Official Title of Study:

A Randomized, Open-label Phase 2 Clinical Trial of BMS-986012 in Combination with Carboplatin, Etoposide, and Nivolumab as First-line Therapy in Extensive-stage Small Cell Lung Cancer

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CLINICAL PROTOCOL CA001050

A Randomized, Open-label Phase 2 Clinical Trial of BMS-986012 in Combination with Carboplatin, Etoposide, and Nivolumab as First-line Therapy in Extensive-stage Small Cell Lung Cancer

Short Title:

A Randomized Study of BMS-986012 in Combination with Carboplatin, Etoposide, and Nivolumab in Participants with Extensive-stage Small Cell Lung Cancer

Protocol Amendment Number: 03

[redacted]
Clinical Trial Physician - Medical Monitor
Bristol-Myers Squibb Company
3401 Princeton Pike
Lawrenceville, NJ 08648
Telephone (office): [redacted]
email: [redacted]

[redacted]
Clinical Scientist
Bristol-Myers Squibb Company
Isaac Newton 4
Sevilla, Spain 41092
Telephone (mobile): [redacted]
email: [redacted]

24-hr Emergency Telephone Number
USA: 1-866-470-2267
International: +1-248-844-7390

Bristol-Myers Squibb Company
3401 Princeton Pike
Lawrenceville, NJ 08648

Avenue de Finlande 4
B-1420 Braine-l'Alleud, Belgium

1-2-1 Otemachi, Chiyoda-ku,
Tokyo 100-0004, Japan

DOCUMENT HISTORY

Document	Date of Issue	Summary of Change
Protocol Amendment 03	22-Mar-2023	The primary reasons for this protocol amendment are: • to update the blinding section to allow the Sponsor to have full access to treatment information from the time of the planned interim analysis • to clarify timing for local safety laboratory tests • for those participants treated beyond 2 years, the collection of biomarkers, pharmacokinetic, immunogenicity, and patient-reported outcomes has been limited to approximately the first 2 years • collection of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) serologies has been removed
Protocol Amendment 02	22-Jul-2022	[redacted]
Protocol Amendment 01	02-Jul-2021	• Aligned dose modification criteria and immuno-oncology agent management algorithms with the current Common Terminology Criteria for Adverse Event version 5. • Provided additional guidance on the management of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection prior to entering the study and during the study and added additional serologic testing for SARS-CoV-2 status. • Incorporated additional updates to improve alignment across protocol sections and/or clarify expectations for eligibility, assessments, sample collections, treatment administration, and country-specific requirements.
Original Protocol	02-Sep-2020	Not applicable

OVERALL RATIONALE FOR PROTOCOL AMENDMENT 03:

The primary reasons for this protocol amendment are:

- to update the blinding section to allow the Sponsor to have full access to treatment information from the time of the planned interim analysis
- to clarify timing for local safety laboratory tests
- for those participants treated beyond 2 years, the collection of biomarkers, pharmacokinetic, immunogenicity, and patient-reported outcomes has been limited to approximately the first 2 years
- collection of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) serologies has been removed

Additional administrative revisions and minor edits were also made.

SUMMARY OF KEY CHANGES FOR PROTOCOL AMENDMENT 03

Section Number & Title	Description of Change	Brief Rationale
Section 1: Synopsis	Exclusion criteria has been updated to clarify that previously treated limited stage small cell lung cancer (LS-SCLC) participants are excluded.	To align with the changes made in the body of the protocol in Protocol Amendment 02.
Table 2-1: Screening Procedural Outline (CA001050) Table 2-2: On-treatment Procedural Outline (CA001050) Table 2-3: Follow-up Procedural Outline (CA001050) Section 3.3: Benefit/Risk Assessment Table 4-1: Objectives and Endpoints Section 9.8: Biomarkers Table 9.8-1 Biomarker Sampling Schedule for Arms A and B Section 9.8.3.6: Serum for Anti-SARS-CoV-2 Serology	Removed severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) serology language.	Based on the significant advancements in understanding SARS-CoV-2 and available treatment options, including monoclonal antibodies and effective vaccination, the collection of SARS-CoV-2 serologies is no longer warranted.

SUMMARY OF KEY CHANGES FOR PROTOCOL AMENDMENT 03		
Section Number & Title	**Description of Change**	**Brief Rationale**
Table 2-2: On-treatment Procedural Outline (CA001050)	• Laboratory tests "Notes" column has been updated to clarify that local laboratory testing should be within 72 hours prior to each dose, and that for the first treatment visit, labs need not be repeated if they were performed within 72 hours and the results are available and have been reviewed for eligibility.	• To clarify timing for local safety laboratory tests.
	• Patient-reported outcomes (PROs) collection has been limited to Cycle 28 during treatment period (approximately 2 years of treatment). Follow-up collection remains unchanged.	• Collection of PROs is sufficient over the course of 2 years of treatment.
Table 4-1: Objectives and Endpoints Table 9.8-1: Biomarker Sampling Schedule for Arms A and B [redacted]	• Removed sampling of [redacted] circulating tumor cell (CTC). [redacted]	Exploratory analysis of CTC samples will not be performed.
Table 4-1: Objectives and Endpoints [redacted]	• Added [redacted] analysis in [redacted]. • Added [redacted] in tumor using [redacted] samples. • Removed histamine analysis in [redacted].	• [redacted] analysis helps understand the mechanism of action associated with the treatment. • [redacted] characterization of the cells in the tumor micro-environment helps understand mechanism of action and the relationship between [redacted] and efficacy. • The analysis of histamine level may not give a clear answer to the occurrence of pruritus.
Section 7.3: Blinding	Wording had been updated to clarify that the Sponsor will have full access to treatment information at the time of and following the planned interim analysis.	This study is a randomized, open-label phase 2 study. The decision to sponsor-blind this study was to minimize the introduction of bias and maintain integrity of the study. The decision to unblind at the time of the interim analysis (approximately 75% of information available, ie, 77 progression-free survival [PFS] events) has been taken with the utmost consideration to allow the Sponsor to also be able to make global program decisions without jeopardizing the integrity of the data.

SUMMARY OF KEY CHANGES FOR PROTOCOL AMENDMENT 03		
Section Number & Title	**Description of Change**	**Brief Rationale**
Table 9.5-1: Pharmacokinetic and Immunogenicity Sampling Schedule for Arm A Table 9.5-2: Pharmacokinetic and Immunogenicity Sampling Schedule for Arm B	Pharmacokinetic (PK) and immunogenicity sample collection has been limited to Cycle 26 Day 1 during treatment period (approximately 2 years of treatment). Follow-up collection remains unchanged.	Collection of PK and immunogenicity is sufficient over the course of 2 years of treatment.
Table 9.8-1 Biomarker Sampling Schedule for Arms A and B	• Changed last sample collection of [redacted] to C26D1 during treatment period. Follow-up collection remains unchanged. • Updated footnote "d" • Add footnote "f".	• Collection and analysis of samples [redacted] is sufficient over the course of 2 years of treatment. Sample collection for more than 2 years (beyond C26D1) would unnecessarily burden the participant and affect the participant's quality of life. • Updated to clarify that upon-progression samples should be collected within 30 days of documented disease progression unless they are already collected during a visit that falls under the defined window. • If a participant discontinues study drug treatment during the treatment/sampling period, the participant will move to sampling at the follow-up visits.

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1 SYNOPSIS

Protocol Title: A Randomized, Open-Label Phase 2 Clinical Trial of BMS-986012 in Combination with Carboplatin, Etoposide, and Nivolumab as First-Line Therapy in Extensive-Stage Small Cell Lung Cancer

Short Title:

A Randomized Study of BMS-986012 in Combination with Carboplatin, Etoposide, and Nivolumab in Participants with Extensive-stage Small Cell Lung Cancer

Study Phase:

Phase 2

Rationale:

The standard treatment for extensive-stage small cell lung cancer (ES-SCLC) for decades has been platinum-etoposide combination chemotherapy. Both the National Comprehensive Cancer Network guidelines and European Society of Medical Oncology guidelines recommend 4 to 6 cycles of etoposide plus cisplatin or carboplatin for first-line treatment of ES-SCLC. Treatment beyond 6 cycles is not recommended based on several trials that did not show benefit in overall survival (OS) and demonstrated increased toxicity. No differences in efficacy between cisplatin and carboplatin in the first-line treatment of SCLC have been identified, with carboplatin shown to have a favorable toxicity profile. Based on the limited sample size of the current study and favorable toxicity profile, carboplatin has been the chemotherapy agent selected for the conduct of the study.

Although initial response rates to platinum-etoposide chemotherapy are up to 78%, most patients relapse within 6 months, and median OS is approximately 10 months. Over the past several years, immunotherapy targeting immune checkpoint pathways, including the programmed cell death 1 (PD-1) and programmed cell death-ligand 1 (PD-L1) pathways, have shown anti-tumor responses and improved OS of patients of multiple cancers, including ES-SCLC. This has led to the approvals of 2 regimens of immune checkpoint inhibitors in combination with chemotherapy in first-line ES-SCLC, namely atezolizumab and durvalumab.

Atezolizumab, an anti-PD-L1 monoclonal antibody (mAb), was investigated as part of the IMpower133 study in combination with carboplatin plus etoposide, followed by atezolizumab in maintenance, as initial treatment for ES-SCLC resulted in a 0.9-month benefit in median progression-free survival (PFS) from 4.3 to 5.2 months and a 2-month benefit in median OS from 10.3 to 12.3 months.

Additionally, a Phase 3 randomized, multicenter, active-controlled, open-label trial investigated durvalumab, another anti-PD-L1 human immunoglobulin G1 (IgG1) mAb, in combination with etoposide and either carboplatin or cisplatin as part of the CASPIAN study. A planned interim analysis demonstrated a significant improvement is OS in the durvalumab plus platinum-etoposide treatment arm with a hazard ratio (HR) of 0.73 (95% confidence interval [CI]: 0.59 0.9; p = 0.0047). Median OS was 13.0 months (95% CI: 11.5-14.8) in the durvalumab plus

platinum-etoposide arm compared with 10.3 months (95% CI: 9.3-11.2) in the platinum-etoposide arm.

Also, in a recent randomized Phase 2 trial conducted by the Eastern Cooperative Oncology Group (ECOG) and the American College of Radiology Imaging Network Cancer Research Group, EA5161, patients received carboplatin or cisplatin (at investigator discretion) and etoposide alone or in combination with nivolumab, an anti-PD-1 mAb, as first-line therapy for ES-SCLC. Nivolumab in combination with platinum-etoposide significantly improved PFS compared to platinum-etoposide alone, with a HR of 0.68 (95% CI: 0.48-1.00; p = 0.047) and a median PFS of 5.5 versus 4.7 months, respectively. OS was also improved in the nivolumab with platinum-etoposide arm, with a HR of 0.73 (95% CI: 0.49-1.1; p = 0.14) and a median OS of 11.3 versus 9.3 months, respectively, showing comparable efficacy data to current approved therapies.

Although the addition of anti-PD-L1 regimens to chemotherapy in first-line ES-SCLC has shown benefit, it is only modest at best. Innovative combinations are needed to combat this disease, with targeted therapy a desirable path forward.

Fucosyl-monosialoganglioside-1 (fuc-GM1) offers a cell surface target known [redacted] in approximately [redacted] of SCLC tumors [redacted].

BMS-986012, a first-in-class, fully human IgG1 that specifically binds to the fuc-GM1 ganglioside, is being developed for the treatment of SCLC. BMS-986012 binds to fuc-GM1 on the tumor cell, and the fragment crystallizable (Fc) portion of the antibody binds to natural killer (NK) cells, macrophages, or complement, resulting in tumor cell death by antibody-dependent cellular cytotoxicity (ADCC), antibody-dependent cellular phagocytosis (ADCP), or complement-dependent cytotoxicity (CDC), respectively. BMS-986012 in combination with nivolumab may provide clinical benefit to subjects with SCLC by combining the immune-based mechanisms of action (MOAs) of both compounds.

Clinical support for the combination of BMS-986012 with nivolumab was demonstrated in the first-in-human study CA001-030, a Phase 1/2 multicenter study of BMS-986012 in participants with relapsed/refractory SCLC. In this study, a total of 29 participants were treated with the combination of BMS-986012 and nivolumab, the majority of which were in the second-line setting. Dose escalation evaluated 400 mg and 1,000 mg in the combination setting, where 400 mg was ultimately selected based on a slightly better safety profile and similar efficacy to the 1,000 mg dose level. As of data cut-off (08-May-2020), clinical benefit has been observed in 13 of 29 participants across both dose levels in dose escalation and expansion, including 9 partial responses (PRs), 1 complete response (CR), and 3 stable disease (SD) responses, with 1 subject achieving a PR after treatment beyond progression. Efficacy data are preliminary and subject to change. In general, pruritus was the main adverse event (AE) observed, generally Grade 1 or 2 in severity and considered an on-target treatment effect of BMS-986012. Other AEs were similar to those seen in nivolumab, again the majority of which were Grade 1 or 2 in severity. Based on the preliminary data, BMS-986012, either administered as monotherapy or in combination with nivolumab, appears to be well tolerated with an acceptable safety profile.

BMS-986012 has shown to have a tolerable safety profile both as monotherapy and in combination with chemotherapy or nivolumab and has shown a potential efficacy signal when combined with nivolumab, as per data from the CA001-030 study. Given the fact that anti-PD-(L)1 therapy in combination with standard-of-care chemotherapy has led to improved survival rates in patients with ES-SCLC in the first-line setting and the potential areas of synergy between BMS-986012 and nivolumab the addition of targeted therapy seems a logical approach to treat patients in this indication.

This randomized study is designed to demonstrate that treatment with BMS-986012 in combination with carboplatin, etoposide, and nivolumab will have acceptable safety and tolerability and will improve PFS compared with carboplatin, etoposide, and nivolumab alone in newly diagnosed participants with ES-SCLC.

Study Population:

Key Inclusion Criteria:

- Adult participants ages ≥ 18 years or local age of majority.
- Participants must have histologically or cytologically documented ES-SCLC. Participants must present with extensive-stage disease (American Joint Committee on Cancer, 8th edition, Stage IV [T any, N any, M1a, M1b, or M1c] or T3-4 due to multiple lung nodules that are too extensive or tumor or nodal volume that is too large to be encompassed in a tolerable radiation plan)
- Participants taking part in the separate PET tracer sub-study must provide a [redacted] from any disease site (primary or metastatic). [redacted]
- [redacted]
- ECOG performance status (PS) 0 or 1.
- Participants must have at least 1 measurable lesion by computed tomography (CT) or magnetic resonance imaging per Response Evaluation Criteria in Solid Tumors version 1.1 (RECIST v1.1) criteria.
- Participants must be suitable to receive a platinum-based chemotherapy regimen as per locally approved drug labels and institutional guidelines.
- Adequate hematologic and end organ function as defined below:
  - Absolute neutrophil count ≥ 1,500/mm^3 (stable off any growth factor within 2 weeks of the first study drug administration)
  - Platelets ≥ 100,000/mm^3 (transfusion to achieve this level is not permitted within 2 weeks of the first study drug administration)
  - Hemoglobin ≥ 9 g/dL (transfusion to achieve this level is not permitted within 2 weeks of the first study drug administration)

- White blood cells ≥ 2000/mm^3
- Total bilirubin ≤ 1.5 x upper limit of normal (ULN)
- Aspartate aminotransferase (serum glutamic-oxaloacetic transaminase) and alanine aminotransferase (serum glutamic-pyruvic transaminase) ≤ 3 x ULN
- Serum creatinine ≤ 1.5 x ULN or calculated creatinine clearance > 50 mL/min (using the Cockcroft-Gault formula)

Key Exclusion Criteria:

- Participants cannot have had prior chemotherapy, radiation therapy, or biologic therapy for SCLC. Previously treated limited stage SCLC (LS-SCLC) participants are also excluded.
- Participants with symptomatic brain or other central nervous system (CNS) metastases. Participants are eligible if brain or other CNS metastases are asymptomatic and do not require immediate treatment or have been adequately treated and participants have neurologically returned to baseline (except for residual signs or symptoms related to the CNS treatment) for at least 2 weeks prior to randomization. In addition, participants must be either off corticosteroids or on a stable or decreasing dose of ≤ 10 mg daily prednisone (or equivalent) for at least 2 weeks prior to randomization.
- Paraneoplastic autoimmune syndrome requiring systemic treatment.
- History of idiopathic pulmonary fibrosis, drug-induced pneumonitis, idiopathic pneumonitis, organizing pneumonia, or evidence of active pneumonitis on screening chest CT scan. History of radiation pneumonitis is permitted.
- Grade ≥ 2 peripheral sensory neuropathy at study entry.

