Official Title of Study:

An Exploratory Study of the Biologic Effects and Biomarkers of Nivolumab in combination with Ipilimumab in Subjects with Treatment-Naive Stage IV or recurrent Non-Small Cell Lung Cancer (NSCLC)

(CheckMate 592: CHECKpoint pathway and nivoluMAb clinical Trial Evaluation 592)

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# CLINICAL PROTOCOL CA209592

An Exploratory Study of the Biologic Effects and Biomarkers of Nivolumab in combination with Ipilimumab in Subjects with Treatment-Naive Stage IV or recurrent Non-Small Cell Lung Cancer (NSCLC)

(CheckMate 592: CHECKpoint pathway and nivoluMAb clinical Trial Evaluation 592)

**Revised Protocol Number: 05**

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## DOCUMENT HISTORY

| Document | Date of Issue | Summary of Change |
|---|---|---|
| Revised Protocol 05 | 18-Dec-2019 | • Removed restriction of Part 1 enrollment from US sites only<br>• Allowed less frequent imaging for long-term responders<br>• Clarified laboratory collection for TSH and albumin<br>• Updated interim analyses<br>• Added myocarditis to Management Algorithms |
| Revised Protocol 04 | 03-May-2019 | • Updated objectives, endpoints, and analyses for tissue and blood TMB<br>• Updated and reorganized biomarker collection and removed receptor occupancy<br>[redacted]<br>• Allowed skipped dosing on D15 and D29 only<br>• Required brain imaging at screening and when clinically indicated<br>• Updated schemas, interim analyses, dosing details, and appendices<br>• Removed communication with medical monitor for insufficient tissue |
| Revised Protocol 03 | 02-Mar-2018 | Incorporates Amendment 05 |
| Amendment 05 | 02-Mar-2018 | • Added Part 2 of protocol to include new participants for additional biomarker collection, objectives, endpoints, Procedural Outlines, [redacted]<br>• Updated to allow for archival tissue in Part 1 for PD-L1 screening assessment/group assignment only<br>• Added 2 year maximum duration of treatment<br>• Removed fine needle aspirate tissue collection<br>• Updated exclusion criteria, prohibited treatments, and discontinuation criteria to align with current nivolumab program standards<br>• Added EudraCT number<br>• Added Appendix 8 Country Specific Amendment for HIV testing |
| Revised Protocol 02 | 29-Mar-2017 | Incorporates Amendment 04 |
| Amendment 04 | 29-Mar-2017 | Protocol amendment is being implemented to include a co-primary objective to evaluate tumor mutational burden (TMB) as a candidate biomarker of clinical efficacy of nivolumab and ipilimumab combination therapy. [redacted] Dosing for nivolumab was changed to a flat dose of 240mg every 2 weeks. Women of Childbearing Potential definitions and methods of contraception were updated to align with program level guidance<br><br>1) Synopsis Updated:<br>a) Objectives and Endpoints: Updated to include a co-primary objective/endpoint to evaluate tumor mutational burden as a candidate |

| Document | Date of Issue | Summary of Change |
|---|---|---|
| | | biomarker of clinical efficacy of nivolumab and ipilimumab combination therapy.<br>b) Overall Design, Study Schematic, and Study Treatment: Updated to reflect nivolumab flat dose of 240mg every 2 weeks. Treatment and follow-up period were added to Schematic.<br>2) Table 2-1, Screening Procedural Outline:<br>a) Timing of pregnancy test for WOCBP clarified.<br>b) Body Surface Area removed from Physical Measurements.<br>c) Laboratory Tests clarified. Phosphorus required at screening and TSH + Free T3/T4 required within 72 hours of C1D1.<br>d) Paired Fine Needle Aspiration (FNA) added.<br>3) Table 2-2, On Treatment Procedural Outline:<br>a) Physical Exam: Removed reference to nivolumab weight based dosing and added reference to nivolumab flat dosing.<br>b) Laboratory Tests clarified. Phosphorus added for consistency with Section 9.4.1.TSH + Free T3/T4 required within 72 hours of C1D1 and TSH with reflexive Free T3/T4 on Day 1 of each Cycle thereafter (every 6 weeks).<br>c) Paired FNA to be collected from biopsies at Cycle 1 Day 29 (Week 5) and upon documented progression.<br>[redacted]<br>g) Reference to RO added for Whole Blood Collection.<br>4) Table 2-3, Follow-Up and Survival Procedural Outline:<br>a) Laboratory Tests clarified. Phosphorus and Albumin added for consistency with Section 9.4.1.<br>b) Reference to Biomarker assessments/PD Sampling removed.<br>5) Section 3.1, Study Rationale: Added rationale for inclusion of tumor mutational burden as a study objective.<br>6) Section 3.2.2, Rationale for combination of nivolumab and ipilimumab: Updated to reflect nivolumab flat dose of 240mg every 2 weeks.<br>7) Section 3.2.2.1, Rationale for Nivolumab Flat Dosing: Section added.<br>8) Section 3.2.5, Research Hypothesis: Added reference to TMB.<br>9) Table 4-1, Objectives and Endpoints: Updated to include a co-primary objective/enpoint to evaluate tumor mutational burden as a candidate biomarker of clinical efficacy of nivolumab and ipilimumab combination therapy.<br>10) Section 5.1, Overall Design: Updated to reflect nivolumab flat dosing.<br>11) Figure 5.1-1, Study Design Schematic: Updated to reflect nivolumab flat dose of 240mg every 2 weeks. Treatment and follow-up period were added to Schematic.<br>12) Section 5.5 , Justification for Dose: Updated to reflect nivolumab flat dose of 240mg every 2 weeks. |

| Document | Date of Issue | Summary of Change |
|---|---|---|
| | | 13) Table 7.1-1, Selection and Timing of Dose: Updated to reflect nivolumab flat dose of 240mg every 2 weeks.<br>14) Section 7.1.1, Dosing Details: Updated to reflect nivolumab flat dose of 240mg every 2 weeks.<br>[redacted]<br>16) Table 9.4.1-1 Laboratory Assessment Panels<br>a) TSH and Free T3/Free T4 testing clarified.<br>b) Testing for Drugs of Abuse Removed.<br>17) Table 9.6-1, Biomarker Assessment Schedule:<br>a) Paired FNA collection added.<br>[redacted]<br>19) Section 9.6.11, Paired FNA Collection: Section added.<br>[redacted]<br>21) Section 10.1, Sample Size Determination: Updated to reflect tumor mutational burden as a co-primary objective.<br>22) Section 10.2, Populations for Analysis: Defined tumor mutational burden evaluable patients.<br>23) Section 10.3, Statistical and Computational Analyses: Updated to reflect the association between ORR and tumor mutational burden will be explored using logistic regression model among treated patients evaluable for tumor mutational burden.<br>24) Section 10.3.1, Efficacy Analyses: Updated to reflect the association between ORR and TMB will be explored using logistic regression model.<br>25) Appendix 4, Women of Childbearing Potential definitions and methods of contraception: Appendix was updated to align with program level guidance. |
| Revised Protocol 01 | 03-Nov-2016 | Incorporates Amendment 02 |
| Amendment 02 | 03-Nov-2016 | Protocol amendment is being implemented to include a blood collection for Receptor Occupancy Measurements and language to align with program level standards for dosing administration.<br>1) Section 2, Screening Procedural Outline: Tumor tissue samples from biopsies will be divided into FFPE and a fresh sample in preservative, not frozen.<br>2) Section 7.4.5.1, Criteria to Resume nivolumab Dosing: Removed repeated criteria.<br>3) Section 8.1.1, Nivolumab or Ipilimumab Dose Discontinuation: Criteria updated to reflect program standards. |

| Document | Date of Issue | Summary of Change |
|---|---|---|
| | | 4) Section 8.1.3, Post Treatment Study Follow-Up: Updated to reflect program language.<br>5) Section 9.6, Biomarkers: Tumor tissue samples from biopsies will be divided into FFPE and a fresh sample in preservative, not frozen.<br>6) Table 9.6-1, Biomarker Assessment Schedule: Receptor Occupancy Whole Blood Collection Added.<br>7) Section 9.6.10, Receptor Occupancy Measurements: Section added.<br>8) Various typographical errors corrected. |
| Original Protocol | 28-Sep-2016 | Not Applicable |

## OVERALL RATIONALE FOR REVISED PROTOCOL 05:

The CA209592 protocol was revised to allow addition enrollment at non-US sites for Part 1 and update the timing of the interim analyses. Additional updates provided internal consistency in the document.

**SUMMARY OF KEY CHANGES FOR REVISED PROTOCOL 05**

| Section Number & Title | Description of Change | Brief Rationale |
|---|---|---|
| Synopsis<br>Study Schema<br>Figure 5.1-1: Study Design Schematic Part 1 and Part 2 | Removed restriction of Part 1 enrollment from US sites only<br>Rationale: | Allows for additional enrollment for non-US sites for part 1. |
| Table 2-2: On Treatment Procedural Outline (CA209592) for Part 1<br>Table 2-3: On Treatment Procedural Outline (CA209592) for Part 2<br>Table 2-4: Follow-Up and Survival Procedural Outline CA209592 (All Treatment Groups Part 1 and Part 2) | Clarified laboratory collection for TSH and albumin | Updated document for internal consistency in document |
| Table 2-4: Follow-Up and Survival Procedural Outline CA209592 (All Treatment Groups Part 1 and Part 2)<br>Section 9.1.1.1 Efficacy Assessments using CT scan or MRI<br>Table 9.1.1.1-1: Imaging Assessment Schedule (Part 1 and Part 2) | After 3 years on study, tumor assessments for long-term survivors can be performed at a frequency per institutional guidelines or every 24 weeks based on NCCN surveillance guidelines. | Aligns imaging assessments with clinical practice for long-term responders. |
| Table 9.6-1: Biomarker Assessment Schedule for Part 1 | Updated biomarker collection | Provides internal consistency in the document |
| Table 2-1 Screening Procedural Outline (CA209592) for Part 1 and Part 2 9.1.1.1<br>Table 2.-2: On Treatment Procedural Outline (CA209592) for Part 1<br>Table 2.-3: On Treatment Procedural Outline (CA209592) for Part 2<br>Section 9.1.1.1 Efficacy Assessments using CT scan or MRI | Updated clinical laboratory collection | Provides internal consistency in the document |
| Section 5.1 Overall Design<br>Section 10.3.5 Interim Analyses | Updated language for Part 2 interim analysis sample size: | Updates document with original planned analysis with sample size (~150 pts). |
| Appendix | Added myocarditis to Management Algorithms | Aligns with program standards |

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# 1 SYNOPSIS

**Protocol Title:** An Exploratory Study of the Biologic Effects and Biomarkers of Nivolumab in combination with Ipilimumab in Subjects with Treatment-Naive Stage IV or recurrent Non-Small Cell Lung Cancer (NSCLC)
(CheckMate 592: CHECKpoint pathway and nivoluMAb clinical Trial Evaluation 592)

**Study Phase:**

Phase 2, exploratory

**Rationale:**

Immune checkpoint signaling through the programmed death 1 (PD-1) axis to its ligand (PD-L1) with or without CTLA-4 inhibition significantly dampens anti-tumor immune responses in different tumor types including NSCLC. Unfortunately, not all patients respond to immune checkpoint blockade, therefore there is a compelling need for a better understanding of factors that would predict response and progression.

Emerging science and evidence from multiple studies, including exploratory analyses from the phase 2 study CA209568 (nivolumab + ipilimumab) and phase 3 study CA209026 (nivolumab monotherapy), tumor mutational burden (TMB) was identified as an important potential biomarker (independent of PD-L1) to help identify patients most likely to benefit from immunotherapy.

CA209592 is a two-part, exploratory, phase 2 open-label study aiming to explore potential biomarkers of response, including tumor mutational burden, and their association with clinical benefit when nivolumab + ipilimumab combination is given as primary therapy for advanced or metastatic NSCLC, regardless of PD-L1 expression (Part 1). Part 2 of the study explores the association between TMB (blood and tissue) and clinical efficacy.

In Part 1, changes occurring in candidate biomarkers within the tumor or within the peripheral blood during treatment, or at the time of disease progression, may provide an understanding of the mechanism of action, and the biology of underlying response (efficacy/safety) and/or underlying acquired resistance, which may help inform future combination strategies.

Based on the Part 2 expansion cohort in this study, tumor TMB and blood TMB will be collected at baseline. The association of tissue and blood TMB analyses with clinical outcomes will be assessed independently.

**Study Population:**

Participants with Stage IV or recurrent NSCLC, with no prior systemic anticancer therapy given as primary therapy for advanced or metastatic disease.

## Part 1 Objectives and Endpoints:

| Objectives | Endpoints |
|---|---|
| **Primary** | |
| • To evaluate baseline tumor mutational burden as a candidate biomarker of clinical efficacy of nivolumab and ipilimumab combination therapy.<br>• To investigate the potential association between candidate biomarkers in peripheral blood and tumor tissue at baseline and on-treatment with clinical efficacy measures. | • The clinical efficacy will be measured by the analysis endpoint of objective response rate (ORR). The association of ORR with candidate biomarkers in peripheral blood and tumor tissue at baseline and on-treatment will be assessed. Candidate biomarkers may include:<br>○ Baseline tissue TMB and blood TMB<br>○ Potential biomarkers/signatures (including PD-L1 expression) both at baseline and on treatment<br>○ Immunomodulatory and pharmacodynamic activity |
| **Secondary** | |
| • To evaluate efficacy in patient subgroups defined by baseline discovery biomarkers. | • ORR, disease control rate (DCR)<br>• Duration of response (DOR) and time to response (TTR)<br>• Progression free survival (PFS)<br>• Overall survival (OS) |
| [redacted] | |

**Part 2 Objectives and Endpoints:**

| Objectives | Endpoints |
|---|---|
| **Primary** | |
| • To evaluate the association between baseline tissue TMB/blood TMB and clinical efficacy (ORR) for participants in Part 2 | • The clinical efficacy will be measured by the analysis endpoint of objective response rate (ORR). The association of ORR with baseline tissue TMB and blood TMB will be assessed. |
| **Secondary** | |
| • To investigate bacterially-generated and human components enteric biomarkers and identify potential associations with clinical outcomes, including safety and efficacy, for subjects in Part 2. | • ORR, PFS, OS<br>• Incidence of AES, SAEs, and select AEs |
| [redacted] | [redacted] |

**Overall Design:**

Protocol CA209592 is an open-label, exploratory trial evaluating nivolumab in combination with ipilimumab in participants ≥ 18 years old with histologically confirmed advanced or metastatic NSCLC, with no prior systemic anticancer therapy given as primary therapy for advanced disease.

In Part 1, participants will undergo screening evaluations to determine eligibility within 28 days prior to cohort assignment, and approximately 100 patients will be treated. Tumor sample for PD-L1 status assessment is required at screening for group assignment.

Upon determination of PD-L1 status (cut-off of 1%), 2 cohorts will be defined: PD-L1 positive and negative, and patients in each cohort (n= 50 ea.) will receive nivolumab + ipilimumab.

In Part 2, approximately 150 participants will be assigned to a single cohort and treated with nivolumab + ipilimumab regardless of their PD-L1 status.

All participants will be treated with the following:

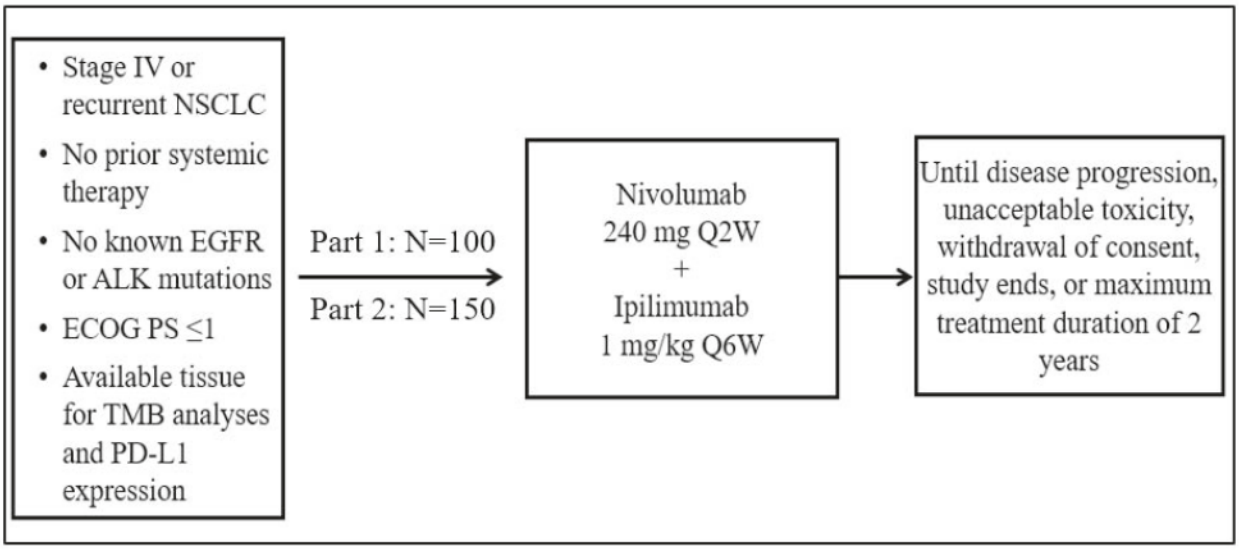
- nivolumab 240mg IV every 2 weeks + ipilimumab 1 mg/kg IV every 6 weeks until disease progression, unacceptable toxicity, withdrawal of consent, the study ends, or maximum treatment duration of 2 years, whichever occurs first. Participants will be permitted to continue on nivolumab +/- ipilimumab beyond initial RECIST 1.1 defined progression, as long as they meet the criteria described in Section 8.1.2.

**Number of Participants:**

**Part 1**: Approximately 150 participants are expected to be enrolled to achieve approximately 100 treated participants in the trial.

**Part 2**: Approximately 200 participants are expected to be enrolled to achieve 150 treated participants. Sites in US and Europe may participate in Part 2.

**Study Schematic Part 1 and Part 2:**




**Study treatment:**

| Study Drug for CA209592 | | | |
|---|---|---|---|
| **Medication** | **Dosage level(s)** | **Frequency of Administration** | **Route of Administration** |
| nivolumab | 240mg | Every 2 weeks | IV |
| ipilimumab | 1 mg/kg | Every 6 weeks | IV |

# 2 SCHEDULE OF ACTIVITIES

**Table 2-1: Screening Procedural Outline (CA209592) for Part 1 and Part 2**

| Procedure | Screening Visit[a] | Notes |
|---|---|---|
| **Eligibility Assessments** | | |
| Informed Consent | X | ICF signed during screening for protocol participation prior to any study specific procedures. Study allows for re-enrollment of a participant that has discontinued the study as a pre-treatment failure. If re-enrolled, the participant must be re-consented and assigned a new patient ID number from IWRS. |
| Inclusion/Exclusion Criteria | X | All inclusion/exclusion criteria should be assessed at screening and confirmed prior to dosing. Section 6. |
| Medical History | X | |
| Body Imaging | X | Contrast enhanced CT of the chest, CT/MRI of the abdomen, pelvis, and all other known and/or suspected sites of disease, within 28 days prior to the first dose [redacted] |
| Brain Imaging | X | MRI of the brain without and with contrast is required for ALL participants during screening to rule out brain metastases. CT of the brain (without and with contrast) can be performed if MRI is contraindicated. See Section 9.1.1 and Appendix 6 for further details. |
| Prior Systemic Therapy | X | Any prior medications received to treat cancer. |
| ECOG Performance Status | X | ECOG Status of 0 or 1 required for treatment assignment. Appendix 5. |
| **Safety Assessments** | | |
| Physical Measurements | X | Includes height and weight |
| Full Physical Examination | X | Within 14 days prior to first dose. |
| Vital Signs | X | Including seated blood pressure, heart rate, and temperature. |
| Assessment of Signs and Symptoms | X | Within 14 days prior to first dose. |

**Table 2-1: Screening Procedural Outline (CA209592) for Part 1 and Part 2**

| Procedure | Screening Visit[a] | Notes |
|---|---|---|
| Concomitant Medication Collection | X | Within 14 days prior to first dose. |
| Laboratory Tests | X | Section 9.4.1, Within 14 days prior to first dose.<br>CBC w/differential, Chemistry panel including: Albumin, LDH, AST, ALT, ALP, T.Bili, BUN or serum urea level, creatinine, Ca, Mg, Na, K, Cl, Phosphorus, Glucose, amylase, lipase.<br>TSH and Free T4/Free T3 required within 72 hours of C1D1.<br>Hepatitis B surface antigen (HBV sAg), and hepatitis C antibody (HCV Ab) or Hepatitis C RNA (HCV RNA).<br>Participants who test positive for hepatitis C but test negative for ribonucleic acid are allowed to enroll. |
| Pregnancy Test (WOCBP Only) | X | Section 9.2.5. Negative pregnancy test required within 24 hours prior to first dose. |
| **Biomarker Assessments** | | |
| Tumor Tissue Sample **(Part 1)**<br>Archived Tumor Tissue or Recent Tumor Biopsy | X | **Part 1 only:** Fresh biopsy required. Archival sample obtained within 3 months of enrollment acceptable for PD-L1 assessment only. See Section 9.6.<br>One (1) formalin-fixed paraffin embedded tumor tissue block or a minimum of 15unstained tumor tissue sections are acceptable.<br>Specimens must be tested by third party lab to determine PD-L1 status prior to group assignment. |
| Tumor Tissue Sample **(Part 2)**<br>Archived Tumor Tissue or Recent Tumor Biopsy | | **Part 2 only:** Recent sample/fresh biopsy or archival, obtained within 3 months of enrollment.<br>One (1) formalin-fixed paraffin embedded tumor tissue block or a minimum of 15 unstained tumor tissue sections are acceptable. Fresh biopsy tissue is preferred.<br>Specimen collection and shipment to central vendor must be verified prior to treatment assignment. See Section 9.6 |
| [redacted] | | |
| EGFR Mutation Status/ ALK Translocation Status (**Part 1 and Part 2**) | X | **Part 1 and Part 2**: To be performed by the local lab prior to first dose in all non-squamous participants. |

**Table 2-1: Screening Procedural Outline (CA209592) for Part 1 and Part 2**

| Procedure | Screening Visit[a] | Notes |
|---|---|---|
| [redacted] | | |
| **Study Treatment** | | |
| Enrollment in IWRS | X | Section 7.2. For participant number assignment at the time informed consent is obtained. |

[a] All screening assessments must be completed and participant should be registered for treatment assignment in IWRS within 28 days, unless otherwise noted.

