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# CLINICAL PROTOCOL CA209032

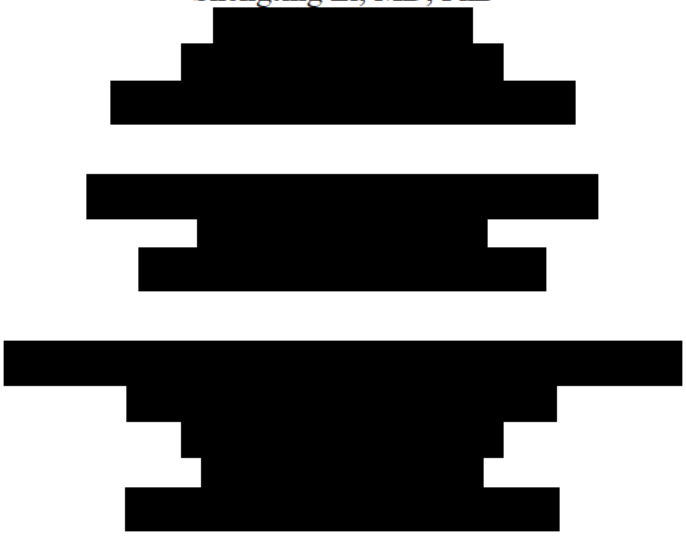
A Phase 1/2, Open-label Study of Nivolumab Monotherapy or Nivolumab combined with Ipilimumab in Subjects with Advanced or Metastatic Solid Tumors

(CheckMate 032: CHECKpoint pathway and nivoluMAb clinical Trial Evaluation 032)

**Revised Protocol 07d - USA Specific**

**Medical Monitor / Study Director**

Shengting Li, MD, PhD



## DOCUMENT HISTORY

| Document | Date of Issue | Summary of Change |
|---|---|---|
| Revised Protocol 07d - USA | 03-Oct-2019 | • Updated personnel with Medical Monitor<br>• Added live/attenuated vaccines and complementary medications (eg, herbal supplements) to Prohibited and/or Restricted Treatments<br>• Clarified tumor assessment language<br>• Updated Appendix 2 (Management Algorithms) with addition of myocarditis AE management algorithm to reflect update in the Nivolumab IB<br>• Added survival visits time window (from Administrative letter 5, dated 27-Aug-2018) |
| Revised Protocol 07c - USA | 27-Jan-2017 | **Incorporates Amendment 16** |
| Amendment 16 | 27-Jan-2017 | To remove one inclusion criteria for the bladder cohort |
| Revised Protocol 07b - USA | 27-Oct-2016 | **Incorporates Amendment 14 and 15** |
| Amendment 15 | 27-Oct-2016 | • To clarify that for the pancreatic cohort, shorter infusion times of nivolumab and ipilimumab will be implemented. |
| Amendment 14 | 26-Oct-2016 | • To expand the bladder cohort (Nivolumab 1 mg/kg combined with Ipilimumab 3 mg/kg). |
| Revised Protocol 07a - USA | 11-Aug-2016 | **Incorporates Amendment 13** |
| Amendment 13 | 11-Aug-2016 | • Implementation of the additional pancreatic cohort treated with a combination of nivolumab, ipilimumab and cobimetinib. |
| Revised Protocol 07 | 10-Aug-2016 | **Incorporates Amendment 12** |
| Amendment 12 | 10-Aug-2016 | • Changed the primary objective for the expansion SCLC cohort to require evaluation by BICR.<br>• Removed the limitation of enrolling subjects with 1 or 2 prior lines of therapy in the same fixed proportion of 50% for each subgroup.<br>• Added permission to use palliative radiation therapy to other non-target lesions<br>• Added permission to use surgical resection or stereotactic radiotherapy following initial response or long-term stable disease<br>• Limited PK and immunogenicity samples collection up to 2 years<br>• Updated Appendix 2 (Management Algorithms) to reflect updates in the nivolumab IB.<br>• Added Appendix 6 (Methods of Contraception) to reflect updates in the nivolumab IB. |

| Document | Date of Issue | Summary of Change |
|---|---|---|
| Revised Protocol 06 | 18-Nov-2015 | **Incorporates Amendment 11** |
| Amendment 11 | 18-Nov-2015 | • Clarification regarding the local lab assessment timing was added.<br>• For Ovarian Cancer cohort, specification of minimum tissue sample collection for ovarian cancer due to the fact that additional analyses of Homologous Recombination Deficiency (HRD) status and Breast Cancer genes 1 and 2 (BRCA1 and BRCA2) mutation status will be conducted in this cohort.<br>• For SCLC expansion cohort, exact language regarding number of prior treatment lines added for consistency with Section 3.1.5 and the study synopsis.<br>• Specification of the crossover option: This option refers only to the original cohorts and not the new cohorts enrolled under or after Amendment 09 implementation.<br>• To increase flexibility in obtainment of tumor samples, for subjects with only one site of measurable disease tumor sampling criteria for biopsies from NOT the only site of measurable disease were widened.<br>• Clarification regarding requirement for baseline CT and MRI brain scans.<br>• Updated biomarker timepoint requirements for Day 8, 15, 22 and 29 sample collections.<br>• For Ovarian Cancer cohort, due to the low risk of development of new safety signals on the combination arms confirmed by the additional information from the combination studies in melanoma, lung, renal cell carcinoma, and glioblastomas as well as the clinical study with ipilimumab 10 mg/kg monotherapy in ovarian cancer, which did not reveal any new safety signals, the Safety Evaluation Phase will be removed. Ovarian cancer subjects will be followed for related toxicities and decisions to stop enrollment will be made on an ongoing basis. |
| Revised Protocol 05 | 23-Sep-2015 | **Incorporates Amendment 10** |
| Amendment 10 | 23-Sep-2015 | • Clarification regarding PK/immunogenicity sampling and pregnancy test was added.<br>• Regimen NI2c was added for treatment of ovarian cancer, including PK/immunogenicity and pregnancy sampling clarifications<br>• Safety assessments in all indications and treatment cohorts is harmonized: D4 W2 and W5 safety assessments are deleted from the NI cohorts consistent with nivolumab monotherapy and nivolumab 3 mg/kg Q2W/ipilimumab 1 mg/kg Q6W cohorts<br>• For options of treatment beyond progression and crossover to NI combination arm, specification of unequivocal disease progression based on non-target lesions only is added<br>• Specification of response to platinum-based therapy in SCLC and Ovarian cancer is added to appendices<br>• Regimen NI2c was removed from the flowchart for Bladder cancer (correction)<br>• For SCLC expansion cohort, clarification of stratified randomization is |

| Document | Date of Issue | Summary of Change |
|---|---|---|
| | | added<br>• For subjects from NI combination who undergo a re-exposure if they achieved an initial objective response (PR or CR) or stable disease of > 3 months and had a subsequent documented progression, an option to continue treatment with nivolumab monotherapy if ipilimumab treatment was stopped due to toxicity is added |
| Revised Protocol 04 | 06-Aug-2015 | **Incorporates Amendment 09** |
| Amendment 09 | 06-Aug-2015 | This global amendment includes:<br>- Updates to Medical Monitor/Study Director<br>- SCLC and Bladder: cohorts Nivo 3 mg/kg and Nivo 1/ Ipi 3 mg/kg, increase sample size.<br>- Addition of Ovarian tumor type: cohorts Nivo 3 / Ipi 1 mg/kg and Nivo 1/ Ipi 3 mg/kg.<br>- Updates to Blinded Independent Central Review (BICR) information<br>Allowing brain radiation prior to cross over<br>- Allowing retreatment upon PD for patients with long lasting PR or CR and who had treatment held by investigator<br>- For the combination arm, subjects who meet discontinuation criteria will be allowed to continue with nivolumab treatment should the study related toxicities be attributed to ipilimumab. Ipilimumab would be discontinued.<br>- Updates to Primary, Secondary [redacted] Objectives<br>- Updates to Discontinuation criteria to include Grade 4 lymphocytopenia |
| Revised Protocol 03 | 07-Aug-2014 | **Incorporates Amendment 07 and 08** |
| Amendment 08 | 07-Aug-2014 | This amendment is to add nivolumab 3 mg/kg in combination with ipilimumab 1 mg/kg to the dose levels being investigated in study CA209-032, change the bladder cohort to a One Stage Design, and to add an optional external evaluation of CT or MRI scans for tumor types where data from study CA209-032 will potentially be used for future NDA submissions. Other changes were made to resolve minor inconsistencies and clarifications. |
| Amendment 07 | 04-Jun-2014 | Pharmacogenetics blood sample update to include all current and future tumor types |

| Document | Date of Issue | Summary of Change |
|---|---|---|
| Revised Protocol 02 | 17-Apr-2014 | **Incorporates Amendment 06** |
| Amendment 06 | 17-Apr-2014 | This global amendment includes adjustments to the treatment guidelines for patients with endocrinopathy events, adds a new cohort for subjects with Bladder Cancer, updates laboratory test requirements, and updates the sample size determination, populations for analyses and interim analysis sections. Other changes were made to resolve minor inconsistencies and clarifications:<br>• Bladder cancer is the most common malignancy of the urinary tract. Immunotherapy with Bacillus Calmette-Guerin in patients with superficial urothelial carcinoma is part of the standard treatment. It has been shown that CD8 tumor-infiltrating lymphocytes (TILs) are predictive of survival in muscle-invasive urothelial carcinoma. Active immunotherapeutic strategies have been investigated for bladder cancer including CTLA-4 blockade. In conclusion, a check point inhibitor therapy with nivolumab or nivolumab in combination with ipilimumab appears to be a promising experimental approach for patients with advanced urothelial carcinoma. This amendment adds a cohort enrolling subjects with advanced bladder cancer to the protocol aligned with the existing study design.<br>• Adjustments to the treatment guidelines for subjects who experience endocrinopathy events are implemented. Subjects who experience endocrinopathy events which resolve or are adequately controlled with physiologic hormone replacement (steroids, thyroid hormones) or glucose controlling agents, may undergo retreatment. A recurrence of the endocrinopathy event under ongoing physiologic hormone replacement therapy appears to be unlikely what justifies a retreatment with potential therapeutic benefit.<br>• The definition of the all immunogenicity population was changed in order to align it with the core safety SAP for the Nivolumab program. Other minor changes in the populations for analyses were made in order to align it with the SAP for 032.<br>• The interim analysis section was updated to allow for IAs based on either a “super” response or if it is necessary to make decisions regarding further development (eg, the SCLC cohort). |

| Document | Date of Issue | Summary of Change |
|---|---|---|
| Revised Protocol 01 | 11-Dec -2013 | **Incorporates Amendment 05** |
| Amendment 05 | 11-Dec-2013 | **Study Design:**<br>• Clarification on need for subject safety follow up before dose escalation and staggered enrollment for Dose Cohort Level 2.<br>• Clarification on number of subjects with objective response and number of enrolled subjects before proceeding from Stage 1 to Stage 2.<br>**Eligibility Criteria**<br>• Clarified wording that subjects with Breast Cancer, Gastric or Gastro-Esophageal Junction Carcinoma, or SCLC must have progressive or refractory disease at study entry.<br>• Adjusted eligibility, treatment delay and discontinuation criteria for subjects with lipase or amylase > 1.5 ULN: Subjects with asymptomatic elevations in amylase or lipase not associated with symptoms, clinical manifestations, or radiographic sings of pancreatitis are eligible. Based on clinical experience in ongoing studies with nivolumab and ipilimumab, asymptomatic elevations of amylase or lipase have not been proven to have to have independent clinical consequence or predict for development or severity of pancreatitis. A wide variation of asymptomatic elevations in amylase or lipase can occur on a day-to-day basis, limiting the utility of interpreting the amylase or lipase elevations in isolation.<br>• Clarifications on eligibility for women of childbearing potential and effective methods of contraception.<br>• Clarification on eligibility of subjects with prior malignancy not interfering with the primary and secondary study endpoints.<br>[redacted] |
| Original Protocol | 10-Jul-2013 | Not applicable |

## OVERALL RATIONALE FOR REVISED PROTOCOL 07D

This revised protocol provides clarity on the tumor assessments during treatment and follow-up. Additional changes were made for prohibited and restricted treatments. The changes apply for all participants in the study.

**SUMMARY OF KEY CHANGES FOR REVISED PROTOCOL 07D**

| Section Number & Title | Description of Change | Brief Rationale |
|---|---|---|
| Section 3.4.1 Prohibited and/or Restricted Treatments<br><br>Section 3.4.2.3 Permitted Therapy | Updated language for permitted therapy and additional prohibited and/or restricted treatments were added:<br>• Any complementary medications (eg, herbal supplements or traditional Chinese medicines) intended to treat the disease under study. Such medications are allowed if they are used as supportive care.<br>• Any live / attenuated vaccine (eg varicella, zoster, yellow fever, rotavirus, oral polio and measles, mumps, rubella (MMR)) during treatment and until 100 days post last dose. | Prohibited and/or restricted treatments were updated to align with program standards for safety. |
| Section 5 Study Assessments and Procedures<br>On-study Assessment tables:<br>Table 5.1-2<br>Table 5.1-3<br>Table 5.1-4<br>Table 5.1-5<br>Section 5.3.1 Imaging Assessment for the Study | Tumor assessment language was added to tables:<br><br>Additionally, with the exception of crossover participants, tumor assessments will not be required upon initiation of subsequent anti-cancer therapy. | On-treatment tables were updated to provide clarity that tumor assessments are not required after subjects receive subsequent anti-cancer therapy. |
| Appendix 2 | Management Algorithms were updated to include AE management for myocarditis | Appendix aligns with revised Nivolumab IB for safety. |

# SYNOPSIS

## Clinical Protocol CA209032

**Protocol Title: A Phase 1/2, Open-label Study of Nivolumab Monotherapy or Nivolumab combined with Ipilimumab in Subjects with Advanced or Metastatic Solid Tumors**

**Investigational Product(s), Dose and Mode of Administration, Duration of Treatment with Investigational Product(s):**

- Nivolumab monotherapy administered IV over 60 minutes at 3 mg/kg every 2 weeks until progression

or

- Nivolumab administered IV over 60 minutes at 1 mg/kg combined with ipilimumab administered IV over 90 minutes at 1 mg/kg every 3 weeks for 4 doses followed by nivolumab administered IV over 60 minutes at 3 mg/kg every 2 weeks until progression.

or

- Nivolumab administered IV over 60 minutes at 1 mg/kg combined with ipilimumab administered IV over 90 minutes at 3 mg/kg every 3 weeks for 4 doses followed by nivolumab administered IV over 60 minutes at 3 mg/kg every 2 weeks until progression.

or

- Nivolumab administered IV over 60 minutes at 3 mg/kg combined with ipilimumab administered IV over 90 minutes at 1 mg/kg every 3 weeks for 4 doses followed by nivolumab administered IV over 60 minutes at 3 mg/kg every 2 weeks until progression.

or

- Nivolumab administered IV over 60 minutes at 3 mg/kg every 2 weeks combined with ipilimumab administered IV over 90 minutes at 1 mg/kg every 6 weeks until progression.

or

- Nivolumab administered IV over 30 minutes at 3 mg/kg every 2 weeks combined with ipilimumab administered IV over 30 minutes at 1 mg/kg every 6 weeks and cobimetinib 60 mg po qd 21 days on/7 days off until progression in patients with pancreatic cancer.

**Study Phase:** 1/2

**Research Hypothesis:** Treatment with nivolumab monotherapy, nivolumab combined with ipilimumab, or nivolumab combined with ipilimumab and cobimetinib will have clinical activity in subjects with advanced or metastatic tumors.

**Objectives:**

Primary Objective

SCLC Expansion Cohort:

- To compare the objective response rate (ORR) as assessed by a Blinded Independent Central Review (BICR) for nivolumab monotherapy versus nivolumab combined with ipilimumab (nivolumab 1 mg/kg + ipilimumab 3 mg/kg)

Other Cohorts:

- To evaluate the objective response rate (ORR) of nivolumab monotherapy, nivolumab combined with ipilimumab in subjects with advanced or metastatic tumors, or nivolumab combined with ipilimumab and cobimetinib in subjects from the additional pancreatic cancer cohort only. ORR will be assessed by the BICR in selected tumor types.

Secondary Objective

- To assess the safety of nivolumab monotherapy, nivolumab combined with ipilimumab in subjects with advanced or metastatic tumors or nivolumab combined with ipilimumab and cobimetinib in subjects from the additional pancreatic cancer cohort only.
- To assess Overall Survival (OS), OS-rate, Progression Free Survival (PFS), PFS-rate, and Duration of Response (DOR) with nivolumab monotherapy, nivolumab combined with ipilimumab in subjects with advanced or metastatic tumors or nivolumab combined with ipilimumab and cobimetinib in subjects from the additional pancreatic cancer cohort only. PFS and DOR will be assessed by the BICR in selected tumor types.

[redacted]

**Study Design:**

This is a multicenter Phase 1/2, two stage, open label study of nivolumab monotherapy, nivolumab combined with ipilimumab in adult (≥ 18 years) subjects with advanced or metastatic cancer of one of the following tumor types:

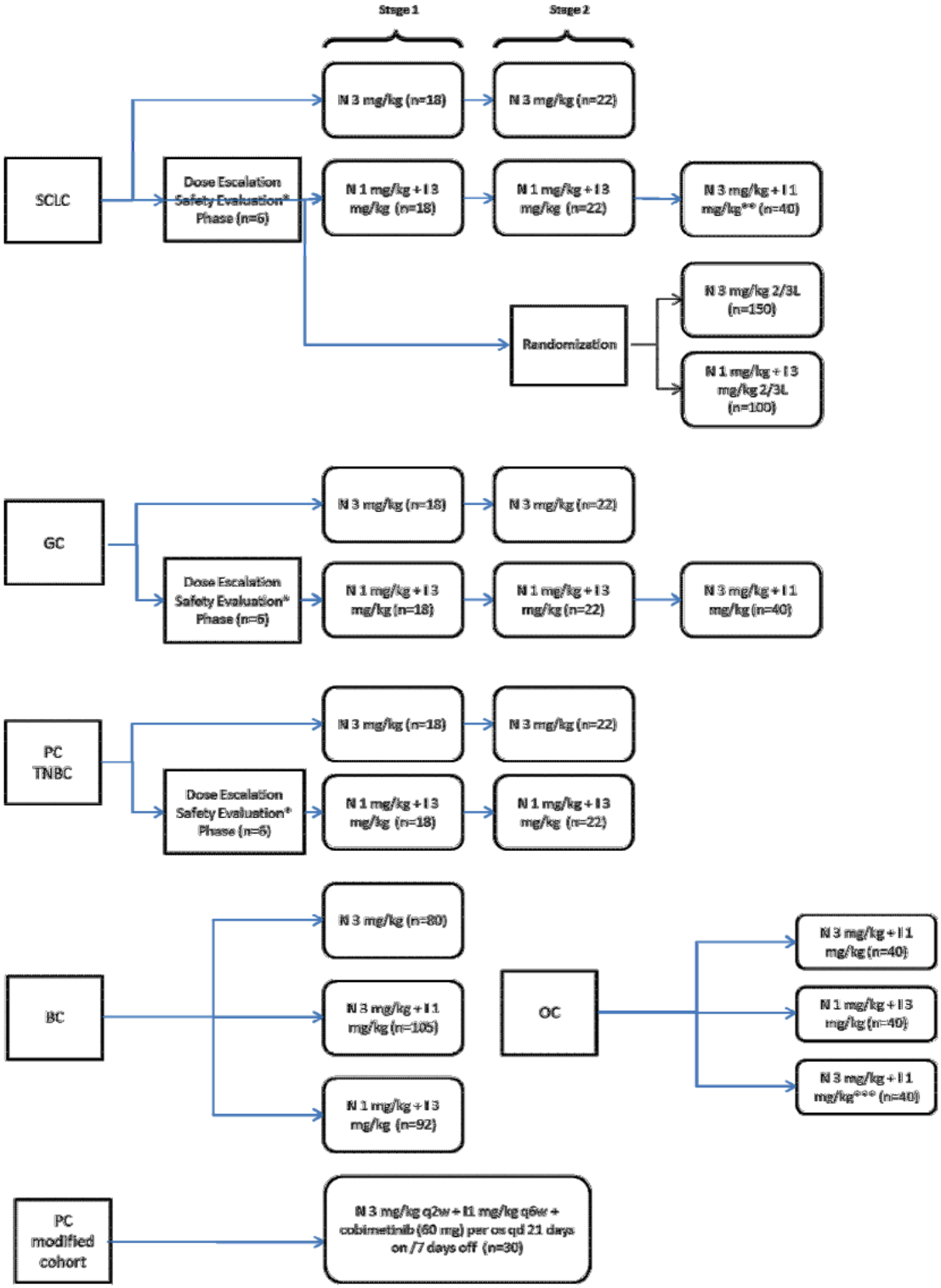
1) Triple Negative Breast Cancer (TNBC)
2) Gastric Cancer (GC)
3) Pancreatic Cancer (PC)
4) Small Cell Lung Cancer (SCLC)
5) Bladder Cancer (BC)
6) Ovarian Cancer (OC)

Or nivolumab combined with ipilimumab and cobimetinib in adult (≥ 18 years) subjects from the additional pancreatic cancer cohort only.

**Treatment assignment**: The assignment to treatment arm and evaluation of safety and activity will be performed independently for each tumor type. For each tumor type, subjects will be assigned to one of the following treatment arms:

| | |
|---|---|
| **Arm N:** | **Nivolumab monotherapy (3 mg/kg) Q2W** |
| **Arm N-I Dose Level 1:** | **Nivolumab (1 mg/kg) + ipilimumab (1 mg/kg) Q3W for 4 doses, then nivolumab (3 mg/kg) Q2W** |
| **Arm N-I Dose Level 2:** | **Nivolumab (1 mg/kg) + ipilimumab (3 mg/kg) Q3W for 4 doses, then nivolumab (3 mg/kg) Q2W** |
| **Arm N-I Dose Level 2b:** | **Nivolumab (3 mg/kg) + ipilimumab (1 mg/kg) Q3W for 4 doses, then nivolumab (3 mg/kg) Q2W** |
| **Arm N-I Dose Level 2c:** | **Nivolumab (3 mg/kg) Q2W + ipilimumab (1 mg/kg) Q6W** |
| **Arm N-I Dose Level 2d:** | **Nivolumab 3 mg/kg Q2W + ipilimumab (1 mg/kg) Q6W + cobimetinib 60 mg po qd 21 days on/7 days off for pancreatic cancer only** |

**Figure -1: Study Design for Each Tumor Type**




*dose level 1 (N1 mg/kg Q3W +I1 mg/kg Q2W) and dose level 2 (N1 mg/kg Q3W + I3 mg/kg Q2W); ** dose level 2b (N3 mg/kg Q3W + I1 mg/kg Q2W); *** dose level 2c (N3 Q2W + I1 Q6W); **** dose level 2d (N3 Q2W + I1 Q6W + cobimetinib 60 mg po qd 21 days on/7 days off)

**Dose-escalating Safety Evaluation Phase for Combination Arm:** Although the regimen currently used in the phase 3 melanoma study, nivolumab 1 mg/kg IV + ipilimumab 3 mg/kg, was expected to also be tolerable in the tumors studied here, an initial dose-escalating safety evaluation for the combination arms was conducted with GC, PC, TNBC, or SCLC (described in protocol Section 3.1.3). The BC cohort was added to this protocol following the completion of the safety evaluations in GC, PC, TNBC, and SCLC at dose level 1 (nivolumab 1 mg/kg, ipilimumab 1 mg/kg) which did not reveal safety concerns. Thereby the starting dose level for the BC cohort was dose level 2 (nivolumab 1 mg/kg, ipilimumab 3 mg/kg). Six BC patients were initially randomized to Dose Level 2, after which enrollment to Dose Level 2b (nivolumab 3 mg/kg, ipilimumab 1 mg/kg) began.

Enrollment to Stage 1 for Arm N occurred in parallel to the safety evaluation for Arm N-I.

**Two Stage Design:** GC, PC, TNBC, or SCLC Arms N and N-I will follow a two-stage design to test whether nivolumab monotherapy or nivolumab combined with ipilimumab yields an objective response rate (ORR) that is of clinical interest in the investigated tumor types. For each tumor type, only treatment arms which meet an ORR threshold will proceed from Stage 1 to Stage 2 (described in protocol Section 3.1.4). Enrollment to Stage 2 in a given treatment arm can continue even if the other treatment arm is still in Stage 1.

**Table 1: Efficacy criteria to proceed from Stage 1 to Stage 2**

| Efficacy criteria | Next Step |
|---|---|
| 2 or more of 18 subjects in a given arm have confirmed PR or CR | Go into Stage 2 |
| 1 or no of 18 subjects in a given arm have confirmed PR or CR. | No Go into Stage 2 |

For Stage 2, upon completion of enrollment of the initial 40 subjects, additional subjects may be assigned into Arm N and Arm N-I up to a total of 100 subjects (including those assigned in Stage 1) in each treatment arm of the given tumor type. For tumor types where nivolumab monotherapy or nivolumab 1 mg/kg plus ipilimumab 3 mg/kg proceeded to Stage 2, assessment of Dose Level 2b in Stage 2 (nivolumab 3 mg/kg + ipilimumab 1 mg/kg, n=up to 70 subjects) may be initiated for that tumor type. For SCLC, an additional 250 subjects (second- or third-line) will be randomized in a 3:2 ratio to one of the 2 expansion groups: nivolumab 3 mg/kg every 2 weeks or nivolumab 1 mg/kg + ipilimumab 3 mg/kg every 3 weeks for 4 cycles followed by nivolumab 3 mg/kg.

**Modified Design for Bladder Cancer Cohort:**

Bladder arms N and N-I (Dose Levels 2 and 2b) will be conducted as a One Stage Design with the treatment of 26-105 subjects in each arm. The Safety Evaluation Phase for the N-I arm will start at Dose Level 2 (nivolumab 1 mg/kg, ipilimumab 3 mg/kg) and will evaluate safety and tolerability after the first 6 randomized subjects. Following the N-I safety evaluation phase, Dose Level 2 will treat approximately 92 subjects and 2b will treat up to a total of 105 subjects. Based on the safety evaluations thus far on study, no dose escalation phase is necessary for bladder cohort N-I Dose Level 2b (nivolumab 3 mg/kg, ipilimumab 1 mg/kg).

**Modified Design for Ovarian Cancer Cohort:**

Ovarian arm N-I (Dose Levels 2, 2b and 2c) will be conducted as a One Stage Design with the treatment of 40 subjects in each arm. Due to the low risk of development of new safety signals on the combination arms no safety evaluation phase will be employed. Ovarian cancer subjects will be followed for related toxicities and decisions to stop treatment will be made on an ongoing basis.

**Design for Additional Pancreatic Cancer Cohort:**

Enrollment in the additional pancreatic cancer cohort will be initiated for one dose level N-I in combination with cobimetinib (Dose Level 2d) and will be conducted as a One Stage Design with the treatment of approximately 30 subjects in one arm. Given that the toxicity profile of the combination of nivolumab and ipilimumab is well-characterized and cobimetinib has demonstrated a tolerable profile when combined with an similar agent in the PD-1/PD-L1 pathway, as well as that cobimetinib does not have overlapping toxicity profiles with nivolumab or ipilimumab, the combination of these 3 agents is not expected to increase frequency and/or severity of drug associated toxicities. Pancreatic cancer subjects will be followed for related toxicities and decisions to stop treatment will be made on an ongoing basis.

Safety of the triplet combination in the proposed indication will be monitored continuously on a daily basis by the Medical Monitor, and enrollment will be staggered given the timing of amendment approval differ at individual sites as well as the limited number of eligible patients available at each site. No more than 6 patients will be enrolled in the first week of the study with subsequent enrollment of ≤ 6 subjects per week during the first month. A scheduled safety review by the Medical Monitor will occur after 12 patients are treated and have been followed for at least 1 month and regular safety telephone conferences will be performed with the investigators participating in studying the triplet combination in the proposed indication.

**SCLC expansion:**

SCLC cohorts Arm N and Arm N-I met the pre-specified safety and efficacy criteria and proceeded to Stage 2. Based on an interim data review, disease control rates (SD + PR + CR) of 36% and 57% for Arms N and N-I, respectively, were estimated. In order to further investigate nivolumab and nivolumab combined with ipilimumab activity in specific SCLC subpopulations, the SCLC expansion cohorts will enroll additional subjects based on response to prior treatment and the number of previous therapies. Up to 250 second or third line subjects will be randomized in a 3:2 ratio to one of 2 expansion groups: Arm A (150 subjects treated with nivolumab 3 mg/kg every 2 weeks (Q2W)) or Arm B (100 subjects treated with nivolumab 1 mg/kg + ipilimumab 3 mg/kg every 3 weeks (Q3W) for 4 cycles followed by nivolumab 3 mg/kg (Q2W) and will be stratified for number of prior treatment lines (1 vs 2 prior chemotherapy regimens). The crossover option refers only to the original cohorts and not the new cohorts enrolled under or after Amendment 09 implementation.

**Crossover for subjects in Arm N:** Subjects in Arm N may crossover to Arm N-I if all of the following criteria are met:

- The Safety Evaluation Phase for the N-I regimen has been completed and at least 6 subjects have been exposed to the dose level used for Stage 1 of the N-I regimen. In case Dose Level 2b has been activated and the safety assessment completed, subjects for cross over will be assigned to Dose Level 2b.
- Subject has confirmed radiologic disease progression (investigator-assessed RECIST 1.1 defined progression confirmed at least 4 weeks after the initial tumor assessment showing progression) in the absence of clinical deterioration. For subjects with clear evidence of new or progressing brain metastases a confirmation is not required. These subjects may proceed with brain radiation therapy and after having completed the radiation therapy a cross over to Arm N-I can be considered.
- Subjects with rapidly progressing tumors under nivolumab monotherapy may undergo radiation treatment first before initiation of the cross over after discussion between the sponsor and investigator.
- Subject has not experienced nivolumab related adverse events leading to permanent discontinuation.
- Subject is not continuing to derive any clinical benefit from nivolumab single agent therapy as assessed by the investigator which would allow continuation of nivolumab monotherapy.
- Subject is not a SCLC patient enrolled based on the Amendment 09 expansion.
- The individual case must be discussed with the medical monitor prior to cross over.

Subjects crossing over to Arm N-I will start treatment at Day 1 Week 1 as described for subjects originally randomized to Arm N-I. Subjects who cross over and subsequently have an objective response in Arm N-I will not be considered in the decision making for Arm N I proceeding to Stage 2.

**Study Population:**

*Key Inclusion Criteria*

- Subjects with histologically confirmed locally advanced or metastatic disease of one of the following tumor types and who meet the eligibility criteria:
  - Triple Negative Breast Cancer
  - Gastric Cancer
  - Pancreatic Cancer
  - Small Cell Lung Cancer

- Bladder Cancer
- Ovarian Cancer

- Subjects must have measurable disease by CT or MRI per RECIST 1.1 criteria (radiographic tumor assessment must be performed within 28 days prior to first dose)
- Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1

*Key Exclusion Criteria*

- Active brain metastases or leptomeningeal metastases. Subjects with brain metastases are eligible if these have been treated and there is no magnetic resonance imaging (MRI) evidence of progression for at least 4 weeks after treatment is complete and within 28 days prior to first dose of study drug administration. There must also be no requirement for immunosuppressive doses of systemic corticosteroids (> 10 mg/day prednisone equivalents) for at least 2 weeks prior to study drug administration.
- Subjects with active, known or suspected autoimmune disease. Subjects with vitiligo, type I diabetes mellitus, residual hypothyroidism due to autoimmune condition only requiring hormone replacement, or conditions not expected to recur in the absence of an external trigger are permitted to enroll.
- Subjects with a condition requiring systemic treatment with either corticosteroids (> 10 mg daily prednisone equivalents) or other immunosuppressive medications within 14 days of study drug administration. Inhaled or topical steroids, and adrenal replacement doses are permitted in the absence of active autoimmune disease.
- Prior therapy with experimental anti-tumor vaccines; any T cell co-stimulation or checkpoint pathways, such as anti-PD-1, anti-PD-L1, anti-PD-L2, anti-CD137, or anti-CTLA-4 antibody, including ipilimumab; or other medicines specifically targeting T cell is also prohibited.

**Study Assessments:**

***Tumor assessments***

The primary endpoint of this study, ORR, is based on tumor assessments at baseline and then at 6 weeks from first dose. Tumor assessments continue every 6 weeks for the first 24 weeks and every 12 weeks thereafter while on treatment or on treatment hold for any reason until disease progression (investigator-assessed RECIST 1.1-defined progression) or treatment discontinuation, except for subjects treated beyond progression or who discontinued treatment for other reasons than PD.

**Statistical Considerations:**

***Sample Size Determination***

*Sample size determination in the original protocol*

This study comprises a Dose Escalating Safety Evaluation Phase for the Combination Arm, followed by a Staged Enrollment for Arm N, and Arm N-I.

In the original protocol, gastric cancer, small cell lung cancer, triple negative breast cancer, and pancreatic cancer are included and the Staged Enrollment Part utilizes a modified Simon two-stage design with the treatment of 40 subjects to evaluate whether nivolumab, or the combination of nivolumab/ipilimumab yields an objective response rate (ORR) that is of clinical interest. In this study, an ORR of 10% or less is considered not of clinical value, and an ORR of 25% or greater is considered of strong clinical interest. The modified Simon design evaluates the null hypothesis that the true response rate is ≤ 10% versus the alternative hypothesis that the true response rate is > 10%. The 2-stage testing within each cohort targets a Type I error rate of 5% and has 80% power to reject the null hypothesis if the true response rate is 25%.

*Sample size determination for bladder cancer cohort*

In Amendment 06, the bladder cohort is added. A one stage design with the treatment of 60-100 subjects is used for nivolumab monotherapy and the dose level 2b. These sample sizes will provide 90% to 97% power to reject the null hypothesis of 10% response rate if the true response rate is 25% with a two-sided Type I error rate of 5%.

In Amendment 14, the dose level 2 arm (nivolumab 1 mg/kg + ipilimumab 3 mg/kg) of the bladder cancer cohort is to enroll and treat a total of 92 subjects. A one stage design will be used. Based on a 19.6% ORR for nivolumab monotherapy (CA209275), the sample size of 92 in this arm will provide 93% power to reject the null hypothesis of 19.6% response rate if the true response rate is 35% with a two-sided Type I error rate of 5%.

*Sample size determination for SCLC expansion cohort*

In Amendment 09, in addition to the original two-stage design of SCLC subjects, additional SCLC expansion cohort subjects will be randomized in a 3:2 ratio to one of 2 expansion groups: Arm A (150 subjects, nivolumab mono) or Arm B (100 subjects, nivolumab 1 mg/kg + ipilimumab 3 mg/kg) and will be stratified for number of prior treatment lines (1 vs 2 prior chemotherapy regimens).

Based on SCLC data so far observed in this study with an ORR of about 10% for nivolumab monotherapy and about 23% for nivolumab / ipilimumab combination therapy, sample sizes of N = 150 for nivolumab monotherapy and N = 100 for nivolumab / ipilimumab combination therapy (nivolumab 1 mg/kg + ipilimumab 3 mg/kg) will target a Type I error rate of 5% (two-sided) and will have 78% power to detect the difference between these two arms, if the true ORR rates are 10% and 23%, respectively.

*Sample size determination for ovarian cancer cohort*

Also in Amendment 09, an ovarian cancer cohort is added and a one stage design with the treatment of 40 subjects for each arm is used. These sample sizes provide 79% power to reject the null hypothesis of 10% response rate if the true response rate is 25% with a two-sided Type I error rate of 5%.

*Sample size determination for the additional pancreatic cancer cohort*

In this Amendment, pancreatic cancer cohort is re-opened and one stage design with the treatment of 30 subjects will be used. This sample size will provide 70% power to reject the null hypothesis of 10% response rate if the true response rate is 25% with a two-sided Type I error rate of 5%.

***Primary Endpoint:***

Objective Response Rate

*Analyses:*

ORR will be summarized for each cohort by a binomial response rate and corresponding two-sided 95% exact CI using the method proposed by Atkinson and Brown for cohorts using a two-stage design and the Clopper-Pearson method for cohorts using a one stage design.

For SCLC expansion cohort, the estimated difference including 95% CI of the estimated difference along with its corresponding p-value of ORR assessed by BICR between nivolumab monotherapy and nivolumab/ipilimumab combination therapy (nivolumab 1 mg/kg + ipilimumab 3 mg/kg) will be presented with 95% CI. Similar methods will be used to summarize ORR for each stratification factor. However, the p-value will not be provided for each stratification factor.

DOR as determined by the investigator or BICR for selected tumor types will be summarized for subjects who achieve confirmed PR or CR using the Kaplan-Meier (KM) product-limit method. Median values of DOR, along with two-sided 95% CI using the Brookmeyer and Crowley method will also be calculated by cohort. In addition, the percentage of responders still in response at different time points (3, 6, and 12 months) will be presented based on the KM plot.

The magnitude of reduction in tumor burden will be summarized descriptively.

***Secondary Endpoints:***

Safety will be assessed on all treated subjects. The rate of treatment-related adverse events leading to drug discontinuation within the first 12 weeks of treatment will be assessed.

PFS is defined as the time from treatment assignment in IVRS to the date of the first documented tumor progression or death due to any cause, whichever occurs first.

OS is defined as the time between the date of treatment assignment in IVRS and the date of death due to any cause. A subject who has not died will be censored at the last known alive date.

*Analysis:*

Treatment-related AEs leading to discontinuation will be tabulated using worst grade per NCI CTCAE v 4.0 criteria by system organ class and preferred term. All on-study AEs, Grade 3-4 AEs, treatment-related AEs, Grade 3 4 treatment-related AEs, SAEs, treatment-related SAEs, and AEs leading to discontinuation will be tabulated using worst grade per NCI CTCAE v 4.0 criteria by system organ class and preferred term. On-study lab parameters including hematology, chemistry, liver function, and renal function and Grade 3-4 Lab Abnormalities will be summarized using worst grade NCI CTCAE v 4.0 criteria.

PFS and OS will be summarized descriptively using Kaplan-Meier methodology. Median values of PFS and OS, along with two-sided 95% CIs using the Brookmeyer and Crowley method, will be calculated for each cohort. PFS rates at 6 and 12 months, and OS rates at 12 and 24 months will also be estimated. Associated two-sided 95% CIs will be calculated using the Greenwood formula. Additional survival analysis may be conducted for up to 5 years beyond analysis of the primary endpoint.

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# 1 INTRODUCTION AND STUDY RATIONALE

Nivolumab (BMS-936558; anti-PD-1 mAb) is a fully human monoclonal immunoglobulin (Ig) G4 antibody that binds to the programmed death-1 (PD-1) cell surface membrane receptor, a negative regulatory molecule expressed by activated T and B lymphocytes. Inhibition of the interaction between PD-1 and its ligands promotes immune responses and antigen-specific T cell responses to both foreign antigens as well as self antigens. PD-1 receptor blockade by nivolumab is a new approach for immunotherapy of tumors. Results from a Phase 1/2 study (CA209003)[1] indicate that nivolumab is active in multiple tumor types. Nivolumab 3 mg/kg monotherapy is currently approved for the treatment of advanced melanoma and non-small-cell lung cancer, metastatic renal carcinoma, and Hodgkin lymphoma, and is being studied in several Phase 3 and 2 clinical trials in advanced and metastatic solid and hematologic malignancies.

Ipilimumab is a fully humanized IgG1 monoclonal antibody binding to the anti-cytotoxic T-cell lymphoma-4 antigen (CTLA-4). Ipilimumab is an approved therapy for metastatic melanoma [Yervoy® Prescribing Information, 2011] and has demonstrated improved overall survival as monotherapy and in combination with dacarbazine.[2,3] Ipilimumab has been studied in combination with multiple standard of care (SOC) therapies including chemotherapy for squamous and non-squamous NSCLC and radiotherapy for hormone resistant prostate cancer.[4] Ipilimumab is currently also approved as adjuvant therapy in stage III melanoma.

Preclinical and clinical 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. 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.[5]

In the Phase 1 dose escalation study CA209004, the combination of nivolumab and ipilimumab has been studied in subjects with unresectable or metastatic melanoma. In this study, a safe dose level for the combination of ipilimumab and nivolumab was established for the treatment of advanced melanoma. At this dose level, 1 mg/kg nivolumab plus 3 mg/kg ipilimumab, an objective response rate of 53% was observed. This regimen was studied in a global, randomized Phase 3 study in advanced melanoma, CA209067.[6] Based on the results of the CA209067 study, the combination therapy of 1 mg/kg nivolumab plus 3 mg/kg ipilimumab is approved for the treatment of patients with unresectable or metastatic melanoma regardless of BRAF mutational status.

The combination of nivolumab with ipilimumab has been investigated in NSCLC (study CA209012)[7], metastatic clear cell renal cell carcinoma (mRCC) (study CA209016[8]). Data from these Phase 1/2 studies show, that the dose level of 3 mg/kg nivolumab plus 1 mg/kg ipilimumab is well tolerated while preserving the tumor efficacy[9,10]

Based on the promising results in study CA209004, study CA209032 is designed as a signal detection study for safety and efficacy in a variety of tumor types investigating nivolumab as a single agent or in combination with ipilimumab.

Pancreatic cancer is included in the tumor types that have been evaluated in CA209032. The combination of nivolumab and ipilimumab has been shown to be more effective than either agent in monotherapy in the treatment of a variety of tumors including melanoma, lung, and renal cell carcinoma.[6,7,8] Given the mechanism of anti-tumor activity of immuno-oncology agents is indirect and functions through the host immune system, there is good rationale that nivolumab and ipilimumab would be effective in pancreatic cancer. However, there was modest activity observed for nivolumab and nivolumab combined with ipilimumab in this indication. This lack of response to immune therapies may be related to the KRAS/MEK pathway. Recent published data have suggested that KRAS mutant tumors may be predisposed to combined therapy with a mitogen/extracellular signal regulating kinase (MEK) and agents targeting PD-1 and CTLA-4 pathways.[11] Therefore, the cohort aims to continue investigating the original hypothesis of whether nivolumab and ipilimumab can treat pancreatic cancer, but leveraging additional pathways which may enhance the ability for a clinically effective anti-tumor immune response.

## 1.1 Study Rationale

Study CA209032 is an open label multi-center Phase 1/2 study to investigate the safety and efficacy of nivolumab monotherapy or nivolumab and ipilimumab in combination in 6 tumor types - triple-negative breast cancer (TNBC), gastric cancer (GC), pancreatic adenocarcinoma (PC), small cell lung cancer (SCLC), bladder cancer (BC) and ovarian cancer (OC).

### *1.1.1 Rationale for Investigating Unresectable Locally Advanced or Metastatic Triple Negative Breast Cancer (TNBC)*

Breast cancer is classified by clinicopathological features based on the expression of hormone receptors for estrogen (ER) and progesterone (PR) as well as the human epidermal growth factor receptor 2 (HER2).[12] Triple negative breast cancer is an aggressive disease characterized by the lack of ER/PR and HER2 expression. TNBC is mostly of the basal type and accounts for 15 - 20% of cases of breast cancer.[13,14] Most BRCA1 mutation associated tumors are basal type and triple-negative.[15]

While TNBC is not responsive to hormonal or HER2-targeted agents, these tumors are responsive to anthracycline/taxane based chemotherapy in the adjuvant and neo-adjuvant setting which may induce complete pathological response (pCR).[16,17] However, the majority of TNBC patients have residual disease with high risk of relapse and rapid decrease in survival within the 3 - 5 year post-treatment.[18,19]

There are no standard chemotherapy regimens for previously treated TNBC patients. Treatment with capecitabine, gemcitabine, vinorelbine or nab-paclitaxel - either alone or in combination - has been used in second line therapy for metastatic breast cancer. Positive results for the subset of TNBC are obtained from the Phase 3 trials for ixabepilone approval in the USA and eribulin approval in the EMA for metastatic breast cancer prior-treated with anthracyclines

and taxanes. In the subset of TNBC patients from a 752 patient trial with anthracycline/taxane pre-treated breast cancer patients, improved PFS (4.2 vs 1.7 months for ixabepilone plus capecitabine compared to capecitabine alone, HR = 0.63, 95% CI 0.52-0.77, P < 0.0001) and ORR (27%) was observed.[20] In the Phase 3 EMBRACE study (N = 762), of eribulin versus treatment of physician's choice (TPC), eribulin demonstrated statistically significant OS increase (median OS 13 versus 11 months, HR = 0.81, P = 0.041).[21] In TNBC patients, the experimental arm conferred a 29% decreased risk of death.[22]

Among other agents, platinum-based regimens and PARP inhibitors (olaparib, iniparib, BSI-201) have shown promising results in TNBC, particularly in association with BRCA-mutation in the tumors. Vascular endothelial growth factor targeted therapy (bevacizumab, sunitinib, sorafenib) have also shown some activity.[23] However, true estimation of benefit from large trials is still awaited.

Establishing a standard of care with significant benefit in metastatic TNBC with prior anthracycline/taxane failure is an urgent unmet need. Immunotherapy may provide a path forward. A meta-analysis of 996 patients receiving neoadjuvant chemotherapy indicated an association of response to high scores for immune modules assessed by gene expression analysis.[24] In a preliminary BMS immuno-histochemistry survey of breast cancer tumor bank samples, TNBC has the highest percentage (18%) of samples positive for PD-L1 expression. Therefore, a monotherapy with a checkpoint inhibitor or the combination of check-point inhibitors like nivolumab may offer improved benefit for metastatic TNBC.

### *1.1.2 Rationale for Investigating Unresectable Locally Advanced or Metastatic Limited or Extensive Stage Small Cell Lung Cancer (SCLC)*

SCLC accounts for 15 - 20% of new cases of lung cancer, and nearly 33,900 new cases are expected in the US in 2012. [25] SCLC is traditionally classified as Limited Stage Disease (LD-SCLC - tumor tissue encompassed within a single radiation port) and Extensive Stage Disease (ED-SCLC - tumor that extends beyond the boundaries of a single radiation port).[26] For LD-SCLC, a combined therapeutic approach of radiotherapy, chemotherapy and rarely surgery is used with curative intent.[27] Most patients at diagnosis have ED-SCLC and are treated with four to six cycles of platinum plus etoposide (PE) which remains the standard chemotherapy regimen for LD- and ED-SCLC. Initial response rate is robust with 70-90% response seen in LD-SCLC and 50 - 70% response seen in ED-SCLC.[27] Whenever, overall survival remains poor with median survival for LD-SCLC at 18-30 months[28] and for ED-LCSC in the range of 10-12 months.[29]

Following platinum-based first line therapy, about 80% LD-LSC patients and all of ED-SCLC patients have disease progression.[30] Patients whose response after first line platinum-based therapy last beyond 180 days are the best candidates for re-challenge with platinum-doublet therapy. Others are treated with single-agent topotecan - the only approved second-line therapy in the US. Approval was based on a Phase 3 study showing superiority of single-agent intravenous topotecan over a regimen consisting of cyclophosphamide, doxorubicin and

vincristine (CAV) with an improved ORR (24.3% vs 18.3%, p= 0.285) and mOS similar between two arms (25 weeks vs 24.7 weeks). [31]

New treatments for SCLC are required. An analysis of peripheral blood mononuclear cells (PBMCs) from SCLC patients has shown that T-effector cells are more in LD-SCLC compared to ED-SCLC subjects and long-term survivors of SCLC have a higher T-effector to T-regulator ratio.[32] In a Phase 2 randomized study, ipilimumab in combination with carboplatin and paclitaxel showed improved PFS versus carboplatin and paclitaxel (5.7 months vs 4.6 months, HR = 0.72, P = 0.05), though there was no improvement when used concurrently.[33] Nivolumab at doses of 1, 3, and 10 mg/kg has been shown to be effective against NSCLC in a Phase 1 study (N = 122) with ORR of 6%, 27%, and 17% and PFS rates at 24 weeks of 25%, 44%, and 31%.[34,35] Considering the immune response seen in SCLC patients, and the results of checkpoint inhibitors nivolumab and ipilimumab in NSCLC patients, it is reasonable to expect that nivolumab alone or in combination with ipilimumab is likely to provide benefit in second-line and further lines of treatment of SCLC.

### *1.1.3 Rationale for Investigating Unresectable Locally Advanced or Metastatic Gastric and Gastro-Esophageal-Junction Cancer (GC)*

Globally, gastric cancer is the 4th leading cancer with over 900,000 diagnosed new cases and is the second leading cause of cancer-related death with 700,000 deaths reported annually. The geographic distribution is varied across the globe with the highest burden of disease seen in Eastern Europe, South America and Asia.[36] Gastro-esophageal junction (GEJ) cancer anatomically straddles the distal esophagus and proximal stomach. Due to the location and since the majority of GEJ tumors are adenocarcinomas, these tumors are frequently grouped together with gastric cancer. Until optimal treatment strategies are defined, advanced and metastatic GEJ cancer is treated and managed in a similar fashion to gastric cancer.[37,38]

Gastric cancer often presents with advanced disease upon diagnosis (except in countries like Japan and Korea where early detection is common). In about 20-30% of cases, subjects will present with resectable disease but in many of these, intraoperative discovery of lymph node metastasis is common and where curative surgery is possible, the recurrence rate after resection is high. For subjects developing advanced and metastatic disease, the reported 1-year survival is approximately 30%.[39] With first-line treatment, the median survival for these subjects is approximately 8 to 14 months and with best supportive care alone is approximately 3 months.

First-line chemotherapy generally consists of a fluroropyrimidine and or a platinum combination regimen.[40] There is still no universal consensus on the standard or reference regimen resulting in regional and even institutional differences seen in the choice of backbone chemotherapy.[41,42] Options for first-line therapy would include S1, 5FU or capecitabine for the fluroropyrimidine agent, and cisplatin or oxaliplatin for the platinum agent. Of note, no doublet combination of fluroropyrimidine plus platinum has been demonstrated to be superior to another in a Phase 3 randomized controlled trial in terms of efficacy although there are reported differences in the toxicity profiles between the regimens.[43,44] Though the results of the V325 Phase 3 trial

showed that the addition of docetaxel to cisplatin and 5FU combination improved time to progression with a small improvement in median survival, this is at the expense of increased toxicity.[45] As a consequence, docetaxel is limited to the first line treatment of gastric cancer.

Trastuzumab has been shown to have survival benefit in combination with chemotherapy for Her2 positive gastric cancer and improved median survival to 13.8 months.[46] This treatment is only applicable to those who exhibit Her2 positive disease comprising 10 - 30% of all the gastric cancer population.[47]

For patients after failure of first line platinum-fluoropyrimidine based chemotherapy there is an urgent medical need to find new therapeutic approaches. In gastric cancer, CTLA-4 blockade has been reported to induce antitumor response. Tremelimumab, a fully humanized anti-CTLA4 monoclonal antibody was assessed for its activity as second-line treatment for subjects with gastric cancer.[48] In a Phase 2 trial tremelimumab was administered on a 3-monthly schedule to a small group (n = 18) of subjects. Although the objective response rate was noted to be only 5%, the median survival was 4.8 months similar to other reported second-line chemotherapies for gastric cancer. Therefore, a checkpoint inhibitor (nivolumab) alone or in combination with each other (nivolumab plus ipilimumab) may offer improved benefit for patients with locally advanced or metastatic Gastric and Gastro-Esophageal-Junction Cancer.

### *1.1.4 Rationale for Investigating Unresectable Locally Advanced or Metastatic Pancreatic Adenocarcinoma Cancer (PC)*

Pancreatic adenocarcinoma is one of the deadliest forms of cancer with rising incidence during the past several decades. It is estimated that 45,200 new cases will be diagnosed and 38,460 people will die of pancreatic carcinoma in the United States in 2013.[49] The 1-year and 5-year survival rates for newly diagnosed patients are 15% and < 5% respectively.[50]

Radical surgery in early stage disease (Stage I and some Stage II) maybe the only treatment with curative intent in pancreatic cancer.[51] For locally advanced or metastatic disease (Stage IV), gemcitabine has been the standard of care with a median survival of 6.2 months and a 1 year survival rate of 20%.[52] The Phase 3 PRODIGE trial [N = 342] comparing FOLFIRINOX (combination of 5-FU, leucovorin, irinotecan, oxaliplatin) to gemcitabine in metastatic pancreatic cancer patients of good performance status (PS 0 in ≤ 75 year olds) showed significant improvement in median PFS (6.4 months vs 3.3 months, P < 0.001) and median OS (11.1 months vs 6.8 months, p < 0.001) with FOLFIRINOX.[53]

No established standard of care exists for subjects who progress after first line therapy in the advanced or metastatic therapy. There is an urgent need to find better treatment for pancreatic cancer. The NCCN Guideline for the treatment of pancreatic cancer state that all subjects with pancreatic cancer - irrespective of their line of treatment - should be considered for clinical trials.[54] Since nivolumab and ipilimumab act through a mechanism that is directed towards activating inactive T-cells, and has been shown to be active across multiple tumor types, it is reasonable to test the hypothesis that nivolumab alone or in combination with ipilimumab will

provide a response rate and depth of response (tumor shrinkage) that may translate to improved overall survival or provide quality of life benefits.

However, there was modest activity observed for nivolumab and nivolumab combined with ipilimumab in this indication on this clinical study. This lack of response to immune therapies may be related to the KRAS/MEK pathway. MEK inhibition alone in immunocompetent mice harboring a colon carcinoma cell line with mutant KRAS-G12D treated with the highly potent and specific MEK-inhibitor G-38963 (which is similar to cobimetinib) resulted in intratumoral CD8+ T cell accumulation and class I MHC upregulation.[55] In additional experiments in preclinical models, MEK inhibition synergized with anti-PD1 to promote durable tumor regression while promoting the effector phenotype and longevity of tumor-infiltrating CD8+ T cells. Investigations conducted by Liu and coworkers showed that MEK inhibitors in combination with PD-1 and CTLA 4 receptor blockade exhibit synergistic antitumor activity in mouse models with increased tumor-infiltrating CD8+ T cells in CD26 tumors.[11]

The MEK pathway is a critical mediator of the constitutively active mutant form of KRAS, KRAS-G12D, in many tumors including colorectal cancer (CRC) and pancreatic cancer. The clinical activity and safety of cobimetinib, an MEK inhibitor, were recently reported in results of a Phase1/2 clinical study in patients with advanced and metastatic CRC with a median of 3 prior treatment lines.[56] Cobimetinib when combined with an anti-PD-L1 antibody, azetolizumab, achieved an ORR of 17% in all treated CRC patients and 20% in patients with KRAS mutation; the 6-month OS rates were 72% and 77%, respectively. The most common adverse effects associated with this combination treatment were diarrhea, fatigue, and skin toxicities. Cobimetinib (Cotellic®) is currently approved in combination with vemurafenib for the treatment of metastatic melanoma.[57]

In addition to CRC, pancreatic cancer is also associated with KRAS mutations, with the most common mutation being KRAS-G12D[58], and the activation of several effector pathways downstream of KRAS, including MEK kinases MEK1/2[59]. Hence, study CA209032 is adding a pancreatic cancer cohort to detect safety and efficacy signals in this tumor type investigating nivolumab in combination with ipilimumab and cobimetinib.

### *1.1.5 Rationale for Investigating Unresectable Locally Advanced or Metastatic Bladder Cancer (BC)*

Bladder cancer is the most common malignancy of the urinary tract. Five percent (5%) of the patients have Stage IV disease at presentation.[60] Immunotherapy with Bacillus Calmette-Guerin in patients with superficial urothelial carcinoma reduces the risk of local recurrence by ~60% and can lead to 5-year survival rates of ~90% in patients with unifocal.[61] CD8 tumor-infiltrating lymphocytes (TILs) are predictive of survival in muscle-invasive urothelial carcinoma. Patients with advanced urothelial cancer (pT2, pT3, or pT4) and higher numbers of CD8 TILs within the tumor (> 8) had better disease-free survival ($P < 0.001$) and overall survival ($P = 0.018$) than did patients with similar-staged urothelial carcinoma and fewer intratumoral CD8 TILs.[62]

Active immunotherapeutic strategies have been investigated for bladder cancer showing that immune and antitumor responses are induced.[63] The safety of pre-operative CTLA-4 blockade in patients with bladder cancer has been demonstrated.[64] The efficacy and safety of first-line gemcitabine, cisplatin + ipilimumab for metastatic urothelial carcinoma is currently being investigated in a Phase 2 trial (NCT01524991). Recently, inhibition of PD-L1 by MPDL3280A was shown to have clinical activity in patients with metastatic urothelial bladder cancer.[65]

Based on the study results, Tecentriq® (atezolizumab, MPDL3280A) was granted approval for the treatment of patients with advanced urothelial carcinoma by the FDA. Nivolumab has also demonstrated meaningful antitumor activity in advanced urotheilal carcinoma[66].

In conclusion, a check point inhibitor therapy with nivolumab alone or nivolumab in combination with ipilimumab appears to be a promising experimental approach for patients with advanced urothelial carcinoma.

### *1.1.6 Rationale for Investigating Unresectable Locally Advanced or Metastatic Ovarian Cancer (OC)*

The term ovarian cancer includes not only epithelial ovarian cancer but also primary peritoneal and fallopian tube cancer. The latter two are less common neoplasms, which, however, are managed in a similar manner to epithelial ovarian cancer. Epithelial ovarian cancer is the leading cause of death from gynecologic cancer in the United States and is the country's fifth most common cause of cancer mortality in women.[67] Nearly 75 % of the patients present with advanced stage OC.[68] According to the International Federation of Gynecology and Obstetrics (FIGO), 5-year survival rates are approximately 46.7% for Stage IIIa, 41.5% for Stage IIIb, 32.5% for Stage IIIc, and 18.6% for Stage IV.[69] Whereas patients with platinum-sensitive OC treated with platinum-based frontline therapy have a high response rates up to 81% and a mPFS and mOS of 19.1 and 44.1 months, respectively[70], subjects with subsequent relapses, either platinum-sensitive or -resistant, have a significantly worse prognosis with a mPFS between 10.2 and 4.1 months and a mOS between 17.6 and 5.0 months, respectively.[71] Immunotherapy with weekly intraperitoneal IL-2 produced a ~ 17% complete pathologic response rate in patients with platinum-resistant OC.[72] A threefold prolongation of PFS was observed in patients treated with rhIFN-γ combined with MTD cisplatin and cyclophosphamide chemotherapy, with minimal added toxicity.[73],[74] The presence of tumor-infiltrating lymphocytes (TILs) in advanced stage OC correlates with an improved outcome. Patients with Stage III and IV OC and the presence of TILs within the tumor (either grade) had better disease-free survival and overall survival ($P < 0.001$) than did patients with similar-staged ovarian cancer and absence of TILs.[75] Therefore, use of immunotherapeutic agents in treatment of advanced OC is justified.

Indeed, active immunotherapeutic strategies with check point inhibitors have been investigated for ovarian cancer showing encouraging clinical activity signals with a good tolerability of nivolumab, PD-1 inhibitor.[76] The efficacy and safety of ipilimumab 10 mg/kg monotherapy for recurrent ovarian cancer is currently being investigated in a Phase 2 trial.[77] No new safety

signals have been identified in this clinical study, so far. Recently, inhibition of PD-1 by MK-3475 has been shown to be well tolerated and have clinical activity in patients with PD-L1 positive advanced ovarian cancer.[78] In conclusion, a check point inhibitor therapy with nivolumab or nivolumab in combination with ipilimumab appears to be a promising experimental approach for patients with advanced ovarian carcinoma.

### 1.1.7 Rationale for Investigating Nivolumab Combined with Ipilimumab and Cobimetinib in Pancreatic Cancer

The combination of nivolumab and ipilimumab is more effective than either agent in monotherapy in the treatment of a variety of tumors including melanoma, lung, and renal cell carcinoma.[6,7,8] Given the mechanism of anti-tumor activity of immuno-oncology agents is indirect and functions through the host immune system, there is good rationale that nivolumab and ipilimumab would be effective in pancreatic cancer. Nivolumab and ipilimumab have only had modest activity in the treatment of metastatic pancreatic cancer. Recent data in KRAS mutant tumors has suggested that MEK pathway inhibition can augment the effectiveness of PD-1/PD-L1 pathway targeted therapies.[79] Therefore, this cohort continues to interrogate the original hypothesis of whether nivolumab and ipilimumab can generate effective clinical activity in pancreatic cancer (a tumor with high prevalence of KRAS mutations) through the addition of a MEK inhibitor.

Cotellic® (cobimetinib) is an orally bioavailable, potent, selective MEK inhibitor. Preclinical observations and initial results of a Phase 1b trial combining cobimetinib and anti-PD-1 agent atezolizumab in patients with KRAS-mutant metastatic CRC indicate that metastatic cancer can be sensitized for immunotherapy by inhibition of MEK-dependent intracellular signaling.[56] It is expected that the combination of nivolumab with ipilimumab and cobimetinib will have a synergistic effect in pancreatic cancer without overlapping toxicities.

The most common toxic events associated with single-agent use of cobimetinib in Phase 1 testing were diarrhea, rash, fatigue, and edema; Grade 3 or higher events included diarrhea, rash, and fatigue.[80]

Drug-drug interactions between nivolumab/ipilimumab and cobimetinib are not expected. It is not likely that other drugs will affect the PK of nivolumab or ipilimumab because nivolumab is an IgG4 monoclonal antibody, and ipilimumab is an IgG1 monoclonal antibody, which are eliminated by non-specific catabolism (often by reticuloendothelial system proteases). This elimination process is not known to be inhibited or induced by small molecule drugs. Nivolumab is also unlikely to impact the PK of other companion drugs when used in combination regimens. A Phase 1 study in metastatic clear cell renal cell carcinoma (CA209009) demonstrated that nivolumab at all dose levels (0.3, 2, and 10 mg/kg) did not modulate cytokine levels (IL6, IL2, and IL10). Because no change in cytokine level was observed, nivolumab is not considered to mediate CYP induction, and has no or low potential for modulating CYP enzymes, and thereby a low risk of interaction with small molecule drugs. Similarly, ipilimumab is not expected to have drug-drug interaction with cobimetinib because ipilimumab, as a monoclonal antibody is unlikely to have an effect on CYPs or other drug-metabolizing enzymes.

The pancreatic cancer cohort will enroll subjects to a combination of Nivolumab administered IV at 3 mg/kg every 2 weeks combined with ipilimumab administered IV at 1 mg/kg every 6 weeks with cobimetinib 60 mg po qd 21 days on/7 days off.

The dose level of cobimetinib used in this clinical study is based on the dose approved for the combination of cobimetinib with vemurafenib for the treatment of patients with unresectable or metastatic melanoma with a BRAF V600E or V600K mutation.[57] This dose was also used in the Phase I clinical study of cobimetinib combined with 800 mg atezolizumab conducted by Bendell.[56] In this study, the dose of 60 mg of cobimetinib per os daily in combination with a PD-L1 antibody was safe and well tolerated.

### *1.1.8 Summary of Results from the Ipilimumab and Nivolumab Programs*

#### *1.1.8.1 Preclinical Summary of Nivolumab Combined with 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.[81]

In a 4-week toxicity study of nivolumab in combination with ipilimumab conducted in cynomolgus monkeys demonstrated that the combination of nivolumab and ipilimumab resulted in dose-dependent gastrointestinal (GI) toxicity. Histologic findings included inflammatory changes in the large intestine, which increased in incidence and severity in a dose-dependent manner. GI toxicity/colitis was not observed in cynomolgus monkeys administered nivolumab alone, but was observed in monkeys receiving ipilimumab. Nivolumab in combination with ipilimumab was also associated with lymphoid hypocellularity of the cortex and/or medulla of the thymus and with acinar cell degranulation in the pancreas. Additional findings included interstitial mononuclear cell infiltrates in the kidneys, portal mononuclear cell infiltrates in the liver and myeloid hypercellularity in the bone marrow. Nivolumab in combination with ipilimumab at the high-dose level (ie, 50 mg/kg and 10 mg/kg, respectively) was associated with the death of 1 animal, attributed to acute gastric dilatation without histopathological evidence of colitis upon pathology evaluation of the GI tract.

#### *1.1.8.2 Summary of Safety*

**Ipilimumab Monotherapy**

Ipilimumab 3 mg/kg is globally approved for advanced melanoma based on the results of a phase study, MDX010-20. In MDX010-20, the ipilimumab monotherapy arm was administered 3 mg/kg ipilimumab every 3 weeks for four doses. In this arm, there were 79% drug related adverse events, with 21% being Grade 3/4 and 3/131 (2%) Grade 5. The most frequent adverse events of interest were rash (30%), pruritis (33%), diarrhea (33%), colitis (8%),

endocrine disorders (9%), AST/ALT increased (2%), and hepatitis (1%). Any grade immune related adverse events were 60% and the Grade 3/4 immune related adverse events for the same cohort was 13% with the most frequent adverse events being diarrhea (5%), colitis (5%), rash (2%), and endocrine disorders (3%).

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

**Nivolumab Monotherapy**

CA209003 is an ongoing Phase 1 open label, multiple dose escalation study in 306 subjects with select previously treated advanced solid tumors, including melanoma, RCC, NSCLC, colorectal cancer, and hormone-refractory prostate cancer. Subjects received nivolumab at doses of 0.1, 0.3, 1, 3, or 10 mg/kg intravenously every 2 weeks, up to a maximum of 2 years of total therapy. As of 18-Mar-2013, a total of 306 melanoma subjects were treated with nivolumab in the dose range of 0.1 - 10 mg/kg.

No maximal tolerated dose was identified in CA209003. The incidence, severity and relationship of AEs were generally similar across dose levels and tumor types. Nivolumab related AEs of any grade occurred in 75.2% of subjects. Of the 306 treated subjects, 303 (99.0%) subjects have at least 1 reported AE regardless of causality. The most frequently reported AEs were fatigue (54.9%), decreased appetite (35.0%), diarrhea (34.3%), nausea (30.1%), and cough (29.4%). Treatment-related AEs were reported in 230 (75.2%) of the 306 subjects. The most frequently reported treatment-related AEs were fatigue (28.1%), rash (14.7%), diarrhea (13.4%), and pruritus (10.5%). Most treatment-related AEs were low grade. Treatment-related high grade (Grade 3-4) AEs were reported in 52 (17.0%) of subjects. The most common treatment-related high grade AEs were fatigue (2.3%) and diarrhea (1%).

Drug-related SAEs occurred in 11.5% of subjects. Grade 3-4 drug-related SAEs reported in at least 2 subjects included: diarrhea (3 subjects, 1.0%), pneumonitis (3 subjects, 1.0%), pneumonia (2 subjects, 0.7%), and lipase increased (2 subjects, 0.7%).

Select AE categories (events with a potential inflammatory mechanism requiring more frequent monitoring and/or unique intervention such as immunosuppressants and/or endocrine replacement therapy) include: GI AEs, pulmonary AEs, renal AEs, hepatic AEs, skin AEs, and endocrinopathies. In addition, Select AEs include a category for infusion reactions. Each category is composed of a discrete set of preferred terms, including those of greatest clinical relevance. These Select AEs are considered events of interest based on the mechanism of action and were previously referred to as immune-related AEs or immune-mediated AEs.

The 10 mg/kg cohort had numerically greater frequency of high-grade select AEs including the subcategories of endocrinopathies, GI, pulmonary, and infusion reactions (Table 1.1.8.2-1). Most high grade events resolved following the treatment guidelines for the treatment of pulmonary events, GI events, hepatic events, renal events, and endocrine events, respectively.