Objectives and Endpoints:

Objectives	Endpoints
Primary	
• Assess the safety and tolerability for participants randomized to BMS-986012 in combination with carboplatin, etoposide, and nivolumab for 4 cycles (induction) followed by BMS-986012 and nivolumab maintenance (Arm A) vs those randomized to carboplatin, etoposide, and nivolumab for 4 cycles (induction) followed by nivolumab maintenance (Arm B).	• Incidence of AEs, SAEs, AEs leading to discontinuation, deaths.
• To compare the PFS as assessed by BICR of participants treated in the combination induction and maintenance therapies of Arms A and B described above.	• PFS by BICR based on RECIST v1.1 criteria.

Objectives	Endpoints
Secondary	
• To estimate the PFSR at 6 and 12 months in each treatment arm, based on PFS by RECIST v1.1 as assessed by BICR.	• PFSR at 6 and 12 months. PFS by BICR based on RECIST v1.1 criteria.
• To compare PFS as assessed by investigator of participants treated in the combination induction and maintenance therapies of Arms A and B described above.	• PFS by investigator based on RECIST v1.1 criteria.
• To estimate the PFSR at 6 and 12 months in each treatment arm based on PFS by RECIST v1.1 assessed by investigator.	• PFSR at 6 and 12 months. PFS by investigator based on RECIST v1.1 criteria.
• To estimate the ORR, TTR, and DOR by RECIST v1.1 criteria by BICR and by investigator.	• ORR, TTR, and DOR based on RECIST v1.1 criteria.
• To assess OS of Arm A and Arm B and estimate OSR at 12 and 24 months by treatment arm.	• OS and OSR at 12 and 24 months, by arm.
• To characterize the immunogenicity of BMS-986012 in combination with carboplatin, etoposide, and nivolumab in Arm A.	• The immunogenicity of BMS-986012 measured by assessment of the presence of specific ADAs to BMS-986012. The incidence of positive ADAs will be calculated.

Abbreviations: ADA = anti-drug antibody; AE = adverse event; BICR = blinded independent central review; CPS = combined positive score; DOR = duration of response; fuc-GM1 = fucosyl-GM1; [redacted] ORR = objective response rate; OS = overall survival; OSR = overall survival rate; PD-L1 = programmed cell death-ligand 1; PFS = progression-free survival; PFSR = progression-free survival rate; RECIST = Response Evaluation Criteria in Solid Tumors; SAE = serious adverse event; TTR = time to response.

Overall Design:

This is a Phase 2, randomized, open-label study of BMS-986012 in combination with carboplatin, etoposide, and nivolumab as first-line therapy in ES-SCLC.

Participants will be randomized to receive either 4 cycles of induction therapy (21 days per cycle) of carboplatin/etoposide in combination with BMS-986012 and nivolumab followed by BMS-986012 and nivolumab as maintenance (28 days per cycle) or 4 cycles of induction therapy (21 days per cycle) of carboplatin/etoposide in combination with nivolumab followed by nivolumab as maintenance (28 days per cycle).

Number of Participants:

Approximately 120 participants will be randomized in a 1:1 ratio to receive treatment into 1 of the 2 arms. The sample size of the study is based on assessing the primary efficacy objective.

Treatment Arms and Duration:

Study treatment:

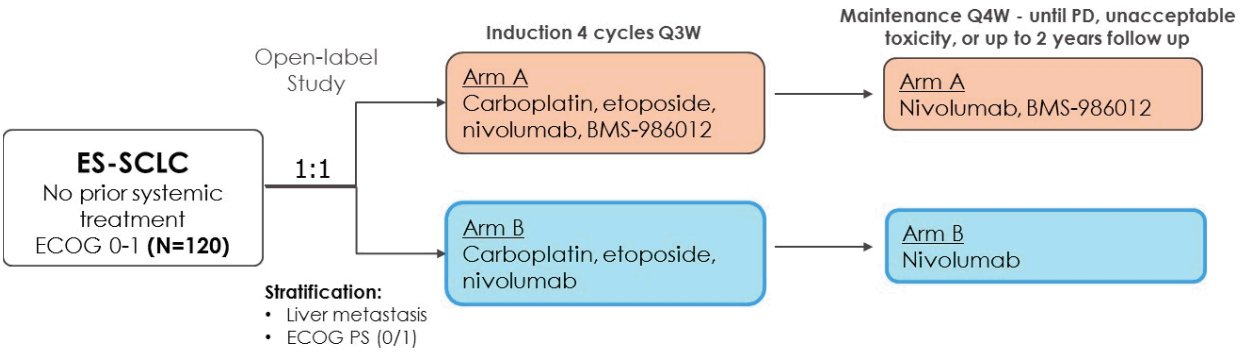
Study Drug for CA001050		
Medication	**Potency**	**IP/Non-IP**
BMS-986012 Concentrate for Solution for Infusion	120 mg (30 mg/mL)	IP
Nivolumab (BMS-936558) Solution for Injection	100 mg or 40 mg (10 mg/mL)	IP
Carboplatin[a,b]	450 mg (10 mg/mL)	Non-IMP
Etoposide[a,b]	100 mg (20 mg/mL)	Non-IMP

Abbreviation: IP/IMP = investigational [medicinal] product.

[a] These products may be obtained by the investigational site as local commercial product in certain countries if allowed by local regulations. In these cases, products may be a different pack size/potency than listed in the tables. These products should be prepared/stored/administered in accordance with the package insert or summary of product characteristics.

[b] Comparator may be supplied by BMS centrally or through site standard prescribing procedure.

Figure 1-1: Study Design Schematic



Abbreviations: ECOG = Eastern Cooperative Oncology Group; ES-SCLC = extensive-stage small cell lung cancer; PD = progressive disease; PS = performance status; Q3W = every 3 weeks; Q4W = every 4 weeks.

Screening:

- Up to 28 days and begins when the participant signs the main informed consent form.

[redacted]

[redacted] The [redacted] will be used to assess [redacted] however, results are not required in order to randomize a participant into the study.

Treatment:

- Begins after contacting the Interactive Response Technology system for randomization. All participants will be treated for up to 2 years or until disease progression, unacceptable toxicity, or participant withdrawal of consent, whichever comes first.
- Randomization will be stratified based on the presence of liver metastases and ECOG PS 0 or 1.
- Participants will be randomized in a 1:1 ratio into 1 of the 2 following arms:
  - Arm A:
    - Induction (3-week cycle - 21 days): Cycles 1 to 4
      - Carboplatin Day 1: area under the curve (AUC) 5 mg/mL/min intravenous (IV)
      - Etoposide Days 1, 2, 3: 100 mg/m^2 IV
      - BMS-986012 Day 1: 420 mg IV
      - Nivolumab Day 1: 360 mg IV
    - Maintenance (4-week cycle - 28 days): Cycle 5 and beyond
      - BMS-986012 Day 1: 560 mg IV
      - Nivolumab Day 1: 480 mg IV
  - Arm B
    - Induction (3-week cycle - 21 days): Cycles 1 to 4
      - Carboplatin Day 1: AUC 5 mg/mL/min IV
      - Etoposide Days 1, 2, 3: 100 mg/m^2 IV
      - Nivolumab Day 1: 360 mg IV
    - Maintenance (4-week cycle - 28 days): Cycle 5 and beyond:
      - Nivolumab Day 1: 480 mg IV
- No participant crossover between treatment arms will be allowed.

Follow-up

Begins when the decision is made to discontinue a participant from study therapy.

- Safety follow-up visits will be performed 30, 60, and 100 days (± 7 days) from the last dose of study treatment. All safety follow-up visits should be conducted in person. However, telemedicine may be allowed if circumstances require it after discussion with the study Medical Monitor.

- In parallel with the safety follow-up period, all participants will start the survival follow-up period. Participants will be followed up every 12 weeks (± 14 days) from the last dose or last safety follow-up visit, whichever occurs later, until death, lost to follow-up, withdrawal of consent, or conclusion of the study, whichever comes first. The duration of this follow up is up to 3 years following the first dose of study treatment, although a longer follow-up period could be considered in selected cases if an efficacy signal is apparent. Subsequent therapies will also be recorded in this survival follow-up period. Survival follow-up visits may be conducted in clinic or by phone.

Dosage Modification

- For AEs that are deemed to be related to BMS-986012 or nivolumab ONLY by the treating physician, dose delays are permitted. Dose reductions are not permitted. The chemotherapy should continue as scheduled.
- For AEs that are deemed to be related to the chemotherapy ONLY by the treating physician, dose modifications are permitted according to local standard or local package insert. BMS-986012 or nivolumab administration should continue as scheduled.
- For AEs that are possibly related to the combination regimen (BMS-986012 and/or nivolumab PLUS chemotherapy), the most conservative toxicity management guidelines must be followed.
- If there is a delay in administration of study drug(s) due to toxicity, treatment with the other study agent(s) should continue as scheduled. Resumption of treatment should be at the next scheduled time point if criteria to resume treatment are met.

Data Monitoring Committee: Yes

A Data Monitoring Committee (DMC) will be established to provide oversight of safety and efficacy considerations for the study. DMC membership and meeting frequency will be provided in the DMC charter. The DMC will evaluate the first 12 participants in each arm for a period of 8 weeks (2 cycles and 2 weeks follow-up) from start of treatment to assess if additional safety concerns occur with the 4-drug regimen during induction phase. The DMC will also conduct the interim efficacy analysis.

In addition to the periodic DMC meetings, BMS has in place a multilayered process for ensuring participant safety through close collaboration of study site Investigators, the BMS study team, and the BMS Worldwide Patient Safety-led Safety Medical Team.

2 SCHEDULE OF ACTIVITIES

An overview of the schedule of major assessments in this study are provided in Table 2-1 (Screening), Table 2-2 (On-treatment), and Table 2-3 (Follow-up).

Table 2-1: Screening Procedural Outline (CA001050)

Procedure[a]	Screening Visit[b] (Days -28 to -1)	Notes
Eligibility Assessments		
Informed Consent	X	A participant is considered enrolled only when a protocol-specific informed consent is signed. Register in Interactive Response Technology (IRT) system to obtain participant number. Study allows for re-enrollment of a participant that has discontinued the study as a pre-treatment failure. If re-enrolled, the participant must be re-consented and assigned a new participant number from IRT.
Inclusion/Exclusion Criteria	X	Must be confirmed prior to randomization.
Medical History	X	All medical history relevant to the disease under study, such as hematological and neurological history and symptoms, infusion or hypersensitivity reactions, smoking history, alcohol use, and SARS-CoV-2 vaccination received more than 30 days prior to randomization. Include any toxicities or allergy related to previous treatments for prior malignancies, if applicable.
Safety Assessments		
Physical Examination (PE)	X	If the screening PE is performed within 72 hours prior to dosing on Day 1, then a single exam may count as both the screening and predose evaluation. PEs must include a baseline neurological assessment at screening.
Physical Measurements	X	Includes height, weight, and body surface area.
Vital Signs	X	Includes body temperature, respiratory rate, and seated blood pressure and heart rate. Blood pressure and heart rate should be measured after the participant has been resting quietly for at least 5 minutes. Consider alternate position(s) for vital sign collection.
Eastern Cooperative Oncology Group Performance Status	X	See Appendix 7.
Assessment of Signs and Symptoms	X	Must be performed within 14 days prior to randomization.
Concomitant Medication Use	X	Must be collected within 28 days prior to randomization. Include vaccine use within 30 days prior to randomization.
Electrocardiogram (ECG)	X	ECGs should be recorded after the participant has been supine for at least 5 minutes.

Table 2-1: Screening Procedural Outline (CA001050)

Procedure[a]	Screening Visit[b] (Days -28 to -1)	Notes
Laboratory Tests	X	Hematology, serum chemistry. See Section 9.4.4 for list of laboratory tests to conduct. Must be performed within 28 days prior to randomization.
Serology	X	Includes hepatitis C virus (HCV) antibody or HCV ribonucleic acid and hepatitis B surface antigen. For human immunodeficiency virus (HIV): testing at sites where locally mandated; see Appendix 8 and Section 9.4.4.
Urinalysis	X	Microscopic examination of the sediment if blood, protein, or leukocytes esterase are positive on the dipstick. See Section 9.4.4.
Pregnancy Test	X	For women of childbearing potential only. Serum or urine pregnancy test (minimum sensitivity 25 IU/L or equivalent units of human chorionic gonadotropin) to be done at screening visit and within 24 hours of first dose of study therapy.
Follicle-stimulating Hormone	X	Women only. Refer to Appendix 4.
Efficacy Assessments		
Body Imaging	X	Contrast enhanced computed tomography (CT) of the chest, CT/magnetic resonance imaging (MRI) of the abdomen, pelvis, and all other known and/or suspected sites of disease within 28 days prior to randomization. See Section 9.1.1 for further details.
Brain Imaging	X	MRI of the brain (without and with contrast) is required for ALL participants during screening to rule out brain metastases. MRI is the preferred method of brain imaging, but CT of the brain (without and with contrast) can be performed if MRI is contraindicated or unavailable. See Section 9.1.1 for further details.

Table 2-1: Screening Procedural Outline (CA001050)

Procedure[a]	Screening Visit[b] (Days -28 to -1)	Notes
Adverse Event (AE) Reporting		
Monitor for Serious Adverse Events (SAEs)	X	All SAEs must be collected from the date of participant's written consent until 100 days after discontinuation of dosing, except in cases where a study participant has started a new anti-neoplastic therapy. However, any SAE occurring after the start of a new treatment that is suspected to be related to study treatment by the investigator will be reported. For participants randomized and never treated with study drug, SAEs should be collected for 30 days from the date of randomization. Both adverse events (AEs) and SAEs will be graded using the National Cancer Institute Common Terminology Criteria for Adverse Events v5.0. All AEs (SAEs and non-serious SAEs) associated with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection should be collected from the time of consent. See Section 9.2.1.
Biomarker Assessments		
[redacted]		
[redacted] Pharmacodynamic Sampling	X	See Section 9.8.
Health Outcomes		
Lung Cancer Symptom Scale	X	Must be collected within 14 days prior to randomization.
Patient Global Impression of Severity	X	Must be collected within 14 days prior to randomization.

Abbreviations: AE = adverse event; CT = computed tomography; ECG = electrocardiogram; HCV = hepatitis C virus; HIV = human immunodeficiency virus; Ig = immunoglobulin; IRT = Interactive Response Technology; MRI = magnetic resonance imaging; PE = Physical Examination; [redacted]; SAE = serious adverse event; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2.

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

[b] If a participant exceeds the 28-day screening period due to a study-related procedure (eg, scheduling of a [redacted] or waiting for a study-related laboratory value), the participant must be re-consented but does not require a new participant identification number. In this situation, safety laboratory tests should be repeated, and the Bristol-Myers Squibb (BMS) Medical Monitor or designee should be notified. Any additional procedures and tests should only be repeated if needed to maintain participant safety and confirm eligibility after discussion with the BMS Medical Monitor or designee.

