGFR mutations (including, but not limited to, deletions in exon 19 and exon 21 [L858R] substitution). Participants who are positive on sensitizing EGFR mutations should have received EGFR inhibitors prior to study entry.

f) Experimental therapies when given as separate regimen are considered as separate line of therapy.

   i) Participants must be naïve to IO therapy. Should not have received prior treatment with an anti-PD-1, anti-PD-L1, anti-PD-L2, anti-CD137, or anti-CTLA-4 antibody, or any other antibody or drug specifically targeting T-cell co-stimulation or checkpoint pathways.

g) Participants must have a life expectancy of at least 3 months following their most recent chemotherapy.

h) Participants receiving prior palliative radiotherapy to a non-central nervous system (CNS). Lesion must have completed that therapy at least 2 weeks prior to the first dose of study drug.

i) Participants with symptomatic tumor lesions at baseline who may require palliative radiotherapy within 4 weeks of the first dose of study drug are strongly encouraged to receive palliative radiotherapy prior to enrollment. Lesions which have received or are anticipated to receive palliative RT may not be designated as target or non-target lesions in the baseline tumor assessment.

j) Evaluable disease by CT or MRI; radiographic tumor assessment performed within 28 days of start of study treatment.

k) Participants must have at least 1 lesion with measurable disease as defined by RECIST v1.1 criteria for solid tumors response assessment. Participants with lesions in a previously irradiated field as the sole site of measurable disease will be permitted to enroll, provided the lesion(s) have demonstrated clear progression and can be measured accurately.

l) Participants with toxicity from any prior anti-cancer therapy must have their toxicity returned to Grade ≤ 1 (NCI Common Terminology Criteria for Adverse Events [CTCAE] Version 4.03) or baseline before administration of study drug.

   i) Participants Grade ≥ 2 with toxicities attributed to prior anti-cancer therapy that are not expected to resolve and result in long-lasting sequela, such as neuropathy after a platinum-based therapy, are eligible.

   ii) Grade >1 alopecia is permitted.

m) Participants must have tissue submitted prior to study start

   i) Either a formalin-fixed, paraffin-embedded (FFPE) tissue block or unstained tumor tissue sections, with an associated pathology report, must be submitted for biomarker evaluation prior to treatment assignment. The tumor tissue sample may be fresh or archival if obtained preferably within 6 months prior to enrollment. Submission of archival tissue from time of diagnosis may be acceptable in some circumstances following a discussion with the BMS Study Director (or Medical Monitor).

   ii) Tissue must be a core needle biopsy, excisional, or incisional biopsy. Fine needle biopsies or drainage of pleural effusions with cytospins are not considered adequate for biomarker review. Biopsies of bone lesions that do not have a soft tissue component or decalcified bone tumor samples are also not acceptable.

   iii) Samples collected via other procedures, including, but not limited to, Endobronchial Ultrasound (EBUS) guided biopsy, transbronchial lung biopsy (TBLB) may be approved by the BMS MM/SD on a case by case basis.

**3) Age and Reproductive Status**

a) Males and Females, ages 18 or age of majority

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 treatment.

c) Women must not be breastfeeding

d) Women of childbearing potential (WOCBP) must agree to follow instructions for method(s) of contraception during treatment and for a period of 5 months after the last dose of nivolumab (ie, 30 days for duration of ovulatory cycle plus the time required for nivolumab to undergo five half-lives).

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

f) Azoospermia males are exempt from contraceptive requirements.

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

Investigators shall counsel WOCBP, and male participants who are sexually active with WOCBP, on the importance of pregnancy prevention and the implications of an unexpected pregnancy. Investigators shall advise on the use of highly effective methods of contraception (Appendix 5), which have a failure rate of < 1% when used consistently and correctly.

## 6.2 Exclusion Criteria

1) **Target Disease Exceptions**
   a) Active brain metastases or leptomeningeal metastases. Participants with brain metastases are eligible if these have been treated there is no magnetic resonance imaging (MRI) - evidence of progression for at least 8 weeks after treatment is complete and within 28 days prior to first dose of study drug administration. When MRI is contraindicated, the results of the CT scan with IV contrast is acceptable.
   b) There must also be no requirement for immunosuppressive doses of systemic corticosteroids (> 10 mg/day prednisone equivalents) for at least 2 weeks prior to study drug administration.

2) **Medical Conditions**
   a) Participants must have recovered from the effects of major surgery or significant traumatic injury at least 14 days prior to treatment.
   b) Participants with previous malignancies (except non-melanoma skin cancers, and in situ cancers such as the following: bladder, gastric, colon, cervical/dysplasia, melanoma, or breast) are excluded unless a complete remission was achieved at least 3 years prior to treatment and no additional therapy is required or anticipated to be required during the study period.
   c) Other active malignancy requiring concurrent intervention.
   d) Participants with an active, known or suspected autoimmune disease. Participants with type I diabetes mellitus, hypothyroidism only requiring hormone replacement, skin disorders (such as vitiligo, psoriasis, or alopecia) not requiring systemic treatment, or conditions not expected to recur in the absence of an external trigger are permitted to enroll.
   e) Participants with a condition requiring systemic treatment with either corticosteroids (> 10 mg daily prednisone equivalent) or other immunosuppressive medications within 14 days of first dose. Inhaled or topical steroids, and adrenal replacement steroid > 10 mg daily prednisone equivalent, are permitted in the absence of active autoimmune disease.
   f) Participants with interstitial lung disease that is symptomatic or may interfere with the detection or management of suspected drug-related pulmonary toxicity.
   g) Known history of testing positive for human immunodeficiency virus (HIV) or known acquired immunodeficiency syndrome (AIDS). NOTE: Testing for HIV must be performed at sites where mandated locally.

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

i) Known medical condition that, in the investigator's opinion, would increase the risk associated with study participation or study drug administration or interfere with the interpretation of safety results.

**3) Prior/Concomitant Therapy**

a) Prior treatment with an anti-PD-1, anti-PD-L1, anti-PD-L2, anti-CD137, or anti-CTLA-4 antibody, or any other antibody or drug specifically targeting T-cell co-stimulation or checkpoint pathways

b) Treatment with botanical preparations (eg herbal supplements or traditional Chinese medicines) intended for general health support or to treat the disease under study within 4 weeks prior to first treatment.

**4) Physical and Laboratory Test Findings**

a) WBC < 2000/μL

b) Neutrophils < 1500/μL

c) Platelets < 100 x 103/μL

d) Hemoglobin < 9.0 g/dL

e) Serum creatinine > 1.5 x ULN, unless creatinine clearance ≥ 40 mL/min (measured or calculated using the Cockroft-Gault formula)

f) AST/ALT: > 3.0 x ULN

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

**5) Allergies and Adverse Drug Reaction**

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

**6) Other Exclusion Criteria**

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

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

c) Any other serious or uncontrolled medical disorder, active infection, physical exam finding, laboratory findings, altered mental status, or psychiatric condition that, in the opinion of the investigator, would limit a participant's ability to comply with the study requirements, substantially increase risk to the participant, or impact the interpretability of study results.

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

## 6.3 Lifestyle Restrictions

Not applicable. No restrictions are required

## 6.4 Screen Failures

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

### *6.4.1 Retesting During Screening or Lead-In Period*

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

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

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

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

# 7. TREATMENT

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

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

- Nivolumab as IP/IMP.

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

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

| Table 7.-1: Study treatments for CA209907 | | | | | |
|---|---|---|---|---|---|
| **Product Description / Class and Dosage Form** | **Potency** | **IP/Non-IMP** | **Blinded or Open Label** | **Packaging / Appearance** | **Storage Conditions (per label)** |
| BMS-936558-01 Solution for Injection/ Nivolumab [a] | 10 mg/mL | IP | Open-label | Clear to opalescent, colorless to pale yellow liquid. May contain particles. | 2° to 8° C. Protect form light, and freezing. |

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

## 7.1 Treatments Administered

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

**Table 7.1-1: Selection and Timing of Dose**

| Study Treatment | Unit dose strength/Dosage level | Dosage formulation Frequency of Administration | Route of Administration |
|---|---|---|---|
| **Nivolumab** | 10 mg/mL/ 480 mg | Every 4 weeks | IV Infusion |

### *7.1.1 Nivolumab Dosing*

Participants should receive nivolumab at a dose of 480 mg as a 30-minute infusion on Day 1 of each treatment cycle until progression, unacceptable toxicity, withdrawal of consent, death, or for maximum treatment duration of 2 years, whichever occurs first. Participants should begin study treatment within 3 days of treatment assignment.

There will be no dose escalations or reductions of nivolumab allowed. Participants may be dosed no less than 25 days from the previous dose during cycles. For every 4 week dosing cycles, participants may be dosed within a ± 3 day window. Premedications are not recommended for the first dose of nivolumab.

Participants should be carefully monitored for infusion reactions during nivolumab administration. If an acute infusion reaction is noted, participants should be managed according to Section 7.4.2**.**

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

Nivolumab Injection, 10 mg/mL is to be administered as an IV infusion through a 0.2-micron to 1.2-micron pore size, low-protein binding in-line filter at the protocol-specified doses. It is not to be administered as an IV push or bolus injection. Nivolumab injection can be infused undiluted (10 mg/mL) or diluted with 0.9% Sodium Chloride Injection, USP or 5% Dextrose Injection, USP to protein concentrations as low as 1 mg/mL. Instructions for dilution and infusion of nivolumab injection may be provided in the clinical protocol, pharmacy binder, or pharmacy reference sheet. Care must be taken to assure sterility of the prepared solution as the product does not contain any antimicrobial preservative or bacteriostatic agent.

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

## 7.2 Method of Treatment Assignment

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

Study treatment will be dispensed at the study visits as listed in Schedule of Activities (Section 2).

## 7.3 Blinding

Not applicable.

## 7.4 Dosage Modification

Dose reductions or modification of nivolumab are not permitted.

### *7.4.1 Nivolumab Dose Delay Criteria*

Nivolumab administration should be delayed for the following:

- Grade 2 non-skin, drug-related adverse event, with the exception of fatigue
- Grade 2 drug-related creatinine, AST, ALT and/or Total Bilirubin abnormalities
- Grade 3 skin, drug-related adverse event
- Grade 3 drug-related laboratory abnormality, with the following exceptions:
  - Grade 3 lymphopenia or asymptomatic amylase or lipase does not require dose delay
  - Grade ≥ 3 AST, ALT, Total Bilirubin will require dose discontinuation (see Section 8.1.1)
- Any adverse event, laboratory abnormality, or intercurrent illness which, in the judgment of the investigator, warrants delaying the dose of study medication.

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

### *7.4.2 Treatment of Nivolumab Related Infusion Reactions*

Since nivolumab contains only human immunoglobulin protein sequences, it is unlikely to be immunogenic and induce infusion or hypersensitivity reactions. However, if such a reaction were to occur, it might manifest with fever, chills, rigors, headache, rash, pruritus, arthralgias, hypotension, hypertension, bronchospasm, or other allergic-like reactions. All Grade 3 or 4 infusion reactions should be reported within 24 hours to the study medical monitor and reported as an SAE if it meets the criteria. Infusion reactions should be graded according to NCI CTCAE (Version 4.0) guidelines.

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

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

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

**For Grade 2 symptoms: (Moderate reaction requires therapy or infusion interruption but responds promptly to symptomatic treatment [eg, antihistamines, non-steroidal anti-**

**inflammatory drugs, narcotics, corticosteroids, bronchodilators, IV fluids]; prophylactic medications indicated for ≤ 24 hours).**

- Stop the nivolumab infusion, begin an IV infusion of normal saline, and treat the participant with diphenhydramine 50 mg IV (or equivalent) and/or acetaminophen/paracetamol 325 to 1000 mg; remain at bedside and monitor participant until resolution of symptoms. Corticosteroid and/or bronchodilator therapy may also be administered as appropriate. If the infusion is interrupted, then restart the infusion at 50% of the original infusion rate when symptoms resolve; if no further complications ensue after 30 minutes, the rate may be increased to 100% of the original infusion rate. Monitor participant closely. If symptoms recur, then no further nivolumab will be administered at that visit.
- For future infusions, the following prophylactic premedications are recommended: diphenhydramine 50 mg (or equivalent) and/or acetaminophen/paracetamol 325 to 1000 mg should be administered at least 30 minutes before nivolumab infusions. If necessary, corticosteroids (up to 25 mg of SoluCortef or equivalent) may be used.

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

- Immediately discontinue infusion of nivolumab. Begin an IV infusion of normal saline and treat the participant as follows: Recommend bronchodilators, epinephrine 0.2 to 1 mg of a 1:1000 solution for subcutaneous administration or 0.1 to 0.25 mg of a 1:10,000 solution injected slowly for IV administration, and/or diphenhydramine 50 mg IV with methylprednisolone 100 mg IV (or equivalent), as needed. Participant 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 participant until recovery of the symptoms.

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

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

Immuno-oncology (I-O) agents are associated with AEs that can differ in severity and duration than AEs caused by other therapeutic classes. Nivolumab and ipilimumab are considered immuno-oncology agents in this protocol. Early recognition and management of AEs 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 AEs:

- Gastrointestinal

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

The above algorithms are found in the nivolumab Investigator Brochure, as well as in **Appendix 4**.