**Table 1.1.8.2-1: Treatment-related Select Adverse Events by Treatment - All CTC Grades Reported in at Least 10 Treated Subjects in CA209003**

| Preferred Term | 0.1 mg/kg n=17 | | 0.3 mg/kg n=18 | | 1 mg/kg n=86 | | 3 mg/kg n=54 | | 10 mg/kg n=131 | | Total N=306 | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Any Grade | Grade 3-4 | Any Grade | Grade 3-4 | Any Grade | Grade 3-4 | Any Grade | Grade 3-4 | Any Grade | Grade 3-4 | Any Grade | Grade 3-4 |
| **Any Select AE** | **8 (47)** | **1 (5.9)** | **9 (50)** | **0** | **42 (49)** | **3 (4)** | **23 (43)** | **2 (4)** | **58 (44)** | **13 (10)** | **140 (46)** | **19 (6)** |
| **Any Endocrinopathies** | **4 (24)** | **0** | **2 (11)** | **0** | **9 (11)** | **0** | **4 (7)** | **0** | **10 (8)** | **3 (2)** | **29 (10)** | **3 (1)** |
| Endocrinopathies Thyroid | 3 (18) | 0 | 2 (11) | 0 | 9 (11) | | 4 (7) | 0 | 8 (6) | 2 (2) | 26 (9) | 2 (1) |
| Blood TSH increased | 2 (12) | 0 | 1 (6) | 0 | 2 (2) | 0 | 2 (4) | 0 | 4 (3) | 1 (1) | 11 (4) | 1 (0.3) |
| Hypothyroidism | 1 (6) | 0 | 1 (6) | 0 | 5 (6) | 0 | 1 (2) | 0 | 3 (2) | 1 (1) | 11 (4) | 1 (0.3) |
| **Any Skin AEs** | **3 (18)** | **0** | **5 (28)** | **0** | **27 (31)** | **0** | **12 (22)** | **0** | **28 (21)** | **1 (1)** | **75 (25)** | **1 (0.3)** |
| Rash | 3 (18) | 0 | 3 (17) | 0 | 20 (23) | 0 | 5 (9) | 0 | 14 (11) | 0 | 45 (15) | 0 |
| Pruritus | 0 | 0 | 1 (6) | 0 | 15 (17) | 0 | 3 (6) | 0 | 13 (10) | 1 (1) | 32 (11) | 1 (0.3) |
| **Any GI AE** | **1 (6)** | **0** | **2 (11)** | **0** | **19 (22)** | **0** | **7 (13)** | **0** | **14 (11)** | **3 (2)** | **43 (14)** | **3 (1)** |
| Diarrhea | 1 (6) | 0 | 2 (11) | 0 | 19 (22) | 0 | 6 (11) | 0 | 13 (10) | 3 (2) | 41 (13) | 3 (1) |
| **Any hepatic AE** | **0** | **0** | **2 (11)** | **0** | **8 (9)** | **0** | **3 (6)** | **2 (4)** | **5 (4)** | **2 (2)** | **18 (6)** | **4 (1)** |
| ALT increased | 0 | 0 | 1 (6) | 0 | 6 (7) | 0 | 1 (2) | 0 | 3 (2) | **1 (1)** | 11 (4) | 1 (0.3) |
| **Any Pulmonary AE** | 1 (6) | **0** | 1 (6) | **0** | **6 (7)** | **3 (4)** | **2 (4)** | **0** | **7 (5)** | **3 (2)** | **17 (6)** | **6 (2)** |
| Pneumonitis | 1 (6) | 0 | 1 (6) | 0 | 4 (5) | 2 (2) | 1 (2) | 0 | 6 (5) | 2 (2) | 12 (4) | 4 (1) |
| **Other Select AE** | **0** | **0** | 1 (6) | **0** | **3 (4)** | **0** | **3 (6)** | **0** | **8 (6)** | **2 (2)** | **15 (5)** | **2 (1)** |
| Infusion-related reaction | 0 | 0 | 1 (6) | 0 | 3 (4) | 0 | 3 (6) | 0 | 5 (4) | 0 | 12 (4) | 0 |

Abbreviations: ALT: alanine aminotransferase, TSH: thyroid stimulating hormone

Source: Preliminary data, MDX1106-03. Clinical data cut-off date: 18-Mar-2013

Treatment-related AEs leading to discontinuation were reported in 32 (10.5%) of the 306 treated subjects on CA209003. The most frequent of these were pneumonitis (8 subjects; 2.6%) and colitis (3 subjects; 1.0%). There were 3 (1%) drug related deaths; each occurred after development of pneumonitis.

The Phase 3 dose for nivolumab monotherapy is 3 mg/kg. Additional details on the safety profile of nivolumab, including results from other clinical studies, are also available in the BMS-936558 (nivolumab) IB.

**Nivolumab Combined with Ipilimumab**

As of 15-Feb-2013, in the Phase 1 study CA209004 of 86 subjects with unresectable or metastatic melanoma, ascending doses of nivolumab have been studied as monotherapy in sequence with ipilimumab (N = 33) or in combination with ascending doses of ipilimumab (N = 53).

In the sequential cohorts, 1 mg/kg and 3 mg/kg nivolumab cohorts have been studied. Subjects were required to have prior ipilimumab and their last treatment must have occurred within 4 - 12 weeks. As such, based on ipilimumab pharmacokinetics, pharmacodynamically active ipilimumab was present at the outset of treatment in all subjects. Based on this, the monotherapy safety profile in the sequential cohorts was expected to differ from the monotherapy safety profile reported in CA209003. Therefore, the most relevant safety data for nivolumab monotherapy is from CA209003 (described above). The pooled safety data from CA209004 is only provided below for reference.

In each of the combination cohorts in this multi-arm study, ipilimumab was administered once every 3 weeks for 4 doses with nivolumab administered once every 3 weeks for 8 doses. Starting at week 24, ipilimumab and nivolumab were administered once every 12 weeks for 8 doses. The three initial dose escalation cohorts consisted of Cohort 1 (nivolumab 0.3 mg/kg plus ipilimumab 3 mg/kg; n = 14), Cohort 2 (nivolumab 1 mg/kg plus ipilimumab 3 mg/kg; n = 17) and Cohort 3 (nivolumab 3 mg/kg plus ipilimumab 3 mg/kg; n = 6). The study was subsequently amended to include Cohort 2a which evaluated nivolumab 3 mg/kg plus ipilimumab 1 mg/kg (n = 16). Safety data were pooled to summarize the overall findings.

At least one AE, regardless of whether they were attributed to the therapy, has been reported in 81 (94.2%) of the 86 subjects (Table 1.1.8.2-2). A numerically higher number of subjects in the combination therapy treatment groups experienced severe AEs, regardless of causality and treatment related, than those in the monotherapy treatment group.

In the combination treatment groups, the following dose-limiting toxicities (DLTs) were observed during the dose escalation in the combination cohorts:

- Cohort 1: Grade 3 elevated AST/ALT (1 subject);
- Cohort 2 : Grade 3 uveitis (1 subject) and Grade 3 elevated AST/ALT (1 subject);
- Cohort 3: Grade 4 elevated lipase (2 subjects) and Grade 3 elevated lipase (1 subject).

Based on these data, Cohort 2 was identified as the maximum tolerated dose (MTD) and Cohort 3 exceeded the MTD.

The most frequent treatment related AEs were rash (54.7%), pruritis (47.2%) and fatigue (37.7%). The most frequently reported treatment related severe AEs in the combination group were lipase and AST elevation (13.2% each), ALT elevation (11.3%), followed by diarrhea (5.7%) and rash (3.8%).

Treatment related serious adverse events (SAEs) were reported in 49% of patients in the combination treated subjects (N = 53) and were most frequently severe SAEs were: AST elevation (13.2%), ALT elevation (11.3%), lipase elevation (5.7%) and diarrhea, colitis and renal failure (3.8% each). Ten of the 53 (18.9%) treated subjects in the combination cohort discontinued therapy due treatment-related adverse events, the most frequent of which were ALT, AST elevation, lipase elevation, renal failure or pneumonitis. No drug-related deaths were reported.

**Table 1.1.8.2-2: Summary of Adverse Events Reported in ≥ 10% of Subjects Treated with Nivolumab in Combination with Ipilimumab Compared to Sequential Nivolumab Monotherapy**

| No. of Subjects (N) | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| | Combination Therapy n=53 | | | | Sequential (Nivo Monotherapy) n=33 | | | |
| | Regardless of Causality | | Treatment-related | | Regardless of Causality | | Treatment-related | |
| Preferred Term | Any Grade | Grade 3-4 | Any Grade | Grade 3-4 | Any Grade | Grade 3-4 | Any Grade | Grade 3-4 |
| **Any AE** | **52 (98.1)** | **38 (71.7)** | **49 (92.5)** | **28 (52.8)** | **29 (87.9)** | **11 (33.4)** | **24 (72.7)** | **6 (18.2)** |
| Rash | 32 (60.4) | 3 (5.7) | 29 (54.7) | 2 (3.8) | 7 (21.2) | 0 | 3 (9.1) | 0 |
| Fatigue | 31 (58.5) | 0 | 20 (37.7) | 0 | 12 (36.4) | 14 (42.4) | 3 (9.1) | 0 |
| Pruritus | 28 (52.8) | 1 (1.9) | 25 (47.2) | 0 | 6 (18.2) | | 6 (18.2) | 0 |
| Diarrhea | 22 (41.5) | 3 (5.7) | 18 (34.0) | 3 (5.7) | 4 (12.1) | 0 | 3 (9.1) | 0 |
| Cough | 19 (35.8) | 0 | 7 (13.2) | 0 | 8 (24.2) | 0 | 2 (6.1) | 0 |
| Nausea | 19 (35.8) | 1 (1.9) | 11 (20.8) | 0 | 6 (18.2) | 0 | 1 (3.0) | 0 |
| Pyrexia | 18 (34.0) | 0 | 11 (20.8) | 0 | 6 (18.2) | 0 | 0 | 0 |
| Headache | 18 (34.0) | 0 | 6 (11.3) | 0 | 3 (9.1) | 0 | 0 | 0 |
| AST increased | 13 (24.5) | 8 (15.1) | 11 (20.8) | 7 (13.2) | 1 (3.0) | 0 | 0 | 0 |
| Vomiting | 13 (24.5) | 3 (5.7) | 6 (11.3) | 1 (1.9) | 1 (3.0) | 0 | 0 | 0 |
| ALT increased | 12 (22.6) | 7 (13.2) | 11 (20.8) | 6 (11.3) | 1 (3.0) | 0 | 1 (3.0) | 0 |
| Abdominal pain | 11 (20.8) | 0 | 5 (9.4) | 0 | 1 (3.0) | 1 (3.0) | 0 | 0 |
| Arthralgia | 11 (20.8) | 0 | 4 (7.5) | 0 | 7 (21.2) | 1 (3.0) | 3 (9.1) | 0 |
| Lipase increased | 11 (20.8) | 9 (17.0) | 10 (18.9) | 7 (13.2) | 4 (12.1) | 2 (6.1) | 4 (12.1) | 2 (6.1) |
| Constipation | 10 (18.9) | 0 | 0 | 0 | 4 (12.1) | 0 | 1 (3.0) | 0 |
| Back pain | 9 (17.0) | 0 | 0 | 0 | 4 (12.1) | 0 | 0 | 0 |
| Decreased appetite | 9 (17.0) | 0 | 5 (9.4) | 0 | 3 (9.1) | 0 | 1 (3.0) | 0 |

**Table 1.1.8.2-2: Summary of Adverse Events Reported in ≥ 10% of Subjects Treated with Nivolumab in Combination with Ipilimumab Compared to Sequential Nivolumab Monotherapy**

| No. of Subjects (N) | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| | Combination Therapy n=53 | | | | Sequential (Nivo Monotherapy) n=33 | | | |
| | Regardless of Causality | | Treatment-related | | Regardless of Causality | | Treatment-related | |
| Preferred Term | Any Grade | Grade 3-4 | Any Grade | Grade 3-4 | Any Grade | Grade 3-4 | Any Grade | Grade 3-4 |
| Dyspnea | 9 (17.0) | 1 (1.9) | 3 (5.7) | 0 | 3 (9.1) | 1 (3.0) | 0 | 0 |
| Chills | 9 (17.0) | 0 | 3 (5.7) | 0 | 2 (6.1) | 0 | 0 | 0 |
| Amylase increased | 9 (17.0) | 3 (5.7) | 8 (15.1) | 3 (5.7) | 1 (3.0) | 1 (3.0) | 1 (3.0) | 1 (3.0) |
| Pain in extremity | 7 (13.2) | 0 | 0 | 0 | 2 (6.1) | 0 | 0 | 0 |

Abbreviations: AE: adverse event, ALT: alanine aminotransferase, AST: aspartate aminotransferase

Source: Preliminary data, MDX1106-04. Clinical cut-off date 15-Feb-2013.

**Treatment-related AEs of Special Interest:** A greater number of treatment-related Select AEs including pulmonary AEs, GI AEs, hepatic AEs, endocrinopathy, skin AEs, renal AEs, and others, provided in Table 1.1.8.2-3, were reported in subjects treated with nivolumab + ipilimumab combination therapy than in sequential nivolumab monotherapy.

The most frequently reported treatment-related Select AEs in the combination therapy group included rash, pruritus, diarrhea, AST increased, and ALT increased. With the exception of hepatic AEs, the events were reported were Grade 1-2. Isolated cases of pneumonitis and uveitis were observed, a finding that is consistent with previous experience with monotherapy.

The most frequently reported treatment-related Select AEs in the monotherapy treatment group were pruritus, rash, and diarrhea; all were Grade 1-2.

**Table 1.1.8.2-3: Summary of Treatment-related Events of Special Interest Reported in at Least 2 Subjects Treated with Nivolumab in Combination with Ipilimumab Compared to Sequential Nivolumab Monotherapy**

| No. of Subjects (N) | | | | |
|---|---|---|---|---|
| | Combination Therapy n=53 | | Sequential (Nivo Monotherapy) n=33 | |
| **Preferred Term** | **Any Grade** | **Grade 3-4** | **Any Grade** | **Grade 3-4** |
| **Any pulmonary AEs** | **3 (5.7)** | **1 (1.9)** | **1 (3.0)** | **0** |
| Pneumonitis | 3 (5.7) | 1 (1.9) | 1 (3.0) | 0 |
| **Any GI AE** | **20 (37.7)** | **5 (9.4)** | **3 (9.1)** | **0** |
| Colitis | 5 (9.4) | 2 (3.8) | 0 | 0 |
| Diarrhea | 19 (35.8) | 3 (5.7) | 3 (9.1) | 0 |
| **Any hepatic AE** | **12 (22.6)** | **8 (15.1)** | **1 (3.0)** | **0** |
| ALT increased | 11 (20.8) | 6 (11.3) | 1 (3.0) | 0 |
| AST increased | 11 (20.8) | 7 (13.2) | 0 | 0 |
| **Any endocrinopathy** | **7 (13.2)** | **1 (1.9)** | **3 (9.1)** | **1 (3.0)** |
| Adrenal insufficiency | 2 (3.8) | 0 | 1 (3.0) | 1 (3.0) |
| Hyperthyroidism | 2 (3.8) | 0 | 0 | 0 |
| Hypophysitis | 2 (3.8) | 1 (1.9) | 2 (6.1) | 1 (3.0) |
| Hypothyroidism | 2 (3.8) | 0 | 2 (6.1) | 1 (3.0) |
| Thryoiditis | 3 (5.7) | 0 | 0 | 0 |
| **Any skin AE** | **37 (69.8)** | **2 (3.8)** | **8 (24.2)** | **0** |
| Pruritus | 25 (47.2) | 0 | 6 (18.2) | 0 |
| Rash | 29 (54.7) | 2 (3.8) | 3 (9.1) | 0 |
| **Any Renal AE** | **3 (5.7)** | **3 (5.7)** | **0** | **0** |
| Blood creatinine increased | 3 (5.7) | 3 (5.7) | 0 | 0 |

**Table 1.1.8.2-3: Summary of Treatment-related Events of Special Interest Reported in at Least 2 Subjects Treated with Nivolumab in Combination with Ipilimumab Compared to Sequential Nivolumab Monotherapy**

| No. of Subjects (N) | | | | |
|---|---|---|---|---|
| | Combination Therapy n=53 | | Sequential (Nivo Monotherapy) n=33 | |
| **Preferred Term** | **Any Grade** | **Grade 3-4** | **Any Grade** | **Grade 3-4** |
| Renal failure acute | 2 (3.8) | 2 (3.8) | 0 | 0 |
| **Other** | 1 (1.9) | 0 | 0 | 0 |
| Infusion-related reaction | 1 (1.9) | 0 | 0 | 0 |

Abbreviations: AE: adverse event, ALT: alanine aminotransferase, AST: aspartate aminotransferase, ipi: ipilimumab, nivo: nivolumab

Source: Preliminary data, MDX1106-04. Clinical cut-off date 15-Feb-2013.

Recently, data from a Phase 1 study of nivolumab in combination with ipilimumab in metastatic renal cell carcinoma (mRCC) showed an incidence of 28.6% grade 3-4 treatment related adverse events for patients treated at nivolumab 3 mg/kg plus ipilimumab 1 mg/kg, while patients treated at nivolumab 1 mg/kg plus ipilimumab 3 mg/kg had grade 3-4 treatment related adverse events in 60.9%.[9] Median PFS based on an interim analysis was in the same range for both dose levels.

**Adverse Event Management Algorithms**

Because of the potential for clinically meaningful nivolumab or ipilimumab related AEs requiring early recognition and prompt intervention, management algorithms have been developed for suspected pulmonary toxicity, GI, hepatotoxicity, endocrinopathy, skin toxicity, neurological toxicity, and nephrotoxicity. The algorithms recommended for utilization in CA209032 are contained in Appendix 2.

### *1.1.8.3 Summary of Clinical Activity*

**Ipilimumab Monotherapy**

In melanoma, two completed Phase 3 studies have demonstrated clinically meaningful and statistically significant survival benefit in advanced melanoma. The completed Phase 3 study MDX010-20 demonstrated improved survival in pre-treated advanced melanoma. The study compared the overall survival (OS) of ipilimumab (3 mg/kg) plus a melanoma-specific vaccine (gp100) to that of gp100 alone. A second comparison defined the OS of ipilimumab alone vs gp100 alone. Both comparisons demonstrated statistically significant improvements in OS ($p = 0.0004$ and 0.0026, respectively). The median OS was 10, 10.1, and 6.4 months, for ipilimumab plus gp100, ipilimumab monotherapy, and gp100 monotherapy, respectively. The objective response rate was 5.7% (95% CI: 3.7, 8.4), 10.9% (95% CI: 6.3, 17.4), and 1.5% (95% CI: 0.2, 5.2) on the ipilimumab arm, the ipilimumab plus gp100 arm, and the gp100 arm, respectively.

The completed Phase 3 study CA184024 demonstrated improved survival in treatment-naive melanoma. The study compared the OS of ipilimumab (10 mg/kg) plus dacarbazine vs dacarbazine plus placebo. OS was improved in the ipilimumab plus dacarbazine group compared to the dacarbazine plus placebo group (11.2 months vs 9.1 months, respectively, HR 0.72, $p < 0.001$). The objective response rate was 15.2% on the ipilimumab plus dacarbazine arm compared to 10.3% on the dacarbazine plus placebo arm.

The approved ipilimumab regimen in advanced melanoma is 3 mg/kg ipilimumab monotherapy.

**Nivolumab Monotherapy**

In CA209003 (MDX1106-03), the clinical activity of nivolumab was demonstrated in a variety of tumor types and across a range of doses (0.1 mg/kg, 0.3 mg/kg, 1 mg/kg, 3 mg/kg, 10 mg/kg). As of the clinical cut-off date of 05-Mar-2013, a total of 306 subjects with melanoma, RCC, and NSCLC have been treated with nivolumab. All subjects initiated treatment at least one year prior to analysis. A response of either CR or PR, as determined by investigator assessed tumor evaluations based on modified RECIST 1.0, has been reported at all dose levels.

Among 107 patients with advanced melanoma who received nivolumab, the preliminary objective response rate was 33/107 (31%). Responses occurred at each dose level, with 6/17 (35%), 5/18 (28%), 11/35 (31%), 7/17 (41%), and 4/20 (20%) melanoma subjects responding at 0.1, 0.3, 1, 3, and 10 mg/kg, respectively. Duration of response range from 24.1 to 48.7+, 18.4 to 66.3+, 32.4 to 108.1+, 40.1+ to 115.4+, and 73.9 to 117.0+ months in melanoma subjects treated at 0.1, 0.3, 1, 3, and 10 mg/kg, respectively. An additional 7% of melanoma subjects had stable disease for 24 weeks or longer. Across dose levels, melanoma subjects achieved a median overall survival of 16.8 months (95% CI: 12.5, 31.6), with a 2-year overall survival rate of 43%.

**Nivolumab Combined with Ipilimumab**

As of 15-Feb-2013, in the combination cohorts of CA209004, ipilimumab was administered once every 3 weeks for 4 doses with nivolumab administered once every 3 weeks for 8 doses. Starting at week 24, ipilimumab and nivolumab were administered once every 12 weeks for 8 doses. The three initial dose-escalation cohorts consisted of Cohort 1 (nivolumab 0.3 mg/kg plus ipilimumab 3 mg/kg; n = 14), Cohort 2 (nivolumab 1.0 mg/kg plus ipilimumab 3 mg/kg; n = 17) and Cohort 3 (nivolumab 3.0 mg/kg plus ipilimumab 3 mg/kg; n = 6). Later, the study was amended to include Cohort 2a which evaluated nivolumab 3 mg/kg plus ipilimumab 1 mg/kg (n = 15).

In the combination cohorts, across all dose levels (N = 53), confirmed objective responses according to modified WHO criteria were observed in 21 of 52 patients (40%; 95% CI, 27 to 55) who had a response that could be evaluated. In addition, 4 patients had an objective response according to immune-related response criteria and 2 had an unconfirmed partial response. These patients were not included in the calculation of objective response rates. In the 1 mg/kg nivolumab + 3 mg/kg ipilimumab group, the ORR was 53% (see Table 1.1.8.3-1).

**Table 1.1.8.3-1: Objective Response Rate and Progression Free Survival 24 Weeks Rate in Melanoma Subjects - MDX1106-04**

| Treatment Group[a] | Nivo Dose (mg/kg) | N | ORR | 95% CI of ORR | PFS at 24 weeks (%) | 95% CI of PFS |
|---|---|---|---|---|---|---|
| Nivo + 3 Ipi | 0.3 | 14 | 3 (21) | 5 - 51 | 43 | 17 - 69 |
| Nivo + 3 Ipi | 1.0 | 17 | 9 (53) | 28 - 77 | 58 | 34 - 82 |
| Nivo + 1 Ipi | 3.0 | 15 | 6 (40) | 16 - 68 | 59 | 26 - 92 |
| Nivo + 3 Ipi | 3.0 | 6 | 3 (50) | 12 - 88 | 50 | 10 - 90 |

[a] Subjects received ipilimumab immediately prior to study entry, within 4 - 12 weeks of initiating nivolumab monotherapy on the protocol.

Abbreviations: CI: confidence interval, Ipi: ipilimumab, Nivo: nivolumab, ORR: objective response rate, PFS: progression-free survival

Source: Preliminary data, MDX1106-04. Clinical cut-off date 15-Feb-2013.

After noting that several patients had very deep responses (approaching complete response), a post hoc analysis of the number of patients with tumor reduction of 80% or more was done (Figure 1.1.8.3-1 and Figure 1.1.8.3-2). This depth of response was uncommon in published studies of ipilimumab or nivolumab.[2,34] A total of 16 out of 52 evaluable patients had tumor reduction of 80% or more at 12 weeks, including 5 with a complete response.

In the combination cohorts, overall evidence of clinical activity (conventional, unconfirmed, or immune-related response or stable disease for ≥ 24 weeks) was observed in 65% of patients (95% CI, 51 to 78). Responses were ongoing in 19 of 21 patients who had a response, with the duration ranging from 6.1 to 72.1 weeks at the time of data analysis.[82]

**Figure 1.1.8.3-1: Study CA209004 Clinical Activity - Tumor Shrinkage over Time**

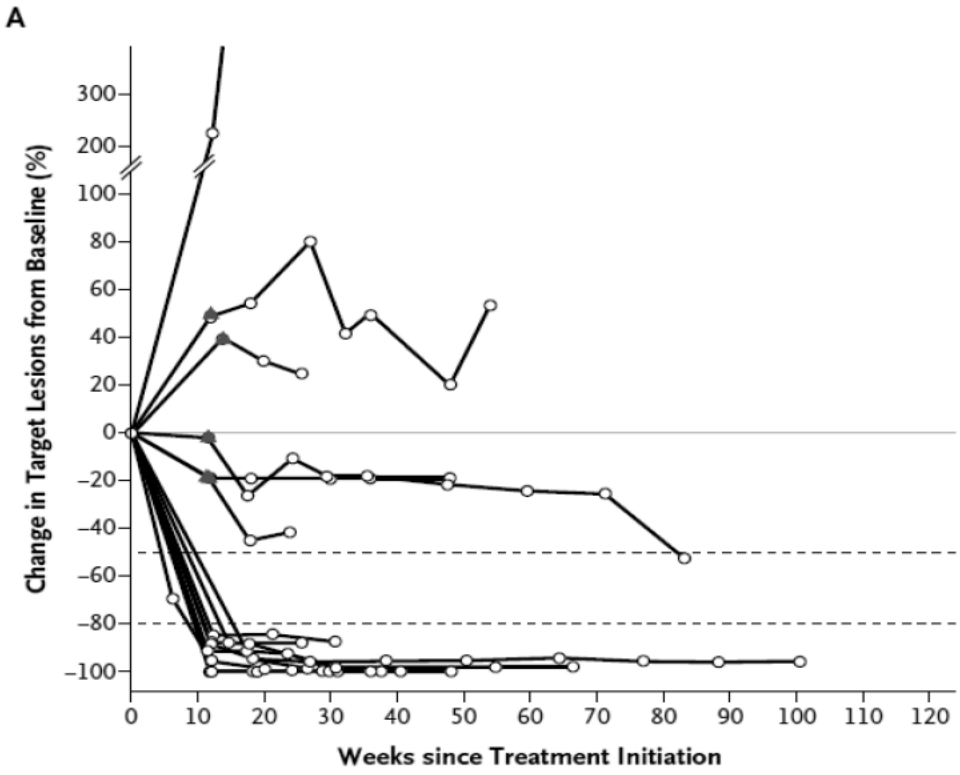
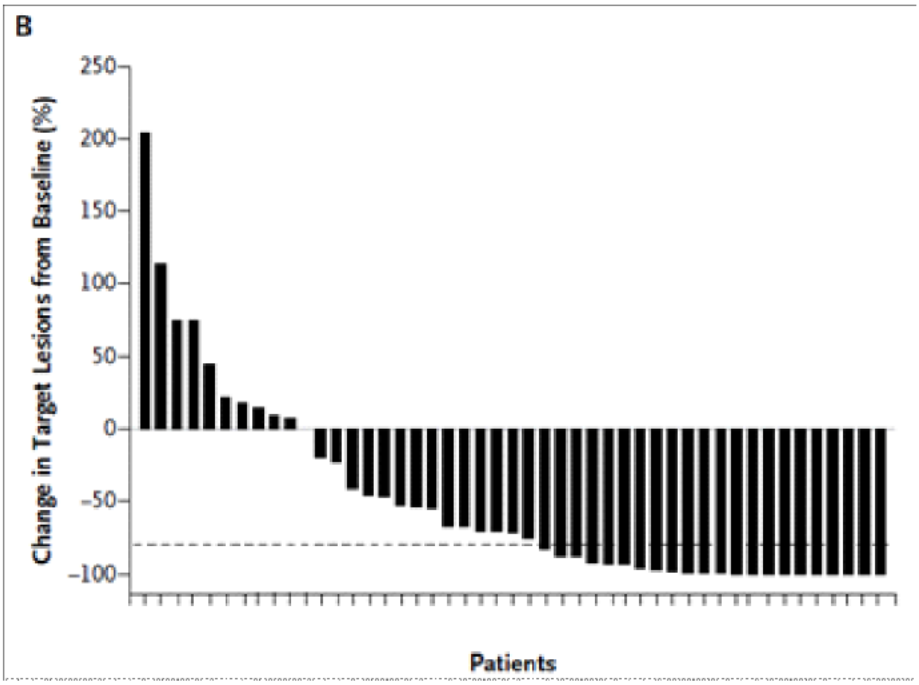



**Figure 1.1.8.3-2: Study CA209004 Clinical Activity - Maximum Tumor Shrinkage**



Representative spider plots in Figure 1.1.8.3-1 show changes from baseline in the tumor burden, measured as the sum of the products of perpendicular diameters of all target lesions, in patients who received the concurrent regimen of nivolumab (at a dose of 1 mg per kilogram of body weight) and ipilimumab (3 mg per kilogram), the maximum doses that were associated with an acceptable level of adverse events. Triangles indicate the first occurrence of a new lesion. Dashed lines indicate 50% and 80% improvement from baseline (gray line) in target lesions, as assessed by means of modified World Health Organization criteria. Figure 1.1.8.3-2 shows a representative waterfall plot of the maximum percentage change in target lesions, as compared with baseline measurements, in patients who received the concurrent regimen. A total of 47 patients had a response that could be evaluated in this analysis; 46 had a positive or negative change in target lesions from baseline, and 1 had no change. The dashed line denotes 80% tumor reduction in target lesions from baseline.[83]

### *1.1.9 Rationale to Support Dose/Schedule of Nivolumab Combined with Ipilimumab*

In CA209004, the 3 mg/kg nivolumab plus 3 mg/kg ipilimumab dosing regimen exceeded the maximum tolerated dose per protocol. In CA209004, while both Cohort 2 (1 mg/kg nivolumab plus 3 mg/kg ipilimumab) and Cohort 2a (3 mg/kg nivolumab plus 1 mg/kg ipilimumab) had similar Week 24 PFS rate, a dose of 3 mg/kg of ipilimumab every 3 weeks for a total of four doses and 1 mg/kg nivolumab every 3 weeks for four doses followed by nivolumab 3 mg/kg every 2 weeks until progression was chosen. Based on preliminary data, this group had a numerically higher ORR than Cohort 2a, although the significance of this difference is not clear.

The rationale for maximizing the ipilimumab dose over the nivolumab dose is primarily based on a well-defined dose and exposure response for ipilimumab (10 mg/kg > 3 mg/kg > 0.3 mg/kg). In contrast, analysis of nivolumab monotherapy across dose ranges of 1 mg/kg to 10 mg/kg reveals similar clinical activity with no clear evidence of dose or exposure response. Therefore, the selection of 3 mg/kg of ipilimumab (Cohort 2) may be more clinically impactful than selection of 3 mg/kg of nivolumab (Cohort 2a).

The combination arm in Study CA209032 is expected to use the same dose and schedule as that in Cohort 2 of CA209004 for the first 12 weeks (nivolumab 1 mg/kg plus ipilimumab 3 mg/kg). This is the same regimen currently being studied in the Phase 3 study in advanced melanoma, CA209067 and in ongoing studies in RCC and NSCLC. In CA209067 and in this current protocol, ipilimumab will be limited to 4 doses in the first 12 weeks since this is the currently approved dosing regimen.

To ensure that this regimen is tolerable across other tumors, an initial dose escalating safety evaluation step for the combination arm will be instituted. The starting dose in this evaluation will be 1 mg/kg each nivolumab and ipilimumab. If this regimen is tolerable, then Dose level 2, 1 mg/kg nivolumab + 3 mg/kg ipilimumab will be evaluated. The criteria for determining tolerability are based on the AE profile observed for the combination in CA209004.

Recently, data from a Phase 1 study of nivolumab in combination with ipilimumab in metastatic renal cell carcinoma (mRCC) showed an incidence of 28.6% grade 3-4 treatment related adverse

events for patients treated at nivolumab 3 mg/kg plus ipilimumab 1 mg/kg, while patients treated at nivolumab 1 mg/kg plus ipilimumab 3 mg/kg had grade 3-4 treatment related adverse events in 60.9%.[9] Median PFS based on an interim analysis was in the same range for both dose levels. Similarly, data from a Phase 1 study of nivolumab in combination with ipilimumab in first line NSCLC patients showed that the nivolumab 3 mg/kg plus ipilimumab 1 mg/kg dose level was well tolerated while sustaining clinical activity.[10] Based on these data, Study CA209032 will also investigate the nivolumab 3 mg/kg plus ipilimumab 1 mg/kg dose level.

Based on the clinical activity in CA209004, the majority of responses to the combination of nivolumab and ipilimumab occur in the first 12 weeks. Nivolumab 3 mg/kg monotherapy treatment every two weeks until progression was studied in CA209003 and was associated with durable responses. Thus, starting at week 12, which is after the completion of the four doses of combined nivolumab and ipilimumab, nivolumab at 3 mg/kg will be administered every two weeks until progression.

In summary, nivolumab and ipilimumab combinations have shown additive or synergistic activities across the tumor types investigated. To further improve the tolerability profile, other combination dosing regimens were also explored in the nivolumab development program. Less frequent dosing of ipilimumab at 1 mg/kg q6week when given with nivolumab 3 mg/kg q2week was found to have a similar discontinuation rate to that observed in nivolumab monotherapy (11% vs 10%) while yielding a ORR of 39% and a 12-month PFS rate of 35% in preliminary data from CA209012 in NSCLC. The median OS was 18.1 months. Based on these efficacy and safety data, nivolumab 3 mg/kg q 2 weeks + ipilimumab 1 mg/kg q 6 weeks dosing regimen will be evaluated in the current study.

### *1.1.10 Rationale for Shorter Nivolumab and Ipilimumab Infusion Times in Additional Pancreatic Cancer Cohort*

Long infusion times place a burden on patients and treatment centers. Establishing that nivolumab and ipilimumab can be safely administered using shorter infusion times of approximately 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 approximately 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.

Shortened infusion times will be implemented only in the additional re-opened pancreatic cancer cohort.

### *1.1.11 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 has also been reported for ipilimumab monotherapy.[84] 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 will 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 (Section 4.5.7). Such subjects must discontinue study therapy upon evidence of further progression.

## 1.2 Research Hypothesis

Treatment with nivolumab monotherapy, nivolumab combined with ipilimumab, or nivolumab combined with ipilimumab and cobimetinib will have clinical activity in subjects with advanced or metastatic tumors.

## 1.3 Objectives(s)

### *1.3.1 Primary Objective*

SCLC Expansion Cohort

- To compare the objective response rate (ORR) as assessed by a Blinded Independent Central Review (BICR) for nivolumab monotherapy versus nivolumab combined with ipilimumab (nivolumab 1 mg/kg + ipilimumab 3 mg/kg).

Other Cohorts

- To evaluate the objective response rate (ORR) of nivolumab monotherapy, nivolumab combined with ipilimumab in subjects with advanced or metastatic tumors, or nivolumab combined with ipilimumab and cobimetinib in subjects from the additional pancreatic cancer cohort only. ORR will be assessed by the BICR in selected tumor types.

### *1.3.2 Secondary Objective*

- To assess the safety of nivolumab monotherapy, nivolumab combined with ipilimumab in subjects with advanced or metastatic tumors, or nivolumab combined with ipilimumab and cobimetinib in subjects from the additional pancreatic cancer cohort only.
- To assess Overall Survival (OS), OS-rate, Progression Free Survival (PFS), PFS-rate, and Duration of Response (DOR) with nivolumab monotherapy, nivolumab combined with ipilimumab in subjects with advanced or metastatic tumors, or nivolumab combined with ipilimumab and cobimetinib in subjects from the additional pancreatic cancer cohort only. PFS and DOR will be assessed by the BICR in selected tumor types.

## 1.4 Product Development Background

As of Jun-2013, approximately 12,300 subjects have been treated with nivolumab monotherapy in single- or multiple-dose Phase 1/2/3 studies or studies with nivolumab in combination with other therapeutics (ipilimumab, cytotoxic chemotherapy, anti-angiogenics, and targeted therapies). Nivolumab as mono or combination therapy is currently being studied in multiple Phase 3 studies in squamous and non-squamous non-small cell lung cancer (NSCLC), malignant melanoma, and renal (clear) cell carcinoma (RCC).

Ipilimumab is an approved therapy for metastatic melanoma[85] and has demonstrated improved overall survival as monotherapy and in combination with dacarbazine[2,3]. An extensive clinical development program for ipilimumab, encompassing more than 14,000 subjects in several cancer types in completed and ongoing studies, as well as a compassionate use program have been conducted. Ipilimumab has been studied in combination with multiple standard of care (SOC) therapies including chemotherapy for squamous and non-squamous NSCLC and radiotherapy for hormone resistant prostate[4]. Phase 3 studies are ongoing in NSCLC, SCLC, and prostate carcinoma.

## 1.5 Overall Risk/Benefit Assessment

There continues to be a significant unmet clinical need for patients with the advanced or metastatic tumors selected for this study (see 1.1 Study Rationale). Nivolumab monotherapy has demonstrated clinical activity across several tumor types, including advanced melanoma, NSCLC, and RCC. Nivolumab has demonstrated a manageable safety profile in patients > 700 patients across all clinical trials. The most common AEs included fatigue, rash, pruritis, diarrhea, and nausea. The AE profile for nivolumab monotherapy does not appear to be dose dependent and appears to be similar across a range of solid tumors studied.

Ipilimumab 3 mg/kg is approved for use in the US (advanced melanoma) and in the EU (for previously treated advanced melanoma) based on OS benefit in randomized trials. Furthermore, clinical activity with ipilimumab has been observed in patients with NSCLC, SCLC, and prostate carcinoma. The efficacy of ipilimumab in these tumor types is being investigated in ongoing Phase 3 studies. The currently approved dose for ipilimumab in melanoma patients is 3 mg/kg every 3 weeks for up to 4 doses. Ipilimumab has demonstrated a manageable safety profile and treatment guidelines for immune related adverse events are established based on > 14,000 patients treated in clinical trials.

The combination of nivolumab and ipilimumab has the potential for increased benefit compared to both ipilimumab monotherapy and nivolumab monotherapy. In Study CA209004, 53% of the subjects with advanced melanoma treated at the dose level of nivolumab 1 mg/kg combined with ipilimumab 3 mg/kg had an objective response, the majority of which had deep tumor reduction of 80% or more. This deep response compares favorably to results with 3 mg/kg ipilimumab monotherapy or nivolumab monotherapy and is the basis for an ongoing randomized Phase 3 study in advanced melanoma (CA209067). Studies investigating the efficacy and safety of nivolumab in combination with ipilimumab are ongoing in NSCLC and RCC.

The combination of nivolumab and ipilimumab has the potential for increased frequencies of adverse events compared to ipilimumab monotherapy or nivolumab monotherapy. The most common (reported at > 10% incidence) treatment related AEs are fatigue, rash, pruritus, diarrhea, lipase increased, pyrexia, ALT increase, AST increased, amylase increased, and vitiligo. This class of AEs are expected for the combination of nivolumab and ipilimumab based on the known AE profile of each drug alone. In addition, many of the Grade 3-4 adverse events were laboratory in nature (ie, LFTs, lipase, amylase), were without clinical sequalae and have been manageable and reversible following intervention dose delays or with systemic steroid treatment. However, these AEs have the potential to be fatal if not detected early and managed per the established algorithm and fatal AEs have been reported for both ipilimumab and nivolumab monotherapy. As of June 2013, one subject died because of a study treatment related adverse event (toxic epidermal necrolysis, TEN) in the nivolumab + ipilimumab development program. Fatal TEN has previously been reported for ipilimumab monotherapy.

Evaluating nivolumab monotherapy and the combination of nivolumab and ipilimumab in subjects with advanced or metastatic solid tumors for which no standard of care in advanced lines of treatment exists, will potentially generate efficacy signals as a basis for further clinical development in these tumor types.

Across multiple tumors, 3 mg/kg nivolumab as well as 3 mg/kg ipilimumab monotherapy have demonstrated a tolerable AE profile in hundreds, respectively thousands of subjects that appears to be independent of tumor type. The combination of 1 mg/kg nivolumab + 3 mg/kg ipilimumab has demonstrated an acceptable AE profile in melanoma and is currently in Phase 3. The same regimen is currently being studied in RCC and NSCLC. The following safety measures have been employed to ensure safety of the subjects in this current study:

- Intense toxicity monitoring will help to ensure the subjects' safety in Study CA209032, including frequent safety conference calls with investigators and representatives of the sponsor
- A BMS medical safety team (MST) routinely reviews safety signals across the entire nivolumab program, including all ongoing combinations with ipilimumab
- Two stage design used which will stop an individual arm for lack of sufficient activity
- For the combination arm, an initial dose escalating safety evaluation phase will be performed to determine the optimal dose for each tumor type independently

Cobimetinib as monotherapy or in combination with other targeted therapy is well tolerated.[86] Safety data from the Phase 3 coBRIM trial demonstrated that the combination of vemurafenib and cobimetinib was associated with a nonsignificantly higher incidence of adverse events of Grade 3 or higher, as compared with vemurafenib and placebo (65% vs 59%).[87] The recommended dosage of oral cobimetinib is 60 mg once daily for 21 consecutive days, followed by a 7-day break, for a total cycle length of 28 days.

Emerging preliminary data on safety and efficacy of the PD-1 inhibitor atezolizumab in combination with cobimetinib in advanced CRC have demonstrated a clinical benefit and was well tolerated.[56] Being a PD-1 inhibitor, nivolumab is expected to have an acceptable tolerability profile in combination with cobimetinib similar to that of atezolizumab.

Given that the toxicity profile of the combination of nivolumab and ipilimumab is well-characterized and that cobimetinib does not have overlapping toxicity profiles with nivolumab or ipilimumab, the combination of these three agents is not expected to increase frequency and/or severity of drug associated toxicities.

Based on the above assessment, the potential benefit of combining nivolumab with ipilimumab and cobimetinib appears to outweigh the potential risk. The overall risk/benefit assessment supports the evaluation of these combinations in this setting.

In conclusion, the overall risk-benefit assessment for Study CA209032 does justify the conduct of the trial.

# 2 ETHICAL CONSIDERATIONS

## 2.1 Good Clinical Practice

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

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

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

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

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

## 2.2 Institutional Review Board/Independent Ethics Committee

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

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

## 2.3 Informed Consent

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

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

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

Investigators must:

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

subject's willingness to continue participation in the study. This communication should be documented.

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

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

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

# 3 INVESTIGATIONAL PLAN

## 3.1 Study Design and Duration

This is a multicenter Phase 1/2, two stage, open label study of nivolumab monotherapy, nivolumab combined with ipilimumab, in adult (≥ 18 years) subjects with advanced or metastatic cancer of one of the following tumor types:

1) Triple Negative Breast Cancer (TNBC)
2) Gastric Cancer (GC)
3) Pancreatic Cancer (PC)
4) Small Cell Lung Cancer (SCLC)
5) Bladder Cancer (BC)
6) Ovarian Cancer (OC)

Or nivolumab combined with ipilimumab and cobimetinib in adult (≥ 18 years) subjects from the additional pancreatic cancer cohort only.

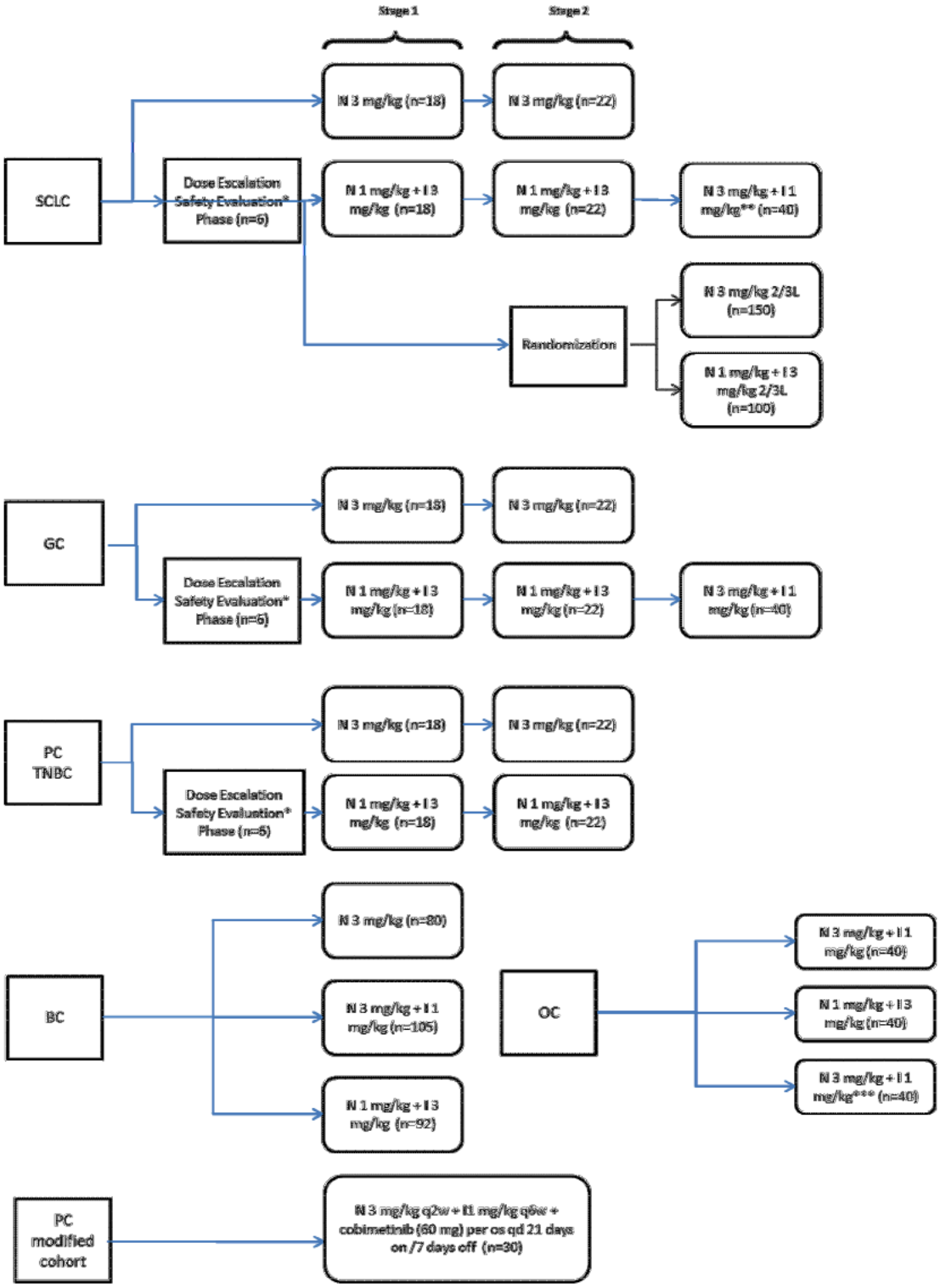
**Treatment assignment**: The assignment to treatment arm and evaluation of safety and activity will be performed independently for each tumor type (Figure 3.1-1). For each tumor type, subjects will be assigned (described in Section 4.3.4) to one of the following treatment arms:

| | |
|---|---|
| **Arm N:** | Nivolumab monotherapy (3 mg/kg) Q2W |
| **Arm N-I Dose Level 1:** | Nivolumab (1 mg/kg) + ipilimumab (1 mg/kg) Q3W for 4 doses, then nivolumab (3mg/kg) Q2W |
| **Arm N-I Dose Level 2:** | Nivolumab (1 mg/kg) + ipilimumab (3 mg/kg) Q3W for 4 doses, then nivolumab (3 mg/kg) Q2W |
| **Arm N-I Dose Level 2b**: | Nivolumab (3 mg/kg) + ipilimumab (1 mg/kg) Q3W for 4 doses, then nivolumab (3 mg/kg) Q2W |

**Arm N-I Dose Level 2c**: Nivolumab (3 mg/kg) Q2W + ipilimumab (1 mg/kg) Q6W

**Arm N-I Dose Level 2d:** Nivolumab 3 mg/kg Q2W + ipilimumab (1 mg/kg) Q6W + cobimetinib 60 mg po qd 21 days on/7 days off for the additional pancreatic cancer cohort only

**Figure 3.1-1: Study Design for Each Tumor Type**




*dose level 1 (N1 mg/kg Q2W +I1 mg/kg Q2W) and dose level 2 (N1 mg/kg Q3W + I3 mg/kg Q2W); ** dose level 2b (N3 mg/kg Q3W + I1 mg/kg Q2W); *** dose level 2c (N3 mg/kg Q2W + I1 mg/kg Q6W); ****dose level 2d (N3 mg/kg Q2W +I1 mg/kg Q6W +cobimetinib 60 mg po QD 21 days on/7 days off

**Dose-escalation Safety Evaluation Phase for Combination Arm:** Although the regimen currently used in the Phase 3 melanoma study, nivolumab 1 mg/kg IV + ipilimumab 3 mg/kg, was expected to also be tolerable in the tumors studied here, an initial dose-escalating safety evaluation for the combination arms was conducted with GC, PC, TNBC, or SCLC (described in protocol Section 3.1.2). The BC cohort was added to this protocol following the completion of the safety evaluations in GC, PC, TNBC, and SCLC at dose level 1 (nivolumab 1 mg/kg, ipilimumab 1 mg/kg) which did not reveal safety concerns. Thereby the starting dose level for the BC cohort was dose level 2 (nivolumab 1 mg/kg, ipilimumab 3 mg/kg). Six BC patients were initially randomized to Dose Level 2, after which enrollment to Dose Level 2b (nivolumab 3 mg/kg, ipilimumab 1 mg/kg) began.

Enrollment to Stage 1 for Arm N occurred in parallel to the safety evaluation for Arm N-I.

**Two Stage Design:** GC, PC, TNBC, SCLC Arms will follow a two-stage design to test whether nivolumab monotherapy or nivolumab combined with ipilimumab yields an objective response rate (ORR) that is of clinical interest in the investigated tumor types. For each tumor type, only treatment arms which meet an ORR threshold will proceed from Stage 1 to Stage 2 (described in protocol Section 3.1.3). Enrollment to Stage 2 in a given treatment arm can continue even if the other treatment arm is still in Stage 1.

For Stage 2, upon completion of enrollment for the initial 40 subjects, additional subjects may be assigned into Arm N and Arm N-I up to a total of 100 subjects (including those assigned in Stage 1) in each treatment arm of the given tumor type. For tumor types where nivolumab monotherapy or nivolumab 1 mg/kg plus ipilimumab 3 mg/kg proceeded to Stage 2, assessment of Dose Level 2b in Stage 2 (nivolumab 3 mg/kg + ipilimumab 1 mg/kg, n=up to 70 subjects) may be initiated for that tumor type. For SCLC, an additional 250 subjects (second- or third-line) will be randomized in a 3:2 ratio to one of the 2 expansion groups: nivolumab 3 mg/kg every 2 weeks or nivolumab 1 mg/kg + ipilimumab 3 mg/kg every 3 weeks for 4 cycles followed by nivolumab 3 mg/kg.

### *3.1.1 Modified Designs*

**Bladder Cancer Cohort**

The enrollment for the BC cohorts N and N-I (Dose Level 2b) will be conducted as a One Stage Design:

- Recently, inhibition of PD-L1 by MPDL3280A was shown to have clinical activity in patients with metastatic urothelial bladder cancer, leading to approval of the drug in this indication by the FDA.[88] The overall response rate in all treated subjects was 15%.
- Nivolumab has recently demonstrated meaningful antitumor activity with an overall response rate of 19.6% in all treated subjects
- As these data show that checkpoint inhibition has potential to be an active treatment for patients with advanced bladder cancer, a Two Stage design with the intent of avoiding to expose too many patients to a potentially ineffective treatment does not appear to be necessary for this specific tumor type.[66]

- Bladder arms N and N-I (Dose Levels 2 and 2b) will be conducted as a One Stage Design with the treatment of 26-105 subjects in each arm. The Safety Evaluation Phase for the N-I arm will start at Dose Level 2 (nivolumab 1 mg/kg, ipilimumab 3 mg/kg) and will evaluate safety and tolerability after the first 6 randomized subjects. Following the N-I safety evaluation phase, Dose Levels 2 will treat approximately 92 subjects and 2b will treat up to a total of 105 subjects. Based on the safety evaluations thus far on study, no dose escalation phase is necessary for bladder cohort N-I Dose Level 2b (nivolumab 3 mg/kg, ipilimumab 1 mg/kg).

**Ovarian Cancer Cohort**

The OC cohorts N-I (Dose Level 2, 2b, 2c) will be conducted as a One Stage Design with the enrollment of 40 subjects in each arm. The Dose Level 2c was added to Ovarian Cancer Cohort based on the results of CA209003 and CA209012 clinical studies mentioned above. The efficacy and tolerability of nivolumab monotherapy observed in CA209003 study with longer follow-up of previously treated NSCLC patients suggested a strategy in which nivolumab serves as the "base" of a combination regimen, with ipilimumab exposure limited by lower doses and/or less frequent administration. This strategy is the basis for new nivolumab and ipilimumab combination regimens with nivolumab 3 mg/kg Q2W combined with ipilimumab 1 mg/kg Q6W. This regimen was used in CA209012 study with preliminary data showing a promising activity and a good safety profile of the combination.

The enrollment to the N-I arm to Dose Levels 2, 2b, and 2c will be conducted simultaneously. Due to the low risk of development of new safety signals on the combination arms confirmed by the additional information from the combination studies in melanoma, lung, renal cell carcinoma, and glioblastoma as well as the clinical study with ipilimumab 10 mg/kg monotherapy in ovarian cancer, which did not reveal any new safety signals (please refer to Section 1.1 Study Rationale and Sections 5.5.1.2, 5.5.2.2, 5.5.3.2, 5.5.4.2, and 5.6.1.3 in the current version of the Investigator Brochure), no Safety Evaluation Phase will be employed. Ovarian cancer subjects will be followed for related toxicities and decisions to stop treatment will be made on an ongoing basis.

**Additional Pancreatic Cancer Cohort**

Enrollment in the PC cohort will be initiated for one dose level N-I in combination with cobimetinib (Dose Level 2d) and will be conducted as a One-Stage Design:

The safety profile of all agents proposed for the triplet combination are well defined as either monotherapy or in combination and the products are already commercially available for the treatment of several advanced and metastatic tumor types. The safety profile of the combination of nivolumab with ipilimumab (3 mg/kg) is well characterized and it is approved for treatment of unresectable or metastatic melanoma. The toxicity profile of the nivolumab + ipilimumab combination has been shown to correlate with the ipilimumab dose: With increasing doses of ipilimumab there has been an increase in frequency of adverse events, and potentially the severity of these events, however no novel toxicities have been demonstrated versus either agent

alone.[82,89,90,91,92] In the current regimen for this protocol cohort, the dose of ipilimumab will be cumulatively lower than on prior cohorts studied in the proposed indication as well as the approved dose level for the combination for the treatment of advanced and metastatic melanoma. The toxicity profile with lower doses of ipilimumab has been established to be very similar to that of nivolumab monotherapy.[93]

The safety of a PD-L1 agent combined with cobimetinib is already established and safe. For the triplet combination, non-overlapping toxicities are expected. Therefore, if there were to be an increase in toxicity, no new toxicities are anticipated and it is not expected to be significantly different that that seen in the combination of nivolumab with the higher dose of ipilimumab, which has already been demonstrated to be tolerable.

Safety of the triplet combination in the proposed indication will be monitored continuously on a daily basis by the Medical Monitor, and enrollment will be staggered given the timing of amendment approval differ at individual sites as well as the limited number of eligible patients available at each site. No more than 6 patients will be enrolled in the first week of the study with subsequent enrollment of ≤ 6 subjects per week during the first month. A scheduled safety review by the Medical Monitor will occur after 12 patients are treated and have been followed for at least 1 month and regular safety telephone conferences will be performed with the investigators participating in studying the triplet combination in the proposed indication.

### *3.1.2 Dose-Escalating Safety Evaluation Phase for Arm N-I*

The combination of 1 mg/kg nivolumab + 3 mg/kg ipilimumab is already approved for the treatment of advanced and metastatic melanoma regardless of BRAF mutational status and has more recently been tested in NSCLC and RCC. This regimen is expected to also be tolerable in the tumors being studied in this protocol. However, as an added safety precaution, the combination of N-I will first be assessed in a dose escalating safety phase. This safety evaluation will be conducted for each of the investigated tumor types independently (Table 3.1.2-1). Recently, data from Phase 1/2 studies in NSCLC and RCC have shown, that the dose level of 1 mg/kg ipilimumab plus 3 mg/kg nivolumab is well tolerated while potentially preserving the tumor efficacy.[9,10] Therefore, a Dose Level 2b (nivolumab 3 mg/kg, ipilimumab 1 mg/kg) will be investigated in the Dose-Escalating Safety Evaluation Phase in case Dose Level 2 is not tolerable for any of the tumor types being studied.

**Table 3.1.2-1: Dose Cohort for Arm N-I**

| Dose Cohort Level | Nivolumab (mg/kg) | Ipilimumab (mg/kg) |
|---|---|---|
| -1 | 0.3 | 1 |
| 1 | 1 | 1 |
| 2 | 1 | 3 |
| 2b | 3 | 1 |

The first dose cohort will be Level 1. If this is deemed tolerable, then Level 2 will be initiated. If Level 1 is not tolerable, then Level -1 will be initiated. The BC cohort will start at Level 2. If Dose Level 2 is not tolerable for a certain tumor type, Dose Level 2b will be investigated. There will be no dose escalation beyond Level 2 or Level 2b. Once the highest dose level for further investigation has been confirmed in the Dose-Escalating Safety Evaluation Phase, Arm N-I will continue enrolling with Stage 1 (Section 3.1.3).

Subjects on active treatment need to be followed up for at least 6 weeks after start of study treatment before determination of the tolerability of a dose level. However, tolerability beyond 6 weeks may also be taken into consideration. The criteria for tolerability (Table 3.1.2-2) are based on drug related adverse events leading to permanent discontinuation (listed in Section 4.5.5) and include:

- If none of the first 3 subjects in a given dose level permanently discontinue treatment due to study drug related adverse events within the first 6 weeks, then this dose cohort will be deemed as tolerable. For Dose Cohort Level 2 or Dose Cohort Level 2b, at least 6 subjects need to have been exposed to this dose level and followed up for at least 6 weeks after start of study treatment before the enrollment will proceed in Stage 1. The enrollment of these 6 subjects will occur in a staggered mode, first 3 subjects will be enrolled and followed up for at least 6 weeks before the next 3 subjects will be enrolled and followed up for at least 6 weeks.
- If one or two of the first 3 subjects in a dose cohort permanently discontinue treatment within the first 6 weeks due to study drug related adverse events, this cohort will be expanded to 6 subjects.
- If one of 6 subjects in a dose cohort permanently discontinue treatment due to study drug related adverse events within the first 6 weeks, then dose cohort will be deemed as tolerable.
- If two of 6 subjects in a dose cohort permanently discontinue treatment within the first 6 weeks due to study treatment related adverse events, this cohort may be expanded to 9 subjects. If an expansion is not possible because of the severity of the adverse events leading to permanent discontinuation, then this dose cohort will be deemed not tolerable.
- If no more than two of 9 subjects in a dose cohort permanently discontinue treatment due to study treatment related adverse events within the first 6 weeks, then this dose cohort will be deemed as tolerable.
- If at least three of the first 9 subjects in a dose cohort permanently discontinue treatment within the first 6 weeks due to study treatment related adverse events, a Dose -1 Cohort (in case of toxicities at Dose Level 1) or a Dose 2b Cohort (in case of toxicities at Dose Level 2) may proceed.

For the decision to enroll a Dose -1 or Dose 2b Cohort, the clinical severity of the adverse events leading to permanent discontinuation in the previous Dose Cohort will be taken into consideration.

**Table 3.1.2-2: Dose Cohort for Arm N-I**

| Number of subjects treated and followed up for at least 6 weeks after start of study treatment | Number of subjects with permanent discontinuation due to treatment related adverse events | Next Step |
|---|---|---|
| 3 | 0 | Dose tolerable |
| 3 | 1-2 | Expand to 6 subjects |
| 6 | ≤ 1 | Dose tolerable |
| 6 | 2 | Expand to 9 subjects |
| 9 | ≤ 2 | Dose tolerable |
| 9 | ≥ 3 | Dose not tolerable[a] |

[a] discussion with investigators to review risk/benefit taking into account reversibility of AEs and depth of response

#### *3.1.2.1 Evaluation of Risk/Benefit for Doses that do not meet Tolerable Criteria*

In the event of ≥ 3 of the first 9 subjects requiring permanent discontinuation, a discussion with investigators may be held to review the risk/benefit of this regimen. The rationale for this evaluation is that the most frequent severe drug related AEs for the combination in melanoma have been asymptomatic, reversible laboratory events (ie, LFTs and lipase) and there is preliminary evidence of deep and durable responses in the N-I arm in advanced melanoma (CA209004). Therefore, a discussion of the risk/benefit of the regimen will be triggered if the following criteria are met:

- A majority of subjects who discontinue due to treatment related AEs have deep tumor response (ie, > 80% reduction)
- All treatment related AEs leading to discontinuation are non-fatal, reversible and without severe sequela (ie, GI perforation)
- A majority of the treatment related AEs are laboratory in nature, asymptomatic, and monitorable via routine blood draws

If a decision is made to continue with a regimen because of a favorable risk/benefit profile (ie, non-fatal AEs in subjects with near CRs that are durable) and despite meeting the 'not tolerable' criteria above, then IRBs must be notified, ICFs must be updated, and discussion of the risk/benefit must be documented with all future subjects who enroll on this regimen.

### *3.1.3 Staged Enrollment (Stage 1 and Stage 2)*

#### *3.1.3.1 Stage 1*

This Stage is intended to assess the efficacy in 18 subjects per treatment arm per tumor type to determine whether enrollment should continue to Stage 2. For efficacy determination, each Arm within each tumor type will be assessed independently.

**Arm N**: The enrollment and treatment of 18 subjects to Arm N per tumor type can begin while the initial Dose Cohort for Arm N-I in this tumor type is still ongoing. The dose level in Arm N is 3 mg/kg nivolumab IV every two weeks (Q2W). This dose has been established in more than 700 subjects with various tumor types exposed to nivolumab monotherapy with a tolerable AE profile. Therefore no dose adjustments for Arm N are planned.

**Arm N-I:** Up to 18 subjects will be enrolled and treated in this arm per tumor type at the highest tolerated Dose Level determined during the Dose Escalating Safety Evaluation phase. The 3-9 subjects treated at the highest dose level confirmed for further investigation from the Dose Escalating Safety Evaluation phase will be counted as part of the 18 required subjects.

#### *3.1.3.2 Criteria to proceed from Stage 1 to Stage 2*

The decision to proceed from Stage 1 to Stage 2 will be made for each tumor and for each treatment arm independently and include (Table 3.1.3.2-1):

- 2 or more of 18 subjects in a given arm must have confirmed PR or CR before enrollment for that arm will be continued in Stage 2. The tolerability of the regimen will continue to be evaluated by the Sponsor with the investigators to ensure that it is acceptable for continued enrollment.
  - Subjects with initial PD per RECIST 1.1 who continue treatment in their initially assigned treatment arm beyond progression (Section 4.5.7) and subsequently reach confirmed immune related CR or PR (relative to initial tumor assessment) and including any new measurable lesions within the sum of all target lesions, will be considered as having an objective response for the purposes of meeting criteria for moving from Stage 1 to Stage 2. Although not standard RECIST 1.1, these immune related response criteria using unidimensional measurements account for the unusual immune related tumor response patterns reported for both ipilimumab and nivolumab.
- Once the last subject in a given treatment arm has permanently discontinued treatment for any reason or has reached the Week 48 Tumor Assessment, and the above criteria are not met, then this treatment arm will not proceed to Stage 2. Ongoing subjects will continue to be followed up for efficacy and safety.
- In case that 2 or more of subjects in a given arm enrolling in Stage 1 have confirmed PR or CR, but the enrollment of 18 subjects for Stage 1 has not been completed or 18 subjects have been enrolled but have not been randomized and started treatment at that timepoint, the following applies:
  - Arm N: the enrollment for that arm can be continued in Stage 2. The tolerability of the regimen will continue to be evaluated by the Sponsor with the investigators to ensure that it is acceptable for continued enrollment.
  - Arm N-I: at least 9 subjects need to have been exposed to the highest dose level which has been confirmed for Stage 1 and followed up for at least 6 weeks after start of study treatment before the enrollment for that arm can be continued in Stage 2. The tolerability of the regimen will continue to be evaluated by the Sponsor with the investigators to ensure that it is acceptable for continued enrollment.

**Table 3.1.3.2-1: Efficacy criteria to proceed from Stage 1 to Stage 2**

| Efficacy criteria | Next Step |
|---|---|
| 2 or more of 18* subjects in a given arm have confirmed PR or CR | Go into Stage 2 |
| 1 or no of 18* subjects in a given arm have confirmed PR or CR. | No Go into Stage 2 |

* see Section 3.1.3.2 last bullet point for further clarification

### *3.1.3.3 Stage 2*

**Arm N:** For treatment **Arm N** of the given tumor type that continues to Stage 2, additional subjects will be assigned to a total of 40 subjects, inclusive of those enrolled in Stage 1. For tumor types where nivolumab monotherapy proceeded to Stage 2, assessment of Dose Level 2b in Stage 2 (nivolumab 3 mg/kg + ipilimumab 1 mg/kg, n=40 subjects) will be initiated for that tumor type. A separate evaluation of Dose Level 2b may be necessary if the safety and tolerability of Dose Level 2 has not been confirmed.

**Arm N-I (Dose Level 2):** In case treatment Arm N-I at Dose Level 2 proceeds to Stage 2, additional subjects will be assigned to a total of 40 subjects at Dose Level 2, inclusive of those enrolled in Stage 1. In order to investigate the Dose Level 2b with a potentially better tolerability while preserving tumor efficacy, an additional 40 subjects at Dose Level 2b will be enrolled once Arm N-I Dose Level 2 proceeds to Stage 2. In this case, a separate safety evaluation of Dose Level 2b is not necessary, as the safety and tolerability of Dose Level 2 had already been confirmed previously.

Within a given tumor type, the treatment arms can proceed to Stage 2 independent of the status of the other treatment arm.

For Stage 2, upon completion of enrollment of the initial 40 subjects, additional subjects may be assigned into Arm N and Arm N-I up to a total of 100 subjects (including those assigned in Stage 1) in each treatment arm of the given tumor type. For tumor types where nivolumab monotherapy or nivolumab 1 mg/kg plus ipilimumab 3 mg/kg proceeded to Stage 2, assessment of Dose Level 2b in Stage 2 (nivolumab 3 mg/kg + ipilimumab 1 mg/kg, n=up to 70 subjects) may be initiated for that tumor type.

### *3.1.3.4 Modified Design Bladder Cancer Cohort*

Bladder arms N and N-I (Dose Levels 2 and 2b) will be conducted as a One Stage Design with the treatment of 26-105 subjects in each arm. The Safety Evaluation Phase for the N-I arm will start at Dose Level 2 (nivolumab 1 mg/kg, ipilimumab 3 mg/kg) and will evaluate safety and tolerability after the first 6 randomized subjects. Following the N-I safety evaluation phase, Dose Levels 2 will treat approximately 92 subjects and 2b will treat up to a total of 105 subjects. Based on the safety evaluations thus far on study, no dose escalation phase is necessary for bladder cohort N I Dose Level 2b (nivolumab 3 mg/kg, ipilimumab 1 mg/kg).

#### 3.1.3.5 Arm N-I (Dose Level 2b)

Based on the safety evaluations thus far on study, no dose escalation phase is necessary for bladder cohort N-I Dose Level 2b (nivolumab 3 mg/kg, ipilimumab 1 mg/kg).

### 3.1.4 SCLC Expansion

SCLC cohorts Arm N and Arm N-I met the pre-specified safety and efficacy criteria and proceeded to Stage 2. Based on an interim data review, disease control rates (SD + PR + CR) of 36% and 57% for Arms N and N-I, respectively, were estimated. In order to further investigate nivolumab and nivolumab combined with ipilimumab activity in specific SCLC subpopulations, the SCLC expansion cohorts will enroll additional subjects based on response to prior treatment and the number of previous therapies. Up to 250 second or third line subjects will be randomized in a 3:2 ratio to one of 2 expansion groups: Arm A (150 subjects treated with nivolumab 3 mg/kg every 2 weeks (Q2W)) or Arm B (100 subjects treated with nivolumab 1 mg/kg + ipilimumab 3 mg/kg every 3 weeks (Q3W) for 4 cycles followed by nivolumab 3 mg/kg (Q2W) and will be stratified for number of prior treatment lines (1 vs 2 prior chemotherapy regimens).

The study population for the SCLC expansion cohort is specified as follows:

- Histopathologically or cytologically confirmed diagnosis of SCLC.
- All subjects had platinum-based first-line treatment. Subjects with previous second-line chemotherapy treatment are eligible as well.
- Subjects with platinum refractory, resistant, or sensitive disease are eligible.
- Subjects with initial diagnosis of limited or extensive disease are eligible.
- Documented objective radiographic disease progression at study entry.

Tumor assessments for subjects in the SCLC expansion cohort will undergo a BICR assessment. The crossover option refers only to the original cohorts and not the new cohorts enrolled under or after Amendment 09.