[redacted]

Table 2-2: On-treatment Procedural Outline (CA001050)

Procedure Study Cycle	**Cycles 1 and 2 (N = 21 days)**				**Cycles 3 and 4 (N = 21 days)**	**Cycle 5 and beyond (N = 28 days)**	**EOT[a]**	**Notes**
Study Cycle Day	**D1 (± 3 days)**	**D2 (± 3 days)**	**D8 (± 3 days)**	**D15 (± 3 days)**	**D1 (± 3 days)**	**D1 (± 3 days)**		
Safety Assessments								
Physical Examination	X	X	X	X	X	X	X	All physical examinations must include a neurological assessment.
Eastern Cooperative Oncology Group Performance Status	X				X	X	X	See Appendix 7.
Physical Measurements	X	X			X	X	X	Weight and body surface area only up to Cycle 4. Weight only Cycle 5 and beyond.
Vital Signs	X		X	X	X	X	X	See note in screening procedures.
Electrocardiogram	X				X (Cycle 3 only)		X	As noted, otherwise as clinically indicated. See note in screening procedures.
Concomitant Medication Use	Continuously							
Prophylactic G-CSF	X							Prophylactic use of G-CSF is mandated starting from Cycle 1 and during the chemotherapy treatment period, ie, induction phase for participants aged >65 years and/or other risk factors as per NCCN guidelines.

Table 2-2: On-treatment Procedural Outline (CA001050)

Procedure Study Cycle	Cycles 1 and 2 (N = 21 days)				Cycles 3 and 4 (N = 21 days)	Cycle 5 and beyond (N = 28 days)	EOT[a]	Notes
Study Cycle Day	D1 (± 3 days)	D2 (± 3 days)	D8 (± 3 days)	D15 (± 3 days)	D1 (± 3 days)	D1 (± 3 days)		
Laboratory Tests	X		X	X	X	X	X	Perform on site/local laboratory testing within 72 hours prior to each dose. For the first treatment visit (C1D1), labs need not be repeated if they were performed within 72 hours and the results are available and have been reviewed for eligibility. Hematology, serum chemistry. See Section 9.4.4 for list of laboratory tests to conduct. Only hematology is required on Days 8 and 15 of Cycles 1 and 2.
Urinalysis	X	As clinically indicated						Refer to Section 9.4.4 for list of laboratory tests.
Pregnancy Test	X				X	X	X	For women of childbearing potential (WOCBP) only. WOCBP must have a negative pregnancy test within 24 hours prior to the start of each cycle and results also must be evaluated prior to study therapy administration. Urine pregnancy test: minimum sensitivity 25 IU/L or equivalent units of human chorionic gonadotropin.

Table 2-2: On-treatment Procedural Outline (CA001050)

Procedure **Study Cycle**	**Cycles 1 and 2 (N = 21 days)**				**Cycles 3 and 4 (N = 21 days)**	**Cycle 5 and beyond (N = 28 days)**	**EOT**[a]	**Notes**
Study Cycle Day	**D1 (± 3 days)**	**D2 (± 3 days)**	**D8 (± 3 days)**	**D15 (± 3 days)**	**D1 (± 3 days)**	**D1 (± 3 days)**		
Efficacy Assessments								
Body Imaging					Week 7 (see notes)	Week 13, then every 8 weeks (see notes)		Contrast-enhanced computed tomography (CT) of the chest, CT/magnetic resonance imaging (MRI) of the abdomen, pelvis, and all other known and/or suspected sites of disease should occur in Week 7 (± 7 days), Week 13 (± 7 days), and then every 8 weeks (± 7 days) for 2 years, and then every 12 weeks until blinded independent central review-confirmed disease progression or treatment discontinuation, whichever occurs later. See Section 9.1.1 for further details.
Brain Imaging						Week 13, then every 12 weeks (see notes)		Participants with a history of brain metastasis or symptoms should have a surveillance MRI (without and with contrast) study per standard of care (approximately every 12 weeks), or sooner if clinically indicated. MRI is the preferred method of brain imaging, but CT of the brain without and with contrast can be performed if MRI is contraindicated or unavailable. See Section 9.1.1 for further details.

Table 2-2: On-treatment Procedural Outline (CA001050)

Procedure **Study Cycle**	**Cycles 1 and 2 (N = 21 days)**				**Cycles 3 and 4 (N = 21 days)**	**Cycle 5 and beyond (N = 28 days)**	**EOT**[a]	**Notes**
Study Cycle Day	**D1 (± 3 days)**	**D2 (± 3 days)**	**D8 (± 3 days)**	**D15 (± 3 days)**	**D1 (± 3 days)**	**D1 (± 3 days)**		
Adverse Event (AE) Reporting								
Monitor for Nonserious AEs	Continuously							Nonserious AEs will be collected starting with the first dose of study drug (except those associated with severe acute respiratory syndrome coronavirus 2 [SARS-CoV-2] infection that should be collected from the time of consent) and for a minimum of 100 days following discontinuation of study treatment, except in cases where a study participant has started a new anti-neoplastic therapy. However, any AE occurring after the start of a new treatment that is suspected to be related to study treatment by the investigator or associated with SARS-CoV-2 infection will be reported. See Section 9.2.1.
Monitor for Serious AEs	Continuously							See note in screening procedures.
Pharmacokinetic (PK) and Immunogenicity Assessments								
Serial Serum PK Sampling	See note							See Section 9.5.
Biomarker Assessments								
[redacted] Pharmacodynamic Sampling	See note							See Section 9.8, including upon progression samples.

Table 2-2: On-treatment Procedural Outline (CA001050)

Procedure **Study Cycle**	**Cycles 1 and 2 (N = 21 days)**				**Cycles 3 and 4 (N = 21 days)**	**Cycle 5 and beyond (N = 28 days)**	**EOT[a]**	**Notes**
Study Cycle Day	**D1 (± 3 days)**	**D2 (± 3 days)**	**D8 (± 3 days)**	**D15 (± 3 days)**	**D1 (± 3 days)**	**D1 (± 3 days)**		
[redacted]	See note							See Section 9.8. Upon-progression [redacted] is optional, but strongly encouraged, at time of disease progression.
Health Outcomes								
Lung Cancer Symptom Scale	X				X	X	X	To be completed prior to treatment on Day 1 of each cycle up to Cycle 28.
A Single Item From the Functional Assessment of Chronic Therapy – General	X (Cycle 2)				X	X	X	To be completed prior to treatment on Day 1 of each cycle starting at Cycle 2 up to Cycle 28.
Patient Global Impression of Severity	X				X	X	X	To be completed prior to treatment on Day 1 of each cycle up to Cycle 28.
Patient Global Impression of Change	Cycle 2 only				X	X	X	To be completed prior to treatment on Day 1 of each cycle starting from Cycle 2 Day 1 up to Cycle 28.
Clinical Drug Supplies								
Randomize	X (Cycle 1)							Participant must receive the first dose of study treatment within 3 calendar days of randomization.
Carboplatin Administration	X				X			
Etoposide Administration	Days 1, 2, and 3				Days 1, 2, and 3			

Table 2-2: On-treatment Procedural Outline (CA001050)

Procedure Study Cycle	**Cycles 1 and 2 (N = 21 days)**				**Cycles 3 and 4 (N = 21 days)**	**Cycle 5 and beyond (N = 28 days)**	**EOT[a]**	**Notes**
Study Cycle Day	**D1 (± 3 days)**	**D2 (± 3 days)**	**D8 (± 3 days)**	**D15 (± 3 days)**	**D1 (± 3 days)**	**D1 (± 3 days)**		
Nivolumab Administration	X				X	X		
BMS-986012 Administration	X				X	X		If assigned to treatment Arm A.

Abbreviations: AE = adverse event; C = cycle; CT = computed tomography; D = Day; EOT = end of treatment; G-CSF = granulocyte-colony stimulating factor; Ig = immunoglobulin; MRI = magnetic resonance imaging; PK = pharmacokinetic; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2; WOCBP = women of childbearing potential.

[a] EOT is defined as the visit where the decision is made to discontinue the participant from treatment and will be considered as the start of the safety follow-up period. EOT visit should be completed within 28 days after the decision to permanently discontinue treatment has been made. EOT visit may be skipped if coincides with the Safety Follow-up Visit 1.

Table 2-3: Follow-up Procedural Outline (CA001050)

Procedure	Safety Follow-up			Survival FU[a]	Notes
	FU1 30 Days (± 7 Days)	FU2 60 Days (± 7 Days)	FU3 100 Days (± 7 Days)		
Safety Assessments					
Physical Examination	X	X	X		
Eastern Cooperative Oncology Group Performance Status	X	X	X		See Appendix 7.
Physical Measurements	X	X	X		Weight only.
Vital Signs	X	X	X		See note in screening procedures.
Electrocardiogram	X				
Concomitant Medication Use	X	X	X		
Laboratory Tests	X	X	X		Hematology, serum chemistry. See Section 9.4.4 for list of laboratory tests to conduct.
Urinalysis	As clinically indicated				See Section 9.4.4.
Pregnancy Test	X	X	X		See Section 9.4.4 and Section 9.2.5.
Review of Subsequent Cancer Therapy	X	X	X	X	Includes systemic therapy, tumor-directed surgery, or radiation therapy.
Adverse Event (AE) Reporting					
Monitor for Nonserious AEs	X	X	X		See note in on-treatment procedures. Participants will be followed for all non-serious AEs associated with confirmed or suspected severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection until resolution, the condition stabilizes, the event is otherwise explained, the event is deemed irreversible, the participant is lost to follow-up (as defined in Section 8.3), or for suspected cases, until SARS-CoV-2 infection is ruled-out. See Section 9.2.3.

Table 2-3: Follow-up Procedural Outline (CA001050)

Procedure	Safety Follow-up			Survival FU[a]	Notes
	FU1 30 Days (± 7 Days)	FU2 60 Days (± 7 Days)	FU3 100 Days (± 7 Days)		
Monitor for Serious AEs	X	X	X		See note in screening procedures. Participants will be followed for all serious adverse events (SAEs) associated with confirmed or suspected SARS-CoV-2 infection until resolution, the condition stabilizes, the event is otherwise explained, the event is deemed irreversible, the participant is lost to follow-up (as defined in Section 8.3), or for suspected cases, until SARS-CoV-2 infection is ruled-out. See Section 9.2.3.
Efficacy Assessments					
Body Imaging	See notes				Contrast-enhanced computed tomography (CT) of the chest, CT/magnetic resonance imaging (MRI) of the abdomen, pelvis, and all other known and/or suspected sites of disease should occur in Week 7 (± 7 days), Week 13 (± 7 days), and then every 8 weeks (± 7 days) for 2 years, and then every 12 weeks until blinded independent central review-confirmed disease progression or treatment discontinuation, whichever occurs later. See Section 9.1.1 for further details.

Table 2-3: Follow-up Procedural Outline (CA001050)

Procedure	Safety Follow-up			Survival FU[a]	Notes
	FU1 30 Days (± 7 Days)	FU2 60 Days (± 7 Days)	FU3 100 Days (± 7 Days)		
Brain Imaging	See notes				Participants with a history of brain metastasis or symptoms should have a surveillance MRI (without and with contrast) study per standard of care (approximately every 12 weeks), or sooner if clinically indicated. MRI is the preferred method of brain imaging, but CT of the brain without and with contrast can be performed if MRI is contraindicated or unavailable. See Section 9.1.1 for further details.
Pharmacokinetic and Immunogenicity Assessments					
	X	X	X		See Section 9.5.
Biomarker Assessments					
	X	X	X		See Section 9.8.
Health Outcomes					
Lung Cancer Symptom Scale	X	X	X		
A Single Item From the Functional Assessment of Chronic Therapy – General	X	X	X		
Patient Global Impression of Severity	X	X	X		
Patient Global Impression of Change	X	X	X		

Abbreviations: AE = adverse event; CT = computed tomography; FU = follow-up; Ig = immunoglobulin; MRI = magnetic resonance imaging; SAE = serious adverse event; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2.

[a] In parallel with the safety follow-up period, all participants will start the survival follow-up period. Participants will be followed up every 12 weeks (± 14 days) from the last dose or last safety follow-up visit, whichever occurs later, until death, lost to follow-up, withdrawal of consent, or conclusion of the study, whichever

comes first. The duration of this follow-up is up to 3 years following the first dose of study treatment, although a longer follow-up period could be considered in selected cases if an efficacy signal is apparent.

In the event multiple procedures are required at a single time point, the following is a list of procedures from highest priority to low:

- Safety (clinical labs)
- Safety (electrocardiogram [ECG])
- Biomarker and immunogenicity sampling
- Pharmacokinetic (PK) sampling

3 INTRODUCTION

BMS-986012 has previously been investigated in 3 separate studies, [redacted] These 3 studies were: CA001-030 (an open-label, Phase 1/2, first-in-human [FIH], multicenter study of BMS-986012 in participants with relapsed/refractory small cell lung cancer [SCLC] where participants were administered BMS-986012 both as monotherapy and in combination with nivolumab); CA001-044 (an open-label, Phase 1/2 randomized study of BMS-986012 administered in combination with platinum and etoposide in participants with extensive-stage SCLC [ES-SCLC]); and CA001-045 (an open-label study of BMS-986012 administered as monotherapy or in combination with chemotherapy to Japanese participants with SCLC).

[redacted] As data in the CA001-030 study matured, a potential efficacy signal emerged in the nivolumab combination cohort in not only the response rate but also the durability of the response, a signal that provides the basis for further investigation in SCLC, for which treatment remains an unmet need.

3.1 Study Rationale

The standard treatment for ES-SCLC for decades has been platinum-etoposide combination chemotherapy. Both the National Comprehensive Cancer Network (NCCN) guidelines and European Society of Medical Oncology guidelines recommend 4 to 6 cycles of etoposide plus cisplatin or carboplatin for first-line treatment of ES-SCLC.[1] Treatment beyond 6 cycles is not recommended based on several trials that did not show benefit in overall survival (OS) and demonstrated increased toxicity.[1] For ES-SCLC patients who respond to initial chemotherapy, prophylactic cranial irradiation (PCI) is recommended.[1] PCI decreases risk of symptomatic brain metastases and increases OS.[2] However, a recent study showed that PCI did not result in longer OS compared with observation in patients with ES-SCLC.[3]

No differences in efficacy between cisplatin and carboplatin in the first-line treatment of SCLC have been identified,[4] with carboplatin shown to have a favorable toxicity profile.[5] Based on the limited sample size of the current study and favorable toxicity profile, carboplatin has been the chemotherapy agent selected for the conduct of the study.

Although initial response rates to platinum-etoposide chemotherapy are up to 78%, most patients relapse within 6 months, and median OS is approximately 10 months.[4] Over the past several years, immunotherapy targeting immune checkpoint pathways, including the programmed cell death 1 (PD-1) and programmed cell death-ligand 1 (PD-L1) pathways, have shown anti-tumor responses and improved OS of patients of multiple cancers, including ES-SCLC. This has led to the approvals of 2 regimens of immune checkpoint inhibitors in combination with chemotherapy in first-line ES-SCLC, namely atezolizumab and durvalumab.