**Table 2-2: On Treatment Procedural Outline (CA209592) for Part 1**

| Procedure | On Treatment Visits | Notes<br>1 Cycle = 6 weeks<br>Visits occur every 2 weeks (± 3days) to align with nivolumab dose administration. |
|---|---|---|
| **Safety Assessments** | | |
| Physical Examination/Physical Measurements (including performance status) | X | Appendix 5.<br>Weight and ECOG status. Dosing calculations for ipilimumab should be based on the body weight. If the participant's weight on the day of dosing differs by > 10% from the weight used to calculate the dose, the dose must be recalculated. All doses should be rounded to the nearest milligram. Note: nivolumab dosing is 240 mg flat dosing. |
| Vital Signs | X | Obtain BP, HR, and temperature just prior to dosing. |
| Adverse Events Assessment | X | Section 9.2. |
| Review of Concomitant Medications | X | |
| Laboratory Tests | X | Section 9.4.1.<br>On-study local laboratory assessments should be done within 72 hours prior to each dose.<br>CBC w/differential, LFTs (ALT, AST, total bilirubin, alkaline phosphatase), BUN or serum urea level, creatinine, Ca, Mg, Na, K, Cl, Phosphorus, LDH, glucose, amylase, lipase. |
| Thyroid Function Testing | X | TSH + Free T3/T4 required within 72 hours of C1D1,<br>If TSH is abnormal, then TSH with reflexive Free T4, Free T3 is to be performed on Day 1 of each Cycle (every 6 weeks). |
| Pregnancy Test (WOCBP Only) | X | Serum or urine within 24 hours prior to first dose (C1D1) and then every 4 weeks (± 1 week) regardless of dosing schedule. |
| **Biomarker Assessments** | | |
| On Treatment Tumor Biopsy | X<br>See Note. | Section 9.6.<br>To be performed at Cycle 1 Day 29 (Week 5 ± 1 Week) AND upon documented progression. |
| [redacted] | | |

**Table 2-2: On Treatment Procedural Outline (CA209592) for Part 1**

| Procedure | On Treatment Visits | Notes<br>1 Cycle = 6 weeks<br>Visits occur every 2 weeks (± 3days) to align with nivolumab dose administration. |
|---|---|---|
| [redacted] | | |
| **Efficacy Assessments** | | |
| Body Imaging | See note. | Section 9.1.1.<br>Tumor assessments should occur every 8 weeks (± 1 week) for the first 12 months on treatment, then every 12 weeks (± 1 week) until documented radiographic disease progression.<br>An additional and optional CT scan is planned at W5, to guide tumor biopsy as needed and to support predicting tumor response based on early tumor growth characteristics using a mathematical tumor growth model.<br>CT chest and CT/MRI abdomen and pelvis (with contrast, unless contraindicated), plus any area that is being monitored. Use same imaging method as was used at screening.<br>For participants who discontinue study treatment for reasons other than radiographic PD, follow-up scans should continue to be performed according to the on-study assessment schedule until PD, withdrawal of consent, start of subsequent therapy, death, or lost to follow-up.<br>Participants who remain on therapy beyond initial progression, will have an assessment performed within 6 weeks to confirm progression (see section 8.1.2)<br>[redacted]<br>All PET/CT scans should be before any scheduled biopsy at the same time point, if possible. |
| Brain Imaging | X | Participants with a history of brain metastasis or symptoms should have a surveillance MRI study per standard of care (approximately every 12 weeks), or sooner if clinically indicated. CT of the brain without and with contrast can be performed if MRI is contraindicated. See Section 9.1.1.1 for further details. |

**Table 2-2: On Treatment Procedural Outline (CA209592) for Part 1**

| Procedure | On Treatment Visits | | | Notes<br>1 Cycle = 6 weeks<br>Visits occur every 2 weeks (± 3days) to align with nivolumab dose administration. |
|---|---|---|---|---|
| [redacted] | | | | |
| **Study Treatment** | **Day 1** | **Day 15** | **Day 29** | |
| Dispense Study Treatment | X | X | X | Within 3 days of the treatment assignment in IWRS, the participant must receive the first dose of study medication. Participants may be dosed no less than 19 days between doses during administration of ipi/nivo in combination and no less than 12 days between doses nivo if is administered alone. |
| Nivolumab Administration | X | X | X | Treatment is administered every 2 weeks (+/- 3 days). Refer to Section 7.1.1. |
| Ipilimumab Administration | X | | | Treatment is administered every 6 weeks (+/- 5 days). Refer to Section 7.1.1. |

**Table 2-3: On Treatment Procedural Outline (CA209592) for Part 2**

| Procedure | On Treatment Visits | Notes<br>1 Cycle = 6 weeks<br>Visits occur every 2 weeks (± 3days) to align with nivolumab dose administration. |
|---|---|---|
| **Safety Assessments** | | |
| Physical Examination/Physical Measurements (including performance status) | X | Appendix 5.<br>Weight and ECOG status. Dosing calculations for ipilimumab should be based on the body weight. If the participant's weight on the day of dosing differs by > 10% from the weight used to calculate the dose, the dose must be recalculated. All doses should be rounded to the nearest milligram.<br>Note: nivolumab dosing is 240mg flat dosing. |
| Vital Signs | X | Obtain BP, HR, and temperature just prior to dosing. |
| Adverse Events Assessment | X | Section 9.2. |
| Review of Concomitant Medications | X | |
| Laboratory Tests | X | Section 9.4.1.<br>On-study local laboratory assessments should be done within 72 hours prior to each dose.<br>CBC w/differential, LFTs (ALT, AST, total bilirubin, alkaline phosphatase), BUN or serum urea level, creatinine, Ca, Mg, Na, K, Cl, Phosphorus, LDH, glucose, amylase, lipase. |
| Thyroid Function Testing | X | TSH + Free T3/T4 required within 72 hours of C1D1,<br>If TSH is abnormal, then TSH with reflexive Free T4, Free T3 is to be performed on Day 1 of each Cycle (every 6 weeks). |
| Pregnancy Test (WOCBP Only) | X | Serum or urine within 24 hours prior to first dose (C1D1) and then every 4 weeks (± 1 week) regardless of dosing schedule. |

**Table 2-3: On Treatment Procedural Outline (CA209592) for Part 2**

| Procedure | On Treatment Visits | Notes<br>1 Cycle = 6 weeks<br>Visits occur every 2 weeks (± 3days) to align with nivolumab dose administration. |
|---|---|---|
| **Efficacy Assessments** | | |
| Body Imaging | See note. | Section 9.1.1.<br>Tumor assessments should occur every 8 weeks (± 1 week) for the first 12 months on treatment, then every 12 weeks (± 1 week) until documented radiographic disease progression.<br>CT chest and CT/MRI abdomen and pelvis (with contrast, unless contraindicated), plus any area that is being monitored. Use same imaging method as was used at screening.<br>For participants who discontinue study treatment for reasons other than radiographic PD, follow-up scans should continue to be performed according to the on-study assessment schedule until PD, withdrawal of consent, start of subsequent therapy, death, or lost to follow-up.<br>Participants who remain on therapy beyond initial progression, will have an assessment performed within 6 weeks to confirm progression (see Section 8.1.2) |
| Brain Imaging | See note. | Participants with a history of brain metastasis or symptoms should have surveillance MRIs per standard of care (approximately every 12 weeks) or sooner if clinically indicated. CT of the brain without and with contrast can be performed if MRI is contraindicated. See Section 9.1.1.1 for further details. |
| [redacted] | | |
| **Study Treatment** | **Day 1** / **Day 15** / **Day 29** | |
| Dispense Study Treatment | X / X / X | Within 3 days of the treatment assignment in IWRS, the participant must receive the first dose of study medication. Participants may be dosed no less than 19 days between doses during administration of ipi/nivo in combination and no less than 12 days between doses nivo if is administered alone. |
| Nivolumab Administration | X / X / X | Treatment is administered every 2 weeks (+/- 3 days). Refer to Section 7.1.1. |
| Ipilimumab Administration | X / | Treatment is administered every 6 weeks (+/- 5 days). Refer to Section 7.1.1. |

**Table 2-4: Follow-Up and Survival Procedural Outline CA209592 (All Treatment Groups Part 1 and Part 2)**

| Procedure | Follow-Up Visits 1[a] & 2[b] | Survival Follow-up Visits[c] | Notes |
|---|---|---|---|
| **Safety Assessments** | | | |
| Targeted Physical Examination | X | | To assess for potential late emergent study drug related issues. |
| Vital Signs | X | | |
| Adverse Events Assessment | X | | 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. |
| Laboratory Tests | X | | To be done at FU1, to be repeated at FU2, if study related toxicity persists.<br>CBC w/ differential, LFTs, BUN or serum urea level, creatinine, Ca, Mg, Na, K, Cl, Phosphorus, LDH, Glucose, amylase, lipase.<br>If TSH is abnormal, then TSH with reflexive Free T4, Free T3 is to be performed |
| Pregnancy Test (WOCBP Only) | X | | Section 9.2.5. |
| **Efficacy Assessments** | | | |
| Radiographic Tumor Assessments | X | | For participants who discontinue study treatment for reasons other than radiographic PD, follow-up scans should continue to be performed according to the on-study assessment schedule (Table 2-2 and Table 2-3) until PD, withdrawal of consent, or start of subsequent therapy, death, or lost to follow-up<br>After 3 years on study, tumor assessments for long-term survivors can be performed at a frequency per institutional guidelines or every 24 weeks based on NCCN surveillance guidelines. |
| Collection of Survival Status and Subsequent Therapy Information | X | X | Every 3 months after FU2; May be completed by office visit, phone contact or email, to assess subsequent anti-cancer therapy. |

[a] Follow-up visit 1 (FU1) = 30 days from the last dose +/- 7 days or coincides with the date of discontinuation (+/- 7 days) if date of discontinuation is greater than 35 days after last dose.

[b] Follow-up visit 2 (FU2) = 100 days (+/- 7 days) from follow-up visit 1

[c] Every 3 months (+/- 7 days) from FU2

# 3 INTRODUCTION

CA209592 is an open-label, exploratory Phase 2 trial aiming to investigate the biologic effects and biomarkers of nivolumab in combination ipilimumab in subjects, with no prior systemic anticancer therapy given as primary therapy for advanced or metastatic non-small cell lung cancer (NSCLC).

## 3.1 Study Rationale

Immune checkpoint signaling through the programmed death 1 (PD-1) axis to its ligand (PD-L1) with or without CTLA-4 inhibition significantly dampens anti-tumor immune responses in different tumor types including NSCLC.

Clinical activity of nivolumab and ipilimumab combination was evaluated in patients with advanced NSCLC as first line treatment in CA209012. Dual inhibition (PD-1 and CTLA-4) was associated with higher response rate over nivolumab monotherapy with very acceptable safety profile. Data from the same study are also showing better outcome in patients with tumors expressing PD-L1 versus those with no expression. ORR was higher with increasing PD-L1 expression, with response rates of the combination exceeding response rates with monotherapy at each expression level.

Unfortunately, not all patients respond to immune checkpoint blockade, therefore there is a compelling need for a better understanding of factors that would predict response and progression.

CA209592 is an exploratory Phase 2, open-label, trial aiming to evaluate response in patients with no prior systemic anticancer therapy given as primary therapy for advanced or metastatic NSCLC, with or without PD-L1 expression and addresses the following objectives in Part 1:

- To evaluate tumor mutational burden as a candidate biomarker of clinical efficacy of nivolumab and ipilimumab combination therapy;
- Characterize the immunomodulatory and pharmacodynamic activity of nivolumab in combination with ipilimumab, within the tumor microenvironment and in the periphery;
- Evaluate/identify potential biomarkers/signatures within pre-treatment and within on-treatment samples that are correlated with primary response/non-response and/or safety;

[redacted]

Part 2 will address the following primary objectives:

- Evaluate the association between baseline tissue TMB/blood TMB with clinical efficacy (ORR) for participants

Tumor mutational burden (TMB) refers to the total number of nonsynonymous somatic mutations that exist within a tumor's genome. A subset of these mutations, termed neo-antigens, may result in an expressed protein that is not recognized by the host's immune system as self, and therefore has the potential to be immunogenic, leading to an anti-tumor immune-mediated response. Tumors with a high mutation burden may have a higher rate of neo-antigens which, in principle, would be expected to be more immunogenic than tumors with comparatively low mutation burden.[1] Therefore, high TMB has been hypothesized to correlate with improved efficacy in patients treated with I-O therapies. This hypothesis has been supported in multiple publications across IO therapies, tumor types, and lines of treatment. The first published study of TMB as a biomarker of clinical outcomes was reported by Snyder et al (2014), where high TMB was found to be associated with efficacy in metastatic melanoma patients treated with anti-CTLA-4 therapy. Further studies by Rizvi et al (2015) reported TMB as a biomarker of pembrolizumab efficacy in second-line NSCLC patients. Additional studies of pembrolizumab and atezolizumab in NSCLC have been generally consistent with these results.[2]

In 2017, TMB was evaluated in an exploratory post hoc analysis in the BMS-sponsored first line NSCLC study, CheckMate 026, which represents the first Phase III study to retrospectively demonstrate the impact of TMB on efficacy of a PD-1/L1 inhibitor.[3] This analysis demonstrated that in patients with high TMB, ORR was numerically higher in the nivolumab arm versus the chemotherapy arm (47% vs. 28%) and median PFS was longer in the nivolumab arm compared to the chemotherapy arm (9.7 vs. 5.8 mo., HR 0.62; 95% CI 0.38, 1.00). OS was notable, though similar (18.3 vs. 18.8 mo. and 1 year OS rates of 64% vs 60%, respectively), between the arms in patients with high TMB, although of note, 68% of patients in the chemotherapy arm received subsequent nivolumab.[3] Interestingly, the ORR and mPFS rates observed in the high TMB subgroup within CheckMate 026 were similar to those reported in the first line NSCLC study of pembrolizumab (Keynote-024), where ORR and mPFS were 45% and 10.3 months, respectively, in patients with ≥50% PD-L1 expression treated with pembrolizumab monotherapy.[4]

Recent data released in the ongoing phase 3 CA209227 study had met its co-primary endpoint of PFS with the nivolumab plus ipilimumab combination versus chemotherapy in first-line advanced NSCLC patients whose tumors have high TMB (≥10 mutations/megabase), regardless of PD-L1 expression. In the study, TMB was evaluated using Foundation Medicine's analytically validated assay FoundationOne CDx. Additionally, based on an interim analysis for overall survival (OS), the Data Monitoring Committee recommended that the study continue. The safety profile was consistent with previously reported findings in first-line NSCLC for the combination schedule of nivolumab 3 mg/kg every two weeks and low-dose ipilimumab (1 mg/kg) every six weeks.

CA209568 (CheckMate 568) is a two-part, phase 2 open-label study evaluating efficacy and safety of first-line treatment with nivolumab and ipilimumab in Stage IV NSCLC (Part 1), as well as the safety of combining nivolumab and ipilimumab plus platinum doublet chemotherapy (Part 2). The objective of Part 1 is to determine if the administration of nivolumab in combination with ipilimumab as first line treatment will lead to clinical benefit as demonstrated by a clinically meaningful ORR in PD-L1 positive (membranous staining in ≥1% tumor cells) and PD-L1

negative (< 1% tumor cells) Stage IV NSCLC. An unpublished interim analysis in 2017 demonstrated that TMB is predictive of clinical response in such population.

Recently the phase 2 POPLAR and phase 3 OAK studies, from Roche/Genentech confirmed retrospective data analysis reported analytic and clinical validation for the blood TMB (bTMB) assay.[5] Using the Foundation Medicine's assay, these studies indicated that high bTMB associated with response to atezolizumab in individuals with previously-treated non-small cell lung cancer.

These results indicate that TMB may be an important, predictive independent biomarker that can identify a population of first-line NSCLC patients who can potentially benefit from I-O therapy. Changes occurring in candidate biomarkers within the tumor and peripheral blood during treatment or at the time of disease progression may provide an understanding of the mechanism of action underlying response (efficacy/safety) and/or underlying acquired resistance. This may help to inform on the biology of response to nivolumab + ipilimumab therapy and may inform future combination strategies.

## 3.2 Background

Non-small cell lung cancer (NSCLC) remains the leading cause of cancer-related mortality worldwide, accounting for approximately 18% of all cancer deaths.[6] Despite treatment with platinum-based chemotherapy, the standard of care for first-line therapy, patients with metastatic NSCLC have a median survival of approximately 10 months, and a 5-year survival rate of less than 5%.[7]

Immunotherapeutic approaches recently have demonstrated clinical efficacy in several cancer types, including melanoma and hormone-refractory prostate cancer.[8] 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 disruption 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 prevents 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. In early clinical trials, nivolumab has demonstrated activity in several tumor types, including melanoma, renal cell cancer (RCC), and NSCLC.[9] In particular, substantial activity has been noted in previously treated NSCLC subjects, where objective response rates approached 25%, and the progression-free survival (PFS) rate at 24 weeks approached 45%, with no clear differences between squamous and non-squamous histology.[10] In general, nivolumab also has been well tolerated to date, with a favorable safety profile relative to anticipated toxicities based on an immunostimulatory mechanism of action.[11]

Similar clinical activity and safety have also been observed among a cohort of chemotherapy-naive NSCLC subjects treated with nivolumab monotherapy in another trial, and preliminary data suggest that PD-L1 tumor expression may be predictive for response to nivolumab.[12]

Immunotherapies with or without chemotherapy have been recently reported to show clinical benefit as first-line therapy for the following patient populations. In metastatic NSCLC with ≥50% PD-L1 expression, first-line PD-1 checkpoint inhibition as monotherapy has been associated with clinical benefit (KEYNOTE-024 pembrolizumab vs chemotherapy). However, first-line PD-1 checkpoint inhibition as monotherapy did not prove to be superior to chemotherapy in a broader, PD-L1 selected population in CA209026 (CheckMate-026). These results together show the limitations of first-line chemotherapy-free immunotherapy regimen to a relatively small group of patients with high (± 50%) PD-L1 expression.

Other drug combination studies evaluated immunotherapy + chemotherapy (± bevacizumab) combinations have shown PFS benefit in metastatic nonsquamous NSCLC patients. In the phase 2 KEYNOTE-021 study, randomized patients with stage IIIB/IV, chemotherapy-naive, nonsquamous NSCLC received chemotherapy with or without 24 months treatment with pembrolizumab. After a median follow-up of 10.6 months, a significantly greater objective response rate (55% vs. 29%, P = 0.0016) was observed in the patients who received pembrolizumab as well as chemotherapy, compared to those treated with chemotherapy alone. While patients were not selected by the amount of PD-L1 expression in their tumor, researchers did note a higher response rate (around 80%) for the pembrolizumab and chemotherapy combination in tumors with PD-L1 expression greater than or equal to 50%.[13]

The IMpower150, a controlled phase 3 study evaluated the efficacy and safety of tezolizumab in combination with chemotherapy with or without bevacizumab in people with stage IV non-squamous NSCLC who had not been treated with chemotherapy for their advanced disease. The study met its co-primary endpoint of PFS and demonstrated that the combination of atezolizumab and bevacizumab plus chemotherapy provided a statistically significant and clinically meaningful reduction in the risk of disease worsening or death (PFS) compared to bevacizumab plus chemotherapy in the first-line treatment of people with advanced non-squamous non-small cell lung cancer (NSCLC).[14]

### 3.2.1 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.[15,16,17] 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).[18] Collectively, these signals govern the balance between T-cell activation and tolerance.

#### 3.2.1.1 Mechanism of Action of Nivolumab

PD-1 is a member of the CD28 family of T-cell co-stimulatory receptors that also includes CD28, CTLA-4, ICOS, and BTLA.[19] 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.[20] 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.[21]

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 re stimulation 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 result in tumor rejection in several immunocompetent mouse tumor models (MC38, SA1/N, and PAN02).[21]

Single dose pharmacokinetics (PK) of nivolumab was evaluated in subjects with multiple tumor types in CA209001, whereas multiple dose PK was evaluated in subjects in CA209003. In addition, a population pharmacokinetic (PPK) model was developed with data from subjects in CA209001, CA209002, and CA209003.