### 3.1.5 Duration of Study Treatment

The study treatment will be continued until disease progression (investigator-assessed RECIST 1.1-defined progression) or occurrence of unacceptable toxicity as defined in Section 4.5.5. For subjects achieving confirmed CR or a PR for more than 3 months (long lasting PR) the investigator may decide to hold treatment for this subject after discussion with the medical monitor of the sponsor. During the treatment hold subjects should follow all study procedures as specified in Section 5.1. Subjects for which treatment was held following long lasting responses and who experience a recurrence of disease progression may reinitiate their last study treatment. Before reinitiating treatment, the investigator should discuss the individual case with the medical monitor and document in the study records.

### 3.1.6 Crossover for Subjects in Arm N

Subjects in Arm N may crossover to Arm N-I if all of the following criteria are met:

- The Safety Evaluation Phase for the N-I regimen has been completed and at least 6 subjects have been exposed to the dose level used for Stage 1 of the N-I regimen. In case Dose Level 2b has been activated and completed the safety assessment, subjects for cross over will be assigned to Dose Level 2 or Dose Level 2b after discussion between the sponsor and investigator taking into consideration previous safety and efficacy signals at these dose levels and the status of the individual subject planned for cross over.
- Subject has further disease progression (investigator-assessed RECIST 1.1-defined progression according to description provided in Section 4.5.7, confirmed at least 4 weeks after the initial tumor assessment showing progression (definition of confirmed progression see Appendix 3)) in the absence of clinical deterioration. For subjects with clear evidence of new or progressing brain metastases a confirmation is not required. These subjects may proceed with brain radiation therapy and, if necessary, with gamma-knife or surgical resection, after having completed the therapy a cross over to Arm N-I can be considered (see Section 3.4.2.1).
- Subjects with rapidly progressing tumors under nivolumab monotherapy may undergo radiation treatment first before initiation of the cross over after discussion between the sponsor and investigator.
- Subject has not experienced nivolumab related adverse events leading to permanent discontinuation as described in Section 4.5.5.
- Subject is not continuing to derive any clinical benefit from nivolumab single agent therapy as assessed by the investigator which would allow continuation of nivolumab monotherapy (see Section 4.5.8).
- Subject is not a SCLC patient enrolled based on the Amendment 09 expansion.
- The individual case must be discussed with the medical monitor prior to cross over.

Subjects crossing over to Arm N-I will start treatment at Day 1 Week 1 as described for subjects originally randomized to Arm N-I. Subjects who crossed over and subsequently have an objective response in Arm N-I will not be considered in the decision making for Arm N-I proceeding to Stage 2. Subjects in Arm N-I cannot crossover to Arm N.

### 3.1.7 Re-exposure with Nivolumab/Ipilimumab for Subjects in Arm N-I

Subjects in Arm N-I may undergo a re-exposure with nivolumab/ipilimumab if they achieved an initial objective response (PR or CR) or stable disease of ≥ 3 months and had a subsequent documented progression. Subjects must fulfill the following criteria:

- Subjects have not experienced any related adverse events as described in Section 4.5.5 (discontinuation criteria).
- Eligible subjects will receive up to four doses of nivolumab/ipilimumab (based on treatment assigned at randomization) during Re-exposure. Subjects can receive nivolumab monotherapy, if ipilimumab caused toxicities leading to its discontinuation (section 4.5.5)

- Dosing may be delayed for toxicity (see Section 4.5.2).
- Subjects who have permanently discontinued study therapy for any reason and are in the follow up phase may not receive any re-exposure dosing.

### 3.1.8 Review of Safety

The subjects' safety will be monitored on an ongoing basis as described fully in Section 7. Safety conference calls with investigators and representatives of the sponsor will be held approximately every other week with additional meetings as necessary. Decisions for the safety evaluation phase of Arm N-I and for continuing from Stage 1 to Stage 2 in both treatment arms will be made in conjunction with the investigators. In addition, a BMS medical safety team (MST) routinely reviews safety signals across the entire nivolumab program including combination studies with ipilimumab.

### 3.1.9 Treatment Beyond Progression

Treatment beyond investigator-assessed RECIST 1.1-defined progression will be permitted if the subject experiences investigator-assessed clinical benefit and the subject is tolerating the study treatment (Section 4.5.7). No treatment beyond progression with cobimetinib is permitted.

### 3.1.10 Intrapatient Dose Reductions for Nivolumab, Ipilimumab and/or Cobimetinib

Intrapatient dose reduction for nivolumab and/or ipilimumab is not permitted for any reason. Dose delays for the management of study treatment related adverse events are described in Section 4.5.2.

Intrapatient dose reductions for cobimetinib should be undertaken as presented in Table 3.1.10-1 and based on the prescribing information.[57]

**Table 3.1.10-1: Recommended Dose Reductions for COTELLIC (Cobimetinib)**

| | |
|---|---|
| First Dose Reduction | 40 mg orally once daily |
| Second Dose Reduction | 20 mg orally once daily |
| Subsequent Modifications | Permanently discontinue cobimetinib if unable to tolerate 20 mg once daily |

### 3.1.11 Mandatory Availability of Tumor Material

Tumor tissue from fresh tumor biopsies must be submitted prior to treatment for retrospective biomarker analyses. Tumor biopsies may be done during the screening period prior to study treatment start. Tumor material from biopsies done before the screening period is acceptable if the biopsy was performed within 3 months prior to the planned treatment start and no other systemic cancer therapy was administered in the meanwhile. Baseline tumor biopsies should preferably be performed from a tumor site that is NOT the only site of measurable disease. For subjects with only one site of measurable disease, tumor biopsies from this one tumor site are allowed if at least one of the following criteria is met:

- CT imaging performed after biopsy and there is still measurable disease or
- The type of biopsy is not expected to impact the measurability (eg, core needle biopsy) regardless on when imaging occurred, prior to or after biopsy.

### 3.1.12 Study Phases

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

Screening Phase:

- Begins by establishing the subject's initial eligibility and signing of the informed consent form (ICF).
- Subject is enrolled using the Interactive Voice Response System (IVRS).

Treatment Phase:

- Begins with the vial assignment call to the IVRS.
- A negative pregnancy test must be documented within 24 hours prior to the start of investigational product.
- Within 3 days from treatment assignment, the subject must receive the first dose of study medication:
  - **Arm N (nivolumab monotherapy):**
    Nivolumab 3 mg/kg IV every two weeks (Q2W). See Table 4.5-1
  - **Arm N-I (nivolumab + ipilimumab)**
    - Dose Escalation Phase:

*Staged Enrollment Phase*: Dose Level determined in Dose Escalation Phase. See Table 4.5-2 and Table 4.5-3.

- **Dose Level 1**, Nivolumab 1 mg/kg IV combined with ipilimumab 1 mg/kg IV Q3W for 4 doses, then nivolumab 3 mg/kg IV Q2W. See Table 4.5-2 and Table 4.5-3.
- **Dose Level 2:** Nivolumab 1 mg/kg IV combined with ipilimumab 3 mg/kg IV Q3W for 4 doses, then nivolumab 3 mg/kg IV Q2W.

- **Dose Level 2b:** Nivolumab 3 mg/kg IV combined with ipilimumab 1 mg/kg IV Q3W for 4 doses, then nivolumab 3 mg/kg IV Q2W.
- **Dose Level 2c:** Nivolumab 3 mg/kg IV Q2W combined with ipilimumab 1 mg/kg Q6W.
- **Dose Level 2d**: Nivolumab 3 mg/kg IV Q2W combined with ipilimumab 1 mg/kg Q6W + cobimetinib 60 mg per os qd 21 days on/7 days off for the additional pancreatic cancer cohort only.

- Adverse event assessments will be documented at each visit throughout the study.

On-study laboratory assessments (after D1W1) should be drawn within 72 hours prior to dosing according to the schedule in Table 5.1-2, Table 5.1-3, Table 5.1-4, and Table 5.1-5.

- Women of child bearing potential (WOCBP) must have a negative pregnancy test documented as follows:
  - Arm N and Arm N-I2c: before every other nivolumab administration, within 24 hours prior to dosing.
  - Arm N-I: before every combined nivolumab / ipilimumab administration, within 24 hours prior to dosing. Thereafter every 4 weeks, within 24 hours prior to nivolumab dosing.
- PK samples and immunogenicity samples will be collected according to the schedule in Section 5.5.
- Study drug dosing may be delayed for toxicity. See Section 4.5.2.
- Treated subjects will be evaluated for response according to the RECIST 1.1 guidelines beginning 6 weeks (± 1 week) after first dose and continuing every 6 weeks (± 1 week) for the first 24 weeks, and then every 12 weeks (± 1 week) while on treatment or on treatment hold for any reason until disease progression (investigator-assessed RECIST 1.1-defined progression) or treatment discontinuation, except for subjects treated beyond progression or who discontinued treatment for other reasons than PD.

This phase ends when the subject is discontinued from study therapy. For a complete list of reasons for treatment discontinuation, see Section 4.5.5.

Follow-Up Phase

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

Two follow-up visits include collection of PK/immunogenicity samples Table 5.1-7, Table 5.5.1-1, and Table 5.5.1-2.

- Subjects who discontinue treatment for reasons other than tumor progression will continue to have tumor assessments beginning 6 weeks (± 1week) after first dose and continuing every 6 weeks (± 1 week) for the first 24 weeks from first dose, and every 12 weeks (± 1 week) thereafter until disease progression (investigator-assessed RECIST 1.1-defined progression).

This does also apply to subjects whose treatment was put on hold after achieving confirmed CR or PR for more than 3 month (long lasting PR).

- Subjects will be followed for drug-related toxicities until these toxicities resolve, return to baseline or are deemed irreversible. All adverse events will be documented for a minimum of 100 days after last dose.
- Follow up visits should be made in-person. If a subject is unable to make an in-person visit, the reason should be clearly documented at the site.
- Follow-up visit 1 (FU1) = 35 days from the last dose ± 7 days or coincide with the date of discontinuation (± 7 days) if date of discontinuation is greater than 42 days after last dose, Follow-up visit 2 (FU2) = 80 days (± 7 days) from follow-up visit 1.
- After completion of the first two follow-up visits, subjects will be followed every 3 months for survival via in-person visits, phone or email. Ad hoc survival data requests may be made during the study as well, particularly during database locks.

### *3.1.13 Total Study Duration*

It is projected that the accrual for the Initial Dose Cohort and the Efficacy Signal Detection - Stage 1 of the study will be completed within 4 months after FPFV and that the results of the interim analysis will be available 9 months after FPFV. The final analysis is expected at 60 months after FPFV. The total study duration is not expected to be affected by the implementation of the additional pancreatic cancer cohort.

## 3.2 Post Study Access to Therapy

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

## 3.3 Study Population

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

### *3.3.1 Inclusion Criteria*

**1. Signed Written Informed Consent**

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

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

## 2. Target Population

a) Subjects with pathologically confirmed locally advanced or metastatic disease of the following tumor types:

i) Women with histologically or cytologically confirmed breast carcinoma who must meet all of the following:

(1) Tumor must be "triple receptor negative" defined as ER/PR negative per local lab and HER-2 negative defined as HER-2 0 or 1+ by IHC, or IHC 2+ and ISH not amplified, or ISH-non amplified.

AND

(2) Subjects must have progression or refractory disease. Subjects must have had at least 1 chemotherapy regimen for the treatment of metastatic (Stage IV) or locally advanced disease.

OR

(3) Subject actively refuses chemotherapy for the treatment of metastatic (Stage IV) or locally advanced disease considered as standard treatment for this disease stage, despite being informed by the investigator about the treatment options. Subjects actively refusing chemotherapy must have had progression or refractory disease prior to starting study treatment. The subject's refusal must be thoroughly documented. The investigator will discuss each individual subject refusing chemotherapy with the sponsor's medical monitor to confirm eligibility.

ii) Subjects with histologically confirmed Gastric or Gastro-Esophageal Junction Carcinoma (including adenocarcinoma arising from the lower esophagus) who must meet all of the following:

(1) Subjects must have progression or refractory disease. Subjects must have had at least 1 chemotherapy regimen for the treatment of metastatic (Stage IV) or locally advanced disease. Subjects with HER-2 positive tumors must have had previous treatment with trastuzumab.

OR

(2) Subject actively refuses chemotherapy or biological therapy for the treatment of metastatic (Stage IV) or locally advanced disease considered as standard treatment for this disease stage, despite being informed by the investigator about the treatment options. Subjects actively refusing chemotherapy must have had progression or refractory disease prior to starting study treatment. The subject's refusal must be thoroughly documented. The investigator will discuss each individual subject refusing chemotherapy with the sponsor's medical monitor to confirm eligibility.

iii) Subjects with histologically confirmed Pancreatic adenocarcinoma who must meet all of the following (Not applicable per Amendment 13):

(1) Subjects must not have clinically relevant ascites at baseline, such as ascites in need of paracentesis.

AND

(2) Subjects must have had best response of stable disease, or progression or refractory disease during or after at least 1 chemotherapy regimen for the treatment of metastatic (Stage IV) or locally advanced disease

OR

(3) Subject actively refuses chemotherapy for the treatment of metastatic (Stage IV) or locally advanced disease considered as standard treatment for this disease stage, despite being informed by the investigator about the treatment options. Subjects actively refusing chemotherapy must have had best response of stable disease, or progression or refractory disease prior to starting study treatment. The subject's refusal must be thoroughly documented. The investigator will discuss each individual subject refusing chemotherapy with the sponsor's medical monitor to confirm eligibility.

iv) Subjects with histologically or cytologically confirmed small cell lung cancer. Subjects must have progression or refractory disease. Subjects must have had at least 1 platinum based chemotherapy regimen for the treatment of limited or extensive stage disease, but not more than 2 prior chemotherapy regimens. For subjects to be enrolled in the SCLC expansion cohorts to following eligibility criteria apply:

(1) All subjects must have had platinum-based first-line treatment. Subjects with previous second-line chemotherapy treatment are eligible as well.

(2) Subjects with platinum refractory, resistant, or sensitive disease are eligible (Appendix 4).

(3) Subjects with initial diagnosis of limited or extensive disease are eligible.

(4) Documented objective radiographic disease progression at study entry.

v) Subjects with histologically or cytologically confirmed urothelial carcinoma (including mixed histologies of urothelial carcinoma with elements of other subtypes) of the renal pelvis, ureter, bladder, or urethra, who must meet all of the following:

(1) Subjects must have progression or refractory disease. Subjects must have had at least 1 platinum based chemotherapy regimen for the treatment of metastatic (Stage IV) or locally advanced unresectable disease.

OR

(2) Subjects with disease recurrence within 1 year of completing a platinum based neoadjuvant or adjuvant therapy.

OR

(3) Subject actively refuses chemotherapy for the treatment of metastatic (Stage IV) or locally advanced unresectable disease considered as standard treatment for this disease stage, despite being informed by the investigator about the treatment options. Subjects actively refusing chemotherapy must have had progression or refractory disease prior to starting study treatment. The subject's refusal must be thoroughly documented. The investigator will discuss each individual subject

refusing chemotherapy with the sponsor's medical monitor to confirm eligibility. NA for subject enrolling per protocol amendment 16.

AND

(4) Metastatic or surgically unresectable (cT4b, or any N+ [N1-3], or any M-1) disease.

vi) Subjects with histologically confirmed ovarian carcinoma (including epithelial ovarian cancer (OC), primary peritoneal, or fallopian tube carcinoma) who must meet all of the following:

(1) Subjects must have received one platinum-based chemotherapeutic regimen for management of primary disease, possibly including intraperitoneal therapy, consolidation, biologic/targeted (non-cytotoxic) agents (eg, bevacizumab) or extended therapy administered after surgical or non-surgical assessment. Subjects are allowed to have received, but are not required to have received subsequent cytotoxic regimens for management of recurrent or persistent disease. For the purposes of this study, PARP inhibitors given for recurrent or progressive disease will be considered cytotoxic. A line of therapy is defined as a regimen used to treat initial disease (frontline) or following disease progression (second and subsequent lines). A change in regimen for reasons of toxicity or consolidation/maintenance in the absence of disease progression does not constitute a new line of therapy.

(2) Subjects must have documented disease progression after completion of their most recent regimen.

(3) Subjects with platinum refractory, resistant, or sensitive disease are eligible (Appendix 5).

vii) Additional pancreatic cancer cohort: Subjects with histologically confirmed pancreatic adenocarcinoma who must meet all of the following:

(1) Subjects must not have clinically relevant ascites at baseline, such as ascites in need of paracentesis.

AND

(2) Treatment with at least one, but not more than 2 previous lines of chemotherapy in the metastatic/advanced setting.

(3) Documented objective radiographic disease progression at study entry.

(4) Royal Marsden score 0 or 1 (Appendix 6) [94]

OR

(5) Subject actively refuses chemotherapy for the treatment of metastatic (Stage IV) or locally advanced disease considered as standard treatment for this disease stage, despite being informed by the investigator about the treatment options. Subjects actively refusing chemotherapy must have had best response of stable disease, or progression or refractory disease prior to starting study treatment. The

subject's refusal must be thoroughly documented. The investigator will discuss each individual subject refusing chemotherapy with the sponsor's medical monitor to confirm eligibility.

**A line of therapy is defined as a regimen used to treat initial disease (frontline) or following disease progression (second and subsequent lines). A change in regimen for reasons of toxicity or consolidation/maintenance in the absence of disease progression does not constitute a new line of therapy.**

b) Subjects must have measurable disease by CT or MRI per RECIST 1.1 criteria (see Appendix 3). (Radiographic tumor assessment must be performed within 28 days prior to first dose).

c) Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1 (refer to Appendix 1).

d) Subjects must consent to allow for a baseline tumor biopsy. Baseline tumor biopsies should preferably be performed from a tumor site that is NOT the only site of measurable disease. For subjects with only one site of measurable disease, tumor biopsies are allowed if at least one of the following criteria is met:

- CT imaging performed after biopsy and there is still measurable disease or
- The type of biopsy is not expected to impact the measurability (eg, core needle biopsy) regardless on when imaging occurred, prior to or after biopsy.

Tumor material from biopsies done before the screening period is acceptable if the biopsy was performed within 3 months prior to the planned treatment start and no other systemic cancer therapy was administered in the meanwhile.

e) All baseline laboratory requirements will be assessed and should be obtained within 14 days of first dose. Screening laboratory values must meet the following criteria:

i) WBCs ≥ 2000/μL

ii) Neutrophils ≥ 1500/μL

iii) Platelets ≥ 100 x $10^3$/μL

iv) Hemoglobin ≥ 9.0 g/dL

v) Serum creatinine ≤ 1.5 x ULN or calculated creatinine clearance (CrCl) ≥ 40 mL/minute (using Cockcroft/Gault formula)

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

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

vi) AST ≤ 3 x ULN

vii) ALT ≤ 3 x ULN

viii) Total Bilirubin ≤ 1.5 x ULN (except subjects with Gilbert Syndrome who can have total bilirubin < 3.0 mg/dL)

ix) Albumin ≥ 3 g/dL

x) Lipase ≤ 1.5 ULN. Subjects with Lipase > 1.5 ULN may enroll if there are neither clinical nor radiographic signs of a pancreatitis.

xi) Amylase ≤ 1.5 ULN. Subjects with Amylase > 1.5 ULN may enroll if there are neither clinical nor radiographic signs of a pancreatitis.

f) Prior focal radiotherapy to an isolated bony or soft tissue metastasis must be completed at least 2 weeks before study drug administration.

g) Subject Re-enrollment: This study permits the re-enrollment of a subject that has discontinued the study as a pre-treatment failure (ie, subject has not been assigned / has not been treated). If re-enrolled, the subject must be re-consented and assigned a new subject number from IVRS.

**3. Age and Reproductive Status**

a) Men and women ≥ 18 years of age

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

c) Women must not be breastfeeding

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

e) Men who are sexually active with WOCBP must agree to follow instructions for method(s) of contraception for the duration of treatment with study drug (s) plus approximately 5 half-lives of study drug (s) plus 90 days (duration of sperm turnover) for a total of 7 months post-treatment completion.

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

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

At a minimum, subjects must agree to use one highly effective method of contraception. See Appendix 7 for details on highly effective methods of contraception.

### *3.3.2 Exclusion Criteria*

**1. Target Disease Exceptions**

a) Active brain metastases or leptomeningeal metastases. Subjects with brain metastases are eligible if these have been treated and there is no magnetic resonance imaging (MRI) evidence of progression for at least 4 weeks after treatment is complete and within 28-days prior to first dose of study drug administration. There must also be no requirement for immunosuppressive doses of systemic corticosteroids (> 10 mg/day prednisone equivalents) for at least 2 weeks prior to study drug administration. Subjects with incidental findings of asymptomatic brain metastases at screening may start study treatment without prior radiation treatment after discussion between the sponsor and investigator.

**2. Medical History and Concurrent Diseases**

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

b) Other prior malignancy active within the previous 3 years except for local or organ confined early stage cancer that has been definitively treated with curative intent, does not require ongoing treatment, has no evidence of residual active disease, and has a negligible risk of recurrence and is therefore unlikely to interfere with the primary and secondary endpoints of the study, including response rate and safety.

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

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

e) Prior therapy with experimental anti-tumor vaccines; any T cell co-stimulation or checkpoint pathways, such as anti-PD-1, anti-PD-L1, anti-PD-L2, anti-CD137, or anti-CTLA-4 antibody, including ipilimumab; or other medicines specifically targeting T cell is also prohibited.

f) All toxicities attributed to prior anti-cancer therapy other than alopecia and fatigue must have resolved to grade 1 (NCI CTCAE version 4) or baseline before administration of study drug. Subjects with toxicities attributed to prior anti-cancer therapy which are not expected to resolve and result in long lasting sequelae, such as neuropathy after platinum-based therapy, are permitted to enroll.

g) Treatment with any chemotherapy, radiation therapy, biologics for cancer, or investigational therapy within 28 days of first administration of study treatment (subjects with prior cytotoxic or investigational products < 4 weeks prior to treatment might be eligible after discussion between investigator and sponsor, if toxicities from the prior treatment have been resolved to CTC grade 1 level).

h) Subjects which have been previously enrolled and randomized in Studies BMS CA209331 or BMS CA209451 are not eligible.

i) Inability to take oral medication or significant nausea and vomiting, malabsorption, external biliary shunt, significant bowel resection that would preclude adequate absorption of oral medication for subjects in the additional pancreatic cancer cohort only.

**3. Physical and Laboratory Test Findings**

a) Positive test for hepatitis B virus (HBV) using HBV surface antigen (HBV sAg) test or positive test for hepatitis C virus (HCV) using HCV ribonucleic acid (RNA) or HCV antibody test indicating acute or chronic infection.

b) Known history of testing positive for human immunodeficiency virus (HIV) or known acquired immunodeficiency syndrome (AIDS). NOTE: Testing for HIV must be performed at sites where mandated locally.

c) Subjects must not be dependent on continuous supplemental oxygen use.

d) For subjects assigned to the additional pancreatic cancer cohort: baseline echocardiogram showing left ventricular ejection fraction (LVEF) below the institutional lower limit of normal (LLN) or < 50%, whichever is lower, and electrocardiogram with corrected QT ≥ 450 ms should be excluded.

**4. Allergies and Adverse Drug Reaction**

a) History of allergy to study drug components.

b) History of severe hypersensitivity reaction to any monoclonal antibody.

**5. Sex and Reproductive Status**

a) WOCBP who are pregnant or breastfeeding.

b) Women with a positive pregnancy test at enrollment or prior to administration of study medication.

**6. Other Exclusion Criteria**

a) Prisoners or subjects who are involuntarily incarcerated

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

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

### *3.3.3 Women of Childbearing Potential*

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

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

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

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

[redacted]

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

### 3.4.2 Other Restrictions and Precautions

It is the local imaging facility's responsibility to determine, based on subject attributes (eg, allergy history, diabetic history and renal status), the appropriate imaging modality and contrast regimen for each subject. Imaging contraindications and contrast risks should be considered in this assessment. Subjects with renal insufficiency should be assessed as to whether or not they should receive contrast and if so, what type and dose of contrast is appropriate. Specific to MRI, subjects with severe renal insufficiency (ie, estimated glomerular filtration rate (eGFR) $< 30$ mL/min/1.73m$^2$) are at increased risk of nephrogenic systemic fibrosis. MRI contrast should not be given to this subject population. In addition, subjects are excluded from MRI if they have tattoos, metallic implants, pacemakers, etc.

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

#### 3.4.2.1 Palliative Radiation Therapy

Palliative (limited-field) radiation therapy is permitted for pain control to sites of bone disease or other non-target lesions present at baseline or new lesions. For subjects with new or progressing brain metastases or other lesions, except SCLC subjects from the expansion cohorts under or after Amendment 09, radiation therapy is permitted before a crossover to Arm N-I can be considered.

1) Bone and other metastases
   a) For bone or other disease sites present at baseline or new, the lesion being considered for palliative radiation is not a target lesion.
   b) The case is discussed with the BMS medical monitor, and the medical monitor agrees that the conditions required to receive palliative radiation are met.
2) Brain metastases or other lesions
   a) Subject is enrolled in the nivolumab monotherapy arm.
   b) The case is discussed with the BMS medical monitor, and the medical monitor agrees that the conditions required to receive palliative radiation are met.
   c) After completion of the brain or other lesions radiation therapy, the BMS Medical Monitor must be consulted before a crossover to Arm N-I can be permitted. Treatment in the crossover arm can only be started after there is no MRI evidence of progression for at least 2 weeks after brain radiation treatment is complete.

#### 3.4.2.2 Surgical Resection or Stereotactic Radiotherapy Following Initial Response or Long-Term Stable Disease

Investigators may choose to resect solitary lesions in subjects with residual or new disease following initial response or stable disease of $\geq 3$ months (long-term stable disease) and render the subject free of macroscopic disease. Subjects enrolled in this study may have lesions treated surgically or by stereotactic radiotherapy only following consultation with the Medical Monitor

[redacted]

## 3.5 Discontinuation of Subjects from Treatment

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

- Subject's request to stop study treatment
- Any clinical adverse event (AE), laboratory abnormality or intercurrent illness which, in the opinion of the investigator, indicates that continued participation in the study is not in the best interest of the subject

- Termination of the study by Bristol-Myers Squibb (BMS)
- Loss of ability to freely provide consent through imprisonment or involuntarily incarceration for treatment of either a psychiatric or physical (eg, infectious disease) illness
- Additional protocol specified reasons for discontinuation (see Section 4.5.5).

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

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

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

For subjects achieving confirmed CR or a PR for more than 3 month (long lasting PR) the investigator may decide to hold treatment for this subject after discussion with the medical monitor of the sponsor. Subjects for which treatment was held following long lasting responses and who experience a recurrence of disease progression may reinitiate their last study treatment. Before reinitiating treatment, the investigator should discuss the individual case with the medical monitor and document in the study records.

## 3.6 Post Treatment Study Follow up

In this study, objective response rate is a key endpoint of the study. Tumor responses initiated by immunotherapy with nivolumab, nivolumab combined with ipilimumab, or nivolumab combined with ipilimumab and cobimetinib may evolve after treatment discontinuation. Therefore, post treatment study follow-up is of critical importance and is essential to preserving subject safety and the integrity of the study. Subjects who discontinue study treatment must continue to be followed for collection of outcome and/or survival follow-up data as required and in line with Section 5 until death or the conclusion of the study.

### *3.6.1 Withdrawal of Consent*

Subjects who request to discontinue study treatment will remain in the study and must continue to be followed for protocol specified follow-up procedures. The only exception to this is when a subject specifically withdraws consent for any further contact with him/her or persons previously authorized by subject to provide this information. Subjects should notify the investigator of the decision to withdraw consent from future follow-up **in writing**, whenever possible. The withdrawal of consent should be explained in detail in the medical records by the investigator, as

to whether the withdrawal is from further treatment with study drug only or also from study procedures and/or post treatment study follow-up, and entered on the appropriate CRF page. In the event that vital status (whether the subject is alive or dead) is being measured, publicly available information should be used to determine vital status only as appropriately directed in accordance with local law.

### *3.6.2 Lost to Follow-Up*

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

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

## 4 STUDY DRUG

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

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

## 4.1 Investigational Product

**Table 4.1-1: Product Description: Treatment Period**

| Product Description and Dosage Form | Potency | Primary Packaging (Volume)/ Label Type | Secondary Packaging (Qty) /Label Type | Appearance | Storage Conditions (per label) |
|---|---|---|---|---|---|
| BMS-936558-01 Solution for Injection[a] | 100 mg (10 mg/mL) | 10 mL per vial/ Open-label | 10 vials per carton/ Open-label | Clear to opalescent colorless to pale yellow liquid. May contain particles | 2 to 8°C. Protect from light and freezing |
| Ipilimumab Solution for Injection | 200 mg (5 mg/mL) | 40 mL per vial/Open-label | 4 vials per carton/Open-label | Clear, colorless to pale yellow liquid. May contain particles | 2 to 8°C. Protect from light and freezing |
| Cobimetinib tablet | 20 mg | 63 tablets per bottle | n/a | White, round, film-coated, debossed on one side with "COB" | 15-30°C |

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

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

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.

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

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

## 4.2 Non-investigational Product

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

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

## 4.3 Storage and Dispensing

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

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

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

Please refer to the current version of the Investigator Brochure, pharmacy reference sheets or pharmacy manual for complete storage, handling, dispensing, and infusion information for BMS-936558 (nivolumab) and ipilimumab. Please refer to the current version of the Prescribing Information for Cotellic (cobimetinib) for complete storage, handling, dispensing, and administration information.[57]

### *4.3.1 BMS-936558 (Nivolumab)*

BMS-936558 (nivolumab) vials must be stored at a temperature of 2°C to 8°C and should be protected from light, freezing and shaking. If stored in a glass front refrigerator, vials should be stored in the carton. Recommended safety measures for preparation and handling of nivolumab include laboratory coats and gloves.

For details on prepared drug storage and use time of nivolumab under room temperature/light and refrigeration, please refer to the BMS-936558 (nivolumab) Investigator Brochure sections 3.2.2 and 3.2.3 and/or pharmacy reference sheets.

Nivolumab injection is to be administered as a 60-minute IV infusion in Arm N, Arms N-I, dose levels 1, 2, 2b, and 2c. Nivolumab injection is to be administered as a 30-minute IV infusion in Arm N-I, dose level 2d. During drug product preparation and handling, vigorous mixing or shaking is to be avoided. Care must be taken to assure sterility of the prepared solution as the product does not contain any antimicrobial preservative or bacteriostatic agent. Please refer to the nivolumab IB and/or pharmacy reference sheets for further details regarding preparation/administration.

### *4.3.2 Ipilimumab*

Ipilimumab injection can be used for IV administration without dilution after transferring to a PVC (polyvinyl chloride), non-PVC/non-DEHP (di-(2-ethylhexyl)phthalate) or glass containers and is stable for 24 hours at 2-8ºC or room temperature/room light (RT/RL). For additional ipilimumab storage instructions, please refer to the ipilimumab IB and/or pharmacy reference sheets.

Recommended safety measures for preparation and handling include protective clothing, gloves, and safety cabinets.

Ipilimumab is to be administered as a 90-minute IV infusion in Arm N, Arms N-I, dose levels 1, 2, 2b, and 2c. Ipilimumab is to be administered as a 30-minute IV infusion in Arm N-I, dose level 2d. Care must be taken to assure sterility of the prepared solutions, since the drug product does not contain any antimicrobial preservatives or bacteriostatic agents. Please refer to the ipilimumab IB and/or pharmacy reference sheets for further details regarding preparation/administration.

### *4.3.3 Nivolumab and Ipilimumab Combination*

When both BMS-936558 (nivolumab) and ipilimumab are to be administered on the same day, separate infusion bags and filters must be used for each infusion. Nivolumab is to be administered first. The nivolumab infusion must be promptly followed by a saline flush to clear the line of nivolumab before starting the ipilimumab infusion.

### *4.3.4 COTELLIC (Cobimetinib)*

The recommended dose of cobimetinib is 60 mg (three 20 mg tablets) orally taken once daily for the first 21 days of each 28-day cycle until disease progression or unacceptable toxicity. No treatment beyond progression with this compound is permitted.

## 4.4 Method of Assigning Subject Identification

The subject number will be assigned through an interactive voice response system (IVRS) once the subject has signed the informed consent form and is registered. Every subject that signs the informed consent form must be assigned a subject number in IVRS. Specific instructions for using IVRS will be provided to the investigational site in a separate document.

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

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

Once enrolled in IVRS, enrolled subjects that have met all eligibility criteria will be ready for treatment assignment and drug vial assignment through the IVRS. The following information is required for drug vial assignment and randomization:

- Subject number
- Date of birth
- Tumor Type
- Date tumor tissue sample was shipped to central lab

Subjects meeting all eligibility criteria will be assigned to Arm N (nivolumab), Arm N-I (nivolumab + ipilimumab), Arm N-I Dose level 2b (nivolumab 3 mg/kg + ipilimumab 1 mg/kg), Arm N-I Dose level 2c (nivolumab 3 mg/kg every 2 weeks + ipilimumab 1 mg/kg every 6 weeks), or Arm N-I Dose level 2d (nivolumab 3 mg every 2 weeks + ipilimumab 1 mg/kg every 6 weeks) combined with cobimetinib 60 mg orally qd 21 days on/7 days off, according to their tumor type and treatment arm availability:

- Within a given tumor type, subjects will be assigned to a treatment arm (N or N-I Dose Level 2 or N-I Dose Level 2b) in a 1:1:1 ratio guided by randomization schedule if all arms are open.
- The computer-generated randomization schemas will be prepared by a Randomization Coordinator within the Drug Supply Management Department of BMS Research and Development.
- If only one or two treatment arms are open for enrollment (ie., when enrollment in Arm N-I is paused for an interim safety assessment, or when either arm is paused for decision making to proceed from Stage 1 to Stage 2 in the Efficacy Signal Detection part), then all newly to be assigned subjects will go into the remaining open arm(s).
- Once the subject has a treatment assignment, study treatment should be initiated within 3 working days.
- Specific instructions (including an enrollment worksheet) for central enrollment and treatment assignment procedure will be provided to the site.

Subjects to be enrolled in the SCLC expansion cohort will be randomized in a 3:2 ratio to one of 2 expansion groups: Arm A (150 subjects, nivolumab 3 mg/kg every 2 weeks (Q2W) or Arm B (100 subjects, nivolumab 1 mg/kg + ipilimumab 3 mg/kg every 3 weeks (Q3W) for 4 cycles

followed by nivolumab 3 mg/kg Q2W) and will be stratified for number of prior treatment lines (1 vs 2 prior chemotherapy regimens).

Subjects to be enrolled in the OC expansion cohort will be randomized in a 1:1:1 ratio to one of 3 dose level groups:

- Arm A (40 subjects, nivolumab 1 mg/kg + ipilimumab 3 mg/kg every 3 weeks (Q3W) for 4 cycles followed by nivolumab 3 mg/kg Q2W)
- Arm B (40 subjects, nivolumab 3 mg/kg + ipilimumab 1 mg/kg every 3 weeks (Q3W) for 4 cycles followed by nivolumab 3 mg/kg Q2W)
- Arm C (40 subjects, Nivolumab (3 mg/kg) Q2W + ipilimumab (1 mg/kg) Q6W)

Subjects to be enrolled in the PC additional cohort will be assigned to one regimen consisting of nivolumab 3 mg/kg Q2W + ipilimumab (1 mg/kg) Q6W + cobimetinib 60 mg orally QD 21 days on/7 days off.

## 4.5 Selection and Timing of Dose for Each Subject

The dosing regimen and schedule for **Arm N, Arm N-I Dose Level -1, Dose Level 1, Dose Level 2, Dose Level 2b, and Dose Level 2c** are detailed in Table 4.5-1 (Arm N), Table 4.5-2 (N-I Arms -1, 1, 2, and 2b, Week 1-12), Table 4.5-3 (N-I Arms -1, 1, 2, and 2b, Week 13 and following), Table 4.5-4 (N-I Arm 2c), and Table 4.5-5 (N-I Arm 2d combined with cobimetinib).

**Table 4.5-1: Dosing Schedule for Arm N - Nivolumab (BMS-936558) Monotherapy**

| Every 2 Week Dosing | | |
|---|---|---|
| **Day 1, Week 1** | **Day 1, Week 3** | **Day 1, Week 5, 7, 9, and every other week thereafter** |
| 3 mg/kg Nivolumab | 3 mg/kg Nivolumab | 3 mg/kg Nivolumab |

**Table 4.5-2: Dosing Schedule for N-I Arms -1, 1, 2, and 2b (Week 1-12) - Nivolumab (BMS-936558) + Ipilimumab Combination**

| Every 3 Week Dosing | | | | |
|---|---|---|---|---|
| **Study Part** | **Day 1 Week 1** | **Day 1 Week 4** | **Day 1 Week 7** | **Day 1 Week 10** |
| **Dose Escalation Phase Dose Level -1** | 0.3 mg/kg Nivolumab<br>1 mg/kg Ipilimumab | 0.3 mg/kg Nivolumab<br>1 mg/kg Ipilimumab | 0.3 mg/kg Nivolumab<br>1 mg/kg Ipilimumab | 0.3 mg/kg Nivolumab<br>1 mg/kg Ipilimumab |
| **Dose Escalation Phase Dose Level 1** | 1 mg/kg Nivolumab<br>1 mg/kg Ipilimumab | 1 mg/kg Nivolumab<br>1 mg/kg Ipilimumab | 1 mg/kg Nivolumab<br>1 mg/kg Ipilimumab | 1 mg/kg Nivolumab<br>1 mg/kg Ipilimumab |
| **Dose Escalation Phase Dose Level 2** | 1 mg/kg Nivolumab<br>3 mg/kg Ipilimumab | 1 mg/kg Nivolumab<br>3 mg/kg Ipilimumab | 1 mg/kg Nivolumab<br>3 mg/kg Ipilimumab | 1 mg/kg Nivolumab<br>3 mg/kg Ipilimumab |
| **Efficacy, Staged Phase**[a] | | | | |
| **Dose Level 2** | 1 mg/kg Nivolumab<br>3 mg/kg Ipilimumab | 1 mg/kg Nivolumab<br>3 mg/kg Ipilimumab | 1 mg/kg Nivolumab<br>3 mg/kg Ipilimumab | 1 mg/kg Nivolumab<br>3 mg/kg Ipilimumab |
| **Dose Level 2b** | 3 mg/kg Nivolumab<br>1 mg/kg Ipilimumab | 3 mg/kg Nivolumab<br>1 mg/kg Ipilimumab | 3 mg/kg Nivolumab<br>1 mg/kg Ipilimumab | 3 mg/kg Nivolumab<br>1 mg/kg Ipilimumab |

[a] The staged phase uses maximum tolerable dose identified in escalation phase since it might be different for each tumor type

**Table 4.5-3: Dosing Schedule for N-I Arms -1, 1, 2, and 2b (Week 13 and following) - Nivolumab (BMS-936558) + Ipilimumab Combination**

| Every 2 Week Dosing | | |
|---|---|---|
| **Day 1<br>Week 13** | **Day 1<br>Week 15** | **Day 1, Week 17, 19, 21<br>and every other week thereafter** |
| 3 mg/kg Nivolumab | 3 mg/kg Nivolumab | 3 mg/kg Nivolumab |

**Table 4.5-4: Dosing Schedule for N-I Arm Dose Level 2c - Nivolumab (BMS-936558) + Ipilimumab Combination**

| Every 2 or 6 Week Dosing | | |
|---|---|---|
| **Day 1<br>Week 1** | **Day 1, Week 3, 5, 7, 9<br>and every other week thereafter** | **Day 1 Week 7, 13, 19 and every 6 weeks thereafter** |
| 3 mg/kg Nivolumab | 3 mg/kg Nivolumab | |
| 1 mg/kg Ipilimumab | | 1 mg/kg Ipilimumab |

**Table 4.5-5: Dosing Schedule for N-1 Arm Dose Level 2d Combined with Cobimetinib - Nivolumab (BMS-936558) + Ipilimumab + Cobimetinib Combination**

| Every 2 or 6 Week Dosing | | |
|---|---|---|
| **Day 1<br>Week 1** | **Day 1, Week 3, 5, 7, 9<br>and every other week thereafter** | **Day 1, Week 7, 13, 19<br>and every 6 weeks thereafter** |
| 3 mg/kg Nivolumab | 3 mg/kg Nivolumab | |
| 1 mg/kg Ipilimumab | | 1 mg/kg Ipilimumab |
| 60 mg cobimetinib | Once daily, 21 days on/7 days off | Once daily, 21 days on/7 days off |

Nivolumab and Ipilimumab combination:

When study drugs (nivolumab or ipilimumab) are to be administered on the same day, separate infusion bags and filters must be used for each infusion. Nivolumab is to be administered first. The second infusion will always be ipilimumab, and will start no sooner than 30 minutes after completion of the nivolumab infusion.

When cobimetinib is taken on the same day with nivolumab alone or nivolumab in combination with ipilimumab, dose timimg for cobimetinib should remain the same as on any other days from the 21 consecutive days treatment schedule and should follow the 21 day on/7 days off schedule.

Dosing calculation based on weight:

The dosing calculations should be based on the body weight. If the subject's weight on the day of dosing differs by > 10% from the weight used to calculate the dose, the dose must be recalculated. All doses should be rounded to the nearest milligram.

Dosing modifications:

There will be no dose modifications of nivolumab and ipilimumab allowed for the management of toxicities of individual subjects.

Dosing window Arm N-I Dose Levels 2 and 2b (Week 1-12): subjects may be dosed no less than 19 days between doses and no more than 3 days from scheduled dose. If dosing is delayed, both nivolumab and ipilimumab must be delayed together. If dosing is resumed after a delay, both nivolumab and ipilimumab must be resumed on the same day.

Dosing window Arm N and Arm N-I Dose Levels 2 and 2b (Week 13 and following): subjects may be dosed no less than 12 days between doses and no more than 3 days from scheduled dose.

Dosing window Arm N-I Dose Levels 2c: subjects may be dosed no less than 12 days between doses and no more than 3 days from scheduled dose. If dosing is delayed, both nivolumab and ipilimumab must be delayed together.

Dosing window Arm N-I Dose Level 2d: Cotellic (cobimetinib) will be administered at 60 mg (three 20 mg tablets) orally taken once daily with or without food 21 days on/7 days off until disease progression or unacceptable toxicity. If a dose of Cotellic is missed or if vomiting occurs when the dose is taken, dosing with the next scheduled dose should be resumed. Recommended dose reductions are summarized in Sections 3.1.10 and 4.5.3 and provided in the Prescribing Information for Cotellic.[57]

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

### *4.5.1 Antiemetic Premedications*

Antiemetic medications should not be routinely administered prior to dosing of drugs. See Section 4.5.6 for subsequent premedication recommendations following a nivolumab- or ipilimumab-related infusion reaction.

### 4.5.2 Dose Delay Criteria

**Nivolumab and Ipilimumab**

These dose delay criteria apply for all drug-related adverse events attributed to nivolumab, ipilimumab, or both. All study drugs must be delayed until treatment can resume (see Section 4.5.4).

Nivolumab and ipilimumab administration should be delayed for the following:

- Any Grade ≥ 2 non-skin, drug-related adverse event, with the following exceptions:
  - Grade 2 drug-related fatigue or laboratory abnormalities do not require a treatment delay
- Any Grade 3 skin drug-related adverse event
  - Any Grade 3 drug-related laboratory abnormality, with the following exceptions for asymptomatic amylase or lipase, lymphocytopenia, AST, ALT, or total bilirubin:
    - Grade 3 amylase or lipase abnormalities that are not associated with symptoms or clinical manifestations, or radiographic signs of pancreatitis do not require a dose delay. It is recommended to consult with the BMS Medical Monitor for Grade 3 amylase or lipase abnormalities.
    - If a subject has a baseline AST, ALT, or total bilirubin that is within normal limits, delay dosing for drug-related Grade ≥ 2 toxicity
    - If a subject has baseline grade 1 AST, ALT, or total bilirubin elevation, delay dosing for drug-related Grade ≥ 3 toxicity
    - Grade 3 lymphocytopenia not associated with symptoms or clinical manifestations. It is recommended to consult with the BMS Medical Monitor for Grade 3 lymphocytopenia before treatment continuation.
- Any adverse event, laboratory abnormality, or concurrent illness which, in the judgment of the investigator, warrants delaying the dose of study medication.

Because of the potential for nivolumab- or ipilimumab-related AEs requiring early recognition and prompt intervention, management algorithms have been developed for suspected pulmonary toxicity, GI toxicity, hepatotoxicity, endocrinopathy, skin toxicity, neurological toxicity, and nephrotoxicity.

In order to standardize the management of adverse events for all subjects, treatment management algorithms recommended for utilization in Study CA209032 are included in Appendix 2. Adverse event treatment management algorithms included in the Nivolumab IB or Ipilimumab IB might be considered for individual cases.

**Cobimetinib**

Dose delay criteria for the management of toxicities of individual subjects taking cobimetinib are summarized in Section 4.5.3 and in the prescribing information.[57]

### *4.5.3 Dose Modifications*

Intrapatient dose reductions for nivolumab and ipilimumab for the management of toxicities of individual subjects or dose escalations are not permitted.

Intrapatient dose modifications for cobimetinib for the management of toxicities of individual subjects are summarized in Table 4.5.3-1 and in the prescribing information.

**Table 4.5.3-1: Recommended Dose Modifications for COTELLIC for Adverse Reactions**

| Severity of Adverse Reaction[a] | Dose Modification for COTELLIC |
|---|---|
| **Hemorrhage** | |
| Grade 3 | Withhold COTELLIC for up to 4 weeks<br>• If improved to Grade 0 or 1, resume next lower dose level<br>• If not improved within 4 weeks, permanently discontinue |
| Grade 4 | Permanently discontinue |
| **Cardiomyopathy** | |
| Asymptomatic, absolute decrease in LVEF from baseline of greater than 10% and less than institutional lower limit of normal (LLN) | Withhold COTELLIC for 2 weeks; repeat LVEF.<br>Resume at next lower dose if all of the following are present<br>• LVEF is at or above LLN AND<br>• Absolute decrease from baseline LVEF is 10% or less.<br>Permanently discontinue if any of the following are present<br>• LVEF is less than LLN OR<br>• Absolute decrease from baseline LVEF is more than 10%. |
| Symptomatic LVEF decrease from baseline | Withhold COTELLIC for up to 4 weeks, repeat LVEF.<br>Resume at next lower dose if all of the following are present:<br>• Symptoms resolve and<br>• LVEF is at or above LLN AND<br>• Absolute decrease from baseline LVEF is 10% or less.<br>Permanently discontinue if any of the following are present<br>• Symptoms persist, OR<br>• LVEF is less than LLN, OR<br>• Absolute decrease from baseline LVEF is more than 10%. |
| Dermatologic Reactions | |
| Grade 2 (intolerable), Grade 3 or 4 | Withhold or reduce dose. |

**Table 4.5.3-1: Recommended Dose Modifications for COTELLIC for Adverse Reactions**

| Severity of Adverse Reaction[a] | Dose Modification for COTELLIC |
|---|---|
| **Severe Retinopathy or Retinal Vein Occlusion** | |
| Serious retinopathy | Withhold COTELLIC for up to 4 weeks.<br>• If signs and symptoms improve, resume at the next lower dose level.<br>• If not improved or symptoms recur at the lower dose within 4 weeks, permanently discontinue. |
| Retinal vein occlusion | Permanently discontinue COTELLIC. |
| **Liver Laboratory Abnormalities and Hepatotoxicity** | |
| First occurrence Grade 4 | Withhold COTELLIC for up to 4 weeks.<br>• If improved to Grade 0 or 1, then resume at the next lower dose level.<br>If not improved to Grade 0 or 1 within 4 weeks, permanently discontinue |
| Recurrent Grade 4 | Permanently discontinue COTELLIC. |
| **Rhabdomyolysis and Creatine Phosphokinase (CPK) elevations** | |
| • Grade 4 CPK elevation<br>• Any CPK elevation and myalgia | Withhold COTELLIC for up to 4 weeks.<br>• If improved to Grade 3 or lower, resume at the next lower dose level.<br>• If not improved within 4 weeks, permanently discontinue. |
| **Photosensitivity** | |
| Grade 2 (intolerable), Grade 3 or Grade 4 | Withhold COTELLIC for up to 4 weeks.<br>• If improved to Grade 0 or 1, resume at the next lower dose level.<br>• If not improved within 4 weeks, permanently discontinue. |
| **Other** | |
| • Grade 2 (intolerable) adverse reactions<br>• Any Grade 3 adverse reactions | Withhold COTELLIC for up to 4 weeks.<br>• If improved to Grade 0 or 1, resume at the next lower dose level.<br>• If not improved within 4 weeks, permanently discontinue. |
| First occurrence of any Grade 4 adverse reaction | • Withhold COTELLIC until adverse reaction improves to Grade 0 or 1. Then resume at the next lower dose level, OR<br>• Permanently discontinue |
| Recurrent Grade 4 adverse reaction | Permanently discontinue COTELLIC. |

[a] NCI CTCAE v 4.0

### 4.5.4 Criteria to Resume Treatment

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

- Subjects may resume treatment in the presence of Grade 2 fatigue.
- Subjects with baseline Grade 1 AST/ALT or total bilirubin who require dose delays for reasons other than a 2-grade shift in AST/ALT or total bilirubin may resume treatment in the presence of Grade 2 AST/ALT OR total bilirubin. Subjects with combined Grade 2 AST/ALT AND total bilirubin values meeting discontinuation parameters (Section 4.5.5) should have treatment permanently discontinued.
- Drug-related pulmonary toxicity, diarrhea, or colitis must have resolved to baseline before treatment is resumed.
- Drug-related endocrinopathies adequately controlled with only physiologic hormone replacement or glucose controlling agents may resume treatment.

If the criteria to resume treatment are met, the subject should restart treatment at the next scheduled timepoint per protocol. However, if the treatment is delayed past the scheduled timepoint per protocol, the scheduled study treatment administration will be delayed, but not skipped, until dosing resumes. In particular, this is to ensure that subjects in Arm N-I will receive 4 administrations of combined nivolumab and ipilimumab treatment if toxicity allows.

If dose delay is necessary for subjects in Arm N-I during Week 1-12, both nivolumab and ipilimumab must be delayed until treatment can resume. However, if a nivolumab-related infusion reaction prevents subsequent infusion of ipilimumab on the same day, the dose of ipilimumab should be replaced as soon as possible. In such instances, at least 19 days must elapse between the replacement dose of ipilimumab and the administration of the next dose of nivolumab combined with ipilimumab.

If treatment is delayed > 6 weeks from the last dose, the subject must be permanently discontinued from study therapy, except as specified in Section 4.5.5.

Cobimetinib will be resumed in accordance with the Prescribing Information for Cotellic and dose modification summary provided in Section 4.5.3.

### 4.5.5 Discontinuation Criteria

**Nivolumab and Ipilimumab**

Discontinuation criteria apply for all drug-related adverse events attributed to nivolumab, ipilimumab, or both.

Treatment should be permanently discontinued for the following:

- Any Grade 2 drug-related uveitis, eye pain, or blurred vision that does not respond to topical therapy and does not improve to Grade 1 severity within the re-treatment period OR requires systemic treatment.

- Any Grade 3 non-skin, drug-related adverse event lasting > 7 days, with the following exceptions for drug-related laboratory abnormalities, uveitis, pneumonitis, bronchospasm, diarrhea, colitis, neurologic toxicity, hypersensitivity reactions, and infusion reactions:
  - Grade 3 drug-related uveitis, pneumonitis, bronchospasm, diarrhea, colitis, neurologic toxicity, hypersensitivity reaction, or infusion reaction of any duration requires discontinuation
  - For Grade 3 endocrinopathy adverse events such as adrenal insufficiency, ACTH deficiency, hyper- or hypothyroidosis, or glucose intolerance, which resolve or are adequately controlled with physiologic hormone replacement (steroids, thyroid hormones) or glucose controlling agents, respectively, do not require treatment discontinuation
  - Grade 3 drug-related laboratory abnormalities do not require treatment discontinuation except:
    - Grade 3 drug-related thrombocytopenia > 7 days or associated with bleeding requires discontinuation
    - Any drug-related liver function test (LFT) abnormality that meets the following criteria require discontinuation:
      - AST or ALT > 8 x ULN
      - Total bilirubin > 5 x ULN
      - Concurrent AST or ALT > 3 x ULN and total bilirubin > 2 x ULN
- Any Grade 4 drug-related adverse event or laboratory abnormality, except for the following events which do not require discontinuation:
  - Grade 4 amylase or lipase abnormalities that are not associated with symptoms or clinical manifestations, or radiographic signs of pancreatitis. Consult with the BMS Medical Monitor for Grade 4 amylase or lipase abnormalities.
  - 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.
  - For Grade 4 endocrinopathy adverse events such as adrenal insufficiency, ACTH deficiency, hyper- or hypothyroidosis, or glucose intolerance, which resolve or are adequately controlled with physiologic hormone replacement (steroids, thyroid hormones) or glucose controlling agents, respectively, retreatment can be considered after discussion with the BMS Medical Monitor.
  - Grade 4 lymphocytopenia not associated with symptoms or clinical manifestations. It is recommended to consult with the BMS Medical Monitor for Grade 4 lymphocytopenia before treatment continuation.

- Any dosing interruption lasting > 6 weeks with the following exceptions:
  - Dosing interruptions to allow for prolonged steroid tapers to manage drug-related adverse events are allowed. Prior to re-initiating treatment in a subject with a dosing interruption lasting > 6 weeks, the BMS medical monitor must be consulted. Tumor assessments should continue as per protocol even if dosing is interrupted.
  - Dosing interruptions > 6 weeks that occur for non-drug-related reasons may be allowed if approved by the BMS medical monitor. Prior to re-initiating treatment in a subject with a dosing interruption lasting > 6 weeks, the BMS medical monitor must be consulted. Tumor assessments should continue as per protocol even if dosing is interrupted.
- Any adverse event, laboratory abnormality, or concurrent illness which, in the judgment of the Investigator, presents a substantial clinical risk to the subject with continued nivolumab, ipilimumab, or cobimetinib dosing.

If a subject in Arm N-I meets criteria for discontinuation of nivolumab, the subject should discontinue both nivolumab and ipilimumab and be taken off the treatment phase of the study entirely. However, if the investigator assesses the drug-related AE to be related to ipilimumab only and not related to nivolumab, ipilimumab dosing alone may be discontinued while nivolumab dosing is delayed until the subject meets criteria to resume nivolumab treatment (specified in Section 4.5.4). Nivolumab would be continued at 3 mg/kg with an every 2 week dosing interval. The relationship to ipilimumab should be well documented in the source documents and the BMS medical monitor needs to be contacted prior to continuation with nivolumab therapy.

**Cobimetinib**

Discontinuation criteria for cobimetinib are specified in Section 4.5.3 and in the Prescribing Information.[57]

For subjects on Arm N-I dose level 2d, if the investigator assesses drug related AEs to be related to ipilimumab or cobimetinib only and not related to other study drugs, treatment with the agent causing the AE alone may be permanently discontinued and treatment with the remaining drugs will continue. Treatment with the remaining drugs may only be resumed when the subject meets criteria to resume treatment according to section 4.5.4. If a subject in Arm N-I dose level 2d meets criteria for discontinuation of nivolumab or nivolumab and ipilimumab, the subject should discontinue all agents, nivolumab, ipilimumab, and cobimetinib and be taken off the treatment phase of the study entirely.

### *4.5.6 Treatment of Nivolumab- or Ipilimumab-Related Infusion Reactions*

Since nivolumab and ipilimumab contain only human immunoglobulin protein sequences, each is unlikely to be immunogenic and induce an infusion or hypersensitivity reaction. However, if such a reaction were to occur, it might manifest with fever, chills, rigors, headache, rash, pruritis, arthralgias, hypo- or hypertension, bronchospasm, or other symptoms. All Grade 3 or 4 infusion reactions should be reported within 24 hours to the BMS Medical Monitor and reported as an

SAE if criteria are met. Infusion reactions should be graded according to NCI CTCAE (version 4.0) guidelines.

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

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

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

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

Stop the nivolumab or ipilimumab infusion, begin an IV infusion of normal saline, and treat the subject with diphenhydramine 50 mg IV (or equivalent) and/or paracetamol 325 to 1000 mg (acetaminophen); remain at bedside and monitor subject until resolution of symptoms. Corticosteroid or bronchodilator therapy may also be administered as appropriate. If the infusion is interrupted, restart the infusion at 50% of the original infusion rate when symptoms resolve; if no further complications ensue after 30 minutes, the rate may be increased to 100% of the original infusion rate. Monitor subject closely. If symptoms recur then no further nivolumab or ipilimumab will be administered at that visit. Administer diphenhydramine 50 mg IV, and remain at bedside and monitor the subject until resolution of symptoms. The amount of study drug infused must be recorded on the electronic case report form (eCRF). The following prophylactic premedications are recommended for future infusions: diphenhydramine 50 mg (or equivalent) and/or paracetamol 325 to 1000 mg (acetaminophen) should be administered at least 30 minutes before additional nivolumab or ipilimumab administrations. If necessary, corticosteroids (recommended dose: up to 25 mg of IV hydrocortisone or equivalent) may be used.

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

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

investigator is comfortable that the symptoms will not recur. Nivolumab or ipilimumab will be permanently discontinued. Investigators should follow their institutional guidelines for the treatment of anaphylaxis. Remain at bedside and monitor subject until recovery from symptoms. In the case of late-occurring hypersensitivity symptoms (eg, appearance of a localized or generalized pruritis within 1 week after treatment), symptomatic treatment may be given (eg, oral antihistamine, or corticosteroids).

### *4.5.7 Treatment Beyond Disease Progression*

As described in Section 1.1.11 accumulating evidence indicates that subjects treated with immunotherapy may derive clinical benefit despite evidence of PD.[84]

Subjects will be permitted to continue with treatment beyond initial RECIST 1.1 defined PD as long as they meet the following criteria:

- Investigator-assessed clinical benefit

and

- Subject is tolerating study drug.

The assessment of clinical benefit should take into account whether the subject is clinically deteriorating and unlikely to receive further benefit from continued treatment. The following criteria need to be taken into consideration:

- Absence of clinical symptoms and signs (including worsening of laboratory values) indicating disease progression.
- No decline in ECOG performance status.
- Absence of rapid progression of disease or of progressive tumor at critical anatomical sites (eg, cord compression) requiring urgent alternative medical intervention.

Treatment with cobimetinib beyond progression as monotherapy or as part of the combination with nivolumab and ipilimumab is not permitted.

All decisions to continue treatment beyond progression must be discussed with the BMS Medical Monitor and documented in the study records.

Subjects must be re-consented in order to continue treatment.

Subjects should discontinue study therapy upon evidence of further progression, defined as an additional 10% or greater increase in tumor burden from time of initial progression (including all target lesions and new measurable lesions). Progression in non-target lesions should only be unequivocal as defined and described in Appendix 3 compared to initial progression.

New lesions are considered measurable 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).

For statistical analyses that include the investigator-assessed progression date, subjects who continue treatment beyond initial investigator-assessed, RECIST 1.1-defined progression will be considered to have investigator-assessed progressive disease at the time of the initial progression event. Subjects who have tumor shrinkage following RECIST-defined progression (ie, immune related response; Section 5.4.4 will be also descriptively summarized separately since these immune responses may be used in determining Go to Stage 2.

### *4.5.8 Crossover to Arm N-I*

Subjects in Arm N may crossover to Arm N-I if all of the criteria defined in Section 3.1.6 are met. Subjects from the SCLC expansion cohort enrolled under or after Amendment 09 are excluded from the crossover option. In case Dose Level 2b-has been activated and completed the safety assessment, subjects for cross over will be assigned to Dose Level 2 or Dose Level 2b after discussion between the sponsor and investigator taking into consideration previous safety and efficacy signals at these dose levels and the status of the individual subject planned for cross over.

Before crossover, the investigator should discuss the individual case with the medical monitor and document in the study records.

Subjects must be re-consented prior to crossing over to Arm N-I.

Subjects crossing over to Arm N-I will start treatment at Day 1 Week 1 as described for subjects originally randomized to Arm N-I. Subjects who crossed over and subsequently have an objective response in Arm N-I, will not be considered in respect to the decision making for Arm N-I of proceeding to Stage 2. Subjects in Arm N-I cannot crossover to Arm N.

New lesions are considered measurable 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).

For statistical analyses that include the investigator-assessed progression date, subjects who crossover after initial investigator-assessed, RECIST 1.1-defined progression will be considered to have investigator-assessed progressive disease at the time of the initial progression event in Arm N. The tumor assessment confirming PD in Arm N will serve as the baseline for tumor assessments in Arm N-I.

## 4.6 Blinding/Unblinding

Not applicable.

## 4.7 Treatment Compliance

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

## 4.8 Destruction of Study Drug

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

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

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

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

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

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

## 4.9 Return of Study Drug

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

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

## 4.10 Retained Samples for Bioavailability / Bioequivalence

Not applicable.