Atezolizumab, an anti-PD-L1 monoclonal antibody (mAb), was investigated as part of the IMpower133 study in combination with carboplatin plus etoposide, followed by atezolizumab in maintenance, as initial treatment for ES-SCLC resulted in a 0.9-month benefit in median progression-free survival (PFS) from 4.3 to 5.2 months and a 2-month benefit in median OS from 10.3 to 12.3 months.[6] Analysis showed that objective tumor responses to immune checkpoint inhibitors occur in tumors with a high mutational burden and antigen load. SCLC has one of the highest rates of mutation burden, suggesting that this disease could be particularly susceptible to immune-based therapeutic approaches.[7,8,9] Atezolizumab was added to the NCCN guidelines in October 2018 for the first-line treatment of ES-SCLC in combination with carboplatin and etoposide, followed by atezolizumab maintenance.[10]

Additionally, a Phase 3, randomized, multicenter, active-controlled, open-label trial investigated durvalumab, another anti-PD-L1 human immunoglobulin G1 (IgG1) mAb, in combination with etoposide and either carboplatin or cisplatin as part of the CASPIAN study. A planned interim analysis demonstrated a significant improvement is OS in the durvalumab plus platinum-etoposide treatment arm with a hazard ratio (HR) of 0.73 (95% confidence interval [CI]: 0.59-0.9; p = 0.0047). Median OS was 13.0 months (95% CI: 11.5-14.8) in the durvalumab plus platinum-etoposide arm compared with 10.3 months (95% CI: 9.3-11.2) in the platinum-etoposide arm.[11]

Also, in a recent randomized Phase 2 trial conducted by the Eastern Cooperative Oncology Group (ECOG) and the American College of Radiology Imaging Network Cancer Research Group, EA5161, patients received carboplatin or cisplatin (at investigator discretion) and etoposide alone or in combination with nivolumab, an anti-PD-1 mAb, as first-line therapy for ES-SCLC.[12] As per data presented at the American Society of Clinical Oncology 2020 annual meeting, nivolumab in combination with platinum-etoposide significantly improved PFS compared to platinum-etoposide alone, with a HR of 0.68 (95% CI: 0.48-1.00; p = 0.047) and a median PFS of 5.5 versus 4.7 months, respectively. OS was also improved in the nivolumab with platinum-etoposide arm, with a HR of 0.73 (95% CI: 0.49-1.1; p = 0.14) and a median OS of 11.3 versus 9.3 months, respectively,[12] showing comparable efficacy data to current approved therapies.

Although the addition of anti-PD-L1 regimens to chemotherapy in first-line ES-SCLC has shown benefit, it is only modest at best. Innovative combinations are needed to combat this disease, with targeted therapy a desirable path forward.

Fucosyl-monosialoganglioside-1 (fuc-GM1) offers a cell surface target known [redacted] in approximately [redacted] of SCLC tumors by [redacted][13,14,15]

BMS-986012, a first-in-class, fully human IgG1 that specifically binds to the fuc-GM1 ganglioside, is being developed for the treatment of SCLC. BMS-986012 binds to fuc-GM1 on the tumor cell, and the fragment crystallizable (Fc) portion of the antibody binds to natural killer (NK) cells, macrophages, or complement, resulting in tumor cell death by antibody-dependent cellular cytotoxicity (ADCC), antibody-dependent cellular phagocytosis (ADCP), or complement-dependent cytotoxicity (CDC), respectively. [16] BMS-986012 in combination with nivolumab may provide clinical benefit to subjects with SCLC by combining the immune-based mechanisms of action (MOAs) of both compounds. Potential areas of synergy include the following:

- Providing antigens to antigen-presenting cells (APCs) to induce T-cell activity: BMS-986012 has been shown in preclinical models to lead to cancer cell death, including by ADCP. Processing and presentation of antigens by APCs, such as macrophages, has been shown to increase T-cell responses in tumor models. Furthermore, suboptimal tumor antigen delivery and presentation have been postulated as another mechanism by which tumors can successfully evade immune system recognition. As nivolumab is known to increase T-cell activation, synergy is expected via this mechanism.
- Reducing tumor cell-derived immune inhibition: Tumors and tumor microenvironment are known to express a variety of factors that impede a robust immune response from eliminating the tumor. Soluble and membrane-bound factors have been shown to inhibit the cytolytic activity of tumor-infiltrating T cells (eg, [redacted], transforming growth factor-beta). In addition, some tumor-derived factors are able to enhance immune system counterregulatory systems (eg, increased T-regulatory cells). BMS-986012 monotherapy has demonstrated preclinical tumor growth inhibition and clinical activity, including tumor reduction.[16] This anti-tumor activity may lead to reduced immune inhibition and synergistic activity with the anti-PD-1 effects of nivolumab.
- Supporting immune-based MOA of BMS-986012: BMS-986012 demonstrated dose-dependent ADCC and ADCP in SCLC cell lines.[16] Because BMS-986012 acts via multiple immune cell-based mechanisms, enhancement of the overall immune activation via the T-cell stimulatory effects of nivolumab may increase BMS-986012 anti-tumor activity.

Clinical support for the combination of BMS-986012 with nivolumab was demonstrated in the FIH study CA001-030, a Phase 1/2 multicenter study of BMS-986012 in participants with relapsed/refractory SCLC. In this study, a total of 29 participants were treated with the combination of BMS-986012 and nivolumab, the majority of which were in the second-line setting. Dose escalation evaluated 400 mg and 1,000 mg in the combination setting, where 400 mg was ultimately selected based on a slightly better safety profile and similar efficacy to the 1,000 mg dose level. As of data cut-off (08-May-2020), clinical benefit has been observed in 13 of 29 participants across both dose levels in dose escalation and expansion, including 9 partial responses (PRs), 1 complete response (CR), and 3 stable disease (SD) responses, with 1 subject achieving a PR after treatment beyond progression. Efficacy data are preliminary and subject to change. In general, pruritus was the main adverse event (AE) observed, generally Grade 1 or 2 in severity, and considered an on-target treatment effect of BMS-986012. Other AEs were similar to those seen in nivolumab, again the majority of which were Grade 1 or 2 in severity. Based on the

preliminary data, BMS-986012, either administered as monotherapy or in combination with nivolumab, appears to be well tolerated with an acceptable safety profile.[16]

In addition to clinical support for combining BMS-986012 with nivolumab, there is both preclinical and clinical support for the use of BMS-986012 in combination with chemotherapy to treat SCLC. Preclinical support comes from xenograft models: [redacted] Clinically, Study CA001-044 (an open-label, Phase 1/2 randomized study of BMS-986012 administered in combination with platinum and etoposide in participants with ES-SCLC) evaluated escalating doses of BMS-986012 in combination with cisplatin/etoposide (Part 1) and carboplatin/etoposide (Part 2). As of data cut-off (28-Jan-2020), a total of 14 participants had been treated collectively in Parts 1 and 2, with 12 participants treated at the 400-mg dose level and 2 participants treated at the 1,000-mg dose level. AEs considered related to study treatment were pruritus (12 participants) and generalized pruritus, dizziness, xerosis, conjunctivitis, and urticaria (1 participant each). All related AEs were Grade 1 or 2, except for the AEs of urticaria and pruritus (1 participant each), which were Grade 3. There were no dose-limiting toxicities reported. Out of the 14 participants treated, 10 participants achieved a PR as their best overall response (BOR; the other 1 participant had progressive disease [PD] as their BOR and 2 participants had no BOR determined). One participant died prior to disease assessment. One participant remains on therapy at the time of the database lock.[16]

BMS-986012 has shown to have a tolerable safety profile both as monotherapy and in combination with chemotherapy or nivolumab and has shown a potential efficacy signal when combined with nivolumab, as per data from the CA001-030 study. Given the fact that anti-PD-(L)1 therapy in combination with standard-of-care chemotherapy has led to improved survival rates in patients with ES-SCLC in the first-line setting and the potential areas of synergy between BMS-986012 and nivolumab, as previously described, the addition of targeted therapy seems a logical approach to treat patients in this indication.

This randomized study is designed to demonstrate that treatment with BMS-986012 in combination with carboplatin, etoposide, and nivolumab will have acceptable safety and tolerability and will improve PFS compared with carboplatin, etoposide, and nivolumab alone in newly diagnosed participants with ES-SCLC.

3.2 Background

A detailed description of the chemistry, pharmacology, efficacy, and safety of BMS-986012 is provided in the BMS-986012 Investigator Brochure (IB),[16] and information for nivolumab is provided in the nivolumab IB.[17] Refer to locally approved product labels for carboplatin/etoposide details.

3.2.1 Indication Background

Lung cancer has been the most common cancer in the world for several decades, and in 2018, there were an estimated 2 million new cases, representing 11.6% of all new cancers. It is also the most common cause of death from cancer, with 1.76 million deaths (18.4% of the total).[18] These statistics include SCLC, which has an even poorer prognosis, and the 5-year OS rate is around 6%.[19] SCLC accounts for 12% to 16% of all lung cancers in the United States (US) and Europe and is distinguished by its rapid growth rate, early dissemination to regional lymph nodes and distant sites, and sensitivity to chemotherapy and radiotherapy.[20] Historically, SCLC is staged by the Veterans' Affairs Administration Lung Cancer Study Group classification.[21] At time of diagnosis, 70% of the patients have ES-SCLC, meaning that the tumor has spread outside of the hemithorax with presence of metastases.[21,22,23]

3.2.2 BMS-986012 Mechanism of Action

BMS-986012 is a first-in-class, fully human IgG1 mAb produced in Chinese hamster ovary (CHO) cells by recombinant DNA technology that specifically binds to the fuc-GM1 ganglioside. BMS-986012 is being developed for the treatment of SCLC, as [redacted] analysis of tumor samples with anti-fuc-GM1 mAb has demonstrated antigen expression in a high percentage of SCLC cases and little or no expression in normal tissues.[13,14,15,24,25,26]

BMS-986012 exhibits high-affinity and dose-dependent saturable binding to fuc-GM1 and shows no detectable antigen-specific binding to the closely related molecule GM1. BMS-986012 was optimized to have enhanced effector functions by elimination of the fucosylation on the Fc domain. The absence of this fucosyl group in BMS-986012 (resulting from its expression in a cell line deficient in fucosyl transferase) confers higher affinity for Fc receptors, resulting in enhanced ADCC.[27] Furthermore, the antibody was shown to mediate potent CDC as well as ADCP.

3.2.3 Nivolumab Mechanism of Action

Cancer immunotherapy rests on the premise that tumors can be recognized as foreign rather than as self and can be effectively attacked by an activated immune system. An effective immune response in this setting is thought to rely on immune surveillance of tumor antigens expressed on cancer cells that ultimately results in an adaptive immune response and cancer cell death. Meanwhile, tumor progression may depend upon acquisition of traits that allow cancer cells to

evade immunosurveillance and escape effective innate and adaptive immune responses.[28,29,30] Current immunotherapy efforts attempt to break the apparent tolerance of the immune system to tumor cells and antigens by either introducing cancer antigens by therapeutic vaccination or by modulating regulatory checkpoints of the immune system. T-cell stimulation is a complex process involving the integration of numerous positive as well as negative co-stimulatory signals in addition to antigen recognition by the T-cell receptor (TCR).[31] Collectively, these signals govern the balance between T-cell activation and tolerance.

PD-1 is a member of the cluster of differentiation 28 (CD28) family of T-cell co-stimulatory receptors that also includes CD28, cytotoxic T-lymphocyte-associated protein 4 (CTLA-4), inducible costimulatory molecule (ICOS), and B- and T-lymphocyte attenuator (BTLA).[32] PD-1 signaling has been shown to inhibit CD28-mediated upregulation of interleukin (IL)-2, IL-10, IL-13, interferon-γ (IFN-γ) and B-cell lymphoma-extra large (Bcl-xL). [redacted] also been noted to inhibit T-cell activation, and expansion of previously activated cells. Evidence for a negative regulatory role of PD-1 comes from studies of PD-1 deficient mice, which develop a variety of autoimmune phenotypes.[33] These results suggest that PD-1 blockade has the potential to activate anti-self T-cell responses, but these responses are variable and dependent upon various host genetic factors. Thus, PD-1 deficiency or inhibition is not accompanied by a universal loss of tolerance to self-antigens.

Nivolumab (BMS-936558) is produced in CHO cells by recombinant DNA technology. In vitro, nivolumab binds to PD-1 with high affinity (half maximal effective concentration 0.39-2.62 nM) and inhibits the binding of PD-1 to its ligands PD-L1 and PD-L2 (half maximal inhibitory concentration ± 1 nM). Nivolumab binds specifically to PD-1 and not to related members of the CD28 family such as CD28, ICOS, CTLA-4 and BTLA. Blockade of the PD-1 pathway by nivolumab results in a reproducible enhancement of both proliferation and IFN-γ release in the mixed lymphocyte reaction. Using a cytomegalovirus (CMV) restimulation assay with human peripheral blood mononuclear cells (PBMC), the effect of nivolumab on antigen-specific recall response indicates that nivolumab augmented IFN-γ secretion from CMV-specific memory T cells in a dose-dependent manner versus isotype-matched control. In vivo blockade of PD-1 by a murine analog of nivolumab enhances the anti-tumor immune response and result in tumor rejection in several immunocompetent mouse tumor models (MC38, SA1/N, and PAN02).[34]

3.3 Benefit/Risk Assessment

[redacted]

[redacted]

Fucosyl-GM1 has very limited tissue expression in primates but is detected in peripheral sensory nerves and dorsal root ganglion cells of monkeys and humans. To address concerns of peripheral neuropathy as a target liability of BMS-986012, an investigative study was conducted in cynomolgus monkeys of BMS-986012 in combination with cisplatin. There were no neurotoxicities or nerve conduction velocity defects observed with BMS-986012 alone, and there were no observed exacerbations of cisplatin-induced neuropathy when BMS-986012 was given in combination with cisplatin.

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

A pattern of immune-related AEs has been defined, for which management algorithms have been developed; these are provided in Appendix 5. Most high-grade events were manageable with the use of corticosteroids or hormone replacement therapy (endocrinopathies) as instructed in these algorithms.

The safety profile of anti-PD-(L)1 therapy with chemotherapy in SCLC is well established to be well tolerated and manageable from 4 trials thus far:

1) IMpower133 (atezolizumab plus carboplatin and etoposide versus carboplatin and etoposide in first-line ES-SCLC) showed a safety profile consistent with the previously reported safety profile of the individual agents, with no new findings observed and similar rates of hematologic side effects in the 2 groups, and incidence and types of immune-related AEs were similar to those seen with atezolizumab monotherapy.[6]
2) The CASPIAN trial (durvalumab plus platinum–etoposide versus platinum–etoposide in first-line ES-SCLC) demonstrated a similar safety profile between the 2 groups, with similar frequencies of Grade 3 or 4 AEs, AEs leading to discontinuation, and AEs leading to death. The most common AEs were hematological toxicities consistent with those of chemotherapy alone. Immune-mediated AEs (IMAEs) were mostly low grade and manageable with standard treatment guidelines and were numerically higher in the durvalumab group but consistent with the known safety profile of durvalumab.[11]
3) KEYNOTE-604 (pembrolizumab plus platinum–etoposide versus platinum–etoposide in first-line ES-SCLC) had similar safety profiles as above, where the most frequently observed AEs in both treatment groups were hematologic events, rates of which did not seem to be increased by pembrolizumab and were consistent with those of chemotherapy alone. The incidence and types of IMAEs observed in the pembrolizumab group were consistent with those observed for pembrolizumab monotherapy in SCLC.[35]

4) ECOG-ACRIN EA5161 (cisplatin/carboplatin and etoposide alone or in combination with nivolumab in first-line ES-SCLC) again had similar safety profiles as above. Hematological toxicities were the most frequently observed AEs. The combination of nivolumab and chemotherapy was well tolerated with manageable toxicities.[12]

In terms of the clinical experience with BMS-986012, a manageable safety profile has been established from the 3 protocols CA001-030, CA001-044, and CA001-045, where a total of 126 particpants have been treated as either monotherapy or combination with platinum/etoposide or nivolumab. A comprehensive summary of safety is available in the most recent version of the IB.[16]

Pruritus is the most common study treatment-related AE (TRAE) across the BMS-986012 program and has occurred in nearly all participants treated with BMS-986012 as of the cut-off date (08-May-2020). Pruritus related to study treatment is often acute in onset and can occur during the infusion, although it is usually not associated with other findings typical of an infusion-related reaction. Reported pruritus events have been generally mild to moderate in intensity, although the mechanism of action remains unclear. Some participants reported symptomatic relief with antihistamines, whereas others required a short course of low-dose corticosteroids. There does not appear to be a relationship between dose of BMS-986012 and grade or duration of pruritus. In the majority of all cases, pruritus resolved within 1 to 2 cycles despite continued dosing of BMS-986012, and most participants did not experience recurrent pruritus once an episode had resolved, even with repeated dosing.