Single dose PK of nivolumab was evaluated in 39 subjects with multiple tumor types in study CA209001 in the dose range of 0.3 to 10 mg/kg. The median Tmax across single doses ranged from 1.6 to 3 hours with individual values ranging from 0.9 to 7 hours. The geometric means of Cmax and AUC(INF) of nivolumab administered at dosages of 0.3 mg/kg, 1 mg/kg, 3 mg/kg, and 10 mg/kg demonstrated approximate dose proportionality. The geometric mean of clearance (CL), after a single intravenous (IV) dose, ranged from 0.13 to 0.19 mL/h/kg, while mean volume of distribution during the terminal phase (Vz) varied between 83 to 113 mL/kg across doses. There was moderate variability in PK parameters among subjects, with coefficient of variation (CV) of 20% to 32% in Cmax, 39% to 47% in AUC(INF), 17% to 43% in clearance, and 23% to 40% in Vz. The mean terminal elimination half-life of nivolumab is 17 to 25 days, which is consistent with the half-life of endogenous IgG4, indicating that the elimination mechanism of nivolumab may be similar to that of IgG4. Both elimination and distribution of nivolumab appear to be

independent of dose in the dose range studied. Additional details are provided in the investigator brochure. A preliminary PPK model was developed by nonlinear mixed effect modeling using data from 379 subjects in CA209001, CA209002 and CA209003. Clearance (CL) of nivolumab is independent of dose in the dose range (0.1 to 10 mg/kg) and tumor types studied. The body weight normalized dosing produces approximately constant trough concentrations over a wide range of body weights, and hence is appropriate for future clinical trials of nivolumab.

#### 3.2.1.2 Mechanism of Action of Ipilimumab

Cytotoxic T-lymphocyte-associated protein 4 (CTLA-4), an activation-induced T-cell surface molecule, is a member of the CD28:B7 immunoglobulin superfamily that competes with CD28 for B7. CTLA-4 mediated signals are inhibitory and turn off T cell-dependent immune responses. ipilimumab is a fully human monoclonal IgG1κ that binds to the CTLA-4 antigen expressed on a subset of T cells from human and nonhuman primates. The proposed mechanism of action for ipilimumab is interference of the interaction of CTLA-4 with B7 molecules on APCs, with subsequent blockade of the inhibitory modulation of T-cell activation promoted by the CTLA 4/B7 interaction.[22]

### 3.2.2 Rationale for Combination of Nivolumab and Ipilimumab

Preclinical data indicate that the combination of PD-1 and CTLA-4 receptor blockade may improve antitumor activity. In vitro combinations of nivolumab plus ipilimumab increase IFN-γ production 2- to 7-fold over either agent alone in a mixed lymphocyte reaction. Increased antitumor activity of the combination was also observed in 3 of 5 syngeneic murine cancer models. In a murine melanoma vaccine model, blockade with either CTLA-4 or PD-1 antibodies increased the proportion of CTLA-4 and PD-1-expressing CD4/CD8 tumor infiltrating T effector cells, and dual blockade increased tumor infiltration of T effector cells and decreased intratumoral T regulatory cells, as compared to either agent alone.[23]

In the clinical setting, the combination of nivolumab and ipilimumab was evaluated in CA209004 (MDX1106-04), a Phase 1b multiple ascending dose study in subjects with treatment naive and previously treated advanced melanoma. Results showed promising activity with higher, tolerable toxicity profile compared to ipilimumab alone. Based on this, CA209069 was conducted, a randomized double blind Phase 2 study of nivolumab in combination with ipilimumab versus ipilimumab monotherapy in subjects with BRAF-wild type (WT) and mutant, with untreated unresectable or metastatic melanoma. The regimens used were: nivolumab 1mg/kg plus ipilimumab 3 mg/kg every 3 weeks for 4 doses followed by nivolumab 3 mg/kg every 2 weeks versus ipilimumab 3 mg/kg every 3 weeks for 4 doses.[24]

In subjects with BRAF-WT tumors treated with nivolumab and ipilimumab combination, there was improved ORR at 61% (44/72), with 22% (16/72) complete responses (CR), as compared to 11% (4/37) ORR with 0 CRs in those treated with ipilimumab alone. The median PFS was not reached in the combination versus 4.4 months for ipilimumab alone (HR = 0.4). Improved clinical outcomes (PFS and ORR) with nivolumab and ipilimumab combination was confirmed by CA209067, a randomized Phase 3 study. In subjects with previously untreated, unresectable or metastatic melanoma (n = 945), the median PFS was 11.5 months (95% CI, 8.9 to 16.7) in the

nivolumab plus-ipilimumab group, 6.9 months (95% confidence interval [CI], 4.3 to 9.5) in the nivolumab group, and 2.9 months (95% CI, 2.8 to 3.4) in the ipilimumab group. Significantly longer progression-free survival was observed in the nivolumab-plus-ipilimumab group than in the ipilimumab group (hazard ratio for death or disease progression, 0.42; 99.5% CI, 0.31 to 0.57; $P < 0.001$) and in the nivolumab group than in the ipilimumab group (hazard ratio, 0.57; 99.5% CI, 0.43 to 0.76; $P < 0.001$). The hazard ratio for the comparison between the nivolumab plus ipilimumab group and the nivolumab group was 0.74 (95% CI, 0.60 to 0.92).[25]

**Table 3.2.2-1: Treatment-related adverse events from selected cohorts in CA209012 (NSCLC)**

| Arm[a] | No. Subjects / arm | Follow-up time (median, wks) | No. Subjects still on treatment | Subjects with drug-related AEs | No. Subjects with Grade 3-4 drug-related AEs | No. subjects d/c due to drug-related AEs (all Grades) |
|---|---|---|---|---|---|---|
| N[b] | 31 | 88.1 | 5 (16%) | 26 (83.9%) | 9 (29%) | 4 (13%) |
| O[b] | 40 | 46.9 | 7 (18%) | 29 (72.5%) | 16 (40%) | 3 (8%) |
| P[b] | 38 | 55.9 | 9 (24%) | 31 (81.6%) | 14 (36.8%) | 4 (10.5%) |
| Q[b] | 39 | 51.1 | 7 (18%) | 28 (71.8%) | 13 (33.3%) | 5 (12.8%) |
| F[c] | 52 | 62.2 | 5 (13%) | 37 (71%) | 10 (19%) | 5 (10%) |

[a] N: nivolumab 1 mg/kg plus ipilimumab 1 mg/kg every 3 weeks x 4, followed by nivolumab 3 mg/kg every 2 weeks; O: nivolumab 1 mg/kg every 2 weeks plus ipilimumab 1 mg/kg every 6 weeks; P: Nivolumab 3 mg/kg every 2 weeks plus ipilimumab 1 mg/kg every 12 weeks; Q: nivolumab 3 mg/kg every 2 weeks plus ipilimumab 1 mg/kg every 6 weeks; F: nivolumab 3 mg/kg every 2 weeks

[b] based on February 2016 database lock

[c] based on March 2015 database lock

**Table 3.2.2-2: Efficacy of First-Line Treatment of Nivolumab/Ipilimumab Combination in CA209012 (NSCLC)**

| | Nivo 1 + Ipi 1 Q3W N (n=31) | Nivo 1 + Ipi 1 Q6W O (n=40) | Nivo 3 Q2W + Ipi 1 Q12W P (n=38) | Nivo 3 Q2W+ Ipi 1 Q6W Q (n=39) |
|---|---|---|---|---|
| Confirmed ORR, % (95% CI) | **19** (7.5, 37.5) | **33** (19, 49) | **47** (31, 64) | **39** (23, 55) |
| PFS rate at 24 wks (95% CI) | 52 (33, 68) | 47 (31, 62) | 65 (47, 78) | 47 (31, 62) |
| mPFS, mos (95% CI) | 7.8 (2.1, 11.7) | 5.6 (2.7, 9.7) | 8.1 (5.6, 11.6) | 3.9 (2.6, 13.2) |
| 1 year OS rate, % (95% CI) | 65 (45, 79) | NC | NC | 69 (52, 81) |

**Table 3.2.2-2: Efficacy of First-Line Treatment of Nivolumab/Ipilimumab Combination in CA209012 (NSCLC)**

| | Nivo 1 + Ipi 1 Q3W N (n=31) | Nivo 1 + Ipi 1 Q6W O (n=40) | Nivo 3 Q2W + Ipi 1 Q12W P (n=38) | Nivo 3 Q2W+ Ipi 1 Q6W Q (n=39) |
|---|---|---|---|---|
| Median length of follow-up, months | 20.3 (2-28) | 10.8 (0.4-19) | 12.9 (1, 18) | 11.7 (1, 18.2) |

Clinical activity was observed in all combination cohorts (Table 3.2.2-2), but numerically higher response rates were observed in cohorts evaluating the approved dose of nivolumab 3 mg/kg, with confirmed response rates of 39 - 47% (cohorts P and Q). Some differences in terms of response rate and PFS were observed between cohort P and Q, which is possibly due to different factors such as the small sample size in both cohorts, limited follow-up as well as the imbalance between the two arms in terms of smoking status.

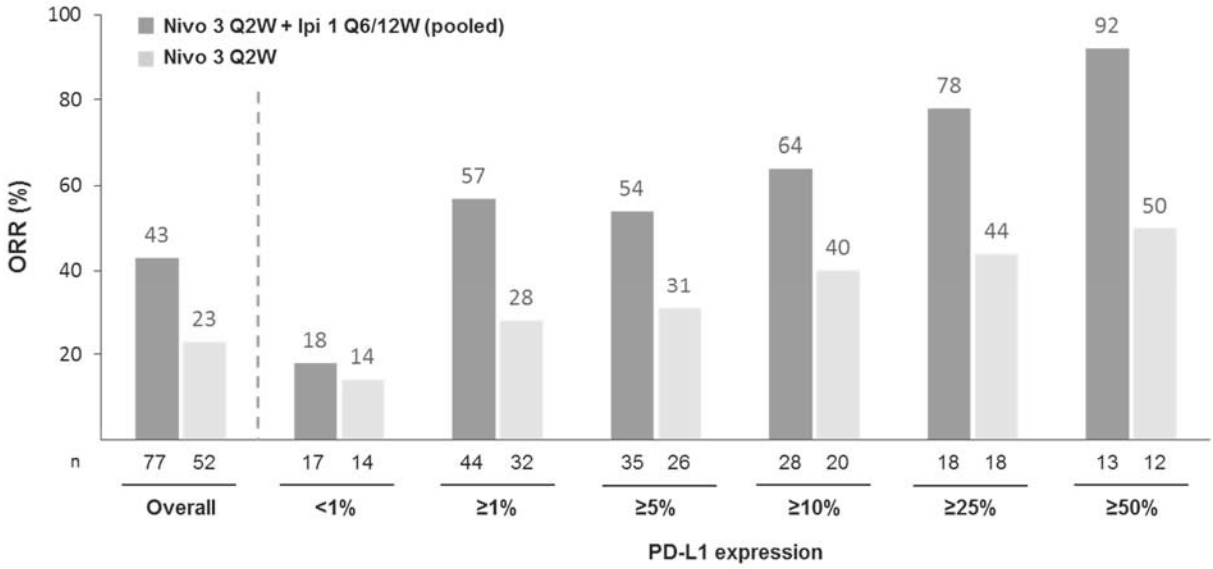
**Table 3.2.2-3: Efficacy by Tumor with PD-L1 Expression (≥ 1%) in CA209012**

| | Nivo 1 + Ipi 1 Q3W (Arm N n=12) | Nivo 1 Q2W + Ipi 1 Q6W (Arm O n=21) | Nivo 3 Q2W + Ipi 1 Q12W (Arm P n=21) | Nivo 3 Q2W + Ipi 1 Q6W (Arm Q n=23) |
|---|---|---|---|---|
| ORR, % | 25 | 36 | 57 | 57 |
| mPFS, months (95% CI) | 2.6 (1.6, ) | 5.1 (2.6, ) | 8.1 (5.6, ) | 10.6 (3.6, ) |
| PFS rate at 24 wks, % (95% CI) | 42 (15, 67) | 43 (21, 63) | 75 (50, 89) | 65 (42, 81) |
| 1 year OS rate, % (95% CI) | 58 (27, 80) | NC | 90 (66, 97) | 83 (60, 93) |

When clinical activity was analyzed by PD-L1 expression, there appeared to be higher efficacy in subjects with PD-L1 expressing tumors, however interpretation is limited by the small number of subjects. Those with PD-L1 ≥ 1% expressing tumors treated with nivolumab and ipilimumab combination in cohorts P and Q had response rates of 57%. PFS appeared to be also higher in these subsets as well.

Using different cutoff levels for PD-L1 expression, the ipilimumab + nivolumab combination is consistently superior to nivolumab monotherapy in terms of ORR.

**Figure 3.2.2-1: Nivolumab Plus Ipilimumab in First-line NSCLC (CA209012): Efficacy Across All Tumor PD-L1 Expression Levels**




Combination data based on a February 2016 database lock; monotherapy data based on a March 2015 database lock

In this study, patients with first line PD-L1 negative NSCLC will also receive the combination of nivolumab and ipilimumab.

In CA209012 study, given that the number of patients receiving nivolumab 3mg/kg combined with ipilimumab 1mg/kg every 6 or 12 weeks was too small, the interpretation of the efficacy data reported in this study is challenging.

There is an ongoing phase III CA209227 trial that has included a large cohort of PD-L1 < 1% patients receiving nivolumab 3 mg/kg Q2w + ipilimumab 1 mg/kg Q6w. This study is under the oversight of an independent DMC, which has recommended that the trial continue as planned. Recently, BMS announced that study CA209227 has met its co-primary endpoint of PFS comparing nivolumab + ipilimumab in high TMB NSCLC, regardless of PD-L1 expression.

Although follow-up is still limited, the PFS and ORRs observed in these cohorts are highly encouraging. With comparable efficacy and safety data from cohorts P and Q, the nivolumab plus ipilimumab every 6 week dosing schedule (cohort Q) is the selected regimen moving forward.[26] Aside from utilizing the approved nivolumab dose in NSCLC, it would also provide the highest dose and frequency of ipilimumab feasible in a combination regimen.

In updated data from CA209012 as of 18-Feb-2016 indicate 21% of subjects remain on therapy in cohorts P+Q. The primary reason for treatment discontinuation was disease progression in 18 subjects (47.4%) in cohort P, and 20 subjects (51.3%) in cohort Q. The median number of doses of nivolumab and ipilimumab was 17 and 3 on cohort P (range 1 to 40/1 to 7), with 8 and 2 in cohort Q (range 1-40/1 - 14). There were 8 subjects in cohort P and 15 in cohort Q with disease progression within 3 months of study start. Subject characteristics were consistent with a typical

advanced/metastatic NSCLC population and roughly balanced across cohorts considering the small sample size.

In view of the safety and efficacy data seen with nivolumab every 2 weeks and ipilimumab every 6 weeks in subjects with NSCLC, it is recommended to proceed with combination dosing for the Study CA209592. See Section 3.2.2.1 for nivolumab Q2Week 240 mg dosing rationale.

#### 3.2.2.1 Rationale for Nivolumab Flat Dosing

Nivolumab has been extensively studied in the NSCLC patient population in studies CA209003, CA209063, CA209017, and CA209057, with body weight normalized dosing (mg/kg). Nivolumab pharmacokinetics (PK) and exposures of participants in these studies have been characterized by population pharmacokinetic (PPK) analysis of data collected from these studies, together with PK data from several phase 1, 2, and 3 clinical studies of nivolumab monotherapy in solid tumors. 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 a mg/kg dose represents an over-adjustment for the effect of body weight on nivolumab PK.

Flat dosing offers several advantages over body weight normalized dosing, including reduced potential for dosing errors and shortened dosage preparation time. A flat dose of 240 mg every 2 weeks is expected to produce the equivalent average exposure to 3 mg/kg every 2 weeks at the median body weight of ~80 kg in nivolumab-treated participants.

A PPK model predicted overall nivolumab exposures across participants with a wide range of body weight (35-160 kg) for a 240 mg every 2 weeks flat dose to be similar to that from 3 mg/kg every 2 weeks. 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 from these regimens are maintained well below those in 10 mg/kg every 2 weeks, which was established as a safe and well-tolerated dose.

In addition, the relationship between nivolumab exposure produced by 3 mg/kg and efficacy has been found to be relatively flat. Taken together, the PK, safety, and efficacy data indicate that the safety and efficacy profile of 240 mg nivolumab will be similar to that of 3 mg/kg nivolumab.

### 3.2.3 Rationale for Shorter Infusion Times for Nivolumab and Ipilimumab

Long infusion times place a burden on subjects and treatment centers. Establishing that nivolumab and ipilimumab can be safely administered using shorter infusion times of 30 minutes duration in subjects will diminish the burden provided no change in safety profile. Previous clinical studies of nivolumab monotherapy and ipilimumab monotherapy and the combination of nivolumab and ipilimumab have used a 60 minute infusion duration for nivolumab and 90-minute infusion duration for ipilimumab (1 - 3 mg/kg dosing for both). However, both nivolumab and ipilimumab have been administered at up to 10 mg/kg with the same infusion duration.

Nivolumab has been administered safely over 60 minutes at doses ranging up to 10 mg/kg safely over long treatment duration. In Study CA209010, (a Phase 2, randomized, double blinded, dose ranging study of nivolumab in subjects with advanced/metastatic clear cell RCC) a dose

association was observed for infusion site reactions and hypersensitivity reactions (1.7% at 0.3 mg/kg, 3.7% at 2 mg/kg and 18.5% at 10 mg/kg). All the events were Grade 1 - 2 and were manageable. An infusion duration of 30 minutes for 3 mg/kg nivolumab (30% of the dose provided at 10 mg/kg) is not expected to present any safety concerns compared to the prior experience at 10 mg/kg nivolumab dose infused over a 60-minute duration.

Similarly, ipilimumab at 10 mg/kg has been safely administered over 90 minutes. In the CA184022 study, where ipilimumab was administered up to a dose of 10 mg/kg, on-study drug related hypersensitivity events (Grade 1 - 2) were reported in 1 (1.4%) subject in the 0.3 mg/kg and in 2 (2.8%) subjects in the 10 mg/kg group. There were no drug-related hypersensitivity events reported in the 3 mg/kg group. Across the 3 treatment groups, no Grade 3 - 4 drug-related hypersensitivity events were reported and there were no reports of infusion reactions. Ipilimumab 10 mg/kg monotherapy has also been safely administered as 90 minute infusion in large Phase 3 studies in prostate cancer (CA184043) and as adjuvant therapy for Stage 3 melanoma (CA184029), with infusion reactions occurring in subjects. Administering 1 mg/kg of ipilimumab represents one-tenth of the 10 mg/kg dose.

Overall, infusion reactions including high-Grade hypersensitivity reactions have been uncommon across nivolumab or ipilimumab clinical studies or the combination of nivolumab and ipilimumab. Furthermore, a 30-minute break after the first infusion for the combination cohort will ensure the appropriate safety monitoring before the start of the second infusion. Overall, a change in safety profile is not anticipated with 30-minute infusion of nivolumab, ipilimumab or combination.

### 3.2.4 Rationale for Permitting Continued Treatment in Select Cases of Progressive Disease

Accumulating clinical evidence indicates some subjects treated with immune system stimulating agents may develop progression of disease (by conventional response criteria) before demonstrating clinical objective responses and/or stable disease. This phenomenon was observed in approximately 10% of subjects in the Phase 1 study of nivolumab and also with ipilimumab monotherapy.[21]

Two hypotheses have been put forth to explain this phenomenon. First, enhanced inflammation within tumors could lead to an increase in tumor size which would appear as enlarged index lesions and as newly visible small non-index lesions. Over time, both the malignant and inflammatory portions of the mass may then decrease leading to overt signs of clinical improvement. Alternatively, in some individuals, the kinetics of tumor growth may initially outpace anti-tumor immune activity. With sufficient time, the anti-tumor activity may dominate and become clinically apparent. Therefore subjects will be allowed to continue study therapy after initial investigator assessed RECIST 1.1 defined progression if they are assessed to be deriving clinical benefit and tolerating study drug. Such subjects must discontinue study therapy upon evidence of further progression as defined in Section 8.1.2.

### 3.2.5 Rationale for Tumor Mutational Burden Testing

In patients with advanced disease, access to tumor tissue can be challenging and often results in limited collection for investigation in clinical trials. This challenge underscores the value for

investigating surrogate biomarkers of clinical outcomes using less invasive sampling techniques, such as blood collection. Recently the phase 2 POPLAR and phase 3 OAK studies, from Roche/Genentech confirmed retrospective data analysis reported analytic and clinical validation for the blood TMB (bTMB) assay.[27] Using the Foundation Medicine's assay, these studies indicated that high bTMB associated with response to atezolizumab in individuals with previously-treated non-small cell lung cancer.

Next Generation Sequencing (NGS), also known as Ultra-deep sequencing allows the detection of multiple mutations in several genes through parallel sequencing of several DNA fragments. [redacted] bTMB data will be generated using NGS, through generation of a short fragment DNA library, single fragment clonal amplification and massive parallel sequencing and data analysis.

Based on the Part 2 expansion cohort in this study, tumor TMB and blood TMB will be collected at baseline. The association of tissue and blood TMB analyses with clinical outcomes will be assessed independently.

### *3.2.6 Research Hypothesis*

Immunomodulatory and pharmacodynamic changes in the peripheral blood and tumor tissue are expected in subjects with advanced or metastatic NSCLC receiving nivolumab + ipilimumab. Although no hypotheses will be formally tested, the CA209592 study will characterize the potential association between biomarkers, including tumor mutational burden, in peripheral blood and tumor tissue with clinical efficacy measures, and generate hypotheses for future studies.