### *7.4.4 Nivolumab Treatment Beyond Disease Progression*

Accumulating evidence indicates a minority of participants treated with immunotherapy may derive clinical benefit despite initial evidence of PD. Participants will be permitted to continue study treatment beyond initial RECIST 1.1 defined PD as long as the following criteria are met:

1) Investigator-assessed clinical benefit
2) Tolerance of study drug
3) Stable performance status
4) Treatment beyond progression will not delay an imminent intervention to prevent serious complications of disease progression (eg, CNS metastases)
5) Participant provides written informed consent prior to receiving additional study treatment, using an ICF describing any reasonably foreseeable risks or discomforts, or other alternative treatment options.

The decision to continue treatment beyond initial progression should be discussed with the BMS Medical Monitor and documented in the study records.

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

If the investigator feels that the participant continues to achieve clinical benefit by continuing treatment, the participant should remain on the trial and continue to receive monitoring according to the Time and Events Schedule (Section 2).

For the participants who continue study therapy beyond progression, further progression is defined as an additional 10% increase in tumor burden volume from time of initial PD. This includes an increase in the sum of all target lesions and/ or the development of new measurable lesions. Treatment should be discontinued permanently upon documentation of further disease progression.

New lesions are considered measureable at the time of initial progression if the longest diameter is at least 10 mm (except for pathological lymph nodes which must have a short axis of at least 15 mm). Any new lesion considered non-measureable at the time of initial progression may

become measureable and therefore included in the tumor burden volume if the longest diameter increases to at least 10 mm (except for pathological lymph nodes which must have a short axis of at least 15 mm).

Participants with global deterioration of health status (as determined by the investigator) who require discontinuation of treatment without objective evidence of disease progression at the time of treatment discontinuation should be reported as 'symptomatic deterioration.' Every effort should be made to document objective progression (ie, radiographic confirmation) even after discontinuation of treatment.

## 7.5 Preparation/Handling/Storage/Accountability

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

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

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

Investigational product documentation (whether supplied by BMS or not) must be maintained that includes all processes required to ensure drug is accurately administered. This includes documentation of drug storage, administration and, as applicable, storage temperatures, reconstitution, and use of required processes (eg, required diluents, administration sets).

Further guidance and information for final disposition of unused study treatment are provided in Appendix 6 (study governance).

### *7.5.1 Retained Samples for Bioavailability / Bioequivalence*

Not Applicable.

## 7.6 Treatment Compliance

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

## 7.7 Concomitant Therapy

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

The following medications are prohibited during the study (unless utilized to treat a drug-related adverse event):

- Immunosuppressive agents
- Immunosuppressive doses of systemic corticosteroids (except as stated in Section 7.7.3)

- Any concurrent anti-neoplastic therapy (ie, chemotherapy, hormonal therapy, immunotherapy, extensive, non-palliative radiation therapy, or standard or investigational agents for treatment of NSCLC)
- Any botanical preparation (eg herbal supplements or traditional Chinese medicines) intended to treat the disease under study or provide supportive care. Use of marijuana and its derivatives for treatment of symptoms related to cancer or cancer treatment are permitted if obtained by medical prescription or if its use (even without a medical prescription) has been legalized locally

### *7.7.2 Other Restrictions and Precautions*

Participants with a condition requiring systemic treatment with either corticosteroids (> 10 mg daily prednisone equivalent) or other immunosuppressive medications within 14 days of treatment assignment are excluded. Inhaled or topical steroids, and adrenal replacement steroid doses > 10 mg daily prednisone equivalent, are permitted in the absence of active autoimmune disease.

### *7.7.3 Permitted Therapy*

Participants are permitted the use of topical, ocular, intra-articular, intranasal, and inhalational corticosteroids (with minimal systemic absorption). Adrenal replacement steroid doses > 10 mg daily prednisone are permitted. A brief (less than 3 weeks) course of corticosteroids for prophylaxis (eg, contrast dye allergy) or for treatment of non-autoimmune conditions (eg, delayed-type hypersensitivity reaction caused by a contact allergen) is permitted.

Pre-enrollment palliative radiotherapy must have been completed at least 2 weeks prior to first dose and all signs of toxicity must have remitted. Lesions which have received or are anticipated to receive palliative RT may not be designated as target or non-target lesions in the baseline tumor assessment. 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.

Supportive care for disease-related symptoms may be offered to all participants on the trial. Palliative (limited-field) radiation therapy and palliative surgical resection are permitted if the following criteria are met:

1) The lesion being considered for palliative therapy is not a target lesion or a non-target lesion used for tumor assessment.
2) The case is discussed with the BMS Medical Monitor (including discussion of whether progression has occurred).

#### *7.7.3.1 Imaging Restriction and Precautions*

If a participant has a known allergy to contrast material, local prophylaxis standards may be used to obtain the assessment with contrast if at all possible, or use the alternate modality. In cases where contrast is strictly contraindicated, a non-contrast scan will suffice. Should a participant

have a contraindication for CT IV contrast, a non-contrast CT chest and a contrast enhanced MRI of the abdomen and pelvis may be obtained.

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

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

### 7.8 Treatment After the End of the Study

At the conclusion of the study, participants who continue to demonstrate clinical benefit will be eligible to receive BMS supplied study treatment for the maximum treatment duration specified in protocol (see Section 7.1.1). Study treatment will be provided via an extension of the study, a rollover study requiring approval by responsible health authority and ethics committee, or through another mechanism at the discretion of BMS.

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

## 8. DISCONTINUATION CRITERIA

### 8.1 Discontinuation from Study Treatment

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

- Participant's request to stop study treatment. Participants who request to discontinue study treatment will remain in the study and must continue to be followed for protocol specified follow-up procedures. The only exception to this is when a participant specifically withdraws

consent for any further contact with him/her or persons previously authorized by participant to provide this information

- Any clinical adverse event (AE), laboratory abnormality or intercurrent illness which, in the opinion of the investigator, indicates that continued participation in the study is not in the best interest of the participant
- 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 criteria for discontinuation (Section 8.1.1)

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

In the case of pregnancy, the investigator must immediately notify the BMS Medical Monitor/designee of this event. In the event a normal healthy female participant becomes pregnant during a clinical trial, the study treatment must be discontinued immediately. In most cases, the study treatment will be permanently discontinued in an appropriate manner (eg, dose tapering if necessary for participant safety). Please call the BMS Medical Monitor within 24 hours of awareness of the pregnancy. If the investigator determines a possible favorable benefit/risk ratio that warrants continuation of study treatment, a discussion between the investigator and the BMS Medical Monitor/designee must occur.

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

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

### *8.1.1 Nivolumab Dose Discontinuation*

Nivolumab treatment should be permanently discontinued for the following:

- Any Grade 2 drug-related uveitis, eye pain or blurred vision that does not respond to topical therapy and does not improve to Grade 1 severity within the re-treatment period OR requires systemic treatment
- Any Grade 3 non-skin, drug-related adverse event lasting > 7 days or recurs, with the following exceptions for laboratory abnormalities, drug-related uveitis, pneumonitis, bronchospasm, neurologic toxicity, hypersensitivity reactions, infusion reactions, and endocrinopathies:
  - Grade 3 drug-related uveitis, pneumonitis, bronchospasm, neurologic toxicity, hypersensitivity reaction, or infusion reaction of any duration requires discontinuation

- Grade 3 drug-related endocrinopathies, adequately controlled with only physiologic hormone replacement do not require discontinuation. Adrenal insufficiency requires discontinuation regardless of control with hormone replacement.
- Grade 3 drug-related laboratory abnormalities do not require treatment discontinuation except:
  - Grade 3 drug-related thrombocytopenia > 7 days or associated with bleeding requires discontinuation
  - Grade ≥ 3 drug-related AST, ALT or Total Bilirubin requires discontinuation*
  - Concurrent AST or ALT > 3 x ULN and total bilirubin > 2x ULN

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

- Any Grade 4 drug-related adverse event or laboratory abnormality (including but not limited to creatinine, AST, ALT, or Total Bilirubin), except for the following events which do not require discontinuation:
  - Grade 4 neutropenia ≤ 7 days
  - Grade 4 lymphopenia or leukopenia or asymptomatic amylase or lipase
  - Isolated Grade 4 electrolyte imbalances/abnormalities that are not associated with clinical sequelae and are corrected with supplementation/appropriate management within 72 hours of their onset
  - Grade 4 drug-related endocrinopathy adverse events, such as, hyper- or hypothyroidism, or glucose intolerance, which resolve or are adequately controlled with physiologic hormone replacement (corticosteroids, thyroid hormones) or glucose-controlling agents, respectively, may not require discontinuation after discussion with and approval from the BMS Medical Monitor.
- Any event that leads to delay in dosing lasting > 10 weeks from the previous dose requires discontinuation, with the following exceptions:
  - Dosing delays to allow for prolonged steroid tapers to manage drug-related adverse events are allowed.
  - Dosing delays lasting > 10 weeks from the previous dose that occur for non-drug-related reasons may be allowed if approved by the BMS medical monitor.

Prior to re-initiating treatment in a participant with a dosing delay lasting > 10 weeks, the BMS medical monitor must be consulted. Tumor assessments should continue as per protocol even if dosing is delayed. Periodic study visits to assess safety and laboratory studies should also continue every 6 weeks or more frequently if clinically indicated during such dosing delays.

Any adverse event, laboratory abnormality, or intercurrent illness which, in the judgment of the Investigator, presents a substantial clinical risk to the participant with continued nivolumab dosing.

### 8.1.2 Criteria to Resume Treatment

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

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

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

### 8.1.3 Post Study Treatment Study Follow-up

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

Participants who discontinue study treatment may continue to be followed.

## 8.2 Discontinuation from the Study

Participants who request to discontinue study treatment will remain in the study and must continue to be followed for protocol specified follow-up procedures. The only exception to this is when a participant specifically withdraws consent for any further contact with him/her or persons previously authorized by participant to provide this information.

- Participants should notify the investigator of the decision to withdraw consent from future follow-up **in writing**, whenever possible.
- The withdrawal of consent should be explained in detail in the medical records by the investigator, as to whether the withdrawal is from further treatment with study treatment only or also from study procedures and/or post treatment study follow-up, and entered on the appropriate CRF page.
- In the event that vital status (whether the participant is alive or dead) is being measured, publicly available information should be used to determine vital status only as appropriately directed in accordance with local law.
- If the participant withdraws consent for disclosure of future information, the sponsor may retain and continue to use any data collected before such a withdrawal of consent.

## 8.3 Lost to Follow-Up

- All reasonable efforts must be made to locate participants to determine and report their ongoing status. This includes follow-up with persons authorized by the participant.
- Lost to follow-up is defined by the inability to reach the participant after a minimum of **three** documented phone calls, faxes, or emails as well as lack of response by participant to one registered mail letter. All attempts should be documented in the participant's medical records.
- If it is determined that the participant has died, the site will use permissible local methods to obtain date and cause of death.
- If investigator's use of third-party representative to assist in the follow-up portion of the study has been included in the participant's informed consent, then the investigator may use a Sponsor retained third-party representative to assist site staff with obtaining participant's contact information or other public vital status data necessary to complete the follow-up portion of the study.
- The site staff and representative will consult publicly available sources, such as public health registries and databases, in order to obtain updated contact information.
- If after all attempts, the participant remains lost to follow-up, then the last known alive date as determined by the investigator should be reported and documented in the participant's medical records.

# 9. STUDY ASSESSMENTS AND PROCEDURES

- Study procedures and timing are summarized in the Schedule of Activities.
- Protocol waivers or exemptions are not allowed.
- All immediate safety concerns must be discussed with the Sponsor immediately upon occurrence or awareness to determine if the participant should continue or discontinue treatment.
- Adherence to the study design requirements, including those specified in the Schedule of Activities, is essential and required for study conduct.
- All screening evaluations must be completed and reviewed to confirm that potential participants meet all eligibility criteria before treatment assignment. The investigator will maintain a screening log to record details of all participants screened and to confirm eligibility or record reasons for screening failure, as applicable.
- Procedures conducted as part of the participant's routine clinical management (eg, blood count) and obtained before signing of informed consent may be utilized for screening or baseline purposes provided the procedure meets the protocol-defined criteria and has been performed within the timeframe defined in the Schedule of Activities.

Additional measures, including non-study laboratory tests should be performed as clinically indicated or to comply with local regulations. Laboratory toxicities (eg, suspected drug induced

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

If a participant shows pulmonary-related signs (hypoxia, fever) or symptoms (eg. dyspnea, cough, fever) consistent with possible pulmonary adverse events, the participant should be immediately evaluated to rule out pulmonary toxicity, according to the suspected pulmonary toxicity management algorithm in the BMS-936558 (nivolumab) Investigator Brochure and Appendix 4.

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

## 9.1 Efficacy Assessments

Study evaluations will take place in accordance with the Schedule of Activities (Section 2), according to RECIST 1.1 criteria.[25] High resolution CT with oral/intravenous contrast or contrast-enhanced MRI is the preferred imaging modalities for assessing radiographic tumor response. If a participant has a known allergy to contrast material, please use local prophylaxis standards to obtain the assessment with contrast if at all possible, or use the alternate modality. In cases where contrast is strictly contraindicated, a non-contrast scan will suffice. Screening assessments should be performed within 28 days of start of study treatment. Brain MRI is the preferred imaging method for evaluating CNS metastasis, and assessment is required during screening in participants with a known history of treated brain metastases. All known or suspected sites of disease (including CNS) should be assessed at screening and at subsequent assessments using the same imaging method and technique. If more than one method is used at screening, then the most accurate method according to RECIST 1.1 should be used when recording data, and should again be used for all subsequent assessments. Bone scan, PET scan, or ultrasound are not adequate for assessment of RECIST response. In selected circumstances where such modalities are the sole modality used to assess certain non-target organs, those non-target organs may be evaluated less frequently. For example, bone scans may need to be repeated only when complete response is identified in target disease or when progression in bone is suspected. Previously treated CNS metastases are not considered measurable lesions for purposes of RECIST determined response. Participants with a history of brain metastasis should have surveillance MRI approximately every 12 weeks, or sooner if clinically indicated.