# 5 STUDY ASSESSMENTS AND PROCEDURES

## 5.1 Flow Chart/Time and Events Schedule

**Table 5.1-1: Screening Procedural Outline (CA209032)**

| Procedure | Screening Visit | Notes |
|---|---|---|
| **Eligibility Assessments** | | |
| Informed Consent | X | May be performed more than 28 days prior to the first dose (must be completed prior to any study related procedures)<br>Original IC in screening for protocol participation;<br>Study allows for re-enrollment of a subject that has discontinued the study as a pre-treatment failure. If re-enrolled, the subject must be re-consented and assigned a new subject number from IVRS. |
| Inclusion/Exclusion Criteria | X | All inclusion/exclusion criteria should be assessed at screening and confirmed prior to first dose. |
| Demographics and Medical History | X | For SCLC and Ovarian cancer subjects, evaluation of Platinum-free interval (PFI) from the completion of any platinum-based chemotherapy and subsequent disease progression, and Treatment-free-interval (TFI) from the completion of any other cytotoxic or targeted based prior treatment line and subsequent disease progression will be collected. For Ovarian Cancer, information about BRCA and Homologous Recombinant Deficiency (HRD), if available, will be collected |
| Tumor Tissue Samples | X | Sufficient tumor tissue obtained before start of study treatment in the metastatic setting or from an unresectable site (block or minimum of 10 slides for bladder and SCLC subjects and a minimum of 15 slides for ovarian subjects (if medically justified), obtained from core biopsy, punch biopsy, excisional biopsy or surgical specimen). Tumor tissue samples must be shipped from site to central laboratory prior to randomization. |
| Screening/Baseline Tumor Assessment | X | CT chest, CT or MRI brain, abdomen, pelvis and all known sites of disease within 28 days prior to first dose. For patients with known brain metastasis, an MRI brain is required at baseline. A CT brain is not allowed for patients with a history or evidence of known brain metastasis at baseline. |
| **Safety Assessments** | | |
| Physical Examination | X | Within 14 days prior to first dose |

**Table 5.1-1: Screening Procedural Outline (CA209032)**

| Procedure | Screening Visit | Notes |
|---|---|---|
| Vital Signs and oxygen saturation | X | Including BP, HR, temperature, and oxygen saturation by pulse oximetry (at rest). Obtain vital signs at the screening visit and within 72 hours prior to first dose. |
| Physical Measurements (including performance status) | X | Height, Weight and ECOG status. Within 14 days prior to first dose |
| Echocardiogram (additional pancreatic cancer cohort only) | X | Subjects with LVEF below the institutional LLN or < 50%, whichever is lower, and corrected QT ≥ 450 ms are to be excluded |
| ECG | X | Within 14 days prior to first dose |
| Assessment of Signs and Symptoms | X | Within 14 days prior to first dose |
| [redacted] | [redacted] | [redacted] |
| Laboratory Tests | X | CBC w/differential, Chemistry panel including: LDH, AST, ALT, ALP, T.Bili, BUN or serum urea level, creatinine, albumin, Ca, Mg, Na, K, Cl, glucose, amylase, lipase, TSH, Free T4, Free T3, hepatitis B surface antigen (HBV sAg), and hepatitis C antibody (HCV Ab) or Hepatitis C RNA (HCV RNA), CPK (additional pancreatic cancer cohort only) within 14 days prior to first dose. Screening labs done within 72 hours prior to first dose can also be used for on treatment lab purposes at Day 1 dosing. |
| Pregnancy Test (WOCBP only) | X | Serum or urine within 24 hours of first dose |
| Ophthalmological evaluation (additional pancreatic cancer cohort only) | X | |

| Table 5.1-2: On-Study Assessments - Arm N, Nivolumab Monotherapy (CA209032) | | |
|---|---|---|
| **Procedure** | **For Arm N, Nivolumab is administered every 2 weeks**<br>**Day 1**<br>**Week 1, 3, 5, 7, 9, etc** | **Notes** |
| **Safety Assessments** | | |
| Targeted Physical Examination | X | Within 72 hours prior to dosing. During treatment hold to be conducted every 12 weeks to adjust to the tumor assessment schedule (see Section 3.1.6). |
| Vital Signs and Oxygen Saturation | X | Including BP, HR, temperature, and oxygen saturation by pulse oximetry. Pulse oximetry at rest and within 72 hours prior to dosing. During treatment hold to be conducted every 12 weeks to adjust to the tumor assessment schedule (see Section 3.1.6). |
| Physical Measurements (including performance status) | X | Weight and ECOG status.<br>The dosing calculations should be based on the body weight. If the subject's weight on the day of dosing differs by > 10% from the weight used to calculate the dose, the dose must be recalculated. All doses should be rounded to the nearest milligram.<br>During treatment hold to be conducted every 12 weeks to adjust to the tumor assessment schedule (see Section 3.1.5). |
| Adverse Events Assessment | Continuously | eSAEs should be approved in TAO within 5 days from entry |
| [redacted] | [redacted] | [redacted] |
| Laboratory Tests | X | On-study local laboratory assessments should be done within 72 hours prior to each dose up to and including Week 25 and then every other dose thereafter (Week 29, Week 33, Week 37 etc.) and include: CBC w/differential, LFTs (ALT, AST, total bilirubin, alkaline phosphatase), BUN or serum urea level, creatinine, albumin, Ca, Mg, Na, K, Cl, LDH, glucose, amylase, lipase, TSH (if TSH result abnormal, subsequent testing of Free T4 and Free T3 required).<br>During treatment hold to be conducted every 12 weeks to adjust to the tumor assessment schedule (see Section 3.1.5). |
| Pregnancy Test (WOCBP only) | X | Serum or urine within 24 hours prior to first dose and then every 4 weeks. During treatment hold to be conducted every 12 weeks and resume per protocol testing once treatment resumes (see Section 3.1.5). |

**Table 5.1-2: On-Study Assessments - Arm N, Nivolumab Monotherapy (CA209032)**

| Procedure | For Arm N, Nivolumab is administered every 2 weeks<br>Day 1<br>Week 1, 3, 5, 7, 9, etc | Notes |
|---|---|---|
| **Outcomes Research Assessment** | | |
| QoL | X | Collect EQ-5D prior to study drug administration through Week 13, then at the same time of subsequent tumor assessments, during Follow Up 1 and 2 and survival visits. The EQ-5D can be done via a phone contact when a clinic visit is not feasible (ie., follow up scans are being done at another facility or department) in order to not miss the assessment.<br>During treatment hold to be conducted every 12 weeks to adjust to the tumor assessment schedule (see Section 3.1.5). |
| **Pharmacokinetic Assessments** | | |
| PK Samples | See Section 5.5.1 for details regarding specific sample timing | |
| [redacted] | | |
| [redacted] | [redacted] | |
| [redacted] | [redacted] | |
| [redacted] | [redacted] | |
| [redacted] | [redacted] | [redacted] |

| Table 5.1-2: On-Study Assessments - Arm N, Nivolumab Monotherapy (CA209032) | | |
|---|---|---|
| **Procedure** | **For Arm N, Nivolumab is administered every 2 weeks**<br>**Day 1**<br>**Week 1, 3, 5, 7, 9, etc** | **Notes** |
| [redacted] | [redacted] | |
| [redacted] | | [redacted] |
| **Efficacy Assessment** | | |
| Tumor Assessment | See Notes | • Tumor assessments should occur every 6 weeks (± 1 wk) from first dose for the first 24 weeks, then every 12 wks (± 1 wk) while on treatment or on treatment hold for any reason until disease progression and treatment discontinuation, whichever occurs later. Additionally, with the exception of crossover participants, tumor assessments will not be required upon initiation of subsequent anti-cancer therapy.<br>• CT chest, CT or MRI abdomen, pelvis and all known sites of disease. Use same imaging method as was used at screening/baseline.<br>• Subjects with a history of brain metastasis should have surveillance MRI approximately every 12 weeks, or sooner if clinically indicated |
| **Clinical Drug Supplies** | | |
| IVRS Drug Vial Assignment | X | |
| Administer Study Treatment | X | See Section 4.5, Note: Within 3 days from vial allocation, the subject must receive the first dose of study medication. Subjects may be dosed no less than 12 days between doses and no more than 3 days from the scheduled dose. |

**Table 5.1-3: On-Study Assessments for N-I Arms (Dose Levels 2 and 2b) Week 1-12, Nivolumab + Ipilimumab Combination (CA209032)**

| Procedure | Week 1-12, nivolumab and ipilimumab are administered every 3 weeks for 4 doses.<br>Day 1, Week 1, 4, 7, 10 | Notes |
|---|---|---|
| **Safety Assessments** | | |
| Targeted Physical Examination | X | Within 72 hours prior to dosing. During treatment hold to be conducted every 12 weeks to adjust to the tumor assessment schedule (see Section 3.1.5). |
| Vital Signs and Oxygen Saturation | X | Including BP, HR, temperature, and oxygen saturation by pulse oximetry. Pulse oximetry at rest within 72 hours prior to dosing. During treatment hold to be conducted every 12 weeks to adjust to the tumor assessment schedule (see Section 3.1.5). |
| Physical Measurements (including performance status) | X | Weight and ECOG status<br>The dosing calculations should be based on the body weight. If the subject's weight on the day of dosing differs by > 10% from the weight used to calculate the dose, the dose must be recalculated. All doses should be rounded to the nearest milligram.<br>During treatment hold to be conducted every 12 weeks to adjust to the tumor assessment schedule (see Section 3.1.5). |
| Adverse Events Assessment | Continuously | eSAEs should be approved in TAO within 5 days from entry |
| [redacted] | [redacted] | [redacted] |
| Laboratory Tests | X | Within 72 hours prior to re-dosing to include CBC w/ differential, LFTs, BUN or serum urea level, creatinine, albumin, Ca, Mg, Na, K, Cl, LDH, glucose, amylase, lipase, TSH (if TSH result abnormal, subsequent testing of Free T4 and Free T3 required).<br>During treatment hold to be conducted every 12 weeks to |

| **Table 5.1-3:** | **On-Study Assessments for N-I Arms (Dose Levels 2 and 2b) Week 1-12, Nivolumab + Ipilimumab Combination (CA209032)** | |
|---|---|---|
| **Procedure** | **Week 1-12, nivolumab and ipilimumab are administered every 3 weeks for 4 doses.**<br>**Day 1, Week 1, 4, 7, 10** | **Notes** |
| | | adjust to the tumor assessment schedule (see Section 3.1.5). |
| Pregnancy Test *(WOCBP only)* | X | Serum or urine within 24 hours prior to first dose and then every 3 weeks at Week 1-12, then every 4 weeks. During treatment hold to be conducted every 12 weeks and resume per protocol testing once treatment resumes (see Section 3.1.5). |
| **Outcomes Research Assessments** | | |
| QoL | X | Collect EQ-5D prior to study drug administration through Week 13, then at the same time of subsequent tumor assessments, during Follow Up 1 and 2 and survival visits. The EQ-5D can be done via a phone contact when a clinic visit is not feasible (ie, follow up scans are being done at another facility or department) in order to not miss the assessment.<br>During treatment hold to be conducted every 12 weeks to adjust to the tumor assessment schedule (see Section 3.1.5). |
| **Pharmacokinetic Assessments** | | |
| PK Samples | See Section 5.5.1 for details regarding specific sample timing | |
| [redacted] | | |
| [redacted] | [redacted] | |
| [redacted] | [redacted] | |
| [redacted] | [redacted] | |

| **Table 5.1-3:** | **On-Study Assessments for N-I Arms (Dose Levels 2 and 2b) Week 1-12, Nivolumab + Ipilimumab Combination (CA209032)** | |
|---|---|---|
| **Procedure** | **Week 1-12, nivolumab and ipilimumab are administered every 3 weeks for 4 doses.**<br>**Day 1, Week 1, 4, 7, 10** | **Notes** |
| [redacted] | [redacted] | [redacted] |
| [redacted] | [redacted] | |
| [redacted] | | [redacted] |
| **Efficacy Assessment** | | |
| Tumor Assessment | See Notes | • Tumor assessments should occur every 6 weeks (± 1 wk) from first dose for the first 24 weeks, then every 12 wks (± 1 wk) while on treatment or on treatment hold due to any reason until disease progression and treatment discontinuation, whichever occurs later. Additionally, with the exception of crossover participants, tumor assessments will not be required upon initiation of subsequent anti-cancer therapy.<br>• CT chest, CT or MRI abdomen, pelvis and all known sites of disease. Use same imaging method as was used at screening/baseline.<br>• Subjects with a history of brain metastasis should have surveillance MRI approximately every 12 weeks, or sooner if clinically indicated |
| **Clinical Drug Supplies** | | |
| IVRS Drug Vial Assignment | X | |
| Administer Study Treatment | X | See Section 4.5, Note: Within 3 days from vial allocation, the subject must receive the first dose of study medication. Subjects may be dosed no less than 19 days between doses and no more than 3 days from the scheduled dose. |

**Table 5.1-4: On-Study Assessments - N-I Arms (Dose Levels 2 and 2b), Week 13 and following, Nivolumab + Ipilimumab Combination (CA209032)**

| Procedure | Week 13 and following, Nivolumab is administered every 2 weeks<br>Day 1<br>Week 13, 15, 17, 19, 21, etc | Notes |
|---|---|---|
| **Safety Assessments** | | |
| Targeted Physical Examination | X | Within 72 hours prior to dosing. During treatment hold to be conducted every 12 weeks to adjust to the tumor assessment schedule (see Section 3.1.5). |
| Vital Signs and Oxygen Saturation | X | Including BP, HR, temperature and oxygen saturation by pulse oximetry. Pulse oximetry at rest within 72 hours prior to dosing. During treatment hold to be conducted every 12 weeks to adjust to the tumor assessment schedule (see Section 3.1.5). |
| Physical Measurements (including performance status) | X | Weight and ECOG status<br>The dosing calculations should be based on the body weight. If the subject's weight on the day of dosing differs by > 10% from the weight used to calculate the dose, the dose must be recalculated. All doses should be rounded to the nearest milligram.<br>During treatment hold to be conducted every 12 weeks to adjust to the tumor assessment schedule (see Section 3.1.5). |
| Adverse Events Assessment | Continuously | eSAEs should be approved in TAO within 5 days from entry |
| [redacted] | [redacted] | [redacted] |

**Table 5.1-4: On-Study Assessments - N-I Arms (Dose Levels 2 and 2b), Week 13 and following, Nivolumab + Ipilimumab Combination (CA209032)**

| Procedure | Week 13 and following, Nivolumab is administered every 2 weeks<br>Day 1<br>Week 13, 15, 17, 19, 21, etc | Notes |
|---|---|---|
| Laboratory Tests | X | On-study local laboratory assessments should be done within 72 hours prior to each dose up to and including Week 25 and then every other dose thereafter (Week 29, Week 33, Week 37 etc.) and include: CBC w/differential, LFTs (ALT, AST, total bilirubin, alkaline phosphatase), BUN or serum urea level, creatinine, albumin, Ca, Mg, Na, K, Cl, LDH, glucose, amylase, lipase, TSH (if TSH result abnormal, subsequent testing of Free T4 and Free T3 required).<br>During treatment hold to be conducted every 12 weeks to adjust to the tumor assessment schedule (see Section 3.1.5). |
| Pregnancy Test (WOCBP only) | X | Serum or urine within 24 hours prior to dosing every 4 weeks. During treatment hold to be conducted every 12 weeks and resume per protocol testing once treatment resumes (see Section 3.1.5). |
| **Outcomes Research Assessments** | | |
| QoL | X | Collect EQ-5D prior to study drug administration through Week 13, then at the same time of subsequent tumor assessments, during Follow Up 1 and 2 and survival visits. The EQ-5D can be done via a phone contact when a clinic visit is not feasible (ie., follow up scans are being done at another facility or department) in order to not miss the assessment.<br>During treatment hold to be conducted every 12 weeks to adjust to the tumor assessment schedule (see Section 3.1.5). |
| [redacted] | | |
| [redacted] | [redacted] | |
| [redacted] | [redacted] | |

| **Table 5.1-4: On-Study Assessments - N-I Arms (Dose Levels 2 and 2b), Week 13 and following, Nivolumab + Ipilimumab Combination (CA209032)** | | |
|---|---|---|
| **Procedure** | **Week 13 and following, Nivolumab is administered every 2 weeks**<br>**Day 1**<br>**Week 13, 15, 17, 19, 21, etc** | **Notes** |
| Peripheral Blood RNA | See Section 5.6.8.6 for details regarding specific sample timing | |
| Peripheral Blood Mononuclear Cells (PBMCs) | See Section 5.6.8.6 for details regarding specific sample timing | Any time PBMC is performed please also draw CBC for white blood cell counts, if not already part of the visit lab draws. |
| Whole Blood Sample (DNA) | See Section 5.6.8.6 for details regarding specific sample timing | |
| **Pharmacokinetic Assessments** | | |
| PK Samples | See Section 5.5.1 for details regarding specific sample timing | |
| **Efficacy Assessment** | | |
| Tumor Assessment | See Notes | • Tumor assessments should occur every 6 weeks (± 1 wk) from first dose for the first 24 weeks, then every 12 wks (± 1 wk) while on treatment or on treatment hold due to any reason until disease progression and treatment discontinuation, whichever occurs later. Additionally, with the exception of crossover participants, tumor assessments will not be required upon initiation of subsequent anti-cancer therapy.<br>• CT chest, CT or MRI abdomen, pelvis and all known sites of disease. Use same imaging method as was used at screening/baseline.<br>• Subjects with a history of brain metastasis should have surveillance MRI approximately every 12 weeks, or sooner if clinically indicated |
| **Clinical Drug Supplies** | | |
| IVRS Drug Vial Assignment | X | |
| Administer Study Treatment | X | Subjects may be dosed no less than 12 days between doses and no more than 3 days from the scheduled dose. |

| **Table 5.1-5: On-Study Assessments for N-I Arms (Dose Level 2c) Nivolumab + Ipilimumab Combination (CA209032)** | | |
|---|---|---|
| **Procedure** | **For Arm N-I Dose level 2c, Nivolumab is administered every 2 weeks, Ipilimumab is administered every 6 weeks**<br>**Day 1**<br>**Week 1, 3, 5, 7, 9, etc** | **Notes** |
| **Safety Assessments** | | |
| Targeted Physical Examination | X | Within 72 hours prior to dosing. During treatment hold to be conducted every 12 weeks to adjust to the tumor assessment schedule (see Section 3.1.5). |
| Vital Signs and Oxygen Saturation | X | Including BP, HR, temperature, and oxygen saturation by pulse oximetry. Pulse oximetry at rest within 72 hours prior to dosing. During treatment hold to be conducted every 12 weeks to adjust to the tumor assessment schedule (see Section 3.1.5). |
| Physical Measurements (including performance status) | X | Weight and ECOG status<br>The dosing calculations should be based on the body weight. If the subject's weight on the day of dosing differs by > 10% from the weight used to calculate the dose, the dose must be recalculated. All doses should be rounded to the nearest milligram.<br>During treatment hold to be conducted every 12 weeks to adjust to the tumor assessment schedule (see Section 3.1.5). |
| Adverse Events Assessment | Continuously | eSAEs should be approved in TAO within 5 days from entry |
| [redacted] | [redacted] | [redacted] |

| **Table 5.1-5: On-Study Assessments for N-I Arms (Dose Level 2c) Nivolumab + Ipilimumab Combination (CA209032)** | | |
|---|---|---|
| **Procedure** | **For Arm N-I Dose level 2c, Nivolumab is administered every 2 weeks, Ipilimumab is administered every 6 weeks**<br>**Day 1**<br>**Week 1, 3, 5, 7, 9, etc** | **Notes** |
| Laboratory Tests | X | Within 72 hours prior to each dose up to and including Week 25 and then every other dose thereafter (Week 29, Week 33, Week 37 etc.). Dosing to include CBC w/ differential, LFTs, BUN or serum urea level, creatinine, albumin, Ca, Mg, Na, K, Cl, LDH, glucose, amylase, lipase, TSH (if TSH result abnormal, subsequent testing of Free T4 and Free T3 required).<br>During treatment hold to be conducted every 12 weeks to adjust to the tumor assessment schedule (see Section 3.1.5). |
| Pregnancy Test *(WOCBP only)* | X | Serum or urine within 24 hours prior to first dose and then every 4 weeks. During treatment hold to be conducted every 12 weeks and resume per protocol testing once treatment resumes (see Section 3.1.5). |
| **Outcomes Research Assessments** | | |
| QoL | X | Collect EQ-5D prior to study drug administration through Week 13, then at the same time of subsequent tumor assessments, during Follow Up 1 and 2 and survival visits. The EQ-5D can be done via a phone contact when a clinic visit is not feasible (ie., follow up scans are being done at another facility or department) in order to not miss the assessment.<br>During treatment hold to be conducted every 12 weeks to adjust to the tumor assessment schedule (see Section 3.1.5). |
| **Pharmacokinetic Assessments** | | |
| PK Samples | See Section 5.5.1 for details regarding specific sample timing | |
| [redacted] | | |
| [redacted] | [redacted] | |

**Table 5.1-5: On-Study Assessments for N-I Arms (Dose Level 2c) Nivolumab + Ipilimumab Combination (CA209032)**

| Procedure | For Arm N-I Dose level 2c, Nivolumab is administered every 2 weeks, Ipilimumab is administered every 6 weeks<br>Day 1<br>Week 1, 3, 5, 7, 9, etc | Notes |
|---|---|---|
| | specific sample timing | |
| [redacted] | [redacted] | |
| [redacted] | [redacted] | |
| [redacted] | [redacted] | [redacted] |
| [redacted] | [redacted] | |
| [redacted] | | [redacted] |
| **Efficacy Assessment** | | |
| Tumor Assessment | See Notes | • Tumor assessments should occur every 6 weeks (± 1 wk) from first dose for the first 24 weeks, then every 12 wks (± 1 wk) while on treatment or on treatment hold due to any reason until disease progression and treatment discontinuation, whichever occurs later. Additionally, with the exception of crossover participants, tumor assessments will not be required upon initiation of subsequent anti-cancer therapy.<br>• CT chest, CT or MRI abdomen, pelvis and all known sites of disease. Use same imaging method as was used at screening/baseline.<br>• Subjects with a history of brain metastasis should have surveillance MRI approximately every 12 weeks, or sooner if clinically indicated |

| **Table 5.1-5:** | **On-Study Assessments for N-I Arms (Dose Level 2c) Nivolumab + Ipilimumab Combination (CA209032)** | |
|---|---|---|
| **Procedure** | **For Arm N-I Dose level 2c, Nivolumab is administered every 2 weeks, Ipilimumab is administered every 6 weeks**<br>**Day 1**<br>**Week 1, 3, 5, 7, 9, etc** | **Notes** |
| **Clinical Drug Supplies** | | |
| IVRS Drug Vial Assignment | X | |
| Administer Study Treatment | X | See Section 4.5, Note: Within 3 days from vial allocation, the subject must receive the first dose of study medication. Subjects may be dosed no less than 12 days between doses and no more than 3 days from the scheduled dose. |

| **Table 5.1-6:** | **On-Study Assessments for N-I Arms (Dose Level 2d) Nivolumab + Ipilimumab + Cobimetinib Combination (CA209032)** | |
|---|---|---|
| **Procedure** | **For Arm N-I Dose level 2d, Nivolumab is administered every 2 weeks, Ipilimumab is administered every 6 weeks, cobimetinib is administered orally 21 days on/7 days off**<br>**Day 1**<br>**Week 1, 3, 5, 7, 9, etc** | **Notes** |
| **Safety Assessments** | | |
| Targeted Physical Examination | X | Within 72 hours prior to dosing. During treatment hold to be conducted every 12 weeks to adjust to the tumor assessment schedule (see Section 3.1.6). |
| Vital Signs and Oxygen Saturation | X | Including BP, HR, temperature, and oxygen saturation by pulse oximetry. Pulse oximetry at rest within 72 hours prior to dosing. During treatment hold to be conducted every 12 weeks to adjust to the tumor assessment schedule (see Section 3.1.6). |

**Table 5.1-6: On-Study Assessments for N-I Arms (Dose Level 2d) Nivolumab + Ipilimumab + Cobimetinib Combination (CA209032)**

| Procedure | For Arm N-I Dose level 2d, Nivolumab is administered every 2 weeks, Ipilimumab is administered every 6 weeks, cobimetinib is administered orally 21 days on/7 days off<br>Day 1<br>Week 1, 3, 5, 7, 9, etc | Notes |
|---|---|---|
| Physical Measurements (including performance status) | X | Weight and ECOG status<br>The dosing calculations should be based on the body weight. If the subject's weight on the day of dosing differs by > 10% from the weight used to calculate the dose, the dose must be recalculated. All doses should be rounded to the nearest milligram.<br>During treatment hold to be conducted every 12 weeks to adjust to the tumor assessment schedule (see Section 3.1.6). |
| Echocardiogram (additional pancreatic cancer cohort only) | After the first month of treatment, then every 3 months or as clinically indicated until treatment discontinuation | In case of decrease in LVEF from baseline of greater than 10% and less than institutional LLN, follow requirements for dose modification, Section 4.5.3.<br>All patients restarting treatment with a dose reduction of cobimetinib should have LVEF measurements 2, 4, 10, and 16 weeks after re-start, and then as clinically indicated |
| Ophthalmological evaluation | X | Every 12 weeks and any time a patient reports new or worsening visual disturbances |
| Adverse Events Assessment | Continuously | eSAEs should be approved in TAO within 5 days from entry |
| [redacted] | [redacted] | [redacted] |
| Laboratory Tests | X | Within 72 hours prior to each dose up to and including Week 25 and then every other dose thereafter (Week 29, Week 33, Week 37 etc.). Dosing to include CBC w/ differential, LFTs, BUN or serum urea level, creatinine, albumin, Ca, Mg, Na, K, Cl, LDH, glucose, amylase, lipase, TSH (if TSH result abnormal, subsequent testing of Free T4 and Free T3 required) and CPK.<br>During treatment hold to be conducted every 12 weeks to adjust to |

**Table 5.1-6: On-Study Assessments for N-I Arms (Dose Level 2d) Nivolumab + Ipilimumab + Cobimetinib Combination (CA209032)**

| Procedure | For Arm N-I Dose level 2d, Nivolumab is administered every 2 weeks, Ipilimumab is administered every 6 weeks, cobimetinib is administered orally 21 days on/7 days off<br>Day 1<br>Week 1, 3, 5, 7, 9, etc | Notes |
|---|---|---|
| | | the tumor assessment schedule (see Section 3.1.6). |
| Pregnancy Test *(WOCBP only)* | X | Serum or urine within 24 hours prior to first dose and then every 4 weeks. During treatment hold to be conducted every 12 weeks and resume per protocol testing once treatment resumes (see Section 3.1.6). |
| **Outcomes Research Assessments** | | |
| QoL | X | Collect EQ-5D prior to study drug administration through Week 13, then at the same time of subsequent tumor assessments, during Follow Up 1 and 2 and survival visits. The EQ-5D can be done via a phone contact when a clinic visit is not feasible (ie., follow up scans are being done at another facility or department) in order to not miss the assessment.<br>During treatment hold to be conducted every 12 weeks to adjust to the tumor assessment schedule (see Section 3.1.6). |
| **Pharmacokinetic Assessments** | | |
| PK Samples | See Section 5.5 for details regarding specific sample timing | |
| [redacted] | | |
| [redacted] | [redacted] | |
| [redacted] | [redacted] | |
| [redacted] | [redacted] | |

**Table 5.1-6: On-Study Assessments for N-I Arms (Dose Level 2d) Nivolumab + Ipilimumab + Cobimetinib Combination (CA209032)**

| Procedure | For Arm N-I Dose level 2d, Nivolumab is administered every 2 weeks, Ipilimumab is administered every 6 weeks, cobimetinib is administered orally 21 days on/7 days off<br>Day 1<br>Week 1, 3, 5, 7, 9, etc | Notes |
|---|---|---|
| | sample timing | |
| Peripheral Blood Mononuclear Cells (PBMCs) | See Section 5.6 for details regarding specific sample timing | Any time PBMC is performed please also draw CBC for white blood cell counts, if not already part of the visit lab draws. |
| Whole Blood Sample (DNA) | See Section 5.6 for details regarding specific sample timing | |
| Pharmacogenetic research | | Optional (refer to Amendment 01 and 07) |
| **Efficacy Assessment** | | |
| Tumor Assessment | See Notes | For participants who discontinue treatment for reasons other than disease progression.<br>Tumor assessments should occur every 6 weeks (± 1 wk) from first dose for the first 24 weeks, then every 12 wks (± 1 wk) while on treatment or on treatment hold due to any reason until disease progression and treatment discontinuation, whichever occurs later.<br>Additionally, with the exception of crossover participants, tumor assessments will not be required upon initiation of subsequent anti-cancer therapy.<br>• CT chest, CT or MRI abdomen, pelvis and all known sites of disease. Use same imaging method as was used at screening/baseline.<br>• Subjects with a history of brain metastasis should have surveillance MRI approximately every 12 weeks, or sooner if clinically indicated |

**Table 5.1-6: On-Study Assessments for N-I Arms (Dose Level 2d) Nivolumab + Ipilimumab + Cobimetinib Combination (CA209032)**

| Procedure | For Arm N-I Dose level 2d, Nivolumab is administered every 2 weeks, Ipilimumab is administered every 6 weeks, cobimetinib is administered orally 21 days on/7 days off<br>Day 1<br>Week 1, 3, 5, 7, 9, etc | Notes |
|---|---|---|
| **Clinical Drug Supplies** | | |
| IVRS Drug Vial Assignment | X | |
| Administer Study Treatment | X<br>Nivolumab is administered every 2 weeks, Ipilimumab is administered every 6 weeks, cobimetinib is administered orally at 60 mg (three 20 mg tablets) qd 21 days on/7 days off | See Section 4.5, Note: Within 3 days from vial allocation, the subject must receive the first dose of study medication. Subjects may be dosed with nivolumab alone or nivolumab and ipilimumab no less than 12 days between doses and no more than 3 days from the scheduled dose.<br>Nivolumab and Ipilimumab both administered as 30-min IV infusion. |

**Table 5.1-7: Follow-up Assessments (CA209032) - All Subjects**

| Procedure | Follow Up,[a] Visits 1 and 2 | Survival,[b] Follow up Visits | Notes |
|---|---|---|---|
| **Safety Assessments** | | | |
| Targeted Physical Examination | X | | To assess for potential late emergent study drug related issues |
| Adverse Event Assessments | X | X | eSAEs should be approved in TAO within 5 days from entry. AEs during the survival follow up visits considered study drug related should be followed until resolution, stabilization, or returned to baseline. |
| Laboratory Tests | X | | CBC w/ differential, LFTs, BUN or serum urea level, creatinine, albumin, Ca, Mg, Na, K, Cl, LDH, glucose, amylase, lipase, TSH (if TSH result abnormal, subsequent testing of Free T4 and Free T3 required). |
| Pregnancy Test (WOCBP Only) | X | | Serum or urine |
| [redacted] | [redacted] | | [redacted] |
| [redacted] | [redacted] | | [redacted] |
| [redacted] | [redacted] | [redacted] | [redacted] |
| **Efficacy Assessments** | | | |
| Tumor Assessments | See Notes | | Only for subjects without progression on study therapy and even if they receive subsequent treatment.<br>Tumor assessments should occur every 6 weeks (± 1 wk) from first dose for the first 24 weeks, then every 12 wks (± 1 wk) until disease progression or treatment is discontinued, except for subjects who discontinued treatment for other reasons than PD.<br>CT chest, CT or MRI abdomen, pelvis and all known sites of disease. Use same imaging method as was used at screening/baseline.<br>Subjects with a history of brain metastasis should have surveillance MRI approximately every 12 weeks, or sooner if clinically indicated |

| **Table 5.1-7: Follow-up Assessments (CA209032) - All Subjects** | | | |
|---|---|---|---|
| **Procedure** | **Follow Up,[a] Visits 1 and 2** | **Survival,[b] Follow up Visits** | **Notes** |
| **Outcomes Research Assessments** | | | |
| QoL | X | X | Collect EQ-5D prior to study drug administration through Week 13, then at the same time of subsequent tumor assessments, during Follow Up 1 and 2 and survival visits. The EQ-5D can be done via a phone contact when a clinic visit is not feasible (ie, follow up scans are being done at another facility or department) in order to not miss the assessment. |
| **Pharmacokinetic Samples** | | | |
| PK Samples | X | | See Section 5.5.1 for schedule of assessments |

[a] Follow-up visit 1 (FU1) = 35 days from the last dose ± 7 days or coincide with the date of discontinuation (± 7 days) if date of discontinuation is greater than 42 days after last dose, Follow-up visit 2 (FU2) = 80 days (± 7 days) from follow-up visit 1

[b] Survival visits = every 3 months from FU2 (±14 days) from FU2.

### *5.1.1 Retesting During Screening or Lead-in Period*

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

## 5.2 Study Materials

- NCI CTCAE version 4.0
- BMS-936558 (nivolumab) Investigator Brochure
- Ipilimumab Investigator Brochure
- Laboratory manuals for collection and handling of blood (including biomarker and immunogenicity) and tissue specimens
- Site manual for operation of interactive voice response system, including enrollment worksheets
- Site manual for imaging process and requirements
- Manual for entry of local laboratory data
- Serious Adverse Events (or eSAE) case report form pages
- Pregnancy surveillance forms
- RECIST 1.1 pocket guide

## 5.3 Safety Assessments

At baseline, a medical history will be obtained to capture relevant underlying conditions. The baseline examinations should include signs and symptoms, weight, height, ECOG Performance Status, BP, HR, temperature, and oxygen saturation by pulse oximetry at rest should be performed within 14 days prior to first dose except where noted in [redacted]

Baseline local laboratory assessments should be done within 14 days prior to the first dose and include: CBC w/differential, LFTs (ALT, AST, total bilirubin, alkaline phosphatase), BUN or serum urea level, creatinine, albumin, Ca, Mg, Na, K, Cl, LDH, glucose, amylase, lipase, TSH, Free T4, Free T3, and Hep B and C testing (HBV sAg and HCV RNA or Ab) and CPK (additional pancreatic cancer cohort only) (see Table 5.1-1). Pregnancy testing for WOCBP (done locally) must be performed within 24 hours prior to the initial administration of study drug at baseline and then every 3 weeks for subjects in Arm N-I at Week 1-12, then every 4 weeks, and at the safety follow up visits. For subjects in Arm N and N-I 2c pregnancy testing for WOCBP (done locally) must be performed within 24 hours prior to the initial administration of study drug at baseline and then every 4 weeks, and at each safety follow up visit. During treatment hold, pregnancy testing must be performed every 12 weeks and resumed per protocol testing once treatment resumes.

Subjects will be evaluated for safety if they have received any study drug. Toxicity assessments will be performed continuously during the treatment phase. During the safety follow-up phase (Table 5.1-4) toxicity assessments should be done in person. Once subjects reach the survival follow-up phase, either in-person visits or documented telephone calls to assess the subject's status are acceptable.

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

On-study weight, ECOG performance status, and vital signs should be assessed at each on-study visit prior to nivolumab dosing. Vital signs should also be taken as per institutional standard of care prior to, during and after dosing. Oxygen saturation by pulse oximetry at rest should be assessed at each on study visit prior to nivolumab dosing. The start and stop time of the nivolumab and the ipilimumab infusion should be documented. Physical examinations are to be performed as clinically indicated. If there are any new or worsening clinically significant changes since the last exam, report changes on the appropriate non-serious or serious adverse event page.

Additional measures, including non-study required laboratory tests, should be performed as clinically indicated or to comply with local regulations. Laboratory toxicities (eg, suspected drug inducted liver enzyme elevations) will be monitored during the follow-up phase via on site/local labs until all study drug related toxicities resolve, return to baseline or are deemed irreversible.

Oxygen saturation by pulse oximetry should be obtained prior to each dose of nivolumab or ipilimumab and at any time a subject has any new or worsening respiratory symptoms. A reading at rest should be obtained at each time point. If a subject shows changes on pulse oximetry or other pulmonary-related signs (eg, hypoxia, fever) or symptoms (eg, dyspnea, cough) consistent with possible pulmonary adverse events, the patient subject should be immediately evaluated to rule out pulmonary toxicity. An algorithm for the management of suspected pulmonary toxicity can be found in Appendix 2.

Echocardiogram and ophthalmologic examination (including retinal evaluation) to be conducted by an ophthalmologist will be performed for the additional pancreatic cancer cohort only.

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

### *5.3.1 Imaging Assessment for the Study*

Images will be submitted to an imaging core lab for central review. Sites will be trained prior to scanning the first study subject. Image acquisition guidelines and submission process will be outlined in the CA209032 Imaging Manual to be provided by the core lab. 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.

**CT/MRI**

Contrast-enhanced Computed Tomography (CT) scans acquired on dedicated CT equipment is preferred for this study. CT with contrast of the chest, abdomen and pelvis are to be performed for tumor assessments at baseline and beginning 6 weeks (+/- 1 week) from first dose and continuing every 6 weeks (+/- 1 week) for the first 24 weeks and every 12 weeks (+/- 1 week) thereafter, while on treatment or on treatment hold for any reason until disease progression and treatment discontinuation, whichever occurs later. Additionally, with the exception of crossover participants, tumor assessments will not be required upon initiation of subsequent anti-cancer therapy. CT scans should be acquired with 5mm slices with no intervening gap (contiguous). Although a contrast enhanced CT in particular for the chest is the preferred technique, a contrast enhanced MRI may be used based on local standards.

Should a subject have a contraindication for CT IV contrast, a non-contrast CT of the chest and a contrast enhanced MRI of the abdomen and pelvis may be obtained. MRI's should be acquired with slice thickness of £5 mm with no gap (contiguous).

Every attempt should be made to image each subject using an identical acquisition protocol on the same scanner for all imaging time points.

**Note: Use of CT component of a PET/CT scanner:**

Combined modality scanning such as with FDG-PET/CT is increasingly used in clinical care, and is a modality/technology that is in rapid evolution; therefore, the recommendations outlined here may change rather quickly with time. At present, low dose or attenuation correction CT portions of a combined FDG-PET/CT are of limited use in anatomically based efficacy assessments and it is therefore suggested that they should not be substituted for dedicated diagnostic contrast enhanced CT scans for anatomically based RECIST measurements. However, if a site can document that the CT performed as part of a FDG-PET/CT is of identical diagnostic quality to a diagnostic CT (with IV and oral contrast) then the CT portion of the FDG-PET/CT can be used for RECIST 1.1measurements. Note, however, that the FDG-PET portion of the CT introduces additional data which may bias an investigator if it is not routinely or serially performed.

**MRI Brain**

MRI or CT of brain is required at screening in order to rule out active metastatic disease. For patients with a history of known brain metastasis, an MRI brain is required at baseline. A CT brain is not allowed for patients with known brain metastasis at baseline. Subjects with a history of brain metastasis should have surveillance MRI approximately every 12 weeks, or sooner if clinically indicated.

## 5.4 Efficacy Assessments

Study evaluations will take place in accordance with the flow charts in Section 5.1. Baseline assessments should be performed within 28 days prior to the first dose utilizing CT or MRI. In addition to chest, abdomen, pelvis, and brain, all known sites of disease should be assessed at baseline. Subsequent assessments should include chest, abdomen, and pelvis, and all known sites

of disease and should use the same imaging method as was used at baseline. Subjects will be evaluated for tumor response beginning 6 weeks (± 1 week) from first dose and continuing every 6 weeks (± 1 week) for the first 24 weeks and every 12 weeks (± 1 week) thereafter, while on treatment or on treatment hold for any reason until disease progression and treatment discontinuation, whichever occurs later. Additionally, with the exception of crossover participants, tumor assessments will not be required upon initiation of subsequent anti-cancer therapy. Tumor assessments for ongoing study treatment decisions will be completed by the investigator using RECIST (Response Evaluation Criteria in Solid Tumors) 1.1 criteria (Appendix 3).

### 5.4.1 Primary Efficacy Assessment

The primary endpoint is objective response rate (ORR) in all assigned subjects as determined by the investigators. ORR is defined as the number of subjects with a best overall response (BOR) of complete response (CR) or partial response (PR) divided by the number of assigned subjects. The investigator-determined ORR will be further characterized by the investigator-determined duration of response (DOR) and the magnitude of reduction in tumor volume. ORR and DOR will be assessed by BICR in selected tumor types.

### 5.4.2 Best Overall Response

The best overall response is determined once all the data for the subject is known. It is defined as the best response designation, as determined by the investigator or BICR for selected tumor types, recorded between the date of first treatment and the date of objectively documented progression per RECIST1.1 or the date of subsequent therapy, whichever occurs first. For subjects without documented progression or subsequent therapy, all available response designations will contribute to the BOR assessment. The subject'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.

Complete or partial responses may be claimed only if the criteria for each are met at a subsequent time point (minimum 4 weeks after criteria of objective response are first met). In this circumstance, the best overall response can be interpreted as in Table 5.4.2-1.

**Table 5.4.2-1: Best overall response when confirmation of CR and PR required**

| Overall Response First Timepoint | Overall Response Subsequent Timepoint | Best Overall response |
|---|---|---|
| CR | CR | CR |
| CR | PR | SD, PD or PR[a] |
| CR | SD | SD provided minimum criteria for SD duration met, otherwise, PD |
| CR | PD | SD provided minimum criteria for SD duration met, otherwise, PD |
| CR | NE | SD provided minimum criteria for SD duration met, |

**Table 5.4.2-1: Best overall response when confirmation of CR and PR required**

| Overall Response First Timepoint | Overall Response Subsequent Timepoint | Best Overall response |
|---|---|---|
| | | otherwise NE |
| PR | CR | PR |
| PR | PR | PR |
| PR | SD | SD |
| PR | PD | SD provided minimum criteria for SD duration met, otherwise, PD |
| PR | NE | SD provided minimum criteria for SD duration 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.

For purposes of this study, the minimum scan time from baseline for determination of SD will be 6 weeks.

### *5.4.3 Duration of Objective Response*

The duration of objective response is measured from the time measurement criteria are first met for confirmed CR/PR (whichever is first recorded) until the first date that progressive disease is objectively documented (taking as reference for progressive disease the smallest measurements recorded on study).

### *5.4.4 Immune related Response Criteria*

Immune related response criteria using unidimensional measurements may be used to describe tumor shrinkage following RECIST 1.1 defined disease progression.[83] The methodology is the same as described above for RECIST 1.1 except for:

- New lesions do not automatically denote disease progression
- The measurement of longest diameter of new measurable lesions are in included in the sum of the measurements of the original target lesions.

Best immune related responses, for subjects who have progression followed by tumor shrinkage are classified as irCR (disappearance of all lesions) or irPR (≥ 30% reduction from baseline).

## 5.5 Pharmacokinetic Assessments

Serum samples for nivolumab and ipilimumab PK and immunogenicity assessments will be collected for all subjects.

### *5.5.1 Pharmacokinetics: Collection and Processing*

A detailed schedule of PK and immunogenicity evaluations is provided in Table 5.5.1-1, Table 5.5.1-2, Table 5.5.1-3, and Table 5.5.1-4. All timepoints are relative to the start of study drug administration. Pre-dose samples should be taken within 30 minutes prior to the start of the first infusion for the day (prior to the nivolumab dose). All on-treatment PK timepoints are intended to align with days on which study drug is administered, if dosing occurs on a different day due to minor scheduling shifts, the PK sampling should be adjusted accordingly. If PK and immunogenicity samples are drawn but study drug(s) is not administered on the same day, samples will be retained and analyzed as planned. There is no need to collect another sample when the dose is resumed. Further details of sample collection, processing, and shipment will be provided in the laboratory procedures manual.

**Table 5.5.1-1: Pharmacokinetic & Immunogenicity Sampling Schedule - Arm N-I (Dose level 2 and 2b)**

| Study Day[a] | Event | Time (Relative to Start of Infusion) Hour: Min | Nivolumab PK Blood Sample | Nivolumab Immunogenicity Sample | Ipilimumab PK Blood Sample | Ipilimumab Immunogenicity Sample |
|---|---|---|---|---|---|---|
| D1 Week 1 | Predose[b] | 00:00 | X | X | X | X |
| D1 Week 4 | Predose | 00:00 | X | X | X | X |
| D1 Week 10 | Predose | 00:00 | X | X | X | X |
| D1 Week 13 | Predose | 00:00 | X | X | | |
| D1 Week 25 | Predose | 00:00 | X | X | | |
| Day 1 of every 16th week until discontinuation of study treatment or completion of 2 years of study treatment | Predose | 00:00 | X | X | | |

[a] If ipilimumab is discontinued and nivolumab continues, ipilimumab PK and Immunogenicity should be collected only for the next 2 timepoints (corresponding to ipilimumab sample collection) according to the PK table. If ipilimumab is discontinued, nivolumab will follow the same schedule as originally planned for that subject.

[b] Predose samples for nivolumab and ipilimumab should both be collected prior to start of nivolumab infusion (preferably within 30 minutes). If the infusion is delayed and a pre-dose sample is already collected, there is no need to collect an additional pre-dose sample.

**Table 5.5.1-2: Pharmacokinetic & Immunogenicity Sampling Schedule - Arm N**

| Study Day | Event | Time (Relative to Start of Infusion) Hour: Min | Nivolumab PK Blood Sample | Nivolumab Immunogenicity Sample | Ipilimumab PK Blood Sample | Ipilimumab Immunogenicity Sample |
|---|---|---|---|---|---|---|
| **All Subjects in Arm N** | | | | | | |
| D1 Week 1 | Predose | 00:00 | X | X | | |
| D1 Week 3 | Predose | 00:00 | X | X | | |
| D1 Week 5 | Predose | 00:00 | X | X | | |
| D1 Week 13 | Predose | 00:00 | X | X | | |
| Day 1 of every 16th week until discontinuation of study treatment or completion of 2 years of study treatment | Predose | 00:00 | X | X | | |
| **Crossover Subjects Only (SCLC subjects from the expansion cohorts under or after Amendment 09 are excluded from this option)** | | | | | | |
| Crossover D1 Week 1 | Predose[a] | 00:00 | X | X | X | X |
| Crossover D1 Week 4 | Predose | 00:00 | X | X | X | X |
| Crossover D1 Week 10 | Predose | 00:00 | X | X | X | X |
| Crossover D1 Week 13 | Predose | 00:00 | X | X | | |
| Crossover D1 Week 25 | Predose | 00:00 | X | X | | |
| Day 1 of every 16th week until discontinuation of study treatment or completion of 2 years of study treatment | Predose | 00:00 | X | X | | |

[a] Predose samples for nivolumab and ipilimumab should both be collected prior to start of nivolumab infusion (preferably within 30 minutes). If the infusion is delayed and a pre-dose sample is already collected, there is no need to collect an additional pre-dose sample.

**Table 5.5.1-3: Pharmacokinetic & Immunogenicity Sampling Schedule - Arm N-I (Dose level 2c)**

| Study Day[a] | Event | Time (Relative to Start of Infusion) Hour: Min | Nivolumab PK Blood Sample | Nivolumab Immunogenicity Sample | Ipilimumab PK Blood Sample | Ipilimumab Immunogenicity Sample |
|---|---|---|---|---|---|---|
| D1 Week 1 | Predose[b] | 00:00 | X | X | X | X |
| D1 Week 7 | Predose | 00:00 | X | X | X | X |
| D1 Week 19 | Predose | 00:00 | X | X | X | X |
| After Week 19 Day 1, Day 1 of every 18th week until discontinuation of study treatment or completion of 2 years of study treatment | Predose | 00:00 | X | X | X | X |

[a] If ipilimumab is discontinued and nivolumab continues, ipilimumab PK and Immunogenicity should be collected only for the next 2 timepoints (corresponding to ipilimumab sample collection) according to the PK table.

[b] Predose samples for nivolumab and ipilimumab should both be collected prior to start of nivolumab infusion (preferably within 30 minutes). If the infusion is delayed and a pre-dose sample is already collected, there is no need to collect an additional pre-dose sample.

**Table 5.5.1-4: Pharmacokinetic & Immunogenicity Sampling Schedule for Arm N-I Combined with Cobimetinib (Dose level 2d) (Nivolumab and Ipilimumab Sample Collections)**

| Study Day (1 Cycle =6 Weeks) | Event | Time (Relative to Start of Infusion) Hour: Min | Nivolumab PK Blood Sample | Nivolumab Immunogenicity Sample | Ipilimumab PK Blood Sample | Ipilimumab Immunogenicity Sample |
|---|---|---|---|---|---|---|
| D1 Week 1 (D1 Cycle 1) | predose | 00:00 | X | X | X | X |
| D1 Week 3 (D15 Cycle 1) | predose | 00:00 | X | X | X | X |
| D1 Week 9 (D15 Cycle 2) | predose | 00:00 | X | X | X | X |
| D1 Week 15 (D15 Cycle 3) | predose | 00:00 | X | X | X | X |
| D1 Week 21 (D15 Cycle 4) | predose | 00:00 | X | X | X | X |
| Day 1 of every 24th (4 cycles) week after week 21 until discontinuation of study treatment or completion of 2 years of study treatment | predose | 00:00 | X | X | X | X |

Note: Predose samples should be collected just prior to the start of infusion on the day the study drug is administered

## 5.6 Biomarker Assessments

### *5.6.1 Rationale and Aims for Biomarker Assessments*

The biological basis of nivolumab and ipilimumab in the treatment of oncological disease is to modulate the immune system to both generate and restore a durable anti-tumor response leading to clearance of tumor. The clinical data generated with the monotherapy and combination therapy supports the hypothesis that blockade of PD-1 and CTLA-4 pathways results in rejection of tumor by the host immune system.

The precise mechanisms by which nivolumab and ipilimumab exert their anti-tumor activity is unclear, however, particular cell types, such as effector T cells and regulatory T cells are critical for the anti-tumor response. Nivolumab and ipilimumab appear to have distinct mechanisms of action, based on signaling of the PD-1 and CTLA-4 pathways, and the observations of a rise in Absolute Lymphocyte Count elevations in ipilimumab, but not nivolumab, therapy. In addition,

the role of the MEK inhibitor cobimetinib in recruiting intratumoral CD8 T cells and the upregulation of class I MHC may be investigated.

Therefore, the major hypotheses that will be addressed by the biomarker plan for CA209032 are:

- Does Expression of PD-L1 on tumor cells prior to therapy correlate with clinical efficacy to monotherapy or combination therapy?
- Does the mutational status of tumor cells (ie KRAS, EGFR) or tumor infectivity (H. pylori, HPV) correlate with clinical efficacy to monotherapy or combination therapy?
- Can we define distinct pharmacodynamic markers of monotherapy and combination therapy in the peripheral compartment?
- How does monotherapy or combination therapy alter the activating and negative costimulatory molecules on immune cells in the periphery and at the tumor site? Are there distinct mechanisms of resistance to monotherapy and combination therapy?
- Is the intratumoral or peripheral T cell repertoire predictive of response to monotherapy or combination therapy?
- Does the composition and phenotype of the tumor microenvironment, at baseline, or on-treatment, correlate with clinical efficacy?

Peripheral blood and tumor tissue will be collected prior to therapy and at selected timepoints on treatment. Additionally, blood and tumor samples of ovarian cancer patients will be evaluated for Breast Cancer 1 and 2 (BRCA1/BRCA2) and Homologous Recombinant Deficiency (HRD) gene expression. Residual sample material available after completion of the designated analyses may be used in the future for identification of additional pharmacodynamic or predictive markers or to enhance understanding of disease biology. If biomarker samples are drawn but study drug(s) is not administered, samples will be retained. A detailed description of each assay system is described below and a schedule of pharmacodynamic evaluations are provided in Table 5.6.8.6-1.

### 5.6.2 Biomarker Sampling in Crossover Patients

Mandatory peripheral blood and serum will be drawn if crossing over into Arm N-I from Arm N. SCLC subjects from the expansion cohorts under or after Amendment 09 are excluded from the crossover option. The timing of these draws will occur on the day of, but prior to, the first N-I dose. Biomarker draws do not have to be taken from crossover patients if sampling was performed within 7 days of the first combination dose. Follow-up biomarker collections will occur according to Table 5.6.8.6-1.

Tumor biopsy samples are optional, but encouraged, and can occur at any point before the first dose of N-I and after the last dose of N.

[redacted]

[redacted]

## 5.8 Other Assessments

[redacted]

### *5.8.2 Pharmacogenetic Research*

Pharmacogenetic sample collection will be performed at sites that permit pharmacogenetic studies to be conducted in compliance with all applicable laws, rules, and regulations. To participate in the Pharmacogenetic Sample Amendment, subjects must provide a signed Pharmacogenetic Blood DNA informed consent and must have consented to participate in this main clinical trial. Please refer to Amendment 01 and 07 for further information.

### *5.8.3 Demographics and Medical History*

At Screening, information regarding subject's demographics and medical history including date of birth, gender, race and ethnicity, general medical history, tobacco use, potential risk factors for pulmonary related events, disease diagnosis including diagnosis itself, date of initial diagnosis, disease stage at initial diagnosis, cell type, disease classification for SCLC only, current disease diagnosis with date and stage, HER-2 status, receptor status, prior surgery, radiotherapy, and all prior lines of systemic cancer therapies with agents, start and stop dates, best response to the therapy and date of progression after each treatment line will be collected. For SCLC and Ovarian cancer subjects, evaluation of Platinum-free interval (PFI) from the completion of any platinum-based chemotherapy and subsequent disease progression, and Treatment-free-interval (TFI) from the completion of any other cytotoxic or targeted based prior treatment line and subsequent disease progression will be collected. For Ovarian Cancer, information about BRCA and Homologous Recombinant Deficiency (HRD), if available, will be collected.

## 5.9 Blinded Independent Central Review (BICR)

A Blinded Independent Central Review (BICR) will be performed for randomized subjects in selected tumor types to determine RECIST 1.1 response for the analysis of ORR, DOR, and PFS. Details of the Imaging responsibilities and procedures will be specified in the Imaging charter.

Sites will be informed of quality issues or the need for repeat scanning via queries from the central imaging vendor. Results of Central Imaging analysis will not be returned to the site.

# 6 ADVERSE EVENTS

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

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

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

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

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

## 6.1 Serious Adverse Events

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

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

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

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

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

**NOTE**:

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

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

- admission encountered for another life circumstance that carries no bearing on health status and requires no medical/surgical intervention (eg, lack of housing, economic inadequacy, caregiver respite, family circumstances, administrative reason)
- hospitalizations for the administration of subsequent anticancer therapy.

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

Following the subject's written consent to participate in the study, all SAEs, whether related or not related to study drug, must be collected, including those thought to be associated with protocol-specified procedures. All SAEs must be collected that occur during the screening period and within 100 days of discontinuation of dosing. Subjects who are randomized but never treated with study drug, must have SAEs collected for 30 days from the date of randomization. If applicable, SAEs must be collected that relate to any later protocol-specified procedure (eg, a follow-up skin biopsy).

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

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

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

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

**SAE Email Address:** See Contact Information list.

**SAE Facsimile Number:** See Contact Information list.

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

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

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

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

All SAEs should be followed to resolution or stabilization.

## 6.2 Nonserious Adverse Events

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

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

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

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

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

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

Immune-mediated adverse events 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.

## 6.3 Laboratory Test Result Abnormalities

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

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

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

## 6.4 Pregnancy

If, following initiation of the investigational product, it is subsequently discovered that a study subject is pregnant or may have been pregnant at the time of study exposure, including during at least 5 half lives after product administration, the investigator must immediately notify the BMS

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

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

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

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

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

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

## 6.5 Overdose

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

## 6.6 Potential Drug Induced Liver Injury (DILI)

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

Potential drug induced liver injury is defined as:

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

## 6.7 Other Safety Considerations

Any significant worsening noted during interim or final physical examinations, electrocardiogram, x-ray filming, any other potential safety assessment required or not required

by protocol should also be recorded as a nonserious or serious AE, as appropriate, and reported accordingly.

### 6.8 Safety Assessments

Safety assessments including targeted physical examination, vital signs and oxygen saturation, physical measurements including weight and ECOG performance status, and laboratory tests including Cell Blood Count (CBC) with differential, Liver Function Tests (LFTs), Blood Urea Nitrogen (BUN) or serum urea level, creatinine, albumin, Ca, Mg, Na, K, Cl, LDH, glucose, amylase, lipase, TSH (if TSH result is abnormal, subsequent testing of Free T4 and Free T3 is required) will be conducted in each treatment cohort as specified in the flow chart in section 5.1.

## 7 DATA MONITORING COMMITTEE AND OTHER EXTERNAL COMMITTEES

Ipilimumab has been studied in > 13,800 patients in clinical trials while nivolumab has been studied in more than 700 patients in clinical trials. The AE profile of nivolumab appears to be independent of tumor type. The safety of the combination of nivolumab and ipilimumab has been reported in 53 melanoma subjects and the spectrum of adverse events observed among patients treated with the concurrent regimen was qualitatively similar to previous experience with nivolumab or ipilimumab monotherapy. Adverse events observed with the combination therapy were manageable and generally reversible with the use of existing treatment algorithms. In addition, this is an open label study. Therefore, a data monitoring committee will not be utilized for this Phase 1/2 study.

The subjects' safety will be monitored on an ongoing basis. Safety conference calls with investigators and representatives of the sponsor will be held approximately once a month with additional meetings as necessary. The BMS medical monitor is a physician responsible for reviewing, on a systematic and continuous basis, the safety of patients on this study. This includes a review of serious and non-serious adverse events, which includes all hematological and non-hematological events.

In addition, a BMS medical safety team (MST) routinely reviews safety signals across the entire nivolumab program including combination studies with ipilimumab. The MST is independent from the BMS medical monitor. The MST has the primary responsibility within Bristol-Myers Squibb for assessing emerging safety trends, identifying potential safety signals, notifying appropriate stakeholders of relevant findings, and implementing risk management plans.

The MST is responsible for reviewing data from all sources including non-clinical studies and clinical trials, monitoring the progress of various nivolumab safety support activities, and recommending and implementing necessary changes to the safety plan and any other specific safety-related activities.

# 8 STATISTICAL CONSIDERATIONS

## 8.1 Sample Size Determination

**Sample Size determination in the original protocol**

This study comprises a Dose Escalating Safety Evaluation Phase for the Combination Arm, followed by a Staged Enrollment for Arm N and Arm N-I.

In the original protocol, gastric cancer, SCLC, TNBC, and pancreatic cancer are included and the Staged Enrollment Part utilizes a modified Simon two-stage design[95] with the treatment of 40 subjects to evaluate whether nivolumab or the combination of nivolumab/ipilimumab yields an objective response rate (ORR) that is of clinical interest. In this study, an ORR of 10% or less is considered not of clinical value, and an ORR of 25% or greater is considered of strong clinical interest. The modified Simon design evaluates the null hypothesis that the true response rate is ≤ 10% versus the alternative hypothesis that the true response rate is > 10%. The 2-stage testing within each cohort targets a Type I error rate of 5% and has 80% power to reject the null hypothesis if the true response rate is 25%.

**Sample Size determination for bladder cancer cohort**

In Amendment 06, the bladder cohort is added. A one stage design with the treatment of 60 - 100 subjects is used for nivolumab monotherapy and the dose level 2b. These sample sizes will provide 90% to 97% power to reject the null hypothesis of 10% response rate if the true response rate is 25% with a two-sided Type I error rate of 5%.

In Amendment 14, the dose level 2 arm (nivolumab 1 mg/kg + ipilimumab 3 mg/kg) of the bladder cancer cohort is to enroll and treat a total of 92 subjects. A one stage design will be used. Based on a 19.6% ORR for nivolumab monotherapy (CA209275), the sample size of 92 in this arm will provide 93% power to reject the null hypothesis of 19.6% response rate if the true response rate is 35% with a two-sided Type I error rate of 5%.

**Sample Size determination for SCLC expansion cohort**

In Amendment 09, in addition to the original two-stage design in the SCLC cohort, additional SCLC expansion cohort subjects will be randomized in a 3:2 ratio to one of two expansion groups: Arm A (150 subjects, nivolumab mono 3 mg/kg q2w) or Arm B (100 subjects, nivolumab 1 mg/kg + ipilimumab 3 mg/kg q3w) and will be stratified by number of prior treatment lines (1 vs 2 prior chemotherapy regimens).

Based on SCLC data so far observed in this study with an ORR of about 10% for nivolumab monotherapy and about 23% for the nivolumab + ipilimumab combination therapy, sample sizes of N = 150 for nivolumab monotherapy and N = 100 for nivolumab + ipilimumab combination therapy (nivolumab 1 mg/kg + ipilimumab 3 mg/kg) will target a Type I error rate of 5% (two-sided) and will have 78% power to detect the difference between these two arms if the true response rates are 10% and 23%, respectively.

**Sample Size determination for ovarian cancer cohort**

Also in Amendment 09, an ovarian cancer cohort is added and a one stage design with the treatment of 40 subjects for each combination will be used. These sample sizes will provide 79% power to reject the null hypothesis of 10% response rate, if the true response rate is 25% with a two-sided Type I error rate of 5%.

**Sample Size determination for the additional pancreatic cancer cohort**

A one stage design will be used, with the treatment of 30 subjects with nivolumab 3 mg/kg every 2 weeks, ipilimumab 1 mg/kg every 6 weeks, and cobimetinib 60 mg po qd 21 days on/7 days off. This sample size will provide 70% power to reject the null hypothesis of 10% response rate if the true response rate is 25% with a two-sided Type I error rate of 5%.

## 8.2 Populations for Analyses

- All Enrolled Subjects: All subjects who signed an informed consent form and were registered into the IVRS.
- All Assigned Subjects: All subjects who were assigned to the highest tested tolerated dose level in the Dose Escalating Safety Evaluation Phase or to any treatment group during the Staged Enrollment Phase.
- All Treated Subjects: All subjects who received at least one dose of any study medication.
- All PK Subjects: All assigned subjects with available serum time-concentration data.
- All Immunogenicity Subjects: All treated subjects with baseline and at least 1 post baseline immunogenicity assessment.
- All Crossover Subjects: All treated subjects who crossed over from Arm N to Arm N-I. SCLC subjects from the expansion cohorts under or after Amendment 09 are excluded from the crossover option.
- All PD-L1 tested subjects: All subjects who had a tumor tissue sample available for assessment of PD-L1 expression at baseline.
- All treated, PD-L1 tested subjects: All PD-L1 tested subjects who received at least one dose of study treatment.
- All PD-L1 evaluable subjects: All treated PD-L1 tested subjects with quantifiable PD-L1 expression.

*Those subjects in the Dose Escalation Safety Evaluation Phase who received at least one dose of the highest dose level confirmed for further investigation will be counted as part of the required 18 treated subjects for Stage 1. In addition to being included in the All Treated Subjects population, those subjects will also be included in the All Dose Escalation Subjects population. Those subjects in the Dose Escalation Safety Evaluation Phase who received at least one dose of a dose level that was not confirmed for further investigation will not be included in the All Treated Subjects population.

## 8.3 Endpoints

The endpoint definitions apply to all cohorts, unless otherwise specified.

### 8.3.1 Primary Endpoint(s)

The primary endpoint is the objective response rate (ORR). The ORR is defined as the number of subjects with a best overall response (BOR) of complete response (CR) or partial response (PR) divided by the number of treated subjects. The BOR is defined as the best response designation, as determined by the investigator or BICR for selected tumor types, recorded between the date of randomization or treatment assignment and the date of objectively documented progression per RECIST 1.1 or the date of subsequent anti-cancer therapy, whichever occurs first. CR or PR determinations included in the BOR assessment must be confirmed by a second scan no less than 4 weeks after the criteria for response are first met. For subjects without documented progression or subsequent therapy, all available response designations will contribute to the BOR assessment. For subjects who continue treatment beyond progression, the BOR should be determined based on response designations recorded up to the time of the initial RECIST 1.1-defined progression.

For the SCLC expansion cohort, the estimated difference along with its corresponding p-value of ORR assessed by BICR between nivolumab monotherapy and nivolumab / ipilimumab combination therapy (nivolumab 1 mg/kg + ipilimumab 3 mg/kg) will be provided. In addition, 95% CI (two-sided) will also be presented for the estimated difference of ORR between nivolumab monotherapy and nivolumab / ipilimumab combination therapy.

Similar methods will be used to summarize ORR for each stratification factor (no p-value will be provided).

ORR will be further characterized by the duration of response (DOR) and the magnitude of reduction in tumor volume. DOR will be computed for subjects with a BOR of PR or CR and is defined as the time from first confirmed response (CR or PR) to the date of the first documented tumor progression as determined using RECIST 1.1 criteria or death due to any cause, whichever occurs first. For subjects who neither progress nor die, the DOR will be censored using the same censoring algorithm as used for PFS in Section 8.3.2. The magnitude of reduction in tumor volume is defined as the percent decrease in tumor volume from baseline to nadir, observed up until the time of the first documented tumor progression or death.

These measures of response will be interpreted in the context of historical responses observed following treatment with approved agents.

### 8.3.2 Secondary Endpoint(s)

The secondary objective (to assess the safety and tolerability of nivolumab monotherapy, nivolumab combined with ipilimumab in subjects with advanced or metastatic tumors, or nivolumab combined with ipilimumab and cobimetinib in subjects from the additional pancreatic cancer cohort only will be primarily assessed by the rate of treatment-related AEs leading to drug discontinuations during the first 12 weeks of treatment. In addition, safety and tolerability will be analyzed through the incidence of adverse events, serious adverse events, and specific laboratory abnormalities (worst grade) in each cohort. Toxicities will be graded using the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) version 4.0.

PFS is defined as the time from treatment assignment in IVRS to the date of the first documented tumor progression, as determined by the investigator or BICR for selected tumor types (per RECIST 1.1), or death due to any cause, whichever occurs first. Subjects who die without a reported prior progression will be considered to have progressed on the date of their death. Subjects who did not progress or die will be censored on the date of their last evaluable tumor assessment. Subjects who did not have any on-study tumor assessments and did not die will be censored on the date they were assigned treatment in the IVRS. Subjects who started anti-cancer therapy either prior to death or without a prior reported progression will be censored on the date of their last evaluable tumor assessment prior to the initiation of subsequent anti-cancer therapy.

OS is defined as the time between the date of treatment assignment in IVRS and the date of death due to any cause. A subject who has not died will be censored at the last known alive date. OS will be followed continuously while subjects are on the study drug and every 3 months via in-person or phone contact after subjects discontinue the study drug.

[redacted]
index.

## 8.4 Analyses

### *8.4.1 Demographics and Baseline Characteristics*

Demographic and baseline characteristics will be summarized in all treated subjects by cohort, as randomized or assigned, using descriptive statistics.

### *8.4.2 Efficacy Analyses*

#### *8.4.2.1 Primary Endpoint Methods*

The efficacy analyses will be performed on the all treated population. ORR will be summarized for each cohort by a binomial response rate and corresponding two-sided 95% exact CI using the method proposed by Atkinson and Brown[96] for cohorts using two-stage design and the Clopper-Pearson method for cohorts using the one stage design[97].

For SCLC expansion cohort, the estimated difference along with its corresponding p-value of ORR assessed by BICR between nivolumab monotherapy and nivolumab/ipilimumab combination therapy (nivolumab 1 mg/kg + ipilimumab 3 mg/kg) will also be presented with 95% CI. Similar methods will be used to summarize ORR for each stratification factor. However the p-value will not be provided for each stratification factor.

DOR as determined by the investigator or BICR for selected tumor types will be summarized for subjects who achieve confirmed PR or CR using the Kaplan-Meier (KM) product-limit method. The median value, along with two-sided 95% CI using the Brookmeyer and Crowley method,

will also be calculated by cohort. In addition, the percentage of responders still in response at different time points (3, 6, and 12 months) will be presented based on the KM plot.

The magnitude of reduction in tumor burden will be summarized descriptively. Immune related responses will be summarized descriptively.

#### *8.4.2.2 Secondary Endpoint Methods*

PFS and OS will be summarized descriptively using Kaplan-Meier methodology. Median values of PFS and OS, along with two-sided 95% CIs using the Brookmeyer and Crowley method, will be calculated for each cohort. PFS rates at 6 and 12 months, and OS rates at 12 and 24 months will also be estimated. Associated two-sided 95% CIs will be calculated using the Greenwood formula. Additional survival analysis may be conducted for up to 5 years beyond analysis of the primary endpoint.

[redacted]

### *8.4.3 Safety Analyses*

Safety analyses will be performed in all treated subjects. Descriptive statistics of safety will be presented using National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) version 4.0. All on-study AEs, Grade 3-4 AEs, treatment-related AEs, Grade 3-4 treatment-related AEs, SAEs, treatment-related SAEs, and AEs leading to discontinuation will be tabulated using worst grade per NCI CTCAE v 4.0 criteria by system organ class and preferred term. On-study lab parameters including hematology, chemistry, liver function, and renal function and Grade 3-4 Lab Abnormalities will be summarized using worst grade NCI CTCAE v 4.0 criteria.

### *8.4.4 Pharmacokinetic Analyses*

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

[redacted].

### *8.4.6 Outcomes Research Analyses*

Subject's overall health state on a visual analog scale (EQ-VAS) at each assessment time point will be summarized using descriptive statistics by treatment arm (N and N-I), as randomized or assigned.

Proportion of subjects reporting problems for the 5 EQ-5D dimensions at each assessment time point will be summarized by level of problem and by treatment group, as randomized or assigned. Percentages will be based on number subjects assessed at assessment time point.

A by-subject listing of EQ-5D with the problem levels for each of the 5 dimensions (mobility, self-care, usual activities, pain/discomfort and anxiety/depression), health state (5 dimensions digits combined in a 5-digit number) and EQ-VAS will be provided.

[redacted]

## 8.5 Interim Analyses

Data will be reviewed during the Dose Escalation Safety Evaluation Phase to determine the maximum tolerated dose level for arm N-I and to make decisions about Stage 2 for each cohort using Simon's 2-stage design. The decision to proceed from Stage 1 to Stage 2 will be conducted for each tumor type and for each treatment arm independently.

An interim analysis may be conducted after Stage 1, by cohort. This interim analysis may be triggered if a "super" response (ie, 8 or more responders out of 18 subjects) is observed or if it is necessary in order to make decisions regarding further development. Summaries and listings of efficacy and safety will be provided. This interim analysis will not impact the study duration and the trial will continue as planned.

Interim analyses may be conducted for supporting internal decision making or for external data disclosure purposes by cohort, depending upon the maturity of the data.

# 9 STUDY MANAGEMENT

## 9.1 Compliance

### *9.1.1 Compliance with the Protocol and Protocol Revisions*

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

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

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

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

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

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

### *9.1.2 Monitoring*

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

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

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

### *9.1.3 Investigational Site Training*

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

## 9.2 Records

### *9.2.1 Records Retention*

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

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

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

### 9.2.2 Study Drug Records

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

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

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

### 9.2.3 Case Report Forms

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

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

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

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

The completed CRF, including any paper or electronic SAE/pregnancy CRFs, must be promptly reviewed, signed, and dated by the investigator or qualified physician who is a subinvestigator and who is delegated this task on the Delegation of Authority Form For electronic CRFs, review

and approval/signature is completed electronically through the BMS electronic data capture tool. The investigator must retain a copy of the CRFs including records of the changes and corrections.