## 3.3 Benefit/Risk Assessment

Patients with advanced or metastatic NSCLC represent an important unmet medical need. The clinical activity of nivolumab plus ipilimumab observed to date suggests the potential for improved clinical outcomes in .subjects with NSCLC.

Published data from CA209012 study in first line NSCLC, showed confirmed response rates of 39-47% with nivolumab 3 mg/kg Q2w and ipilimumab 1 mg/kg Q6w or Q12w. Activity was observed in both PD-L1 expressing and non-expressing tumors. However, higher response rates were observed in patients whose tumors express PD-L1 (≥ 1%) with a confirmed response rate of 57%).

The safety profile of nivolumab and nivolumab plus ipilimumab is characterized by immune-related toxicities, such as diarrhea, rash, pneumonitis, liver toxicity, and endocrinopathies. The frequencies and intensities of these events in the combination are variable and depend on the specific doses and schedule used. In the dosing schedules selected, these events were mostly low grade, and manageable with the use of corticosteroids.

To assure an ongoing favorable risk/benefit assessment for participants enrolled into CA209592, high-grade, treatment-related adverse events will be closely monitored throughout the conduct of the trial. The Medical Monitor will be responsible for reviewing, on a systematic and continuous

basis, the safety of participants on this study. This includes a review of serious and non-serious adverse events.

More detailed information about the known and expected benefits and risks and reasonably anticipated adverse events (AEs) of nivolumab and ipilimumab may be found in the Investigator's Brochures.

# 4 OBJECTIVES AND ENDPOINTS

**Table 4-1: Objectives and Endpoints for Part 1**

| Objectives | Endpoints |
|---|---|
| **Primary** | |
| • To evaluate baseline tumor mutational burden as a candidate biomarker of clinical efficacy of nivolumab and ipilimumab combination therapy.<br>• To investigate the potential association between candidate biomarkers in peripheral blood and tumor tissue at baseline and on-treatment with clinical efficacy measures. | • The clinical efficacy will be measured by the analysis endpoint of objective response rate (ORR). The association of ORR with candidate biomarkers in peripheral blood and tumor tissue at baseline and on-treatment will be assessed. Candidate biomarkers may include:<br>o Baseline tissue TMB and blood TMB<br>o Potential biomarkers/signatures (including PD-L1 expression) both at baseline and on treatment<br>o Immunomodulatory and pharmacodynamic activity |
| **Secondary** | |
| • To evaluate efficacy in patient subgroups defined by baseline discovery biomarkers. | • ORR, disease control rate (DCR)<br>• Duration of response (DOR) and time to response (TTR)<br>• Progression free survival (PFS)<br>• Overall survival (OS) |
| [redacted] | |

| Table 4-1: Objectives and Endpoints for Part 1 | |
|---|---|
| **Objectives** | **Endpoints** |
| [redacted] | |

The objectives and endpoints for Part 2 are listed in Table 4-2.

| Table 4-2: Objectives and Endpoints for Part 2. | |
|---|---|
| **Objectives** | **Endpoints** |
| **Primary** | |
| • To evaluate the association between baseline tissue TMB/bTMB and clinical efficacy (ORR) for participants in Part 2 | • The clinical efficacy will be measured by the analysis endpoint of objective response rate (ORR). The association of ORR with baseline tissue TMB and bTMB will be assessed |
| **Secondary** | |
| • To investigate bacterially generated and human components enteric biomarkers and identify potential associations with clinical outcomes, including safety and efficacy for participants | • ORR, PFS, OS<br>• Incidence of AES, SAEs, and select AEs |
| [redacted] | |

- **Objective response rate (ORR):** The proportion of patients with best overall response (BOR) of RECIST 1.1 defined confirmed complete response (CR) or partial response (PR) in a pre-defined study population.
- **Disease control rate (DCR):** The proportion of patients with best overall response (BOR) of RECIST 1.1 defined complete response (CR), partial response (PR), or stable disease (SD) in a pre-defined study population
- **Duration of response (DOR):** DOR is defined as the time between the date of the first confirmed response (CR/PR) to the date of the first documented tumor progression (per RECIST 1.1) or death due to any cause. Participants who neither progress nor die will be censored on the date of their last evaluable tumor assessment. Participants who started any subsequent anti-cancer therapy without a prior reported progression will be censored at the last evaluable tumor assessment prior to or on the date of initiation of subsequent anti-cancer therapy.

- **Time to response (TTR):** TTR is measured from the time of first dosing date to the time the criteria for CR/PR are first met.
- **Progression free survival (PFS):** PFS is defined as the time from first dosing date to the date of the first documented tumor progression (per RECIST) or death due to any causes. Participants who neither progress nor die will be censored on the date of their last evaluable tumor assessment. Participants who started any subsequent anti-cancer therapy without a prior reported progression will be censored at the last evaluable tumor assessment prior to or on the date of initiation of subsequent anti-cancer therapy.
- **Overall survival (OS):** OS is defined as the time from first dosing date to the date of death. If a participant didn't die, OS will be censored on the last date the participant was known to be alive.

# 5 STUDY DESIGN

## 5.1 Overall Design

Protocol CA209592 is an open-label, exploratory Phase 2 trial evaluating nivolumab combined with ipilimumab in participants ≥ 18 years old with histologically confirmed advanced or metastatic NSCLC, with no prior systemic anticancer therapy given as primary therapy for advanced disease.

In Part 1, participants will undergo screening evaluations to determine eligibility within 28 days prior to treatment assignment, and approximately **100** patients will be treated with at least 50 PD-L1 positive patients and 50 PD-L1 negative patients. Tumor sample for PD-L1 status assessment is required at screening.

Upon determination of PD-L1 status (cut-off of 1%), 2 cohorts will be defined: PD-L1 positive and negative, and patients in each cohort will receive nivolumab + ipilimumab.

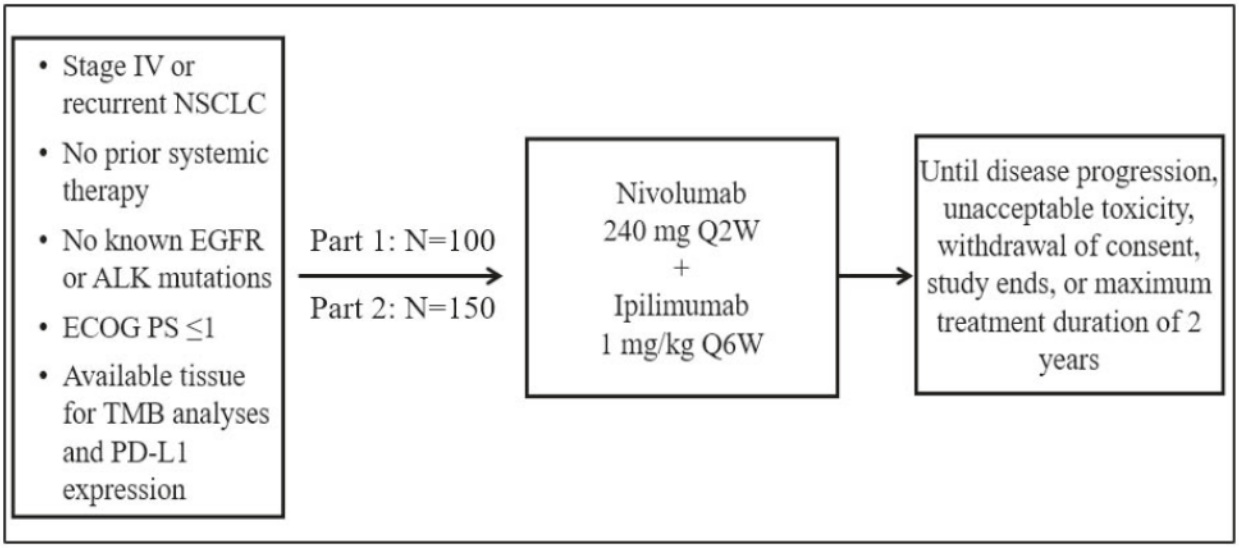
In Part 2, approximately 150 participants will be treated with nivolumab + ipilimumab regardless of their PD-L1 status.

All participants (Part 1 and Part 2) will be treated with the following:

- nivolumab 240mg IV every 2 weeks + ipilimumab 1 mg/kg IV every 6 weeks until disease progression, unacceptable toxicity, withdrawal of consent, the study ends, or a maximum treatment duration of 2 years, whichever occurs first. Participants will be permitted to continue on nivolumab +/- ipilimumab beyond initial RECIST 1.1 defined progression, as long as they meet the criteria described in Section 8.1.2.

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

**Figure 5.1-1: Study Design Schematic Part 1 and Part 2**




The analysis of the primary endpoint ORR will take place after the last treated subject is followed for at least 6 months. Additional survival analysis will be conducted with longer follow-up.

The analysis of the primary endpoint ORR for Part 2 will take place after at least 150 subjects are followed for at least 6 months. Additional survival analysis will be conducted with longer follow-up.

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

A Data Monitoring Committee (DMC) will not be utilized for this study, given the following:

1) This study is an open-label study.
2) Data from the ongoing Phase I CA209012 study has demonstrated a favorable benefit/risk profile and a manageable safety that is consistent with prior experience with these agents.
3) Safety data will be closely monitored by BMS, with real time review and assessment of SAEs as they are received, and periodic review of all adverse events data for potential new safety signals.

## 5.2 Number of Participants

**Part 1:** The planned sample size is approximately 100 patients. Approximately up to 150 participants are expected to be enrolled to achieve 100 treated participants in the trial. For this hypothesis-generating study, the sample size is mainly decided by operational feasibility. No formal hypothesis testing will be conducted. Participation in Part 1 is restricted to sites in the US.

**Part 2**: Approximately 200 participants are expected to be enrolled to achieve 150 treated participants. Sites in US and Europe may participate in Part 2.

## 5.3 End of Study Definition

The duration of the study from start of enrollment to analysis of the primary endpoint is expected to be approximately 48 months. The study will end once additional survival follow-up has concluded.

## 5.4 Scientific Rationale for Study Design

Clinical activity of nivolumab and ipilimumab combination has shown superior efficacy over monotherapy in different tumor types including NSCLC. Although efficacy is superior in PD-L1 positive patients, responses were also observed in subjects with tumors that are not expressing PD-L1 ligand.

Unfortunately, not all patients will respond to immune checkpoint blockade, therefore there is the need for a better understanding of factors that can predict response and progression.

CA209592 study has been designed to explore the immunomodulatory and pharmacodynamic activity of nivolumab and ipilimumab, and potential biomarkers/signatures correlated with response and safety in both PD-L1 positive and negative subjects.

## 5.5 Justification for Dose

The dose and schedule of nivolumab and ipilimumab in this trial was selected in part based on the data observed in the CA209012 study[28], which demonstrated activity of the combination of nivolumab 3 mg/kg every 2 weeks plus ipilimumab 1 mg/kg every 6 weeks in both PD-L1+ and PD-L1- tumors, coupled with a manageable safety profile.

Nivolumab flat dosing offers several advantages over body weight normalized dosing, including reduced potential for do[29]sing errors and shortened dosage preparation time. A flat dose of 240 mg every 2 weeks is expected to produce the equivalent average exposure to 3 mg/kg every 2 weeks at the median body weight of ~80 kg in nivolumab-treated participants.

CA209-592 will include nivolumab 240mg every 2 weeks plus ipilimumab 1 mg/kg every 6 weeks.

## 5.6 Duration of Treatment with Nivolumab plus Ipilimumab

The optimal duration of immunotherapy is an important question and continues to be investigated. Clinical trials across different tumors types in the nivolumab and ipilimumab development program indicate that most of the responses occur early, with a median time to response of 2-4 months, and emerging data suggests that benefit can be maintained in the absence of continued treatment. A recent analysis in a melanoma study suggests the majority of patients who discontinue nivolumab and/or ipilimumab for toxicity maintain disease control in the absence of further treatment.[30] Furthermore, a limited duration of ipilimumab, including only 4 induction doses, resulted in long term survival in patients with metastatic melanoma, with a sustained plateau in survival starting around 2 years after the start of treatment.[31]

Accumulating data suggest that 2 years of PD-1 checkpoint inhibitor treatment may be sufficient for long term benefit. CA209003, a dose-escalation cohort expansion trial evaluating the safety and clinical activity of nivolumab in patients with previously treated advanced solid tumors (including 129 subjects with NSCLC), specified a maximum treatment duration of 2 years. Among 16 subjects with non-small cell lung cancer (NSCLC) who discontinued nivolumab after completing 2 years of treatment, 12 subjects were alive >5 years and remained progression-free without any subsequent therapy. In the CA209003 NSCLC cohort, the overall survival (OS) curve begins to plateau after 2 years, with an OS rate of 25% at 2 years and 18% at 3 years.[32] These

survival outcomes are similar to phase 3 studies in previously treated NSCLC, in which nivolumab treatment was continued until progression or unacceptable toxicity (2 year OS rates of 23% and 29%, and 3 year OS rates of 16%-18% for squamous and non-squamous NSCLC respectively).[33]

Similar results have been reported in clinical studies of pembrolizumab, another PD-1 inhibitor. Keynote-010 was a randomized phase 3 trial of pembrolizumab (at either 2 mg/kg or 10 mg/kg every 3 weeks) versus docetaxel in subjects with previously treated, PD-L1-positive, advanced NSCLC which specified a maximum treatment duration of 2 years for pembrolizumab. OS was significantly longer with both pembrolizumab 2 mg/kg (HR = 0.72, p = 0.00017) and pembrolizumab 10 mg/kg (HR = 0.60, $p < 0.00001$) compared to docetaxel, with an OS plateau developing beyond 2 years in both pembrolizumab arms. Among 690 patients who received pembrolizumab, 47 patients completed 2 years of pembrolizumab and stopped treatment. Most were able to maintain their response, including those with stable disease, with only 2 patients (4%) having confirmed progression after stopping at 2 years.[34]

Keynote-006 was a randomized phase 3 study of pembrolizumab versus ipilimumab in patients with advanced melanoma, which also specified a maximum 2 year duration of pembrolizumab treatment. 104 (19%) of 556 patients randomized to pembrolizumab completed 2 years of treatment. With a median follow-up of 9 months after completion of pembrolizumab, the estimated risk of progression or death was 9% in these patients.[35]

Taken together, these data suggest that treatment beyond 2 years is unlikely to confer additional clinically meaningful benefit and that the risk of progression after discontinuing treatment at 2 years is low.

In contrast, a shorter duration of nivolumab of only 1 year was associated with increased risk of progression in previously treated patients with NSCLC, suggesting that treatment beyond 1 year is likely needed. In CA209153, patients with previously treated advanced NSCLC who completed 1 year of nivolumab therapy were randomized to either continue or stop treatment, with the option of retreatment upon progression. Among 163 patients still on treatment at 1 year and without progression, those who were randomized to continue nivolumab had significant improvement in progression-free survival (PFS) compared to those who were randomized to stop treatment, with median PFS (post-randomization) not reached vs 10.3 months, respectively; HR=0.42 (95% CI, 0.25 to 0.71). With a median follow-up of 14.9 months post-randomization, there also was a trend for patients on continued treatment to live longer (OS HR = 0.63 [95% CI: 0.33, 1.20]). Of note, the PFS curves in both groups plateau approximately 1 year after randomization (ie, 2 years after treatment initiation), suggesting that there may be minimal benefit in extending treatment beyond a total of 2 years.[36]

Collectively, these data suggest that there is minimal if any benefit derived from continuing I-O treatment beyond two years in advanced tumors. However, even though immunotherapy is well tolerated, patients will be at risk for additional toxicity with longer term treatment. Therefore, in this study, treatment will be given for a maximum of 2 years from the start of study treatment.

# 6 STUDY POPULATION

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

## 6.1 Inclusion Criteria

**1) Signed Written Informed Consent**

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

b) Participants must be willing and able to comply with scheduled visits, treatment schedule, and laboratory testing.

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

a) Subjects with histologically confirmed Stage IV or recurrent NSCLC (per the 7th International Association for the Study of Lung Cancer classification [Goldstraw 2007]), squamous or non-squamous histology, with no prior systemic anticancer therapy (including EGFR and ALK inhibitors) given as primary therapy for advanced or metastatic disease.

Prior adjuvant or neoadjuvant chemotherapy is permitted as long as the last administration of the prior regimen occurred at least 6 months prior to enrollment.

Prior chemoradiation for locally advanced disease is also permitted as long as the last administration of chemotherapy or radiotherapy (which ever was given last) occurred at least 6 months prior to enrollment.

b) Measurable disease by CT or MRI per RECIST 1.1 criteria. Tumor assessment performed within 28 days of start of study treatment.

c) All participants must have tissue submitted during screening. This may include either a formalin-fixed paraffin-embedded (FFPE) tissue block or a minimum of 15 unstained tumor tissue slides.

**Part 1**: For cohort assignment purposes (PD-L1 status determination), archival tissue samples $\leq$ 3 months old will be allowed to determine PD-L1 IHC results. Fresh pre-dose biopsy samples (5 cores: 3 in FFPE and 2 in HypoThermosol®) will still need to be submitted.

**Part 2**: a fresh biopsy (preferred) or archival sample ($\leq$ 3 months old) is required for enrollment, but treatment may start before test results are received.

d) ECOG Performance Status 0 or 1.

**3) Age and Reproductive Status**

a) Males and Females, ages 18 years (or age of majority) and older.

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 (Appendix 4) for the duration of treatment followed by a period of 30 days (duration of ovulatory cycle) plus the time required for the investigational drug to undergo five half-lives. WOCBP treated with nivo + ipi combination should use an

adequate method to avoid pregnancy for 5 months (30 days plus the time required for nivolumab to undergo five half-lives) after the last dose of investigational drug.

e) Males who are sexually active with WOCBP must agree to follow instructions for method(s) of contraception (Appendix 4) for the duration of treatment followed by a period of 90 days (duration of sperm turnover) plus the time required for the investigational drug to undergo five half-lives. Males treated with nivo + ipi combination who are sexually active with WOCBP must continue contraception for 7 months (90 days plus the time required for nivolumab to undergo five half-lives) after the last dose of investigational drug. In addition, male participants must be willing to refrain from sperm donation during this time.

f) Azoospermic males are exempt from contraceptive requirements. 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 4) which have a failure rate of < 1% when used consistently and correctly.

## 6.2 Exclusion Criteria

**1) Medical Conditions**

a) Subjects with known EGFR mutations which are sensitive to available targeted inhibitor therapy (including, but not limited to, deletions in exon 19 and exon 21 [L858R] substitution mutations) are excluded. All subjects with non-squamous histology must have been tested for EGFR mutation status; use of an FDA-approved test is strongly encouraged. Non-squamous subjects with unknown or indeterminate EGFR status are excluded.

b) Subjects with known ALK translocations which are sensitive to available targeted inhibitor therapy are excluded. If tested, use of an FDA-approved test is strongly encouraged. Subjects with unknown or indeterminate ALK status may be enrolled.

c) Subjects with untreated CNS metastases are excluded.

   i) Subjects are eligible if CNS metastases are adequately treated and subjects are neurologically returned to baseline (except for residual signs or symptoms related to the CNS treatment) for at least 2 weeks prior to enrollment. In addition, participants must be either off corticosteroids, or on a stable or decreasing dose of ≤ 10 mg daily prednisone (or equivalent) for at least 2 weeks prior to treatment assignment.

d) Prior malignancy active within the previous 3 years except for locally curable cancers that have been apparently cured, such as basal or squamous cell skin cancer, superficial bladder cancer, or carcinoma in situ of the prostate, cervix, or breast.

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

f) Subjects with a condition requiring systemic treatment with either corticosteroids (> 10 mg daily prednisone equivalent) or other immunosuppressive medications within 14 days of

enrollment. Inhaled or topical steroids, and adrenal replacement steroid doses > 10 mg daily prednisone equivalent, are permitted in the absence of active autoimmune disease.

g) Subjects with interstitial lung disease that is symptomatic or may interfere with the detection or management of suspected drug-related pulmonary toxicity.

h) Subjects with serious or uncontrolled medical disorders and any 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.

i) Subjects with a known history of a positive test for human immunodeficiency virus (HIV) or known acquired immunodeficiency syndrome (AIDS). NOTE: Testing for HIV must be performed at sites where mandated locally. See Appendix 8.

**2) Prior/Concomitant Therapy**

a) Prior treatment with an anti-PD-1, anti-PD-L1, anti-PD-L2, anti-CTLA-4 antibody, or any other antibody or drug specifically targeting T-cell 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 2 weeks prior to treatment.

**3) Physical and Laboratory Test Findings**

Screening laboratory values that meet the following criteria (using CTCAE v4):

a) WBC < 2000/μL

b) Neutrophils < 1500/μL

c) Platelets < 100 x $10^3$/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)

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

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

f) AST > 3.0 x ULN

g) ALT > 3.0 x ULN

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

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

**4) Allergies and Adverse Drug Reaction**

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

**5) 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 (e.g., infectious disease) illness

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

## 6.3 Lifestyle Restrictions

Not applicable. No restrictions are required

## 6.4 Screen Failures

Screen failures are defined as participants who consent to participate in the clinical study but are not subsequently registered for treatment. 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 (i.e., participant has not been randomized / has not been treated). If re-enrolled, the participant must be re-consented.