### *9.1.1 Imaging Assessment for the Study*

Radiographic tumor assessments will be conducted at Week 8 (± 7 days) and every 8 weeks (± 7 days) up to 2 years or until disease progression (or until discontinuation of study therapy in patients receiving nivolumab beyond progression), lost to follow-up, or withdrawal of study consent. Participants who discontinue earlier than 2 years or completed 2 years of treatment but achieve SD/PR/CR at the end of Follow-up Visit 2 will have imaging scans every 3 months (12 weeks ± 7 days) until documented radiographic disease progression or up to a maximum duration of 5 years after first dose. Tumor assessments for all participants should continue as per protocol even if dosing is interrupted. Tumor measurements should be made by the same investigator or

radiologist for each assessment whenever possible. Assessment of partial assessment response (PR) and complete response (CR) must be confirmed at least 4 weeks following initial assessment. Changes in tumor measurements and tumor responses to guide ongoing study treatment decisions will be assessed by the investigator using RECIST 1.1 (see Appendix **3** for details of RECIST 1.1).

Central imaging assessments are not planned for this study; however, copies of all scans will be stored for possible future central analysis, if determined to be necessary by BMS. At the Sponsor's discretion, scans may be collected centrally to be reviewed by independent radiologists.

## 9.2 Adverse Events

The definitions of an AE or serious adverse event (SAE) can be found in Appendix 7.

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

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

**Contacts for SAE reporting specified in Appendix 7.**

### *9.2.1 Time Period and Frequency for Collecting AE and SAE Information*

The collection of nonserious AE information should begin at initiation of study treatment until [the follow-up contact], at the timepoints specified in the Schedule of Activities (Section 1). Nonserious AE information should also be collected from the start of a placebo lead-in period or other observational period intended to establish a baseline status for the participants.

Sections 5.6.1 and 5.6.2 in the Investigator Brochure (IB) represent the Reference Safety Information to determine expectedness of serious adverse events for expedited reporting. Following the participant'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 must report any SAE that occurs after these time periods and that is believed to be related to study drug or protocol-specified procedure.

- Medical occurrences that begin before the start of study treatment but after obtaining informed consent will be recorded on the appropriate section of the eCRF section.
- All SAEs will be recorded and reported to Sponsor or designee within 24 hours, as indicated in Appendix 7.
- The investigator will submit any updated SAE data to the sponsor within 24 hours of this being available.

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

The method of evaluating, and assessing causality of AEs and SAEs and the procedures for completing and reporting/transmitting SAE reports are provided in Appendix 7.

#### *9.2.1.1 Adverse Events of Special Interest*

Definition of immune-mediated adverse events (IMAEs)

Immune-mediated AEs are specific events (that include pneumonitis, diarrhea/colitis, hepatitis, nephritis/renal dysfunction, rash, and endocrine [adrenal insufficiency, hypothyroidism/thyroiditis, hyperthyroidism, diabetes mellitus, and hypophysitis]) for which participants received immunosuppressive medication for treatment of the event, with the exception of endocrine events (hypothyroidism/thyroiditis, hyperthyroidism, hypophysitis, diabetes mellitus, adrenal insufficiency), which are included regardless of treatment since these events are often managed without immunosuppression.

Immune-mediated AEs are specific events (or groups of PTs describing specific events) that include pneumonitis, diarrhea/colitis, hepatitis, nephritis/renal dysfunction, rash, endocrine (adrenal insufficiency, hypothyroidism/thyroiditis, hyperthyroidism, diabetes mellitus, and hypophysitis), and other specific events, considered as potential immune-mediated events by investigator, that meet the definition summarized below:

- those occurring within 100 days of the last dose
- regardless of causality
- with no clear alternate etiology based on investigator assessment, or with an immune-mediated component
- treated with immune-modulating medication (Of note, adrenal insufficiency, hypothyroidism/thyroiditis, hyperthyroidism, diabetes mellitus, and hypophysitis are considered IMAEs regardless of immune-modulating medication use, since endocrine drug reactions are often managed without immune-modulating medication).

Table 9.2.1.1-1 below provides a summary of the IMAEs category and their respective preferred terms.

**Table 9.2.1.1-1: Preferred Terms Included in Analysis of IMAEs to Support Warnings and Precautions**

| IMAE Category | PTs included under IMAE Category |
|---|---|
| Pneumonitis | Pneumonitis, interstitial lung disease |
| Diarrhea/Colitis | Diarrhea, colitis, enterocolitis |
| Hepatitis | Hepatotoxicity, hepatitis, hepatitis acute, autoimmune hepatitis, AST increased, ALT increased, bilirubin increased, ALP increased |

**Table 9.2.1.1-1: Preferred Terms Included in Analysis of IMAEs to Support Warnings and Precautions**

| IMAE Category | PTs included under IMAE Category |
|---|---|
| Adrenal insufficiency | Adrenal insufficiency |
| Hypothyroidism/Thyroiditis | Hypothyroidism, thyroiditis<br>Thyroiditis acute (collapsed with thyroiditis for frequency), Autoimmune thyroiditis (collapsed with thyroiditis for frequency) |
| Hyperthyroidism | Hyperthyroidism |
| Hypophysitis | Hypophysitis |
| Diabetes mellitus | Diabetes mellitus, diabetic ketoacidosis |
| Nephritis and renal dysfunction | Nephritis, nephritis allergic, tubulointerstitial nephritis, acute renal failure, renal failure, increased creatinine |
| Rash | Rash, rash maculopapular |

### *9.2.2 Method of Detecting AEs and SAEs*

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

Every adverse event must be assessed by the investigator with regard to whether it is considered immune-mediated. For events which are potentially immune-mediated, additional information will be collected on the participant's case report form.

### *9.2.3 Follow-up of AEs and SAEs*

- Nonserious AEs should be followed to resolution or stabilization, or reported as SAEs if they become serious (see Section Appendix 7).
- Follow-up is also required for nonserious AEs that cause interruption or discontinuation of study treatment and for those present at the end of study treatment as appropriate.
- All identified nonserious AEs must be recorded and described on the nonserious AE page of the CRF (paper or electronic). Completion of supplemental CRFs may be requested for AEs and/or laboratory abnormalities that are reported/identified during the course of the study.

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

Further information on follow-up procedures is given in Appendix 7.

### 9.2.4 Regulatory Reporting Requirements for SAEs

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

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

### 9.2.5 Pregnancy

If, following initiation of the study treatment, it is subsequently discovered that a participant is pregnant or may have been pregnant at the time of study exposure, including during at least 5 half-lives after product administration, the investigator must immediately notify the BMS Medical Monitor/designee of this event and complete and forward a Pregnancy Surveillance Form to BMS Designee within 24 hours of awareness of the event and in accordance with SAE reporting procedures described in Appendix 7.

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

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

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

### 9.2.6 Laboratory Test Result Abnormalities

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

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

- Any laboratory test result abnormality that required the participant to receive specific corrective therapy

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

### *9.2.7 Potential Drug Induced Liver Injury (DILI)*

Wherever possible, timely confirmation of initial liver-related laboratory abnormalities should occur prior to the reporting of a potential DILI event. All occurrences of potential DILIs, meeting the defined criteria, must be reported as SAEs (see Section 9.2 and Appendix 7 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.

### *9.2.8 Other Safety Considerations*

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

## 9.3 Overdose

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

## 9.4 Safety

Planned time points for all safety assessments are listed in the Schedule of Activities. Some of the assessments referred to in this protocol may not be captured as data in the eCRF. They are intended to be used as safety monitoring by the treating physician. Additional testing or assessments may be performed as clinically necessary or where required by institutional or local regulations."

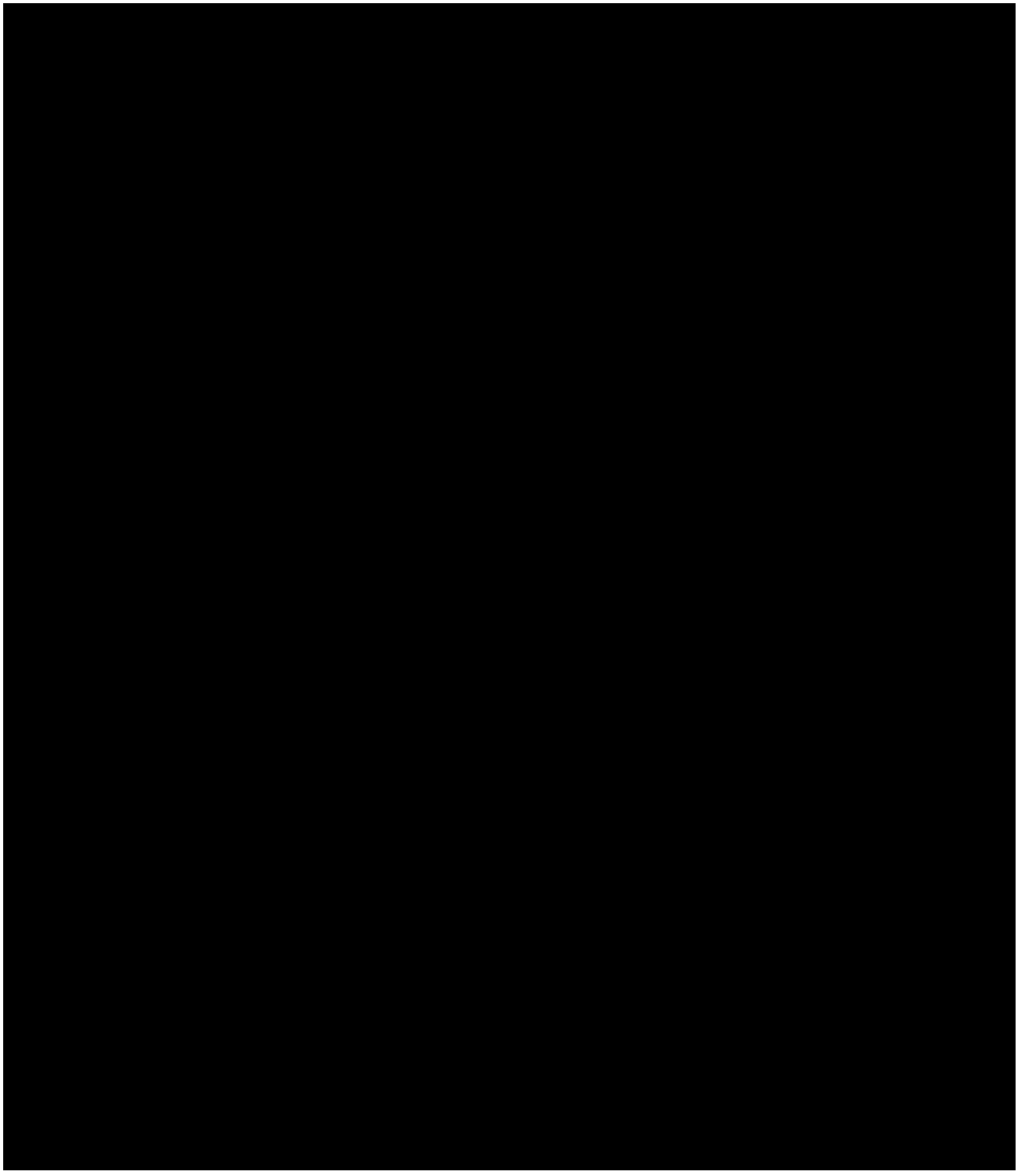
### *9.4.1 Clinical Safety Laboratory Assessments*

Investigators must document their review of each laboratory safety report.

Please refer to the Schedule of Activities in Section 2 for details regarding required laboratory tests.

### 9.4.2 Imaging Safety Assessment

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



[redacted]

## 9.6 Pharmacodynamics

Not applicable.

## 9.7 Pharmacogenomics

Not applicable.

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

## 9.9 Health Economics OR Medical Resource Utilization and Health Economics

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

# 10. STATISTICAL CONSIDERATIONS

## 10.1 Sample Size Determination

Approximately 200 participants will be enrolled in order to treat up to 120 participants. This number of treated participants was chosen to provide descriptive analysis to estimate incidence rate of high-grade (Grades 3-4 or Grade 5), drug-related, select AEs and rate of immune-mediated AEs in all treated participants with nivolumab alternate dosing schedule. Overall, the safety profile of nivolumab monotherapy is manageable and generally consistent across completed and ongoing clinical trials with no MTD reached at any dose tested up to 10 mg/kg. Most AEs were low-grade (Grade 1 to 2) with relatively few related high-grade (Grades 3 to 4) AEs. Rates of high-grade (Grades 3-4 or Grade 5), drug-related, select AEs and rate of immune-mediated AEs by category observed in 2L NSCLC CheckMate 063, 017 and 057 were low and <7%. Nivolumab monotherapy has been extensively studied in multiple tumor types, including melanoma, NSCLC, RCC, cHL, Head and Neck, and UC with body weight normalized dosing (mg/kg). PPK modelling predicted median and 95th percentile of exposures are maintained below those in 10 mg/kg every 2 weeks,[26] which was established as a safe and well-tolerable dose across multiple tumor types. There was no clinical meaningful relationship between nivolumab exposure or body weight and frequency or severity of AEs. Therefore, a 480 mg Q4W is expected to be safe and tolerable in those patients.