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

## 9.3 Clinical Study Report and Publications

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

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

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

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

# 10 GLOSSARY OF TERMS

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

# 11 LIST OF ABBREVIATIONS

| Term | Definition |
|---|---|
| AE | adverse event |
| ACLS | advanced cardiac life support |
| AI | accumulation index |
| AI_AUC | AUC Accumulation Index; ratio of AUC(TAU) at steady state to AUC(TAU) after the first dose |
| AI_Cmax | Cmax Accumulation Index; ratio of Cmax at steady state to Cmax after the first dose |
| AI_Ctau | Ctau Accumulation Index; ratio of Ctau at steady state to Ctau after the first dose |
| ALT | alanine aminotransferase |
| ANC | absolute neutrophil count |
| ANOVA | analysis of variance |
| aPTT | activated partial thromboplastin time |
| AST | aspartate aminotransferase |
| AT | aminotransaminases |
| AUC | area under the concentration-time curve |
| AUC(INF) | area under the concentration-time curve from time zero extrapolated to infinite time |
| AUC(0-T) | area under the concentration-time curve from time zero to the time of the last quantifiable concentration |
| AUC(TAU) | area under the concentration-time curve in one dosing interval |
| A-V | Atrioventricular |
| β-HCG | beta-human chorionic gonadotrophin |
| BA/BE | bioavailability/bioequivalence |
| BC | Breast cancer |
| BCRA1 | Breast cancer type 1 |
| %BE | percent biliary excretion |
| BICR | Blinded Independent Central Review |
| BID, bid | bis in die, twice daily |
| BLQ | below limit of quantification |
| BMI | body mass index |

| Term | Definition |
|---|---|
| BMS | Bristol-Myers Squibb |
| BP | blood pressure |
| BRt | Total amount recovered in bile |
| %BRt | Total percent of administered dose recovered in bile |
| BUN | blood urea nitrogen |
| C | Celsius |
| C12 | concentration at 12 hours |
| C24 | concentration at 24 hours |
| Ca++ | Calcium |
| CAV | cyclophosphamide, doxorubicin and vincristine |
| 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 |
| CLD | Dialysate clearance of drug from plasma/serum |
| CLNR | nonrenal clearance |
| CLR | renal clearance |
| CLT | total body clearance |
| CLT/F (or CLT) | apparent total body clearance |
| CLT/F/fu or CLT/fu | Apparent clearance of free drug or clearance of free if (if IV) |
| cm | Centimeter |
| Cmax, CMAX | maximum observed concentration |
| Cmin, CMIN | trough observed concentration |
| CNS | Central nervous system |
| CR | Complete response |
| CRC | Clinical Research Center |

| Term | Definition |
|---|---|
| CRF | Case Report Form, paper or electronic |
| CT | Computed tomography |
| Ct | Expected concentration at a certain time, usually at the end of an expected future dosing interval (eg, concentration at 24 hours, concentration at 12 hours, etc.) |
| Ctau | Concentration in a dosing interval (eg, concentration at 24 hours, concentration at 12 hours, etc.) |
| CTLA-4 | Cytotoxic T-lymphocyte-associated protein 4 |
| Ctrough | Trough observed plasma concentration |
| CV | coefficient of variation |
| CYP | cytochrome p-450 |
| D/C | Discontinue |
| DCR | Disease control rate |
| dL | Deciliter |
| DLT | Dose limiting toxicity |
| DOR | Duration of response |
| DRt | Total amount recovered in dialysate |
| %DRt | Total percent of administered dose recovered in dialysate |
| DSM IV | Diagnostic and Statistical Manual of Mental Disorders (4th Edition) |
| EA | extent of absorption |
| ECG | Electrocardiogram |
| ECOG | Eastern Cooperative Oncology Group |
| eCRF | Electronic Case Report Form |
| ED | Extensive disease |
| EDC | Electronic Data Capture |
| EEG | electroencephalogram |
| eg | exempli gratia (for example) |
| EMA | European Medicinal Agency |
| EOI | End of Infusion |
| EQ-5D | EuroQol 5 Dimensions Questionnaire |
| ER | Estrogen receptor |

| Term | Definition |
|---|---|
| ESR | Expedited Safety Report |
| EU | European Union |
| F | Bioavailability |
| Fb | fraction of bound drug |
| FDA | Food and Drug Administration |
| FFPE | Formalin-fixed, paraffin-embedded |
| FI | fluctuation Index ([Cmax-Ctau)/Cavg]) |
| FIGO | Federation of Gynecology and Obstetrics |
| FOLFIRINOX | combination of 5-FU, leucovorin, irinotecan, oxaliplatin |
| FRt | total amount recovered in feces |
| %FRt | total percent of administered dose recovered in feces |
| FSH | follicle stimulating hormone |
| %FE | percent fecal excretion |
| fu | fraction of unbound drug |
| FU1 | Follow-up 1 |
| FU2 | Follow-up 2 |
| g | Gram |
| GC | gas chromatography |
| GC | Gastric cancer |
| GCP | Good Clinical Practice |
| G criteria | adjusted R2 value of terminal elimination phase |
| GEJ | Gastro-esophageal junction |
| GEM | Gemcitabine |
| GGT | gamma-glutamyl transferase |
| GFR | glomerular filtration rate |
| h | Hour |
| HBsAg | hepatitis B surface antigen |
| HBV | hepatitis B virus |
| HCV | hepatitis C virus |
| HCO3- | Bicarbonate |

| Term | Definition |
|---|---|
| HER-2 | Human epidermal growth factor receptor 2 |
| HIPAA | ***Health Insurance Portability and Accountability Act*** |
| HIV | Human Immunodeficiency Virus |
| HR | heart rate |
| HRD | homologous recombinant deficiency |
| HRT | hormone replacement therapy |
| IB | Investigator Brochure |
| IC | Informed Consent |
| ICD | International Classification of Diseases |
| ICF | Informed consent form |
| ICH | International Council for Harmonisation |
| ie | id est (that is) |
| IEC | Independent Ethics Committee |
| IFN | Interferon |
| IMP | investigational medicinal products |
| IND | Investigational New Drug Exemption |
| IRB | Institutional Review Board |
| irCR | Immune related complete response |
| irPR | Immune related partial response |
| irPD | Immune related progression |
| IU | International Unit |
| IV | Intravenous |
| K | slope of the terminal phase of the log concentration-time curve |
| K3EDTA | potassium ethylenediaminetetraacetic acid |
| K+ | Potassium |
| kg | Kilogram |
| KM | Kaplan-Meier |
| $\lambda z$ | terminal disposition rate constant |
| L | Liter |
| LC | liquid chromatography |

| Term | Definition |
|---|---|
| LD | Limited disease |
| LDH | lactate dehydrogenase |
| LFT | Liver function test |
| ln | natural logarithm |
| Lz_Start | The time point starting the log-linear elimination phase defining the terminal half life |
| Lz_End | The time point ending the log-linear elimination phase defining the terminal half life |
| Lz_N | Number of time points in the log-linear elimination phase defining the terminal half life |
| MST | medical safety team |
| mg | Milligram |
| Mg++ | Magnesium |
| MIC | minimum inhibitory concentration |
| min | Minute |
| mIU/ml | Milli international units per millimeter |
| mL | Milliliter |
| mmHg | millimeters of mercury |
| mOS | Median overall survival |
| mRCC | Metastatic renal cell carcinoma |
| MR_AUC(0-T) | Ratio of metabolite AUC(0-T) to parent AUC(0-T), corrected for molecular weight |
| MR_AUC(INF) | Ratio of metabolite AUC(INF) to parent AUC(INF), corrected for molecular weight |
| MR_AUC(TAU) | Ratio of metabolite AUC(TAU) to parent AUC(TAU), corrected for molecular weight |
| MR_Cmax | Ratio of metabolite Cmax to parent Cmax, corrected for molecular weight |
| MR_Ctau | Ratio of metabolite Ctau to parent Ctau, corrected for molecular weight |
| MRI | Magnetic resonance imaging |
| MRT | mean residence time |
| MS | mass spectrometry |

| Term | Definition |
|---|---|
| MTD | maximum tolerated dose |
| µg | Microgram |
| N | number of subjects or observations |
| N | Nivolumab monotherapy |
| N-I | Nivolumab in combination with Ipilimumab |
| Na+ | Sodium |
| N/A | not applicable |
| NCCN | ***National Comprehensive Cancer Network*** |
| NCI CTCAE | National Cancer Institute - Common Terminology Criteria for Adverse Events |
| ng | Nanogram |
| NIMP | non-investigational medicinal products |
| NSAID | nonsteroidal anti-inflammatory drug |
| NSCLC | Non-small cell lung cancer |
| ORR | Overall response rate |
| OS | Overall survival |
| PAC | Paclitaxel |
| PARP | ***Poly (ADP-ribose) polymerase*** |
| pAUCe | Extrapolated partial AUC from last quantifiable concentration to infinity |
| Pb | percent of bound drug |
| PBMC | Peripheral blood mononuclear cell |
| PC | Pancreatic cancer |
| pCR | Complete pathological response |
| PD | Pharmacodynamics |
| PD-1 | Programmed death 1 |
| PDL-1 | Programmed cell death 1 ligand 1 |
| PE | Physical Exam |
| PE | Platinum plus etopiside |
| PFI | platinum-free interval |
| PFS | Progression Free Survival |

| Term | Definition |
|---|---|
| PK | Pharmacokinetics |
| PO | per os (by mouth route of administration) |
| PR | Partial response |
| PR | Progesterone receptor |
| PS | Performance status |
| PT | prothrombin time |
| PTT | partial thromboplastin time |
| Pu | percent of unbound drug |
| Q2W | Every two weeks |
| Q3W | Every three weeks |
| QC | quality control |
| QD, qd | quaque die, once daily |
| R2 | coefficient of determination |
| RBC | red blood cell |
| RECIST | Response Evaluation Criteria in Solid Tumors |
| RT-PCR | Reverse transcription-polymerase chain reaction |
| SAE | serious adverse event |
| SCLC | Small cell lung cancer |
| SD | stable disease |
| SD | standard deviation |
| SOC | Standard of care |
| SOP | Standard Operating Procedures |
| sp. | Species |
| Subj | Subject |
| t | Temperature |
| T | Time |
| TAO | Trial Access Online, the BMS implementation of an EDC capability |
| TEN | toxic epidermal necrolysis |
| TFI | Treatment-free-interval |
| T-HALF | Half life |

| Term | Definition |
|---|---|
| T-HALFeff_AUC | Effective elimination half-life that explains the degree of AUC accumulation observed |
| T-HALFeff_Cmax | Effective elimination half-life that explains the degree of Cmax accumulation observed) |
| TID, tid | ter in die, three times a day |
| Tmax, TMAX | time of maximum observed concentration |
| TNBC | Triple negative breast cancer |
| TPC | Treatment of physician's choice |
| TR_AUC(0-T) | AUC(0-T) treatment ratio |
| TR_AUC(INF) | AUC(INF) treatment ratio |
| TR_Cmax | Cmax treatment ratio |
| UR | urinary recovery |
| %UR | percent urinary recovery |
| URt | total amount recovered in urine |
| US | United States |
| %URt | total percent of administered dose recovered in urine |
| UV | Ultraviolet |
| Vss/F (or Vss) | apparent volume of distribution at steady state |
| Vz | Volume of distribution of terminal phase (if IV and if multi-exponential decline) |
| W | Washout |
| WBC | white blood cell |
| WHO | World Health Organization |
| WOCBP | women of childbearing potential |
| x g | times gravity |

# APPENDIX 1 PERFORMANCE STATUS SCALES

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

# APPENDIX 2 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.

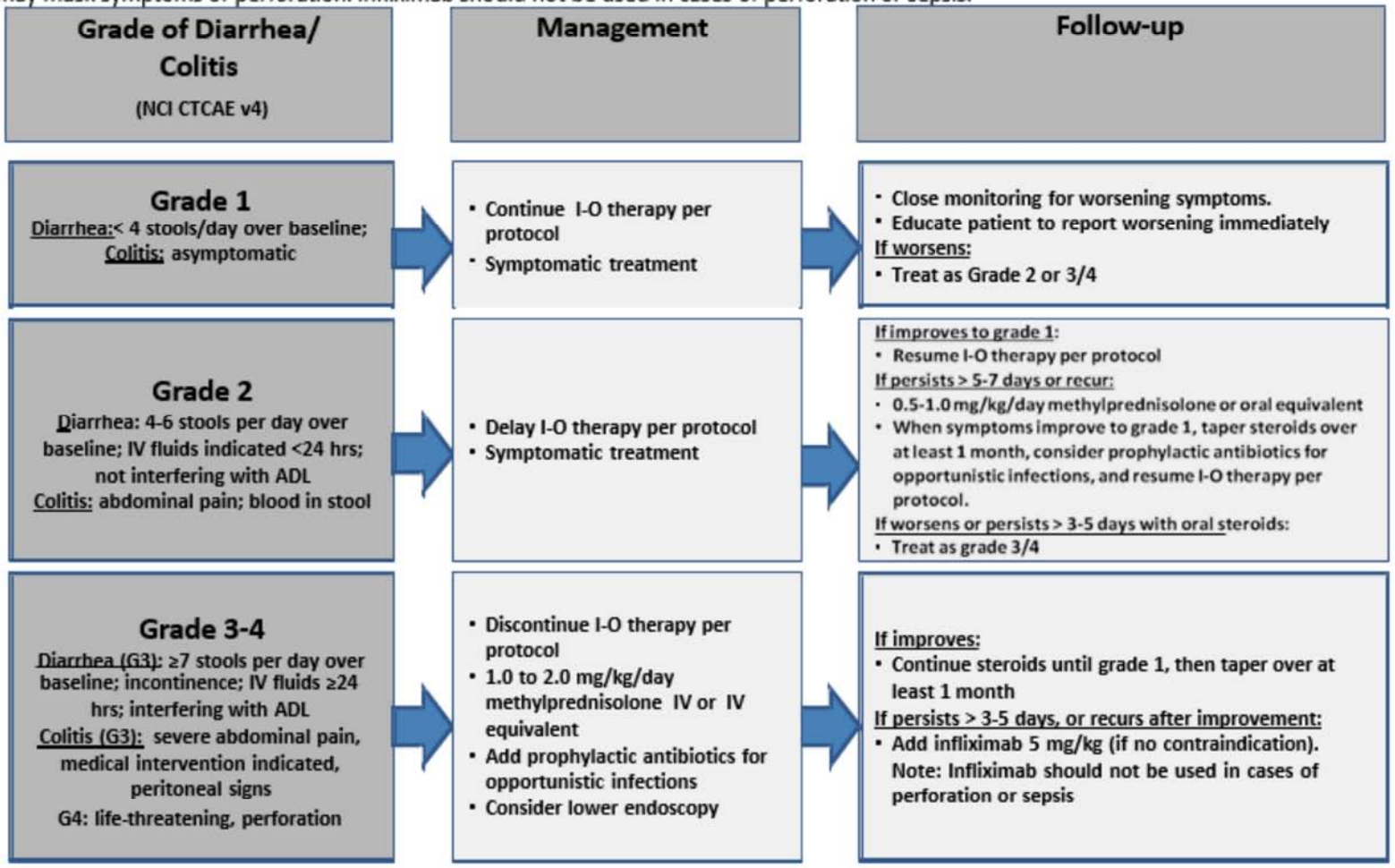
Corticosteroids are a primary therapy for immuno-oncology drug-related adverse events. The oral equivalent of the recommended IV doses may be considered for ambulatory patients with low-grade toxicity. The lower bioavailability of oral corticosteroids should be taken into account when switching to the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

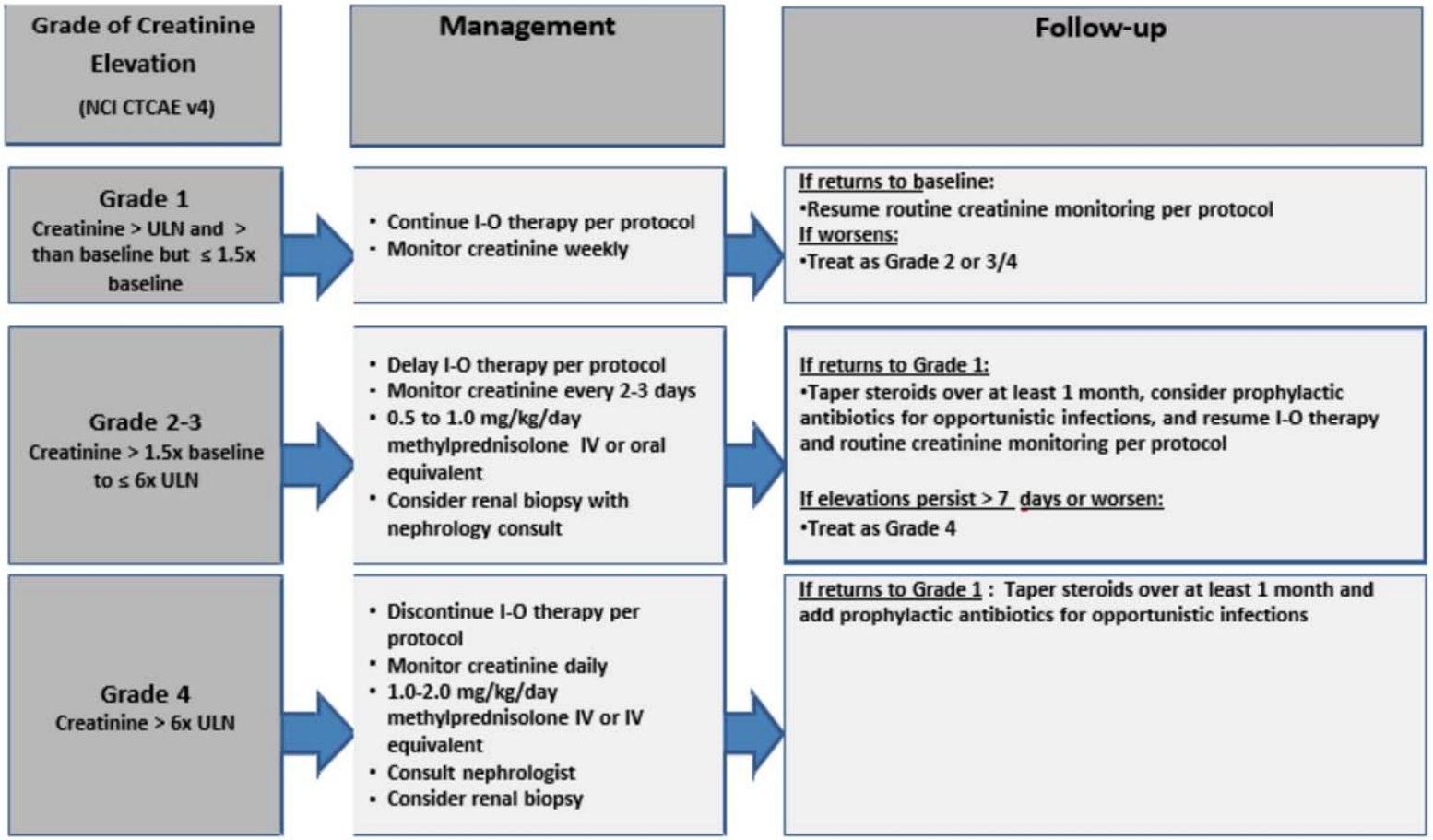



Patients on IV steroids may be switched to an equivalent dose of oral corticosteroids (e.g. prednisone) at start of tapering or earlier, once sustained clinical improvement is observed. Lower bioavailability of oral corticosteroids should be taken into account when switching to the equivalent dose of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

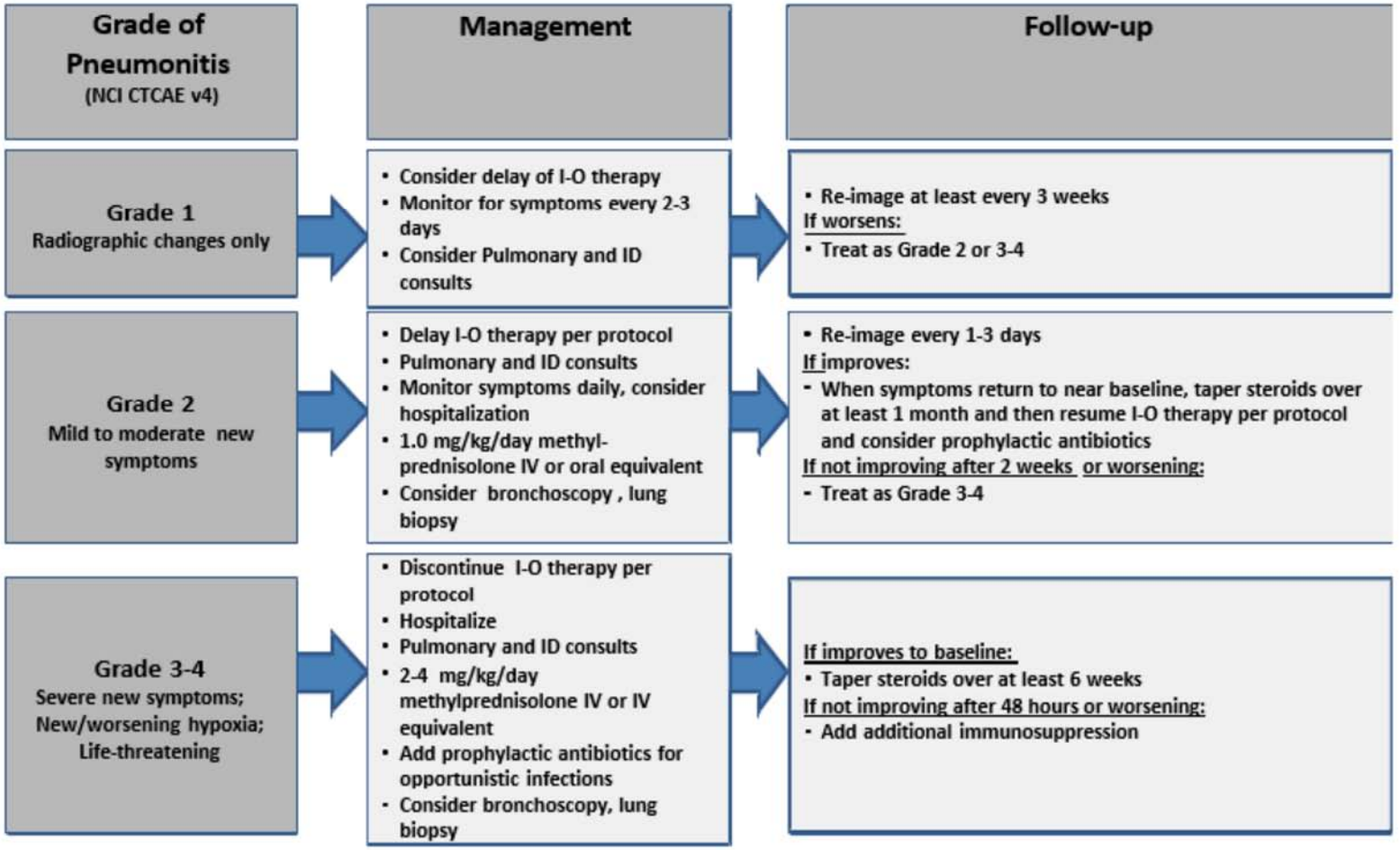



Patients on IV steroids may be switched to an equivalent dose of oral corticosteroids (e.g. prednisone) at start of tapering or earlier, once sustained clinical improvement is observed. Lower bioavailability of oral corticosteroids should be taken into account when switching to the equivalent dose of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

| Grade of Liver Test Elevation (NCI CTCAE v4) | Management | Follow-up |
|---|---|---|
| **Grade 1**<br>AST or ALT > ULN to 3.0 x ULN and/or T. bili > ULN to 1.5 x ULN | • Continue I-O therapy per protocol | • Continue LFT monitoring per protocol<br>If worsens:<br>- Treat as Grade 2 or 3-4 |
| **Grade 2**<br>AST or ALT > 3.0 to ≤ 5 x ULN and/or T. bili > 1.5 to ≤ 3 x ULN | • Delay I-O therapy per protocol<br>- Increase frequency of monitoring to every 3 days | If returns to baseline:<br>•Resume routine monitoring, resume I-O therapy per protocol<br>If elevations persist > 5-7 days or worsen :<br>• 0.5-1 mg/kg/day methylprednisolone or oral equivalent and when LFT returns to grade 1 or baseline, taper steroids over at least 1 month, consider prophylactic antibiotics for opportunistic infections, and resume I-O therapy per protocol |
| **Grade 3-4**<br>AST or ALT > 5 x ULN or T.bili >3 x ULN | • Discontinue I-O therapy*<br>• Increase frequency of monitoring to every 1-2 days<br>• 1.0 to 2.0 mg/kg/day methylprednisolone IV or IV equivalent*<br>• Add prophylactic antibiotics for opportunistic infections<br>- Consult gastroenterologist | If returns to grade 2:<br>- Taper steroids over at least 1 month<br>If does not improve in >3-5 days, worsens or rebounds:<br>• Add mycophenolate mofetil 1 g BID<br>• If no response within an additional 3-5 days, consider other immunosuppressants per local guidelines |

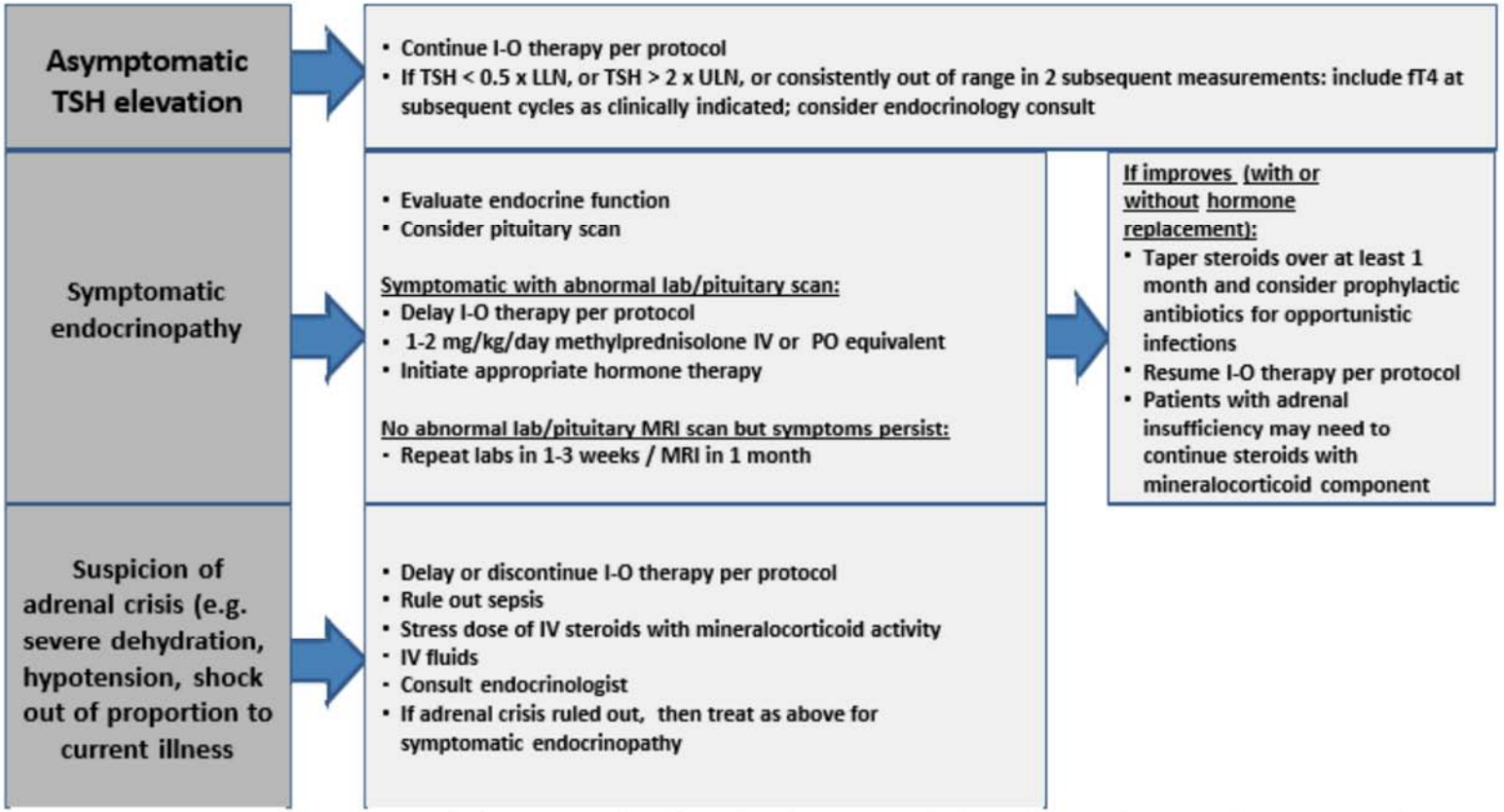
Patients on IV steroids may be switched to an equivalent dose of oral corticosteroids (e.g. prednisone) at start of tapering or earlier, once sustained clinical improvement is observed. Lower bioavailability of oral corticosteroids should be taken into account when switching to the equivalent dose of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

*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.

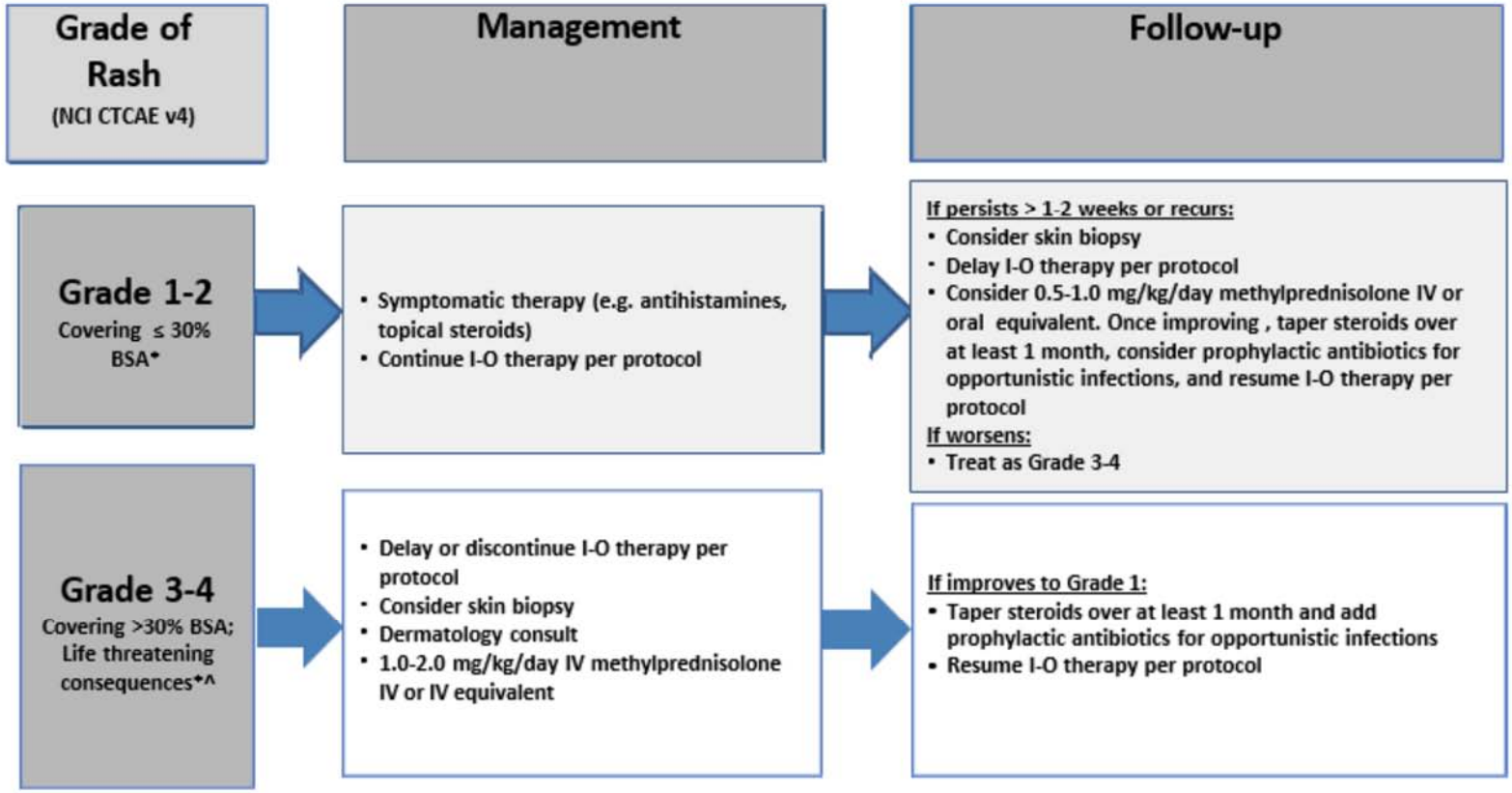



Patients on IV steroids may be switched to an equivalent dose of oral corticosteroids (e.g. prednisone) at start of tapering or earlier, once sustained clinical improvement is observed. Lower bioavailability of oral corticosteroids should be taken into account when switching to the equivalent dose of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

27-Jun-2019

# 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

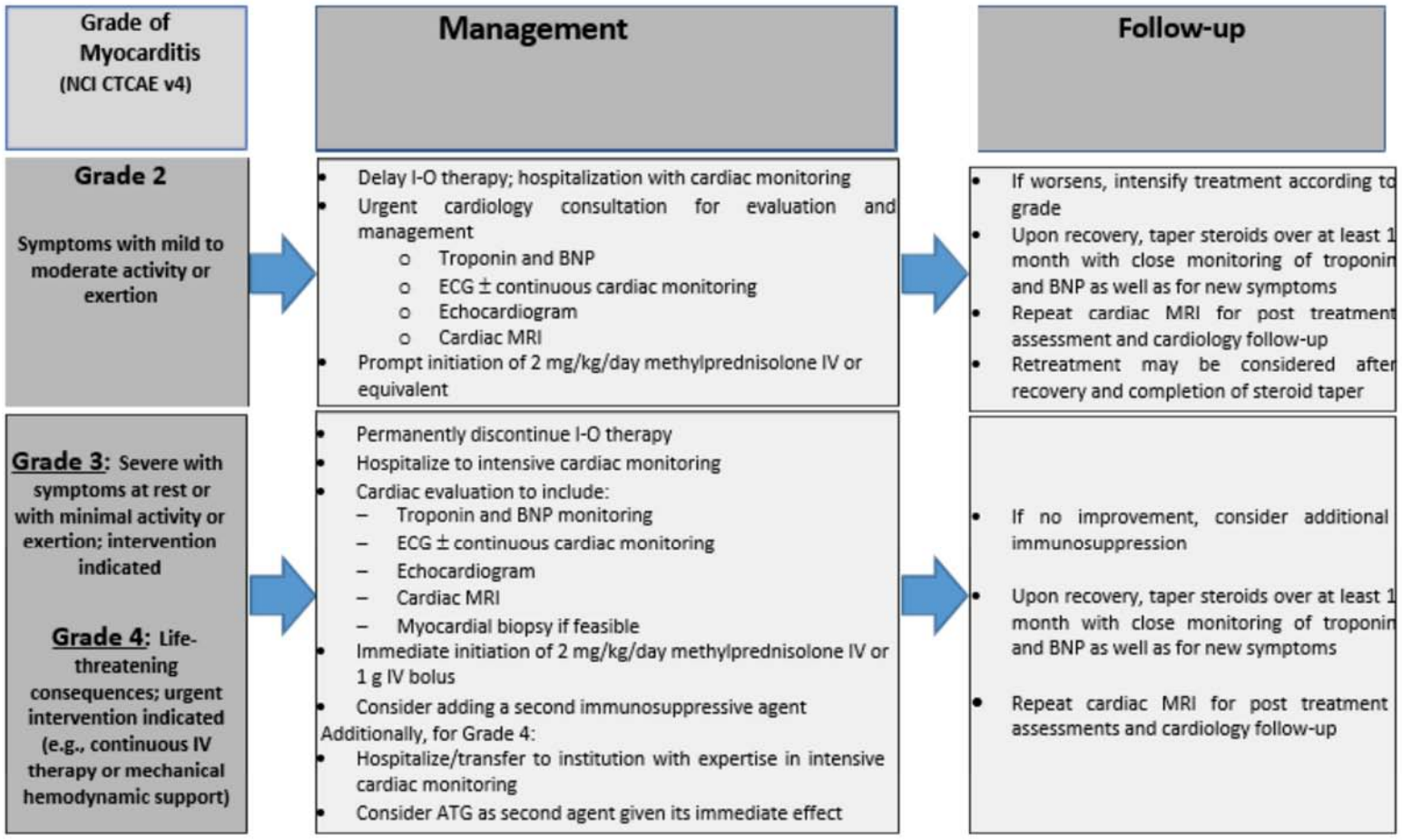
Rule out non-inflammatory causes. If non-inflammatory cause, treat accordingly and continue I-O therapy.

| 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.

27-Jun-2019

# Myocarditis Adverse Event Management Algorithm




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

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

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

27-Jun-2019

# APPENDIX 3 RECIST 1.1

Changes in tumor measurements and tumor responses will be assessed by the investigator using the RECIST 1.1 (Response Evaluation Criteria in Solid Tumors) criteria. (Eisenhauer, et al 2009.)

Source: Eisenhauer et al New response evaluation criteria in solid tumours: Revised RECIST guideline (version 1.1), European Journal of Cancer, 2009, Vol. 45, p 228-247

## 1 ASSESSMENT OF OVERALL TUMOR BURDEN AND MEASURABLE DISEASE

To assess objective response or future progression, it is necessary to estimate the *overall tumor burden at baseline* and use this as a comparator for subsequent measurements. Measurable disease is defined by the presence of at least one measurable tumor lesion. When CT scans have slice thickness greater than 5 mm, the minimum size for a measurable lesion should be twice the slice thickness.

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

### 1.1 Measurable lesions

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

- 10 mm by CT/MRI scan - (CT/MRI scan slice thickness no greater than 5 mm)
- 10 mm caliper measurement by clinical exam (lesions which cannot be accurately measured with calipers should be recorded as non-measurable)
- 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). At baseline and in follow-up, only the ***short*** axis will be measured and followed.

### 1.2 Non-measurable lesions

- All other lesions, including small lesions (longest diameter < 10 mm 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 in not measurable by reproducible imaging techniques.

## 1.3 Special considerations regarding lesion measurability

### *1.3.1 Bone lesions*

- Bone scan, PET scan or plain films are ***not*** considered adequate imaging techniques to measure bone lesions. However, these techniques can be used to confirm the presence or disappearance of bone lesions.
- Lytic bone lesions or mixed lytic-blastic lesions, with *identifiable soft tissue components*, that can be evaluated by cross sectional imaging techniques such as CT or MRI can be considered as measurable lesions if the *soft tissue component* meets the definition of measurability described above.
- Blastic bone lesions are non-measurable.

### *1.3.2 Cystic lesions*

- Lesions that meet the criteria for radiographically defined simple cysts should not be considered as malignant lesions (neither measurable nor non-measurable) since they are, by definition, simple cysts.
- 'Cystic lesions' thought to represent cystic metastases can be considered as measurable lesions, if they meet the definition of measurability described above. However, if non-cystic lesions are present in the same subject, these are preferred for selection as target lesions.

### *1.3.3 Lesions with prior local treatment*

Tumor lesions situated in a previously irradiated area, or in an area subjected to other loco-regional therapy, are usually not considered measurable unless there has been demonstrated progression in the lesion.

## 1.4 Specifications by methods of measurements

### *1.4.1 Measurement of lesions*

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

### *1.4.2 Method of assessment*

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

#### *1.4.2.1 CT/MRI scan*

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

#### *1.4.2.2 Chest X-ray*

Chest CT is preferred over chest X-ray, particularly when progression is an important endpoint, since CT is more sensitive than X-ray, particularly in identifying new lesions. However, lesions on chest X-ray may be considered measurable if they are clearly defined and surrounded by aerated lung.

#### *1.4.2.3 Clinical lesions*

Clinical lesions will only be considered measurable when they are superficial and ≥ 10 mm diameter as assessed using calipers. For the case of skin lesions, documentation by color photography including a ruler to estimate the size of the lesion is suggested. As previously noted, when lesions can be evaluated by both clinical exam and imaging, imaging evaluation should be undertaken since it is more objective and may also be reviewed at the end of the study.

#### *1.4.2.4 Ultrasound*

Ultrasound is ***not*** useful in assessment of lesion size and should not be used as a method of measurement. If new lesions are identified by ultrasound in the course of the study, confirmation by CT or MRI is advised.

#### *1.4.2.5 Endoscopy, laparoscopy*

The utilization of these techniques for objective tumor evaluation is ***not*** advised.

#### *1.4.2.6 Tumor markers*

Tumor markers ***alone*** cannot be used to assess objective tumor response.

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

### 2.1 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.

Target lesions should be selected on the basis of their **size** (lesions with the longest diameter), be representative of all involved organs, and should lend themselves to ***reproducible repeated measurements*.**

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 below, 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.

#### *2.1.1 Lymph nodes*

**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. Nodes that have a short axis < 10 mm are considered non-pathological and should not be recorded or followed.

## 2.2 Non-target lesions

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'.** In addition, it is possible to record multiple non-target lesions involving the same organ as a single item on the case record form (e.g. 'multiple enlarged pelvic lymph nodes' or 'multiple liver metastases').

# 3 TUMOR RESPONSE EVALUATION

## 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 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. Nodes that have a short axis <10 mm are considered non-pathological and should not be recorded or followed.

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

All lesions (nodal and non-nodal) recorded at baseline should have their actual measurements recorded at each subsequent evaluation, even when very small (e.g. 2 mm). If the radiologist is able to provide an actual measurement, that should be recorded, even if it is below 5 mm.

However, when such a lesion becomes difficult to assign an exact measure to then:

- 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: in case of a lymph node believed to be present and 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).

#### *3.1.1.3 Target 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.
- 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

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 (< 10 mm 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* 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 non-target lesions*

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

#### *3.2.1.1 When the subject also has measurable disease*

- 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.
- A modest 'increase' in the size of one or more non-target lesions is usually not sufficient to quality for unequivocal progression status.

#### *3.2.1.2 When the subject has only non-measurable disease*

- To achieve 'unequivocal progression' on the basis of the non-target disease, there must be an overall level of substantial worsening such that the overall tumor burden has increased sufficiently to merit discontinuation of therapy.
- A modest 'increase' in the size of one or more non-target lesions is usually not sufficient to qualify for unequivocal progression status.
- Because worsening in non-target disease cannot be easily quantified (by definition: if all lesions are non-measurable) a useful test that can be applied when assessing subjects 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: i.e. 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 subject should be considered to have had overall PD at that point.

#### *3.2.1.3 Tumor markers*

Tumor markers *alone* cannot be used to assess objective tumor responses. If markers are initially above the upper normal limit, however, they must normalize in order for a subject to be considered as having attained a complete response.

### 3.3 New lesions

The appearance of new malignant lesions denotes disease progression. The finding of a new lesion should be unequivocal: i.e. 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 subject'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 subject who has visceral disease at baseline and while on study has a CT or MRI brain scan ordered which reveals metastases. The subject'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.*

### *3.3.1 FDG-PET evaluation*

While FDG-PET response assessments need additional study, it is sometimes reasonable to incorporate the use of the qualitative assessment of FDG-PET scanning to complement CT scanning in assessment of progression (particularly possible 'new' disease). New lesions on the basis of FDG-PET imaging can be identified according to the following algorithm:

- Negative FDG-PET at baseline, with a positive FDG-PET at follow-up might be a sign of PD based on a new lesion. However, other reasons for newly detected lesions with increased FDG-PET uptake, such as inflammatory lymphnodes, should be taken into consideration.
- No FDG-PET at baseline and a positive FDG-PET at follow-up:
  - If the positive FDG-PET at follow-up corresponds to a new site of disease confirmed by CT, this is PD.
  - If the positive FDG-PET at follow-up is not confirmed as a new site of disease on CT, additional follow-up CT scans are needed to determine if there is truly progression occurring at that site (if so, the date of PD will be the date of the initial positive FDG-PET scan).
  - If the positive FDG-PET at follow-up corresponds to a pre-existing site of disease on CT that is not progressing on the basis of the anatomic images, this is not PD.
  - Other reasons for newly detected lesions with increased FDG-PET uptake, such as inflammatory lymphnodes, should be taken into consideration.

# 4 RESPONSE CRITERIA

## 4.1 Time point response

A response assessment should occur at each time point specified in the protocol.

For subjects who have **measurable disease** at baseline Table 1 provides a summary of the overall response status calculation at each time point.

**Table 1: Time point response: subjects 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 |

| **Table 1: Time point response: subjects with target (+/– non-target) disease.** | | | |
|---|---|---|---|
| **Target lesions** | **Non-target lesions** | **New lesions** | **Overall response** |
| 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, NE =not evaluable.

For subjects who have **non-measurable** (therefore non-target) disease only, Table 2 is to be used.

| **Table 2: Time point response: Subjects 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 |

[a] 'Non-CR/non-PD' is preferred over 'stable disease' 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.

CR = complete response, PD = progressive disease, and NE = not evaluable.

### *4.1.1 Missing assessments and not evaluable designation*

When no imaging/measurement is done at all at a particular time point, the subject is **not evaluable (NE)** at that time point. If only a subset of lesion measurements are made at an

assessment, the case is also considered NE at that time point, unless a convincing argument can be made that the contribution of the individual missing lesion(s) would not have changed the assigned time point response.

### *4.1.2 Confirmation of Scans and External Evaluation*

- **Verification of Response:** Confirmation of response (CR or PR) is required. Confirmed CR or PR will be claimed only if the criteria for each are met at a subsequent timepoint (minimum 4 weeks after criteria for an objective response are first met).
- **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 not to have progressive disease per RECIST 1.1.
- **External Evaluation of scans:** For all subjects, BMS will request the transfer of anonymized scans for a BMS internal or external evaluation through a third party. For tumor types where data from study CA209-032 will potentially be used for future NDA submissions, BMS will request the transfer of anonymized scans from all subjects with this tumor type for a BMS internal or external evaluation through a third party.

## 4.2 Best overall response: All timepoints

The best overall response is determined once all the data for the subject is known. It is defined as the best response designation, as determined by the investigator, recorded between the date of first treatment and the date of objectively documented progression per RECIST1.1 or the date of subsequent therapy, whichever occurs first. For subjects without documented progression or subsequent therapy, all available response designations will contribute to the BOR assessment. The subject'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.

Complete or partial responses may be claimed only if the criteria for each are met at a subsequent time point (minimum 4 weeks after criteria of objective response are first met). In this circumstance, the best overall response can be interpreted as in Table 3.

**Table 3: Best overall response when confirmation of CR and PR IS required.**

| Overall response | Overall response | BEST overall response |
|---|---|---|
| **First time point** | **Subsequent time point** | |
| CR | CR | CR |
| CR | PR | SD, PD or PR[a] |

**Table 3: Best overall response when confirmation of CR and PR IS required.**

| Overall response | Overall response | BEST overall response |
|---|---|---|
| **First time point** | **Subsequent time point** | |
| CR | SD | SD provided minimum criteria for SD duration met, otherwise, PD |
| CR | PD | SD provided minimum criteria for SD duration met, otherwise, PD |
| CR | NE | SD provided minimum criteria for SD duration met, otherwise NE |
| PR | CR | PR |
| PR | PR | PR |
| PR | SD | SD |
| PR | PD | SD provided minimum criteria for SD duration met, otherwise, PD |
| PR | NE | SD provided minimum criteria for SD duration met, otherwise NE |
| NE | NE | NE |

CR = complete response, PR = partial response, SD = stable disease, PD = progressive disease, NE = not evaluable.

[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 subject 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.

For purposes of this study, the minimum scan time from baseline for determination of SD will be 6 weeks.

## 4.3 Duration of response

### *4.3.1 Duration of overall response*

The duration of overall response is measured from the time measurement criteria are first met for CR/PR (whichever is first recorded) until the first date that recurrent or progressive disease is objectively documented (taking as reference for progressive disease the smallest measurements recorded on study).

The duration of overall complete response is measured from the time measurement criteria are first met for CR until the first date that recurrent disease is objectively documented.

### *4.3.2 Duration of stable disease*

Stable disease is measured from the start of the treatment (in randomized trials, from date of randomization) until the criteria for progression are met, taking as reference the smallest sum on study (if the baseline sum is the smallest, this is the reference for calculation of PD).

### *4.3.3 Immune related Response Criteria*

Immune related response criteria using unidimensional measurements may be used to describe tumor shrinkage following RECIST defined disease progression Appendix 3. The methodology is the same as described above for RECIST except:

- New lesions do not automatically denote disease progression
- The measurement of longest diameter of new measurable lesions are in included in the sum of the measurements of the original target lesions.

Best immune related responses, for subjects who have progression followed by tumor shrinkage are classified as irCR (disappearance of all lesions) or irPR (≥ 30% reduction from baseline).

# APPENDIX 4 DEFINITION OF PRIOR RESPONSE TO PLATINUM-BASED CHEMOTHERAPY IN SCLC

**Platinum sensitive**: Progression free interval ≥ 90 days after completion of any platinum-based chemotherapy.

**Platinum resistant**: Progression free interval < 90 days after completion of any platinum-based chemotherapy.

**Platinum refractory**: Progression during platinum-based chemotherapy.

# APPENDIX 5 DEFINITION OF PRIOR RESPONSE TO PLATINUM-BASED CHEMOTHERAPY IN OVARIAN CANCER

**Platinum-sensitive**: Relapse > 6 months after stop of any platinum-based chemotherapy.

**Platinum-resistant**: Relapse > 1 to ≤ 6 months after stop of any platinum-based chemotherapy.

**Platinum-refractory**: Relapse on or within 1 month after stop of any platinum-based chemotherapy.

## APPENDIX 6 ROYAL MARSDEN PROGNOSTIC SCORE

**Table 1.** Prognostic Score

| Variable | Score | HR* |
|---|---|---|
| LDH | | 1.85 |
| < ULN | 0 | |
| > ULN | 1 | |
| Albumin, g/L | | 1.83 |
| > 35 | 0 | |
| < 35 | 1 | |
| Sites of metastasis | | 1.54 |
| 0-2 | 0 | |
| > 2 | 1 | |

NOTE. The prognostic score ranges from 0 to 3. The good-prognosis group comprises patients with a score of 0 to 1, and the poor-prognosis group comprises patients with a score of 2 to 3.

Abbreviations: HR, hazard ratio; LDH, lactate dehydrogenase; ULN, upper limit of normal.

*Hazard ratios are based on the retrospective analysis.

Source: Arkenau HT, Barriuso J, Olmos D, Ang JE, et al. Prospective Validation of a Prognostic Score to Improve Patient Selection for Oncology Phase I Trials. J Clin Oncol. 2009;27:2692-2696

# APPENDIX 7 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.

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

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

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

## 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 in the female participant.

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

| **Highly Effective Contraceptive Methods That Are User Dependent**<br>*Failure rate of <1% per year when used consistently and correctly.*[a] |
|---|
| • Combined (estrogen- and progestogen-containing) hormonal contraception associated with inhibition of ovulation[b]<br>– oral<br>– intravaginal<br>– transdermal |
| • Progestogen-only hormonal contraception associated with inhibition of ovulation[b]<br>– oral<br>– injectable |
| **Highly Effective Methods That Are User Independent** |
| • Implantable progestogen-only hormonal contraception associated with inhibition of ovulation [b]<br>• Intrauterine device (IUD)[c]<br>• Intrauterine hormone-releasing system (IUS)[c]<br>• Bilateral tubal occlusion |
| • Vasectomized partner<br>*A vasectomized partner is a highly effective contraception method provided that the partner is the sole male sexual partner of the WOCBP and the absence of sperm has been confirmed. If not, an additional highly effective method of contraception should be used.* |
| • Sexual abstinence<br>*Sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the study drug. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the study and the preferred and usual lifestyle of the participant.*<br>• It is not necessary to use any other method of contraception when complete abstinence is elected.<br>• WOCBP participants who choose complete abstinence must continue to have pregnancy tests, as specified in the protocol.<br>• Acceptable alternate methods of highly effective contraception must be discussed in the event that the WOCBP participants chooses to forego complete abstinence |

NOTES:

[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.

[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.

[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

## 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 the end of relevant systemic exposure, defined as 7 months after the end of treatment in the male participant.
- Female partners of males participating in the study to consider use of effective methods of contraception until the end of relevant systemic exposure, defined as 7 months after the end of treatment in the male participant.
- Male participants with a pregnant or breastfeeding partner must agree to remain abstinent from penile vaginal intercourse or use a male condom during each episode of penile penetration during the treatment and until 7 months after the end of treatment.
- Refrain from donating sperm for the duration of the study treatment and until 7 months after the end of treatment.

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

## COLLECTION OF PREGNANCY INFORMATION

Guidance for collection of Pregnancy Information and outcome of pregnancy on the Pregnancy Surveillance Form is provided in Section 6.4 and Section 6.1.1 on Serious Adverse Event Collection and Reporting.

Protocol Number: CA209032
IND Number: 104,225
Ex-US Non-IND
EUDRACT Number 2013-002844-10
Date: 10-Jul-2013
Revised Date: 23-Aug-2019

# CLINICAL PROTOCOL CA209032

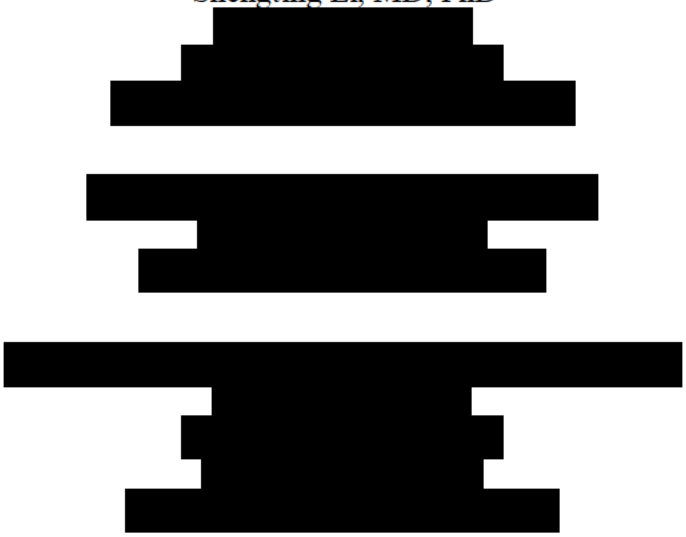
A Phase 1/2, Open-label Study of Nivolumab Monotherapy or Nivolumab combined with Ipilimumab in Subjects with Advanced or Metastatic Solid Tumors

(CheckMate 032: CHECKpoint pathway and nivoluMAb clinical Trial Evaluation 032)

**Revised Protocol 08**
**Incorporates Administrative Letters 02, 03, 04, and 05**

**Medical Monitor / Study Director**

Shengting Li, MD, PhD



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

## DOCUMENT HISTORY

| Document | Date of Issue | Summary of Change |
|---|---|---|
| Revised Protocol 08 | 23-Aug-2019 | • Updated personnel with Medical Monitor<br>• Added live/attenuated vaccines and complementary medications (eg, herbal supplements) to Prohibited and/or Restricted Treatments<br>• Clarified tumor assessment language<br>• Updated Appendix 2 (Management Algorithms) with addition of myocarditis AE management algorithm to reflect update in the Nivolumab IB<br>• Added survival visits time window (from Administrative letter 5, dated 27-Aug-2018) |
| Administrative Letter 05 | 27-Aug-2018 | Updated survival visit information |
| Administrative Letter 04 | 31-Jan-2018 | Updated study personnel |
| Administrative Letter 03 | 11-Jan-2018 | Corrected Date of Issue in Document History for Amendment 10 |
| Administrative Letter 02 | 18-Apr-2017 | Updated study personnel |
| Revised Protocol 07 | 10-Aug-2016 | Incorporates Amendment 12 |
| Amendment 12 | 10-Aug-2016 | • Changed the primary objective for the expansion SCLC cohort to require evaluation by BICR.<br>• Removed the limitation of enrolling subjects with 1 or 2 prior lines of therapy in the same fixed proportion of 50% for each subgroup.<br>• Added permission to use palliative radiation therapy to other non-target lesions<br>• Added permission to use surgical resection or stereotactic radiotherapy following initial response or long-term stable disease<br>• Limited PK and immunogenicity samples collection up to 2 years<br>• Updated Appendix 2 (Management Algorithms) to reflect updates in the nivolumab IB.<br>• Added Appendix 6 (Methods of Contraception) to reflect updates in the nivolumab IB. |
| Revised Protocol 06 | 18-Nov-2015 | Incorporates Amendment 11 |
| Amendment 11 | 18-Nov-2015 | • Clarification regarding the local lab assessment timing was added.<br>• For Ovarian Cancer cohort, specification of minimum tissue sample collection for ovarian cancer due to the fact that additional analyses of Homologous Recombination Deficiency (HRD) status and Breast Cancer genes 1 and 2 (BRCA1 and BRCA2) mutation status will be conducted in this cohort.<br>• For SCLC expansion cohort, exact language regarding number of prior treatment lines added for consistency with Section 3.1.5 and the study synopsis.<br>• Specification of the crossover option: This option refers only to the |

| Document | Date of Issue | Summary of Change |
|---|---|---|
| | | original cohorts and not the new cohorts enrolled under or after Amendment 09 implementation.<br>• To increase flexibility in obtainment of tumor samples, for subjects with only one site of measurable disease tumor sampling criteria for biopsies from NOT the only site of measurable disease were widened.<br>• Clarification regarding requirement for baseline CT and MRI brain scans.<br>• [redacted]<br>• For Ovarian Cancer cohort, due to the low risk of development of new safety signals on the combination arms confirmed by the additional information from the combination studies in melanoma, lung, renal cell carcinoma, and glioblastomas as well as the clinical study with ipilimumab 10 mg/kg monotherapy in ovarian cancer, which did not reveal any new safety signals, the Safety Evaluation Phase will be removed. Ovarian cancer subjects will be followed for related toxicities and decisions to stop enrollment will be made on an ongoing basis. |
| Revised Protocol 05 | 23-Sep-2015 | **Incorporates Amendment 10** |
| Amendment 10 | 23-Sep-2015 | • Clarification regarding PK/immunogenicity sampling and pregnancy test was added.<br>• Regimen NI2c was added for treatment of ovarian cancer, including PK/immunogenicity and pregnancy sampling clarifications<br>• Safety assessments in all indications and treatment cohorts is harmonized: D4 W2 and W5 safety assessments are deleted from the NI cohorts consistent with nivolumab monotherapy and nivolumab 3 mg/kg Q2W/ipilimumab 1 mg/kg Q6W cohorts<br>• For options of treatment beyond progression and crossover to NI combination arm, specification of unequivocal disease progression based on non-target lesions only is added<br>• Specification of response to platinum-based therapy in SCLC and Ovarian cancer is added to appendices<br>• Regimen NI2c was removed from the flowchart for Bladder cancer (correction)<br>• For SCLC expansion cohort, clarification of stratified randomization is added<br>• For subjects from NI combination who undergo a re-exposure if they achieved an initial objective response (PR or CR) or stable disease of > 3 months and had a subsequent documented progression, an option to continue treatment with nivolumab monotherapy if ipilimumab treatment was stopped due to toxicity is added |
| Revised Protocol 04 | 06-Aug-2015 | **Incorporates Amendment 09** |
| Amendment 09 | 06-Aug-2015 | This global amendment includes:<br>- Updates to Medical Monitor/Study Director<br>- SCLC and Bladder: cohorts Nivo 3 mg/kg and Nivo 1/ Ipi 3 mg/kg, |

| Document | Date of Issue | Summary of Change |
|---|---|---|
| | | increase sample size.<br>- Addition of Ovarian tumor type: cohorts Nivo 3 / Ipi 1 mg/kg and Nivo 1/ Ipi 3 mg/kg.<br>- Updates to Blinded Independent Central Review (BICR) information<br>Allowing brain radiation prior to cross over<br>- Allowing retreatment upon PD for patients with long lasting PR or CR and who had treatment held by investigator<br>- For the combination arm, subjects who meet discontinuation criteria will be allowed to continue with nivolumab treatment should the study related toxicities be attributed to ipilimumab. Ipilimumab would be discontinued.<br>- Updates to Primary, Secondary [redacted] Objectives<br>- Updates to Discontinuation criteria to include Grade 4 lymphocytopenia |
| Revised Protocol 03 | 07-Aug-2014 | **Incorporates Amendment 07 and 08** |
| Amendment 08 | 07-Aug-2014 | This amendment is to add nivolumab 3 mg/kg in combination with ipilimumab 1 mg/kg to the dose levels being investigated in study CA209-032, change the bladder cohort to a One Stage Design, and to add an optional external evaluation of CT or MRI scans for tumor types where data from study CA209-032 will potentially be used for future NDA submissions. Other changes were made to resolve minor inconsistencies and clarifications. |
| Amendment 07 | 04-Jun-2014 | Pharmacogenetics blood sample update to include all current and future tumor types |
| Revised Protocol 02 | 17-Apr-2014 | **Incorporates Amendment 06** |
| Amendment 06 | 17-Apr-2014 | This global amendment includes adjustments to the treatment guidelines for patients with endocrinopathy events, adds a new cohort for subjects with Bladder Cancer, updates laboratory test requirements, and updates the sample size determination, populations for analyses and interim analysis sections. Other changes were made to resolve minor inconsistencies and clarifications:<br>• Bladder cancer is the most common malignancy of the urinary tract. Immunotherapy with Bacillus Calmette-Guerin in patients with superficial urothelial carcinoma is part of the standard treatment. It has been shown that CD8 tumor-infiltrating lymphocytes (TILs) are predictive of survival in muscle-invasive urothelial carcinoma. Active immunotherapeutic strategies have been investigated for bladder cancer including CTLA-4 blockade. In conclusion, a check point inhibitor therapy with nivolumab or nivolumab in combination with ipilimumab appears to be a promising experimental approach for patients with advanced urothelial carcinoma. This amendment adds a cohort enrolling subjects with advanced bladder cancer to the protocol aligned with the existing study design.<br>• Adjustments to the treatment guidelines for subjects who experience endocrinopathy events are implemented. Subjects who experience endocrinopathy events which resolve or are adequately controlled with physiologic hormone replacement (steroids, thyroid hormones) or |

| Document | Date of Issue | Summary of Change |
|---|---|---|
| | | glucose controlling agents, may undergo retreatment. A recurrence of the endocrinopathy event under ongoing physiologic hormone replacement therapy appears to be unlikely what justifies a retreatment with potential therapeutic benefit.<br>• The definition of the all immunogenicity population was changed in order to align it with the core safety SAP for the Nivolumab program. Other minor changes in the populations for analyses were made in order to align it with the SAP for 032.<br>• The interim analysis section was updated to allow for IAs based on either a "super" response or if it is necessary to make decisions regarding further development (eg, the SCLC cohort). |
| Revised Protocol 01 | 11-Dec -2013 | **Incorporates Amendment 05** |
| Amendment 05 | 11-Dec-2013 | **Study Design:**<br>• Clarification on need for subject safety follow up before dose escalation and staggered enrollment for Dose Cohort Level 2.<br>• Clarification on number of subjects with objective response and number of enrolled subjects before proceeding from Stage 1 to Stage 2.<br>**Eligibility Criteria**<br>• Clarified wording that subjects with Breast Cancer, Gastric or Gastro-Esophageal Junction Carcinoma, or SCLC must have progressive or refractory disease at study entry.<br>• Adjusted eligibility, treatment delay and discontinuation criteria for subjects with lipase or amylase > 1.5 ULN: Subjects with asymptomatic elevations in amylase or lipase not associated with symptoms, clinical manifestations, or radiographic sings of pancreatitis are eligible. Based on clinical experience in ongoing studies with nivolumab and ipilimumab, asymptomatic elevations of amylase or lipase have not been proven to have to have independent clinical consequence or predict for development or severity of pancreatitis. A wide variation of asymptomatic elevations in amylase or lipase can occur on a day-to-day basis, limiting the utility of interpreting the amylase or lipase elevations in isolation.<br>• Clarifications on eligibility for women of childbearing potential and effective methods of contraception.<br>• Clarification on eligibility of subjects with prior malignancy not interfering with the primary and secondary study endpoints.<br>[redacted].<br>**Study procedures**<br>• Implementation of time windows for study visits and biomarker assessments.<br>In addition, inconsistencies within the protocol for mandatory tumor biopsies were resolved. |
| Original Protocol | 10-Jul-2013 | Not applicable |

## OVERALL RATIONALE FOR REVISED PROTOCOL 08

This revised protocol provides clarity on the tumor assessments during treatment and follow-up. Additional changes were made for prohibited and restricted treatments. The changes apply for all participants in the study.

**SUMMARY OF KEY CHANGES FOR REVISED PROTOCOL 08**

| Section Number & Title | Description of Change | Brief Rationale |
|---|---|---|
| Section 3.4.1 Prohibited and/or Restricted Treatments<br><br>Section 3.4.2.3 Permitted Therapy | Updated language for permitted therapy and additional prohibited and/or restricted treatments were added:<br>• Any complementary medications (eg, herbal supplements or traditional Chinese medicines) intended to treat the disease under study. Such medications are allowed if they are used as supportive care.<br>• Any live / attenuated vaccine (eg varicella, zoster, yellow fever, rotavirus, oral polio and measles, mumps, rubella (MMR)) during treatment and until 100 days post last dose. | Prohibited and/or restricted treatments were updated to align with program standards for safety. |
| Section 5 Study Assessments and Procedures<br>On-study Assessment tables:<br>Table 5.1-2<br>Table 5.1-3<br>Table 5.1-4<br>Table 5.1-5<br>Section 5.3.1 Imaging Assessment for the Study | Tumor assessment language was added to tables:<br><br>Additionally, with the exception of crossover participants, tumor assessments will not be required upon initiation of subsequent anti-cancer therapy. | On-treatment tables were updated to provide clarity that tumor assessments are not required after subjects receive subsequent anti-cancer therapy. |
| Appendix 2 | Management Algorithms were updated to include AE management for myocarditis | Appendix aligns with revised Nivolumab IB for safety. |

# SYNOPSIS

## Clinical Protocol CA209032

**Protocol Title: A Phase 1/2, Open-label Study of Nivolumab Monotherapy or Nivolumab combined with Ipilimumab in Subjects with Advanced or Metastatic Solid Tumors**

**Investigational Product(s), Dose and Mode of Administration, Duration of Treatment with Investigational Product(s):**

- Nivolumab monotherapy administered IV over 60 minutes at 3 mg/kg every 2 weeks until progression

or

- Nivolumab administered IV over 60 minutes at 1 mg/kg combined with ipilimumab administered IV over 90 minutes at 1 mg/kg every 3 weeks for 4 doses followed by nivolumab administered IV over 60 minutes at 3 mg/kg every 2 weeks until progression.

or

- Nivolumab administered IV over 60 minutes at 1 mg/kg combined with ipilimumab administered IV over 90 minutes at 3 mg/kg every 3 weeks for 4 doses followed by nivolumab administered IV over 60 minutes at 3 mg/kg every 2 weeks until progression.

or

- Nivolumab administered IV over 60 minutes at 3 mg/kg combined with ipilimumab administered IV over 90 minutes at 1 mg/kg every 3 weeks for 4 doses followed by nivolumab administered IV over 60 minutes at 3 mg/kg every 2 weeks until progression.

or

- Nivolumab administered IV over 60 minutes at 3 mg/kg every 2 weeks combined with ipilimumab administered IV over 90 minutes at 1 mg/kg every 6 weeks until progression.

**Study Phase:** 1/2

**Research Hypothesis:** Treatment with nivolumab monotherapy or nivolumab combined with ipilimumab will have clinical activity in subjects with advanced or metastatic tumors.

**Objectives:**

Primary Objective

SCLC Expansion Cohort:

- To compare the objective response rate (ORR) as assessed by a Blinded Independent Central Review (BICR) for nivolumab monotherapy versus nivolumab combined with ipilimumab (nivolumab 1 mg/kg + ipilimumab 3 mg/kg).

Other Cohorts:

- To evaluate the objective response rate (ORR) of nivolumab monotherapy or nivolumab combined with ipilimumab in subjects with advanced or metastatic tumors. ORR will be assessed by a BICR in selected tumor types.

Secondary Objective

- To assess the safety of nivolumab monotherapy or nivolumab combined with ipilimumab in subjects with advanced or metastatic tumors.
- To assess Overall Survival (OS), OS-rate, Progression Free Survival (PFS), PFS-rate, and Duration of Response (DOR) with nivolumab monotherapy or nivolumab combined with ipilimumab in subjects with advanced or

metastatic tumors. PFS and DOR will be assessed by a Blinded Independent Central Review (BICR) in selected tumor types.

[redacted]

**Study Design:**

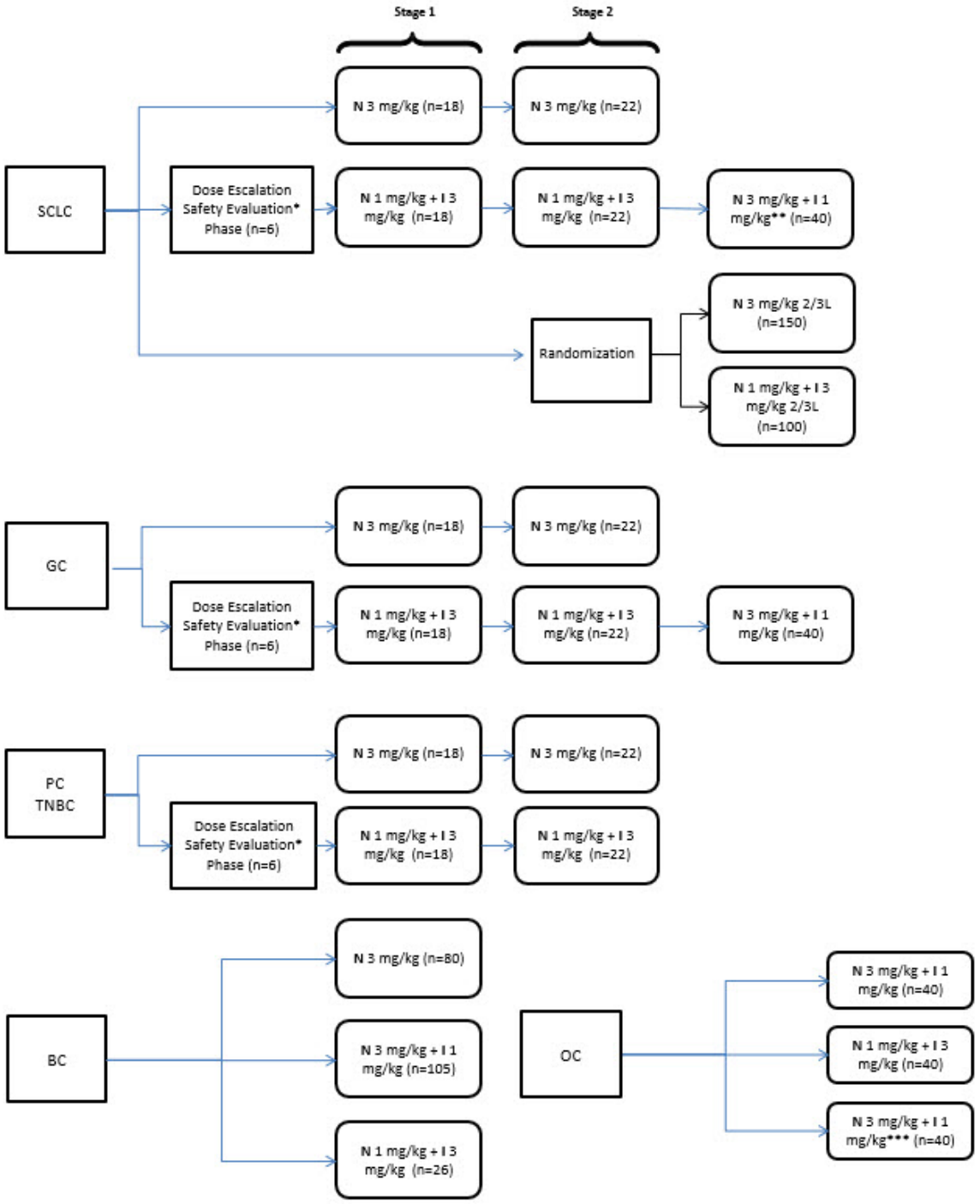
This is a multicenter Phase 1/2, two stage, open label study of nivolumab monotherapy or nivolumab combined with ipilimumab in adult (≥ 18 years) subjects with advanced or metastatic cancer of one of the following tumor types:

1) Triple Negative Breast Cancer (TNBC)
2) Gastric Cancer (GC)
3) Pancreatic Cancer (PC)
4) Small Cell Lung Cancer (SCLC)
5) Bladder Cancer (BC)
6) Ovarian Cancer (OC)

**Treatment assignment**: The assignment to treatment arm and evaluation of safety and activity will be performed independently for each tumor type. For each tumor type, subjects will be assigned (described in Section 4.2) to one of the following treatment arms:

| | |
|---|---|
| **Arm N:** | **Nivolumab monotherapy (3 mg/kg) Q2W** |
| **Arm N-I Dose Level 1:** | **Nivolumab (1 mg/kg) + ipilimumab (1 mg/kg) Q3W for 4 doses, then nivolumab (3 mg/kg) Q2W** |
| **Arm N-I Dose Level 2:** | **Nivolumab (1 mg/kg) + ipilimumab (3 mg/kg) Q3W for 4 doses, then nivolumab (3 mg/kg) Q2W** |
| **Arm N-I Dose Level 2b:** | **Nivolumab (3 mg/kg) + ipilimumab (1 mg/kg) Q3W for 4 doses, then nivolumab (3 mg/kg) Q2W** |
| **Arm N-I Dose Level 2c:** | **Nivolumab (3 mg/kg) Q2W + ipilimumab (1 mg/kg) Q6W.** |

**Figure 1:** **Study Design for Each Tumor Type**




*dose level 1 (N1 mg/kg Q3W +I1 mg/kg Q2W) and dose level 2 (N1 mg/kg Q3W + I3 mg/kg Q2W); ** dose level 2b (N3 mg/kg Q3W + I1 mg/kg Q2W); *** dose level 2c (N3 Q2W + I1 Q6W

**Dose-escalating Safety Evaluation Phase for Combination Arm:** Although the regimen currently used in the phase 3 melanoma study, nivolumab 1 mg/kg IV + ipilimumab 3 mg/kg, was expected to also be tolerable in the

tumors studied here, an initial dose-escalating safety evaluation for the combination arms was conducted with GC, PC, TNBC, or SCLC (described in protocol Section 3.1.3). The BC cohort was added to this protocol following the completion of the safety evaluations in GC, PC, TNBC, and SCLC at dose level 1 (nivolumab 1 mg/kg, ipilimumab 1 mg/kg) which did not reveal safety concerns. Thereby the starting dose level for the BC cohort was dose level 2 (nivolumab 1 mg/kg, ipilimumab 3 mg/kg). Six BC patients were initially randomized to Dose Level 2, after which enrollment to Dose Level 2b (nivolumab 3 mg/kg, ipilimumab 1 mg/kg) began.