Given that fuc-GM1 is expressed in peripheral nerves, peripheral and sensory neuropathy have been events of interest that were carefully monitored in the clinical program. The number of participants who experienced new onset or worsening of preexisting peripheral neuropathy in this program was small, and the events were generally low grade. Factors such as past medical history, prior platinum therapy, and dose/cumulative exposure to BMS-986012 may affect the occurrence, duration, and severity of sensory changes, and continued evaluation of these events is ongoing.

BMS-986012, nivolumab, carboplatin, and etoposide function through distinct mechanisms of action, making overlapping toxicities unlikely. BMS-986012 is a monoclonal antibody targeting fuc-GM1, which is generally not expressed in normal tissue. Nivolumab is a checkpoint inhibitor that blocks the inhibitory signal from PD-1 on effector T cells, stimulating immune-mediated tumor destruction. Carboplatin and etoposide are both chemotherapeutic agents, the former a platinum-based antineoplastic agent that interferes with deoxyribonucleic acid (DNA) replication and the latter a topoisomerase inhibitor. In addition, for potential PK interactions, there are no expected clinical PK drug-drug interactions anticipated with the combination of the above agents. Finally, in CA001-030 and CA001-044, no PK differences were observed when BMS-986012 was given in combination with nivolumab or chemotherapy as compared to monotherapy. In summary, the combination of BMS-986012 with carboplatin/etoposide and nivolumab is expected to have a manageable safety profile with a positive benefit-risk profile.

However, given the novel combination of the 4 drugs, there will be additional safety monitoring conducted by the Data Monitoring Committee (DMC), in addition to the BMS multilayered process for ensuring participant safety, as described in Section 5.1.4.

In terms of potential clinical benefit, this was observed across the program:

In the monotherapy portion of the CA001-030 trial, as of the clinical data cut-off date (08-May-2020), preliminary clinical benefit has been observed in 21 participants out of 77 treated across all dose levels in both dose escalation and dose expansion. One participant receiving 70 mg had a confirmed CR lasting 53 weeks until progression. One participant in the 400-mg dose level had a confirmed PR that lasted for 18 weeks. One participant in the 1,000-mg dose level has a confirmed PR that is ongoing as of the data cut-off date. Eighteen participants had SD in the 160-, 400-, and 1,000-mg dose levels, ranging in duration from 3 to 55 weeks.

In the CA001-030, cohorts evaluating BMS-986012 in combination with nivolumab, as of the clinical data cut-off date (08-May-2020), preliminary clinical benefit has been observed in 13 participants out of 29 treated in both dose escalation and expansion. There have been 9 PRs, 1 CR, and 3 SD responses, with 1 subject achieving a PR after treatment beyond progression. These data are preliminary and subject to change as they are based on investigator-assessed responses.

Finally, in CA001-044, as of the clinical data cut-off date (28-Jan-2020), out of the 14 participants treated, 10 participants achieved a PR as their BOR, 1 participant had PD as their BOR, and 2 participants had no BOR determined. One participant died prior to disease assessment.

Given the experience with BMS-986012, a favorable benefit-risk relationship has been established, and continued investigation of the agent is warranted. However, as BMS-986012 is an investigational agent, it is possible that unforeseen, unknown, or unanticipated reactions may occur. However, based on the nonclinical safety profile of BMS-986012 and the lack of unexpected toxicity observed in the program to date, the potential safety risks are expected to be minimal. An urgent need exists for new therapies for participants with SCLC as it remains a very much unmet need. More detailed information about the known and expected benefits and risks and reasonably anticipated AEs may be found in the BMS-986012 and nivolumab IBs.[16,17]

Whether BMS-986012, nivolumab, carboplatin, or etoposide administration increases the risk for contracting severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection or increases the severity or duration of symptoms is currently unknown. This unknown risk must be considered when enrolling a participant.

Non-live SARS-CoV-2 vaccination is considered a simple concomitant medication within the study. However, the efficacy and safety of non-live vaccines (including non-live COVID-19 vaccines) in participants receiving study treatments is unknown.

No additional safety monitoring or routine screening tests will be required due to the SARS-CoV-2 pandemic. Participants with recent or acute infections will be excluded or delay start of treatment as defined in Section 6.2. If a participant has a confirmed SARS-CoV-2 infection while on study treatment, dose delay or interruption of study treatment is required as described in Section 7.4.

4 OBJECTIVES AND ENDPOINTS

Table 4-1: Objectives and Endpoints

Objectives	Endpoints
Primary	
• Assess the safety and tolerability for participants randomized to BMS-986012 in combination with carboplatin, etoposide, and nivolumab for 4 cycles (induction) followed by BMS-986012 and nivolumab maintenance (Arm A) vs those randomized to carboplatin, etoposide, and nivolumab for 4 cycles (induction) followed by nivolumab maintenance (Arm B).	• Incidence of AEs, SAEs, AEs leading to discontinuation, deaths.
• To compare the PFS as assessed by BICR of participants treated in the combination induction and maintenance therapies of Arms A and B described above.	• PFS by BICR based on RECIST v1.1 criteria.
Secondary	
• To estimate the PFSR at 6 and 12 months in each treatment arm, based on PFS by RECIST v1.1 as assessed by BICR.	• PFSR at 6 and 12 months. PFS by BICR based on RECIST v1.1 criteria.
• To compare PFS as assessed by investigator of participants treated in the combination induction and maintenance therapies of Arms A and B described above.	• PFS by investigator based on RECIST v1.1 criteria.
• To estimate the PFSR at 6 and 12 months in each treatment arm based on PFS by RECIST v1.1 assessed by investigator.	• PFSR at 6 and 12 months. PFS by investigator based on RECIST v1.1 criteria.
• To estimate the ORR, TTR, and DOR by RECIST v1.1 criteria by BICR and by investigator.	• ORR, TTR, and DOR based on RECIST v1.1 criteria.
• To assess OS of Arm A and Arm B and estimate OSR at 12 and 24 months by treatment arm.	• OS and OSR at 12 and 24 months, by arm.
• To characterize the immunogenicity of BMS-986012 in combination with carboplatin, etoposide, and nivolumab in Arm A.	• The immunogenicity of BMS-986012 measured by assessment of the presence of specific ADAs to BMS-986012. The incidence of positive ADAs will be calculated.

Table 4-1: Objectives and Endpoints

Objectives	Endpoints
Tertiary/Exploratory	
• To assess disease-related symptoms measured by LCSS.	• Change from baseline and time to deterioration in LCSS ASBI and 3-item global index.
• To assess the bother associated with the side effects of treatment.	• Participant-perceived bother as measured by the FACIT GP5 item.
• To assess associations of [redacted] in pretreatment [redacted] assessed using [redacted] assays with anti-tumor activity measures.	• Measures of [redacted] by [redacted] and by targeted [redacted] and association with measures of anti-tumor activity measures (eg, ORR, PFS).
• To assess associations of [redacted] (CPS) in pretreatment [redacted] with anti-tumor activity measures.	• Measures of tumor [redacted] (CPS) at baseline and association with measures of anti-tumor activity (eg, ORR, PFS).

• To explore associations with antitumor activity measures in Arms A and B with changes in biomarkers during treatment such as the following:
  • NK cell-mediated ADCC [redacted]
  • [redacted] in [redacted] (ie, NK cell activation)
  • [redacted] levels in [redacted]
  • [redacted] levels in [redacted]
	• Summary measures of NK cell-mediated ADCC [redacted] in [redacted] at baseline and on-treatment and associations with antitumor activity measures.
	• Summary measures [redacted] with their changes from baseline and associations with antitumor activity measures.
	• Summary measures of [redacted] levels at baseline and on-treatment in [redacted] and associations with baseline [redacted] measured by [redacted] and [redacted] and antitumor activity measures.
	• Summary measures of [redacted] levels at baseline and on-treatment in [redacted] and associations with baseline [redacted] measured by [redacted] and [redacted] and antitumor activity measures.

• To explore associations with anti-tumor activity measures in Arms A and B with baseline biomarkers such as the following:
  • [redacted]
  • [redacted]
  • [redacted]
  • [redacted] in the tumor micro-environment
	• Summary measures of [redacted] from [redacted] at baseline [redacted] and associations with baseline [redacted] and antitumor activity measures.
	• Summary of baseline measures of [redacted] in blood and associations with antitumor activity measures.
	• Summary measures of [redacted] and associations with antitumor activity measures.
	• Summary measures of [redacted] and associations with antitumor activity measures.

Table 4-1: Objectives and Endpoints

Objectives	Endpoints
• To characterize PK of BMS-986012 in combination with carboplatin, etoposide, and nivolumab in Arm A. • To characterize PK of nivolumab in Arms A and B.	• Summary statistics of BMS-986012 serum concentrations. • Summary statistics of nivolumab serum concentrations.
• To characterize the immunogenicity of nivolumab in Arms A and B. • To explore the PK-pharmacodynamic relationship(s) of BMS-986012 with select biomarkers and anti-tumor activities. • To explore [redacted] in [redacted] obtained at progression from optiona[redacted]. • Explore associations of the BMS-986279 PET tracer[a] uptake of the [redacted] lesion with [redacted] levels by [redacted] and/or [redacted], and the heterogeneity of BMS-986279 PET tracer uptake in tumor lesions, in a sub-study of participants at select study site(s).	• The immunogenicity of nivolumab measured by assessment of the presence of specific ADAs to nivolumab. The incidence of positive ADAs will be calculated. • Measures of associations between PK exposure and select biomarker or anti-tumor activity changes association measures. • Measures of [redacted] associations with anti-tumor activity. • Association measure of BMS-986279 uptake by quantitative measurements (eg, SUVmax, SUVpeak, SUVmean) with [redacted] by [redacted] in [redacted] and/or [redacted]. • Summary measures of PET-CT uptake signal measured by SUV measurements in tumor lesions, including variability estimates.

Abbreviations: ADA = anti-drug antibody; ADCC = antibody-dependent cellular cytotoxicity; AE = adverse event; ASBI = Average Symptom Burden Index; BICR = blinded independent central review; CPS = combined positive score; CT = computed tomography; CTC = circulating tumor cell; DOR = duration of response; ES-SCLC = extensive stage small cell lung cancer; FACIT GP5 = a single item from the Functional Assessment of Chronic Therapy – General; [redacted]; Ig(G) = immunoglobulin G; [redacted] LCSS = Lung Cancer Symptom Scale; mAb = monoclonal antibody; [redacted]; NK = natural killer; ORR = objective response rate; OS = overall survival; OSR = overall survival rate; [redacted]; PET = positron emission tomography; PFS = progression-free survival; PFSR = progression-free survival rate; PK = pharmacokinetic; RECIST = Response Evaluation Criteria in Solid Tumors; SAE = serious adverse event; SUV = standardized uptake value; [redacted]; TTR = time to response.

[a] BMS-986279 is a PET tracer based on BMS-986012 mAb labeled with 89Zr.

5 STUDY DESIGN

5.1 Overall Design

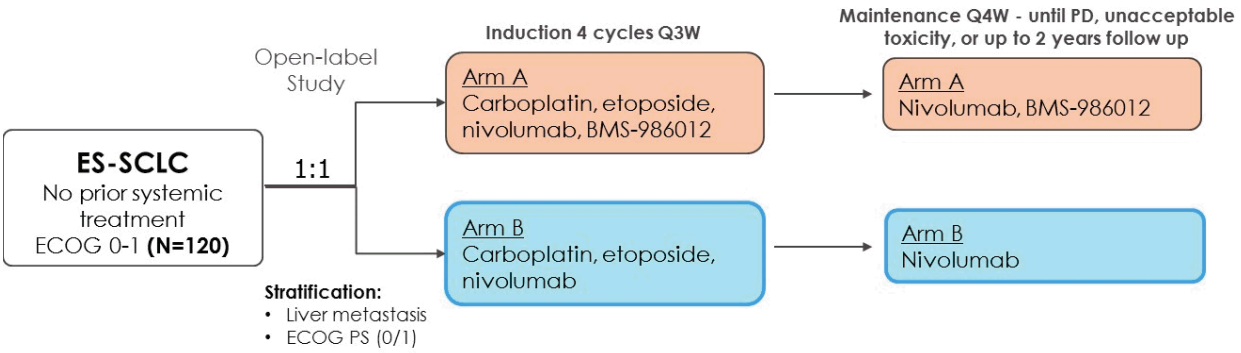
This is a Phase 2, randomized, open-label study of BMS-986012 in combination with carboplatin, etoposide, and nivolumab as first-line therapy in ES-SCLC.

Participants will be randomized to receive either 4 cycles of induction therapy (21 days per cycle) of carboplatin/etoposide in combination with BMS-986012 and nivolumab followed by BMS-986012 and nivolumab as maintenance (28 days per cycle) or 4 cycles of induction therapy (21

days per cycle) of carboplatin/etoposide in combination with nivolumab followed by nivolumab as maintenance (28 days per cycle).

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

Figure 5.1-1: Study Design Schematic



Abbreviations: ECOG = Eastern Cooperative Oncology Group; ES-SCLC = extensive-stage small cell lung cancer; PD = progressive disease; PS = performance status; Q3W = every 3 weeks; Q4W = every 4 weeks.

5.1.1 Screening

The screening period will be up to 28 days and begins when the participant signs the main informed consent form (ICF). During the screening period, [redacted]; however, results are not required in order to randomize a participant into the study. Participants will be enrolled using an Interactive Response Technology (IRT).

This study allows for re-enrollment of a participant that has discontinued the study as a pretreatment failure. If re-enrolled, the participant must be re-consented and assigned a new participant number from IRT.

If a participant exceeds the 28-day screening period due to a study-related procedure (eg, scheduling of a [redacted] or waiting for a study-related laboratory value), the participant must be re-consented but does not require a new participant identification number. In this situation, safety laboratory tests should be repeated, and the Bristol-Myers Squibb (BMS) Medical Monitor or designee should be notified. Any additional procedures and tests should only be repeated if needed to maintain participant safety and confirm eligibility after discussion with the BMS Medical Monitor or designee.

Participant is assessed for study eligibility according to the inclusion (Section 6.1) and exclusion (Section 6.2) criteria. The detailed procedures are described in Table 2-1.

5.1.2 Treatment

The treatment period begins after contacting the IRT system for randomization.