Table 10.1-1 shows the 95% Confidence Intervals for different AE rates for a sample size of 120 participants.

**Table 10.1-1: 95% Confidence Intervals for different AE rates for a sample size of 120**

| Number of participants with AE (%) | Exact 95% CI around proportion |
|---|---|
| 0/120 (0%) | 0%-3.0% |
| 1/120 (0.8%) | 0.8%-4.6% |
| 2/120 (1.7%) | 0.2%-5.9% |
| 3/120 (2.5%) | 0.5%-7.1% |
| 4/120 (3.3%) | 0.9%-8.3% |
| 5/120 (4.2%) | 1.4%-9.5% |
| 6/120 (5.0%) | 1.9%-10.6% |

With a sample size of 120, the chance of observing at least one participant with the event is greater than 80% for true probabilities of events higher than 1.3%.

- If true probability of event is 1%, the chance of observing at least 1 participant with event among 120 treated participants is 70%.
- If true probability of event is 2%, the chance of observing at least 1 participant with event among 120 treated participants is 91%.

Precision of secondary endpoint ORR, when sample size is 120, is provided in Table 10.1-2. If 24 responders are observed among the 120 treated participants (ORR =20%), the 2-sided exact 95% CI will be (13.2%, 28.3%). It is assumed that response rate would be similar to ORR observed in 2L NSCLC CheckMate017 and 057. With a target ORR = 19 %, this study has approximately 90% of power to exclude a 9% ORR (the null hypothesis) with a 0.05 two-sided significance level. The threshold response rate set at 9.0% is based on the response rate of docetaxel reported by Hanna et al[27]. as well as Japanese phase 2 ONO-4538-05 and 06 study.

**Table 10.1-2: Precision of Secondary Endpoint of ORR**

| Number of responders (%) | Exact 95% CI around ORR |
|---|---|
| 10/120 (8.3%) | 7.1-24.7 |
| 11/120 (9.2) | 8.1-26.4 |
| 18/120 (15%) | 9.1%-22.7% |
| 19/120 (15.8%) | 9.8%-23.6% |
| 20/120 (16.7%) | 10.5%-24.6% |
| 21/120 (17.5%) | 11.2%-25.5% |
| 22/120 (18.3%) | 11.9%-26.4% |
| 23/120 (19.2%) | 12.6%-27.4% |
| 24/120 (20.0%) | 13.2%- 28.3% |

## 10.2 Populations for Analyses

For purposes of analysis, the following populations are defined:

| Population | Description |
|---|---|
| Enrolled Participants: | All participants who signed an informed consent form and were registered into the IVRS. |
| Treated Participants: | All participants who received at least 1 dose of nivolumab. |

## 10.3 Statistical Analyses

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

### *10.3.1 Efficacy Analyses*

| Endpoint | Statistical Analysis Methods |
|---|---|
| Primary | NA |
| Secondary | • The PFS/OS curve will be estimated using the Kaplan-Meier (KM) product-limit method. Two-sided 95% confidence intervals for median PFS/OS will be computed by Klein and Moeschberger method. PFS/OS rates at 6, 12, 18, 24, 36, 48, and 60 months will be estimated using KM estimates on the PFS/OS curve. Minimum follow-up must be longer than or equal to the time point to generate the rates. Associated two sided 95% CIs will be calculated using the Greenwood's formula. The status of participants who are censored in the PFS/OS Kaplan Meier analysis will be tabulated.<br>• BOR will be summarized by response category. Objective Response Rate (ORR) and 95% exact CI will be calculated using Clopper-Pearson method. Duration of response will be estimated using KM product-limit method for participants who achieve confirmed PR or CR Two-sided 95% confidence intervals for median DOR will be computed by Klein and Moeschberger method. |
| [redacted] | |

### *10.3.2 Safety Analyses*

| Endpoint | Statistical Analysis Methods |
|---|---|
| Primary | • Incidence of high-grade (worst CTC Grade 3, 4 or 5), drug-related, select AEs by category (subcategory for endocrine events). The select AE consist of a list of preferred terms grouped by specific category (eg, pulmonary events, gastrointestinal events categories) and by subcategory (eg, thyroid disorders, diabetes, pituitary, adrenal disorders subcategories). These categories and subcategories are defined by the Sponsor, and the list that is most current at the time of analysis will be used. Also changes may be made to this list with each new version of MedDRA. Drug-related AEs are those events with relationship to study drug "Related," as recorded on the CRF. If the relationship to study drug is missing, the AE will be considered as drug-related. |

| Endpoint | Statistical Analysis Methods |
|---|---|
| | • Select AEs will be summarized for each category/subcategory using a 30-day safety window and repeated using the 100-day safety window (sensitivity analysis) (refer to core safety SAP).<br>• Overall summary of Grades 3 to 5 drug-related, select AEs by worst CTC grade presented by Category or Subcategory / PT.<br>• Overall summary of drug-related select AEs by worst CTC grade presented by Category or Subcategory / PT (any grade, Grades 3-4, Grade 5).<br>• Overall summary of any select AEs by worst CTC grade presented by Category or Subcategory/PT (any grade, Grades 3-4, Grade 5).<br>• Overall summary of any serious select AEs by worst CTC grade presented by Category or Subcategory /PT (any grade, Grades 3-4, Grade 5).<br>• Overall summary of drug-related serious select AEs by worst CTC grade presented by Category or Subcategory /PT (any grade, Grades 3-4, Grade 5).<br>• Overall summary of any select AEs leading to discontinuation by worst CTC grade presented by Category or Subcategory /PT (any grade, Grades 3-4, Grade 5).<br>• Overall summary of drug-related, select AEs leading to discontinuation by worst CTC Grade presented by Category or Subcategory /PT (any grade, Grades 3-4, Grade 5).<br>• Summary of frequency of unique select AEs<br><br>Time-to onset of Grades 3 to 5 drug-related, select AE (for participants who experienced at least 1 select AE) will be summarized for each category/subcategory of select AEs. Time to onset of select AE for a specific category was defined as the time between the day of the first dose of study treatment and the onset date of the earliest select AE in this category.<br>Time to resolution of Grade 3 to 5 drug-related select AE will be summarized separately for each category/subcategory. Time-to resolution analyses are restricted to treated participants who experienced the specific events. The following summary statistics will be reported: percentage of participants who experienced the specific events, percentage of participants with resolution of the longest select AE, median time-to resolution along with 95% CI (derived from Kaplan-Meier estimation) and ranges.<br><br>• Incidence of immune-mediated AEs by Category. Immune-mediated AEs are AEs consistent with an immune-mediated mechanism or immune-mediated component for which non-inflammatory etiologies (eg, infection or tumor progression) have been ruled out (eg, pneumonitis, diarrhea/colitis, hepatitis, adrenal insufficiency, hypothyroidism, rash). IMAEs can include events with an alternate etiology which were |

| Endpoint | Statistical Analysis Methods |
|---|---|
| | exacerbated by the induction of autoimmunity. Information supporting the assessment will be collected on the participant's case report form.<br>IMAEs will be summarized for each category/subcategory using a 100-day safety window and repeated using the 30-day safety window (sensitivity analysis) (refer to core safety SAP).<br>• Summary of Immune-Mediated Adverse Events by Worst CTC Grade (Any Grade, Grades 3-4, Grade 5).<br>• Summary of Serious immune-mediated AEs Leading to Discontinuation by Worst CTC Grade, by Category.<br>• Summary of Immune-Mediated AEs Leading to Discontinuation by Worst CTC Grade, by Category.<br>• Summary of Any Immune-Mediated AEs Leading to Dose Delay or Reduction by Worst CTC Grade, by category.<br>• Time-to onset of IMAE (for participants who experienced at least 1 IMAE) will be summarized for each category/subcategory of IMAEs.<br>• Time to resolution of IMAEs will be summarized separately for each category/subcategory, for participants who experienced at least 1 immune-mediated AE.<br><br>Select AEs and IMAEs analyses will include AEs with an onset date and time on or after the date and time of the first dose of study treatment (or with an onset date on or after the day of first dose of study treatment if time is not collected or is missing). For participants who are off study treatment, AEs will be included if an event occurred within a safety window of 30/100 days after the last dose of study treatment. No "subtracting rule" will be applied when an AE occurs both pre-treatment and post-treatment with the same preferred term and grade. |
| Secondary | Not Applicable |
| [redacted] | |

[redacted]

[redacted]

### 10.3.5 Interim Analyses

Interim analyses may be performed.

### 10.3.6 Final Analyses

The final analysis will be performed when all participants have completed the study treatment. Data cuts for publication purposes earlier than all participants completing the study are possible.

The Statistical Analysis Plan will further describe the planned analyses.

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# 12. APPENDICES

## APPENDIX 1 ABBREVIATIONS AND TRADEMARKS

| Term | Definition |
|---|---|
| AE | adverse event |
| ALT | alanine aminotransferase |
| [redacted] | |
| AST | aspartate aminotransferase |
| [redacted] | |
| BMS | Bristol-Myers Squibb |
| BP | blood pressure |
| BUN | blood urea nitrogen |
| [redacted] | |
| $Ca^{++}$ | calcium |
| [redacted] | |
| CBC | complete blood count |
| [redacted] | |
| CFR | Code of Federal Regulations |
| CI | confidence interval |
| [redacted] | |
| CNS | Central nervous system |
| CRF | Case Report Form, paper or electronic |
| CR | Complete response |
| C1W1D1 | Cycle 1 Week 1 Day 1 |
| DMC | Data monitoring committee |
| DOR | Duration of response |
| ECG | electrocardiogram |
| eCRF | Electronic Case Report Form |
| EDC | Electronic Data Capture |
| [redacted] | |
| FDA | Food and Drug Administration |

| Term | Definition |
|---|---|
| FSH | follicle stimulating hormone |
| GCP | Good Clinical Practice |
| [redacted] | |
| HBsAg | hepatitis B surface antigen |
| [redacted] | |
| HCV | hepatitis C virus |
| HIV | Human Immunodeficiency Virus |
| HR | heart rate |
| [redacted] | |
| ICH | International Conference on Harmonisation |
| IEC | Independent Ethics Committee |
| IMAE | Immune-mediated adverse event |
| IMP | investigational medicinal products |
| IND | Investigational New Drug Exemption |
| I-O | Immuno-oncology |
| IRB | Institutional Review Board |
| IRT | Interactive Response Technology |
| IV | intravenous |
| $K^+$ | potassium |
| kg | kilogram |
| [redacted] | |
| LDH | lactate dehydrogenase |
| mg | milligram |
| [redacted] | |
| min | minute |
| mL | milliliter |
| MTD | maximum tolerated dose |
| [redacted] | |

| Term | Definition |
|---|---|
| N | number of subjects or observations |
| N/A | not applicable |
| [redacted] | |
| NSCLC | Non-small cell lung cancer |
| ORR | Overall response rate |
| [redacted] | |
| PD | Progressive diseases |
| PFS | Progression-free survival |
| [redacted] | |
| PR | Partial response |
| [redacted] | |
| SAE | serious adverse event |
| SOP | Standard Operating Procedures |
| ULN | Upper limit of normal |
| [redacted] | |
| WBC | white blood cell |
| [redacted] | |
| WOCBP | women of childbearing potential |

# APPENDIX 2 PERFORMANCE STATUS SCALES

| STATUS | SCALES | | STATUS |
|---|---|---|---|
| | KARNOFSKY | ZUBROD-ECOG-WHO | |
| Normal, no complaints | 100 | 0 | Normal activity |
| Able to carry on normal activities Minor signs or symptoms of disease | 90 | 0 | Symptoms, but fully ambulatory |
| Normal activity with effort | 80 | 1 | |
| Cares for self. Unable to carry on normal activity or to do active work | 70 | 1 | Symptomatic, but in bed < 50% of the day. |
| Requires occasional assistance, but able to care for most of his needs | 60 | 2 | |
| Requires considerable assistance and frequent medical care | 50 | 2 | Needs to be in bed > 50% of the day, but not bedridden |
| Disabled. Requires special care and assistance | 40 | 3 | |
| Severely disabled. Hospitalization indicated though death non imminent | 30 | 3 | Unable to get out of bed |
| Very sick. Hospitalization necessary. Active supportive treatment necessary | 20 | 4 | |
| Moribund | 10 | 4 | |
| Dead | 0 | 5 | Dead |

# APPENDIX 3 RECIST 1.1 GUIDELINES

## 1. EVALUATION OF LESIONS

At baseline, tumor lesions/lymph nodes will be categorized measurable or non-measurable as follows:

### 1.1 Measurable

Tumor lesions: Must be accurately measured in at least one dimension (longest diameter in the plane of measurement is to be recorded) with a minimum size of:

1. 10 mm by CT scan (CT scan slice thickness no greater than 5 mm)
2. 10 mm caliper measurement by clinical exam (lesions which cannot be accurately measured with calipers should be recorded as non-measurable)
3. 20 mm by chest x-ray

*Malignant lymph nodes:* To be considered pathologically enlarged and measurable, a lymph node must be ≥ 15 mm in short axis when assessed by CT scan (CT scan slice thickness recommended to be no greater than 5 mm).