Enrollment to Stage 1 for Arm N occurred in parallel to the safety evaluation for Arm N-I.

**Two Stage Design:** GC, PC, TNBC, or SCLC Arms N and N-I will follow a two-stage design to test whether nivolumab monotherapy or nivolumab combined with ipilimumab yields an objective response rate (ORR) that is of clinical interest in the investigated tumor types. For each tumor type, only treatment arms which meet an ORR threshold will proceed from Stage 1 to Stage 2 (described in protocol Section 3.1.4). Enrollment to Stage 2 in a given treatment arm can continue even if the other treatment arm is still in Stage 1.

**Table 1: Efficacy criteria to proceed from Stage 1 to Stage 2**

| Efficacy criteria | Next Step |
|---|---|
| 2 or more of 18 subjects in a given arm have confirmed PR or CR | Go into Stage 2 |
| 1 or no of 18 subjects in a given arm have confirmed PR or CR. | No Go into Stage 2 |

For Stage 2, upon completion of enrollment of the initial 40 subjects, additional subjects may be assigned into Arm N and Arm N-I up to a total of 100 subjects (including those assigned in Stage 1) in each treatment arm of the given tumor type. For tumor types where nivolumab monotherapy or nivolumab 1 mg/kg plus ipilimumab 3 mg/kg proceeded to Stage 2, assessment of Dose Level 2b in Stage 2 (nivolumab 3 mg/kg + ipilimumab 1 mg/kg, n=up to 70 subjects) may be initiated for that tumor type. For SCLC, an additional 250 subjects (second- or third-line) will be randomized in a 3:2 ratio to one of the 2 expansion groups: nivolumab 3 mg/kg every 2 weeks or nivolumab 1 mg/kg + ipilimumab 3 mg/kg every 3 weeks for 4 cycles followed by nivolumab 3 mg/kg.

**Modified Design for Bladder Cancer Cohort:**

Bladder arms N and N-I (Dose Levels 2 and 2b) will be conducted as a One Stage Design with the treatment of 26-105 subjects in each arm. The Safety Evaluation Phase for the N-I arm will start at Dose Level 2 (nivolumab 1 mg/kg, ipilimumab 3 mg/kg) and will evaluate safety and tolerability after the first 6 randomized subjects. Following the N-I safety evaluation phase, Dose Level 2 will enroll 26 subjects and 2b will enroll up to a total of 105 subjects. Based on the safety evaluations thus far on study, no dose escalation phase is necessary for bladder cohort N-I Dose Level 2b (nivolumab 3 mg/kg, ipilimumab 1 mg/kg).

**Modified Design for Ovarian Cancer Cohort:**

Ovarian arm N-I (Dose Levels 2, 2b and 2c) will be conducted as a One Stage Design with the treatment of 40 subjects in each arm. Due to the low risk of development of new safety signals on the combination arms no safety evaluation phase will be employed. Ovarian cancer subjects will be followed for related toxicities and decisions to stop treatment will be made on an ongoing basis.

**SCLC expansion:**

SCLC cohorts Arm N and Arm N-I met the pre-specified safety and efficacy criteria and proceeded to Stage 2. Based on an interim data review, disease control rates (SD + PR + CR) of 36% and 57% for Arms N and N-I, respectively, were estimated. In order to further investigate nivolumab and nivolumab combined with ipilimumab activity in specific SCLC subpopulations, the SCLC expansion cohorts will enroll additional subjects based on response to prior treatment and the number of previous therapies. Up to 250 second or third line subjects will be randomized in a 3:2 ratio to one of 2 expansion groups: Arm A (150 subjects treated with nivolumab 3 mg/kg every 2 weeks (Q2W)) or Arm B (100 subjects treated with nivolumab 1 mg/kg + ipilimumab 3 mg/kg every 3 weeks (Q3W) for 4 cycles followed by nivolumab 3 mg/kg (Q2W) and will be stratified for number of prior treatment lines (1 vs 2 prior chemotherapy regimens). The crossover option refers only to the original cohorts and not the new cohorts enrolled under or after Amendment 09 implementation.

**Crossover for subjects in Arm N:** Subjects in Arm N may crossover to Arm N-I if all of the following criteria are met:

- The Safety Evaluation Phase for the N-I regimen has been completed and at least 6 subjects have been exposed to the dose level used for Stage 1 of the N-I regimen. In case Dose Level 2b has been activated and the safety assessment completed, subjects for cross over will be assigned to Dose Level 2b.
- Subject has confirmed radiologic disease progression (investigator-assessed RECIST 1.1 defined progression confirmed at least 4 weeks after the initial tumor assessment showing progression) in the absence of clinical deterioration. For subjects with clear evidence of new or progressing brain metastases a confirmation is not required. These subjects may proceed with brain radiation therapy and after having completed the radiation therapy a cross over to Arm N-I can be considered.
- Subjects with rapidly progressing tumors under nivolumab monotherapy may undergo radiation treatment first before initiation of the cross over after discussion between the sponsor and investigator.
- Subject has not experienced nivolumab related adverse events leading to permanent discontinuation.
- Subject is not continuing to derive any clinical benefit from nivolumab single agent therapy as assessed by the investigator which would allow continuation of nivolumab monotherapy.
- Subject is not a SCLC patient enrolled based on the Amendment 09 expansion.
- The individual case must be discussed with the medical monitor prior to cross over.

Subjects crossing over to Arm N-I will start treatment at Day 1 Week 1 as described for subjects originally randomized to Arm N-I. Subjects who cross over and subsequently have an objective response in Arm N-I will not be considered in the decision making for Arm N I proceeding to Stage 2.

**Study Population:**

*Key Inclusion Criteria*

- Subjects with histologically confirmed locally advanced or metastatic disease of one of the following tumor types and who meet the eligibility criteria defined in Section 3.4.1:
  - Triple Negative Breast Cancer
  - Gastric Cancer
  - Pancreatic Cancer
  - Small Cell Lung Cancer
  - Bladder Cancer
  - Ovarian Cancer
- Subjects must have measurable disease by CT or MRI per RECIST 1.1 criteria (radiographic tumor assessment must be performed within 28 days prior to first dose)
- Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1

*Key Exclusion Criteria*

- Active brain metastases or leptomeningeal metastases. Subjects with brain metastases are eligible if these have been treated and there is no magnetic resonance imaging (MRI) evidence of progression for at least 4 weeks after treatment is complete and within 28 days prior to first dose of study drug administration. There must also be no requirement for immunosuppressive doses of systemic corticosteroids (> 10 mg/day prednisone equivalents) for at least 2 weeks prior to study drug administration.
- Subjects with active, known or suspected autoimmune disease. Subjects with vitiligo, type I diabetes mellitus, residual hypothyroidism due to autoimmune condition only requiring hormone replacement, or conditions not expected to recur in the absence of an external trigger are permitted to enroll.

- Subjects with a condition requiring systemic treatment with either corticosteroids (> 10 mg daily prednisone equivalents) or other immunosuppressive medications within 14 days of study drug administration. Inhaled or topical steroids, and adrenal replacement doses are permitted in the absence of active autoimmune disease.
- Prior therapy with experimental anti-tumor vaccines; any T cell co-stimulation or checkpoint pathways, such as anti-PD-1, anti-PD-L1, anti-PD-L2, anti-CD137, or anti-CTLA-4 antibody, including ipilimumab; or other medicines specifically targeting T cell is also prohibited.

**Study Assessments:**

***Tumor assessments***

The primary endpoint of this study, ORR, is based on tumor assessments at baseline and then at 6 weeks from first dose. Tumor assessments continue every 6 weeks for the first 24 weeks and every 12 weeks thereafter while on treatment or on treatment hold for any reason until disease progression (investigator-assessed RECIST 1.1-defined progression) or treatment discontinuation, except for subjects treated beyond progression or who discontinued treatment for other reasons than PD.

**Statistical Considerations:**

***Sample Size Determination***

*Sample size determination in the original protocol*

This study comprises a Dose Escalating Safety Evaluation Phase for the Combination Arm, followed by a Staged Enrollment for Arm N, and Arm N-I.

In the original protocol, gastric cancer, small cell lung cancer, triple negative breast cancer, and pancreatic cancer are included and the Staged Enrollment Part utilizes a modified Simon two-stage design with the treatment of 40 subjects to evaluate whether nivolumab, or the combination of nivolumab/ipilimumab yields an objective response rate (ORR) that is of clinical interest. In this study, an ORR of 10% or less is considered not of clinical value, and an ORR of 25% or greater is considered of strong clinical interest. The modified Simon design evaluates the null hypothesis that the true response rate is ≤ 10% versus the alternative hypothesis that the true response rate is > 10%. The 2-stage testing within each cohort targets a Type I error rate of 5% and has 80% power to reject the null hypothesis if the true response rate is 25%.

*Sample size determination for bladder cancer cohort*

In Amendment 06, the bladder cohort is added. A one stage design with the treatment of 60-100 subjects is used. These sample sizes provide 90% to 97% power to reject the null hypothesis of 10% response rate if the true response rate is 25% with a two-sided Type I error rate of 5%.

*Sample size determination for SCLC expansion cohort*

In Amendment 09, in addition to the original two-stage design of SCLC subjects, additional SCLC expansion cohort subjects will be randomized in a 3:2 ratio to one of 2 expansion groups: Arm A (150 subjects, nivolumab mono) or Arm B (100 subjects, nivolumab 1 mg/kg + ipilimumab 3 mg/kg) and will be stratified for number of prior treatment lines (1 vs 2 prior chemotherapy regimens).

Based on SCLC data so far observed in this study with an ORR of about 10% for nivolumab monotherapy and about 23% for nivolumab / ipilimumab combination therapy, sample sizes of N = 150 for nivolumab monotherapy and N = 100 for nivolumab / ipilimumab combination therapy (nivolumab 1 mg/kg + ipilimumab 3 mg/kg) will target a Type I error rate of 5% (two-sided) and will have 78% power to detect the difference between these two arms, if the true ORR rates are 10% and 23%, respectively.

*Sample size determination for ovarian cancer cohort*

Also in Amendment 09, an ovarian cancer cohort is added and a one stage design with the treatment of 40 subjects for each arm is used. These sample sizes will provide 79% power to reject the null hypothesis of 10% response rate if the true response rate is 25% with a two-sided Type I error rate of 5%.

***Primary Endpoint:***

Objective Response Rate

*Analyses:*

ORR will be summarized for each cohort by a binomial response rate and corresponding two-sided 95% exact CI using the method proposed by Atkinson and Brown for cohorts using a two-stage design and the Clopper-Pearson method for cohorts using a one-stage design.

For SCLC expansion cohort, the estimated difference including 95% CI of the estimated difference along with its corresponding p-value of ORR assessed by BICR between nivolumab monotherapy and nivolumab/ipilimumab combination therapy (nivolumab 1 mg/kg + ipilimumab 3 mg/kg) will be presented with 95% CI. Similar methods will be used to summarize ORR for each stratification factor. However, p-value will not be provided for each stratification factor.

DOR as determined by the investigator or BICR for selected tumor types will be summarized for subjects who achieve confirmed PR or CR using the Kaplan-Meier (KM) product-limit method. Median values of DOR, along with two-sided 95% CI using the Brookmeyer and Crowley method will also be calculated by cohort. In addition, the percentage of responders still in response at different time points (3, 6, and 12 months) will be presented based on the KM plot.

The magnitude of reduction in tumor burden will be summarized descriptively. Immune related responses will be summarized descriptively.

***Secondary Endpoints:***

Safety will be assessed in all treated subjects. The rate of treatment-related adverse events leading to drug discontinuation within the first 12 weeks of treatment will be assessed.

PFS is defined as the time from treatment assignment in IVRS to the date of the first documented tumor progression or death due to any cause, whichever occurs first.

OS is defined as the time between the date of treatment assignment in IVRS and the date of death due to any cause. A subject who has not died will be censored at the last known alive date.

*Analysis:*

Treatment-related AEs leading to discontinuation will be tabulated using worst grade per NCI CTCAE v 4.0 criteria by system organ class and preferred term. All on-study AEs, Grade 3-4 AEs, treatment-related AEs, Grade 3 4 treatment-related AEs, SAEs, treatment-related SAEs, and AEs leading to discontinuation will be tabulated using worst grade per NCI CTCAE v 4.0 criteria by system organ class and preferred term. On-study lab parameters including hematology, chemistry, liver function, and renal function and Grade 3-4 Lab Abnormalities will be summarized using worst grade NCI CTCAE v 4.0 criteria.

PFS and OS will be summarized descriptively using Kaplan-Meier methodology. Median values of PFS and OS, along with two-sided 95% CIs using the Brookmeyer and Crowley method, will be calculated for each cohort. PFS rates at 6 and 12 months, and OS rates at 12 and 24 months will also be estimated. Associated two-sided 95% CIs will be calculated using the Greenwood formula. Additional survival analysis may be conducted for up to 5 years beyond analysis of the primary endpoint.

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## 1.2 Research Hypothesis

Treatment with nivolumab monotherapy or nivolumab combined with ipilimumab will have clinical activity in subjects with advanced or metastatic tumors.

## 1.3 Objectives(s)

### *1.3.1 Primary Objective*

SCLC Expansion Cohort

- To compare the objective response rate (ORR) as assessed by a Blinded Independent Central Review (BICR) for nivolumab monotherapy versus nivolumab combined with ipilimumab (nivolumab 1 mg/kg + ipilimumab 3 mg/kg).

Other Cohorts

- To evaluate the objective response rate (ORR) of nivolumab monotherapy or nivolumab combined with ipilimumab in subjects with advanced or metastatic tumors. ORR will be assessed by the BICR in selected tumor types.

### *1.3.2 Secondary Objective*

- To assess the safety of nivolumab monotherapy or nivolumab combined with ipilimumab in subjects with advanced or metastatic tumors.
- To assess Overall Survival (OS), OS-rate, Progression Free Survival (PFS), PFS-rate, and Duration of Response (DOR) with nivolumab monotherapy or nivolumab combined with ipilimumab in subjects with advanced or metastatic tumors. PFS and DOR will be assessed by the BICR in selected tumor types.

[redacted]

[redacted]

## 1.4 Product Development Background

As of Jun-2016, approximately 12,300 subjects have been treated with nivolumab monotherapy in single- or multiple-dose Phase 1/2/3 studies or studies with nivolumab in combination with other therapeutics (ipilimumab, cytotoxic chemotherapy, anti-angiogenics, and targeted therapies). Nivolumab as mono or combination therapy is currently being studied in multiple Phase 3 studies in squamous and non-squamous non-small cell lung cancer (NSCLC), malignant melanoma, and renal (clear) cell carcinoma (RCC).

Ipilimumab is an approved therapy for metastatic melanoma[78] and has demonstrated improved overall survival as monotherapy and in combination with dacarbazine[2,3]. An extensive clinical development program for ipilimumab, encompassing more than 14,000 subjects in several cancer types in completed and ongoing studies, as well as a compassionate use program have been conducted. Ipilimumab has been studied in combination with multiple standard of care (SOC) therapies including chemotherapy for squamous and non-squamous NSCLC and radiotherapy for hormone resistant prostate[4]. Phase 3 studies are ongoing in NSCLC, SCLC, and prostate carcinoma.

## 1.5 Overall Risk/Benefit Assessment

There continues to be a significant unmet clinical need for patients with the advanced or metastatic tumors selected for this study ([redacted]). Nivolumab monotherapy has demonstrated clinical activity across several tumor types, including advanced melanoma, NSCLC, and RCC. Nivolumab has demonstrated a manageable safety profile in patients > 700 patients across all clinical trials. The most common AEs included fatigue, rash, pruritis, diarrhea, and nausea. The AE profile for nivolumab monotherapy does not appear to be dose dependent and appears to be similar across a range of solid tumors studied.

Ipilimumab 3 mg/kg is approved for use in the US (advanced melanoma) and in the EU (for previously treated advanced melanoma) based on OS benefit in randomized trials. Furthermore, clinical activity with ipilimumab has been observed in patients with NSCLC, SCLC, and prostate carcinoma. The efficacy of ipilimumab in these tumor types is being investigated in ongoing Phase 3 studies. The currently approved dose for ipilimumab in melanoma patients is 3 mg/kg every 3 weeks for up to 4 doses. Ipilimumab has demonstrated a manageable safety profile and treatment guidelines for immune related adverse events are established based on > 14,000 patients treated in clinical trials.

The combination of nivolumab and ipilimumab has the potential for increased benefit compared to both ipilimumab monotherapy and nivolumab monotherapy. In Study CA209004, 53% of the

subjects with advanced melanoma treated at the dose level of nivolumab 1 mg/kg combined with ipilimumab 3 mg/kg had an objective response, the majority of which had deep tumor reduction of 80% or more. This deep response compares favorably to results with 3 mg/kg ipilimumab monotherapy or nivolumab monotherapy and is the basis for an ongoing randomized Phase 3 study in advanced melanoma (CA209067). Studies investigating the efficacy and safety of nivolumab in combination with ipilimumab are ongoing in NSCLC and RCC.

The combination of nivolumab and ipilimumab has the potential for increased frequencies of adverse events compared to ipilimumab monotherapy or nivolumab monotherapy. The most common (reported at > 10% incidence) treatment related AEs are fatigue, rash, pruritus, diarrhea, lipase increased, pyrexia, ALT increase, AST increased, amylase increased, and vitiligo. This class of AEs are expected for the combination of nivolumab and ipilimumab based on the known AE profile of each drug alone. In addition, many of the Grade 3-4 adverse events were laboratory in nature (ie, LFTs, lipase, amylase), were without clinical sequalae and have been manageable and reversible following intervention dose delays or with systemic steroid treatment. However, these AEs have the potential to be fatal if not detected early and managed per the established algorithm and fatal AEs have been reported for both ipilimumab and nivolumab monotherapy. As of June 2013, one subject died because of a study treatment related adverse event (toxic epidermal necrolysis, TEN) in the nivolumab + ipilimumab development program. Fatal TEN has previously been reported for ipilimumab monotherapy.

Evaluating nivolumab monotherapy and the combination of nivolumab and ipilimumab in subjects with advanced or metastatic solid tumors for which no standard of care in advanced lines of treatment exists, will potentially generate efficacy signals as a basis for further clinical development in these tumor types.

Across multiple tumors, 3 mg/kg nivolumab as well as 3 mg/kg ipilimumab monotherapy have demonstrated a tolerable AE profile in hundreds, respectively thousands of subjects that appears to be independent of tumor type. The combination of 1 mg/kg nivolumab + 3 mg/kg ipilimumab has demonstrated an acceptable AE profile in melanoma and is currently in Phase 3. The same regimen is currently being studied in RCC and NSCLC. The following safety measures have been employed to ensure safety of the subjects in this current study:

- Intense toxicity monitoring will help to ensure the subjects' safety in Study CA209032, including frequent safety conference calls with investigators and representatives of the sponsor
- A BMS medical safety team (MST) routinely reviews safety signals across the entire nivolumab program, including all ongoing combinations with ipilimumab
- Two stage design used which will stop an individual arm for lack of sufficient activity
- For the combination arm, an initial dose escalating safety evaluation phase will be performed to determine the optimal dose for each tumor type independently

In conclusion, the overall risk-benefit assessment for Study CA209032 does justify the conduct of the trial.

# 2 ETHICAL CONSIDERATIONS

## 2.1 Good Clinical Practice

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

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

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

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

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

## 2.2 Institutional Review Board/Independent Ethics Committee

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

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

## 2.3 Informed Consent

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

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

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

Investigators must:

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

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

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

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

# 3 INVESTIGATIONAL PLAN

## 3.1 Study Design and Duration

This is a multicenter Phase 1/2, two stage, open label study of nivolumab monotherapy or nivolumab combined with ipilimumab in adult (≥ 18 years) subjects with advanced or metastatic cancer of one of the following tumor types:

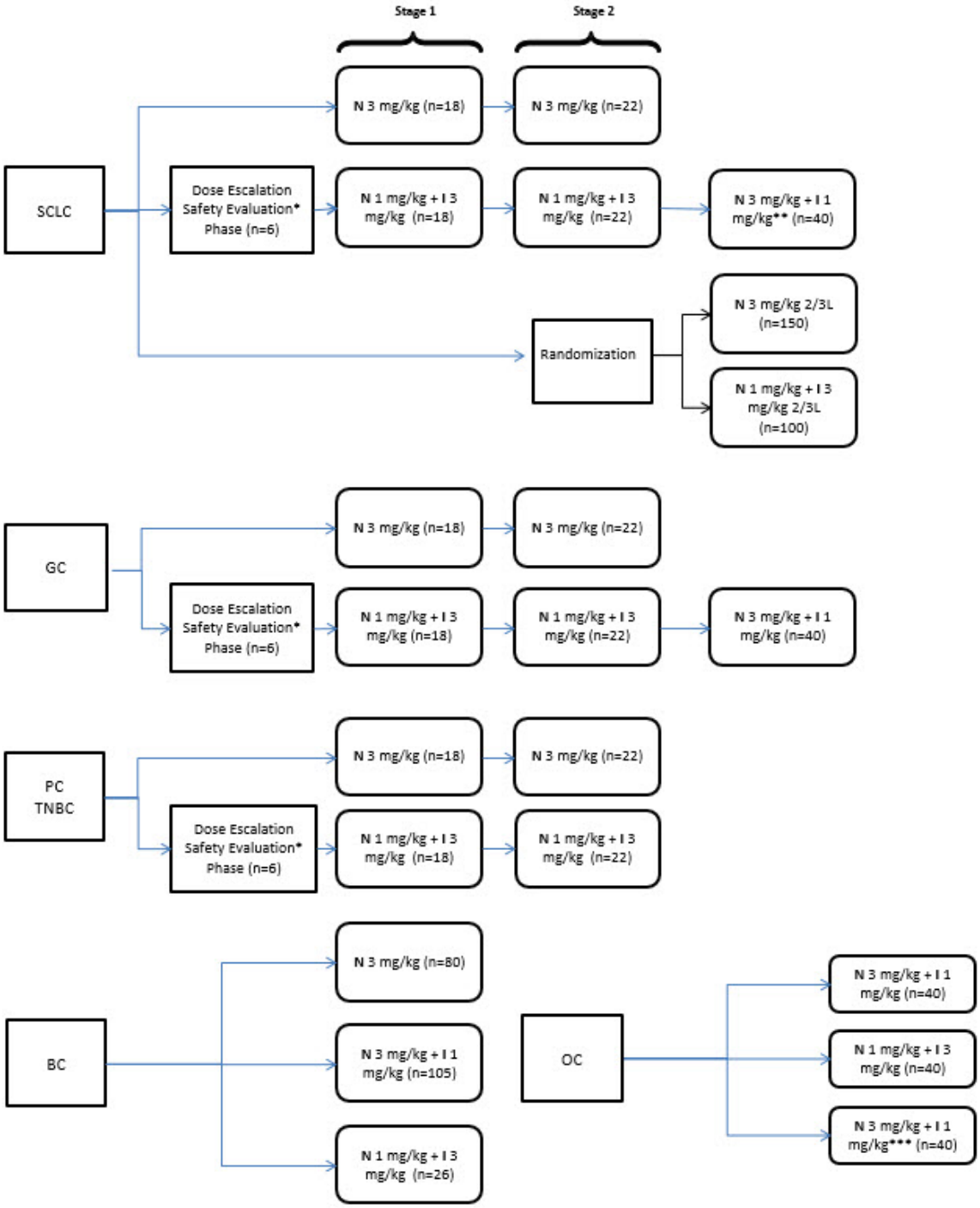
1) Triple Negative Breast Cancer (TNBC)
2) Gastric Cancer (GC)
3) Pancreatic Cancer (PC)
4) Small Cell Lung Cancer (SCLC)

5) Bladder Cancer (BC)
6) Ovarian Cancer (OC)

**Treatment assignment**: The assignment to treatment arm and evaluation of safety and activity will be performed independently for each tumor type (Figure 3.1-1). For each tumor type, subjects will be assigned (described in Section 4.4) to one of the following treatment arms:

| | |
|---|---|
| **Arm N:** | Nivolumab monotherapy (3 mg/kg) Q2W |
| **Arm N-I Dose [redacted] 1:** | Nivolumab (1 mg/kg) + ipilimumab (1 mg/kg) Q3W for 4 doses, then nivolumab (3mg/kg) Q2W |
| **Arm N-I Dose Level 2:** | Nivolumab (1 mg/kg) + ipilimumab (3 mg/kg) Q3W for 4 doses, then nivolumab (3 mg/kg) Q2W |
| **Arm N-I Dose Level 2b**: | Nivolumab (3 mg/kg) + ipilimumab (1 mg/kg) Q3W for 4 doses, then nivolumab (3 mg/kg) Q2W |
| **Arm N-I Dose Level 2c**: | Nivolumab (3 mg/kg) Q2W + ipilimumab (1 mg/kg) Q6W |

**Figure 3.1-1: Study Design for Each Tumor Type**




Notes: N = nivolumab; I = ipilimumab; SCLC = small cell lung cancer; GC = gastric cancer; PC = pancreatic cancer; TNBC = triple-negative breast cancer; BC = bladder cancer; OC = ovarian cancer

*dose level 1 (N1 mg/kg Q3W +I1 mg/kg Q2W) and dose level 2 (N1 mg/kg Q3W + I3 mg/kg Q2W); ** dose level 2b (N3 mg/kg Q3W + I1 mg/kg Q2W); *** dose level 2c (N3 Q2W + I1 Q6W)

**Dose-escalation Safety Evaluation Phase for Combination Arm:** Although the regimen currently used in the Phase 3 melanoma study, nivolumab 1 mg/kg IV + ipilimumab 3 mg/kg, was expected to also be tolerable in the tumors studied here, an initial dose-escalating safety evaluation for the combination arms was conducted with GC, PC, TNBC, or SCLC (described in protocol Section 3.1.2). The BC cohort was added to this protocol following the completion of the safety evaluations in GC, PC, TNBC, and SCLC at dose level 1 (nivolumab 1 mg/kg, ipilimumab 1 mg/kg) which did not reveal safety concerns. Thereby the starting dose level for the BC cohort was dose level 2 (nivolumab 1 mg/kg, ipilimumab 3 mg/kg). Six BC patients were initially randomized to Dose Level 2, after which enrollment to Dose Level 2b (nivolumab 3 mg/kg, ipilimumab 1 mg/kg) began.

Enrollment to Stage 1 for Arm N occurred in parallel to the safety evaluation for Arm N-I.

**Two Stage Design:** GC, PC, TNBC, SCLC Arms will follow a two-stage design to test whether nivolumab monotherapy or nivolumab combined with ipilimumab yields an objective response rate (ORR) that is of clinical interest in the investigated tumor types. For each tumor type, only treatment arms which meet an ORR threshold will proceed from Stage 1 to Stage 2 (described in protocol Section 3.1.3). Enrollment to Stage 2 in a given treatment arm can continue even if the other treatment arm is still in Stage 1.

For Stage 2, upon completion of enrollment for the initial 40 subjects, additional subjects may be assigned into Arm N and Arm N-I up to a total of 100 subjects (including those assigned in Stage 1) in each treatment arm of the given tumor type. For tumor types where nivolumab monotherapy or nivolumab 1 mg/kg plus ipilimumab 3 mg/kg proceeded to Stage 2, assessment of Dose Level 2b in Stage 2 (nivolumab 3 mg/kg + ipilimumab 1 mg/kg, n=up to 70 subjects) may be initiated for that tumor type. For SCLC, an additional 250 subjects (second- or third-line) will be randomized in a 3:2 ratio to one of the 2 expansion groups: nivolumab 3 mg/kg every 2 weeks or nivolumab 1 mg/kg + ipilimumab 3 mg/kg every 3 weeks for 4 cycles followed by nivolumab 3 mg/kg.

### *3.1.1 Modified Designs*

**Bladder Cancer Cohort**

The enrollment for the BC cohorts N and N-I (Dose Level 2b) will be conducted as a One Stage Design:

- Recently, inhibition of PD-L1 by MPDL3280A was shown to have clinical activity in patients with metastatic urothelial bladder cancer, leading to approval of the drug in this indication by the FDA.[59] In particular, in patients with tumors tested positive for PD-L1 expression, the overall response rate was 43%. The overall response rate regardless of PD-L1 expression was 20%.

- As these data show that checkpoint inhibition has potential to be an active treatment for patients with advanced bladder cancer, a Two Stage design with the intent of avoiding to expose too many patients to a potentially ineffective treatment does not appear to be necessary for this specific tumor type.
- Bladder arms N and N-I (Dose Levels 2 and 2b) will be conducted as a One Stage Design with the treatment of 26-105 subjects in each arm. The Safety Evaluation Phase for the N-I arm will start at Dose Level 2 (nivolumab 1 mg/kg, ipilimumab 3 mg/kg) and will evaluate safety and tolerability after the first 6 randomized subjects. Following the N-I safety evaluation phase, Dose Levels 2 will enroll 26 subjects and 2b will enroll up to a total of 105 subjects. Based on the safety evaluations thus far on study, no dose escalation phase is necessary for bladder cohort N-I Dose Level 2b (nivolumab 3 mg/kg, ipilimumab 1 mg/kg).

**Ovarian Cancer Cohort**

The OC cohorts N-I (Dose Level 2, 2b, 2c) will be conducted as a One Stage Design with the enrollment of 40 subjects in each arm. The Dose Level 2c was added to Ovarian Cancer Cohort based on the results of CA209003 and CA209012 clinical studies mentioned above. The efficacy and tolerability of nivolumab monotherapy observed in CA209003 study with longer follow-up of previously treated NSCLC patients suggested a strategy in which nivolumab serves as the "base" of a combination regimen, with ipilimumab exposure limited by lower doses and/or less frequent administration. This strategy is the basis for new nivolumab and ipilimumab combination regimens with nivolumab 3 mg/kg Q2W combined with ipilimumab 1 mg/kg Q6W. This regimen was used in CA209012 study with preliminary data showing a promising activity and a good safety profile of the combination.

The enrollment to the N-I arm to Dose Levels 2, 2b, and 2c will be conducted simultaneously. Due to the low risk of development of new safety signals on the combination arms confirmed by the additional information from the combination studies in melanoma, lung, renal cell carcinoma, and glioblastoma as well as the clinical study with ipilimumab 10 mg/kg monotherapy in ovarian cancer, which did not reveal any new safety signals ([redacted] no Safety Evaluation Phase will be employed. Ovarian cancer subjects will be followed for related toxicities and decisions to stop treatment will be made on an ongoing basis.

### *3.1.2 Dose-Escalating Safety Evaluation Phase for Arm N-I*

The combination of 1 mg/kg nivolumab + 3 mg/kg ipilimumab is already approved for the treatment of advanced and metastatic melanoma regardless of BRAF mutational status and has more recently been tested in NSCLC and RCC. This regimen is expected to also be tolerable in the tumors being studied in this protocol. However, as an added safety precaution, the combination of N-I will first be assessed in a dose escalating safety phase. This safety evaluation will be conducted for each of the investigated tumor types independently (Table 3.1.2-1). Recently, data from Phase 1/2 studies in NSCLC and RCC have shown, that the dose level of 1 mg/kg ipilimumab plus 3 mg/kg nivolumab is well tolerated while potentially preserving the

tumor efficacy.[9,10] Therefore, a Dose Level 2b (nivolumab 3 mg/kg, ipilimumab 1 mg/kg) will be investigated in the Dose-Escalating Safety Evaluation Phase in case Dose Level 2 is not tolerable for any of the tumor types being studied.

**Table 3.1.2-1: Dose Cohort for Arm N-I**

| Dose Cohort Level | Nivolumab (mg/kg) | Ipilimumab (mg/kg) |
|---|---|---|
| -1 | 0.3 | 1 |
| 1 | 1 | 1 |
| 2 | 1 | 3 |
| 2b | 3 | 1 |

The first dose cohort will be Level 1. If this is deemed tolerable, then Level 2 will be initiated. If Level 1 is not tolerable, then Level -1 will be initiated. The BC cohort will start at Level 2. If Dose Level 2 is not tolerable for a certain tumor type, Dose Level 2b will be investigated. There will be no dose escalation beyond Level 2 or Level 2b. Once the highest dose level for further investigation has been confirmed in the Dose-Escalating Safety Evaluation Phase, Arm N-I will continue enrolling with Stage 1 (Section 3.1.3).

Subjects on active treatment need to be followed up for at least 6 weeks after start of study treatment before determination of the tolerability of a dose level. However, tolerability beyond 6 weeks may also be taken into consideration. The criteria for tolerability (Table 3.1.2-2) are based on drug related adverse events leading to permanent discontinuation (listed in Section 4.5.5) and include:

- If none of the first 3 subjects in a given dose level permanently discontinue treatment due to study drug related adverse events within the first 6 weeks, then this dose cohort will be deemed as tolerable. For Dose Cohort Level 2 or Dose Cohort Level 2b, at least 6 subjects need to have been exposed to this dose level and followed up for at least 6 weeks after start of study treatment before the enrollment will proceed in Stage 1. The enrollment of these 6 subjects will occur in a staggered mode, first 3 subjects will be enrolled and followed up for at least 6 weeks before the next 3 subjects will be enrolled and followed up for at least 6 weeks.
- If one or two of the first 3 subjects in a dose cohort permanently discontinue treatment within the first 6 weeks due to study drug related adverse events, this cohort will be expanded to 6 subjects.
- If one of 6 subjects in a dose cohort permanently discontinue treatment due to study drug related adverse events within the first 6 weeks, then dose cohort will be deemed as tolerable.
- If two of 6 subjects in a dose cohort permanently discontinue treatment within the first 6 weeks due to study treatment related adverse events, this cohort may be expanded to 9 subjects. If an expansion is not possible because of the severity of the adverse events leading to permanent discontinuation, then this dose cohort will be deemed not tolerable.

- If no more than two of 9 subjects in a dose cohort permanently discontinue treatment due to study treatment related adverse events within the first 6 weeks, then this dose cohort will be deemed as tolerable.
- If at least three of the first 9 subjects in a dose cohort permanently discontinue treatment within the first 6 weeks due to study treatment related adverse events, a Dose -1 Cohort (in case of toxicities at Dose Level 1) or a Dose 2b Cohort (in case of toxicities at Dose Level 2) may proceed.

For the decision to enroll a Dose -1 or Dose 2b Cohort, the clinical severity of the adverse events leading to permanent discontinuation in the previous Dose Cohort will be taken into consideration.

**Table 3.1.2-2: Dose Cohort for Arm N-I**

| Number of subjects treated and followed up for at least 6 weeks after start of study treatment | Number of subjects with permanent discontinuation due to treatment related adverse events | Next Step |
|---|---|---|
| 3 | 0 | Dose tolerable |
| 3 | 1-2 | Expand to 6 subjects |
| 6 | ≤ 1 | Dose tolerable |
| 6 | 2 | Expand to 9 subjects |
| 9 | ≤ 2 | Dose tolerable |
| 9 | ≥ 3 | Dose not tolerable[a] |

[a] discussion with investigators to review risk/benefit taking into account reversibility of AEs and depth of response

### *3.1.2.1 Evaluation of Risk/Benefit for Doses that do not meet Tolerable Criteria*

In the event of ≥ 3 of the first 9 subjects requiring permanent discontinuation, a discussion with investigators may be held to review the risk/benefit of this regimen. The rationale for this evaluation is that the most frequent severe drug related AEs for the combination in melanoma have been asymptomatic, reversible laboratory events (ie, LFTs and lipase) and there is preliminary evidence of deep and durable responses in the N-I arm in advanced melanoma (CA209004). Therefore, a discussion of the risk/benefit of the regimen will be triggered if the following criteria are met:

- A majority of subjects who discontinue due to treatment related AEs have deep tumor response (ie, > 80% reduction)
- All treatment related AEs leading to discontinuation are non-fatal, reversible and without severe sequela (ie, GI perforation)
- A majority of the treatment related AEs are laboratory in nature, asymptomatic, and monitorable via routine blood draws

If a decision is made to continue with a regimen because of a favorable risk/benefit profile (ie, non-fatal AEs in subjects with near CRs that are durable) and despite meeting the 'not tolerable' criteria above, then IRBs must be notified, ICFs must be updated, and discussion of the risk/benefit must be documented with all future subjects who enroll on this regimen.

### 3.1.3 Staged Enrollment (Stage 1 and Stage 2)

#### 3.1.3.1 Stage 1

This Stage is intended to assess the efficacy in 18 subjects per treatment arm per tumor type to determine whether enrollment should continue to Stage 2. For efficacy determination, each Arm within each tumor type will be assessed independently.

**Arm N**: The enrollment and treatment of 18 subjects to Arm N per tumor type can begin while the initial Dose Cohort for Arm N-I in this tumor type is still ongoing. The dose level in Arm N is 3 mg/kg nivolumab IV every two weeks (Q2W). This dose has been established in more than 700 subjects with various tumor types exposed to nivolumab monotherapy with a tolerable AE profile. Therefore no dose adjustments for Arm N are planned.

**Arm N-I:** Up to 18 subjects will be enrolled and treated in this arm per tumor type at the highest tolerated Dose Level determined during the Dose Escalating Safety Evaluation phase. The 3-9 subjects treated at the highest dose level confirmed for further investigation from the Dose Escalating Safety Evaluation phase will be counted as part of the 18 required subjects.

#### 3.1.3.2 Criteria to proceed from Stage 1 to Stage 2

The decision to proceed from Stage 1 to Stage 2 will be made for each tumor and for each treatment arm independently and include (Table 3.1.3.2-1):

- 2 or more of 18 subjects in a given arm must have confirmed PR or CR before enrollment for that arm will be continued in Stage 2. The tolerability of the regimen will continue to be evaluated by the Sponsor with the investigators to ensure that it is acceptable for continued enrollment.
  - Subjects with initial PD per RECIST 1.1 who continue treatment in their initially assigned treatment arm beyond progression (Section 4.5.7) and subsequently reach confirmed immune related CR or PR (relative to initial tumor assessment) and including any new measurable lesions within the sum of all target lesions, will be considered as having an objective response for the purposes of meeting criteria for moving from Stage 1 to Stage 2. Although not standard RECIST 1.1, these immune related response criteria using unidimensional measurements account for the unusual immune related tumor response patterns reported for both ipilimumab and nivolumab.
- Once the last subject in a given treatment arm has permanently discontinued treatment for any reason or has reached the Week 48 Tumor Assessment, and the above criteria are not met, then this treatment arm will not proceed to Stage 2. Ongoing subjects will continue to be followed up for efficacy and safety.
- In case that 2 or more of subjects in a given arm enrolling in Stage 1 have confirmed PR or CR, but the enrollment of 18 subjects for Stage 1 has not been completed or 18 subjects have

been enrolled but have not been randomized and started treatment at that timepoint, the following applies:

- Arm N: the enrollment for that arm can be continued in Stage 2. The tolerability of the regimen will continue to be evaluated by the Sponsor with the investigators to ensure that it is acceptable for continued enrollment.
- Arm N-I: at least 9 subjects need to have been exposed to the highest dose level which has been confirmed for Stage 1 and followed up for at least 6 weeks after start of study treatment before the enrollment for that arm can be continued in Stage 2. The tolerability of the regimen will continue to be evaluated by the Sponsor with the investigators to ensure that it is acceptable for continued enrollment.

**Table 3.1.3.2-1: Efficacy criteria to proceed from Stage 1 to Stage 2**

| Efficacy criteria | Next Step |
|---|---|
| 2 or more of 18[a] subjects in a given arm have confirmed PR or CR | Go into Stage 2 |
| 1 or no of 18[a] subjects in a given arm have confirmed PR or CR. | No Go into Stage 2 |

[a] see Section 3.1.3.2 last bullet point for further clarification

### *3.1.3.3 Stage 2*

**Arm N:** For treatment **Arm N** of the given tumor type that continues to Stage 2, additional subjects will be assigned to a total of 40 subjects, inclusive of those enrolled in Stage 1. For tumor types where nivolumab monotherapy proceeded to Stage 2, assessment of Dose Level 2b in Stage 2 (nivolumab 3 mg/kg + ipilimumab 1 mg/kg, n=40 subjects) will be initiated for that tumor type. A separate evaluation of Dose Level 2b may be necessary if the safety and tolerability of Dose Level 2 has not been confirmed.

**Arm N-I (Dose Level 2):** In case treatment Arm N-I at Dose Level 2 proceeds to Stage 2, additional subjects will be assigned to a total of 40 subjects at Dose Level 2, inclusive of those enrolled in Stage 1. In order to investigate the Dose Level 2b with a potentially better tolerability while preserving tumor efficacy, an additional 40 subjects at Dose Level 2b will be enrolled once Arm N-I Dose Level 2 proceeds to Stage 2. In this case, a separate safety evaluation of Dose Level 2b is not necessary, as the safety and tolerability of Dose Level 2 had already been confirmed previously.

Within a given tumor type, the treatment arms can proceed to Stage 2 independent of the status of the other treatment arm.

For Stage 2, upon completion of enrollment of the initial 40 subjects, additional subjects may be assigned into Arm N and Arm N-I up to a total of 100 subjects (including those assigned in Stage 1) in each treatment arm of the given tumor type. For tumor types where nivolumab monotherapy or nivolumab 1 mg/kg plus ipilimumab 3 mg/kg proceeded to Stage 2, assessment

of Dose Level 2b in Stage 2 (nivolumab 3 mg/kg + ipilimumab 1 mg/kg, n=up to 70 subjects) may be initiated for that tumor type.

#### *3.1.3.4 Modified Design Bladder Cancer Cohort*

Bladder arms N and N-I (Dose Levels 2 and 2b) will be conducted as a One Stage Design with the treatment of 26-105 subjects in each arm. The Safety Evaluation Phase for the N-I arm will start at Dose Level 2 (nivolumab 1 mg/kg, ipilimumab 3 mg/kg) and will evaluate safety and tolerability after the first 6 randomized subjects. Following the N-I safety evaluation phase, Dose Levels 2 will enroll 26 subjects and 2b will enroll up to a total of 105 subjects. Based on the safety evaluations thus far on study, no dose escalation phase is necessary for bladder cohort N-I Dose Level 2b (nivolumab 3 mg/kg, ipilimumab 1 mg/kg).

#### *3.1.3.5 Arm N-I (Dose Level 2b)*

Based on the safety evaluations thus far on study, no dose escalation phase is necessary for bladder cohort N-I Dose Level 2b (nivolumab 3 mg/kg, ipilimumab 1 mg/kg).

### *3.1.4 SCLC Expansion*

SCLC cohorts Arm N and Arm N-I met the pre-specified safety and efficacy criteria and proceeded to Stage 2. Based on an interim data review, disease control rates (SD + PR + CR) of 36% and 57% for Arms N and N-I, respectively, were estimated. In order to further investigate nivolumab and nivolumab combined with ipilimumab activity in specific SCLC subpopulations, the SCLC expansion cohorts will enroll additional subjects based on response to prior treatment and the number of previous therapies. Up to 250 second or third line subjects will be randomized in a 3:2 ratio to one of 2 expansion groups: Arm A (150 subjects treated with nivolumab 3 mg/kg every 2 weeks (Q2W)) or Arm B (100 subjects treated with nivolumab 1 mg/kg + ipilimumab 3 mg/kg every 3 weeks (Q3W) for 4 cycles followed by nivolumab 3 mg/kg (Q2W) and will be stratified for number of prior treatment lines (1 vs 2 prior chemotherapy regimens).

The study population for the SCLC expansion cohort is specified as follows:

- Histopathologically or cytologically confirmed diagnosis of SCLC.
- All subjects had platinum-based first-line treatment. Subjects with previous second-line chemotherapy treatment are eligible as well.
- Subjects with platinum refractory, resistant, or sensitive disease are eligible.
- Subjects with initial diagnosis of limited or extensive disease are eligible.
- Documented objective radiographic disease progression at study entry.

Tumor assessments for subjects in the SCLC expansion cohort will undergo a BICR assessment. The crossover option refers only to the original cohorts and not the new cohorts enrolled under or after Amendment 09.

### 3.1.5 Duration of Study Treatment

The study treatment will be continued until disease progression (investigator-assessed RECIST 1.1-defined progression) or occurrence of unacceptable toxicity as defined in Section 4.5.5. For subjects achieving confirmed CR or a PR for more than 3 months (long lasting PR) the investigator may decide to hold treatment for this subject after discussion with the medical monitor of the sponsor. During the treatment hold subjects should follow all study procedures as specified in Section 5.1. Subjects for which treatment was held following long lasting responses and who experience a recurrence of disease progression may reinitiate their last study treatment. Before reinitiating treatment, the investigator should discuss the individual case with the medical monitor and document in the study records.

### 3.1.6 Crossover for Subjects in Arm N

Subjects in Arm N may crossover to Arm N-I if all of the following criteria are met:

- The Safety Evaluation Phase for the N-I regimen has been completed and at least 6 subjects have been exposed to the dose level used for Stage 1 of the N-I regimen. In case Dose Level 2b has been activated and completed the safety assessment, subjects for cross over will be assigned to Dose Level 2 or Dose Level 2b after discussion between the sponsor and investigator taking into consideration previous safety and efficacy signals at these dose levels and the status of the individual subject planned for cross over.
- Subject has further disease progression (investigator-assessed RECIST 1.1-defined progression according to description provided in Section 4.5.7, confirmed at least 4 weeks after the initial tumor assessment showing progression (definition of confirmed progression see Appendix 3)) in the absence of clinical deterioration. For subjects with clear evidence of new or progressing brain metastases a confirmation is not required. These subjects may proceed with brain radiation therapy and, if necessary, with gamma-knife or surgical resection, after having completed the therapy a cross over to Arm N-I can be considered (see Section 3.4.2.1).
- Subjects with rapidly progressing tumors under nivolumab monotherapy may undergo radiation treatment first before initiation of the cross over after discussion between the sponsor and investigator.
- Subject has not experienced nivolumab related adverse events leading to permanent discontinuation as described in Section 4.5.5.
- Subject is not continuing to derive any clinical benefit from nivolumab single agent therapy as assessed by the investigator which would allow continuation of nivolumab monotherapy (see Section 4.5.8).
- Subject is not a SCLC patient enrolled based on the Amendment 09 expansion.
- The individual case must be discussed with the medical monitor prior to cross over.

Subjects crossing over to Arm N-I will start treatment at Day 1 Week 1 as described for subjects originally randomized to Arm N-I. Subjects who crossed over and subsequently have an objective response in Arm N-I will not be considered in the decision making for Arm N-I proceeding to Stage 2. Subjects in Arm N-I cannot crossover to Arm N.

### 3.1.7 Re-exposure with Nivolumab/Ipilimumab for Subjects in Arm N-I

Subjects in Arm N-I may undergo a re-exposure with nivolumab/ipilimumab if they achieved an initial objective response (PR or CR) or stable disease of ≥ 3 months and had a subsequent documented progression. Subjects must fulfill the following criteria:

- Subjects have not experienced any related adverse events as described in Section 4.5.5 (discontinuation criteria).
- Eligible subjects will receive up to four doses of nivolumab/ipilimumab (based on treatment assigned at randomization) during Re-exposure. Subjects can receive nivolumab monotherapy, if ipilimumab caused toxicities leading to its discontinuation (section 4.5.5)
- Dosing may be delayed for toxicity (see Section 4.5.2).
- Subjects who have permanently discontinued study therapy for any reason and are in the follow up phase may not receive any re-exposure dosing.

### 3.1.8 Review of Safety

The subjects' safety will be monitored on an ongoing basis as described fully in Section 7. Safety conference calls with investigators and representatives of the sponsor will be held approximately every other week with additional meetings as necessary. Decisions for the safety evaluation phase of Arm N-I and for continuing from Stage 1 to Stage 2 in both treatment arms will be made in conjunction with the investigators. In addition, a BMS medical safety team (MST) routinely reviews safety signals across the entire nivolumab program including combination studies with ipilimumab.

### 3.1.9 Treatment Beyond Progression

Treatment beyond investigator-assessed RECIST 1.1-defined progression will be permitted if the subject experiences investigator-assessed clinical benefit and the subject is tolerating the study treatment (Section 4.5.7).

### 3.1.10 Intrapatient Dose Reductions

Intrapatient dose reduction is not permitted for any reason. Dose delays for the management of study treatment related adverse events are described in Section 4.5.2.

### 3.1.12 Study Phases

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

Screening Phase:

- Begins by establishing the subject's initial eligibility and signing of the informed consent form (ICF).
- Subject is enrolled using the Interactive Voice Response System (IVRS).

Treatment Phase:

- Begins with the vial assignment call to the IVRS.
- A negative pregnancy test must be documented within 24 hours prior to the start of investigational product.
- Within 3 days from treatment assignment, the subject must receive the first dose of study medication:
  - **Arm N (nivolumab monotherapy):**
    Nivolumab 3 mg/kg IV every two weeks (Q2W). See Table 4.5-1
  - **Arm N-I (nivolumab + ipilimumab)**
    - Dose Escalation Phase:

*Staged Enrollment Phase*: Dose Level determined in Dose Escalation Phase. See Table 4.5-2 and Table 4.5-3.

- **Dose Level 1**, Nivolumab 1 mg/kg IV combined with ipilimumab 1 mg/kg IV Q3W for 4 doses, then nivolumab 3 mg/kg IV Q2W. See Table 4.5-2 and Table 4.5-3.
- **Dose Level 2:** Nivolumab 1 mg/kg IV combined with ipilimumab 3 mg/kg IV Q3W for 4 doses, then nivolumab 3 mg/kg IV Q2W.

- **Dose Level 2b:** Nivolumab 3 mg/kg IV combined with ipilimumab 1 mg/kg IV Q3W for 4 doses, then nivolumab 3 mg/kg IV Q2W.
- **Dose Level 2c:** Nivolumab 3 mg/kg IV Q2W combined with ipilimumab 1 mg/kg Q6W.

- Adverse event assessments will be documented at each visit throughout the study.

On-study laboratory assessments (after D1W1) should be drawn within 72 hours prior to dosing according to the schedule in Table 5.1-2, Table 5.1-3, Table 5.1-4, and Table 5.1-5.

- Women of child bearing potential (WOCBP) must have a negative pregnancy test documented as follows:
  - Arm N and Arm N-I2c: before every other nivolumab administration, within 24 hours prior to dosing.
  - Arm N-I: before every combined nivolumab / ipilimumab administration, within 24 hours prior to dosing. Thereafter every 4 weeks, within 24 hours prior to nivolumab dosing.
- PK samples and immunogenicity samples will be collected according to the schedule in Section 5.5.
- Study drug dosing may be delayed for toxicity. See Section 4.5.2.
- Treated subjects will be evaluated for response according to the RECIST 1.1 guidelines beginning 6 weeks (± 1 week) after first dose and continuing every 6 weeks (± 1 week) for the first 24 weeks, and then every 12 weeks (± 1 week) while on treatment or on treatment hold for any reason until disease progression (investigator-assessed RECIST 1.1-defined progression) or treatment discontinuation, except for subjects treated beyond progression or who discontinued treatment for other reasons than PD.

This phase ends when the subject is discontinued from study therapy. For a complete list of reasons for treatment discontinuation, see Section 4.5.5.

Follow-Up Phase

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

Two follow-up visits include collection of PK/immunogenicity samples Table 5.1-6, Table 5.5.1-1, and Table 5.5.1-2.

- Subjects who discontinue treatment for reasons other than tumor progression will continue to have tumor assessments beginning 6 weeks (± 1week) after first dose and continuing every 6 weeks (± 1 week) for the first 24 weeks from first dose, and every 12 weeks (± 1 week) thereafter until disease progression (investigator-assessed RECIST 1.1-defined progression). This does also apply to subjects whose treatment was put on hold after achieving confirmed CR or PR for more than 3 month (long lasting PR).

- Subjects will be followed for drug-related toxicities until these toxicities resolve, return to baseline or are deemed irreversible. All adverse events will be documented for a minimum of 100 days after last dose.
- Follow up visits should be made in-person. If a subject is unable to make an in-person visit, the reason should be clearly documented at the site.
- Follow-up visit 1 (FU1) = 35 days from the last dose ± 7 days or coincide with the date of discontinuation (± 7 days) if date of discontinuation is greater than 42 days after last dose, Follow-up visit 2 (FU2) = 80 days (± 7 days) from follow-up visit 1.
- After completion of the first two follow-up visits, subjects will be followed every 3 months for survival via in-person visits, phone or email. Ad hoc survival data requests may be made during the study as well, particularly during database locks.

### *3.1.13 Total Study Duration*

It is projected that the accrual for the Initial Dose Cohort and the Efficacy Signal Detection - Stage 1 of the study will be completed within 4 months after FPFV and that the results of the interim analysis will be available 9 months after FPFV. The final analysis is expected at 60 months after FPFV.

## 3.2 Post Study Access to Therapy

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

## 3.3 Study Population

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

### *3.3.1 Inclusion Criteria*

**1. Signed Written Informed Consent**

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

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

## 2. Target Population

a) Subjects with pathologically confirmed locally advanced or metastatic disease of the following tumor types:

i) Women with histologically or cytologically confirmed breast carcinoma who must meet all of the following:

(1) Tumor must be "triple receptor negative" defined as ER/PR negative per local lab and HER-2 negative defined as HER-2 0 or 1+ by IHC, or IHC 2+ and ISH not amplified, or ISH-non amplified.

AND

(2) Subjects must have progression or refractory disease. Subjects must have had at least 1 chemotherapy regimen for the treatment of metastatic (Stage IV) or locally advanced disease.

OR

(3) Subject actively refuses chemotherapy for the treatment of metastatic (Stage IV) or locally advanced disease considered as standard treatment for this disease stage, despite being informed by the investigator about the treatment options. Subjects actively refusing chemotherapy must have had progression or refractory disease prior to starting study treatment. The subject's refusal must be thoroughly documented. The investigator will discuss each individual subject refusing chemotherapy with the sponsor's medical monitor to confirm eligibility.

ii) Subjects with histologically confirmed Gastric or Gastro-Esophageal Junction Carcinoma (including adenocarcinoma arising from the lower esophagus) who must meet all of the following:

(1) Subjects must have progression or refractory disease. Subjects must have had at least 1 chemotherapy regimen for the treatment of metastatic (Stage IV) or locally advanced disease. Subjects with HER-2 positive tumors must have had previous treatment with trastuzumab.

OR

(2) Subject actively refuses chemotherapy or biological therapy for the treatment of metastatic (Stage IV) or locally advanced disease considered as standard treatment for this disease stage, despite being informed by the investigator about the treatment options. Subjects actively refusing chemotherapy must have had progression or refractory disease prior to starting study treatment. The subject's refusal must be thoroughly documented. The investigator will discuss each individual subject refusing chemotherapy with the sponsor's medical monitor to confirm eligibility.

iii) Subjects with histologically confirmed Pancreatic adenocarcinoma who must meet all of the following:

(1) Subjects must not have clinically relevant ascites at baseline, such as ascites in need of paracentesis.

AND

(2) Subjects must have had best response of stable disease, or progression or refractory disease during or after at least 1 chemotherapy regimen for the treatment of metastatic (Stage IV) or locally advanced disease

OR

(3) Subject actively refuses chemotherapy for the treatment of metastatic (Stage IV) or locally advanced disease considered as standard treatment for this disease stage, despite being informed by the investigator about the treatment options. Subjects actively refusing chemotherapy must have had best response of stable disease, or progression or refractory disease prior to starting study treatment. The subject's refusal must be thoroughly documented. The investigator will discuss each individual subject refusing chemotherapy with the sponsor's medical monitor to confirm eligibility.

iv) Subjects with histologically or cytologically confirmed small cell lung cancer. Subjects must have progression or refractory disease. Subjects must have had at least 1 platinum based chemotherapy regimen for the treatment of limited or extensive stage disease, but not more than 2 prior chemotherapy regimens. For subjects to be enrolled in the SCLC expansion cohorts to following eligibility criteria apply:

(1) All subjects must have had platinum-based first-line treatment. Subjects with previous second-line chemotherapy treatment are eligible as well.

(2) Subjects with platinum refractory, resistant, or sensitive disease are eligible (Appendix 4).

(3) Subjects with initial diagnosis of limited or extensive disease are eligible.

(4) Documented objective radiographic disease progression at study entry.

v) Subjects with histologically or cytologically confirmed urothelial carcinoma (including mixed histologies of urothelial carcinoma with elements of other subtypes) of the renal pelvis, ureter, bladder, or urethra, who must meet all of the following:

(1) Subjects must have progression or refractory disease. Subjects must have had at least 1 platinum based chemotherapy regimen for the treatment of metastatic (Stage IV) or locally advanced unresectable disease.

OR

(2) Subjects with disease recurrence within 1 year of completing a platinum based neoadjuvant or adjuvant therapy.

OR

(3) Subject actively refuses chemotherapy for the treatment of metastatic (Stage IV) or locally advanced unresectable disease considered as standard treatment for this disease stage, despite being informed by the investigator about the treatment options. Subjects actively refusing chemotherapy must have had progression or refractory disease prior to starting study treatment. The subject's refusal must be

thoroughly documented. The investigator will discuss each individual subject refusing chemotherapy with the sponsor's medical monitor to confirm eligibility.

vi) Subjects with histologically confirmed ovarian carcinoma (including epithelial ovarian cancer (OC), primary peritoneal, or fallopian tube carcinoma) who must meet all of the following:

(1) Subjects must have received one platinum-based chemotherapeutic regimen for management of primary disease, possibly including intraperitoneal therapy, consolidation, biologic/targeted (non-cytotoxic) agents (eg, bevacizumab) or extended therapy administered after surgical or non-surgical assessment. Subjects are allowed to have received, but are not required to have received subsequent cytotoxic regimens for management of recurrent or persistent disease. For the purposes of this study, PARP inhibitors given for recurrent or progressive disease will be considered cytotoxic. A line of therapy is defined as a regimen used to treat initial disease (frontline) or following disease progression (second and subsequent lines). A change in regimen for reasons of toxicity or consolidation/maintenance in the absence of disease progression does not constitute a new line of therapy.

(2) Subjects must have documented disease progression after completion of their most recent regimen.

(3) Subjects with platinum refractory, resistant, or sensitive disease are eligible (Appendix 5).

b) Subjects must have measurable disease by CT or MRI per RECIST 1.1 criteria (see Appendix 3). (Radiographic tumor assessment must be performed within 28 days prior to first dose).

c) Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1 (refer to Appendix 1).

d) Subjects must consent to allow for a baseline tumor biopsy. Baseline tumor biopsies should preferably be performed from a tumor site that is NOT the only site of measurable disease. For subjects with only one site of measurable disease, tumor biopsies are allowed if at least one of the following criteria is met:

- CT imaging performed after biopsy and there is still measurable disease or
- The type of biopsy is not expected to impact the measurability (eg, core needle biopsy) regardless on when imaging occurred, prior to or after biopsy.

Tumor material from biopsies done before the screening period is acceptable if the biopsy was performed within 3 months prior to the planned treatment start and no other systemic cancer therapy was administered in the meanwhile.

e) All baseline laboratory requirements will be assessed and should be obtained within 14 days of first dose. Screening laboratory values must meet the following criteria:

i) WBCs ≥ 2000/μL

ii) Neutrophils ≥ 1500/μL

iii) Platelets ≥ 100 x $10^3$/μL

iv) Hemoglobin ≥ 9.0 g/dL

v) Serum creatinine ≤ 1.5 x ULN or calculated creatinine clearance (CrCl) ≥ 40 mL/minute (using Cockcroft/Gault formula)

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

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

vi) AST ≤ 3 x ULN

vii) ALT ≤ 3 x ULN

viii) Total Bilirubin ≤ 1.5 x ULN (except subjects with Gilbert Syndrome who can have total bilirubin < 3.0 mg/dL)

ix) Albumin ≥ 3 g/dL

x) Lipase ≤ 1.5 ULN. Subjects with Lipase > 1.5 ULN may enroll if there are neither clinical nor radiographic signs of a pancreatitis.

xi) Amylase ≤ 1.5 ULN. Subjects with Amylase > 1.5 ULN may enroll if there are neither clinical nor radiographic signs of a pancreatitis.

f) Prior focal radiotherapy to an isolated bony or soft tissue metastasis must be completed at least 2 weeks before study drug administration.

g) Subject Re-enrollment: This study permits the re-enrollment of a subject that has discontinued the study as a pre-treatment failure (ie, subject has not been assigned / has not been treated). If re-enrolled, the subject must be re-consented and assigned a new subject number from IVRS.

**3. Age and Reproductive Status**

a) Men and women ≥ 18 years of age

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

c) Women must not be breastfeeding

d) WOCBP must agree to follow instructions for method(s) of contraception from the time of enrollment for the duration of treatment with study drug (s) plus approximately 5 half-

lives of study drug (s) plus 30 days (duration of ovulatory cycle) for a total of 5 months post treatment completion.

e) Men who are sexually active with WOCBP must agree to follow instructions for method(s) of contraception for the duration of treatment with study drug (s) plus approximately 5 half-lives of study drug (s) plus 90 days (duration of sperm turnover) for a total of 7 months post-treatment completion.

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

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

At a minimum, subjects must agree to use one highly effective method of contraception. See Appendix 6 for details on highly effective methods of contraception.

### *3.3.2 Exclusion Criteria*

**1. Target Disease Exceptions**

a) Active brain metastases or leptomeningeal metastases. Subjects with brain metastases are eligible if these have been treated and there is no magnetic resonance imaging (MRI) evidence of progression for at least 4 weeks after treatment is complete and within 28-days prior to first dose of study drug administration. There must also be no requirement for immunosuppressive doses of systemic corticosteroids (> 10 mg/day prednisone equivalents) for at least 2 weeks prior to study drug administration. Subjects with incidental findings of asymptomatic brain metastases at screening may start study treatment without prior radiation treatment after discussion between the sponsor and investigator.

**2. Medical History and Concurrent Diseases**

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

b) Other prior malignancy active within the previous 3 years except for local or organ confined early stage cancer that has been definitively treated with curative intent, does not require ongoing treatment, has no evidence of residual active disease, and has a negligible risk of recurrence and is therefore unlikely to interfere with the primary and secondary endpoints of the study, including response rate and safety.

c) Subjects with active, known or suspected autoimmune disease. Subjects with vitiligo, type I diabetes mellitus, residual hypothyroidism due to autoimmune thyroiditis only

requiring hormone replacement, or conditions not expected to recur in the absence of an external trigger are permitted to enroll.

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

e) Prior therapy with experimental anti-tumor vaccines; any T cell co-stimulation or checkpoint pathways, such as anti-PD-1, anti-PD-L1, anti-PD-L2, anti-CD137, or anti-CTLA-4 antibody, including ipilimumab; or other medicines specifically targeting T cell is also prohibited.

f) All toxicities attributed to prior anti-cancer therapy other than alopecia and fatigue must have resolved to grade 1 (NCI CTCAE version 4) or baseline before administration of study drug. Subjects with toxicities attributed to prior anti-cancer therapy which are not expected to resolve and result in long lasting sequelae, such as neuropathy after platinum-based therapy, are permitted to enroll.

g) Treatment with any chemotherapy, radiation therapy, biologics for cancer, or investigational therapy within 28 days of first administration of study treatment (subjects with prior cytotoxic or investigational products < 4 weeks prior to treatment might be eligible after discussion between investigator and sponsor, if toxicities from the prior treatment have been resolved to CTC grade 1 level).

h) Subjects which have been previously enrolled and randomized in Studies BMS CA209331 or BMS CA209451 are not eligible.

**3. Physical and Laboratory Test Findings**

a) Positive test for hepatitis B virus (HBV) using HBV surface antigen (HBV sAg) test or positive test for hepatitis C virus (HCV) using HCV ribonucleic acid (RNA) or HCV antibody test indicating acute or chronic infection.

b) Known history of testing positive for human immunodeficiency virus (HIV) or known acquired immunodeficiency syndrome (AIDS). NOTE: Testing for HIV must be performed at sites where mandated locally.

c) Subjects must not be dependent on continuous supplemental oxygen use.

**4. Allergies and Adverse Drug Reaction**

a) History of allergy to study drug components.

b) History of severe hypersensitivity reaction to any monoclonal antibody.

**5. Sex and Reproductive Status**

a) WOCBP who are pregnant or breastfeeding.

b) Women with a positive pregnancy test at enrollment or prior to administration of study medication.

**6. Other Exclusion Criteria**

a) Prisoners or subjects who are involuntarily incarcerated

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

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

### 3.3.3 Women of Childbearing Potential

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

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

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

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

[redacted]

[redacted]

## 3.5 Discontinuation of Subjects from Treatment

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

- Subject's request to stop study treatment
- Any clinical adverse event (AE), laboratory abnormality or intercurrent illness which, in the opinion of the investigator, indicates that continued participation in the study is not in the best interest of the subject
- Termination of the study by Bristol-Myers Squibb (BMS)
- Loss of ability to freely provide consent through imprisonment or involuntarily incarceration for treatment of either a psychiatric or physical (eg, infectious disease) illness
- Additional protocol specified reasons for discontinuation (see Section 4.5.5).

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

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

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

For subjects achieving confirmed CR or a PR for more than 3 month (long lasting PR) the investigator may decide to hold treatment for this subject after discussion with the medical monitor of the sponsor. Subjects for which treatment was held following long lasting responses and who experience a recurrence of disease progression may reinitiate their last study treatment. Before reinitiating treatment, the investigator should discuss the individual case with the medical monitor and document in the study records.

## 3.6 Post Treatment Study Follow up

In this study, objective response rate is a key endpoint of the study. Tumor responses initiated by immunotherapy with nivolumab or nivolumab combined with ipilimumab may evolve after treatment discontinuation. Therefore, post treatment study follow-up is of critical importance and is essential to preserving subject safety and the integrity of the study. Subjects who discontinue study treatment must continue to be followed for collection of outcome and/or survival follow-up data as required and in line with Section 5 until death or the conclusion of the study.