Participants will be randomized in a 1:1 ratio into 1 of the 2 following arms:

1. Arm A
    a. Induction (3-week cycle - 21 days): Cycles 1 to 4
        i. Carboplatin Day 1: area under the curve (AUC) 5 mg/mL/min intravenous (IV)
        ii. Etoposide Days 1, 2, 3: 100 mg/m^2 IV
        iii. BMS-986012 Day 1: 420 mg IV
        iv. Nivolumab Day 1: 360 mg IV
    b. Maintenance (4-week cycle - 28 days): Cycle 5 and beyond
        i. BMS-986012 Day 1: 560 mg IV
        ii. Nivolumab Day 1: 480 mg IV
2. Arm B
    a. Induction (3-week cycle - 21 days): Cycles 1 to 4
        i. Carboplatin Day 1: AUC 5 mg/mL/min IV
        ii. Etoposide Days 1, 2, 3: 100 mg/m^2 IV
        iii. Nivolumab Day 1: 360 mg IV
    b. Maintenance (4-week cycle - 28 days): Cycle 5 and beyond:
        i. Nivolumab Day 1: 480 mg IV

Randomization will be stratified based on the presence of liver metastases and ECOG performance status (PS) 0 or 1. When study drugs are to be administered on the same day, chemotherapy will be administered first (during induction phase only), followed by BMS-986012 (for Arm A participants only), and finally nivolumab. All participants will be treated for up to 2 years or until disease progression (see Section 7.1), unacceptable toxicity, or participant withdrawal of consent, whichever comes first. No participant crossover between treatment arms will be allowed; that is, participants randomized to Arm B will not be permitted to receive BMS-986012. Upon completion of 4 cycles of induction therapy, participants in both arms may receive radiation therapies, including prophylactic cranial irradiation, as per criteria in Section 7.7.2.1. Other therapies (including maintenance chemotherapies or immunotherapies) are not permitted in either arm until the participant discontinues study treatment.

The DMC will evaluate the first 12 participants in each arm for a period of 8 weeks (2 cycles and 2 weeks follow-up) from start of treatment to assess if additional safety concerns occur with the 4-drug regimen during the induction phase.

After all treated participants have been followed up for a minimum of 8 weeks, the DMC will assess whether the established threshold for the safety evaluable population has been met and make a benefit-risk recommendation to the study team. In addition, continuous monitoring will be conducted throughout the entire study, to evaluate for toxicity or for safety of aggregate data. This is in addition to the standard sponsor-defined process for monitoring participants (see Section 5.1.4) to ensure safety during the whole duration of the study.

Evaluable participants are defined as those who have completed the 8 weeks of treatment or those who discontinued due to study drug toxicity prior to completing the evaluation period.

5.1.3 Follow-up

The follow-up period begins when the decision is made to discontinue a participant from study therapy.

- Safety Follow-up Visit 1 will be performed 30 days from the last dose (± 7 days). End-of-treatment visit may be skipped if it coincides with the Safety Follow-up Visit 1.
- Safety Follow-up Visit 2 will be performed 60 days from the last dose (± 7 days) of study treatment.
- Safety Follow-up Visit 3 will be performed 100 days (± 7 days) from last dose of study treatment. Participants must be followed for at least 100 days after last dose of study treatment.

All safety follow-up visits should be conducted in person due to different sample collection and assessments required as per the Schedule of Activities. However, telemedicine may be allowed if circumstances require it after discussion with the study Medical Monitor.

- Survival follow-up visits: In parallel with the safety follow-up period, all participants will start the survival follow-up period. Participants will be followed up every 12 weeks (± 14 days) from the last dose or last safety follow-up visit, whichever occurs later, until death, lost to follow-up, withdrawal of consent, or conclusion of the study, whichever comes first. The duration of this follow-up is up to 3 years following the first dose of study treatment, although a longer follow-up period could be considered in selected cases if an efficacy signal is apparent. Subsequent therapies will also be recorded in this survival follow-up period. Survival follow-up visits may be conducted in clinic or by phone or telemedicine.

Study follow-up assessment data are to be collected as outlined in Table 2-3.

5.1.4 Data Monitoring Committee and Other External Committees

A DMC will be established to provide oversight of safety and efficacy considerations for the study. DMC membership and meeting frequency will be provided in the DMC charter. The DMC will provide advice to the Sponsor regarding actions the committee deems necessary for the continued protection of participants enrolled in the study. The independent DMC will be charged with assessing such actions in light of an acceptable benefit-risk profile. The independent DMC will act in an advisory capacity to BMS and will monitor participant safety data for the study. The independent DMC will be advisory to the clinical study leadership team. The clinical study

leadership will have responsibility for overall conduct of the study, including managing the communication of study data. The group will be responsible for promptly reviewing the DMC recommendations, for providing guidance regarding the continuation or termination of the study, and for determining whether amendments to the protocol or changes to the study conduct are required. The DMC will evaluate the first 12 participants in each arm for a period of 8 weeks (2 cycles and 2 weeks follow-up) from start of treatment to assess if additional safety concerns occur with the 4-drug regimen during the induction phase. Additional details are provided in Section 10.3.4.2. The DMC will also conduct the interim efficacy analysis.

In addition to the periodic DMC meetings, BMS has in place a multilayered process for ensuring participant safety through close collaboration of study site Investigators, the BMS study team, and the BMS Worldwide Patient Safety (WWPS)-led Safety Medical Team (SMT). This collaborative process constitutes the Data Safety Monitoring Plan for the study as detailed below.

- Study safety is evaluated continuously by representatives of the BMS WWPS, who operate independently from the clinical team and monitor safety across all BMS protocols. AEs are monitored continuously by WWPS. Signal detection is performed at least monthly and ad hoc throughout the study by the SMT, composed, at a minimum, of the WWPS medical safety assessment physician (Chairman of the SMT) and WWPS single-case review physician, the study Medical Monitor(s), the study biostatistician, and the epidemiologist. The SMT monitors actual or potential issues related to participant safety that could result in a significant change in the medical benefit-risk balance associated with the use of study treatments. Furthermore, Investigators will be kept updated of important safety information during teleconferences between Investigators and the BMS clinical team, which will be held on a regularly scheduled basis. If appropriate, select safety issues may be escalated to a senior-level, multidisciplinary, BMS-wide Medical Review Group for further evaluation and action. To support safety oversight, BMS has established ongoing processes for collection, review, analysis, and submission of individual AE reports and their aggregate analyses.
- Aggregate safety will be continuously monitored for both arms and will be informed by a Bayesian framework (see Section 10.3.4.2), which will consider overall safety measures if an excessive number of safety events are observed.

5.1.5 Blinded Independent Central Review

A blinded independent central review (BICR) will be utilized in this study for determination of BICR-assessed endpoints. The BICR will review all available tumor assessment scans for all treated participants. All investigator determinations of PD will be reviewed by the BICR (see Section 9.1.1.2).

5.2 Number of Participants

Approximately 120 participants will be randomized in a 1:1 ratio to receive treatment into 1 of the 2 arms.

The first 24 participants treated across arms will be followed for early safety evaluation by the DMC and the SMT, including via continuous safety monitoring implemented by the Sponsor. For additional details on sample size determination, see Section 10.1.

5.3 End of Study Definition

The start of the trial is defined as the first visit for the first participant screened. End of trial is defined as the last visit or scheduled procedure shown in the Schedule of Activities (see Section 2) for the last participant. Study completion is defined as the final date on which data for the primary endpoint was or is expected to be collected if this is not the same. OS assessment can be terminated at the discretion of the Sponsor.

5.4 Scientific Rationale for Study Design

BMS-986012 will be evaluated in participants with ES-SCLC. The drug targets the fuc-GM1 antigen, which has a [redacted] prevalence in SCLC patients. Preclinically, BMS-986012 was shown to enhance ADCC as well as mediate potent CDC and ADCP. In CA001-030, the antibody showed a potential efficacy signal when combined with nivolumab, potentially due to the synergism between T-cell activation and the above activities. Checkpoint inhibition in combination with standard-of-care chemotherapy has led to improved survival rates in patients with ES-SCLC in the first-line setting, and as such, the addition of targeted therapy seems a logical approach to treat patients in this indication.

The study design includes the following:

- 28-day screening period
- 4 Induction cycles every 3 weeks (Q3W)
- Maintenance every 4 weeks (Q4W) up to 2 years
- Safety follow-up period of 100 days
- Survival follow-up period of up to 3 years

5.4.1 Rationale for Two-year Duration of Treatment

The optimal duration of immunotherapy is an important question and continues to be investigated.

Accumulating data suggest that 2 years of PD-1 checkpoint inhibitor treatment may be sufficient for long term benefit. CA209-003, a dose-escalation cohort expansion trial evaluating the safety and clinical activity of nivolumab in participants with previously treated advanced solid tumors (including 129 participants with non-small cell lung cancer [NSCLC]), specified a maximum treatment duration of 2 years. Among 16 participants with NSCLC who discontinued nivolumab after completing 2 years of treatment, 12 participants were alive > 5 years and remained progression-free without any subsequent therapy. In the CA209-003 NSCLC cohort, the OS curve begins to plateau after 2 years, with an OS rate of 25% at 2 years and 18% at 3 years.[36] These survival outcomes are similar to Phase 3 studies in previously treated NSCLC, in which nivolumab treatment was continued until progression or unacceptable toxicity (2 year OS rates of 23% and 29%, and 3 year OS rates of 16%-18% for squamous and non-squamous NSCLC, respectively).[37]

Similar results have been reported in clinical studies of pembrolizumab, another PD-1 inhibitor. Keynote-010 was a randomized Phase 3 trial of pembrolizumab (at either 2 mg/kg or 10 mg/kg every 3 weeks) versus docetaxel in participants with previously treated, PD-L1-positive, advanced

NSCLC, which specified a maximum treatment duration of 2 years for pembrolizumab. OS was significantly longer with both pembrolizumab 2 mg/kg (HR 0.72, p = 0.00017) and pembrolizumab 10 mg/kg (HR 0.60, p < 0.00001) compared to docetaxel, with an OS plateau developing beyond 2 years in both pembrolizumab arms. Among 690 participants who received pembrolizumab, 47 participants completed 2 years of pembrolizumab and stopped treatment. Most were able to maintain their response, including those with SD, with only 2 participants (4%) having confirmed progression after stopping at 2 years.[38]

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

In contrast, a shorter duration of nivolumab of only 1 year was associated with increased risk of progression in previously treated participants with NSCLC, suggesting that treatment beyond 1 year is likely needed. In CA209-153, participants with previously treated advanced NSCLC who completed 1 year of nivolumab therapy were randomized to either continue or stop treatment, with the option of retreatment upon progression. Among 163 participants still on treatment at 1 year and without progression, those who were randomized to continue nivolumab had significant improvement in PFS compared to those who were randomized to stop treatment, with median PFS (post-randomization) not reached versus 10.3 months, respectively; HR = 0.42 (95% CI, 0.25 to 0.71). With a median follow-up of 14.9 months post-randomization, there also was a trend for participants on continued treatment to live longer (OS HR = 0.63 [95% CI: 0.33, 1.20]). Of note, the PFS curves in both groups plateau approximately 1 year after randomization (ie, 2 years after treatment initiation), suggesting that there may be minimal benefit in extending treatment beyond a total of 2 years.[39]

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

5.5 Justification for Dose

In Arm A of the study, BMS-986012 will be administered at the dose of 420 mg IV Q3W in combination with nivolumab 360 mg IV Q3W and carboplatin/etoposide chemotherapy for 4 induction cycles, followed by BMS-986012 560 mg IV Q4W with nivolumab 480 mg IV Q4W in the maintenance phase. In Arm B, nivolumab 360 mg IV Q3W will be administered in combination with carboplatin/etoposide for 4 cycles followed by nivolumab 480 mg IV Q4W in the maintenance phase.

The dose of carboplatin and etoposide are based on respective reference product labels for treatment in SCLC.

5.5.1 Justification for BMS-986012 Dose

In Study CA001-030, the starting dose of 70 mg was chosen using data from both preclinical toxicology and pharmacology studies and was 10-fold below the monkey no-observed-adverse-effect level and 150-fold below the highest nonseverely toxic dose.

In the dose escalation phase of CA001-030, flat doses of 70, 160, 400, and 1,000 mg Q3W were evaluated in participants with relapsed or refractory SCLC, both as monotherapy and in combination with nivolumab. BMS-986012 was well tolerated as monotherapy and in combination with nivolumab up to 1,000 mg Q3W, and maximum tolerated dose was not established. In the CA001-044 study, flat doses of 400 mg Q3W and 1,000 mg Q3W were evaluated in combination with chemotherapy. BMS-986012 was well tolerated in combination with chemotherapy as well.

BMS-986012 has shown clinical benefit in previous studies at doses of 400 mg and 1,000 mg Q3W, either as monotherapy or in combination with nivolumab or chemotherapy. Preliminary exposure-response (E-R) analysis did not indicate that increase in exposure was associated with increase in efficacy. A dose of 420 mg Q3W is expected to provide similar anti-tumor activity to 400 mg Q3W and is expected to be safe in a combination setting of 4 drugs not tested before. Further, the dose of 420 mg Q3W simplifies dose optimization similar to Q4W regimen (as described below) by direct dose proportionality without issues of rounding off, thereby avoiding dosing errors.

In the maintenance phase, a less frequent dosing regimen of BMS-986012 is designed to afford convenience to the target participant population and allow combination with less frequent nivolumab dosing of 480 mg Q4W. Based on the data available from Studies CA001-030 and CA001-044, the PK of BMS-986012 is shown to be linear and dose proportional across the dose range tested in clinic. Furthermore, there are no apparent PK differences observed when BMS-986012 is given in combination with nivolumab or chemotherapy.

Given the linear and dose-proportional PK, a 560-mg dose of BMS-986012 is expected to produce similar average exposure to 420 mg Q3W upon switch to the less frequent Q4W regimen.

5.5.2 Justification for Nivolumab Dose

The nivolumab doses of 360 mg Q3W and 480 mg Q4W were selected based on clinical data and modeling and simulation approaches using population PK (PPK) and E-R analyses of data from studies in multiple tumor types (melanoma, NSCLC, and renal cell carcinoma [RCC]) where body weight normalized dosing (mg/kg) was used.

Nivolumab PK has been extensively studied in multiple tumor types, including melanoma, NSCLC, RCC, classical Hodgkin lymphoma, squamous cell carcinoma of the head and neck, colorectal cancer, and urothelial carcinoma and has been safely administered at doses up to 10 mg/kg every 2 weeks (Q2W). Nivolumab monotherapy was originally approved as a body weight-based dose of 3 mg/kg Q2W and was updated to 240 mg Q2W or 480 mg Q4W in multiple indications.[40,41] Nivolumab 360 mg Q3W is also under evaluation in monotherapy and in combination therapy studies. Less frequent 360 mg Q3W and 480 mg Q4W dosing regimens can

reduce the burden to patients of frequent, lengthy IV treatments and allow combination of nivolumab with other agents using alternative dosing regimens.

The benefit-risk profiles of nivolumab 240 mg Q2W, 360 mg Q3W, and 480 mg Q4W are predicted to be comparable to 3 mg/kg Q2W. This assessment is based on a comprehensive characterization of nivolumab PK, safety, efficacy, and E-R relationships across indications. PPK analyses have shown that the PK of nivolumab is linear with proportional exposures over a dose range of 0.1 to 10 mg/kg; no clinically meaningful differences in PK across ethnicities and tumor types were observed. Using the PPK model, the exposures following administration of several dosing regimens of nivolumab administered as a flat dose were simulated, including 240 mg Q2W, 360 mg Q3W, and 480 mg Q4W. The simulated average serum concentration at steady state following administration of nivolumab 360 mg Q3W and 480 mg Q4W are predicted to be similar to those following administration of nivolumab 240 mg Q2W and nivolumab 3 mg/kg Q2W administered to participants over a wide body weight range (34 to 180 kg) across tumor types.