Lymph nodes merit special mention since they are normal anatomical structures which may be visible by imaging even if not involved by tumor. Pathological nodes which are defined as measurable and may be identified as target lesions must meet the criterion of a short axis of ≥ 15 mm by CT scan. Only the short axis of these nodes will contribute to the baseline sum. The short axis of the node is the diameter normally used by radiologists to judge if a node is involved by solid tumor. Nodal size is normally reported as two dimensions in the plane in which the image is obtained (for CT scan this is almost always the axial plane; for MRI the plane of acquisition may be axial, saggital or coronal). The smaller of these measures is the short axis. For example, an abdominal node which is reported as being 20 mm x 30 mm has a short axis of 20 mm and qualifies as a malignant, measurable node. In this example, 20 mm should be recorded as the node measurement. All other pathological nodes (those with short axis ≥ 10 mm but < 15 mm) should be considered non-target lesions. Nodes that have a short axis < 10 mm are considered non-pathological and should not be recorded or followed.

### 1.2 Non-Measurable

All other lesions are considered non-measurable, including small lesions (longest diameter < 10mm or pathological lymph nodes with ≥ 10 to < 15 mm short axis) 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.

## 2. BASELINE DOCUMENTATION OF 'TARGET' AND 'NON-TARGET' LESIONS

When more than one measurable lesion is present at baseline all lesions up to a maximum of five lesions total (and a maximum of two lesions per organ) representative of all involved organs should be identified as target lesions and will be recorded and measured at baseline (this means in instances where patients have only one or two organ sites involved a maximum of two and four lesions respectively will be recorded).

Target lesions should be selected on the basis of their size (lesions with the longest diameter), be representative of all involved organs, but in addition should be those that lend themselves to reproducible repeated measurements. It may be the case that, on occasion, the largest lesion does not lend itself to reproducible measurement in which circumstance the next largest lesion which can be measured reproducibly should be selected.

A sum of the diameters (longest for non-nodal lesions, short axis for nodal lesions) for all target lesions will be calculated and reported as the baseline sum diameters. If lymph nodes are to be included in the sum, then as noted above, only the short axis is added into the sum. The baseline sum diameters will be used as reference to further characterize any objective tumor regression in the measurable dimension of the disease.

All other lesions (or sites of disease) including pathological 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' (more details to follow). In addition, it is possible to record multiple nontarget lesions involving the same organ as a single item on the case record form (eg, 'multiple enlarged pelvic lymph nodes' or 'multiple liver metastases').

## 3. RESPONSE CRITERIA

### 3.1 Evaluation of Target Lesions

**Complete Response (CR):** Disappearance of all target lesions. Any pathological lymph nodes (whether target or non-target) must have reduction in short axis to < 10 mm.

**Partial Response (PR):** At least a 30% decrease in the sum of diameters of target lesions, taking as reference the baseline sum diameters.

**Progressive Disease (PD):** At least a 20% increase in the sum of diameters of target lesions, taking as reference the smallest sum on study (this includes the baseline sum if that is the smallest on study). In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 5 mm. (Note: the appearance of one or more new lesions is also considered progression).

**Stable Disease (SD):** Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as reference the smallest sum diameters while on study.

### 3.1.1 Special Notes on the Assessment of Target Lesions

#### 3.1.1.1 Lymph nodes

Lymph nodes identified as target lesions should always have the actual short axis measurement recorded (measured in the same anatomical plane as the baseline examination), even if the nodes regress to below 10 mm on study. This means that when lymph nodes are included as target lesions, the 'sum' of lesions may not be zero even if complete response criteria are met, since a normal lymph node is defined as having a short axis of < 10 mm. Case report forms or other data collection methods may therefore be designed to have target nodal lesions recorded in a separate section where, in order to qualify for CR, each node must achieve a short axis < 10 mm. For PR, SD and PD, the actual short axis measurement of the nodes is to be included in the sum of target lesions.

#### 3.1.1.2 Target lesions that become 'too small to measure'

While on study, all lesions (nodal and non-nodal) recorded at baseline should have their actual measurements recorded at each subsequent evaluation, even when very small (eg, 2 mm). However, sometimes lesions or lymph nodes which are recorded as target lesions at baseline become so faint on CT scan that the radiologist may not feel comfortable assigning an exact measure and may report them as being 'too small to measure'. When this occurs it is important that a value be recorded on the case report form. If it is the opinion of the radiologist that the lesion has likely disappeared, the measurement should be recorded as 0 mm. If the lesion is believed to be present and is faintly seen but too small to measure, a default value of 5 mm should be assigned (Note: It is less likely that this rule will be used for lymph nodes since they usually have a definable size when normal and are frequently surrounded by fat such as in the retroperitoneum; however, if a lymph node is believed to be present and is faintly seen but too small to measure, a default value of 5 mm should be assigned in this circumstance as well). This default value is derived from the 5 mm CT slice thickness (but should not be changed with varying CT slice thickness). The measurement of these lesions is potentially non-reproducible, therefore providing this default value will prevent false responses or progressions based upon measurement error. To reiterate, however, if the radiologist is able to provide an actual measure, that should be recorded, even if it is below 5 mm.

#### 3.1.1.3 Lesions that split or coalesce on treatment

When non-nodal lesions 'fragment', the longest diameters of the fragmented portions should be added together to calculate the target lesion sum. Similarly, as lesions coalesce, a plane between them may be maintained that would aid in obtaining maximal diameter measurements of each individual lesion. If the lesions have truly coalesced such that they are no longer separable, the vector of the longest diameter in this instance should be the maximal longest diameter for the 'coalesced lesion'.

## 3.2 Evaluation of Non-Target Lesions

This section provides the definitions of the criteria used to determine the tumor response for the group of non-target lesions. While some non-target lesions may actually be measurable, they need not be measured and instead should be assessed only qualitatively at the time points specified in the protocol.

- **Complete Response (CR):** Disappearance of all non-target lesions and normalization of tumor marker level. All lymph nodes must be non-pathological in size (< 10mm short axis).
- **Non-CR/Non-PD:** Persistence of one or more non-target lesion(s) and/or maintenance of tumor marker level above the normal limits.
- **Progressive Disease (PD):** Unequivocal progression (see comments below) of existing non-target lesions. (Note: the appearance of one or more new lesions is also considered progression).

### 3.2.1 Special Notes on Assessment of Progression of Non-Target Disease

The concept of progression of non-target disease requires additional explanation as follows:

#### 3.2.1.1 When the patient also has measurable disease

In this setting, to achieve 'unequivocal progression' on the basis of the non-target disease, there must be an overall level of substantial worsening in non-target disease such that, even in presence of SD or PR in target disease, the overall tumor burden has increased sufficiently to merit discontinuation of therapy (see examples in Appendix 2 and further details below). A modest 'increase' in the size of one or more non-target lesions is usually not sufficient to qualify for unequivocal progression status. The designation of overall progression solely on the basis of change in non-target disease in the face of SD or PR of target disease will therefore be extremely rare.

#### 3.2.1.2 When the patient has only non-measurable disease

This circumstance arises in some trials when it is not a criterion of study entry to have measurable disease. The same general concepts apply here as noted above, however, in this instance there is no measurable disease assessment to factor into the interpretation of an increase in non-measurable disease burden. Because worsening in non-target disease cannot be easily quantified (by definition: if all lesions are truly non-measurable) a useful test that can be applied when assessing patients for unequivocal progression is to consider if the increase in overall disease burden based on the change in non-measurable disease is comparable in magnitude to the increase that would be required to declare PD for measurable disease: ie, an increase in tumor burden representing an additional 73% increase in 'volume' (which is equivalent to a 20% increase diameter in a measurable lesion). Examples include an increase in a pleural effusion from 'trace' to 'large', an increase in lymphangitic disease from localized to widespread, or may be described in protocols as 'sufficient to require a change in therapy'. If 'unequivocal progression' is seen, the patient should be considered to have had overall PD at that point. While it would be ideal to have objective criteria to apply to non-measurable disease, the very nature of that disease makes it impossible to do so; therefore the increase must be substantial.

### 3.2.2 New Lesions

The appearance of new malignant lesions denotes disease progression; therefore, some comments on detection of new lesions are important. There are no specific criteria for the identification of new radiographic lesions; however, the finding of a new lesion should be unequivocal: ie, not attributable to differences in scanning technique, change in imaging modality or findings thought to represent something other than tumor (for example, some 'new' bone lesions may be simply

healing or flare of pre-existing lesions). This is particularly important when the patient's baseline lesions show partial or complete response. For example, necrosis of a liver lesion may be reported on a CT scan report as a 'new' cystic lesion, which it is not.

A lesion identified on a follow-up study in an anatomical location that was not scanned at baseline is considered a new lesion and will indicate disease progression. An example of this is the patient who has visceral disease at baseline and while on study has a CT or MRI brain ordered which reveals metastases. The patient's brain metastases are considered to be evidence of PD even if he/she did not have brain imaging at baseline.

If a new lesion is equivocal, for example because of its small size, continued therapy and follow-up evaluation will clarify if it represents truly new disease. If repeat scans confirm there is definitely a new lesion, then progression should be declared using the date of the initial scan. While FDG-PET response assessments need additional study, it is sometimes reasonable to incorporate the use of FDG-PET scanning to complement CT scanning in assessment of progression (particularly possible 'new' disease). New lesions on the basis of FDG-PET imaging can be identified according to the following algorithm:

1. Negative FDG-PET at baseline, with a positive FDG-PET at follow-up is a sign of PD based on a new lesion.
2. No FDG-PET at baseline and a positive FDG-PET at follow-up: If the positive FDG-PET at follow-up corresponds to a new site of disease confirmed by CT, this is PD. If the positive FDG-PET at follow-up is not confirmed as a new site of disease on CT, additional follow-up CT scans are needed to determine if there is truly progression occurring at that site (if so, the date of PD will be the date of the initial abnormal FDG-PET scan). If the positive FDG-PET at follow-up corresponds to a pre-existing site of disease on CT that is not progressing on the basis of the anatomic images, this is not PD.

## 3.3 Response Assessment

### *3.3.1 Evaluation of Best Overall Response*

The best overall response is the best response recorded from the start of the study treatment until the end of treatment taking into account any requirement for confirmation. The patient's best overall response assignment will depend on the findings of both target and non-target disease and will also take into consideration the appearance of new lesions. Furthermore, depending on the nature of the study and the protocol requirements, it may also require confirmatory measurement.

### *3.3.2 Time Point Response*

It is assumed that at each protocol specified time point, a response assessment occurs. Table 3.3.2-1 provides a summary of the overall response status calculation at each time point for patients who have measurable disease at baseline. When patients have non-measurable (therefore non-target) disease only, Table 3.3.2-2 is to be used.

| Table 3.3.2-1: Time Point Response: Patients With Target (+/- Non-Target) Disease | | | |
|---|---|---|---|
| **Target Lesions** | **Non-Target Lesions** | **New Lesions** | **Overall Response** |
| CR | CR | No | CR |
| CR | Non-CR/non-PD | No | PR |
| CR | Not evaluated | No | PR |
| PR | Non-PD or not all evaluated | No | PR |
| SD | Non-PD or not all evaluated | No | SD |
| Not all evaluated | Non-PD | No | NE |
| PD | Any | Yes or No | PD |
| Any | PD | Yes or No | PD |
| Any | Any | Yes | PD |

CR = complete response, PR = partial response, SD = stable disease, PD = progressive disease and NE = inevaluable

| Table 3.3.2-2: Time Point Response: Patients with Non-target Disease Only | | |
|---|---|---|
| **Non-Target Lesions** | **New Lesions** | **Overall Response** |
| CR | No | CR |
| Non-CR/non-PD | No | Non-CR/non-PD[a] |
| Not all evaluated | No | NE |
| Unequivocal PD | Yes or No | PD |
| Any | Yes | PD |
| CR = complete response, PD = progressive disease and NE = inevaluable | | |

[a] Non-CR/non-PD is preferred over SD for non-target disease since SD is increasingly used as endpoint for assessment of efficacy in some trials so to assign this category when no lesions can be measured is not advised.

### *3.3.3 Best Overall Response*

Best response determination of complete or partial response requires confirmation: Complete or partial responses may be claimed only if the criteria for each are met at a subsequent time point of ≥ 4 weeks later. In this circumstance, the best overall response can be interpreted as in Table 3.3.3-1.

**Special note on response assessment:** When nodal disease is included in the sum of target lesions and the nodes decrease to 'normal' size (< 10 mm), they may still have a measurement reported on scans. This measurement should be recorded even though the nodes are normal in order not to

overstate progression should it be based on increase in size of the nodes. As noted earlier, this means that patients with CR may not have a total sum of 'zero' on the case report form (CRF).

**Table 3.3.3-1: Best Overall Response (Confirmation of CR&PR Required)**

| Overall Response First Time Point | Overall Response Subsequent Time Point | BEST Overall Response |
|---|---|---|
| CR | CR | CR |
| CR | PR | SD, PD OR PR[a] |
| CR | SD | SD provided minimum criteria for SD duration[b] met, otherwise, PD |
| CR | PD | SD provided minimum criteria for SD duration[b] met, otherwise, PD |
| CR | NE | SD provided minimum criteria for SD duration[b] met, otherwise, NE |
| PR | CR | PR |
| PR | PR | PR |
| PR | SD | SD |
| PR | PD | SD provided minimum criteria for SD duration[b] met, otherwise, PD |
| PR | NE | SD provided minimum criteria for SD duration [b]met, otherwise, NE |
| NE | NE | NE |

CR = complete response, PR = partial response, SD = stable disease, PD = progressive disease, and NE = inevaluable

[a] If a CR is truly met at first time point, then any disease seen at a subsequent time point, even disease meeting PR criteria relative to baseline, makes the disease PD at that point (since disease must have reappeared after CR). Best response would depend on whether minimum duration for SD was met. However, sometimes 'CR' may be claimed when subsequent scans suggest small lesions were likely still present and in fact the patient had PR, not CR at the first time point. Under these circumstances, the original CR should be changed to PR and the best response is PR.