### 3.6.1 Withdrawal of Consent

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

### 3.6.2 Lost to Follow-Up

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

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

## 4 STUDY DRUG

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

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

## 4.1 Investigational Product

**Table 4.1-1: Product Description: Treatment Period**

| Product Description and Dosage Form | Potency | Primary Packaging (Volume)/ Label Type | Secondary Packaging (Qty) /Label Type | Appearance | Storage Conditions (per label) |
|---|---|---|---|---|---|
| BMS-936558-01 Solution for Injection[a] | 100 mg (10 mg/mL) | 10 mL per vial/ Open-label | 10 vials per carton/ Open-label | Clear to opalescent colorless to pale yellow liquid. May contain particles | 2 to 8°C. Protect from light and freezing |
| Ipilimumab Solution for Injection | 200 mg (5 mg/mL) | 40 mL per vial/ Open-label | 4 vials per carton/ Open-label | Clear, colorless to pale yellow liquid. May contain particles | 2 to 8°C. Protect from light and freezing |

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

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

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.

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

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

## 4.2 Non-investigational Product

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

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

## 4.3 Storage and Dispensing

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

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

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

Please refer to the current version of the Investigator Brochure and/or pharmacy reference sheets for complete storage, handling, dispensing, and infusion information for BMS-936558 (nivolumab) and ipilimumab.

### *4.3.1 BMS-936558 (Nivolumab)*

BMS-936558 (nivolumab) vials must be stored at a temperature of 2°C to 8°C and should be protected from light, freezing and shaking. If stored in a glass front refrigerator, vials should be stored in the carton. Recommended safety measures for preparation and handling of nivolumab include laboratory coats and gloves.

For details on prepared drug storage and use time of nivolumab under room temperature/light and refrigeration, please refer to the BMS-936558 (nivolumab) Investigator Brochure sections 3.2.2 and 3.2.3 and/or pharmacy reference sheets.

Nivolumab injection is to be administered as a 60-minute IV infusion. During drug product preparation and handling, vigorous mixing or shaking is to be avoided. Care must be taken to assure sterility of the prepared solution as the product does not contain any antimicrobial preservative or bacteriostatic agent. Please refer to the nivolumab IB and/or pharmacy reference sheets for further details regarding preparation/administration.

### *4.3.2 Ipilimumab*

Ipilimumab injection can be used for IV administration without dilution after transferring to a PVC (polyvinyl chloride), non-PVC/non-DEHP (di-(2-ethylhexyl)phthalate) or glass containers and is stable for 24 hours at 2-8ºC or room temperature/room light (RT/RL). For additional ipilimumab storage instructions, please refer to the ipilimumab IB and/or pharmacy reference sheets.

Recommended safety measures for preparation and handling include protective clothing, gloves, and safety cabinets.

Ipilimumab is to be administered as a 90-minute IV infusion. Care must be taken to assure sterility of the prepared solutions, since the drug product does not contain any antimicrobial preservatives or bacteriostatic agents. Please refer to the ipilimumab IB and/or pharmacy reference sheets for further details regarding preparation/administration.

### *4.3.3 Nivolumab and Ipilimumab Combination*

When both BMS-936558 (nivolumab) and ipilimumab are to be administered on the same day, separate infusion bags and filters must be used for each infusion. Nivolumab is to be administered first. The nivolumab infusion must be promptly followed by a saline flush to clear the line of nivolumab before starting the ipilimumab infusion.

## 4.4 Method of Assigning Subject Identification

The subject number will be assigned through an interactive voice response system (IVRS) once the subject has signed the informed consent form and is registered. Every subject that signs the informed consent form must be assigned a subject number in IVRS. Specific instructions for using IVRS will be provided to the investigational site in a separate document.

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

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

Once enrolled in IVRS, enrolled subjects that have met all eligibility criteria will be ready for treatment assignment and drug vial assignment through the IVRS. The following information is required for drug vial assignment and randomization:

- Subject number
- Date of birth
- Tumor Type
- Date tumor tissue sample was shipped to central lab

Subjects meeting all eligibility criteria will be assigned to Arm N (nivolumab), Arm N-I (nivolumab + ipilimumab) or Arm N-I Dose level 2b (nivolumab 3 mg/kg + ipilimumab 1 mg/kg), Arm N-I Dose level 2c (nivolumab 3 mg/kg every 2 weeks + ipilimumab 1 mg/kg every 6 weeks) according to their tumor type and treatment arm availability:

- Within a given tumor type, subjects will be assigned to a treatment arm (N or N-I Dose Level 2 or N-I Dose Level 2b) in a 1:1:1 ratio guided by randomization schedule if all arms are open.
- The computer-generated randomization schemas will be prepared by a Randomization Coordinator within the Drug Supply Management Department of BMS Research and Development.
- If only one or two treatment arms are open for enrollment (ie., when enrollment in Arm N-I is paused for an interim safety assessment, or when either arm is paused for decision making to proceed from Stage 1 to Stage 2 in the Efficacy Signal Detection part), then all newly to be assigned subjects will go into the remaining open arm(s).
- Once the subject has a treatment assignment, study treatment should be initiated within 3 working days.
- Specific instructions (including an enrollment worksheet) for central enrollment and treatment assignment procedure will be provided to the site.

Subjects to be enrolled in the SCLC expansion cohort will be randomized in a 3:2 ratio to one of 2 expansion groups: Arm A (150 subjects, nivolumab 3 mg/kg every 2 weeks (Q2W) or Arm B (100 subjects, nivolumab 1 mg/kg + ipilimumab 3 mg/kg every 3 weeks (Q3W) for 4 cycles followed by nivolumab 3 mg/kg Q2W) and will be stratified for number of prior treatment lines (1 vs 2 prior chemotherapy regimens).

Subjects to be enrolled in the OC expansion cohort will be randomized in a 1:1:1 ratio to one of 3 dose level groups:

- Arm A (40 subjects, nivolumab 1 mg/kg + ipilimumab 3 mg/kg every 3 weeks (Q3W) for 4 cycles followed by nivolumab 3 mg/kg Q2W)
- Arm B (40 subjects, nivolumab 3 mg/kg + ipilimumab 1 mg/kg every 3 weeks (Q3W) for 4 cycles followed by nivolumab 3 mg/kg Q2W)
- Arm C (40 subjects, Nivolumab (3 mg/kg) Q2W + ipilimumab (1 mg/kg) Q6W)

## 4.5 Selection and Timing of Dose for Each Subject

The dosing regimen and schedule for **Arm N, Arm N-I Dose Level -1, Dose Level 1, Dose Level 2, Dose Level 2b, and Dose Level 2c** are detailed in Table 4.5-1 (Arm N), Table 4.5-2 (N-I Arms -1, 1, 2, and 2b, Week 1-12), Table 4.5-3 (N-I Arms -1, 1, 2, and 2b, Week 13 and following), and Table 4.5-4 (N-I Arm 2c).

**Table 4.5-1: Dosing Schedule for Arm N - Nivolumab (BMS-936558) Monotherapy**

| Every 2 Week Dosing | | |
|---|---|---|
| **Day 1, Week 1** | **Day 1, Week 3** | **Day 1, Week 5, 7, 9, and every other week thereafter** |
| 3 mg/kg Nivolumab | 3 mg/kg Nivolumab | 3 mg/kg Nivolumab |

**Table 4.5-2: Dosing Schedule for N-I Arms -1, 1, 2, and 2b (Week 1-12) - Nivolumab (BMS-936558) + Ipilimumab Combination**

| Every 3 Week Dosing | | | | |
|---|---|---|---|---|
| **Study Part** | **Day 1 Week 1** | **Day 1 Week 4** | **Day 1 Week 7** | **Day 1 Week 10** |
| **Dose Escalation Phase Dose Level -1** | 0.3 mg/kg Nivolumab<br>1 mg/kg Ipilimumab | 0.3 mg/kg Nivolumab<br>1 mg/kg Ipilimumab | 0.3 mg/kg Nivolumab<br>1 mg/kg Ipilimumab | 0.3 mg/kg Nivolumab<br>1 mg/kg Ipilimumab |
| **Dose Escalation Phase Dose Level 1** | 1 mg/kg Nivolumab<br>1 mg/kg Ipilimumab | 1 mg/kg Nivolumab<br>1 mg/kg Ipilimumab | 1 mg/kg Nivolumab<br>1 mg/kg Ipilimumab | 1 mg/kg Nivolumab<br>1 mg/kg Ipilimumab |
| **Dose Escalation Phase Dose Level 2** | 1 mg/kg Nivolumab<br>3 mg/kg Ipilimumab | 1 mg/kg Nivolumab<br>3 mg/kg Ipilimumab | 1 mg/kg Nivolumab<br>3 mg/kg Ipilimumab | 1 mg/kg Nivolumab<br>3 mg/kg Ipilimumab |
| **Efficacy, Staged Phase**[a] | | | | |
| **Dose Level 2** | 1 mg/kg Nivolumab<br>3 mg/kg Ipilimumab | 1 mg/kg Nivolumab<br>3 mg/kg Ipilimumab | 1 mg/kg Nivolumab<br>3 mg/kg Ipilimumab | 1 mg/kg Nivolumab<br>3 mg/kg Ipilimumab |
| **Dose Level 2b** | 3 mg/kg Nivolumab<br>1 mg/kg Ipilimumab | 3 mg/kg Nivolumab<br>1 mg/kg Ipilimumab | 3 mg/kg Nivolumab<br>1 mg/kg Ipilimumab | 3 mg/kg Nivolumab<br>1 mg/kg Ipilimumab |

[a] The staged phase uses maximum tolerable dose identified in escalation phase since it might be different for each tumor type

**Table 4.5-3: Dosing Schedule for N-I Arms -1, 1, 2, and 2b (Week 13 and following) - Nivolumab (BMS-936558) + Ipilimumab Combination**

| Every 2 Week Dosing | | |
|---|---|---|
| **Day 1<br>Week 13** | **Day 1<br>Week 15** | **Day 1, Week 17, 19, 21<br>and every other week thereafter** |
| 3 mg/kg Nivolumab | 3 mg/kg Nivolumab | 3 mg/kg Nivolumab |

**Table 4.5-4: Dosing Schedule for N-I Arm Dose Level 2c - Nivolumab (BMS-936558) + Ipilimumab Combination**

| Every 2 or 6 Week Dosing | | |
|---|---|---|
| **Day 1<br>Week 1** | **Day 1, Week 3, 5, 7, 9<br>and every other week thereafter** | **Day 1 Week 7, 13, 19 and every 6 weeks thereafter** |
| 3 mg/kg Nivolumab | 3 mg/kg Nivolumab | |
| 1 mg/kg Ipilimumab | | 1 mg/kg Ipilimumab |

Nivolumab and Ipilimumab combination:

When study drugs (nivolumab or ipilimumab) are to be administered on the same day, separate infusion bags and filters must be used for each infusion. Nivolumab is to be administered first. The second infusion will always be ipilimumab, and will start no sooner than 30 minutes after completion of the nivolumab infusion.

Dosing calculation based on weight:

The dosing calculations should be based on the body weight. If the subject's weight on the day of dosing differs by > 10% from the weight used to calculate the dose, the dose must be recalculated. All doses should be rounded to the nearest milligram.

Dosing modifications:

There will be no dose modifications allowed for the management of toxicities of individual subjects.

Dosing window Arm N-I Dose Levels 2 and 2b (Week 1-12): subjects may be dosed no less than 19 days between doses and no more than 3 days from scheduled dose. If dosing is delayed, both nivolumab and ipilimumab must be delayed together. If dosing is resumed after a delay, both nivolumab and ipilimumab must be resumed on the same day.

Dosing window Arm N and Arm N-I Dose Levels 2 and 2b (Week 13 and following): subjects may be dosed no less than 12 days between doses and no more than 3 days from scheduled dose.

Dosing window Arm N-I Dose Levels 2c: subjects may be dosed no less than 12 days between doses and no more than 3 days from scheduled dose. If dosing is delayed, both nivolumab and ipilimumab must be delayed together.

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

### *4.5.1 Antiemetic Premedications*

Antiemetic medications should not be routinely administered prior to dosing of drugs. See Section 4.5.6 for subsequent premedication recommendations following a nivolumab- or ipilimumab-related infusion reaction.

### *4.5.2 Dose Delay Criteria*

These dose delay criteria apply for all drug-related adverse events attributed to nivolumab, ipilimumab, or both. All study drugs must be delayed until treatment can resume (see Section 4.5.4).

Nivolumab and ipilimumab administration should be delayed for the following:

- Any Grade ≥ 2 non-skin, drug-related adverse event, with the following exceptions:
  - Grade 2 drug-related fatigue or laboratory abnormalities do not require a treatment delay

- Any Grade 3 skin drug-related adverse event
  - Any Grade 3 drug-related laboratory abnormality, with the following exceptions for asymptomatic amylase or lipase, lymphocytopenia, AST, ALT, or total bilirubin:
    - Grade 3 amylase or lipase abnormalities that are not associated with symptoms or clinical manifestations, or radiographic signs of pancreatitis do not require a dose delay. It is recommended to consult with the BMS Medical Monitor for Grade 3 amylase or lipase abnormalities.
    - If a subject has a baseline AST, ALT, or total bilirubin that is within normal limits, delay dosing for drug-related Grade ≥ 2 toxicity
    - If a subject has baseline grade 1 AST, ALT, or total bilirubin elevation, delay dosing for drug-related Grade ≥ 3 toxicity
    - Grade 3 lymphocytopenia not associated with symptoms or clinical manifestations. It is recommended to consult with the BMS Medical Monitor for Grade 3 lymphocytopenia before treatment continuation.
- Any adverse event, laboratory abnormality, or concurrent illness which, in the judgment of the investigator, warrants delaying the dose of study medication.

Because of the potential for nivolumab- or ipilimumab-related AEs requiring early recognition and prompt intervention, management algorithms have been developed for suspected pulmonary toxicity, GI toxicity, hepatotoxicity, endocrinopathy, skin toxicity, neurological toxicity, and nephrotoxicity.

In order to standardize the management of adverse events for all subjects, treatment management algorithms recommended for utilization in Study CA209032 are included in Appendix 2. Adverse event treatment management algorithms included in the Nivolumab IB or Ipilimumab IB might be considered for individual cases.

### 4.5.3 Dose Modifications

Intrapatient dose reductions for the management of toxicities of individual subjects or dose escalations are not permitted.

### 4.5.4 Criteria to Resume Treatment

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

- Subjects may resume treatment in the presence of Grade 2 fatigue.
- Subjects with baseline Grade 1 AST/ALT or total bilirubin who require dose delays for reasons other than a 2-grade shift in AST/ALT or total bilirubin may resume treatment in the presence of Grade 2 AST/ALT OR total bilirubin. Subjects with combined Grade 2 AST/ALT AND total bilirubin values meeting discontinuation parameters (Section 4.5.5) should have treatment permanently discontinued.

- Drug-related pulmonary toxicity, diarrhea, or colitis must have resolved to baseline before treatment is resumed.
- Drug-related endocrinopathies adequately controlled with only physiologic hormone replacement or glucose controlling agents may resume treatment.

If the criteria to resume treatment are met, the subject should restart treatment at the next scheduled timepoint per protocol. However, if the treatment is delayed past the scheduled timepoint per protocol, the scheduled study treatment administration will be delayed, but not skipped, until dosing resumes. In particular, this is to ensure that subjects in Arm N-I will receive 4 administrations of combined nivolumab and ipilimumab treatment if toxicity allows.

If dose delay is necessary for subjects in Arm N-I during Week 1-12, both nivolumab and ipilimumab must be delayed until treatment can resume. However, if a nivolumab-related infusion reaction prevents subsequent infusion of ipilimumab on the same day, the dose of ipilimumab should be replaced as soon as possible. In such instances, at least 19 days must elapse between the replacement dose of ipilimumab and the administration of the next dose of nivolumab combined with ipilimumab.

If treatment is delayed > 6 weeks from the last dose, the subject must be permanently discontinued from study therapy, except as specified in Section 4.5.5.

### *4.5.5 Discontinuation Criteria*

Discontinuation criteria apply for all drug-related adverse events attributed to nivolumab, ipilimumab, or both.

Treatment should be permanently discontinued for the following:

- Any Grade 2 drug-related uveitis, eye pain, or blurred vision that does not respond to topical therapy and does not improve to Grade 1 severity within the re-treatment period OR requires systemic treatment.
- Any Grade 3 non-skin, drug-related adverse event lasting > 7 days, with the following exceptions for drug-related laboratory abnormalities, uveitis, pneumonitis, bronchospasm, diarrhea, colitis, neurologic toxicity, hypersensitivity reactions, and infusion reactions:
  - Grade 3 drug-related uveitis, pneumonitis, bronchospasm, diarrhea, colitis, neurologic toxicity, hypersensitivity reaction, or infusion reaction of any duration requires discontinuation
  - For Grade 3 endocrinopathy adverse events such as adrenal insufficiency, ACTH deficiency, hyper- or hypothyroidosis, or glucose intolerance, which resolve or are adequately controlled with physiologic hormone replacement (steroids, thyroid hormones) or glucose controlling agents, respectively, do not require treatment discontinuation
  - Grade 3 drug-related laboratory abnormalities do not require treatment discontinuation except:
    - Grade 3 drug-related thrombocytopenia > 7 days or associated with bleeding requires discontinuation

- ♦ Any drug-related liver function test (LFT) abnormality that meets the following criteria require discontinuation:
  - AST or ALT > 8 x ULN
  - Total bilirubin > 5 x ULN
  - Concurrent AST or ALT > 3 x ULN and total bilirubin > 2 x ULN

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

If a subject in Arm N-I meets criteria for discontinuation of nivolumab, the subject should discontinue both nivolumab and ipilimumab and be taken off the treatment phase of the study entirely. However, if the investigator assesses the drug-related AE to be related to ipilimumab only and not related to nivolumab, ipilimumab dosing alone may be discontinued while nivolumab dosing is delayed until the subject meets criteria to resume nivolumab treatment (specified in Section 4.5.4). Nivolumab would be continued at 3 mg/kg with an every 2 week dosing interval. The relationship to ipilimumab should be well documented in the source

documents and the BMS medical monitor needs to be contacted prior to continuation with nivolumab therapy.

### *4.5.6 Treatment of Nivolumab- or Ipilimumab-Related Infusion Reactions*

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

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

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

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

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

Stop the nivolumab or ipilimumab infusion, begin an IV infusion of normal saline, and treat the subject with diphenhydramine 50 mg IV (or equivalent) and/or paracetamol 325 to 1000 mg (acetaminophen); remain at bedside and monitor subject until resolution of symptoms. Corticosteroid or bronchodilator therapy may also be administered as appropriate. If the infusion is interrupted, restart the infusion at 50% of the original infusion rate when symptoms resolve; if no further complications ensue after 30 minutes, the rate may be increased to 100% of the original infusion rate. Monitor subject closely. If symptoms recur then no further nivolumab or ipilimumab will be administered at that visit. Administer diphenhydramine 50 mg IV, and remain at bedside and monitor the subject until resolution of symptoms. The amount of study drug infused must be recorded on the electronic case report form (eCRF). The following prophylactic premedications are recommended for future infusions: diphenhydramine 50 mg (or equivalent) and/or paracetamol 325 to 1000 mg (acetaminophen) should be administered at least 30 minutes before additional nivolumab or ipilimumab administrations. If necessary, corticosteroids (recommended dose: up to 25 mg of IV hydrocortisone or equivalent) may be used.

For Grade 3 or Grade 4 symptoms (Severe reaction, Grade 3: prolonged [ie, not rapidly responsive to symptomatic medication and/or brief interruption of infusion]; recurrence of

symptoms following initial improvement; hospitalization indicated for other clinical sequelae [eg, renal impairment, pulmonary infiltrates]; Grade 4: (life threatening; pressor or ventilatory support indicated):

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

### *4.5.7 Treatment Beyond Disease Progression*

As described in Section 1.1.9 accumulating evidence indicates that subjects treated with immunotherapy may derive clinical benefit despite evidence of PD[77].

Subjects will be permitted to continue with treatment beyond initial RECIST 1.1 defined PD as long as they meet the following criteria:

- Investigator-assessed clinical benefit

and

- Subject is tolerating study drug.

The assessment of clinical benefit should take into account whether the subject is clinically deteriorating and unlikely to receive further benefit from continued treatment. The following criteria need to be taken into consideration:

- Absence of clinical symptoms and signs (including worsening of laboratory values) indicating disease progression.
- No decline in ECOG performance status.
- Absence of rapid progression of disease or of progressive tumor at critical anatomical sites (eg, cord compression) requiring urgent alternative medical intervention.

All decisions to continue treatment beyond progression must be discussed with the BMS Medical Monitor and documented in the study records.

Subjects must be re-consented in order to continue treatment.

Subjects should discontinue study therapy upon evidence of further progression, defined as an additional 10% or greater increase in tumor burden from time of initial progression (including all

target lesions and new measurable lesions). Progression in non-target lesions should only be unequivocal as defined and described in Appendix 3 compared to initial progression.

New lesions are considered measurable 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).

For statistical analyses that include the investigator-assessed progression date, subjects who continue treatment beyond initial investigator-assessed, RECIST 1.1-defined progression will be considered to have investigator-assessed progressive disease at the time of the initial progression event. Subjects who have tumor shrinkage following RECIST-defined progression (ie, immune related response; Section 5.4.4 will be also descriptively summarized separately since these immune responses may be used in determining Go to Stage 2.

### *4.5.8 Crossover to Arm N-I*

Subjects in Arm N may crossover to Arm N-I if all of the criteria defined in Section 3.1.6 are met. Subjects from the SCLC expansion cohort enrolled under or after Amendment 09 are excluded from the crossover option. In case Dose Level 2b-has been activated and completed the safety assessment, subjects for cross over will be assigned to Dose Level 2 or Dose Level 2b after discussion between the sponsor and investigator taking into consideration previous safety and efficacy signals at these dose levels and the status of the individual subject planned for cross over.

Before crossover, the investigator should discuss the individual case with the medical monitor and document in the study records.

Subjects must be re-consented prior to crossing over to Arm N-I.

Subjects crossing over to Arm N-I will start treatment at Day 1 Week 1 as described for subjects originally randomized to Arm N-I. Subjects who crossed over and subsequently have an objective response in Arm N-I, will not be considered in respect to the decision making for Arm N-I of proceeding to Stage 2. Subjects in Arm N-I cannot crossover to Arm N.

New lesions are considered measurable 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).

For statistical analyses that include the investigator-assessed progression date, subjects who crossover after initial investigator-assessed, RECIST 1.1-defined progression will be considered to have investigator-assessed progressive disease at the time of the initial progression event in Arm N. The tumor assessment confirming PD in Arm N will serve as the baseline for tumor assessments in Arm N-I.

## 4.6 Blinding/Unblinding

Not applicable.

## 4.7 Treatment Compliance

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

## 4.8 Destruction of Study Drug

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

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

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

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

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

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

## 4.9 Return of Study Drug

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

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

## 4.10 Retained Samples for Bioavailability / Bioequivalence

Not applicable.

# 5 STUDY ASSESSMENTS AND PROCEDURES

## 5.1 Flow Chart/Time and Events Schedule

**Table 5.1-1: Screening Procedural Outline (CA209032)**

| Procedure | Screening Visit | Notes |
|---|---|---|
| **Eligibility Assessments** | | |
| Informed Consent | X | May be performed more than 28 days prior to the first dose (must be completed prior to any study related procedures)<br>Original IC in screening for protocol participation;<br>Study allows for re-enrollment of a subject that has discontinued the study as a pre-treatment failure. If re-enrolled, the subject must be re-consented and assigned a new subject number from IVRS. |
| Inclusion/Exclusion Criteria | X | All inclusion/exclusion criteria should be assessed at screening and confirmed prior to first dose. |
| Demographics and Medical History | X | For SCLC and Ovarian cancer subjects, evaluation of Platinum-free interval (PFI) from the completion of any platinum-based chemotherapy and subsequent disease progression, and Treatment-free-interval (TFI) from the completion of any other cytotoxic or targeted based prior treatment line and subsequent disease progression will be collected. For Ovarian Cancer, information about BRCA and Homologous Recombinant Deficiency (HRD), if available, will be collected |
| Tumor Tissue Samples | X | Sufficient tumor tissue obtained before start of study treatment in the metastatic setting or from an unresectable site (block or minimum of 10 slides for bladder and SCLC subjects and a minimum of 15 slides for ovarian subjects (if medically justified), obtained from core biopsy, punch biopsy, excisional biopsy or surgical specimen). Tumor tissue samples must be shipped from site to central laboratory prior to randomization. |
| Screening/Baseline Tumor Assessment | X | CT chest, CT or MRI brain, abdomen, pelvis and all known sites of disease within 28 days prior to first dose. For patients with known brain metastasis, an MRI brain is required at baseline. A CT brain is not allowed for patients with a history or evidence of known brain metastasis at baseline. |
| **Safety Assessments** | | |
| Physical Examination | X | Within 14 days prior to first dose |
| Vital Signs and oxygen saturation | X | Including BP, HR, temperature, and oxygen saturation by pulse oximetry (at rest). Obtain vital signs at the screening visit and within 72 hours prior to first dose. |
| Physical Measurements (including performance status) | X | Height, Weight and ECOG status. Within 14 days prior to first dose |

**Table 5.1-1: Screening Procedural Outline (CA209032)**

| Procedure | Screening Visit | Notes |
|---|---|---|
| ECG | X | Within 14 days prior to first dose |
| Assessment of Signs and Symptoms | X | Within 14 days prior to first dose |
| [redacted] | [redacted] | [redacted] |
| Laboratory Tests | X | CBC w/differential, Chemistry panel including: LDH, AST, ALT, ALP, T.Bili, BUN or serum urea level, creatinine, albumin, Ca, Mg, Na, K, Cl, glucose, amylase, lipase, TSH, Free T4, Free T3, hepatitis B surface antigen (HBV sAg), and hepatitis C antibody (HCV Ab) or Hepatitis C RNA (HCV RNA), within 14 days prior to first dose. Screening labs done within 72 hours prior to first dose can also be used for on treatment lab purposes at Day 1 dosing. |
| Pregnancy Test (WOCBP only) | X | Serum or urine within 24 hours of first dose |

| Table 5.1-2: On-Study Assessments - Arm N, Nivolumab Monotherapy (CA209032) | | |
|---|---|---|
| **Procedure** | **For Arm N, Nivolumab is administered every 2 weeks**<br>**Day 1**<br>**Week 1, 3, 5, 7, 9, etc** | **Notes** |
| **Safety Assessments** | | |
| Targeted Physical Examination | X | Within 72 hours prior to dosing. During treatment hold to be conducted every 12 weeks to adjust to the tumor assessment schedule (see Section 3.1.5). |
| Vital Signs and Oxygen Saturation | X | Including BP, HR, temperature, and oxygen saturation by pulse oximetry. Pulse oximetry at rest and within 72 hours prior to dosing. During treatment hold to be conducted every 12 weeks to adjust to the tumor assessment schedule (see Section 3.1.5). |
| Physical Measurements (including performance status) | X | Weight and ECOG status.<br>The dosing calculations should be based on the body weight. If the subject's weight on the day of dosing differs by > 10% from the weight used to calculate the dose, the dose must be recalculated. All doses should be rounded to the nearest milligram.<br>During treatment hold to be conducted every 12 weeks to adjust to the tumor assessment schedule (see Section 3.1.5). |
| Adverse Events Assessment | Continuously | eSAEs should be approved in TAO within 5 days from entry |
| [redacted] | [redacted] | [redacted] |
| Laboratory Tests | X | On-study local laboratory assessments should be done within 72 hours prior to each dose up to and including Week 25 and then every other dose thereafter (Week 29, Week 33, Week 37 etc.) and include: CBC w/differential, LFTs (ALT, AST, total bilirubin, alkaline phosphatase), BUN or serum urea level, creatinine, albumin, Ca, Mg, Na, K, Cl, LDH, glucose, amylase, lipase, TSH (if TSH result abnormal, subsequent testing of Free T4 and Free T3 required).<br>During treatment hold to be conducted every 12 weeks to adjust to the tumor assessment schedule (see Section 3.1.5). |
| Pregnancy Test (WOCBP only) | X | Serum or urine within 24 hours prior to first dose and then every 4 weeks. During treatment hold to be conducted every 12 weeks and resume per protocol testing once treatment resumes (see Section 3.1.5). |

| Table 5.1-2: On-Study Assessments - Arm N, Nivolumab Monotherapy (CA209032) | | |
|---|---|---|
| **Procedure** | **For Arm N, Nivolumab is administered every 2 weeks**<br>**Day 1**<br>**Week 1, 3, 5, 7, 9, etc** | **Notes** |
| **Outcomes Research Assessment** | | |
| QoL | X | Collect EQ-5D prior to study drug administration through Week 13, then at the same time of subsequent tumor assessments, during Follow Up 1 and 2 and survival visits. The EQ-5D can be done via a phone contact when a clinic visit is not feasible (ie., follow up scans are being done at another facility or department) in order to not miss the assessment.<br>During treatment hold to be conducted every 12 weeks to adjust to the tumor assessment schedule (see Section 3.1.5). |
| **Pharmacokinetic Assessments** | | |
| PK Samples | [redacted] | |
| [redacted] | | |
| [redacted] | [redacted] | |
| [redacted] | [redacted] | |
| [redacted] | [redacted] | |
| [redacted] | [redacted] | [redacted] |

| Table 5.1-2: On-Study Assessments - Arm N, Nivolumab Monotherapy (CA209032) | | |
|---|---|---|
| [redacted] | [redacted] | [redacted] |
| [redacted] | [redacted] | |
| Pharmacogenetic research | | Optional (refer to Amendment 01 and 07) |
| **Efficacy Assessment** | | |
| Tumor Assessment | See Notes | • Tumor assessments should occur every 6 weeks (± 1 wk) from first dose for the first 24 weeks, then every 12 wks (± 1 wk) while on treatment or on treatment hold for any reason until disease progression and treatment discontinuation, whichever occurs later. Additionally, with the exception of crossover participants, tumor assessments will not be required upon initiation of subsequent anti-cancer therapy.<br>• CT chest, CT or MRI abdomen, pelvis and all known sites of disease. Use same imaging method as was used at screening/baseline.<br>• Subjects with a history of brain metastasis should have surveillance MRI approximately every 12 weeks, or sooner if clinically indicated |
| **Clinical Drug Supplies** | | |
| IVRS Drug Vial Assignment | X | |
| Administer Study Treatment | X | See Section 4.5, Note: Within 3 days from vial allocation, the subject must receive the first dose of study medication. Subjects may be dosed no less than 12 days between doses and no more than 3 days from the scheduled dose. |

| **Table 5.1-3: On-Study Assessments for N-I Arms (Dose Levels 2 and 2b) Week 1-12, Nivolumab + Ipilimumab Combination (CA209032)** | | |
|---|---|---|
| **Procedure** | **Week 1-12, nivolumab and ipilimumab are administered every 3 weeks for 4 doses.**<br>**Day 1, Week 1, 4, 7, 10** | **Notes** |
| **Safety Assessments** | | |
| Targeted Physical Examination | X | Within 72 hours prior to dosing. During treatment hold to be conducted every 12 weeks to adjust to the tumor assessment schedule (see Section 3.1.5). |
| Vital Signs and Oxygen Saturation | X | Including BP, HR, temperature, and oxygen saturation by pulse oximetry. Pulse oximetry at rest within 72 hours prior to dosing. During treatment hold to be conducted every 12 weeks to adjust to the tumor assessment schedule (see Section 3.1.5). |
| Physical Measurements (including performance status) | X | Weight and ECOG status<br>The dosing calculations should be based on the body weight. If the subject's weight on the day of dosing differs by > 10% from the weight used to calculate the dose, the dose must be recalculated. All doses should be rounded to the nearest milligram.<br>During treatment hold to be conducted every 12 weeks to adjust to the tumor assessment schedule (see Section 3.1.5). |
| Adverse Events Assessment | Continuously | eSAEs should be approved in TAO within 5 days from entry |
| Review of Concomitant Medications | Continuously | Note: Immunosuppressive agents are recorded on a separate log page |
| Laboratory Tests | X | Within 72 hours prior to re-dosing to include CBC w/ differential, LFTs, BUN or serum urea level, creatinine, albumin, Ca, Mg, Na, K, Cl, LDH, glucose, amylase, lipase, TSH (if TSH result abnormal, subsequent testing of Free T4 and Free T3 required).<br>During treatment hold to be conducted every 12 weeks to adjust to the tumor assessment schedule (see Section 3.1.5). |
| Pregnancy Test *(WOCBP only)* | X | Serum or urine within 24 hours prior to first dose and then every 3 weeks at Week 1-12, then every 4 weeks. During treatment hold to be conducted |

| Table 5.1-3: | On-Study Assessments for N-I Arms (Dose Levels 2 and 2b) Week 1-12, Nivolumab + Ipilimumab Combination (CA209032) | |
|---|---|---|
| **Procedure** | **Week 1-12, nivolumab and ipilimumab are administered every 3 weeks for 4 doses.**<br>**Day 1, Week 1, 4, 7, 10** | **Notes** |
| | | every 12 weeks and resume per protocol testing once treatment resumes (see Section 3.1.5). |
| **Outcomes Research Assessments** | | |
| QoL | X | Collect EQ-5D prior to study drug administration through Week 13, then at the same time of subsequent tumor assessments, during Follow Up 1 and 2 and survival visits. The EQ-5D can be done via a phone contact when a clinic visit is not feasible (ie, follow up scans are being done at another facility or department) in order to not miss the assessment.<br>During treatment hold to be conducted every 12 weeks to adjust to the tumor assessment schedule (see Section 3.1.5). |
| **Pharmacokinetic Assessments** | | |
| PK Samples | See Section 5.5.1 for details regarding specific sample timing | |
| [redacted] | | |
| [redacted] | [redacted] | |
| [redacted] | [redacted] | |
| [redacted] | [redacted] | |
| [redacted] | [redacted] | [redacted] |

| **Table 5.1-3:** | **On-Study Assessments for N-I Arms (Dose Levels 2 and 2b) Week 1-12, Nivolumab + Ipilimumab Combination (CA209032)** | |
|---|---|---|
| **Procedure** | **Week 1-12, nivolumab and ipilimumab are administered every 3 weeks for 4 doses.**<br>**Day 1, Week 1, 4, 7, 10** | **Notes** |
| Whole Blood Sample (DNA) | See Section 5.6.8.6 for details regarding specific sample timing | |
| Pharmacogenetic research | | Optional (refer to Amendment 01 and 07) |
| **Efficacy Assessment** | | |
| Tumor Assessment | See Notes | • Tumor assessments should occur every 6 weeks (± 1 wk) from first dose for the first 24 weeks, then every 12 wks (± 1 wk) while on treatment or on treatment hold due to any reason until disease progression and treatment discontinuation, whichever occurs later. Additionally, with the exception of crossover participants, tumor assessments will not be required upon initiation of subsequent anti-cancer therapy..<br>• CT chest, CT or MRI abdomen, pelvis and all known sites of disease. Use same imaging method as was used at screening/baseline.<br>• Subjects with a history of brain metastasis should have surveillance MRI approximately every 12 weeks, or sooner if clinically indicated |
| **Clinical Drug Supplies** | | |
| IVRS Drug Vial Assignment | X | |
| Administer Study Treatment | X | See Section 4.5, Note: Within 3 days from vial allocation, the subject must receive the first dose of study medication. Subjects may be dosed no less than 19 days between doses and no more than 3 days from the scheduled dose. |

**Table 5.1-4: On-Study Assessments - N-I Arms (Dose Levels 2 and 2b), Week 13 and following, Nivolumab + Ipilimumab Combination (CA209032)**

| Procedure | Week 13 and following, Nivolumab is administered every 2 weeks<br>Day 1<br>Week 13, 15, 17, 19, 21, etc | Notes |
|---|---|---|
| **Safety Assessments** | | |
| Targeted Physical Examination | X | Within 72 hours prior to dosing. During treatment hold to be conducted every 12 weeks to adjust to the tumor assessment schedule (see Section 3.1.5). |
| Vital Signs and Oxygen Saturation | X | Including BP, HR, temperature and oxygen saturation by pulse oximetry. Pulse oximetry at rest within 72 hours prior to dosing. During treatment hold to be conducted every 12 weeks to adjust to the tumor assessment schedule (see Section 3.1.5). |
| Physical Measurements (including performance status) | X | Weight and ECOG status<br>The dosing calculations should be based on the body weight. If the subject's weight on the day of dosing differs by > 10% from the weight used to calculate the dose, the dose must be recalculated. All doses should be rounded to the nearest milligram.<br>During treatment hold to be conducted every 12 weeks to adjust to the tumor assessment schedule (see Section 3.1.5). |
| Adverse Events Assessment | Continuously | eSAEs should be approved in TAO within 5 days from entry |
| [redacted] | [redacted] | [redacted] |

| **Table 5.1-4:** | **On-Study Assessments - N-I Arms (Dose Levels 2 and 2b), Week 13 and following, Nivolumab + Ipilimumab Combination (CA209032)** | |
|---|---|---|
| **Procedure** | **Week 13 and following, Nivolumab is administered every 2 weeks**<br>**Day 1**<br>**Week 13, 15, 17, 19, 21, etc** | **Notes** |
| Laboratory Tests | X | On-study local laboratory assessments should be done within 72 hours prior to each dose up to and including Week 25 and then every other dose thereafter (Week 29, Week 33, Week 37 etc.) and include: CBC w/differential, LFTs (ALT, AST, total bilirubin, alkaline phosphatase), BUN or serum urea level, creatinine, albumin, Ca, Mg, Na, K, Cl, LDH, glucose, amylase, lipase, TSH (if TSH result abnormal, subsequent testing of Free T4 and Free T3 required).<br>During treatment hold to be conducted every 12 weeks to adjust to the tumor assessment schedule (see Section 3.1.5). |
| Pregnancy Test (WOCBP only) | X | Serum or urine within 24 hours prior to dosing every 4 weeks. During treatment hold to be conducted every 12 weeks and resume per protocol testing once treatment resumes (see Section 3.1.5). |
| **Outcomes Research Assessments** | | |
| QoL | X | Collect EQ-5D prior to study drug administration through Week 13, then at the same time of subsequent tumor assessments, during Follow Up 1 and 2 and survival visits. The EQ-5D can be done via a phone contact when a clinic visit is not feasible (ie., follow up scans are being done at another facility or department) in order to not miss the assessment.<br>During treatment hold to be conducted every 12 weeks to adjust to the tumor assessment schedule (see Section 3.1.5). |
| [redacted] | | |
| [redacted] | [redacted] | |
| [redacted] | [redacted] | |

**Table 5.1-4: On-Study Assessments - N-I Arms (Dose Levels 2 and 2b), Week 13 and following, Nivolumab + Ipilimumab Combination (CA209032)**

| | | |
|---|---|---|
| [redacted] | [redacted] | [redacted] |
| [redacted] | [redacted] | |
| [redacted] | [redacted] | [redacted] |
| [redacted] | [redacted] | |
| **Pharmacokinetic Assessments** | | |
| [redacted] | [redacted] | |
| **Efficacy Assessment** | | |
| Tumor Assessment | See Notes | • Tumor assessments should occur every 6 weeks (± 1 wk) from first dose for the first 24 weeks, then every 12 wks (± 1 wk) while on treatment or on treatment hold due to any reason until disease progression and treatment discontinuation, whichever occurs later. Additionally, with the exception of crossover participants, tumor assessments will not be required upon initiation of subsequent anti-cancer therapy.<br>• CT chest, CT or MRI abdomen, pelvis and all known sites of disease. Use same imaging method as was used at screening/baseline.<br>• Subjects with a history of brain metastasis should have surveillance MRI approximately every 12 weeks, or sooner if clinically indicated |
| **Clinical Drug Supplies** | | |
| IVRS Drug Vial Assignment | X | |
| Administer Study Treatment | X | Subjects may be dosed no less than 12 days between doses and no more than 3 days from the scheduled dose. |

| **Table 5.1-5:** | **On-Study Assessments for N-I Arms (Dose Level 2c) Nivolumab + Ipilimumab Combination (CA209032)** | |
|---|---|---|
| **Procedure** | **For Arm N-I Dose level 2c, Nivolumab is administered every 2 weeks, Ipilimumab is administered every 6 weeks**<br>**Day 1**<br>**Week 1, 3, 5, 7, 9, etc** | **Notes** |
| **Safety Assessments** | | |
| Targeted Physical Examination | X | Within 72 hours prior to dosing. During treatment hold to be conducted every 12 weeks to adjust to the tumor assessment schedule (see Section 3.1.5). |
| Vital Signs and Oxygen Saturation | X | Including BP, HR, temperature, and oxygen saturation by pulse oximetry. Pulse oximetry at rest within 72 hours prior to dosing. During treatment hold to be conducted every 12 weeks to adjust to the tumor assessment schedule (see Section 3.1.5). |
| Physical Measurements (including performance status) | X | Weight and ECOG status<br>The dosing calculations should be based on the body weight. If the subject's weight on the day of dosing differs by > 10% from the weight used to calculate the dose, the dose must be recalculated. All doses should be rounded to the nearest milligram.<br>During treatment hold to be conducted every 12 weeks to adjust to the tumor assessment schedule (see Section 3.1.5). |
| Adverse Events Assessment | Continuously | eSAEs should be approved in TAO within 5 days from entry |
| [redacted] | [redacted] | [redacted] |

**Table 5.1-5: On-Study Assessments for N-I Arms (Dose Level 2c) Nivolumab + Ipilimumab Combination (CA209032)**

| Procedure | For Arm N-I Dose level 2c, Nivolumab is administered every 2 weeks, Ipilimumab is administered every 6 weeks<br>Day 1<br>Week 1, 3, 5, 7, 9, etc | Notes |
|---|---|---|
| Laboratory Tests | X | Within 72 hours prior to each dose up to and including Week 25 and then every other dose thereafter (Week 29, Week 33, Week 37 etc.). Dosing to include CBC w/ differential, LFTs, BUN or serum urea level, creatinine, albumin, Ca, Mg, Na, K, Cl, LDH, glucose, amylase, lipase, TSH (if TSH result abnormal, subsequent testing of Free T4 and Free T3 required).<br>During treatment hold to be conducted every 12 weeks to adjust to the tumor assessment schedule (see Section 3.1.5). |
| Pregnancy Test *(WOCBP only)* | X | Serum or urine within 24 hours prior to first dose and then every 4 weeks. During treatment hold to be conducted every 12 weeks and resume per protocol testing once treatment resumes (see Section 3.1.5). |
| **Outcomes Research Assessments** | | |
| QoL | X | Collect EQ-5D prior to study drug administration through Week 13, then at the same time of subsequent tumor assessments, during Follow Up 1 and 2 and survival visits. The EQ-5D can be done via a phone contact when a clinic visit is not feasible (ie., follow up scans are being done at another facility or department) in order to not miss the assessment.<br>During treatment hold to be conducted every 12 weeks to adjust to the tumor assessment schedule (see Section 3.1.5). |
| **Pharmacokinetic Assessments** | | |
| PK Samples | See Section 5.5.1 for details regarding specific sample timing | |
| [redacted] | | |
| [redacted] | [redacted] | |

**Table 5.1-5: On-Study Assessments for N-I Arms (Dose Level 2c) Nivolumab + Ipilimumab Combination (CA209032)**

| Procedure | For Arm N-I Dose level 2c, Nivolumab is administered every 2 weeks, Ipilimumab is administered every 6 weeks<br>Day 1<br>Week 1, 3, 5, 7, 9, etc | Notes |
|---|---|---|
| | specific sample timing | |
| [redacted] | [redacted] | |
| [redacted] | [redacted] | |
| [redacted] | [redacted] | [redacted] |
| [redacted] | [redacted] | |
| [redacted] | | [redacted] |
| **Efficacy Assessment** | | |
| Tumor Assessment | See Notes | • Tumor assessments should occur every 6 weeks (± 1 wk) from first dose for the first 24 weeks, then every 12 wks (± 1 wk) while on treatment or on treatment hold due to any reason until disease progression and treatment discontinuation, whichever occurs later. Additionally, with the exception of crossover participants, tumor assessments will not be required upon initiation of subsequent anti-cancer therapy.<br>• CT chest, CT or MRI abdomen, pelvis and all known sites of disease. Use same imaging method as was used at screening/baseline.<br>• Subjects with a history of brain metastasis should have surveillance MRI approximately every 12 weeks, or sooner if clinically indicated |

| **Table 5.1-5:** | **On-Study Assessments for N-I Arms (Dose Level 2c) Nivolumab + Ipilimumab Combination (CA209032)** | |
|---|---|---|
| **Procedure** | **For Arm N-I Dose level 2c, Nivolumab is administered every 2 weeks, Ipilimumab is administered every 6 weeks**<br>**Day 1**<br>**Week 1, 3, 5, 7, 9, etc** | **Notes** |
| **Clinical Drug Supplies** | | |
| IVRS Drug Vial Assignment | X | |
| Administer Study Treatment | X | See Section 4.5, Note: Within 3 days from vial allocation, the subject must receive the first dose of study medication. Subjects may be dosed no less than 12 days between doses and no more than 3 days from the scheduled dose. |

**Table 5.1-6: Follow-up Assessments (CA209032) - All Subjects**

| Procedure | Follow Up,[a] Visits 1 and 2 | Survival,[b] Follow up Visits | Notes |
|---|---|---|---|
| **Safety Assessments** | | | |
| Targeted Physical Examination | X | | To assess for potential late emergent study drug related issues |
| Adverse Event Assessments | X | X | eSAEs should be approved in TAO within 5 days from entry. AEs during the survival follow up visits considered study drug related should be followed until resolution, stabilization, or returned to baseline. |
| Laboratory Tests | X | | CBC w/ differential, LFTs, BUN or serum urea level, creatinine, albumin, Ca, Mg, Na, K, Cl, LDH, glucose, amylase, lipase, TSH (if TSH result abnormal, subsequent testing of Free T4 and Free T3 required). |
| Pregnancy Test (WOCBP Only) | X | | Serum or urine |
| [redacted] | [redacted] | | [redacted] |
| [redacted] | [redacted] | | [redacted] |
| [redacted] | [redacted] | [redacted] | [redacted] |
| **Efficacy Assessments** | | | |
| Tumor Assessments | See Notes | | For participants who discontinue treatment for reasons other than disease progression.<br>Tumor assessments should occur every 6 weeks (± 1 wk) from first dose for the first 24 weeks, then every 12 wks (± 1 wk) until disease progression and treatment discontinuation, whichever occurs later.<br>Additionally, with the exception of crossover participants, tumor assessments will not be required upon initiation of subsequent anti-cancer therapy.<br>CT chest, CT or MRI abdomen, pelvis and all known sites of disease. Use same imaging method as was used at screening/baseline.<br>Subjects with a history of brain metastasis should have surveillance MRI approximately every 12 weeks, or sooner if clinically indicated |

| **Table 5.1-6: Follow-up Assessments (CA209032) - All Subjects** | | | |
|---|---|---|---|
| **Procedure** | **Follow Up,[a] Visits 1 and 2** | **Survival,[b] Follow up Visits** | **Notes** |
| **Outcomes Research Assessments** | | | |
| QoL | X | X | Collect EQ-5D prior to study drug administration through Week 13, then at the same time of subsequent tumor assessments, during Follow Up 1 and 2 and survival visits. The EQ-5D can be done via a phone contact when a clinic visit is not feasible (ie, follow up scans are being done at another facility or department) in order to not miss the assessment. |
| **Pharmacokinetic Samples** | | | |
| PK Samples | X | | See Section 5.5.1 for schedule of assessments |

[a] Follow-up visit 1 (FU1) = 35 days from the last dose ± 7 days or coincide with the date of discontinuation (± 7 days) if date of discontinuation is greater than 42 days after last dose, Follow-up visit 2 (FU2) = 80 days (± 7 days) from follow-up visit 1

[b] Survival visits = every 3 months from FU2 (±14 days) from FU2.

### *5.1.1 Retesting During Screening or Lead-in Period*

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

## 5.2 Study Materials

- NCI CTCAE version 4.0
- BMS-936558 (nivolumab) Investigator Brochure
- Ipilimumab Investigator Brochure
- Laboratory manuals for collection and handling of blood [redacted]) and tissue specimens
- Site manual for operation of interactive voice response system, including enrollment worksheets
- Site manual for imaging process and requirements
- Manual for entry of local laboratory data
- Serious Adverse Events (or eSAE) case report form pages
- Pregnancy surveillance forms
- RECIST 1.1 pocket guide

## 5.3 Safety Assessments

At baseline, a medical history will be obtained to capture relevant underlying conditions. The baseline examinations should include signs and symptoms, weight, height, ECOG Performance Status, BP, HR, temperature, and oxygen saturation by pulse oximetry at rest should be performed within 14 days prior to first dose except where noted in Table 5.1-1. [redacted]

Baseline local laboratory assessments should be done within 14 days prior to the first dose and include: CBC w/differential, LFTs (ALT, AST, total bilirubin, alkaline phosphatase), BUN or serum urea level, creatinine, albumin, Ca, Mg, Na, K, Cl, LDH, glucose, amylase, lipase, TSH, Free T4, Free T3, and Hep B and C testing (HBV sAg and HCV RNA or Ab) (see Table 5.1-1). Pregnancy testing for WOCBP (done locally) must be performed within 24 hours prior to the initial administration of study drug at baseline and then every 3 weeks for subjects in Arm N-I at Week 1-12, then every 4 weeks, and at the safety follow up visits. For subjects in Arm N and N-I 2c pregnancy testing for WOCBP (done locally) must be performed within 24 hours prior to the initial administration of study drug at baseline and then every 4 weeks, and at each safety follow up visit.

During treatment hold, pregnancy testing must be performed every 12 weeks and resumed per protocol testing once treatment resumes.

Subjects will be evaluated for safety if they have received any study drug. Toxicity assessments will be performed continuously during the treatment phase. During the safety follow-up phase (Table 5.1-4) toxicity assessments should be done in person. Once subjects reach the survival follow-up phase, either in-person visits or documented telephone calls to assess the subject's status are acceptable.

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

On-study weight, ECOG performance status, and vital signs should be assessed at each on-study visit prior to nivolumab dosing. Vital signs should also be taken as per institutional standard of care prior to, during and after dosing. Oxygen saturation by pulse oximetry at rest should be assessed at each on study visit prior to nivolumab dosing. The start and stop time of the nivolumab and the ipilimumab infusion should be documented. Physical examinations are to be performed as clinically indicated. If there are any new or worsening clinically significant changes since the last exam, report changes on the appropriate non-serious or serious adverse event page.

Additional measures, including non-study required laboratory tests, should be performed as clinically indicated or to comply with local regulations. Laboratory toxicities (eg, suspected drug inducted liver enzyme elevations) will be monitored during the follow-up phase via on site/local labs until all study drug related toxicities resolve, return to baseline or are deemed irreversible.

Oxygen saturation by pulse oximetry should be obtained prior to each dose of nivolumab or ipilimumab and at any time a subject has any new or worsening respiratory symptoms. A reading at rest should be obtained at each time point. If a subject shows changes on pulse oximetry or other pulmonary-related signs (eg, hypoxia, fever) or symptoms (eg, dyspnea, cough) consistent with possible pulmonary adverse events, the patient subject should be immediately evaluated to rule out pulmonary toxicity. An algorithm for the management of suspected pulmonary toxicity can be found in Appendix 2.

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

### *5.3.1 Imaging Assessment for the Study*

Images will be submitted to an imaging core lab for central review. Sites will be trained prior to scanning the first study subject. Image acquisition guidelines and submission process will be outlined in the CA209032 Imaging Manual to be provided by the core lab. 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.

**CT/MRI**

Contrast-enhanced Computed Tomography (CT) scans acquired on dedicated CT equipment is preferred for this study. CT with contrast of the chest, abdomen and pelvis are to be performed

for tumor assessments at baseline and beginning 6 weeks (+/- 1 week) from first dose and continuing every 6 weeks (+/- 1 week) for the first 24 weeks and every 12 weeks (+/- 1 week) thereafter, while on treatment or on treatment hold for any reason until disease progression and treatment discontinuation, whichever occurs later. Additionally, with the exception of crossover participants, tumor assessments will not be required upon initiation of subsequent anti-cancer therapy.

CT scans should be acquired with 5mm slices with no intervening gap (contiguous). Although a contrast enhanced CT in particular for the chest is the preferred technique, a contrast enhanced MRI may be used based on local standards.

Should a subject have a contraindication for CT IV contrast, a non-contrast CT of the chest and a contrast enhanced MRI of the abdomen and pelvis may be obtained. MRI's should be acquired with slice thickness of £5 mm with no gap (contiguous).

Every attempt should be made to image each subject using an identical acquisition protocol on the same scanner for all imaging time points.

**Note: Use of CT component of a PET/CT scanner:**

Combined modality scanning such as with FDG-PET/CT is increasingly used in clinical care, and is a modality/technology that is in rapid evolution; therefore, the recommendations outlined here may change rather quickly with time. At present, low dose or attenuation correction CT portions of a combined FDG-PET/CT are of limited use in anatomically based efficacy assessments and it is therefore suggested that they should not be substituted for dedicated diagnostic contrast enhanced CT scans for anatomically based RECIST measurements. However, if a site can document that the CT performed as part of a FDG-PET/CT is of identical diagnostic quality to a diagnostic CT (with IV and oral contrast) then the CT portion of the FDG-PET/CT can be used for RECIST 1.1measurements. Note, however, that the FDG-PET portion of the CT introduces additional data which may bias an investigator if it is not routinely or serially performed.

**MRI Brain**

MRI or CT of brain is required at screening in order to rule out active metastatic disease. For patients with a history of known brain metastasis, an MRI brain is required at baseline. A CT brain is not allowed for patients with known brain metastasis at baseline. Subjects with a history of brain metastasis should have surveillance MRI approximately every 12 weeks, or sooner if clinically indicated.

## 5.4 Efficacy Assessments

Study evaluations will take place in accordance with the flow charts in Section 5.1. Baseline assessments should be performed within 28 days prior to the first dose utilizing CT or MRI. In addition to chest, abdomen, pelvis, and brain, all known sites of disease should be assessed at baseline. Subsequent assessments should include chest, abdomen, and pelvis, and all known sites of disease and should use the same imaging method as was used at baseline. Subjects will be evaluated for tumor response beginning 6 weeks (± 1 week) from first dose and continuing every

6 weeks (± 1 week) for the first 24 weeks and every 12 weeks (± 1 week) thereafter, while on treatment or on treatment hold for any reason until disease progression and treatment discontinuation, whichever occurs later. Additionally, with the exception of crossover participants, tumor assessments will not be required upon initiation of subsequent anti-cancer therapy. Tumor assessments for ongoing study treatment decisions will be completed by the investigator using RECIST (Response Evaluation Criteria in Solid Tumors) 1.1 criteria (Appendix 3).

### 5.4.1 Primary Efficacy Assessment

The primary endpoint is objective response rate (ORR) in all assigned subjects as determined by the investigators. ORR is defined as the number of subjects with a best overall response (BOR) of complete response (CR) or partial response (PR) divided by the number of assigned subjects. The investigator-determined ORR will be further characterized by the investigator-determined duration of response (DOR) and the magnitude of reduction in tumor volume. ORR and DOR will be assessed by BICR in selected tumor types.

### 5.4.2 Best Overall Response

The best overall response is determined once all the data for the subject is known. It is defined as the best response designation, as determined by the investigator or BICR for selected tumor types, recorded between the date of first treatment and the date of objectively documented progression per RECIST1.1 or the date of subsequent therapy, whichever occurs first. For subjects without documented progression or subsequent therapy, all available response designations will contribute to the BOR assessment. The subject'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.

Complete or partial responses may be claimed only if the criteria for each are met at a subsequent time point (minimum 4 weeks after criteria of objective response are first met). In this circumstance, the best overall response can be interpreted as in Table 5.4.2-1.

**Table 5.4.2-1: Best overall response when confirmation of CR and PR required**

| Overall Response First Timepoint | Overall Response Subsequent Timepoint | Best Overall response |
|---|---|---|
| CR | CR | CR |
| CR | PR | SD, PD or PR[a] |
| CR | SD | SD provided minimum criteria for SD duration met, otherwise, PD |
| CR | PD | SD provided minimum criteria for SD duration met, otherwise, PD |
| CR | NE | SD provided minimum criteria for SD duration met, otherwise NE |
| PR | CR | PR |

| Table 5.4.2-1: Best overall response when confirmation of CR and PR required | | |
|---|---|---|
| **Overall Response First Timepoint** | **Overall Response Subsequent Timepoint** | **Best Overall response** |
| PR | PR | PR |
| PR | SD | SD |
| PR | PD | SD provided minimum criteria for SD duration met, otherwise, PD |
| PR | NE | SD provided minimum criteria for SD duration 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.

For purposes of this study, the minimum scan time from baseline for determination of SD will be 6 weeks.

### *5.4.3 Duration of Objective Response*

The duration of objective response is measured from the time measurement criteria are first met for confirmed CR/PR (whichever is first recorded) until the first date that progressive disease is objectively documented (taking as reference for progressive disease the smallest measurements recorded on study).

### *5.4.4 Immune related Response Criteria*

Immune related response criteria using unidimensional measurements may be used to describe tumor shrinkage following RECIST 1.1 defined disease progression.[76] The methodology is the same as described above for RECIST 1.1 except for:

- New lesions do not automatically denote disease progression
- The measurement of longest diameter of new measurable lesions are in included in the sum of the measurements of the original target lesions.

Best immune related responses, for subjects who have progression followed by tumor shrinkage are classified as irCR (disappearance of all lesions) or irPR (≥ 30% reduction from baseline).

## 5.5 Pharmacokinetic Assessments

Serum samples for nivolumab and ipilimumab PK and immunogenicity assessments will be collected for all subjects.

### *5.5.1 Pharmacokinetics: Collection and Processing*

A detailed schedule of PK and immunogenicity evaluations is provided in Table 5.5.1-1, Table 5.5.1-2, and Table 5.5.1-3. All timepoints are relative to the start of study drug administration. Pre-dose samples should be taken within 30 minutes prior to the start of the first infusion for the day (prior to the nivolumab dose). All on-treatment PK timepoints are intended to align with days on which study drug is administered, if dosing occurs on a different day due to minor scheduling shifts, the PK sampling should be adjusted accordingly. If PK and immunogenicity samples are drawn but study drug(s) is not administered on the same day, samples will be retained and analyzed as planned. There is no need to collect another sample when the dose is resumed. Further details of sample collection, processing, and shipment will be provided in the laboratory procedures manual.

**Table 5.5.1-1: Pharmacokinetic & Immunogenicity Sampling Schedule - Arm N-I (Dose level 2 and 2b)**

| Study Day[a] | Event | Time (Relative to Start of Infusion) Hour: Min | Nivolumab PK Blood Sample | Nivolumab Immunogenicity Sample | Ipilimumab PK Blood Sample | Ipilimumab Immunogenicity Sample |
|---|---|---|---|---|---|---|
| D1 Week 1 | Predose[b] | 00:00 | X | X | X | X |
| D1 Week 4 | Predose | 00:00 | X | X | X | X |
| D1 Week 10 | Predose | 00:00 | X | X | X | X |
| D1 Week 13 | Predose | 00:00 | X | X | | |
| D1 Week 25 | Predose | 00:00 | X | X | | |
| Day 1 of every 16th week until discontinuation of study treatment or completion of 2 years of study treatment | Predose | 00:00 | X | X | | |

[a] If ipilimumab is discontinued and nivolumab continues, ipilimumab PK and Immunogenicity should be collected only for the next 2 timepoints (corresponding to ipilimumab sample collection) according to the PK table. If ipilimumab is discontinued, nivolumab will follow the same schedule as originally planned for that subject.

[b] Predose samples for nivolumab and ipilimumab should both be collected prior to start of nivolumab infusion (preferably within 30 minutes). If the infusion is delayed and a pre-dose sample is already collected, there is no need to collect an additional pre-dose sample.

| Table 5.5.1-2: Pharmacokinetic & Immunogenicity Sampling Schedule - Arm N | | | | | | |
|---|---|---|---|---|---|---|
| **Study Day** | **Event** | **Time (Relative to Start of Infusion) Hour: Min** | **Nivolumab PK Blood Sample** | **Nivolumab Immunogenicity Sample** | **Ipilimumab PK Blood Sample** | **Ipilimumab Immunogenicity Sample** |
| **All Subjects in Arm N** | | | | | | |
| D1 Week 1 | Predose | 00:00 | X | X | | |
| D1 Week 3 | Predose | 00:00 | X | X | | |
| D1 Week 5 | Predose | 00:00 | X | X | | |
| D1 Week 13 | Predose | 00:00 | X | X | | |
| Day 1 of every 16th week until discontinuation of study treatment or completion of 2 years of study treatment | Predose | 00:00 | X | X | | |
| **Crossover Subjects Only (SCLC subjects from the expansion cohorts under or after Amendment 09 are excluded from this option)** | | | | | | |
| Crossover D1 Week 1 | Predose[a] | 00:00 | X | X | X | X |
| Crossover D1 Week 4 | Predose | 00:00 | X | X | X | X |
| Crossover D1 Week 10 | Predose | 00:00 | X | X | X | X |
| Crossover D1 Week 13 | Predose | 00:00 | X | X | | |
| Crossover D1 Week 25 | Predose | 00:00 | X | X | | |
| Day 1 of every 16th week until discontinuation of study treatment or completion of 2 years of study treatment | Predose | 00:00 | X | X | | |

[a] Predose samples for nivolumab and ipilimumab should both be collected prior to start of nivolumab infusion (preferably within 30 minutes). If the infusion is delayed and a pre-dose sample is already collected, there is no need to collect an additional pre-dose sample.

**Table 5.5.1-3: Pharmacokinetic & Immunogenicity Sampling Schedule - Arm N-I (Dose level 2c)**

| Study Day[a] | Event | Time (Relative to Start of Infusion) Hour: Min | Nivolumab PK Blood Sample | Nivolumab Immunogenicity Sample | Ipilimumab PK Blood Sample | Ipilimumab Immunogenicity Sample |
|---|---|---|---|---|---|---|
| D1 Week 1 | Predose[b] | 00:00 | X | X | X | X |
| D1 Week 7 | Predose | 00:00 | X | X | X | X |
| D1 Week 19 | Predose | 00:00 | X | X | X | X |
| After Week 19 Day 1, Day 1 of every 18th week until discontinuation of study treatment or completion of 2 years of study treatment | Predose | 00:00 | X | X | X | X |

[a] If ipilimumab is discontinued and nivolumab continues, ipilimumab PK and Immunogenicity should be collected only for the next 2 timepoints (corresponding to ipilimumab sample collection) according to the PK table

[b] Predose samples for nivolumab and ipilimumab should both be collected prior to start of nivolumab infusion (preferably within 30 minutes). If the infusion is delayed and a pre-dose sample is already collected, there is no need to collect an additional pre-dose sample.

[redacted]

[redacted]

1.

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

## 5.7 Outcomes Research Assessments

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

The EQ-5D measure will be collected as follows:

- Nivolumab monotherapy arm: Collect prior to each study drug administration at Week 1, 3, 5, 7, 9, 11, and 13, then at the same time of subsequent tumor assessments, during Follow Up 1 and 2 and survival visits.
- Nivolumab / Ipilimumab combination arm: Collect prior to each study drug administration at Week 1, 4, 7, 10, and 13, then at the same time of subsequent tumor assessments, during Follow Up 1 and 2 and survival visits.
- The EQ-5D can be done via a phone contact when a clinic visit is not feasible (ie, follow up scans are being done at another facility or department) in order to not miss the assessment.

## 5.8 Other Assessments

[redacted]

### *5.8.2 Pharmacogenetic Research*

Pharmacogenetic sample collection will be performed at sites that permit pharmacogenetic studies to be conducted in compliance with all applicable laws, rules, and regulations. To participate in the Pharmacogenetic Sample Amendment, subjects must provide a signed Pharmacogenetic Blood DNA informed consent and must have consented to participate in this main clinical trial. Please refer to Amendment 01 and 07 for further information.

### *5.8.3 Demographics and Medical History*

At Screening, information regarding subject's demographics and medical history including date of birth, gender, race and ethnicity, general medical history, tobacco use, potential risk factors for pulmonary related events, disease diagnosis including diagnosis itself, date of initial diagnosis, disease stage at initial diagnosis, cell type, disease classification for SCLC only, current disease diagnosis with date and stage, HER-2 status, receptor status, prior surgery,

radiotherapy, and all prior lines of systemic cancer therapies with agents, start and stop dates, best response to the therapy and date of progression after each treatment line will be collected. For SCLC and ovarian cancer subjects, evaluation of platinum-free interval (PFI) from the completion of any platinum-based chemotherapy and subsequent disease progression, and Treatment-free-interval (TFI) from the completion of any other cytotoxic or targeted based prior treatment line and subsequent disease progression will be collected. For ovarian cancer, information about BRCA and Homologous Recombinant Deficiency (HRD), if available, will be collected.

### 5.9 Blinded Independent Central Review (BICR)

A Blinded Independent Central Review (BICR) will be performed for randomized subjects in selected tumor types to determine RECIST 1.1 response for the analysis of ORR, DOR, and PFS. Details of the Imaging responsibilities and procedures will be specified in the Imaging charter.

Sites will be informed of quality issues or the need for repeat scanning via queries from the central imaging vendor. Results of Central Imaging analysis will not be returned to the site.

## 6 ADVERSE EVENTS

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

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

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

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

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

## 6.1 Serious Adverse Events

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

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

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

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

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

**NOTE**:

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

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

- admission encountered for another life circumstance that carries no bearing on health status and requires no medical/surgical intervention (eg, lack of housing, economic inadequacy, caregiver respite, family circumstances, administrative reason)
- hospitalizations for the administration of subsequent anticancer therapy.

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

Following the subject's written consent to participate in the study, all SAEs, whether related or not related to study drug, must be collected, including those thought to be associated with protocol-specified procedures. All SAEs must be collected that occur during the screening period and within 100 days of discontinuation of dosing. Subjects who are randomized but never treated with study drug, must have SAEs collected for 30 days from the date of randomization. If applicable, SAEs must be collected that relate to any later protocol-specified procedure (eg, a follow-up skin biopsy).

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

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

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

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

**SAE Email Address:** See Contact Information list.

**SAE Facsimile Number:** See Contact Information list.

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

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

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

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

All SAEs should be followed to resolution or stabilization.

## 6.2 Nonserious Adverse Events

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

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

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

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

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

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

Immune-mediated adverse events 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.

## 6.3 Laboratory Test Result Abnormalities

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

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

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

## 6.4 Pregnancy

If, following initiation of the investigational product, it is subsequently discovered that a study subject is pregnant or may have been pregnant at the time of study exposure, including during at least 5 half lives after product administration, the investigator must immediately notify the BMS

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

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

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

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

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

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

## 6.5 Overdose

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

## 6.6 Potential Drug Induced Liver Injury (DILI)

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

Potential drug induced liver injury is defined as:

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

## 6.7 Other Safety Considerations

Any significant worsening noted during interim or final physical examinations, electrocardiogram, x-ray filming, any other potential safety assessment required or not required

by protocol should also be recorded as a nonserious or serious AE, as appropriate, and reported accordingly.

### 6.8 Safety Assessments

Safety assessments including targeted physical examination, vital signs and oxygen saturation, physical measurements including weight and ECOG performance status, and laboratory tests including Cell Blood Count (CBC) with differential, Liver Function Tests (LFTs), Blood Urea Nitrogen (BUN) or serum urea level, creatinine, albumin, Ca, Mg, Na, K, Cl, LDH, glucose, amylase, lipase, TSH (if TSH result is abnormal, subsequent testing of Free T4 and Free T3 is required) will be conducted in each treatment cohort as specified in the flow chart in section 5.1.

## 7 DATA MONITORING COMMITTEE AND OTHER EXTERNAL COMMITTEES

Ipilimumab has been studied in > 13,800 patients in clinical trials while nivolumab has been studied in more than 700 patients in clinical trials. The AE profile of nivolumab appears to be independent of tumor type. The safety of the combination of nivolumab and ipilimumab has been reported in 53 melanoma subjects and the spectrum of adverse events observed among patients treated with the concurrent regimen was qualitatively similar to previous experience with nivolumab or ipilimumab monotherapy. Adverse events observed with the combination therapy were manageable and generally reversible with the use of existing treatment algorithms. In addition, this is an open label study. Therefore, a data monitoring committee will not be utilized for this Phase 1/2 study.