Extensive E-R analyses of multiple PK measures (maximum serum concentration at Day 1, average serum concentration at Day 28 [Cavg28], and trough serum concentration at Day 28) and efficacy and safety endpoints indicated that the efficacy of the flat-dose 480 mg IV regimen is similar to that of the 3-mg/kg Q2W IV regimen. In E-R efficacy analyses for OS and ORR conducted in melanoma, RCC, and NSCLC using Cavg28 as the exposure measure, the probability of achieving a response and survival probabilities at 1 year and 2 years for IV 480 mg Q4W were similar to that of IV 3 mg/kg Q2W. In E-R safety analyses, it was demonstrated that the exposure margins for safety are maintained following nivolumab 480 mg Q4W, and the predicted risks of discontinuations due to AEs or death, AE Grade ≥ 3, and IMAEs Grade ≥ 2 are similar following nivolumab 480 mg Q4W relative to nivolumab 3 mg/kg Q2W across tumor types. In addition, nivolumab exposures with 240 mg Q2W, 360 mg Q3W, and 480 mg Q4W flat-dose IV regimens across tumor types are maintained well below the corresponding exposures observed with the well-tolerated 10 mg/kg IV nivolumab Q2W dose regimen.

Additional details on nivolumab posologies and benefit-risk can be found in the IB.[17]

6 STUDY POPULATION

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

6.1 Inclusion Criteria

1) Signed Written Informed Consent

a) **Not Applicable per Protocol Amendment 01.** Participants or legally authorized representatives (see Appendix 2) must have signed and dated an Institutional Review Board (IRB)/Independent Ethics Committee (IEC)-approved written ICF in accordance with regulatory and institutional guidelines. This must be obtained before the performance of any protocol-related procedures that are not part of normal participant care.

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

c) Participants must have signed and dated an Institutional Review Board (IRB)/Independent Ethics Committee (IEC)-approved written ICF in accordance with regulatory and institutional guidelines. This must be obtained before the performance of any protocol-related procedures that are not part of normal participant care.

2) Type of Participant and Target Disease Characteristics

a) **Not Applicable per Protocol Amendment 01.** Participants must have histologically or cytologically documented ES-SCLC. Participants must present with extensive-stage disease (American Joint Committee on Cancer, 7th edition, Stage IV [T any, N any, M1a, or M1b], or T3-4 due to multiple lung nodules that are too extensive or tumor or nodal volume that is too large to be encompassed in a tolerable radiation plan).

b) **Not Applicable per Protocol Amendment 01.** [redacted].

c) ECOG PS 0 or 1.

d) Participants must have at least 1 measurable lesion by computed tomography (CT) or magnetic resonance imaging (MRI) per Response Evaluation Criteria in Solid Tumors version 1.1 (RECIST v1.1) criteria.

e) Participants must be suitable to receive a platinum-based chemotherapy regimen as per locally approved drug labels and institutional guidelines.

f) Adequate hematologic and end organ function as defined below:

i) Absolute neutrophil count $\geq$ 1,500/mm^3 (stable off any growth factor within 2 weeks of the first study drug administration)

ii) Platelets $\geq$ 100,000/mm^3 (transfusion to achieve this level is not permitted within 2 weeks of the first study drug administration)

iii) Hemoglobin $\geq$ 9 g/dL (transfusion to achieve this level is not permitted within 2 weeks of the first study drug administration)

iv) White blood cells $\geq$ 2000/mm^3

v) Total bilirubin $\leq$ 1.5x upper limit of normal (ULN)

vi) Aspartate aminotransferase (AST; serum glutamic-oxaloacetic transaminase) and alanine aminotransferase (ALT; serum glutamic-pyruvic transaminase) $\leq$ 3x ULN

vii) Serum creatinine $\leq$ 1.5x ULN or calculated creatinine clearance > 50 mL/min (using the Cockcroft-Gault formula)

g) Participants must have histologically or cytologically documented ES-SCLC. Participants must present with extensive-stage disease (American Joint Committee on Cancer, 8th edition, Stage IV [T any, N any, M1a, M1b, or M1c] or T3-4 due to multiple lung nodules that are too extensive or tumor or nodal volume that is too large to be encompassed in a tolerable radiation plan).

h) **Not Applicable per Protocol Amendment 02.** [redacted]

i) [redacted].

j) Participants taking part in the separate PET tracer sub-study must provide a [redacted] from any disease site (primary or metastatic). [redacted]

3) Age and Reproductive Status

Investigators shall counsel women of childbearing potential (WOCBP) participants, and male participants who are sexually active with WOCBP, on the importance of pregnancy prevention and the implications of an unexpected pregnancy and the potential of fetal toxicity occurring due to transmission of study drug, present in seminal fluid, to a developing fetus, even if the participant has undergone a successful vasectomy or if the partner is pregnant.

- The investigator shall evaluate the effectiveness of the contraceptive method in relationship to the first dose of study intervention.
- Local laws and regulations may require the use of alternative and/or additional contraception methods.

a) Female Participants

i) Females, ages ≥ 18 years or local age of majority.

ii) Women who are not of childbearing potential are exempt from contraceptive requirements.

iii) Women participants must have documented proof that they are not of childbearing potential.

iv) **Not Applicable per Protocol Amendment 01.** WOCBP must have a negative highly sensitive urine or serum pregnancy test (minimum sensitivity 25 IU/L or equivalent units of human chorionic gonadotropin) within 24 hours prior to the start of study treatment.

(1) If a urine test cannot be confirmed as negative (eg, an ambiguous result), a serum pregnancy test is required. In such cases, the participant must be excluded from participation if the serum pregnancy result is positive

v) Additional requirements for pregnancy testing during and after study intervention are located in Section 2, Schedule of Activities.

vi) The investigator is responsible for review of medical history, menstrual history, and recent sexual activity to decrease the risk for inclusion of a woman with an early undetected pregnancy.

vii) WOCBP must agree to follow instructions for method(s) of contraception defined in Appendix 4 and as described below and included in the ICF.

viii) WOCBP are permitted to use hormonal contraception methods (as described in Appendix 4).

ix) A female participant is eligible to participate if she is not pregnant or breastfeeding, and at least 1 of the following conditions applies:

(1) Is not a WOCBP.

OR

(2) Is a WOCBP and using a contraceptive method that is highly effective (with a failure rate of <1% per year), with low user dependency, as described in Appendix 4 during the intervention period and for at least 6 months and agrees not to donate eggs (ova, oocytes) for the purpose of reproduction for the same time period.

x) WOCBP must have a negative highly sensitive urine or serum pregnancy test (minimum sensitivity 25 IU/L or equivalent units of human chorionic gonadotropin) within 24 hours prior to the start of study treatment. An extension up to 72 hours prior to the start of study treatment is permissible in situations where results cannot be obtained within the standard 24-hour window.

(1) If a urine test cannot be confirmed as negative (eg, an ambiguous result), a serum pregnancy test is required. In such cases, the participant must be excluded from participation if the serum pregnancy result is positive.

b) Male Participants

i) Males, ages ≥ 18 years or local age of majority

ii) Males who are sexually active with WOCBP must agree to follow instructions for method(s) of contraception defined in Appendix 4 and as described below.

iii) Azoospermic males are not exempt from contraceptive requirements and will be required to always use a latex or other synthetic condom during any sexual activity (eg, vaginal, anal, oral) with WOCBP even if the participant has undergone a successful vasectomy or if the partner is pregnant.

iv) **Not Applicable per Protocol Amendment 01.** Male participants are required to use a condom during the intervention period and for at least 7 months after the last dose of study intervention.

v) **Not Applicable per Protocol Amendment 01.** Female partners of males participating in the study should be advised to use highly effective methods of contraception during the study intervention period and for at least 7 months after the last dose of study intervention in the male participant.

vi) **Not Applicable per Protocol Amendment 01.** 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 intervention period and for at least 7 months after the last dose of study intervention.

vii) **Not Applicable per Protocol Amendment 01.** Male participants must refrain from donating sperm during the intervention period and for at least 7 months after the last dose of study intervention.

viii) Breastfeeding partners should be advised to consult their health care providers about using appropriate highly effective contraception during the time the participant is required to use condoms.

ix) Male participants are required to use a condom during the induction period (ie, while receiving chemotherapy) and for at least 6 months after the last dose of chemotherapy (ie, carboplatin and etoposide).

x) Female partners of males participating in the study should be advised to use highly effective methods of contraception during the study induction period (ie, while receiving chemotherapy) and for at least 6 months after the last dose of chemotherapy (ie, carboplatin and etoposide) in the male participant.

xi) 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 induction period (ie, while receiving chemotherapy) and for at least 6 months after the last dose of chemotherapy (ie, carboplatin and etoposide).

xii) Male participants must refrain from donating sperm during the induction period (ie, while receiving chemotherapy) and for at least 6 months after the last dose of chemotherapy (ie, carboplatin and etoposide).

6.2 Exclusion Criteria

1) Medical Conditions

a) **Not Applicable per Protocol Amendment 01.** Women who are pregnant or breastfeeding.

b) Any significant acute or chronic medical illness that would interfere with study treatment or follow-up.

c) Inability to be venipunctured and/or tolerate venous access.

d) Any other sound medical, psychiatric, and/or social reason as determined by the investigator.

e) **Not Applicable per Protocol Amendment 02.** Participants cannot have had prior chemotherapy, radiation therapy, or biologic therapy for SCLC for first-line treatment.

f) **Not Applicable per Protocol Amendment 01.** Participants with symptomatic brain or other central nervous system (CNS) metastases. Participants are eligible if brain or other CNS metastases are asymptomatic or have been adequately treated and participants have neurologically returned to baseline (except for residual signs or symptoms related to the CNS treatment) for at least 2 weeks prior to randomization. In addition, participants must be either off corticosteroids or on a stable or decreasing dose of ≤ 10 mg daily prednisone (or equivalent) for at least 2 weeks prior to randomization.

g) Paraneoplastic autoimmune syndrome requiring systemic treatment.

h) History of idiopathic pulmonary fibrosis, drug-induced pneumonitis, idiopathic pneumonitis, organizing pneumonia, or evidence of active pneumonitis on screening chest CT scan. History of radiation pneumonitis is permitted.

i) Grade ≥ 2 peripheral sensory neuropathy at study entry.

j) Participant has uncontrolled or active systemic fungal, bacterial, viral, or other infection despite appropriate anti-infective treatment within 7 days prior to the first dose of study drug.

k) **Not Applicable per Protocol Amendment 01.** Known human immunodeficiency virus (HIV) positive with an acquired immunodeficiency syndrome (AIDS)-defining opportunistic infection within the past year or a current CD4 count < 350 cells/uL. (Participants with known HIV who are randomized should receive antiretroviral therapy (ART) as clinically indicated and be monitored for CD4 counts and viral load per standard of care by a local health care provider.) NOTE: Testing for HIV must be performed at sites where mandated locally. HIV-positive participants must be excluded where mandated locally (see Appendix 8).

l) Significant uncontrolled cardiovascular disease, including, but not limited to, any of the following:
   i) Uncontrolled hypertension, which is defined as systolic blood pressure > 160 mm Hg or diastolic blood pressure > 100 mm Hg despite optimal medical management.
   ii) Active coronary artery disease, including unstable or newly diagnosed angina within 3 months of study enrollment.
   iii) Myocardial infarction in the past 6 months.
   iv) History of congenital long QT syndrome.
   v) History of clinically significant arrhythmias, such as ventricular tachycardia, ventricular fibrillation, or Torsade de pointes.
   vi) Uncontrolled heart failure, defined as Class 3 or 4 by New York Heart Association functional classification.
   vii) History or current diagnosis of myocarditis.

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

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

o) **Not Applicable per Protocol Amendment 01.** Prior malignancy active within the previous 3 years except for locally curable cancers that have been apparently cured, such as basal or squamous cell skin cancer, superficial bladder cancer, or carcinoma in situ of

the prostate, cervix, or breast AND no additional therapy is required during the study period.

p) Participants with history of life-threatening toxicity related to prior immune therapy (eg, anti-CTLA-4 or anti-PD-1/PD-L1 treatment or any other antibody or drug specifically targeting T-cell co-stimulation or immune checkpoint pathways) except those that are unlikely to re-occur with standard countermeasures (eg, hormone replacement after adrenal crisis).

q) **Not Applicable per Protocol Amendment 01.** Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection (either suspected or confirmed) within 12 weeks of screening. Note: Certain participants with resolving mild or asymptomatic SARS-CoV-2 infection > 4 weeks prior to screening may be included; for these participants, the Sponsor's Clinical Trial Physician must be consulted to confirm eligibility. COVID polymerase chain reaction viral testing may be required prior to randomization based on specific country/regional guidelines, and the result of this testing may impact study participation. Testing results should be discussed with the Medical Monitor to confirm eligibility.

r) Women who are pregnant or breastfeeding. Japan only: participation in the study is not allowed even if breastfeeding is suspended.

s) Participants with symptomatic brain or other central nervous system (CNS) metastases. Participants are eligible if brain or other CNS metastases are asymptomatic and do not require immediate treatment or have been adequately treated and participants have neurologically returned to baseline (except for residual signs or symptoms related to the CNS treatment) for at least 2 weeks prior to randomization. In addition, participants must be either off corticosteroids or on a stable or decreasing dose of ≤ 10 mg daily prednisone (or equivalent) for at least 2 weeks prior to randomization.

t) Known human immunodeficiency virus (HIV) positive with an acquired immunodeficiency syndrome (AIDS)-defining opportunistic infection within the last year or a current CD4 count < 350 cells/uL. Participants with HIV are eligible if:

   i) They have received antiretroviral therapy (ART) for at least 4 weeks prior to randomization as clinically indicated while enrolled on study.
   ii) They continue on ART as clinically indicated while enrolled on study.
   iii) CD4 counts and viral load are monitored per standard of care by a local health care provider.

   NOTE: Testing for HIV must be performed at sites where mandated locally. HIV-positive participants must be excluded where mandated locally (see Appendix 8).

u) Concurrent malignancy (present during screening) requiring treatment or history of prior malignancy active within 2 years prior to randomization (ie, participants with a history of prior malignancy are eligible if treatment was completed at least 2 years before randomization and the participant has no evidence of disease). Participants with history of prior early stage basal/squamous cell skin cancer or non-invasive or in situ cancers that have undergone definitive treatment at any time are also eligible.

v) Previous SARS-CoV-2 infection within 10 days for mild or asymptomatic infections or 20 days for severe/critical illness prior to Cycle 1 Day 1.

i) Acute symptoms must have resolved and based on investigator assessment in consultation with the Medical Monitor, there are no sequelae that would place the participant at a higher risk of receiving study treatment.

w) Participants cannot have had prior chemotherapy, radiation therapy, or biologic therapy for SCLC. Previously treated limited stage SCLC (LS-SCLC) participants are also excluded.

2) Prior/Concomitant Therapy

a) Inability to comply with restrictions and prohibited treatments as listed in Section 7.7 Concomitant Therapy.

b) **Not Applicable per Protocol Amendment 01.** Treatment with botanical preparations (eg, herbal supplements or traditional Chinese medicines) intended for general health support or to treat the disease under study within 2 weeks prior to randomization/treatment. Use of marijuana and its derivatives for treatment of symptoms related to cancer or cancer treatment are permitted if obtained by medical prescription or if its use (even without a medical prescription) has been legalized locally. Refer to Section 7.7.1 for prohibited therapies.

c) Treatment with complementary medications (eg, herbal supplements or traditional Chinese medicines) to treat the disease under study within 2 weeks prior to first study treatment. Such medications are permitted if they are used as supportive care. Refer to Section 7.7.1 for prohibited therapies.

d) Treatment with any live/attenuated vaccine within 30 days of first study treatment.

e) Previous SARS-CoV-2 vaccine within 7 days of Cycle 1 Day 1. For vaccines requiring more than one dose, the full series (eg, both doses of a 2-dose series) should be completed prior to enrollment when feasible and when a delay in enrollment would not put the study participant at risk.