[b] Minimum criteria for SD duration is 6 weeks.

### *3.3.4 Confirmation Scans*

Verification of Response: To be assigned a status of CR or PR, changes in tumor measurements must be confirmed by consecutive repeat assessments that should be performed no less than 28 days after the criteria for response are first met. For this study, the next scheduled tumor assessment can meet this requirement.

Verification of Progression: Progression of disease should be verified in cases where progression is equivocal. If repeat scans confirm PD, then progression should be declared using the date of the

initial scan. If repeat scans do not confirm PD, then the subject is considered to not have progressive disease.

## APPENDIX 4 MANAGEMENT ALGORITHIMS

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.

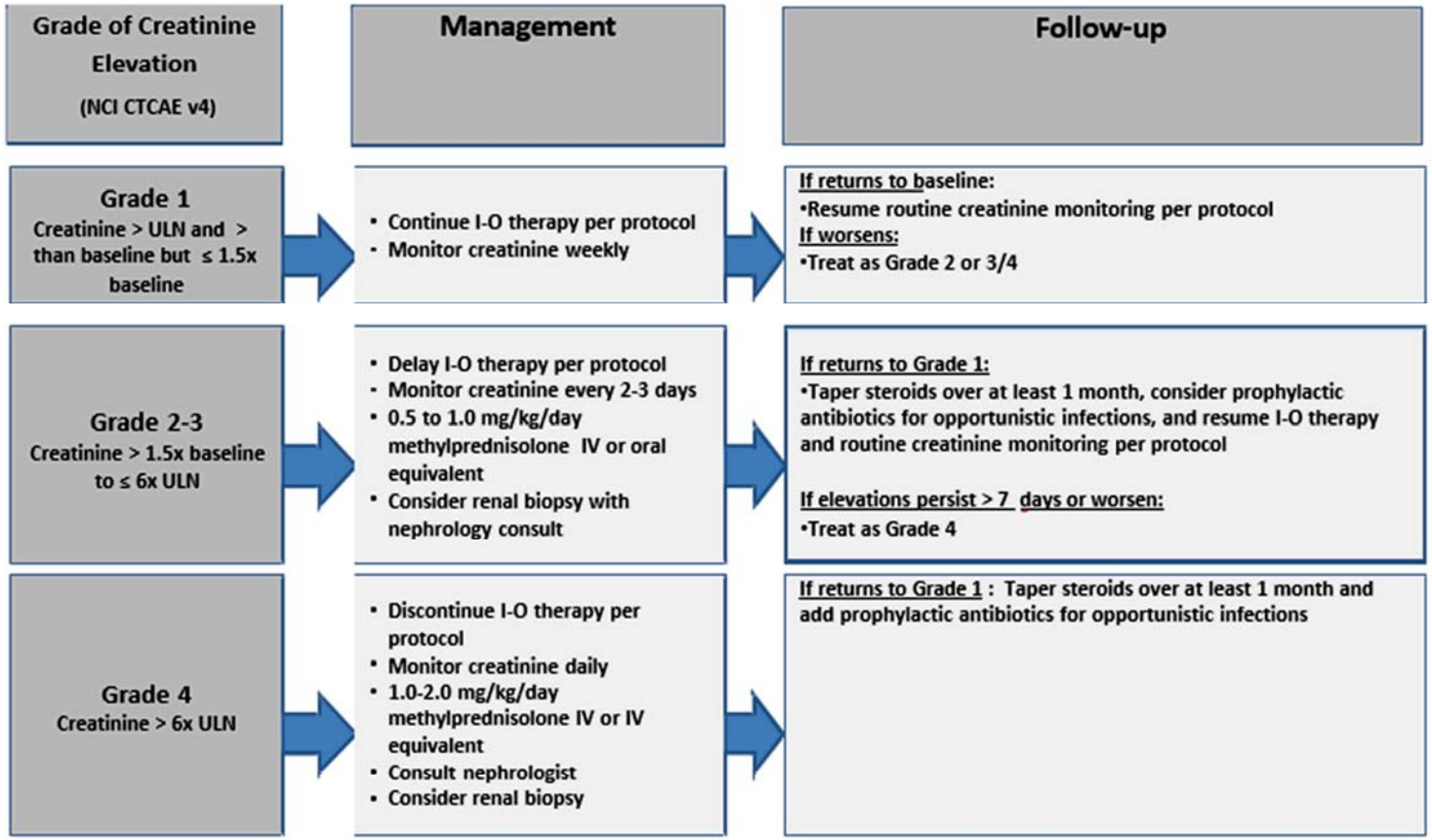
| Grade of Diarrhea/ Colitis (NCI CTCAE v4) | Management | Follow-up |
|---|---|---|
| **Grade 1**<br>Diarrhea:< 4 stools/day over baseline;<br>Colitis: asymptomatic | • Continue I-O therapy per protocol<br>• Symptomatic treatment | • Close monitoring for worsening symptoms.<br>• Educate patient to report worsening immediately<br>If worsens:<br>• Treat as Grade 2 or 3/4 |
| **Grade 2**<br>Diarrhea: 4-6 stools per day over baseline; IV fluids indicated <24 hrs; not interfering with ADL<br>Colitis: abdominal pain; blood in stool | • Delay I-O therapy per protocol<br>• Symptomatic treatment | If improves to grade 1:<br>• Resume I-O therapy per protocol<br>If persists > 5-7 days or recur:<br>• 0.5-1.0 mg/kg/day methylprednisolone or oral equivalent<br>• When symptoms improve to grade 1, taper steroids over at least 1 month, consider prophylactic antibiotics for opportunistic infections, and resume I-O therapy per protocol.<br>If worsens or persists > 3-5 days with oral steroids:<br>• Treat as grade 3/4 |
| **Grade 3-4**<br>Diarrhea (G3): ≥7 stools per day over baseline; incontinence; IV fluids ≥24 hrs; interfering with ADL<br>Colitis (G3): severe abdominal pain, medical intervention indicated, peritoneal signs<br>G4: life-threatening, perforation | • Discontinue I-O therapy per protocol<br>• 1.0 to 2.0 mg/kg/day methylprednisolone IV or IV equivalent<br>• Add prophylactic antibiotics for opportunistic infections<br>• Consider lower endoscopy | If improves:<br>• Continue steroids until grade 1, then taper over at least 1 month<br>If persists > 3-5 days, or recurs after improvement:<br>• Add infliximab 5 mg/kg (if no contraindication). Note: Infliximab should not be used in cases of perforation or sepsis |

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

25-Jun-2019

# Renal Adverse Event Management Algorithm

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

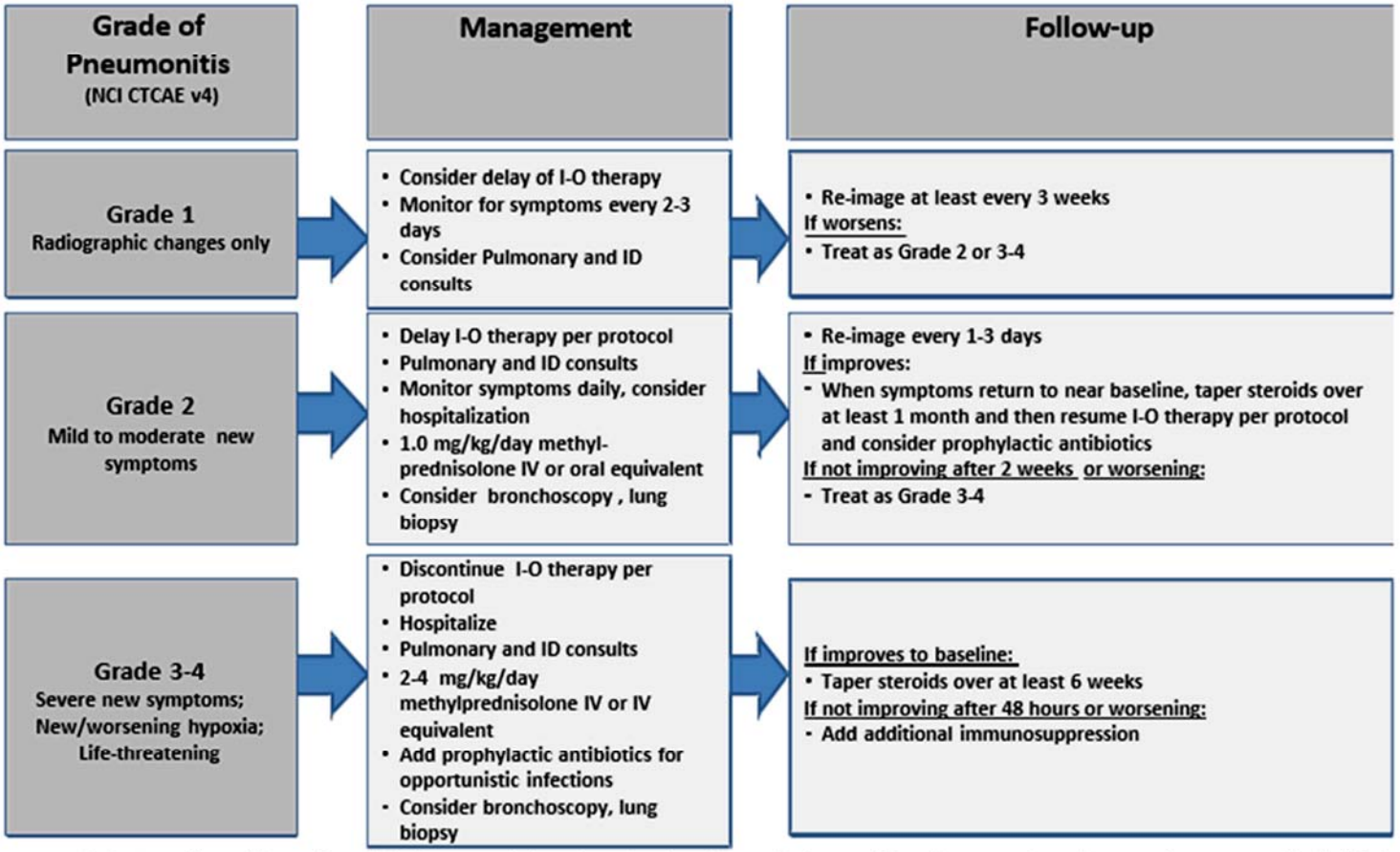



Patients on IV steroids may be switched to an equivalent dose of oral corticosteroids (e.g. prednisone) at start of tapering or earlier, once sustained clinical improvement is observed. Lower bioavailability of oral corticosteroids should be taken into account when switching to the equivalent dose of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

25-Jun-2019

# 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.

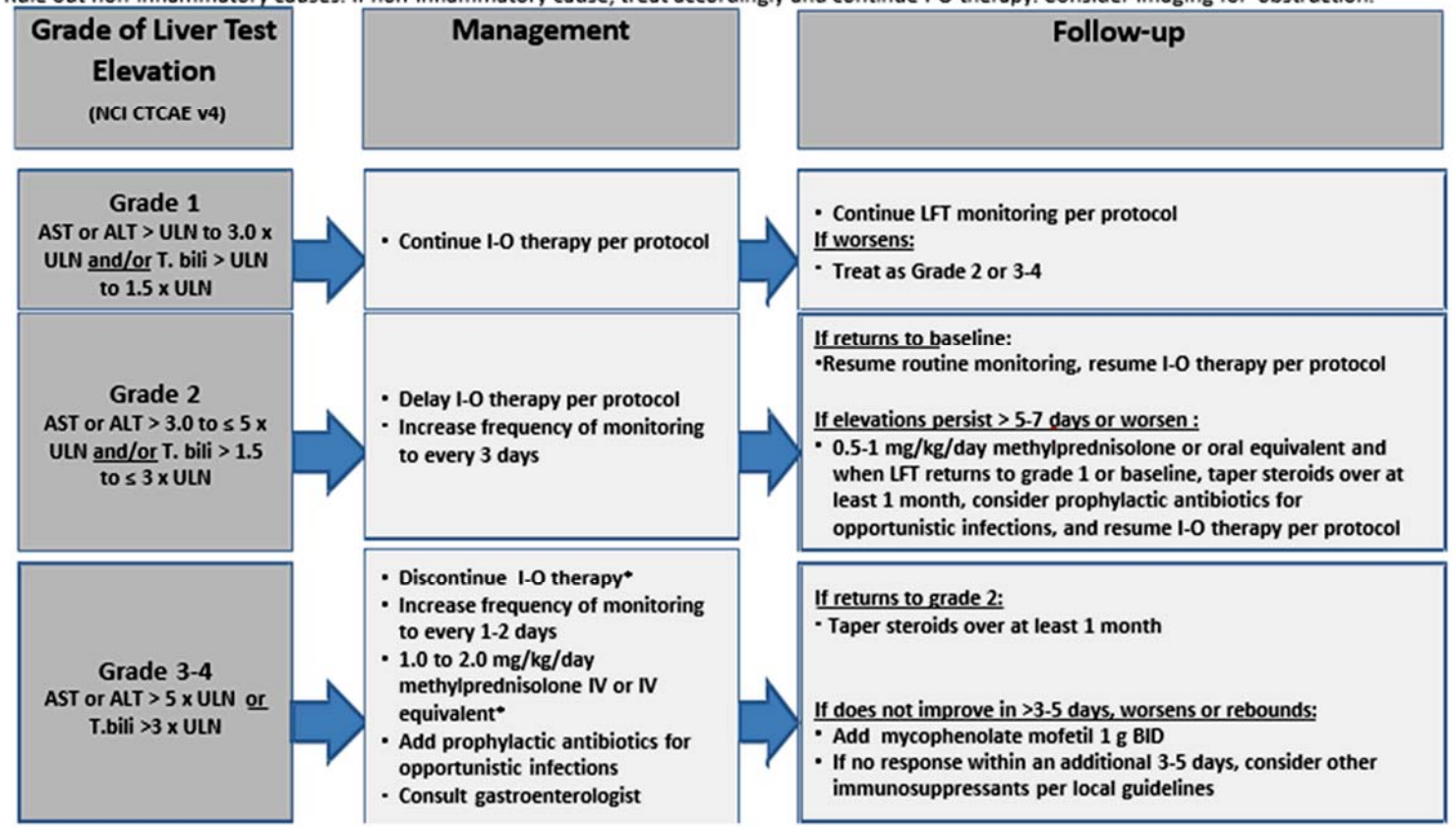



Patients on IV steroids may be switched to an equivalent dose of oral corticosteroids (e.g. prednisone) at start of tapering or earlier, once sustained clinical improvement is observed. Lower bioavailability of oral corticosteroids should be taken into account when switching to the equivalent dose of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