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

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

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

# 7 TREATMENT

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

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

- nivolumab

- ipilimumab

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

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 CA209592**

| Product Description / Class and Dosage Form | Potency | IP/ Non-IMP | Blinded or Open Label | Packaging / Appearance | Storage Conditions (per label) |
|---|---|---|---|---|---|
| nivolumab/BMS -936558-01 Solution for Injection | 10 mg/ml | IP | Open Label | 10 mL vial containing a clear to opalescent, colorless to pale yellow liquid; may contain particulates; 5 vials/carton | Store at 2-8°C; Protect from light and freezing. |
| ipilimumab Solution for Injection | 5 mg/ml | IP | Open Label | 40mL vial containing a clear to slightly opalescent, colorless to pale yellow liquid. May contain particulates; 4 vials/carton | Store at 2-8°C; Protect from light and freezing. |

## 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(s)/ Dosage level(s) | Dosage formulation Frequency of Administration | Route of Administration |
|---|---|---|---|
| **nivolumab** | 240mg | Every 2 weeks | IV |
| + | | | |
| **ipilimumab** | 1 mg/kg | Every 6 weeks | IV |

### *7.1.1 Dosing Details*

Participants should begin study treatment within 3 calendar days of treatment assignment in IWRS. All participants will receive nivolumab at a flat dose of 240mg as a 30 minute IV infusion, on Day 1, Day 15, and Day 29 of each treatment cycle (every 2 weeks), and ipilimumab at a dose of 1 mg/kg as a 30 minute IV infusion on Day 1 and every 6 weeks. Treatment will continue until progression, unacceptable toxicity, withdrawal of consent, the study ends, or a maximum treatment duration of 2 years, whichever occurs first.

Participants may be dosed with nivolumab no less than 12 days from the previous dose. There is no premedication recommended.

Instructions for dilution of nivolumab injection are provided in the nivolumab IB, or pharmacy manual. Care must be taken to assure sterility of the prepared solution as the product does not contain any antimicrobial preservative or bacteriostatic agent.

Instructions for dilution of ipilimumab injection are provided in the ipilimumab IB or pharmacy manual. Ipilimumab is to be administered as a 30 minute IV infusion.

Dosing calculations for ipilimumab should be based on the body weight assessed at baseline. It is not necessary to re-calculate subsequent doses if the participants' weight is within 10% of the weight used to calculate the previous dose. All doses should be rounded up or to the nearest milligram per institutional standard.

When study drugs (nivolumab and ipilimumab) are to be administered on the same day, nivolumab is to be administered first. Nivolumab infusion must be promptly followed by a saline flush to clear the line of nivolumab before starting the ipilimumab infusion. The second infusion will always be the ipilimumab study drug and will start after the infusion line has been flushed, filters changed and patient has been observed to ensure no infusion reaction has occurred. The time in between infusions is expected to be approximately 30 minutes but may be more or less depending on the situation. Separate infusion bags and filters should be used when administering nivolumab and ipilimumab on the same day. Participants should be carefully monitored for infusion reactions. If an acute infusion reaction is noted, participants should be managed according to Section 7.4.3.

Treatment with nivolumab (± ipilimumab) beyond initial investigator-assessed RECIST 1.1 defined progression is permitted if the participant has investigator assessed clinical benefit and is tolerating the study drugs (as specified in Section 8.1.2).

No dose modifications are allowed for nivolumab. Doses of nivolumab and/or ipilimumab may be interrupted, delayed, or discontinued depending on how well the participant tolerates the treatment. Dosing visits for nivolumab can be skipped at D15 and D29 only. For more details, see Section 7.4.1 (dose delays), Section 7.4.5 (resuming treatment), and Section 8. (Discontinuation).

## 7.2 Method of Treatment Assignment

All participants will be centrally enrolled 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 assigned and dispensed at the study visits as listed in Schedule of Activities (Section 2).

## 7.3 Blinding

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

## 7.4 Dosage Modification

### *7.4.1 Dose Delay Criteria*

Dose delay criteria apply to all drug-related AEs. Treatment delays are allowable up to 6 weeks for nivolumab and 12 weeks for ipilimumab from the last dose (any dose delays greater than this will require approval from the medical monitor).

Tumor assessments for all participants should continue as per protocol even if dosing is delayed.

Nivolumab and ipilimumab 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 events
- 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
- Any AE, laboratory abnormality or inter-current illness which, in the judgment of the investigator, warrants delaying the dose of study medication.

Participants that have drug-related toxicities that meet the criteria for dose delay, should have both drugs (ipilimumab and nivolumab) delayed until retreatment criteria are met. (Exceptions apply to the retreatment criteria after dose delay of ipilimumab and nivolumab for Grade ≥ 3 amylase and lipase abnormalities that are not associated with symptoms or clinical manifestations of pancreatitis and that are attributed to ipilimumab alone.)

**Rescheduling:**

Nivolumab may be delayed until the next planned ipilimumab dose if the next ipilimumab dose is scheduled within the next 12 days. This will permit periodic ipilimumab dosing to be synchronized with nivolumab. Dosing for nivolumab can be skipped at D15 and D29 only.

Ipilimumab should be dosed at the specified interval regardless of any delays in intervening nivolumab doses. However, in order to maintain periodic synchronized dosing of ipilimumab and nivolumab, the dosing days of nivolumab (every 2 weeks ± 3 days) and ipilimumab (every 6 weeks ± 5 days) may be adjusted within the permitted window, as long as consecutive nivolumab doses are given at least 12 days apart. Ipilimumab may be delayed beyond the 5 day window if needed to synchronize with the next nivolumab dose.

If an ipilimumab dose is delayed beyond 6 weeks from the prior ipilimumab dose, then subsequent ipilimumab doses should rescheduled to maintain the 6 week interval between consecutive ipilimumab doses.

A dose delay of ipilimumab which results in no ipilimumab dosing for > 12 weeks requires ipilimumab discontinuation, with exceptions as noted in Section 8.1.1.

### 7.4.2 Dose Reductions

There will be no dose reductions for nivolumab or ipilimumab.

### 7.4.3 Treatment of Infusion Reactions

Since nivolumab and ipilimumab contains only human immunoglobulin protein sequences, they are 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) guidelines.

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

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

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

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

- Stop the nivolumab infusion, begin an IV infusion of normal saline, and treat the subject with diphenhydramine 50 mg IV (or equivalent) and/or acetaminophen/paracetamol 325 to 1000 mg; remain at bedside and monitor subject until resolution of symptoms. Corticosteroid and/or bronchodilator therapy may also be administered as appropriate. If the infusion is interrupted, then restart the infusion at 50% of the original infusion rate when symptoms resolve; if no further complications ensue after 30 minutes, the rate may be increased to 100% of the original infusion rate. Monitor subject closely. If symptoms recur, then no further nivolumab or ipilimumab (as applicable) 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 or ipilimumab (as applicable) infusions. If necessary, corticosteroids (up to 25 mg of hydrocortisone or equivalent) may be used.

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

- Immediately discontinue infusion. Begin an IV infusion of normal saline and treat the subject as follows: Recommend bronchodilators, epinephrine 0.2 to 1 mg of a 1:1000 solution for subcutaneous administration or 0.1 to 0.25 mg of a 1:10,000 solution injected slowly for IV administration, and/or diphenhydramine 50 mg IV with methylprednisolone 100 mg IV (or equivalent), as needed. Subject should be monitored until the Investigator is comfortable that the symptoms will not recur. Nivolumab or ipilimumab (as applicable) will be permanently discontinued. Investigators should follow their institutional guidelines for the treatment of anaphylaxis. Remain at bedside and monitor subject until recovery of the symptoms.

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

### *7.4.4 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
- Myocarditis

The above algorithms are found in both the nivolumab and ipilimumab Investigator Brochures, as well as in Appendix 7.

### 7.4.5 Criteria to resume dosing

#### 7.4.5.1 Criteria to resume nivolumab dosing

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

- Subjects may resume treatment in the presence of Grade 2 fatigue
- Subjects who have not experienced a Grade 3 drug-related skin AE may resume treatment in the presence of Grade 2 skin toxicity
- For subjects with Grade 2 AST, ALT, or Total bilirubine elevations, dosing may resume when laboratory values return to baseline and management with corticosteroids, if needed, is complete.
- Subjects with combined Grade 2 AST/ALT AND total bilirubin values meeting discontinuation parameters (Section 8.1.1) should have treatment permanently discontinued.
- Drug-related pulmonary toxicity, diarrhea or colitis must have resolved to baseline before treatment is resumed. Subjects with persistent Grade 1 pneumonitis after completion of a steroid taper over at least 1 month may be eligible for retreatment if discussed with and approved by BMS Medical Monitor.
- Subjects with Grade 1-3 drug-related endocrinopathies adequately controlled with only physiologic hormone replacement may resume treatment after consultation with the BMS Medical Monitor.
- Participants who received systemic corticosteroids for management of any drug-related toxicity must be off corticosteroids or have tapered down to an equivalent dose of prednisone ≤ 10 mg/day.
- Participants who delay study treatment due to any Grade ≥ 3 amylase or lipase abnormality that is not associated with symptoms or clinical manifestations of pancreatitis, and that is assessed by the investigator to be related to ipilimumab and not to nivolumab, may resume nivolumab when the amylase or lipase abnormality has resolved to Grade < 3. The BMS Medical Monitor should be consulted prior to resuming nivolumab in such participants.
- Dose delay of nivolumab which results in treatment interruption of > 6 weeks requires treatment discontinuation, with exceptions as noted in Section 8.1.1.

One exception to note is when ipilimumab and nivolumab doses are delayed due to drug-related Grade ≥ 3 amylase or lipase abnormalities not associated with symptoms or clinical manifestations of pancreatitis. If the investigator assesses the Grade ≥ 3 amylase or lipase abnormality to be related to ipilimumab and not related to nivolumab, nivolumab may be resumed when the amylase or lipase abnormality resolves to Grade < 3 but ipilimumab may only be resumed when the amylase

or lipase abnormality resolves to Grade 1 or baseline. Investigator attribution of this toxicity to the ipilimumab dosing must be clearly noted in the participant's medical chart. The BMS Medical Monitor should be consulted prior to resuming nivolumab in such participants.

See Section 8 for treatment discontinuation criteria.

#### *7.4.5.2 Criteria to resume ipilimumab dosing*

Participants may resume treatment with ipilimumab when drug-related AE(s) resolve(s) 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.
- Participants with baseline Grade 1 AST/ALT or total bilirubin elevations who require dose delays for reasons other than a 2-grade shift in AST/ALT or total bilirubin may resume treatment in the presence of Grade 2 AST/ALT or total bilirubin.
- Participants with combined Grade 2 AST/ALT and total bilirubin values meeting discontinuation parameters (Section 8.1.1) should have treatment permanently discontinued.
- Drug-related pulmonary toxicity, diarrhea or colitis must have resolved to baseline before treatment is resumed. Subjects with persistent Grade 1 pneumonitis after completion of a steroid taper over at least 1 month may be eligible for retreatment if discussed with and approved by BMS Medical Monitor.
- Participants who received systemic corticosteroids for management of any drug-related toxicity must be off corticosteroids or have tapered down to an equivalent dose of prednisone ≤ 10 mg/day.
- Subjects with Grade 1-3 drug-related endocrinopathies adequately controlled with only physiologic hormone replacement may resume treatment after consultation with the BMS Medical Monitor.
- Dose delay of ipilimumab which results in no ipilimumab dosing for > 12 weeks requires ipilimumab discontinuation, with exceptions as noted in Section 8.1.1. Although there is overlap among the discontinuation criteria, if discontinuation criteria are met for ipilimumab, but not for nivolumab, treatment with nivolumab may continue if ipilimumab is discontinued.

Ipilimumab may not be resumed sooner than 6 weeks (± 5days) after the prior ipilimumab dose.

In general, participants who meet criteria to resume ipilimumab will also have met criteria to resume nivolumab, so it should be feasible to synchronize dosing of both drugs when resuming ipilimumab. In order to facilitate this, the dosing days of nivolumab and ipilimumab may be adjusted within the permitted ± 5 day window, as long as consecutive nivolumab doses are given at least 12 days apart.

One exception to note is when ipilimumab and nivolumab doses are delayed due to drug-related Grade ≥ 3 amylase or lipase abnormalities not associated with symptoms or clinical manifestations of pancreatitis. If the investigator assesses the Grade ≥ 3 amylase or lipase abnormality to be related to ipilimumab and not related to nivolumab, nivolumab may be resumed when the amylase or lipase abnormality resolves to Grade < 3 but ipilimumab may only be resumed when the amylase

or lipase abnormality resolves to Grade 1 or baseline. Investigator attribution of this toxicity to the ipilimumab dosing must be clearly noted in the participant's medical chart. The BMS Medical Monitor should be consulted prior to resuming nivolumab in such participants.

See Section 8 for treatment discontinuation criteria.

## 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 (e.g., required diluents, administration sets).

- Required storage conditions for nivolumab and ipilimumab are provided in Table 7-1.
- Further guidance on preparation of nivolumab and ipilimumab for infusion will be provided in a separate Pharmacy Manual.
- Further guidance and information for final disposition of unused study treatment are provided in Appendix 2.

## 7.6 Treatment Compliance

Study treatment compliance will be periodically monitored by drug accountability. Drug accountability should be reviewed by the site study staff at each visit to confirm treatment compliance. Sites should discuss discrepancies with the participant at each on-treatment study visit.

## 7.7 Concomitant Therapy

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

Prohibited and/or restricted medications taken prior to study drug administration in the study are described below. Medications taken within 4 weeks prior to study drug administration and at any time during the study must be recorded on the CRF.

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 7.7.2)
- Any concurrent anti-neoplastic therapy (ie, chemotherapy, hormonal therapy, immunotherapy, extensive, non-palliative radiation therapy, or standard or investigational agents for treatment of the disease under study). Allowable palliative radiation is described in Section 7.7.2.2.
- 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.

No concomitant medications (prescription, over-the-counter or herbal) are to be administered during study unless they are prescribed for treatment of specific clinical events. Any concomitant therapies must be recorded on the CRF.

### 7.7.2 Other Restrictions and Precautions

#### 7.7.2.1 Corticosteroids

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. 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.

#### 7.7.2.2 Palliative Radiotherapy

Prior palliative radiotherapy must have been completed at least 2 weeks prior to treatment.

Non-target bone lesions that do not include lung tissue in the planned radiation field and CNS lesions may be treated with palliative radiotherapy while participants remain on study treatment.

The potential for overlapping toxicities with radiotherapy and nivolumab/ipilimumab currently is not known; however, anecdotal data suggests that it is tolerable. As concurrent radiotherapy and nivolumab/ipilimumab have not been formally evaluated, in cases where palliative radiotherapy is required for a tumor lesion, then nivolumab/ipilimumab should be withheld for at least 1 week before, during, and 1 week after radiation. Subjects should be closely monitored for any potential toxicity during and after receiving radiotherapy, and AEs should resolve to Grade ≤ 1 prior to resuming nivolumab plus ipilimumab. This is also applicable to subjects that discontinue ipilimumab and receive nivolumab alone.

Details of palliative radiotherapy should be documented in the source records and case report form (CRF). Details in the source records should include: dates of treatment, anatomical site, dose administered and fractionation schedule, and AEs.

Participants requiring palliative radiotherapy should be carefully assessed for disease progression. Participants considered as having progressive disease are required to discontinue study therapy, unless eligible to continue treatment beyond progression per the guidance in Section 8.1.2.

#### *7.7.2.3 Imaging Contraindications*

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.

### 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 Section 7.1. 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 and/or ipilimumab is terminated for other reasons, including but not limited to lack of efficacy and/or not meeting the study objectives; c) the participant can obtain medication from a government sponsored or private health program. In all cases BMS will follow local regulations.

## 8 DISCONTINUATION CRITERIA

### 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, as outlined in Section 2. 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.

- 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 (e.g., infectious disease) illness

Discontinuation of the study treatment for abnormal liver tests should be considered by the investigator when a participant meets one of the conditions outlined in Section 9.2.7 OR Appendix 7 or if the investigator believes that it is in best interest of the participant.

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

In the case of pregnancy, the investigator must immediately notify the BMS Medical Monitor/designee of this event. In most cases, the study treatment will be permanently discontinued in an appropriate manner (e.g., 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.

### *8.1.1 Nivolumab or Ipilimumab Dose Discontinuation*

Treatment with nivolumab or ipilimumab must be permanently discontinued for any of 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, myocarditis, 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.
        - Any drug-related liver function test (LFT) abnormality that meets the following criteria require discontinuation:

  - Grade ≥ 3 drug-related AST, ALT or Total Bilirubin requires discontinuation. 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.
  - Concurrent AST or ALT > 3 x ULN and total bilirubin > 2 x ULN
- 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 adverse event, laboratory abnormality, or intercurrent illness which, in the judgment of the Investigator, presents a substantial clinical risk to the subject with continued nivolumab/ ipilimumab dosing.
- Any event that leads to delay in dosing lasting > 6 weeks (or 12 weeks for ipilimumab) from the previous dose requires discontinuation, with the following exceptions:
  1. Dosing delays to allow for prolonged steroid tapers to manage drug-related adverse events are allowed.
  2. Dosing delays lasting > 6 weeks (or 12 weeks for ipilimumab) from the previous dose that occur for non-drug-related reasons may be allowed if approved by the BMS medical monitor.
- In the case of pregnancy, the investigator must immediately notify the Sponsor or designee of this event. In most cases, the study drug will be permanently discontinued in an appropriate manner (eg, dose tapering if necessary for participant safety). Please contact the Sponsor or designee within 24 hours of awareness of the pregnancy. If the investigator determines a possible favorable benefit/risk ratio that warrants continuation of study drug, a discussion between the investigator and the Sponsor or designee must occur.

Prior to re-initiating treatment in a participant with a dosing delay lasting > 6 weeks (or 12 weeks for ipilimumab), 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.

The assessment for discontinuation of nivolumab should be made separately from the assessment made for discontinuation of ipilimumab. Although there is overlap among the discontinuation criteria, if discontinuation criteria are met for ipilimumab but not for nivolumab, treatment with nivolumab may continue if ipilimumab is discontinued.

If a participant meets criteria for discontinuation and investigator is unable to determine whether the event is related to both or one study drug, the participant should discontinue both nivolumab and ipilimumab and be taken off the treatment phase of the study. Continuation of ipilimumab after discontinuation of nivolumab is not allowed on study.

### *8.1.2 Disease Progression*

In general, study treatment must be discontinued at the time of disease progression per RECIST 1.1 criteria. However, accumulating evidence indicates a minority of subjects treated with immunotherapy may derive clinical benefit despite initial evidence of PD.[21]

Participants may be permitted to continue study treatment with nivolumab (with or without ipilimumab) beyond initial investigator assessed RECIST 1.1 defined PD, upon approval by the BMS Medical Monitor or Study Director, as long as they meet the following criteria:

- Investigator-assessed clinical benefit.
- Tolerance of study therapy
- Stable performance status
- Treatment beyond progression will not delay an imminent intervention to prevent serious complications of disease progression (eg, CNS metastases)
- Participant provides written informed consent prior to receiving additional nivolumab treatment. All other elements of the main consent including description of reasonably foreseeable risks or discomforts, or other alternative treatment options will still apply.

Upon progression, a radiographic assessment/scan should be performed within 6 weeks of initial investigator-assessed progression to determine whether there has been a decrease/ limited change 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 (with or without ipilimumab), the participant should remain on the trial and continue according to the Schedule of Activities in Section 2.

For participants who continue nivolumab (with or without ipilimumab) beyond progression, further progression is defined as an additional 10% increase in tumor burden with a minimum 5 mm absolute increase from time of initial PD. This includes an increase in the sum of diameters of all target lesions and/ or the diameters of new measurable lesions compared to the time of initial PD. Nivolumab treatment should be discontinued permanently upon documentation of further 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 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). In situations where the relative increase in total tumor burden by 10% is solely due to inclusion of new lesions which become measurable, these new lesions must demonstrate an absolute increase of at least 5 mm.

### *8.1.3 Post Treatment Study Follow-Up*

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

### *8.1.4 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.

## 8.2 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 (Section 2).

- 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 (e.g., 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 beyond those described in Section 2, including non-study required laboratory tests, should be performed as clinically indicated or to comply with local regulations. Laboratory toxicities (eg, suspected drug induced liver enzyme evaluations) will be monitored during the follow-up phase via on site/local labs until all study drug related toxicities resolve, return to baseline, or are deemed irreversible.

If a participant shows pulmonary-related signs (hypoxia, fever) or symptoms (eg. dyspnea, cough, fever) consistent with possible pulmonary adverse events, the participant should be immediately evaluated to rule out pulmonary toxicity, according to the suspected pulmonary toxicity management algorithm in the BMS-936558 (nivolumab) Investigator Brochure and Appendix 7.

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

Overall survival is one of the secondary endpoints in this study. Every effort will be made to collect survival data on all participant including those withdrawn from treatment for any reason, who are eligible to participate in the study and who have not withdrawn consent for survival data collection.

If the death of a participant is not reported, all dates in this study representing a date of participant contact will be used in determination of the participant's last known date alive.

### 9.1.1 Imaging Assessment for the Study

Any additional imaging that may demonstrate tumor response or progression (including scans performed at unscheduled timepoints and/or at an outside institution) should be collected for RECIST 1.1 tumor assessment and reviewed.

#### 9.1.1.1 Efficacy Assessments using CT scan or MRI

The imaging assessment schedule is provided in Table 9.1.1.1-1.