The subjects' safety will be monitored on an ongoing basis. Safety conference calls with investigators and representatives of the sponsor will be held approximately once a month with additional meetings as necessary. The BMS medical monitor is a physician responsible for reviewing, on a systematic and continuous basis, the safety of patients on this study. This includes a review of serious and non-serious adverse events, which includes all hematological and non-hematological events.

In addition, a BMS medical safety team (MST) routinely reviews safety signals across the entire nivolumab program including combination studies with ipilimumab. The MST is independent from the BMS medical monitor. The MST has the primary responsibility within Bristol-Myers Squibb for assessing emerging safety trends, identifying potential safety signals, notifying appropriate stakeholders of relevant findings, and implementing risk management plans.

The MST is responsible for reviewing data from all sources including non-clinical studies and clinical trials, monitoring the progress of various nivolumab safety support activities, and recommending and implementing necessary changes to the safety plan and any other specific safety-related activities.

## 8 STATISTICAL CONSIDERATIONS

### 8.1 Sample Size Determination

*Sample Size determination in the original protocol*

This study comprises a Dose Escalating Safety Evaluation Phase for the Combination Arm, followed by a Staged Enrollment for Arm N and Arm N-I.

In the original protocol, gastric cancer, SCLC, TNBC, and pancreatic cancer are included and the Staged Enrollment Part utilizes a modified Simon two-stage design[79] with the treatment of 40 subjects to evaluate whether nivolumab or the combination of nivolumab/ipilimumab yields an objective response rate (ORR) that is of clinical interest. In this study, an ORR of 10% or less is considered not of clinical value, and an ORR of 25% or greater is considered of strong clinical interest. The modified Simon design evaluates the null hypothesis that the true response rate is ≤ 10% versus the alternative hypothesis that the true response rate is > 10%. The 2-stage testing within each cohort targets a Type I error rate of 5% and has 80% power to reject the null hypothesis if the true response rate is 25%.

*Sample Size determination for bladder cancer cohort*

In Amendment 06, the bladder cancer cohort is added. A one stage design with the treatment of 60-100 subjects is used. These sample sizes provide 90% to 97% power to reject the null hypothesis of a 10% response rate if the true response rate is 25% with a two-sided Type I error rate of 5%.

*Sample Size determination for SCLC expansion cohort:*

In Amendment 09, in addition to the original two-stage design in the SCLC cohort, additional SCLC expansion cohort subjects will be randomized in a 3:2 ratio to one of two expansion groups: Arm A (150 subject, nivolumab mono 3 mg/kg q2w) or Arm B (100 subjects, nivolumab 1 mg/kg + ipilimumab 3 mg/kg q3w) and will be stratified by number of prior treatment lines (1 vs 2 prior chemotherapy regimens).

Based on SCLC data so far observed in this study with an ORR of about 10% for nivolumab monotherapy and about 23% for the nivolumab + ipilimumab combination therapy, sample sizes of N = 150 for nivolumab monotherapy and N = 100 for nivolumab + ipilimumab combination therapy (nivolumab 1 mg/kg + ipilimumab 3 mg/kg) will target a Type I error rate of 5% (two-sided) and will have 78% power to detect the difference between these two arms if the true response rates are 10% and 23%, respectively.

*Sample Size determination for ovarian cancer cohort*

Also in Amendment 09, an ovarian cancer cohort is added and one stage design with the treatment of 40 subjects for each combination arm will be used. These sample sizes will provide 79% power to reject the null hypothesis of 10% response rate, if the true response rate is 25% with a two-sided Type I error rate of 5%.

## 8.2 Populations for Analyses

- All Enrolled Subjects: All subjects who signed an informed consent form and were registered into the IVRS.
- All Assigned Subjects: All subjects who were assigned to the highest tested tolerated dose level in the Dose Escalating Safety Evaluation Phase or to any treatment group during the Staged Enrollment Phase.
- All Treated Subjects: All subjects who received at least one dose of any study medication.
- All PK Subjects: All assigned subjects with available serum time-concentration data.
- All Immunogenicity Subjects: All treated subjects with baseline and at least 1 post baseline immunogenicity assessment.
- All Crossover Subjects: All treated subjects who crossed over from Arm N to Arm N-I. SCLC subjects from the expansion cohorts under or after Amendment 09 are excluded from the crossover option.
- All PD-L1 tested subjects: All subjects who had a tumor tissue sample available for assessment of PD-L1 expression at baseline.
- All treated, PD-L1 tested subjects: All PD-L1 tested subjects who received at least one dose of study treatment.
- All PD-L1 evaluable subjects: All treated PD-L1 tested subjects with quantifiable PD-L1 expression.

*Those subjects in the Dose Escalation Safety Evaluation Phase who received at least one dose of the highest dose level confirmed for further investigation will be counted as part of the required 18 treated subjects for Stage 1. In addition to being included in the All Treated Subjects population, those subjects will also be included in the All Dose Escalation Subjects population. Those subjects in the Dose Escalation Safety Evaluation Phase who received at least one dose of a dose level that was not confirmed for further investigation will not be included in the All Treated Subjects population.

## 8.3 Endpoints

### *8.3.1 Primary Endpoint(s)*

The primary endpoint is the objective response rate (ORR). The ORR is defined as the number of subjects with a best overall response (BOR) of complete response (CR) or partial response (PR) divided by the number of treated subjects. The BOR is defined as the best response designation, as determined by the investigator or BICR for selected tumor types, recorded between the date of randomization or treatment assignment and the date of objectively documented progression per RECIST 1.1 or the date of subsequent anti-cancer therapy, whichever occurs first. CR or PR determinations included in the BOR assessment must be confirmed by a second scan no less than 4 weeks after the criteria for response are first met. For subjects without documented progression or subsequent therapy, all available response designations will contribute to the BOR assessment. For subjects who continue treatment beyond progression, the BOR should be determined based on response designations recorded up to the time of the initial RECIST 1.1-defined progression.

For the SCLC expansion cohort, the estimated difference along with its corresponding p-value of ORR assessed by BICR between nivolumab monotherapy and nivolumab / ipilimumab combination therapy (nivolumab 1 mg/kg + ipilimumab 3 mg/kg) will be provided. In addition, 95% CI (two-sided) will also be presented for the estimated difference of ORR between nivolumab monotherapy and nivolumab / ipilimumab combination therapy.

Similar methods will be used to summarize ORR for each stratification factor (no p-value will be provided).

ORR will be further characterized by the duration of response (DOR) and the magnitude of reduction in tumor volume. DOR will be computed for subjects with a BOR of PR or CR and is defined as the time from first confirmed response (CR or PR) to the date of the first documented tumor progression as determined using RECIST 1.1 criteria or death due to any cause, whichever occurs first. For subjects who neither progress nor die, the DOR will be censored using the same censoring algorithm as used for PFS in Section 8.3.2. The magnitude of reduction in tumor volume is defined as the percent decrease in tumor volume from baseline to nadir, observed up until the time of the first documented tumor progression or death.

These measures of response will be interpreted in the context of historical responses observed following treatment with approved agents.

### *8.3.2 Secondary Endpoint(s)*

The secondary objective (to assess the safety and tolerability of nivolumab monotherapy or nivolumab combined with ipilimumab in subjects with advanced or metastatic tumors) will be primarily assessed by the rate of treatment-related AEs leading to drug discontinuations during the first 12 weeks of treatment. In addition, safety and tolerability will be analyzed through the incidence of adverse events, serious adverse events, and specific laboratory abnormalities (worst grade) in each cohort. Toxicities will be graded using the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) version 4.0.

PFS is defined as the time from treatment assignment in IVRS to the date of the first documented tumor progression, as determined by the investigator or BICR for selected tumor types (per RECIST 1.1), or death due to any cause, whichever occurs first. Subjects who die without a reported prior progression will be considered to have progressed on the date of their death. Subjects who did not progress or die will be censored on the date of their last evaluable tumor assessment. Subjects who did not have any on-study tumor assessments and did not die will be censored on the date they were assigned treatment in the IVRS. Subjects who started anti-cancer therapy either prior to death or without a prior reported progression will be censored on the date of their last evaluable tumor assessment prior to the initiation of subsequent anti-cancer therapy.

OS is defined as the time between the date of treatment assignment in IVRS and the date of death due to any cause. A subject who has not died will be censored at the last known alive date. OS will be followed continuously while subjects are on the study drug and every 3 months via in-person or phone contact after subjects discontinue the study drug.

[redacted]

index.

## 8.4 Analyses

### *8.4.1 Demographics and Baseline Characteristics*

Demographic and baseline characteristics will be summarized in all treated subjects by cohort, as randomized or assigned, using descriptive statistics.

### *8.4.2 Efficacy Analyses*

#### *8.4.2.1 Primary Endpoint Methods*

The efficacy analyses will be performed on the all treated population. ORR will be summarized for each cohort by a binomial response rate and corresponding two-sided 95% exact CI using the method proposed by Atkinson and Brown[80] for cohorts using the two-stage design and the Clopper-Pearson method for cohorts using the one-stage design[81].

For SCLC expansion cohort, the estimated difference along with its corresponding p-value of ORR assessed by BICR between nivolumab monotherapy and nivolumab/ipilimumab combination therapy (nivolumab 1 mg/kg + ipilimumab 3 mg/kg) will also be presented with 95% CI. Similar methods will be used to summarize ORR for each stratification factor. However the p-value will not be provided for each stratification factor.

DOR as determined by the investigator or BICR for selected tumor types will be summarized for subjects who achieve confirmed PR or CR using the Kaplan-Meier (KM) product-limit method. The median value, along with two-sided 95% CI using the Brookmeyer and Crowley method, will also be calculated by cohort. In addition, the percentage of responders still in response at different time points (3, 6, and 12 months) will be presented based on the KM plot.

The magnitude of reduction in tumor burden will be summarized descriptively. Immune related responses will be summarized descriptively.

#### *8.4.2.2 Secondary Endpoint Methods*

PFS and OS will be summarized descriptively using Kaplan-Meier methodology. Median values of PFS and OS, along with two-sided 95% CIs using the Brookmeyer and Crowley method, will be calculated for each cohort. PFS rates at 6 and 12 months, and OS rates at 12 and 24 months will also be estimated. Associated two-sided 95% CIs will be calculated using the Greenwood formula. Additional survival analysis may be conducted for up to 5 years beyond analysis of the primary endpoint.

[redacted]

### 8.4.3 Safety Analyses

Safety analyses will be performed in all treated subjects. Descriptive statistics of safety will be presented using National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) version 4.0. All on-study AEs, Grade 3-4 AEs, treatment-related AEs, Grade 3-4 treatment-related AEs, SAEs, treatment-related SAEs, and AEs leading to discontinuation will be tabulated using worst grade per NCI CTCAE v 4.0 criteria by system organ class and preferred term. On-study lab parameters including hematology, chemistry, liver function, and renal function and Grade 3-4 Lab Abnormalities will be summarized using worst grade NCI CTCAE v 4.0 criteria.

### 8.4.4 Pharmacokinetic Analyses

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

[redacted]

### 8.4.6 Outcomes Research Analyses

Subject's overall health state on a visual analog scale (EQ-VAS) at each assessment time point will be summarized using descriptive statistics by treatment arm (N and N-I), as randomized or assigned.

Proportion of subjects reporting problems for the 5 EQ-5D dimensions at each assessment time point will be summarized by level of problem and by treatment group, as randomized or assigned. Percentages will be based on number subjects assessed at assessment time point.

A by-subject listing of EQ-5D with the problem levels for each of the 5 dimensions (mobility, self-care, usual activities, pain/discomfort and anxiety/depression), health state (5 dimensions digits combined in a 5-digit number) and EQ-VAS will be provided.

[redacted]

## 8.5 Interim Analyses

Data will be reviewed during the Dose Escalation Safety Evaluation Phase to determine the maximum tolerated dose level for arm N-I and to make decisions about Stage 2 for each cohort using Simon's 2-stage design. The decision to proceed from Stage 1 to Stage 2 will be conducted for each tumor type and for each treatment arm independently.

An interim analysis may be conducted after Stage 1, by cohort. This interim analysis may be triggered if a "super" response (ie, 8 or more responders out of 18 subjects) is observed or if it is necessary in order to make decisions regarding further development. Summaries and listings of efficacy and safety will be provided. This interim analysis will not impact the study duration and the trial will continue as planned.

Interim analyses may be conducted for supporting internal decision making or for external data disclosure purposes by cohort, depending upon the maturity of the data.

# 9 STUDY MANAGEMENT

## 9.1 Compliance

### *9.1.1 Compliance with the Protocol and Protocol Revisions*

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

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

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

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

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

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

### 9.1.2 Monitoring

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

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

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

### 9.1.3 Investigational Site Training

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

## 9.2 Records

### 9.2.1 Records Retention

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

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

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

### 9.2.2 Study Drug Records

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

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

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

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

### *9.2.3 Case Report Forms*

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

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

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

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

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

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

## 9.3 Clinical Study Report and Publications

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

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

- External Principal Investigator designated at protocol development
- National Coordinating Investigator
- Study Steering Committee chair or their designee

- Subject recruitment (eg, among the top quartile of enrollers)
- Involvement in trial design
- Regional representation (eg, among top quartile of enrollers from a specified region or country)
- Other criteria (as determined by the study team)

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

# 10 GLOSSARY OF TERMS

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

# 11 LIST OF ABBREVIATIONS

| Term | Definition |
|---|---|
| AE | adverse event |
| ACLS | advanced cardiac life support |
| AI | accumulation index |
| AI_AUC | AUC Accumulation Index; ratio of AUC(TAU) at steady state to AUC(TAU) after the first dose |
| AI_Cmax | Cmax Accumulation Index; ratio of Cmax at steady state to Cmax after the first dose |
| AI_Ctau | Ctau Accumulation Index; ratio of Ctau at steady state to Ctau after the first dose |
| ALT | alanine aminotransferase |
| ANC | absolute neutrophil count |
| ANOVA | analysis of variance |
| aPTT | activated partial thromboplastin time |
| AST | aspartate aminotransferase |
| AT | aminotransaminases |
| AUC | area under the concentration-time curve |
| AUC(INF) | area under the concentration-time curve from time zero extrapolated to infinite time |
| AUC(0-T) | area under the concentration-time curve from time zero to the time of the last quantifiable concentration |
| AUC(TAU) | area under the concentration-time curve in one dosing interval |
| A-V | Atrioventricular |
| β-HCG | beta-human chorionic gonadotrophin |
| BA/BE | bioavailability/bioequivalence |
| BC | Breast cancer |
| BCRA1 | Breast cancer type 1 |
| %BE | percent biliary excretion |
| BICR | Blinded Independent Central Review |
| BID, bid | bis in die, twice daily |
| BLQ | below limit of quantification |
| BMI | body mass index |

| Term | Definition |
|---|---|
| BMS | Bristol-Myers Squibb |
| BP | blood pressure |
| BRt | Total amount recovered in bile |
| %BRt | Total percent of administered dose recovered in bile |
| BUN | blood urea nitrogen |
| C | Celsius |
| C12 | concentration at 12 hours |
| C24 | concentration at 24 hours |
| Ca++ | Calcium |
| CAV | cyclophosphamide, doxorubicin and vincristine |
| 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 |
| CLD | Dialysate clearance of drug from plasma/serum |
| CLNR | nonrenal clearance |
| CLR | renal clearance |
| CLT | total body clearance |
| CLT/F (or CLT) | apparent total body clearance |
| CLT/F/fu or CLT/fu | Apparent clearance of free drug or clearance of free if (if IV) |
| cm | Centimeter |
| Cmax, CMAX | maximum observed concentration |
| Cmin, CMIN | trough observed concentration |
| CNS | Central nervous system |
| CR | Complete response |
| CRC | Clinical Research Center |

| Term | Definition |
|---|---|
| CRF | Case Report Form, paper or electronic |
| CT | Computed tomography |
| Ct | Expected concentration at a certain time, usually at the end of an expected future dosing interval (eg, concentration at 24 hours, concentration at 12 hours, etc.) |
| Ctau | Concentration in a dosing interval (eg, concentration at 24 hours, concentration at 12 hours, etc.) |
| CTLA-4 | Cytotoxic T-lymphocyte-associated protein 4 |
| Ctrough | Trough observed plasma concentration |
| CV | coefficient of variation |
| CYP | cytochrome p-450 |
| D/C | Discontinue |
| DCR | Disease control rate |
| dL | Deciliter |
| DLT | Dose limiting toxicity |
| DOR | Duration of response |
| DRt | Total amount recovered in dialysate |
| %DRt | Total percent of administered dose recovered in dialysate |
| DSM IV | Diagnostic and Statistical Manual of Mental Disorders (4th Edition) |
| EA | extent of absorption |
| ECG | Electrocardiogram |
| ECOG | Eastern Cooperative Oncology Group |
| eCRF | Electronic Case Report Form |
| ED | Extensive disease |
| EDC | Electronic Data Capture |
| EEG | electroencephalogram |
| eg | exempli gratia (for example) |
| EMA | European Medicinal Agency |
| EOI | End of Infusion |
| EQ-5D | EuroQol 5 Dimensions Questionnaire |
| ER | Estrogen receptor |

| Term | Definition |
|---|---|
| ESR | Expedited Safety Report |
| EU | European Union |
| F | Bioavailability |
| Fb | fraction of bound drug |
| FDA | Food and Drug Administration |
| FFPE | Formalin-fixed, paraffin-embedded |
| FI | fluctuation Index ([Cmax-Ctau)/Cavg]) |
| FIGO | Federation of Gynecology and Obstetrics |
| FOLFIRINOX | combination of 5-FU, leucovorin, irinotecan, oxaliplatin |
| FRt | total amount recovered in feces |
| %FRt | total percent of administered dose recovered in feces |
| FSH | follicle stimulating hormone |
| %FE | percent fecal excretion |
| fu | fraction of unbound drug |
| FU1 | Follow-up 1 |
| FU2 | Follow-up 2 |
| g | Gram |
| GC | gas chromatography |
| GC | Gastric cancer |
| GCP | Good Clinical Practice |
| G criteria | adjusted R2 value of terminal elimination phase |
| GEJ | Gastro-esophageal junction |
| GEM | Gemcitabine |
| GGT | gamma-glutamyl transferase |
| GFR | glomerular filtration rate |
| h | Hour |
| HBsAg | hepatitis B surface antigen |
| HBV | hepatitis B virus |
| HCV | hepatitis C virus |
| HCO3- | Bicarbonate |

| Term | Definition |
|---|---|
| HER-2 | Human epidermal growth factor receptor 2 |
| HIPAA | ***Health Insurance Portability and Accountability Act*** |
| HIV | Human Immunodeficiency Virus |
| HR | heart rate |
| HRD | homologous recombinant deficiency |
| HRT | hormone replacement therapy |
| IB | Investigator Brochure |
| IC | Informed Consent |
| ICD | International Classification of Diseases |
| ICF | Informed consent form |
| ICH | International Council for Harmonisation |
| ie | id est (that is) |
| IEC | Independent Ethics Committee |
| IFN | Interferon |
| IMP | investigational medicinal products |
| IND | Investigational New Drug Exemption |
| IRB | Institutional Review Board |
| irCR | Immune related complete response |
| irPR | Immune related partial response |
| irPD | Immune related progression |
| IU | International Unit |
| IV | Intravenous |
| K | slope of the terminal phase of the log concentration-time curve |
| K3EDTA | potassium ethylenediaminetetraacetic acid |
| K+ | Potassium |
| kg | Kilogram |
| KM | Kaplan-Meier |
| $\lambda z$ | terminal disposition rate constant |
| L | Liter |
| LC | liquid chromatography |

| Term | Definition |
|---|---|
| LD | Limited disease |
| LDH | lactate dehydrogenase |
| LFT | Liver function test |
| ln | natural logarithm |
| Lz_Start | The time point starting the log-linear elimination phase defining the terminal half life |
| Lz_End | The time point ending the log-linear elimination phase defining the terminal half life |
| Lz_N | Number of time points in the log-linear elimination phase defining the terminal half life |
| MST | medical safety team |
| mg | Milligram |
| Mg++ | Magnesium |
| MIC | minimum inhibitory concentration |
| min | Minute |
| mIU/ml | Milli international units per millimeter |
| mL | Milliliter |
| mmHg | millimeters of mercury |
| mOS | Median overall survival |
| mRCC | Metastatic renal cell carcinoma |
| MR_AUC(0-T) | Ratio of metabolite AUC(0-T) to parent AUC(0-T), corrected for molecular weight |
| MR_AUC(INF) | Ratio of metabolite AUC(INF) to parent AUC(INF), corrected for molecular weight |
| MR_AUC(TAU) | Ratio of metabolite AUC(TAU) to parent AUC(TAU), corrected for molecular weight |
| MR_Cmax | Ratio of metabolite Cmax to parent Cmax, corrected for molecular weight |
| MR_Ctau | Ratio of metabolite Ctau to parent Ctau, corrected for molecular weight |
| MRI | Magnetic resonance imaging |
| MRT | mean residence time |
| MS | mass spectrometry |

| Term | Definition |
|---|---|
| MTD | maximum tolerated dose |
| µg | Microgram |
| N | number of subjects or observations |
| N | Nivolumab monotherapy |
| N-I | Nivolumab in combination with Ipilimumab |
| Na+ | Sodium |
| N/A | not applicable |
| NCCN | ***National Comprehensive Cancer Network*** |
| NCI CTCAE | National Cancer Institute - Common Terminology Criteria for Adverse Events |
| ng | Nanogram |
| NIMP | non-investigational medicinal products |
| NSAID | nonsteroidal anti-inflammatory drug |
| NSCLC | Non-small cell lung cancer |
| ORR | Overall response rate |
| OS | Overall survival |
| PAC | Paclitaxel |
| PARP | ***Poly (ADP-ribose) polymerase*** |
| pAUCe | Extrapolated partial AUC from last quantifiable concentration to infinity |
| Pb | percent of bound drug |
| PBMC | Peripheral blood mononuclear cell |
| PC | Pancreatic cancer |
| pCR | Complete pathological response |
| PD | Pharmacodynamics |
| PD-1 | Programmed death 1 |
| PDL-1 | Programmed cell death 1 ligand 1 |
| PE | Physical Exam |
| PE | Platinum plus etopiside |
| PFI | platinum-free interval |
| PFS | Progression Free Survival |

| Term | Definition |
|---|---|
| PK | Pharmacokinetics |
| PO | per os (by mouth route of administration) |
| PR | Partial response |
| PR | Progesterone receptor |
| PS | Performance status |
| PT | prothrombin time |
| PTT | partial thromboplastin time |
| Pu | percent of unbound drug |
| Q2W | Every two weeks |
| Q3W | Every three weeks |
| QC | quality control |
| QD, qd | quaque die, once daily |
| R2 | coefficient of determination |
| RBC | red blood cell |
| RECIST | Response Evaluation Criteria in Solid Tumors |
| RT-PCR | Reverse transcription-polymerase chain reaction |
| SAE | serious adverse event |
| SCLC | Small cell lung cancer |
| SD | stable disease |
| SD | standard deviation |
| SOC | Standard of care |
| SOP | Standard Operating Procedures |
| sp. | Species |
| Subj | Subject |
| t | Temperature |
| T | Time |
| TAO | Trial Access Online, the BMS implementation of an EDC capability |
| TEN | toxic epidermal necrolysis |
| TFI | Treatment-free-interval |
| T-HALF | Half life |

| Term | Definition |
|---|---|
| T-HALFeff_AUC | Effective elimination half-life that explains the degree of AUC accumulation observed |
| T-HALFeff_Cmax | Effective elimination half-life that explains the degree of Cmax accumulation observed) |
| TID, tid | ter in die, three times a day |
| Tmax, TMAX | time of maximum observed concentration |
| TNBC | Triple negative breast cancer |
| TPC | Treatment of physician's choice |
| TR_AUC(0-T) | AUC(0-T) treatment ratio |
| TR_AUC(INF) | AUC(INF) treatment ratio |
| TR_Cmax | Cmax treatment ratio |
| UR | urinary recovery |
| %UR | percent urinary recovery |
| URt | total amount recovered in urine |
| US | United States |
| %URt | total percent of administered dose recovered in urine |
| UV | Ultraviolet |
| Vss/F (or Vss) | apparent volume of distribution at steady state |
| Vz | Volume of distribution of terminal phase (if IV and if multi-exponential decline) |
| W | Washout |
| WBC | white blood cell |
| WHO | World Health Organization |
| WOCBP | women of childbearing potential |
| x g | times gravity |

# APPENDIX 1 PERFORMANCE STATUS SCALES

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

# APPENDIX 2 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.

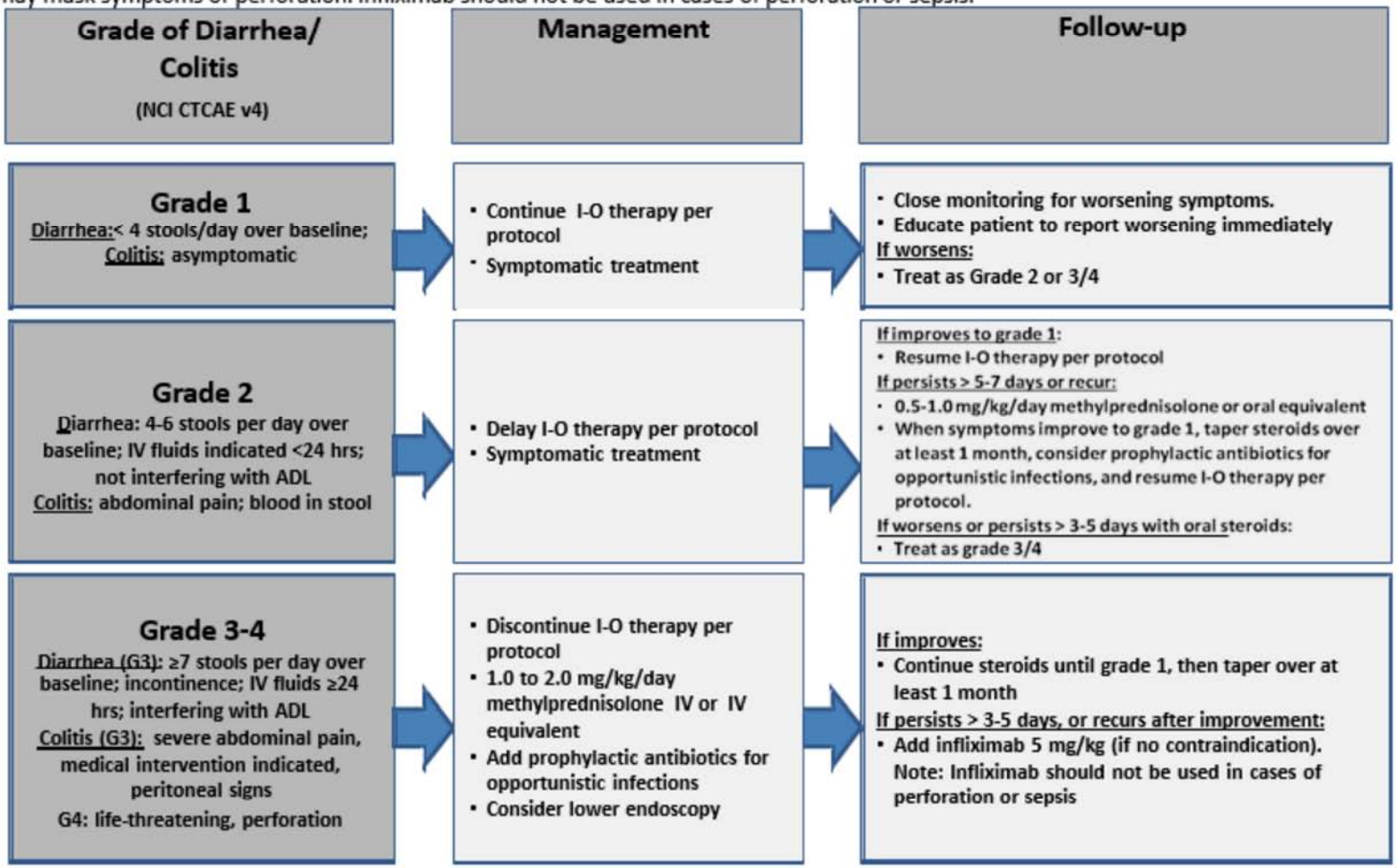
Corticosteroids are a primary therapy for immuno-oncology drug-related adverse events. The oral equivalent of the recommended IV doses may be considered for ambulatory patients with low-grade toxicity. The lower bioavailability of oral corticosteroids should be taken into account when switching to the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

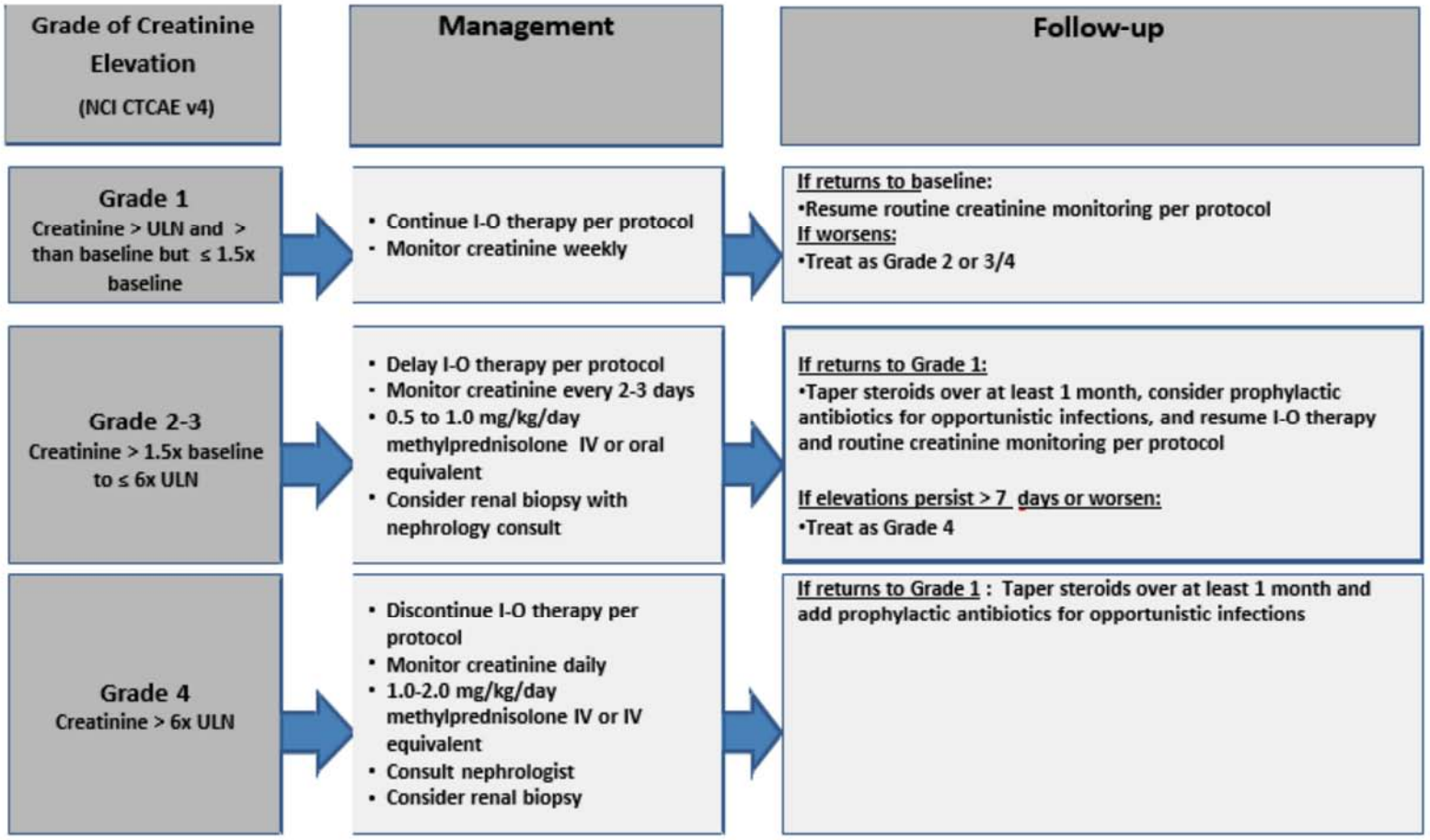



Patients on IV steroids may be switched to an equivalent dose of oral corticosteroids (e.g. prednisone) at start of tapering or earlier, once sustained clinical improvement is observed. Lower bioavailability of oral corticosteroids should be taken into account when switching to the equivalent dose of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

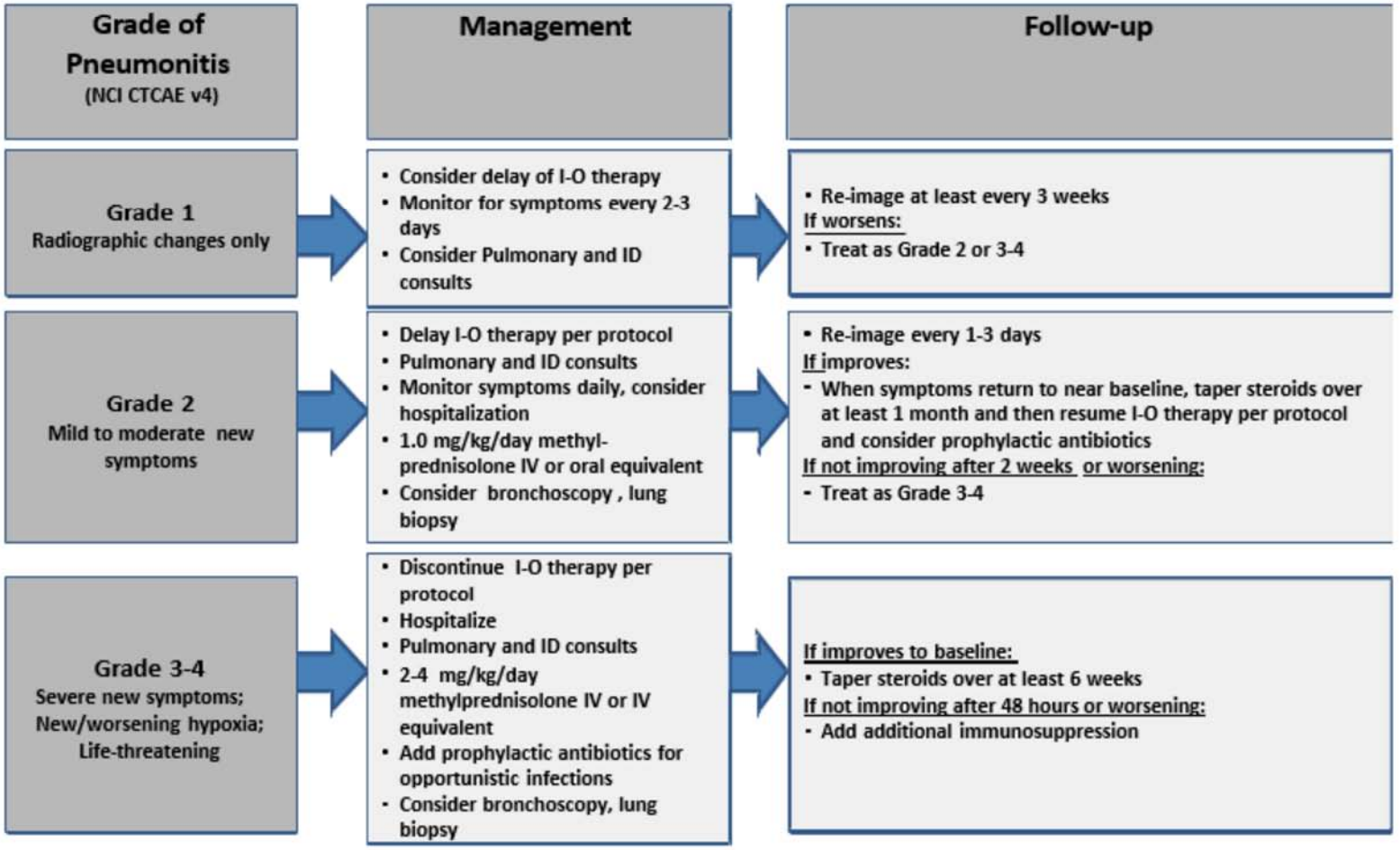



Patients on IV steroids may be switched to an equivalent dose of oral corticosteroids (e.g. prednisone) at start of tapering or earlier, once sustained clinical improvement is observed. Lower bioavailability of oral corticosteroids should be taken into account when switching to the equivalent dose of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

| Grade of Liver Test Elevation (NCI CTCAE v4) | Management | Follow-up |
|---|---|---|
| **Grade 1**<br>AST or ALT > ULN to 3.0 x ULN and/or T. bili > ULN to 1.5 x ULN | • Continue I-O therapy per protocol | • Continue LFT monitoring per protocol<br>If worsens:<br>• Treat as Grade 2 or 3-4 |
| **Grade 2**<br>AST or ALT > 3.0 to ≤ 5 x ULN and/or T. bili > 1.5 to ≤ 3 x ULN | • Delay I-O therapy per protocol<br>• Increase frequency of monitoring to every 3 days | If returns to baseline:<br>•Resume routine monitoring, resume I-O therapy per protocol<br>If elevations persist > 5-7 days or worsen :<br>• 0.5-1 mg/kg/day methylprednisolone or oral equivalent and when LFT returns to grade 1 or baseline, taper steroids over at least 1 month, consider prophylactic antibiotics for opportunistic infections, and resume I-O therapy per protocol |
| **Grade 3-4**<br>AST or ALT > 5 x ULN or T.bili >3 x ULN | • Discontinue I-O therapy*<br>• Increase frequency of monitoring to every 1-2 days<br>• 1.0 to 2.0 mg/kg/day methylprednisolone IV or IV equivalent*<br>• Add prophylactic antibiotics for opportunistic infections<br>• Consult gastroenterologist | If returns to grade 2:<br>• Taper steroids over at least 1 month<br>If does not improve in >3-5 days, worsens or rebounds:<br>• Add mycophenolate mofetil 1 g BID<br>• If no response within an additional 3-5 days, consider other immunosuppressants per local guidelines |

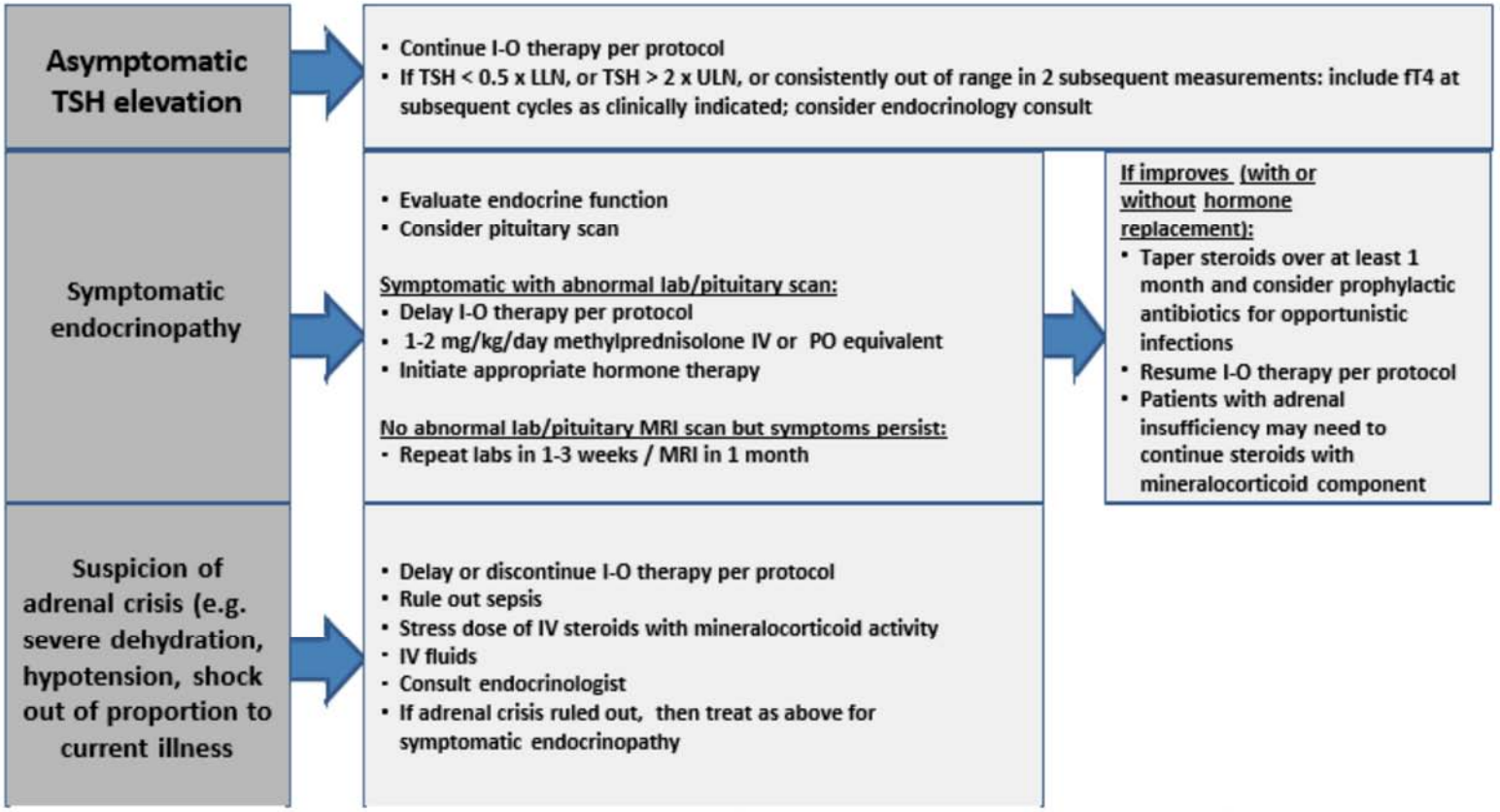
Patients on IV steroids may be switched to an equivalent dose of oral corticosteroids (e.g. prednisone) at start of tapering or earlier, once sustained clinical improvement is observed. Lower bioavailability of oral corticosteroids should be taken into account when switching to the equivalent dose of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

*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.

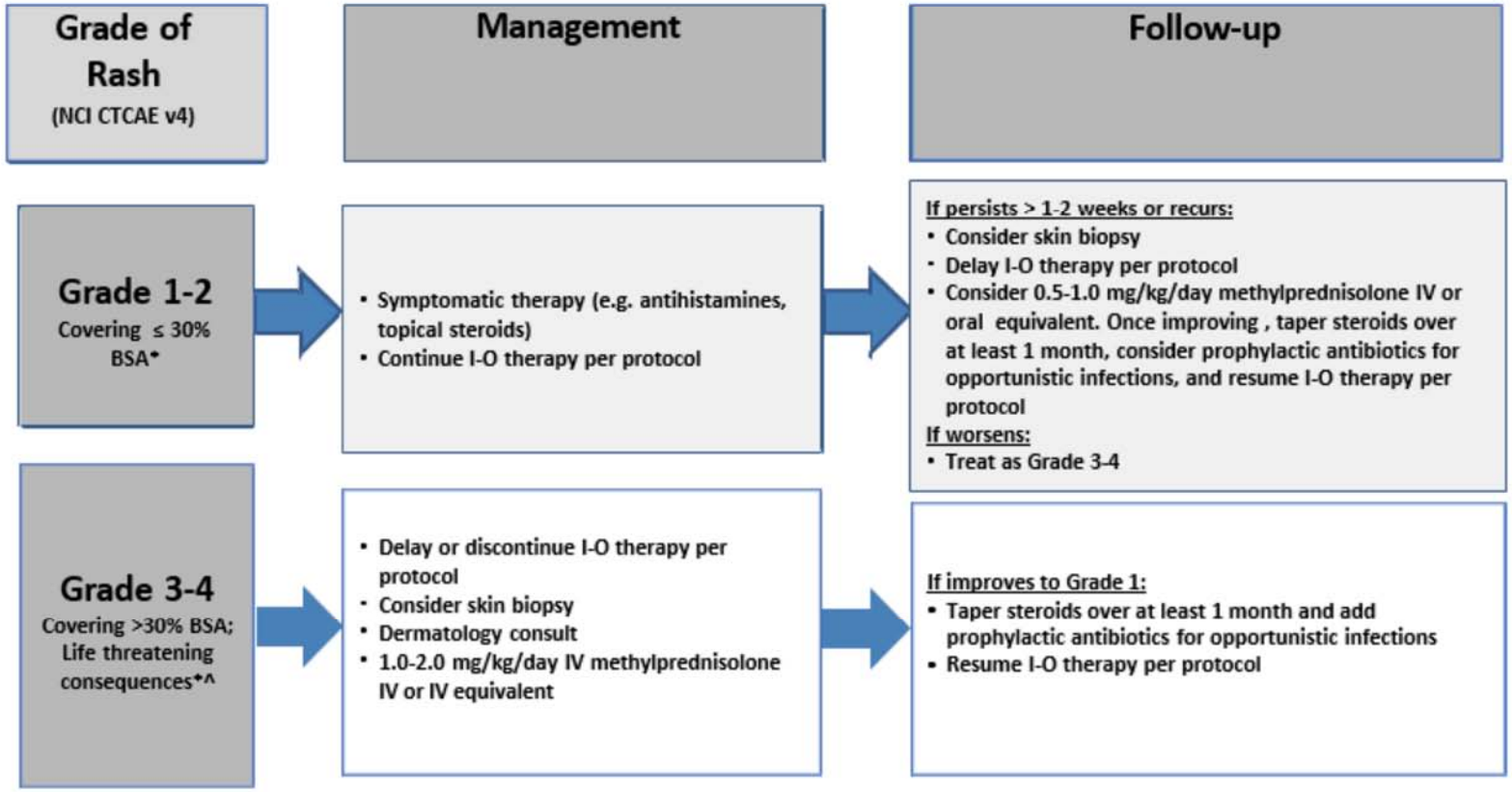



Patients on IV steroids may be switched to an equivalent dose of oral corticosteroids (e.g. prednisone) at start of tapering or earlier, once sustained clinical improvement is observed. Lower bioavailability of oral corticosteroids should be taken into account when switching to the equivalent dose of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

27-Jun-2019

# 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.

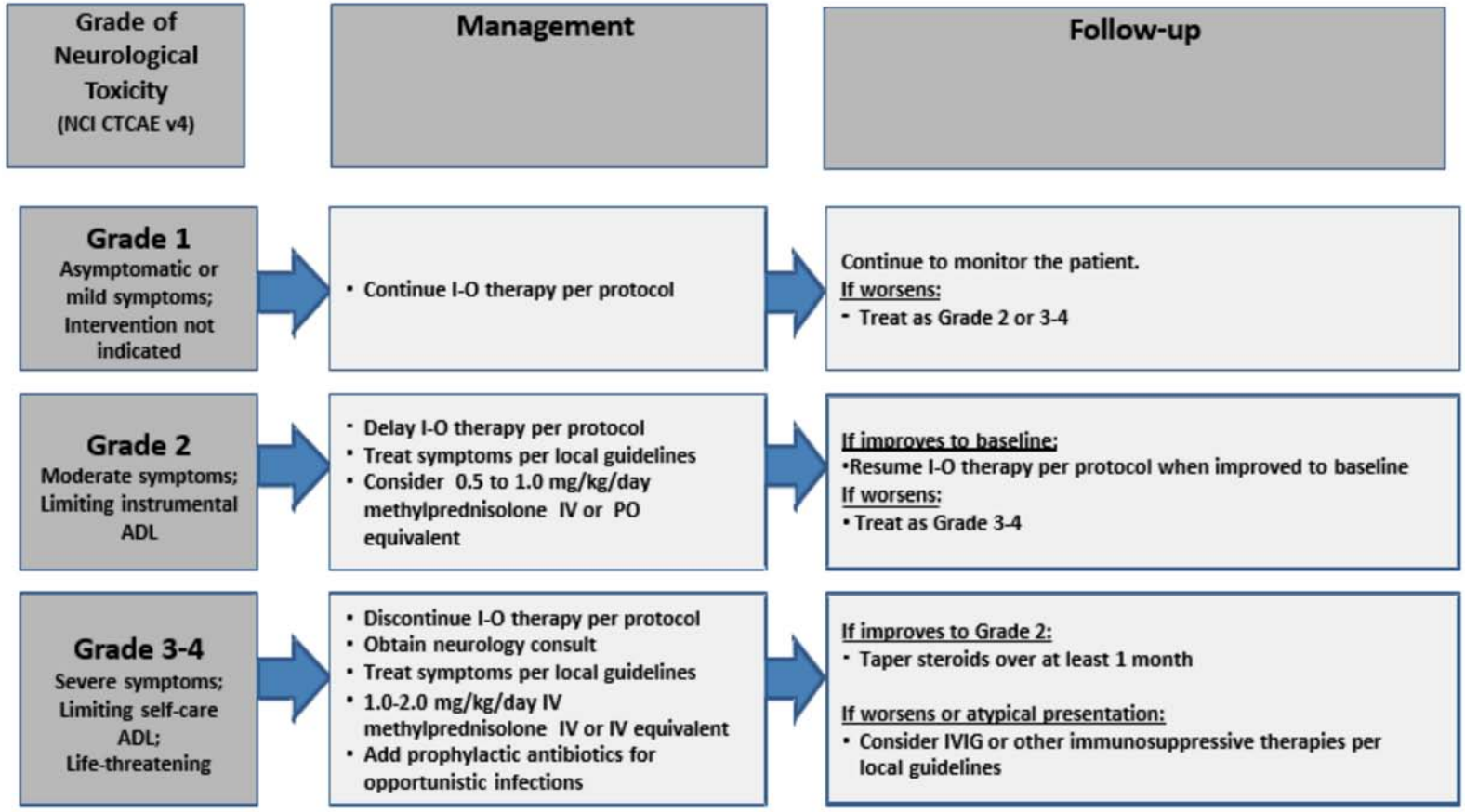
*Refer to NCI CTCAE v4 for term-specific grading criteria.

^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

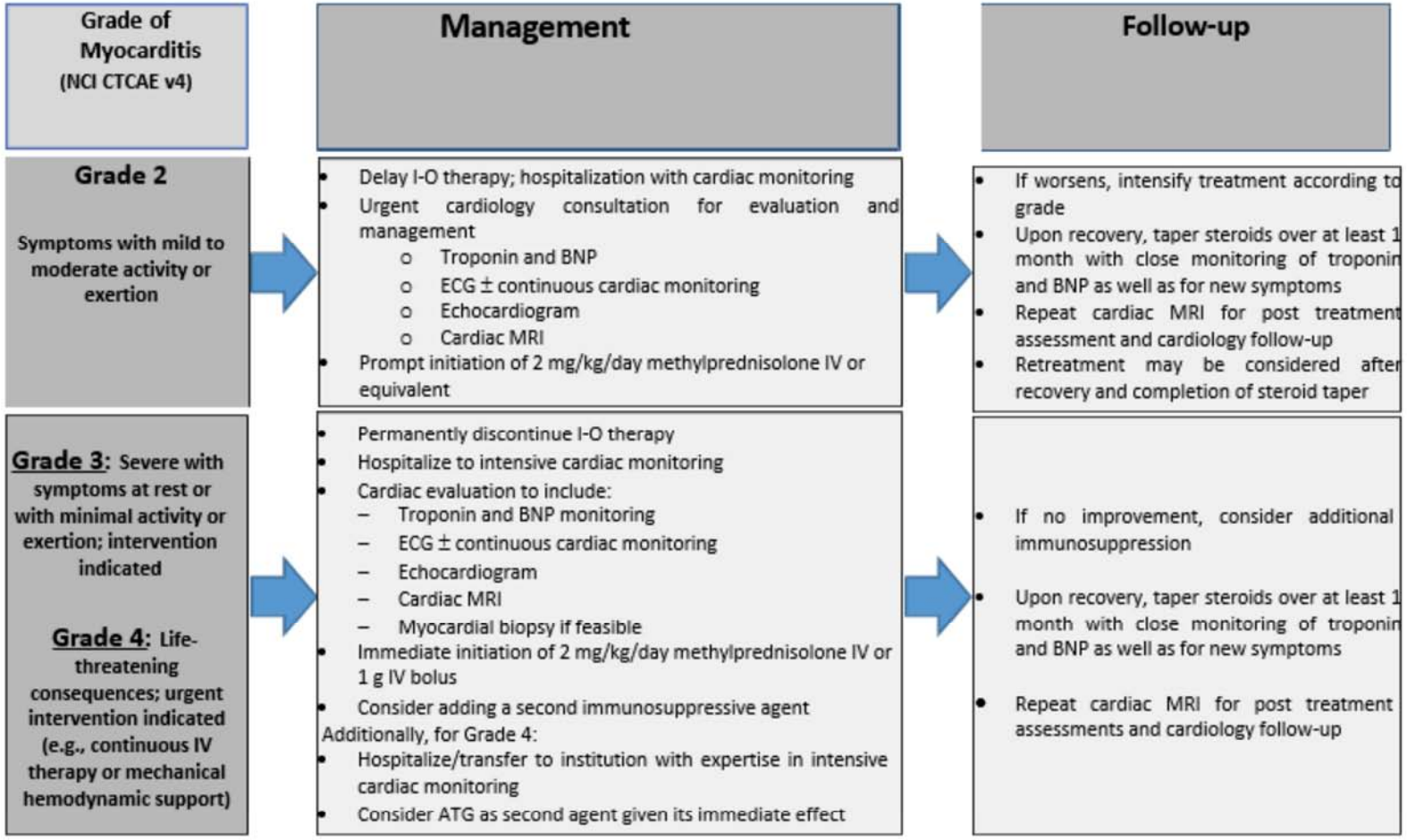
Rule out non-inflammatory causes. If non-inflammatory cause, treat accordingly and continue I-O therapy.




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

# 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 3 RECIST 1.1

Changes in tumor measurements and tumor responses will be assessed by the investigator using the RECIST 1.1 (Response Evaluation Criteria in Solid Tumors) criteria. (Eisenhauer, et al 2009.)

Source: Eisenhauer et al New response evaluation criteria in solid tumours: Revised RECIST guideline (version 1.1), European Journal of Cancer, 2009, Vol. 45, p 228-247

## 1 ASSESSMENT OF OVERALL TUMOR BURDEN AND MEASURABLE DISEASE

To assess objective response or future progression, it is necessary to estimate the *overall tumor burden at baseline* and use this as a comparator for subsequent measurements. Measurable disease is defined by the presence of at least one measurable tumor lesion. When CT scans have slice thickness greater than 5 mm, the minimum size for a measurable lesion should be twice the slice thickness.

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

### 1.1 Measurable lesions

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

- 10 mm by CT/MRI scan - (CT/MRI scan slice thickness no greater than 5 mm)
- 10 mm caliper measurement by clinical exam (lesions which cannot be accurately measured with calipers should be recorded as non-measurable)
- 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). At baseline and in follow-up, only the ***short*** axis will be measured and followed.

### 1.2 Non-measurable lesions

- All other lesions, including small lesions (longest diameter < 10 mm 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 in not measurable by reproducible imaging techniques.

## 1.3 Special considerations regarding lesion measurability

### *1.3.1 Bone lesions*

- Bone scan, PET scan or plain films are ***not*** considered adequate imaging techniques to measure bone lesions. However, these techniques can be used to confirm the presence or disappearance of bone lesions.
- Lytic bone lesions or mixed lytic-blastic lesions, with *identifiable soft tissue components*, that can be evaluated by cross sectional imaging techniques such as CT or MRI can be considered as measurable lesions if the *soft tissue component* meets the definition of measurability described above.
- Blastic bone lesions are non-measurable.

### *1.3.2 Cystic lesions*

- Lesions that meet the criteria for radiographically defined simple cysts should not be considered as malignant lesions (neither measurable nor non-measurable) since they are, by definition, simple cysts.
- 'Cystic lesions' thought to represent cystic metastases can be considered as measurable lesions, if they meet the definition of measurability described above. However, if non-cystic lesions are present in the same subject, these are preferred for selection as target lesions.

### *1.3.3 Lesions with prior local treatment*

Tumor lesions situated in a previously irradiated area, or in an area subjected to other loco-regional therapy, are usually not considered measurable unless there has been demonstrated progression in the lesion.

## 1.4 Specifications by methods of measurements

### *1.4.1 Measurement of lesions*

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

### *1.4.2 Method of assessment*

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

#### *1.4.2.1 CT/MRI scan*

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

#### *1.4.2.2 Chest X-ray*

Chest CT is preferred over chest X-ray, particularly when progression is an important endpoint, since CT is more sensitive than X-ray, particularly in identifying new lesions. However, lesions on chest X-ray may be considered measurable if they are clearly defined and surrounded by aerated lung.

#### *1.4.2.3 Clinical lesions*

Clinical lesions will only be considered measurable when they are superficial and ≥ 10 mm diameter as assessed using calipers. For the case of skin lesions, documentation by color photography including a ruler to estimate the size of the lesion is suggested. As previously noted, when lesions can be evaluated by both clinical exam and imaging, imaging evaluation should be undertaken since it is more objective and may also be reviewed at the end of the study.

#### *1.4.2.4 Ultrasound*

Ultrasound is ***not*** useful in assessment of lesion size and should not be used as a method of measurement. If new lesions are identified by ultrasound in the course of the study, confirmation by CT or MRI is advised.

#### *1.4.2.5 Endoscopy, laparoscopy*

The utilization of these techniques for objective tumor evaluation is ***not*** advised.

#### *1.4.2.6 Tumor markers*

Tumor markers ***alone*** cannot be used to assess objective tumor response.

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

### 2.1 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.

Target lesions should be selected on the basis of their **size** (lesions with the longest diameter), be representative of all involved organs, and should lend themselves to ***reproducible repeated measurements.***

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 below, 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.

#### *2.1.1 Lymph nodes*

**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. Nodes that have a short axis < 10 mm are considered non-pathological and should not be recorded or followed.

## 2.2 Non-target lesions

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'.** In addition, it is possible to record multiple non-target 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 TUMOR RESPONSE EVALUATION

## 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 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. Nodes that have a short axis < 10 mm are considered non-pathological and should not be recorded or followed.

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

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). If the radiologist is able to provide an actual measurement, that should be recorded, even if it is below 5 mm.

However, when such a lesion becomes difficult to assign an exact measure to then:

- 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: in case of a lymph node believed to be present and 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).

#### *3.1.1.3 Target 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.
- 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

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 (< 10 mm 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* 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 non-target lesions*

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

#### *3.2.1.1 When the subject also has measurable disease*

- 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.
- A modest 'increase' in the size of one or more non-target lesions is usually not sufficient to quality for unequivocal progression status.

#### *3.2.1.2 When the subject has only non-measurable disease*

- To achieve 'unequivocal progression' on the basis of the non-target disease, there must be an overall level of substantial worsening such that the overall tumor burden has increased sufficiently to merit discontinuation of therapy.
- A modest 'increase' in the size of one or more non-target lesions is usually not sufficient to qualify for unequivocal progression status.
- Because worsening in non-target disease cannot be easily quantified (by definition: if all lesions are non-measurable) a useful test that can be applied when assessing subjects 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 subject should be considered to have had overall PD at that point.

#### *3.2.1.3 Tumor markers*

Tumor markers *alone* cannot be used to assess objective tumor responses. If markers are initially above the upper normal limit, however, they must normalize in order for a subject to be considered as having attained a complete response.

### 3.3 New lesions

The appearance of new malignant lesions denotes disease progression. 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 subject'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 subject who has visceral disease at baseline and while on study has a CT or MRI brain scan ordered which reveals metastases. The subject'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.*

### *3.3.1 FDG-PET evaluation*

While FDG-PET response assessments need additional study, it is sometimes reasonable to incorporate the use of the qualitative assessment of FDG-PET scanning to complement CT scanning in assessment of progression (particularly possible 'new' disease). New lesions on the basis of FDG-PET imaging can be identified according to the following algorithm:

- Negative FDG-PET at baseline, with a positive FDG-PET at follow-up might be a sign of PD based on a new lesion. However, other reasons for newly detected lesions with increased FDG-PET uptake, such as inflammatory lymphnodes, should be taken into consideration.
- No FDG-PET at baseline and a positive FDG-PET at follow-up:
  - If the positive FDG-PET at follow-up corresponds to a new site of disease confirmed by CT, this is PD.
  - If the positive FDG-PET at follow-up is not confirmed as a new site of disease on CT, additional follow-up CT scans are needed to determine if there is truly progression occurring at that site (if so, the date of PD will be the date of the initial positive FDG-PET scan).
  - If the positive FDG-PET at follow-up corresponds to a pre-existing site of disease on CT that is not progressing on the basis of the anatomic images, this is not PD.
  - Other reasons for newly detected lesions with increased FDG-PET uptake, such as inflammatory lymphnodes, should be taken into consideration.

# 4 RESPONSE CRITERIA

## 4.1 Time point response

A response assessment should occur at each time point specified in the protocol.

For subjects who have **measurable disease** at baseline Table 1 provides a summary of the overall response status calculation at each time point.

**Table 1: Time point response: subjects 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 |

**Table 1: Time point response: subjects with target (+/– non-target) disease.**

| Target lesions | Non-target lesions | New lesions | Overall response |
|---|---|---|---|
| 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, NE =not evaluable.

For subjects who have **non-measurable** (therefore non-target) disease only, Table 2 is to be used.

**Table 2: Time point response: Subjects 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 |

[a] 'Non-CR/non-PD' is preferred over 'stable disease' 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.

CR = complete response, PD = progressive disease, and NE = not evaluable.

### *4.1.1 Missing assessments and not evaluable designation*

When no imaging/measurement is done at all at a particular time point, the subject is **not evaluable (NE)** at that time point. If only a subset of lesion measurements are made at an

assessment, the case is also considered NE at that time point, unless a convincing argument can be made that the contribution of the individual missing lesion(s) would not have changed the assigned time point response.

### *4.1.2 Confirmation of Scans and External Evaluation*

- **Verification of Response:** Confirmation of response (CR or PR) is required. Confirmed CR or PR will be claimed only if the criteria for each are met at a subsequent timepoint (minimum 4 weeks after criteria for an objective response are first met).
- **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 not to have progressive disease per RECIST 1.1.
- **External Evaluation of scans:** For all subjects, BMS will request the transfer of anonymized scans for a BMS internal or external evaluation through a third party. For tumor types where data from study CA209-032 will potentially be used for future NDA submissions, BMS will request the transfer of anonymized scans from all subjects with this tumor type for a BMS internal or external evaluation through a third party.

## 4.2 Best overall response: All timepoints

The best overall response is determined once all the data for the subject is known. It is defined as the best response designation, as determined by the investigator, recorded between the date of first treatment and the date of objectively documented progression per RECIST1.1 or the date of subsequent therapy, whichever occurs first. For subjects without documented progression or subsequent therapy, all available response designations will contribute to the BOR assessment. The subject'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.

Complete or partial responses may be claimed only if the criteria for each are met at a subsequent time point (minimum 4 weeks after criteria of objective response are first met). In this circumstance, the best overall response can be interpreted as in Table 3.

**Table 3: Best overall response when confirmation of CR and PR IS required.**

| Overall response | Overall response | BEST overall response |
|---|---|---|
| **First time point** | **Subsequent time point** | |
| CR | CR | CR |
| CR | PR | SD, PD or PR[a] |

**Table 3: Best overall response when confirmation of CR and PR IS required.**

| Overall response | Overall response | BEST overall response |
|---|---|---|
| **First time point** | **Subsequent time point** | |
| CR | SD | SD provided minimum criteria for SD duration met, otherwise, PD |
| CR | PD | SD provided minimum criteria for SD duration met, otherwise, PD |
| CR | NE | SD provided minimum criteria for SD duration met, otherwise NE |
| PR | CR | PR |
| PR | PR | PR |
| PR | SD | SD |
| PR | PD | SD provided minimum criteria for SD duration met, otherwise, PD |
| PR | NE | SD provided minimum criteria for SD duration met, otherwise NE |
| NE | NE | NE |

CR = complete response, PR = partial response, SD = stable disease, PD = progressive disease, NE = not evaluable.

[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 subject 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.

For purposes of this study, the minimum scan time from baseline for determination of SD will be 6 weeks.

## 4.3 Duration of response

### *4.3.1 Duration of overall response*

The duration of overall response is measured from the time measurement criteria are first met for CR/PR (whichever is first recorded) until the first date that recurrent or progressive disease is objectively documented (taking as reference for progressive disease the smallest measurements recorded on study).

The duration of overall complete response is measured from the time measurement criteria are first met for CR until the first date that recurrent disease is objectively documented.

### *4.3.2 Duration of stable disease*

Stable disease is measured from the start of the treatment (in randomized trials, from date of randomization) until the criteria for progression are met, taking as reference the smallest sum on study (if the baseline sum is the smallest, this is the reference for calculation of PD).

### *4.3.3 Immune related Response Criteria*

Immune related response criteria using unidimensional measurements may be used to describe tumor shrinkage following RECIST defined disease progression Appendix 3. The methodology is the same as described above for RECIST except:

- New lesions do not automatically denote disease progression
- The measurement of longest diameter of new measurable lesions are in included in the sum of the measurements of the original target lesions.

Best immune related responses, for subjects who have progression followed by tumor shrinkage are classified as irCR (disappearance of all lesions) or irPR (≥ 30% reduction from baseline).

# APPENDIX 4 DEFINITION OF PRIOR RESPONSE TO PLATINUM-BASED CHEMOTHERAPY IN SCLC

**Platinum sensitive**: Progression free interval ≥ 90 days after completion of any platinum-based chemotherapy.

**Platinum resistant**: Progression free interval < 90 days after completion of any platinum-based chemotherapy.

**Platinum refractory**: Progression during platinum-based chemotherapy.

# APPENDIX 5 DEFINITION OF PRIOR RESPONSE TO PLATINUM-BASED CHEMOTHERAPY IN OVARIAN CANCER

**Platinum-sensitive**: Relapse > 6 months after stop of any platinum-based chemotherapy.

**Platinum-resistant**: Relapse > 1 to ≤ 6 months after stop of any platinum-based chemotherapy.

**Platinum-refractory**: Relapse on or within 1 month after stop of any platinum-based chemotherapy.

# APPENDIX 6 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.

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

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

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

## 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 in the female participant.

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

| **Highly Effective Contraceptive Methods That Are User Dependent**<br>*Failure rate of <1% per year when used consistently and correctly.*[a] |
|---|
| • Combined (estrogen- and progestogen-containing) hormonal contraception associated with inhibition of ovulation[b]<br>– oral<br>– intravaginal<br>– transdermal |
| • Progestogen-only hormonal contraception associated with inhibition of ovulation[b]<br>– oral<br>– injectable |
| **Highly Effective Methods That Are User Independent** |
| • Implantable progestogen-only hormonal contraception associated with inhibition of ovulation [b]<br>• Intrauterine device (IUD)[c]<br>• Intrauterine hormone-releasing system (IUS)[c]<br>• Bilateral tubal occlusion |
| • Vasectomized partner<br>*A vasectomized partner is a highly effective contraception method provided that the partner is the sole male sexual partner of the WOCBP and the absence of sperm has been confirmed. If not, an additional highly effective method of contraception should be used.* |
| • Sexual abstinence<br>*Sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the study drug. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the study and the preferred and usual lifestyle of the participant.*<br>• It is not necessary to use any other method of contraception when complete abstinence is elected.<br>• WOCBP participants who choose complete abstinence must continue to have pregnancy tests, as specified in the protocol.<br>• Acceptable alternate methods of highly effective contraception must be discussed in the event that the WOCBP participants chooses to forego complete abstinence |

NOTES:

[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.

[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.

[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

## 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 the end of relevant systemic exposure, defined as 7 months after the end of treatment in the male participant.
- Female partners of males participating in the study to consider use of effective methods of contraception until the end of relevant systemic exposure, defined as 7 months after the end of treatment in the male participant.
- Male participants with a pregnant or breastfeeding partner must agree to remain abstinent from penile vaginal intercourse or use a male condom during each episode of penile penetration during the treatment and until 7 months after the end of treatment.
- Refrain from donating sperm for the duration of the study treatment and until 7 months after the end of treatment.

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

## COLLECTION OF PREGNANCY INFORMATION

Guidance for collection of Pregnancy Information and outcome of pregnancy on the Pregnancy Surveillance Form is provided in Section 6.4 and Section 6.1.1 on Serious Adverse Event Collection and Reporting.