25-Jun-2019

# 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.



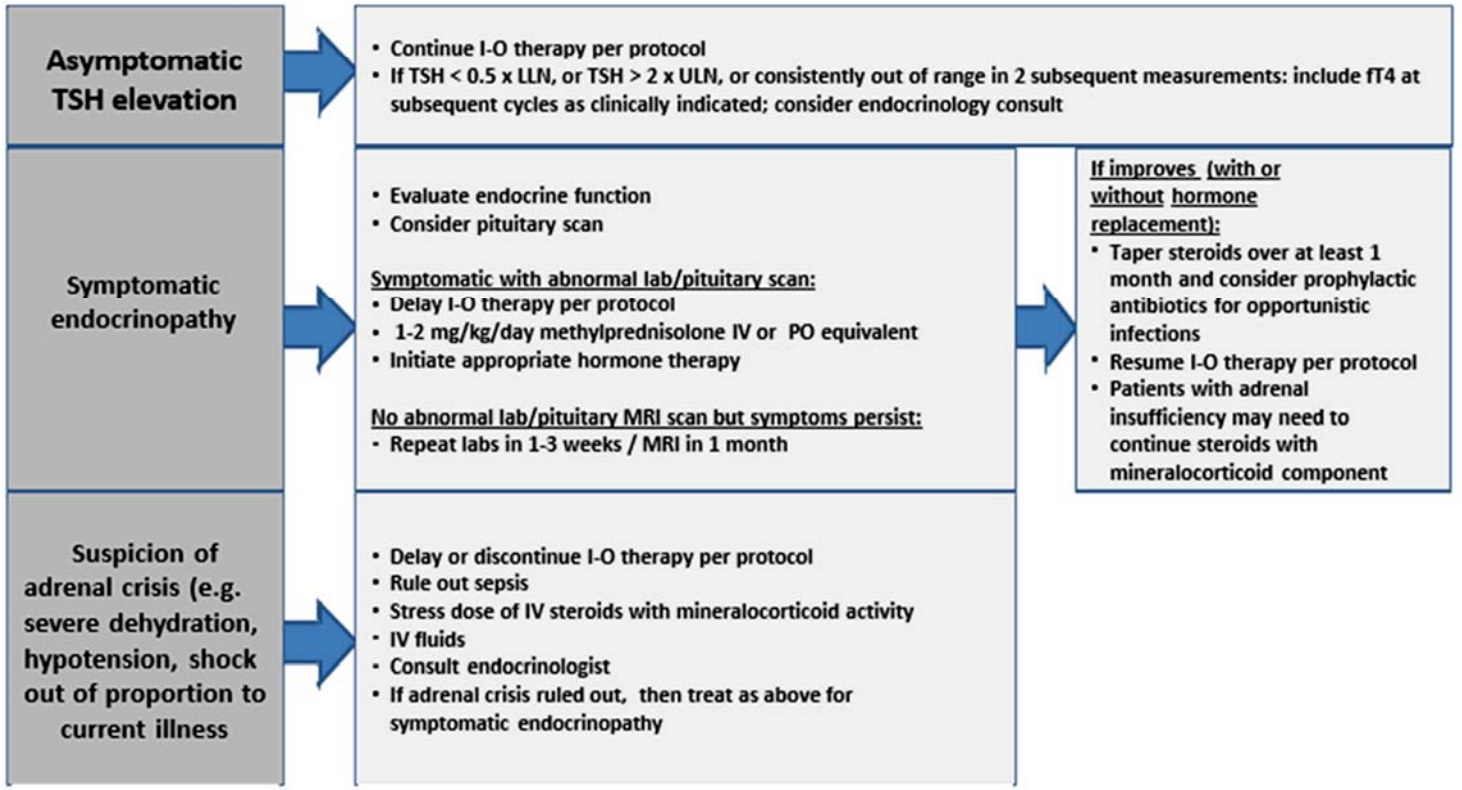

Patients on IV steroids may be switched to an equivalent dose of oral corticosteroids (e.g. prednisone) at start of tapering or earlier, once sustained clinical improvement is observed. Lower bioavailability of oral corticosteroids should be taken into account when switching to the equivalent dose of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

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

25-Jun-2019

# Endocrinopathy Adverse Event 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.

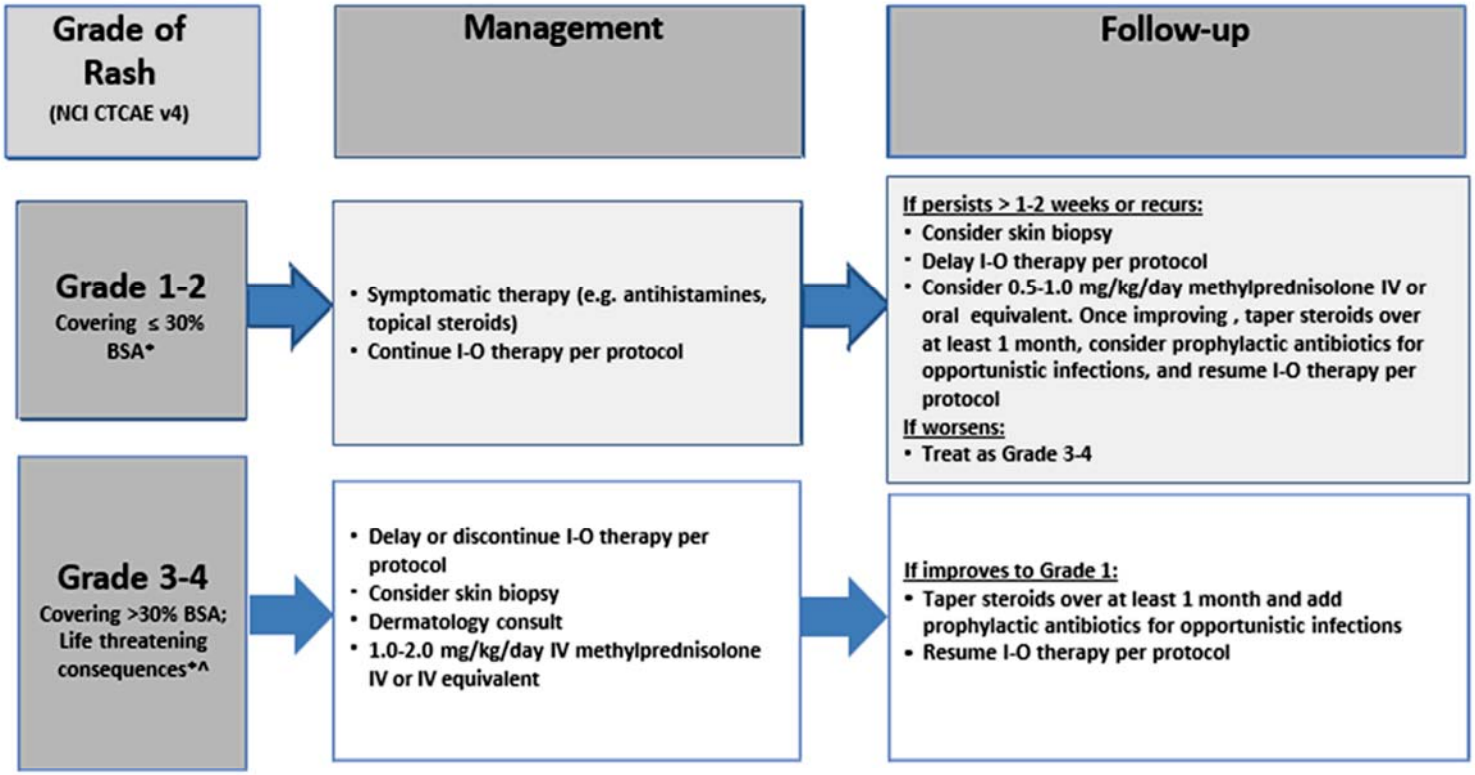



Patients on IV steroids may be switched to an equivalent dose of oral corticosteroids (e.g. prednisone) at start of tapering or earlier, once sustained clinical improvement is observed. Lower bioavailability of oral corticosteroids should be taken into account when switching to the equivalent dose of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

25-Jun-2019

# 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.

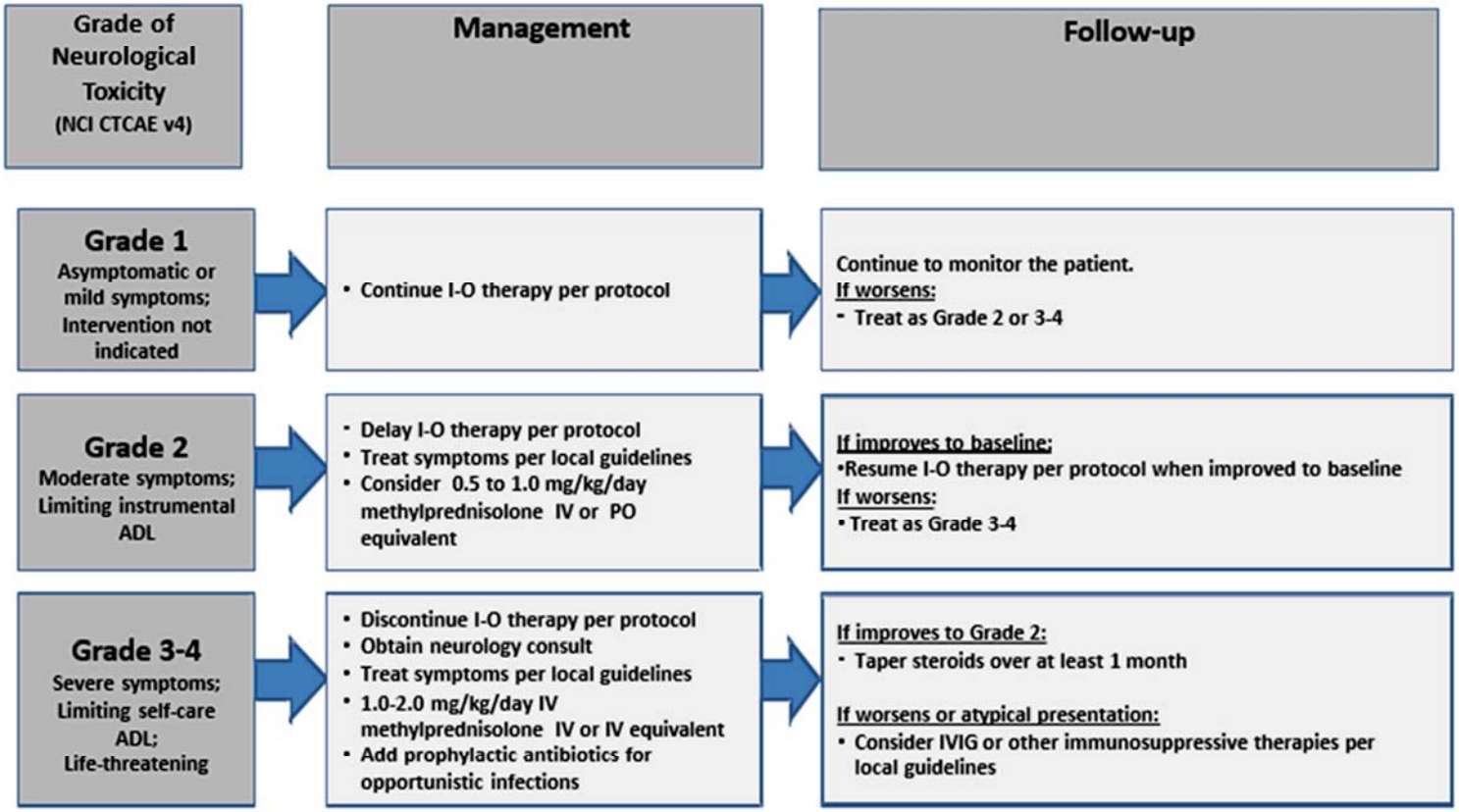
*Refer to NCI CTCAE v4 for term-specific grading criteria.

^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.