Baseline imaging is required within 28 days prior to first dose, including CT chest, CT/MRI abdomen, and pelvis (with contrast, unless contraindicated), plus any area that is being monitored.

Participants must have an MRI of the brain at screening. Participants with a history of brain metastasis should have surveillance MRI approximately every 12 weeks, or sooner if clinically indicated.

Tumor assessments should continue every 8 weeks (± 1 week) from first dose for the first 12 months on treatment, then every 12 weeks (± 1 week) until documented radiographic disease progression. CT chest and CT/MRI abdomen and pelvis (with contrast, unless contraindicated), plus any area that is being monitored. Use the same imaging method as was used at screening. After 3 years on study, tumor assessments for long-term survivors can be performed at a frequency per institutional guidelines or every 24 weeks based on NCCN surveillance guidelines.

In Part 1, an *additional planned optional CT scan is suggested at W5*, to guide tumor biopsy as needed and to support predicting tumor response based on early tumor growth characteristics using a mathematical tumor growth model.

For participants who discontinue study treatment for reasons other than radiographic PD, follow-up scans should continue to be performed according to the on-study assessment schedule until PD, withdrawal of consent, start of subsequent therapy, death, or lost to follow-up.

Participants who remain on therapy beyond initial progression, will have an assessment performed within 6 weeks to confirm progression (see section 8.1.2).

**Table 9.1.1.1-1: Imaging Assessment Schedule (Part 1 and Part 2)**

| Study Day | Event Relative to Dosing | CT | [redacted] | Biopsy[c] |
|---|---|---|---|---|
| **Part 1** | | | | |
| Screening[a,c] | pre-dose | X | | X |
| Cycle 1 Day 15 (Week 3) | pre-dose | | | |
| Cycle 1 Day 29 (Week 5) | - | X[e] | | X |
| Cycle 2 Day 15 | pre-dose | X | | |

**Table 9.1.1.1-1: Imaging Assessment Schedule (Part 1 and Part 2)**

| Study Day | Event Relative to Dosing | CT | [redacted] | Biopsy[c] |
|---|---|---|---|---|
| (Week 9) | | | | |
| **Every 8 weeks** (± 1 week) from first dose, for first 12 months on treatment | - | X | | |
| After 12 months on treatment, **Every 12 weeks** (± 1 week) until documented radiographic disease progression. | - | X | | |
| Progression | - | X | | X |
| **Part 2** | | | | |
| Screening[a,c] | pre-dose | X | | |
| Every 8 weeks (± 1 week) from first dose, for first 12 months on treatment | - | X | | |
| After 12 months on treatment, Every 12 weeks (± 1 week) until documented radiographic disease progression.[f] | - | X | | |

[a] Screening assessments should be performed within 28 days of treatment assignment.

[redacted]

[c] At screening, a fresh biopsy will be taken prior to treatment.

[redacted]

[e] W5 optional CT Scan, to guide biopsy as needed and to support predicting the tumor response based on early tumor growth characteristics using a mathematical tumor growth model.

[f] After 3 years on study, tumor assessments for long-term survivors can be performed at a frequency per institutional guidelines or every 24 weeks based on NCCN surveillance guidelines.

[redacted]

## 9.2 Adverse Events

The definitions of an AE or serious adverse event (SAE) can be found in Appendix 3.

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

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

**Contacts for SAE reporting specified in Appendix 3.**

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

The collection of non-serious AE information should begin at initiation of study treatment until 100 days after the last dose of study therapy, at the timepoints specified in the Schedule of Activities (Section 2). Non-serious 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 (e.g., 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 3.
- The investigator will submit any updated SAE data to the sponsor within 24 hours of this being available.

For participants assigned to treatment and never treated with study drug, SAEs should be collected for 30 days from the date of treatment assignment.

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

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

### 9.2.2 Method of Detecting AEs and SAEs

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

### 9.2.3 Follow-up of AEs and SAEs

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

After the initial AE/SAE report, the investigator is required to proactively follow each participant at subsequent visits/contacts. All SAEs, and non-serious AEs of special interest (as defined in Section 9.2 will be followed until resolution, until the condition stabilizes, until the event is otherwise explained, or until the participant is lost to follow-up (as defined in Section 8.2).

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.

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

### 9.2.4 Regulatory Reporting Requirements for SAEs

- Prompt notification by the investigator to the Sponsor of SAEs is essential so that legal obligations and ethical responsibilities towards the safety of participants and the safety of a product under clinical investigation are met.
- An investigator who receives an investigator safety report describing SAEs or other specific safety information (e.g., 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 3

In most cases, the study treatment will be permanently discontinued in an appropriate manner (e.g., 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 non-serious 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 (e.g., anemia versus low hemoglobin value).

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

Wherever possible, timely confirmation of initial liver-related laboratory abnormalities should occur prior to the reporting of a potential DILI event. All occurrences of potential DILIs, meeting the defined criteria, must be reported as SAEs (see Section 9.2 and Appendix 3 for reporting details).

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.

#### 9.2.8.1 Immune-mediated adverse events

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

## 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 SAEs (see Section 9.2).In the event of an overdose the [investigator/treating physician] should:

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

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

## 9.4 Safety

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

### *9.4.1 Clinical Safety Laboratory Assessments*

- Investigators must document their review of each laboratory safety report.
- Screening laboratory assessments should be done locally within 14 days of first dose.
- On-study laboratory assessments should be done locally within 72 hours prior to each dose, as outlined in the Schedule of Activities in Section 2.
- Laboratory assessments should be performed locally at Follow-Up Visit 1, and should be repeated at Follow-Up Visit 2 if study related toxicity persists.

**Table 9.4.1-1: Laboratory Assessment Panels**

| | |
|---|---|
| **Hematology** | |
| Hemoglobin | |
| Hematocrit | |
| Total leukocyte count, including differential | |
| Platelet count | |
| **Chemistry** | |
| Aspartate aminotransferase (AST) | Sodium |
| Alanine aminotransferase (ALT) | Potassium |
| Total bilirubin | Chloride |
| Alkaline phosphatase | Calcium |
| Lactate dehydrogenase (LDH) | Phosphorus |
| Creatinine | Lipase |
| Blood Urea Nitrogen (BUN) or Serum Urea Level | Amylase |

**Table 9.4.1-1: Laboratory Assessment Panels**

| | |
|---|---|
| Glucose<br>Albumin (screening only) | Magnesium<br>TSH, every 6 weeks (Free T3 and T4 performed at screening and reflex to free T3 and T4 if TSH is abnormal at subsequent timepoints)<br>Creatinine clearance (CLcr)- screening only |
| **Urinalysis (As clinically indicated)** | |
| Protein | |
| Glucose | |
| Blood | |
| Leukocyte esterase | |
| Specific gravity | |
| pH | |
| Microscopic examination of the sediment if blood, protein or leukocytes esterase are positive on the dipstick | |
| **Serology** | |
| Serum for hepatitis C antibody or hepatitis C RNA, hepatitis B surface antigen, HIV-1 and -2 antibody (screening only) Testing for HIV must be performed at sites where mandated locally. See Appendix 8. | |
| Other Analyses | |
| Pregnancy test (WOCBP only: as described in Section 2.) | |

### *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]

[redacted]

[redacted]

## 9.6 Biomarkers

The biomarker sampling schedule is provided in Table 9.6-1 for Part 1 and in Table 9.6-2 for Part 2.

**Part 1**: a biopsy should be taken during the screening period and up to 4-5 core biopsies are recommended at each tumor biopsy collection time point. An assessment of biopsy quality by a pathologist/cytopathologist is encouraged at the time of procedure. [redacted] Please refer to the lab manual for specific tumor collection instructions. Participants must have tissue submitted for PD-L1 IHC testing prior to the start of treatment. Samples should not be taken from target lesions. Samples will be sent to a third party to stain and score for PD-L1 expression using the PD-L1 IHC 28-8 pharmDx kit (Dako). Stained tissue samples will be assessed by a pathologist at a central lab identified by the Sponsor and scored as PD-L1 expressing if membrane staining is observed in ≥ 1% tumor cells among a minimum of 100 evaluable tumor cells.

An additional tumor biopsy will be collected at Cycle 1 Day 29 (Week 5) to evaluate potential pharmacodynamic biomarkers of response/safety to nivolumab + ipilimumab. Changes in candidate biomarkers at this time point may inform of early changes within the tumor microenvironment that contribute to efficacy. PD-L1 will be assessed in this on-treatment biopsy as indicated for the pre-treatment biopsy, above.

A tumor biopsy will be collected in subjects at progression. Changes in candidate biomarkers in this setting may inform of the mechanism(s) underlying acquired resistance and may inform of potential combination approaches to prevent/delay or reverse resistance. PD-L1 will be assessed in biopsy as indicated for the pre-treatment biopsy, above.

Collected tumors may be further analyzed by additional modalities, including, but limited to:

- IHC and/or cytometry (eg, flow-, chip- mass-spec based) to determine the abundance of immunoregulatory and other proteins such as [redacted] PD-L1, [redacted]
- [redacted]
- Genetic mutation detection methods;
- DNA and RNA sequencing (eg, whole exome/genome sequencing, whole transcriptome RNAseq and/or T-cell receptor sequencing);
- [redacted]

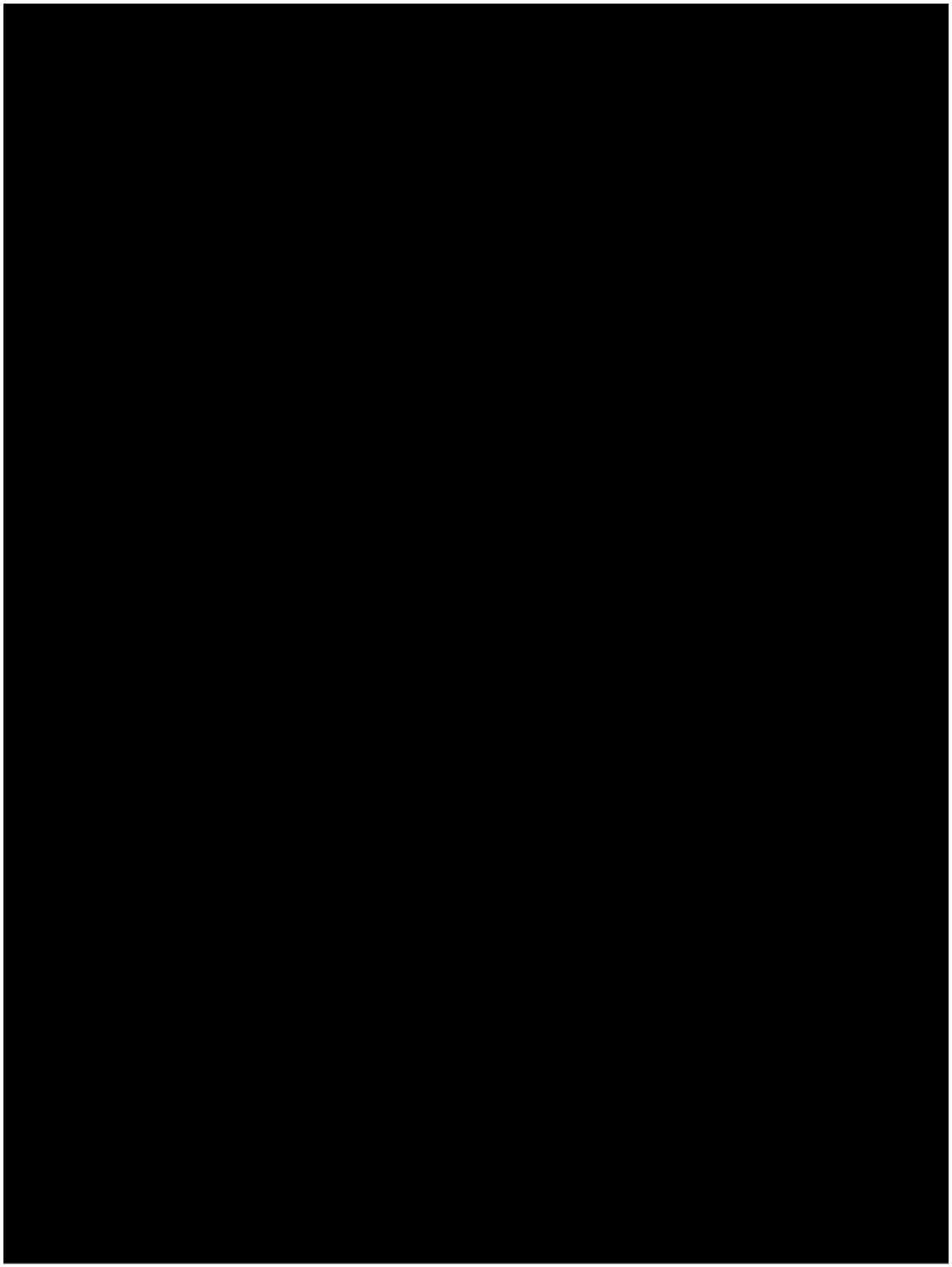
The biomarker sampling schedule is provided in Table 9.6-1 for Part 1.

**Table 9.6-1: Biomarker Assessment Schedule for Part 1**

| Study Day | [redacted] |
|---|---|
| Screening | |
| Cycle 1 Day1 (Week 1) | |
| Cycle 1 Day 29 (Week 5) | |
| Cycle 2 Day 15 (Week 9) | |
| Cycle 3 Day 1 (Week 13) | |
| Progression | |

**Part 2** biomarker samples (blood and tumor tissue) for TMB analyses will be collected at screening. Fresh biopsy tissue is preferred for enrollment; follow lab manual for details. Archival tissue samples that are less than 3 months old may be submitted. For archival tissue, FFPE tissue block (preferred) or submission of 15 unstained tumor tissue sections for PDL-1 and TMB testing will be required. [redacted]

[redacted]



[redacted]

[redacted]

### 9.6.10 Tumor Mutational Burden Evaluation in Tissue and Blood Part 2

Fresh biopsy is preferred or archival sample (≤ 3 months old) are required for enrollment. For archival tissue, FFPE tissue block (preferred) or submission of 15 unstained tumor tissue sections for PDL-1 and TMB testing will be required. If fresh biopsy tissue is obtained, the collection of plasma/serum must be collected within 7 days.

Based on the Part 2 expansion cohort in this study, tumor TMB and blood TMB will be collected at baseline. The association of tissue and blood TMB analyses with clinical outcomes will be assessed independently.

### 9.6.11 Additional Research Collection

Additional research collections and retention are mandatory for all subjects, except where prohibited by local laws or regulations. This protocol will include residual sample storage for additional research (AR).

This collection for additional research is intended to expand the translational R&D capability at Bristol-Myers Squibb, and will support as yet undefined research aims that will advance our understanding of disease and options for treatment. It may also be used to support health authority requests for analysis, and advancement of pharmacodiagnostic development to better target drugs to the right patients. This may also include genetic/genomic exploration aimed at exploring disease pathways, progression and response to treatment etc.

All requests for access to samples or data for additional research will be vetted through a diverse committee of the study sponsor's senior leaders in Research and Development to ensure the research supports appropriate and well-defined scientific research activities.

[redacted]

Samples will be securely stored by the BMS Biorepository in [redacted] or at a BMS approved third party storage management facility.

Samples will be stored in a coded fashion, and no researcher will have access to the key. The key is securely held by the Investigator at the clinical site, so there is no direct ability for a researcher to connect a sample to a specific individual

Additional research samples will be retained for 15 years or the maximum allowed by applicable law. No additional sampling is required for residual collections.

Further details of sample collection and processing will be provided to the site in the procedure manual.

**Table 9.6.11-1: Residual Sample Retention for Additional Research Schedule**

| Sample Type | Timepoints for which residual samples will be retained |
|---|---|
| All | All samples |

## 9.7 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

**Part 1:** The planned sample size is approximately 100. Approximately up to 150 participants are expected to be enrolled to achieve 100 treated participants in the trial. For this hypothesis generating study, the sample size is mainly decided by operational feasibility, and sample size calculation is provided to illustrate the design characteristics of the study. Biomarker hypotheses generated from the study will be validated by analyzing data from other ongoing trials or data from future trials.

One of the co-primary objectives is to evaluate tumor mutational burden as a candidate biomarker of clinical efficacy of nivolumab and ipilimumab combination therapy. For this co-primary objective, the primary endpoint that will be used to measure clinical efficacy is objective response rate (ORR). [redacted].

One of the co-primary objectives of the study is to investigate the potential association between candidate biomarkers in peripheral blood and tumor tissue at baseline and on-treatment with clinical efficacy measures. For this co-primary objective, the primary endpoint that will be used to measure clinical efficacy is objective response rate (ORR). Patients can be divided into sub-groups by candidate biomarkers. No formal hypothesis testing will be conducted on ORR in overall patient population or in patient sub-groups. However, to evaluate the association between candidate biomarkers with ORR while factoring in the correlation among biomarkers, a multiple logistic regression or a penalized regression method (Elastic Net[38], implemented in SAS procedure GLMSELECT) may be used to select important biomarkers simultaneously. More specifically,

patient sub-groups can be identified by biomarkers as covariates in the model, and an important sub-group can be chosen based on biomarker effects estimated from the model. For example, the risk of each patient can be calculated based on estimated covariates, and a suitable cutoff point of patient level risk can be used to identify sub-groups of interest. Other methods can be used to define sub-groups. No matter what methods are used, scientific rationales need to be provided to support the patient sub-groups defined. For patient sub-groups identified, ORR and the associated confidence interval will be calculated, and the estimation bias due to selection bias will be adjusted by re-sampling method.

[redacted]

Although no formal hypothesis testing will be performed, the operating characteristics can also be illustrated in the hypothesis testing framework. [redacted] The power calculation was conducted in EAST 6 using Wald test statistics, and the null response rate of 0.23 was chosen based on data from LUX-Lung 3[39] and 6[40] study.

**Part 2**: The planned sample size is approximately 150 participants. Approximately 200 participants are expected to be enrolled to achieve 150 treated participants. [redacted]

In study CA209568, a TMB analysis determined a TMB cutpoint that subjects at or above the cutpoint were predicted to experience therapeutic benefit from nivolumab in combination with ipilimumab. An exploration will be done for Part 2 subjects to confirm the cutpoint identified in CA209568. Within the TMB-evaluable subjects, it is expected that approximately 1/3 of those providing TMB will be categorized as being above the cutpoint, ie, [redacted] Table 10.1-1 presents the exact 95% CIs for some of the plausible scenarios of observed ORRs for TMB cutpoint positive (TMB+) participants in Part 2 based on blood TMB, as well as TMB based on tumor tissue.

**Table 10.1-1: Part 2 ORR and width of 95% CI** [redacted]

| ORR (# of Responders) | 95% Exact CI |
|---|---|
| [redacted] | |
| | |
| | |
| | |

| Table 10.1-1: Part 2 ORR and width of 95% CI [redacted] | |
|---|---|
| ORR (# of Responders) | 95% Exact CI |
| [redacted] | [redacted] |

95% CI based on Clopper-Pearson method

Combining Part 1 and Part 2 subjects together, about 250*60%*1/3=50 participants will be above the cutpoint.

Table 10.1-2 presents the exact 95% CIs for some scenarios of observed ORRs for TMB cutpoint positive (TMB+) subjects for the entire study.

| Table 10.1-2: Part 1 and Part 2 ORR and width of 95% CI [redacted] | |
|---|---|
| ORR (# of Responders) | 95% Exact CI |
| [redacted] | [redacted] |

## 10.2 Populations for Analyses

For purposes of analysis, the following populations are defined:

| Population or analysis data set | Description |
|---|---|
| All enrolled patients | All subjects who signed an informed consent form and were registered into the IRT system. |
| All treated patients | All patients who received at least one dose of any study medication. |
| All treated patients with evaluable baseline tumor biopsy data | All treated patients with evaluable baseline tumor biopsy data will be included in data analyses. |

| Population or analysis data set | Description |
|---|---|
| Complete biomarker data set | All treated patients with evaluable mandatory baseline tumor biopsy and at least one post baseline tumor biopsy. |
| [redacted] | |
| All baseline TMB evaluable patients | All treated patients with evaluable baseline tumor mutational burden. |

## 10.3 Statistical and Computational Analyses

The association between ORR and tumor mutational burden will be explored using logistic regression model among treated patients evaluable for tumor mutational burden.

Due to limited participants as compared with the number of biomarkers that will be evaluated for the second co-primary objective, a multiple logistic regression model, or penalized regression methods (Elastic Net[38], implemented in SAS procedure GLMSELECT) will be used to assess the potential association between candidate biomarkers in peripheral blood and tumor tissue at baseline and on-treatment with clinical efficacy measures. The primary endpoint will be ORR, and other clinical efficacy measures will be analyzed as part of the secondary endpoints. [redacted]

The analysis of the primary endpoint ORR will take place after the last treated subject is followed for [redacted]. Additional survival analysis will be conducted with longer follow up.

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 | Analysis Methods |
|---|---|
| **Primary:** | |
| ORR | In Part 1, logistic regression model and ROC analysis will be used to evaluate tumor mutational burden as a candidate biomarker of ORR of nivolumab and ipilimumab combination therapy.<br>Multiple logistic regression or penalized regression will be used to screen for (baseline and post baseline) biomarkers simultaneously<br>ORR will be calculated for sub-groups identified by logistic or penalized regression methods, and the confidence interval by Clopper-Pearson method will be provided<br>In Part 2, ROC analysis will be used to confirm cutoffs for baseline tissue TMB and blood TMB that identify subjects who will experience therapeutic benefit based on ORR. Logistic regression will be conducted.<br>ORR will be calculated for TMB (tissue and blood) sub-groups and the confidence interval by Clopper-Pearson method will be provided. |
| **Secondary** | |
| DCR, DOR, TTR, PFS, and OS | The analysis conducted for ORR will be repeated for other efficacy endpoints of interest. For PFS, OS and DOR, for selected patient sub-groups, Kaplan-Meier curves will be provided, and median of time to events and the associated confidence interval will be calculated.<br>Descriptive summary statistics of TTR will be provided for patients with a BOR of CR or PR. |
| **Exploratory** | |
| [redacted] | |

### 10.3.2 Safety Analyses

All safety analyses will be performed on all treated participants.

| Endpoint | Analysis Methods |
|---|---|
| Primary<br>Event rate | AEs, including death, SAE, and AEs defined by safety monitoring test, will be summarized for all treated participants, and by sub-groups when applicable. |

[redacted]

### 10.3.4 Other Analyses

The population pharmacokinetics analysis and pharmacodynamic analyses will be presented separately from the main clinical study report.

[redacted]

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# 12 APPENDICES

## APPENDIX 1 ABBREVIATIONS AND TRADEMARKS

| Term | Definition |
|---|---|
| AE | adverse event |
| ACLS | advanced cardiac life support |
| AI | accumulation index |
| ALT | alanine aminotransferase |
| ANC | absolute neutrophil count |
| AST | aspartate aminotransferase |
| AT | aminotransaminases |
| AUC | area under the concentration-time curve |
| A-V | atrioventricular |
| β-HCG | beta-human chorionic gonadotrophin |
| BID, bid | bis in die, twice daily |
| BLQ | below limit of quantification |
| BMI | body mass index |
| BMS | Bristol-Myers Squibb |
| BP | blood pressure |
| BUN | blood urea nitrogen |
| C | Celsius |
| $Ca^{++}$ | calcium |
| Cavg | average concentration |
| CBC | complete blood count |
| Cexpected-tau | expected concentration in a dosing interval |
| CFR | Code of Federal Regulations |
| CI | confidence interval |
| $C1^{-}$ | chloride |
| CLcr | creatinine clearance |
| cm | centimeter |
| Cmax, CMAX | maximum observed concentration |
| Cmin, CMIN | minimum observed concentration |
| CNS | Central nervous system |

| Term | Definition |
|---|---|
| CRC | Clinical Research Center |
| CRF | Case Report Form, paper or electronic |
| Ctrough | Trough observed plasma concentration |
| CV | coefficient of variation |
| CYP | cytochrome p-450 |
| D/C | discontinue |
| dL | deciliter |
| DMC | Data monitoring committee |
| DSM IV | Diagnostic and Statistical Manual of Mental Disorders ($4^{th}$ Edition) |
| EA | extent of absorption |
| ECG | electrocardiogram |
| eCRF | Electronic Case Report Form |
| EDC | Electronic Data Capture |
| EEG | electroencephalogram |
| eg | exempli gratia (for example) |
| ESR | Expedited Safety Report |
| F | bioavailability |
| FDA | Food and Drug Administration |
| FSH | follicle stimulating hormone |
| g | gram |
| GC | gas chromatography |
| GCP | Good Clinical Practice |
| GGT | gamma-glutamyl transferase |
| GFR | glomerular filtration rate |
| h | hour |
| HBsAg | hepatitis B surface antigen |
| HBV | hepatitis B virus |
| HCV | hepatitis C virus |
| $HCO_3^-$ | bicarbonate |
| HIV | Human Immunodeficiency Virus |

| Term | Definition |
|---|---|
| HR | heart rate |
| HRT | hormone replacement therapy |
| ICD | International Classification of Diseases |
| ICH | International Conference on Harmonisation |
| ie | id est (that is) |
| IEC | Independent Ethics Committee |
| IMP | investigational medicinal products |
| IND | Investigational New Drug Exemption |
| IRB | Institutional Review Board |
| IRT | Interactive Response Technology |
| IU | International Unit |
| IV | intravenous |
| K | slope of the terminal phase of the log concentration-time curve |
| $K_3EDTA$ | potassium ethylenediaminetetraacetic acid |
| $K^+$ | potassium |
| kg | kilogram |
| L | liter |
| LAM | Lactation amenorrhea method |
| LC | liquid chromatography |
| LDH | lactate dehydrogenase |
| ln | natural logarithm |
| mg | milligram |
| $Mg^{++}$ | magnesium |
| min | minute |
| mL | milliliter |
| mmHg | millimeters of mercury |
| MR | medical research |
| MS | mass spectrometry |
| MTD | maximum tolerated dose |
| µg | microgram |

| Term | Definition |
|---|---|
| N | number of subjects or observations |
| $Na^+$ | sodium |
| N/A | not applicable |
| ng | nanogram |
| NIMP | non-investigational medicinal products |
| NSAID | nonsteroidal anti-inflammatory drug |
| PD | pharmacodynamics |
| PK | pharmacokinetics |
| PO | per os (by mouth route of administration) |
| QC | quality control |
| QD, qd | quaque die, once daily |
| $R^2$ | coefficient of determination |
| RBC | red blood cell |
| SAE | serious adverse event |
| SD | standard deviation |
| SOP | Standard Operating Procedures |
| Subj | subject |
| t | temperature |
| T | time |
| TAO | Trial Access Online, the BMS implementation of an EDC capability |
| T-HALF | Half life |
| TID, tid | ter in die, three times a day |
| Tmax, TMAX | time of maximum observed concentration |
| UV | ultraviolet |
| WBC | white blood cell |
| WHO | World Health Organization |
| WOCBP | women of childbearing potential |
| WNOCBP | women **not** of childbearing potential |

# APPENDIX 2 STUDY GOVERANCE CONSIDERATIONS

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

## REGULATORY AND ETHICAL CONSIDERATIONS

## GOOD CLINICAL PRACTICE

This study will be conducted in accordance with:

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

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

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

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

This study will not use the services of study personnel where sanctions have been invoked or where there has been scientific misconduct or fraud (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. The investigator or BMS should also provide the IRB/IEC with a copy of the Investigator Brochure or product labeling information to be provided to subjects and any updates.

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

## COMPLIANCE WITH THE PROTOCOL AND PROTOCOL REVISIONS

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

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

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

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

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

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

## FINANCIAL DISCLOSURE

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

## INFORMED CONSENT PROCESS

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

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

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

Investigators must:

- Provide a copy of the consent form and written information about the study in the language in which the participant is most proficient prior to clinical study participation. The language must be non-technical and easily understood.

- Allow time necessary for participant or participant's legally acceptable representative to inquire about the details of the study.
- Obtain an informed consent signed and personally dated by the participant or the participant's legally acceptable representative and by the person who conducted the informed consent discussion.
- Obtain the IRB/IEC's written approval/favorable opinion of the written informed consent form and any other information to be provided to the subjects, prior to the beginning of the study, and after any revisions are completed for new information.

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

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

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

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

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

## SOURCE DOCUMENTS

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

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

## STUDY TREATMENT RECORDS

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

| If | Then |
|---|---|
| Supplied by BMS (or its vendors): | Records or logs must comply with applicable regulations and guidelines and should include:<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 (eg, lost, wasted)<br>• amount destroyed at study site, if applicable<br>• amount returned to BMS<br>• retain samples for bioavailability/bioequivalence, 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.<br>These records should include:<br>• label identification number or batch number<br>• amount dispensed to and returned by each participant, including unique participant identifiers<br>• dates and initials of person responsible for Investigational Product dispensing/accountability, as per the Delegation of Authority Form. |

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

## CASE REPORT FORMS

An investigator is required to prepare and maintain adequate and accurate case histories designed to record all observations and other data pertinent to the investigation on each individual treated or entered as a control in the investigation. Data that are derived from source documents and reported on the CRF must be consistent with the source documents or the discrepancies must be

explained. Additional clinical information may be collected and analyzed in an effort to enhance understanding of product safety. CRFs may be requested for AEs and/or laboratory abnormalities that are reported or identified during the course of the study.

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

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

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

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

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

## MONITORING

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

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

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

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

## RECORDS RETENTION

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

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

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

## RETURN OF STUDY TREATMENT

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

| If.. | Then |
|---|---|
| Study treatments supplied by BMS (including its vendors | Any unused study treatments supplied by BMS can only be destroyed after being inspected and reconciled by the responsible Study Monitor unless study treatments containers must be immediately destroyed as required for safety, or to meet local regulations (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, ie, incinerator, licensed sanitary landfill, or licensed waste disposal vendor must be documented.
- Accountability and disposal records are complete, up-to-date, and available for the Monitor to review throughout the clinical trial period.

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

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

## CLINICAL STUDY REPORT AND PUBLICATIONS

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

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

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

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

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

## ADVERSE EVENTS

**Adverse Event Definition:**

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

**Events Meeting the AE Definition**

- Any abnormal laboratory test results (hematology, clinical chemistry, or urinalysis) or results from other safety assessments (eg, ECG, radiological scans, vital signs measurements), including those that worsen from baseline, considered clinically significant in the medical and scientific judgment of the investigator. Note that abnormal lab tests or other safety assessments should only be reported as AEs if the final diagnosis is not available. Once the final diagnosis is known, the reported term should be updated to be the diagnosis.
- Exacerbation of a chronic or intermittent pre-existing condition including either an increase in frequency and/or intensity of the condition.
- New conditions detected or diagnosed after study intervention administration even though it may have been present before the start of the study.
- Signs, symptoms, or the clinical sequelae of a suspected drug-drug interaction.
- Signs, symptoms, or the clinical sequelae of a suspected overdose of either study intervention or a concomitant medication. Overdose, as a verbatim term (as reported by the investigator), should not be reported as an AE/SAE unless it is an intentional overdose taken with possible suicidal/self-harming intent. Such overdoses should be reported regardless of sequelae and should specify "intentional overdose" as the verbatim term

**Events NOT Meeting the AE Definition**

- Medical or surgical procedure (eg, endoscopy, appendectomy): the condition that leads to the procedure is the AE.
- Situations in which an untoward medical occurrence did not occur (social and/or convenience admission to a hospital).

## DEFINITION OF SAE

If an event is not an AE per definition above, then it cannot be an SAE even if serious conditions are met.

## 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>• 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>• elective surgery, planned prior to signing consent<br>• admissions as per protocol for a planned medical/surgical procedure<br>• routine health assessment requiring admission for baseline/trending of health status (e.g., routine colonoscopy)<br>• 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>• 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>• 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.) |

Pregnancy and potential drug induced liver injury (DILI) must follow the same transmission timing and processes to BMS as used for SAEs (see section 9.2.5 for reporting pregnancies).

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

## EVALUATING AES AND SAES

**Assessment of Causality**

- The investigator is obligated to assess the relationship between study intervention and each occurrence of each AE/SAE.
- A "reasonable possibility" of a relationship conveys that there are facts, evidence, and/or arguments to suggest a causal relationship, rather than a relationship cannot be ruled out.
- The investigator will use clinical judgment to determine the relationship.
- Alternative causes, such as underlying disease(s), concomitant therapy, and other risk factors, as well as the temporal relationship of the event to study intervention administration will be considered and investigated.
- The investigator will also consult the Investigator's Brochure (IB) and/or Product Information, for marketed products, in his/her assessment.
- For each AE/SAE, the investigator must document in the medical notes that he/she has reviewed the AE/SAE and has provided an assessment of causality.
- There may be situations in which an SAE has occurred and the investigator has minimal information to include in the initial report to Sponsor. However, it is very important that the investigator always make an assessment of causality for every event before the initial transmission of the SAE data to Sponsor.
- The investigator may change his/her opinion of causality in light of follow-up information and send a SAE follow-up report with the updated causality assessment.
- The causality assessment is one of the criteria used when determining regulatory reporting requirements.

**Follow-up of AEs and SAEs**

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

If an ongoing SAE changes in its intensity or relationship to study treatment or if new information becomes available, the SAE report must be updated and submitted within 24 hours to BMS (or designee) using the same procedure used for transmitting the initial SAE report.

All SAEs must be followed to resolution or stabilization.

## REPORTING OF SAES TO SPONSOR OR DESIGNEE

- SAEs, whether related or not related to study treatment, and pregnancies must be reported to BMS (or designee) immediately within 24 hours of awareness of the event.
- SAEs must be recorded on the SAE Report Form.
  - The required method for SAE data reporting is through the eCRF.
  - The paper SAE Report Form is only intended as a back-up option when the electronic data capture (EDC) system is unavailable/not functioning for transmission of the eCRF to BMS (or designee).
    - In this case, the paper form is transmitted via email or confirmed facsimile (fax) transmission
    - When paper forms are used, the original paper forms are to remain on site
- Pregnancies must be recorded on a paper Pregnancy Surveillance Form and transmitted via email or confirmed facsimile (fax) transmission

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

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

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

# APPENDIX 4 WOMEN OF CHILDBEARING POTENTIAL DEFINITIONS AND METHODS OF CONTRACEPTION

## DEFINITIONS

### Woman of Childbearing Potential (WOCBP)

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

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

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

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

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

## CONTRACEPTION GUIDANCE FOR FEMALE PARTICIPANTS OF CHILD BEARING POTENTIAL

One of the highly effective methods of contraception listed below is required during study duration and until the end of relevant systemic exposure, defined as 5 months 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>• Hormonal methods of contraception including oral contraceptive pills containing a combination of estrogen and progesterone, vaginal ring, injectables, implants and intrauterine hormone-releasing system (IUS)[c]<br>• Intrauterine device (IUD)[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 study treatment.
- Female partners of males participating in the study to consider use of effective methods of contraception until the end of relevant systemic exposure, defined as 7 months after the end of treatment in the male participant.
- Male participants with a pregnant or breastfeeding partner must agree to remain abstinent from penile vaginal intercourse or use a male condom during each episode of penile penetration during the treatment and until 7 months after the end of study treatment.
- Refrain from donating sperm for the duration of the study treatment and until 7 months after the end of study treatment.

## COLLECTION OF PREGNANCY INFORMATION

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

## APPENDIX 5 ECOG PERFORMANCE STATUS

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

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

# APPENDIX 6 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. [redacted]

## 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 7 MANAGEMENT ALGORITHMS

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.

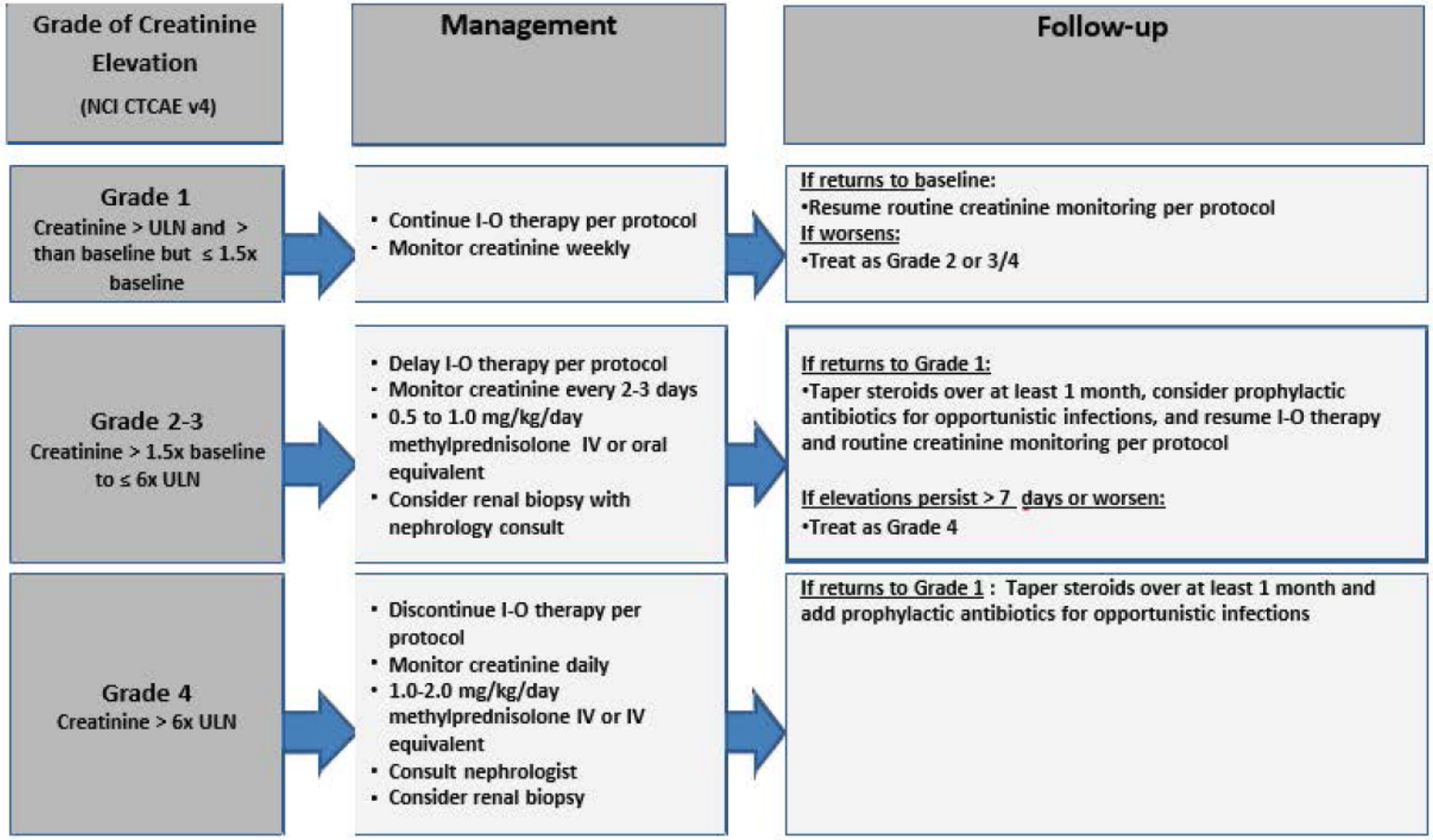
| Grade of Diarrhea/ Colitis (NCI CTCAE v4) | Management | Follow-up |
|---|---|---|
| **Grade 1**<br>Diarrhea:< 4 stools/day over baseline;<br>Colitis: asymptomatic | • Continue I-O therapy per protocol<br>• Symptomatic treatment | • Close monitoring for worsening symptoms.<br>• Educate patient to report 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.

27-Jun-2019

# Renal Adverse Event Management Algorithm

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

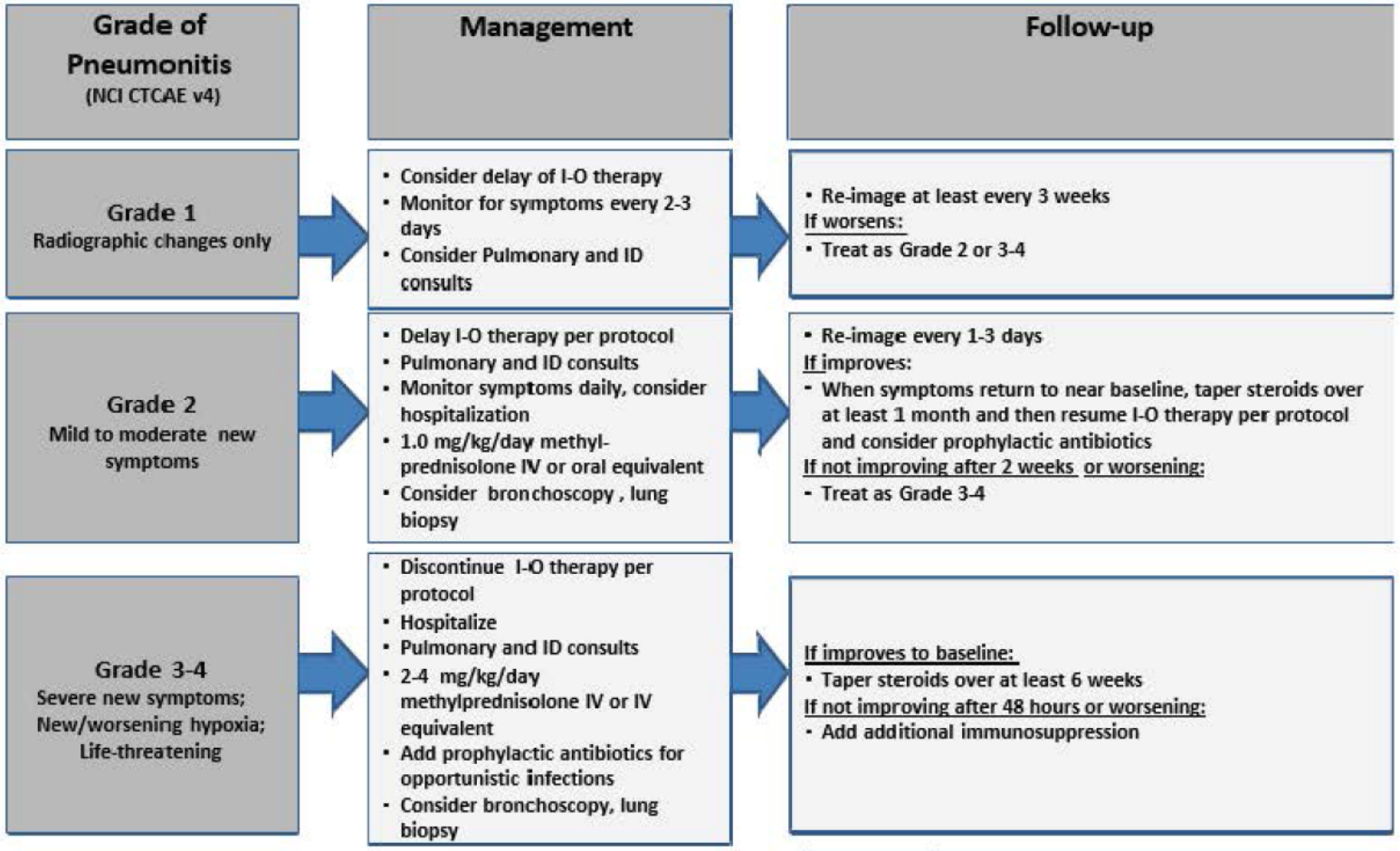



Patients on IV steroids may be switched to an equivalent dose of oral corticosteroids (e.g. prednisone) at start of tapering or earlier, once sustained clinical improvement is observed. Lower bioavailability of oral corticosteroids should be taken into account when switching to the equivalent dose of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

27-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.