25-Jun-2019

# Neurological Adverse Event Management Algorithm

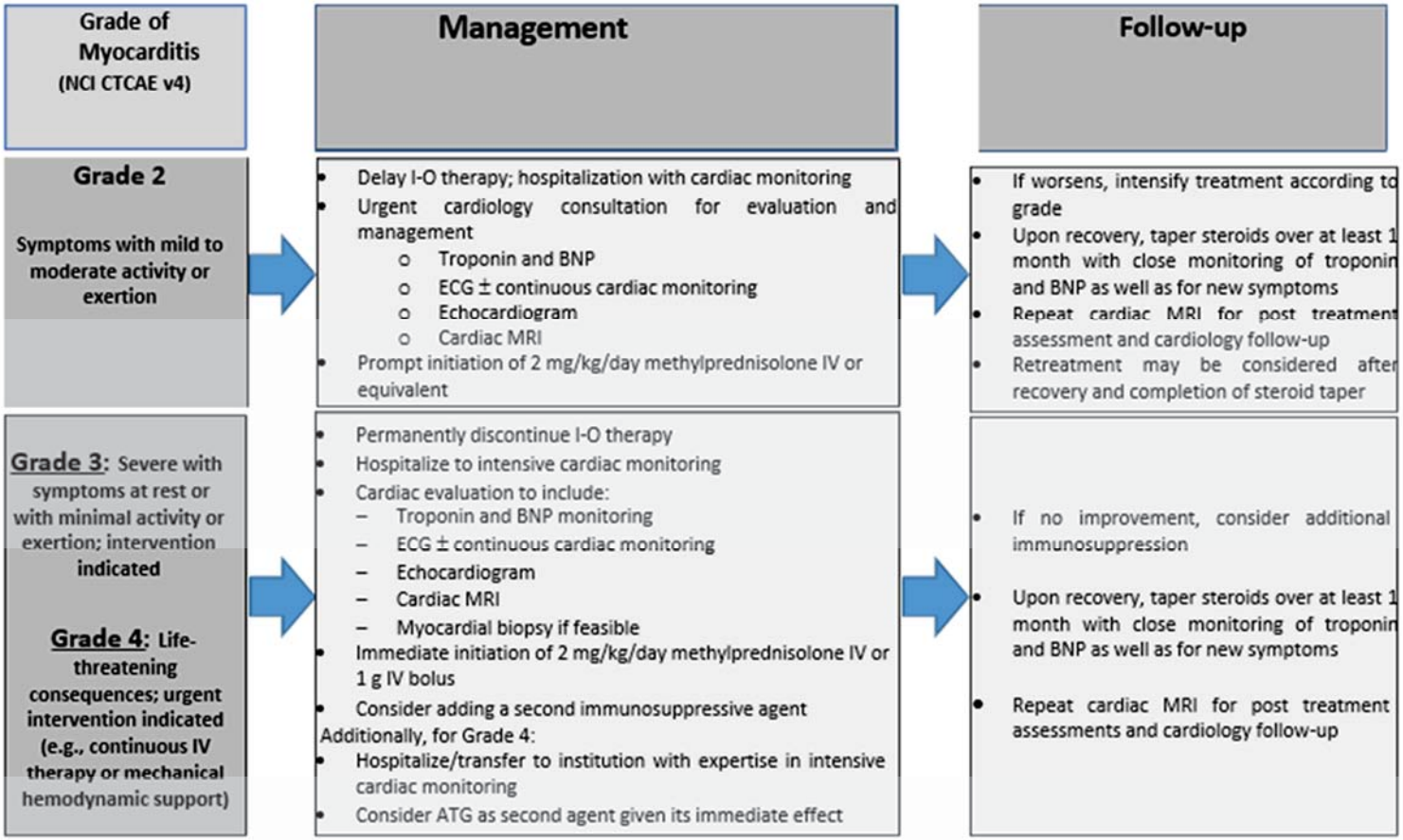
Rule out non-inflammatory causes. If non-inflammatory cause, treat accordingly and continue I-O therapy.




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.

25-Jun-2019

# Myocarditis Adverse Event Management Algorithm




Patients on IV steroids may be switched to an equivalent dose of oral corticosteroids (eg, 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.

Prophylactic antibiotics should be considered in the setting of ongoing immunosuppression.

ATG = anti-thymocyte globulin; BNP = B-type natriuretic peptide; ECG = electrocardiogram; IV = intravenous; MRI = magnetic resonance imaging

25-Jun-2019

# APPENDIX 5 WOMEN OF CHILDBEARING POTENTIAL DEFINITIONS AND METHODS OF CONTRACEPTION

## DEFINITIONS

### Woman of Childbearing Potential (WOCBP)

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

**Women in the following categories are not considered WOCBP**

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

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

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

## CONTRACEPTION GUIDANCE FOR FEMALE PARTICIPANTS OF CHILD BEARING POTENTIAL

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

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

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

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

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

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

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

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

## COLLECTION OF PREGNANCY INFORMATION

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

# APPENDIX 6 STUDY GOVERNANCE CONSIDERATIONS

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

## REGULATORY AND ETHICAL CONSIDERATIONS

## GOOD CLINICAL PRACTICE

This study will be conducted in accordance with:

- Good Clinical Practice (GCP),
- as defined by the International Council on Harmonisation (ICH)
- in accordance with the ethical principles underlying European Union Directive 2001/20/EC
- United States Code of Federal Regulations, Title 21, Part 50 (21CFR50)
- applicable local requirements.

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

All potential serious breaches must be reported to the Sponsor or designee immediately. A potential serious breach is defined as a Quality Issue (eg, protocol deviation, etc) that is likely to affect to a significant degree 1 or more of the following: (1) the physical safety or mental integrity of 1 or more subjects/participants; (2) the scientific value of the trial (eg, reliability and robustness of generated data). Items (1) or (2) can be associated with either GCP Regulation(s) or Trial protocol(s).

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 (e.g., loss of medical licensure, debarment).

## INSTITUTIONAL REVIEW BOARD/INDEPENDENT ETHICS COMMITTEE

Before study initiation, the investigator must have written and dated approval/favorable opinion from the IRB/IEC for the protocol, consent form, participant recruitment materials (eg, advertisements), and any other written information to be provided to subjects/participants. 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/participants and any updates.

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

## COMPLIANCE WITH THE PROTOCOL AND PROTOCOL REVISIONS

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

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

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

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

If an amendment substantially alters the study design or increases the potential risk to the participant: (1) the consent form must be revised and submitted to the IRB(s)/IEC(s) for review and approval/favorable opinion; (2) the revised form must be used to obtain consent from subjects/participants 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/participants prior to enrollment.

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

## FINANCIAL DISCLOSURE

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

## INFORMED CONSENT PROCESS

Investigators must ensure that subjects/participants 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/participants, their legally acceptable representatives (as per country guidelines) are clearly and fully informed about the purpose, potential risks, and other critical issues regarding clinical studies in which the participant volunteers to participate.

Sponsor or designee will provide the investigator with an appropriate (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:

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

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

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

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

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

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

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

## SOURCE DOCUMENTS

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

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

## STUDY TREATMENT RECORDS

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

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

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

## CASE REPORT FORMS

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

For sites using the Sponsor or designee electronic data capture tool, electronic CRFs will be prepared for all data collection fields except for fields specific to SAEs and pregnancy, which will

be reported on the electronic SAE form and Pregnancy Surveillance form, respectively. If electronic SAE form is not available, a paper SAE form can be used.

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

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

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

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

## MONITORING

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

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

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

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

## RECORDS RETENTION

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

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

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

## RETURN OF STUDY TREATMENT

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

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

It is the investigator's or designee's responsibility to arrange for disposal, provided that procedures for proper disposal have been established according to applicable federal, state, local, and institutional guidelines and procedures, and provided that appropriate records of disposal are kept. The following minimal standards must be met:

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

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

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

## CLINICAL STUDY REPORT

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

For each CSR related to this protocol, the following criteria will be used to select the signatory investigator:

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

## SCIENTIFIC PUBLICATIONS

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

Scientific Publications (such as abstracts, congress podium presentations and posters, and manuscripts) of the study results will be a collaborative effort between the study Sponsor and the external authors. No public presentation or publication of any interim results may be made by any principal investigator, sub-investigator, or any other member of the study staff without the prior written consent of the Sponsor.

Authorship of publications at BMS is aligned with the criteria of the International Committee of Medical Journal Editors (ICMJE, www.icmje.org). Authorship selection is based upon significant contributions to the study (ie, ICMJE criterion #1). Authors must meet all 4 ICMJE criteria for authorship:

1) Substantial intellectual contribution to the conception or design of the work; or the acquisition of data (ie, evaluable subjects with quality data), analysis, or interpretation of data for the work (eg, problem solving, advice, evaluation, insights and conclusion); AND
2) Drafting the work or revising it critically for important intellectual content; AND
3) Final approval of the version to be published; AND
4) Agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

Those who make the most significant contributions, as defined above, will be considered by BMS for authorship of the primary publication. Sub-investigators will generally not be considered in the primary publication. Geographic representation will also be considered.

Authors will be listed by order of significant contributions (highest to lowest), with the exception of the last author. Authors in first and last position have provided the most significant contributions to the work.

For secondary analyses and related publications, author list and author order may vary from primary to reflect additional contributions.

# APPENDIX 7 ADVERSE EVENTS AND SERIOUS ADVERSE EVENTS: DEFINITIONS AND PROCEDURES FOR RECORDING, EVALUATING, FOLLOW UP AND REPORTING

## ADVERSE EVENTS

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

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 discontinuation of study treatment.

Every adverse event must be assessed by the investigator with regard to whether it is considered immune-mediated. For events which are potentially immune-mediated, additional information will be collected on the participant's case report form.

## SERIOUS ADVERSE EVENTS

| **Serious Adverse Event (SAE) is defined as any untoward medical occurrence that, at any dose:** |
|---|
| Results in death |
| Is life-threatening (defined as an event in which the participant was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe) |

| |
|---|
| Requires inpatient hospitalization or causes prolongation of existing hospitalization (see NOTE below)<br><br>NOTE:<br><br>The following hospitalizations are not considered SAEs in BMS clinical studies:<br><br>o a visit to the emergency room or other hospital department < 24 hours, that does not result in admission (unless considered an important medical or life-threatening event)<br>o elective surgery, planned prior to signing consent<br>o admissions as per protocol for a planned medical/surgical procedure<br>o routine health assessment requiring admission for baseline/trending of health status (e.g., routine colonoscopy)<br>o medical/surgical admission other than to remedy ill health and planned prior to entry into the study. Appropriate documentation is required in these cases<br>o admission encountered for another life circumstance that carries no bearing on health status and requires no medical/surgical intervention (e.g., lack of housing, economic inadequacy, caregiver respite, family circumstances, administrative reason)<br>o admission for administration of anticancer therapy in the absence of any other SAEs (applies to oncology protocols) |
| Results in persistent or significant disability/incapacity |
| Is a congenital anomaly/birth defect |
| is an important medical event (defined as a medical event(s) that may not be immediately life-threatening or result in death or hospitalization but, based upon appropriate medical and scientific judgment, may jeopardize the participant or may require intervention [e.g., 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 9.2.7 for the definition of potential DILI.) |

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

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

## EVALUATING AES AND SAES

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

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

## REPORTING OF SAES TO SPONSOR OR DESIGNEE

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

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

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

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

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

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

## APPENDIX 8 REVISED PROTOCOL SUMMARY OF CHANGE HISTORY

**Overall Rationale for the Revised Protocol 01, 26-Jan-2018**

The CA209907 protocol is being revised to increase the number of participants on the study.

| **Summary of key changes for Revised Protocol 01** | | |
|---|---|---|
| **Section Number & Title** | **Description of Change** | **Brief Rationale** |
| Synopsis Number or Participants<br>Synopsis Sample Size Determination<br>Figure 5.1-1 Study Design Schematic<br>Section 5.2 Number of Participants<br>Section 10.1 Sample Size Determination | The number of treated participants increased to 120 participants. | Sample size expanded to provide additional data |
| Table 2.-1 Laboratory rest | Added Follicle stimulating hormone (FSH)-only required to confirm menopause in women < age 55 | Align FSH Testing with Women of Childbearing Potential in Appendix |
| Synopsis, Table 2: 95% Confidence Intervals for different AE rates for a sample size of 120 and text<br>Table 10.1-1 Confidence Intervals for different AE rates for a sample size of 70 and text<br>Table 10.1-2 Precision of Secondary Endpoint of ORR<br>Section 10.3.5 Interim Analysis | Statistical analyses were updated. | Change in number of participants requires new confidence intervals and probabilities.<br>Interim analysis may be performed. |
| 6.2 Exclusion Criteria,<br>3) Prior/Concomitant Therapy<br>4) Physical and Laboratory Test Findings | Exclude/prohibit botanical preparations within 4 weeks prior to first treatment. | Botanical preparations are excluded to minimize risks of any interactions with study drugs. |

| Summary of key changes for Revised Protocol 01 | | |
|---|---|---|
| **Section Number & Title** | **Description of Change** | **Brief Rationale** |
| | Serum creatinine parameters changed | Serum creatinine parameters updated for safety at program level. |
| Section 7.7.1 Prohibited and/or Restricted Treatments | Exclude/prohibit botanical preparations | Botanical preparations are excluded to minimize risks of any interactions with study drugs. |
| Section 7.8 Treatment After the End of the Study | Added language for the maximum treatment duration specified in protocol | Consistent with maximum treatment duration throughout protocol |
| Section 8.1.1 Nivolumab Dose Discontinuation | Neurologic toxicity added and adrenal insufficiency/ ACTH deficiency updated | Additional criteria complies with program level standards for drug safety. |
| [redacted] | | |