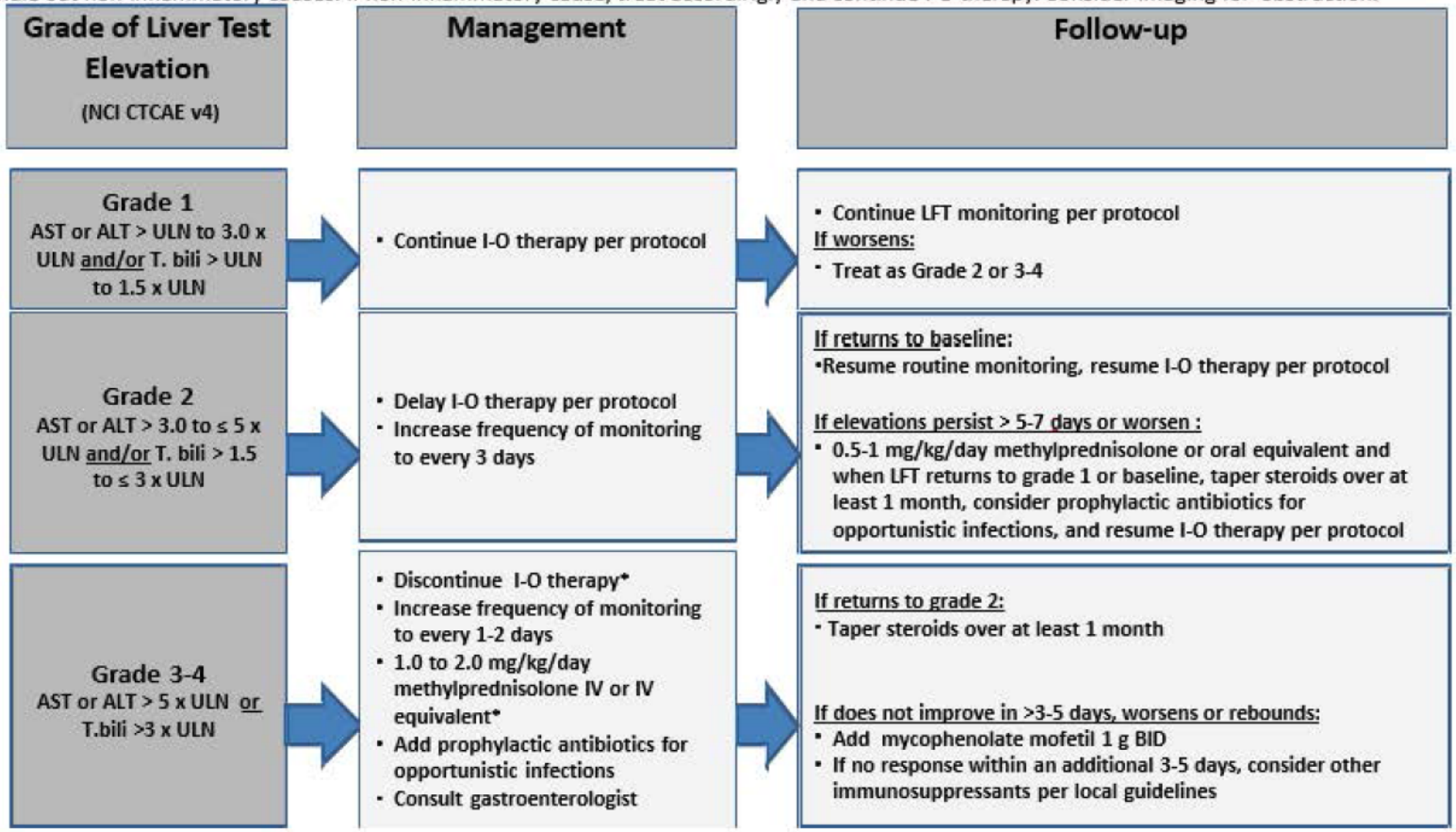



Patients on IV steroids may be switched to an equivalent dose of oral corticosteroids (e.g. prednisone) at start of tapering or earlier, once sustained clinical improvement is observed. Lower bioavailability of oral corticosteroids should be taken into account when switching to the equivalent dose of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

27-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.



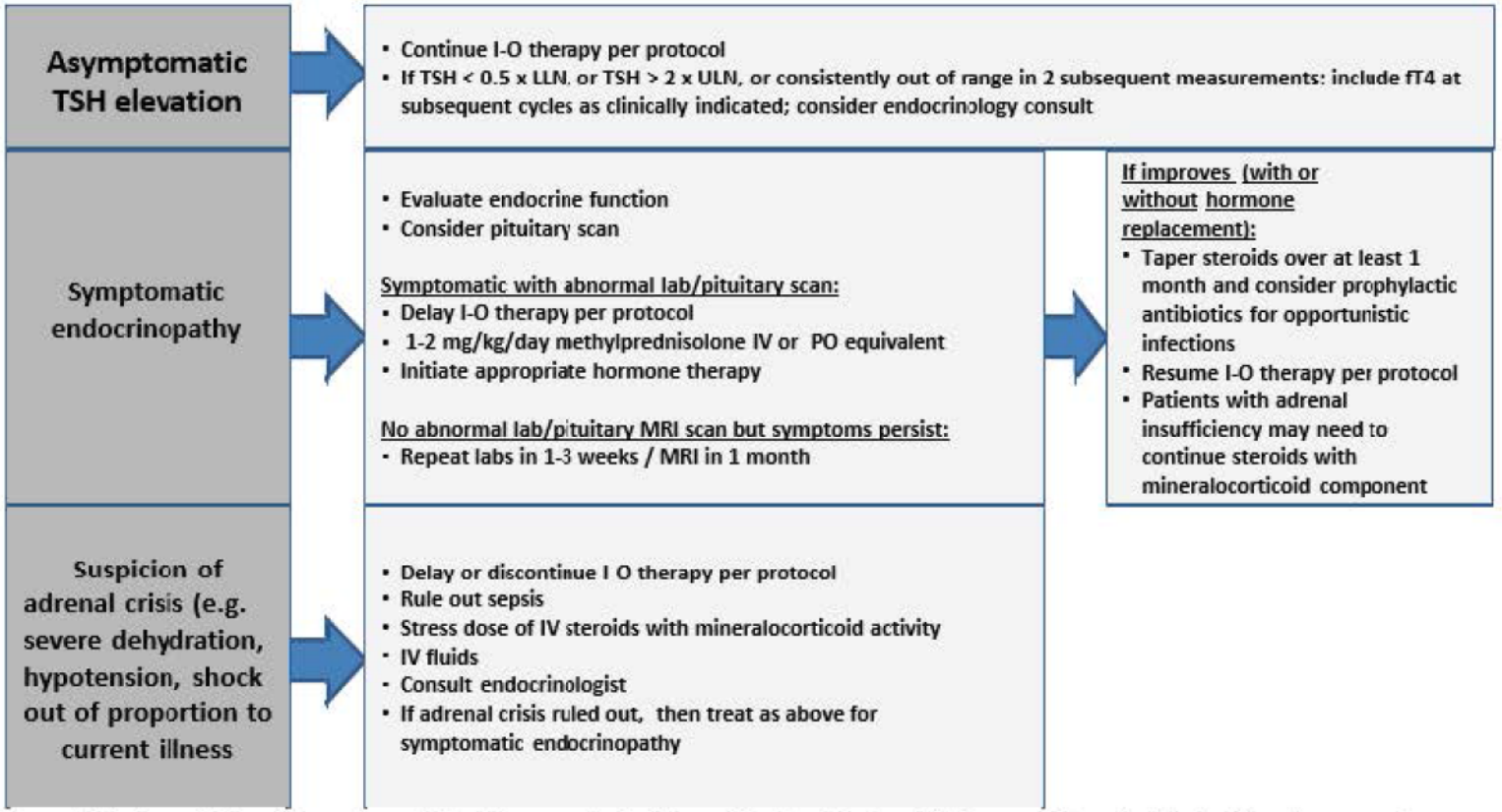

Patients on IV steroids may be switched to an equivalent dose of oral corticosteroids (e.g. prednisone) at start of tapering or earlier, once sustained clinical improvement is observed. Lower bioavailability of oral corticosteroids should be taken into account when switching to the equivalent dose of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

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

27-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.

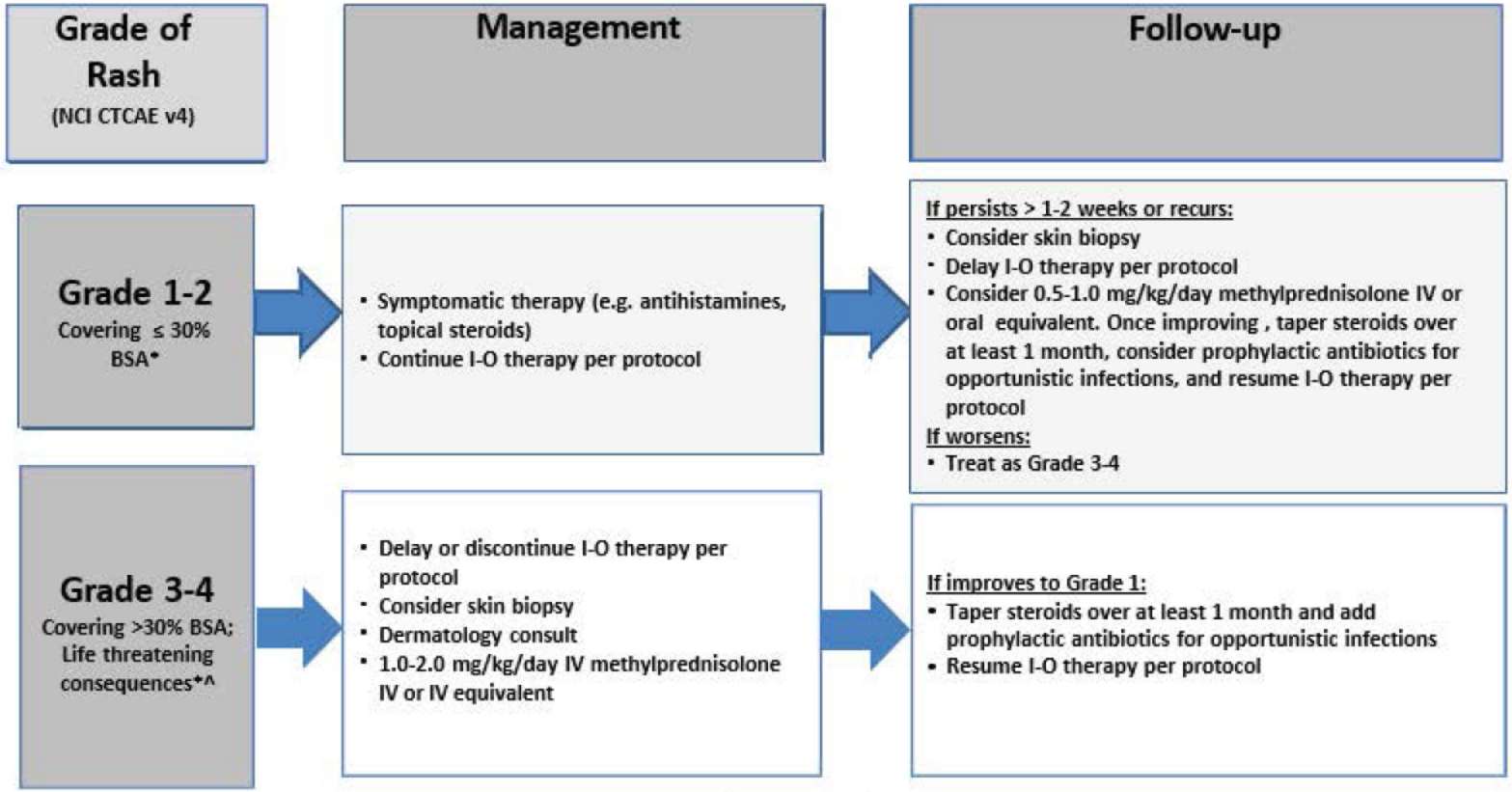



Patients on IV steroids may be switched to an equivalent dose of oral corticosteroids (e.g. prednisone) at start of tapering or earlier, once sustainec clinical improvement is observed. Lower bioavailability of oral corticosteroids should be taken into account when switching to the equivalent dose of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

27-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.

27-Jun-2019

# Neurological Adverse Event Management Algorithm

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

| Grade of Neurological Toxicity (NCI CTCAE v4) | Management | Follow-up |
|---|---|---|
| **Grade 1** Asymptomatic or mild symptoms; Intervention not indicated | • Continue I-O therapy per protocol | Continue to monitor the patient.<br>If worsens:<br>- Treat as Grade 2 or 3-4 |
| **Grade 2** Moderate symptoms; Limiting instrumental ADL | • Delay I-O therapy per protocol<br>• Treat symptoms per local guidelines<br>• Consider 0.5 to 1.0 mg/kg/day methylprednisolone IV or PO equivalent | If improves to baseline:<br>•Resume I-O therapy per protocol when improved to baseline<br>If worsens:<br>• Treat as Grade 3-4 |
| **Grade 3-4** Severe symptoms; Limiting self-care ADL; Life-threatening | • Discontinue I-O therapy per protocol<br>• Obtain neurology consult<br>• Treat symptoms per local guidelines<br>• 1.0-2.0 mg/kg/day IV methylprednisolone IV or IV equivalent<br>• Add prophylactic antibiotics for opportunistic infections | If improves to Grade 2:<br>• Taper steroids over at least 1 month<br>If worsens or atypical presentation:<br>• Consider IVIG or other immunosuppressive therapies per local guidelines |

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.

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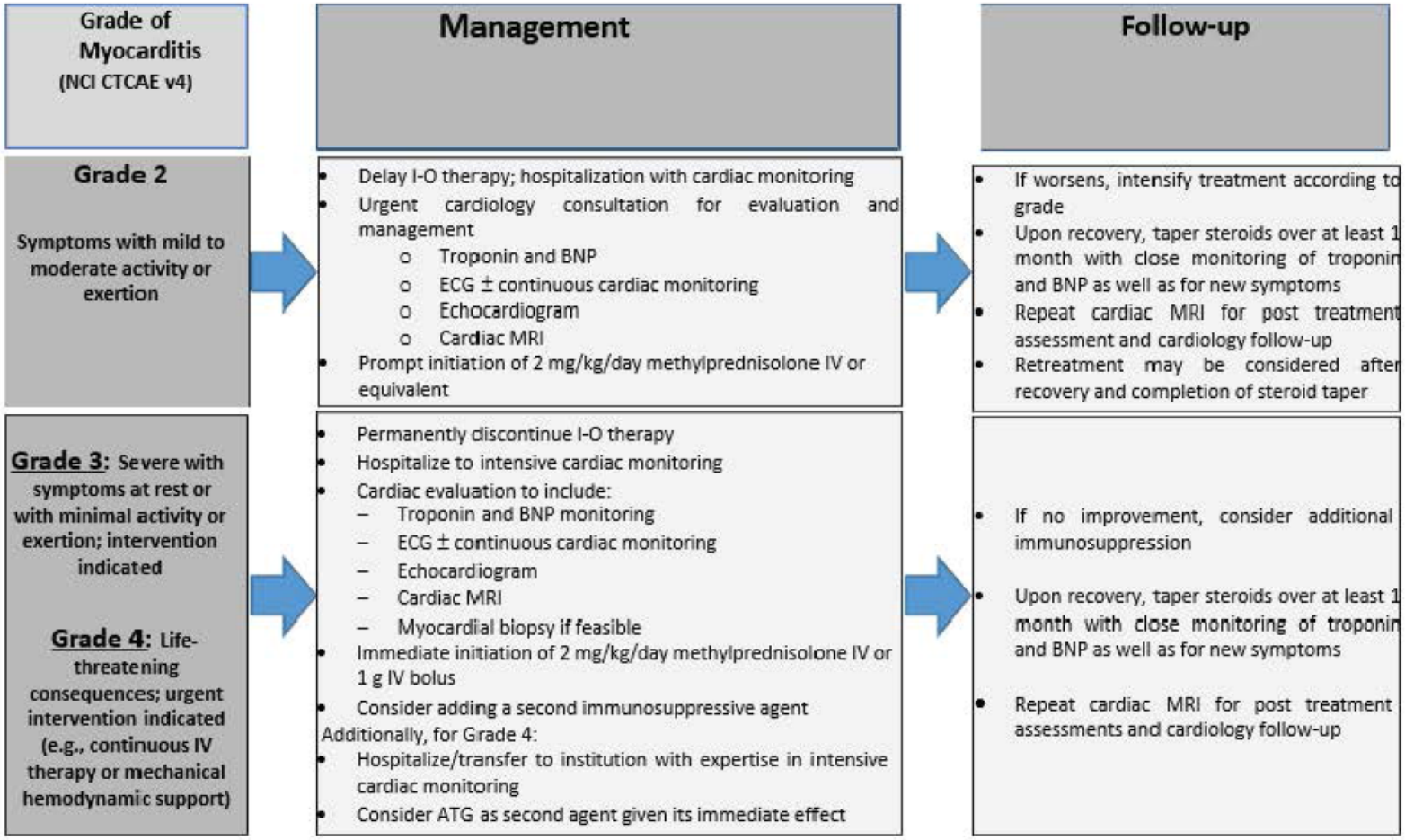
# Myocarditis Adverse Event Management Algorithm




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

27-Jun-2019

# APPENDIX 8 COUNTRY SPECIFIC REQUIREMENTS

## Criteria for exclusion of HIV-positive subjects in GERMANY:

| Section | Country-specific language |
|---|---|
| Section 2 Flow Chart/Time and Events Schedule, Screening Procedural Outline (CA209592) for Part 1 and Part 2 - Laboratory Tests | Add "HIV testing" to the list of laboratory tests |
| Section 6.2 Exclusion Criteria No.1 Letter i) | "Subjects with a known history of a positive test for human immunodeficiency virus (HIV) or known acquired immunodeficiency syndrome (AIDS)" to be replaced with "Positive test for HIV." |
| Section 9.4.1 Clinical Safety Laboratory Assessments Table 9.4.1-1 Laboratory Assessment Panels, Serology | Add "Testing for HIV must be performed at sites where mandated locally." |

# APPENDIX 9 REVISED PROTOCOL SUMMARY OF CHANGE HISTORY

**Overall Rationale for the Revised Protocol 04, 03-May-2019**

The CA209592 protocol was revised to change [redacted] analytical correlation between tissue and blood TMB, and clarified ipilimumab dosing.

| **Summary of key changes for Revised Protocol 04** | | |
|---|---|---|
| **Section Number & Title** | **Description of Change** | **Brief Rationale** |
| Synopsis<br>Table 2-1 Screening Procedural Outline (CA209592) for Part 1 and Part 2<br>Table 2.-2: On Treatment Procedural Outline (CA209592) for Part 1<br>Table 2.-3: On Treatment Procedural Outline (CA209592) for Part 2<br>Table 9.6-1 Biomarker Assessment Schedule for Part 1<br>Table 9.6-2 Biomarker Assessment Schedule for Part 2<br>[redacted] | [redacted] | [redacted] |
| Synopsis Objectives and Endpoints<br>Table 2-1 Screening Procedural Outline (CA209592) for Part 1 and Part 2<br>Section 3.1 Study Rationale<br>Section 3.2.5 3.2.5 Rationale for Tumor Mutation Burden Testing<br>Table 4-2 Objectives and Endpoints for Part 2<br>Section 9.6.10 Tumor Mutation Burden Evaluation in Tissue and Blood Part 2<br>Section 10.1 Sample Size Determination<br>Section 10.3.1 Efficacy Analysis<br>Section 10.3.5 Interim Analyses | Analytical correlation of blood TMB and tissue TMB was removed as a co-primary endpoint. | This endpoint was removed because existing data was sufficient to support correlation. |
| Table 2-1 Screening Procedural Outline (CA209592) for Part 1 and Part 2 9.1.1.1<br>Table 2.-2: On Treatment Procedural Outline (CA209592) for Part 1<br>Table 2.-3: On Treatment Procedural Outline (CA209592) for Part 2<br>Section 9.1.1.1 Efficacy Assessments using CT scan or MRI | Updated brain imaging requirement at screening and during treatment, when clinically indicated. | Brain imaging is required to rule out brain metastasis at screening and during treatment, when clinically indicated for safety. |