3) Physical and Laboratory Test Findings

a) Evidence of organ dysfunction or any clinically significant deviation from normal in physical examination, vital signs, ECGs, or clinical laboratory determinations beyond what is consistent with the target population.

b) Any of the following on 12-lead ECG prior to study drug administration, confirmed by repeat assessment

i) PR interval ≥210 msec

ii) QRS complex ≥ 120 msec

iii) QT interval ≥ 500 msec

iv) Corrected QT interval by Fredericia ≥ 450 msec

c) Any positive test result for hepatitis B virus or hepatitis C virus (HCV) indicating presence of virus, eg, hepatitis B surface antigen (HBsAg, Australia antigen) positive, or hepatitis C antibody (anti-HCV) positive (except if HCV- ribonucleic acid [RNA] negative).

4) Allergies and Adverse Drug Reaction

a) History of allergy, hypersensitivity, or serious adverse reaction to monoclonal antibodies or related compounds.

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

5) Other Exclusion Criteria

a) Prisoners or participants who are involuntarily incarcerated. (Note: Under specific circumstances and only in countries where local regulations permit, a person who has been imprisoned may be included as a participant. Strict conditions apply, and BMS approval is required.)

b) Participants 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 participants and that the results of the study can be used. It is imperative that participants fully meet all eligibility criteria.

6.3 Lifestyle Restrictions

Not applicable. No restrictions are required.

6.4 Screen Failures

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

6.4.1 Retesting During Screening or Lead-in Period

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

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

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

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

Testing for asymptomatic SARS-CoV-2 infection by reverse transcriptase polymerase chain reaction (RT-PCR) or viral antigen is not required. However, some participants may develop suspected or confirmed symptomatic SARS-CoV-2 infection or be discovered to have asymptomatic SARS-CoV-2 infection during the screening period. In such cases, subjects may be

considered eligible for the study after meeting all inclusion/exclusion criteria related to active infection, and after meeting the following criteria:

- At least 10 days (20 days for severe/critical illness) have passed since symptoms first appeared or positive RT-PCR or viral antigen test result, and
- At least 24 hours have passed since last fever without the use of fever-reducing medications, and
- Acute symptoms (eg, cough, shortness of breath) have resolved, and
- In the opinion of the investigator, there are no SARS-CoV-2 infection sequelae that may place the participant at a higher risk of receiving investigational treatment.

In the instance of a SARS-CoV-2 infection during screening, the screening period may be extended beyond the protocol-specified timeframe with Medical Monitor approval. Any screening tests already performed which could potentially be affected by the SARS-CoV-2 infection or its complications on an individual basis and agreed upon with the Medical Monitor (eg, safety labs, chest CT scan) should be repeated within 7 days prior to Cycle 1 Day 1.

7 TREATMENT

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

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

- BMS-986012 Concentrate for Solution for Infusion
- Nivolumab (BMS-936558) Solution for Injection
- Carboplatin
- Etoposide

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

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

Table 7-1: Study Treatments for CA001050

Product Description / Class and Dosage Form	Potency	IP/Non-IMP	Blinded or Open Label	Packaging / Appearance	Storage Conditions (per label)
BMS-986012 Concentrate for Solution for Infusion	120 mg (30 mg/mL)	IP	Open Label	Vial	Refer to the label on container and/or Pharmacy Manual
Nivolumab (BMS-936558) Solution for Injection	100 mg or 40 mg (10 mg/mL)	IP	Open Label	Vial	Refer to the label on container and/or Pharmacy Manual
Carboplatin[a,b]	450 mg (10 mg/mL)	Non-IMP	Open Label	Vial	Refer to the label on container and/or Pharmacy Manual
Etoposide[a,b]	100 mg (20 mg/mL)	Non-IMP	Open Label	Vial	Refer to the label on container and/or Pharmacy Manual

Abbreviation: IP/IMP = investigational [medicinal] product

[a] These products may be obtained by the investigational site as local commercial product in certain countries if allowed by local regulations. In these cases, products may be a different pack size/potency than listed in the tables. These products should be prepared/stored/administered in accordance with the package insert or Summary of Product Characteristics.

[b] Comparator may be supplied by BMS centrally or through site-standard prescribing procedure.

7.1 Treatments Administered

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

Table 7.1-1: Selection and Timing of Dose

Study Treatment	Unit Dose Strength(s)/Dosage Level(s)	Dosage Formulation Frequency of Administration	Route of Administration
BMS-986012	420 mg/560 mg	Day 1 Q3W/Q4W	IV
Nivolumab	360 mg/480 mg	Day 1 Q3W/Q4W	IV
Carboplatin	AUC 5 mg/mL/min	Day 1 Q3W – 4 cycles	IV
Etoposide	100 mg/m^2	Days 1, 2, 3 Q3W – 4 cycles	IV

Abbreviations: AUC = area under the curve; IV = intravenous; Q3W = every 3 weeks; Q4W = every 4 weeks.

When study drugs are to be administered on the same day, chemotherapy will be administered first (during induction phase only), followed by BMS-986012 (for Arm A participants only) and finally nivolumab. Participants will be treated for up to a maximum of 2 years or until disease progression (refer to Section 8.1.4 for treatment beyond disease progression), unacceptable toxicity, or participant withdrawal of consent, whichever comes first. Participants who continue to demonstrate clinical benefit after the maximum 2 years may receive therapy beyond that period after discussion with Sponsor Medical Monitor on a case-by-case basis.

7.1.1 BMS-986012 Dosing

Participants assigned to Arm A should receive BMS-986012 at a dose of 420 mg Q3W on Day 1 of each treatment for the first 4 cycles (induction) and at a dose of 560 mg Q4W for Cycle 5 and beyond over an approximately 60-minute infusion until progression, unacceptable toxicity, withdrawal of consent, completion of 24 months of treatment, or the study ends, whichever occurs first.

There will be no dose escalations or reductions of BMS-986012 allowed. Participants may be treated within a ± 3-day window.

Participants should be carefully monitored for infusion reactions during BMS-986012 administration. If an acute infusion reaction is noted, participants should be managed according to Section 7.7.4.

Doses of BMS-986012 may be interrupted, delayed, skipped, or discontinued depending on how well the participant tolerates the treatment.

For details on prepared drug storage, preparation, and administration, please refer to the respective IBs and/or Pharmacy Manual.

7.1.2 Nivolumab Dosing

Participants should receive nivolumab at a dose of 360 mg Q3W on Day 1 of each treatment for the first 4 cycles (induction) and at a dose of 480 mg Q4W for Cycle 5 and beyond over an

approximately 30-minute infusion until progression, unacceptable toxicity, withdrawal of consent, completion of 24 months of treatment, or the study ends, whichever occurs first. Participants should begin study treatment within 3 calendar days of randomization.

There will be no dose escalations or reductions of nivolumab allowed. Participants may be dosed within a ± 3-day window. Participants may be dosed no less than 19 days from the previous dose during the induction period or 25 days from the previous dose during the maintenance period. Premedications are not recommended for the first dose of nivolumab.

Participants should be carefully monitored for infusion reactions during nivolumab administration. If an acute infusion reaction is noted, participants should be managed according to Section 7.7.4.

Doses of nivolumab may be interrupted, delayed, skipped, or discontinued depending on how well the participant tolerates the treatment.

For details on prepared drug storage, preparation, and administration, please refer to the IBs and/or Pharmacy Manual.

Care must be taken to assure sterility of the prepared solution as the product does not contain any antimicrobial preservative or bacteriostatic agent.

7.1.3 Noninvestigational 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-IPs.

In this protocol, the non-IPs are:

- Carboplatin
- Etoposide

Carboplatin will be administered on Day 1 of each cycle for the first 4 cycles at a dose of AUC 5 mg/mL/min IV. Etoposide will be administered on Days 1, 2, and 3 for the first 4 cycles at a dose of 100 mg/m^2 IV.

Refer to locally approved product labels for carboplatin/etoposide details.

7.2 Method of Treatment Assignment

Study using IRT: All participants will be centrally randomized using an IRT. Before the study is initiated, each user will receive log-in information and directions on how to access the IRT. Randomization will be stratified based on the presence of liver metastases and ECOG PS 0 or 1.

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

Participants will be randomized to receive either Arm A or Arm B according to a computer-generated randomization scheme prepared by a Randomization Coordinator within the Drug Supply Management Department of BMS Research & Development (R&D).

During the screening visit, the investigative site will call into the enrollment option of the IRT designated by BMS for assignment of a 5-digit participant number that will be unique across all sites. Enrolled participants, including those not dosed, will be assigned sequential participant numbers starting with [redacted]. The participant identification number (PID) will ultimately be comprised of the site number and participant number. For example, the first participant screened (ie, enrolled) at site number 1 will have a PID of [redacted] Once it is determined that the participant meets the eligibility criteria following the screening visit, the investigative site will call the IRT to randomize the participant into the open dose panel.

7.3 Blinding

This is a randomized, open-label Phase 2 study. Access to randomized treatment codes will be restricted from BMS personnel (with exceptions noted below) prior to the interim analysis. At the time of and following the interim analysis, the Sponsor will no longer be blinded to randomized treatment codes.

Since this is an open-label study, blinding procedures are not applicable to global sites; however, the specific treatment to be taken by a participant will be assigned using an IRT, which treats open label studies as if they are blinded for the purpose of releasing randomization codes to BMS personnel. The site will contact the IRT prior to the start of study treatment administration for each participant. Only limited BMS personnel may have access to treatment information, until the interim analysis, if needed to help with safety evaluation. In addition, access to treatment codes may be provided to the DMC as specified per the DMC charter.

If treatment information needs to be obtained as recommended by the SMT based on emerging safety data from this Phase 2 study, additional limited designated staff of BMS R&D may access the treatment code at any time to address these needs. This limited BMS personnel may be allowed access to the treatment codes prior to the interim analysis, after appropriate documentation. The release of treatment information will not impact the data integrity of the study. Except as noted above, other members of BMS R&D will not have access to the treatment code until the interim analysis.

Designated staff of BMS R&D may obtain access to the randomization codes prior to the interim analysis to facilitate the bioanalytical analysis of PK samples and immunogenicity. A bioanalytical scientist in the Bioanalytical Sciences department of BMS R&D (or a designee in the external central bioanalytical laboratory) will also obtain access to the randomized treatment assignments in order to minimize unnecessary bioanalytical analysis of samples.

7.4 Dosage Modification

If AEs are considered to be related to study treatment (BMS-986012 or nivolumab or chemotherapy), every attempt must be made to attribute the individual study treatment to the AE, if possible, or to the combination regimen.

- For AEs that are deemed to be related to BMS-986012 or nivolumab ONLY by the treating physician, dose delays are permitted (see Section 7.4.1 and Section 7.4.2). Dose reductions are not permitted. The chemotherapy should continue as scheduled.
- For AEs that are deemed to be related to the chemotherapy ONLY by the treating physician, dose modifications are permitted according to local standard or local package insert. BMS-986012 or nivolumab administration should continue as scheduled.
- For AEs that are possibly related to the combination regimen (BMS-986012 and/or nivolumab PLUS chemotherapy), the most conservative toxicity management guidelines must be followed.
- If there is a delay in administration of study drug(s) due to toxicity, treatment with the other study agent(s) should continue as scheduled. Resumption of treatment should be at the next scheduled time point if criteria to resume treatment are met.

7.4.1 Nivolumab Dose Delay Criteria

Dose delay criteria apply for all drug-related AEs. Delay administration of nivolumab if any of the delay criteria in [redacted] are met.

- Any AE, laboratory abnormality, or intercurrent illness which, in the judgment of the investigator, warrants delaying the dose of study medication.
- Nivolumab should also be delayed during radiotherapy as specified in Section 7.7.2.1.

[redacted]

[redacted]

Participants who require delay of nivolumab should be re-evaluated weekly or more frequently if clinically indicated and resume nivolumab dosing when criteria to resume treatment are met. Continue tumor assessments per protocol even if dosing is delayed.

7.4.2 BMS-986012 Dose Delay Criteria

BMS-986012 administration should be delayed for the following

- Drug related AST or ALT > 3x and ≤ 5x upper limit of normal (ULN) or total bilirubin (T.bili) > 1.5x and ≤ 3x ULN, regardless of baseline value.
- Confirmed SARS-CoV-2 infection.
- Any other Grade ≥ 3 drug-related AE with the following exceptions:
  - Grade ≥ 3 drug-related elevations in amylase and/or lipase without signs or symptoms of pancreatitis.
  - Grade 3 pruritus.

Dose delay of BMS-986012 may occur in the setting of lower-grade toxicity if the investigator believes that it is in the interest of a participant's safety.

BMS-986012 should be delayed until criteria to resume treatment is met (see Section 7.4.5). Treatment with other study agents should not be delayed if a decision to delay BMS-986012 is made, unless the investigator otherwise determines that a delay is justified independent of the delay in BMS-986012 dosing.

Doses of BMS-986012 should also be delayed during radiotherapy as specified in Section 7.7.2.1.

7.4.3 Carboplatin/Etoposide Dose Delay

Carboplatin/etoposide therapy may be delayed for toxicity per investigator's discretion based on locally approved drug labels and institutional guidelines. However, dose delays > 6 weeks are not permitted for this protocol, unless discussed and approved by the Medical Monitor, and, for the purposes of this protocol, participants will be considered to have discontinued carboplatin/etoposide, and the rules outlined in Section 8.1.3 will apply.

7.4.4 Criteria to Resume Treatment with Nivolumab

Participants may resume treatment with nivolumab if they have completed AE management (ie, corticosteroid taper) or are on ≤ 10 mg prednisone or equivalent, and meet the requirements per [redacted]

Prior to re-initiating treatment in a participant with a dosing delay lasting > 6 weeks during induction phase or > 8 weeks during maintenance phase, the Medical Monitor (or designee) must be consulted. Continue tumor assessments per protocol even if dosing is delayed.

7.4.5 Criteria to Resume Treatment with BMS-986012

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

- Participants may resume treatment in the presence of Grade 2 fatigue
- Participants who have not experienced a Grade 3 drug-related skin AE may resume treatment in the presence of Grade 2 skin toxicity

Participants with confirmed SARS-CoV-2 infection may resume treatment after:

1) at least 10 days (20 days for severe/critical illness) have passed since symptoms first appeared, positive RT-PCR test result, or positive viral antigen test result,
2) resolution of acute symptoms (including at least 24 hours has passed since last fever without fever-reducing medications),
3) evaluation by the Investigator with confirmation that there are no sequelae that would place the participant at a higher risk of receiving investigational treatment, and
4) consultation by the Medical Monitor.

For suspected cases, treatment may also resume if SARS-CoV-2 infection is ruled-out and other criteria to resume treatment are met.

Prior to re-initiating treatment in a participant with a dosing delay lasting > 6 weeks during induction phase or > 8 weeks during maintenance phase, the Medical Monitor (or designee) must be consulted. Continue tumor assessments per protocol even if dosing is delayed.

7.4.6 Criteria to Resume Treatment with Carboplatin/Etoposide

Participants may resume treatment with carboplatin/etoposide per investigator's discretion based on locally approved drug labels and institutional guidelines.

7.5 Preparation/Handling/Storage/Accountability

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

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

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

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

For study drugs not provided by BMS and obtained commercially by the site, storage should be in accordance with the product label.

Please refer to the current version of the IBs and/or Pharmacy Manual for complete preparation, storage, and handling information.

Storage facilities for controlled substances must be securely locked and substantially constructed, with restricted access to prevent theft or diversion, as applicable by local regulations.

- Further guidance and information for final disposition of unused study treatment are provided in Appendix 2 and Pharmacy Manual.

7.5.1 Retained Samples for Bioavailability/Bioequivalence/Biocomparability

Not applicable.

7.6 Treatment Compliance

Study treatment compliance will be periodically monitored by drug accountability, as well as the participant's medical records and electronic case report form (eCRF). Study drug will be administered in the clinic by trained personnel. Drug accountability should be reviewed by the site study staff at each visit.

7.7 Concomitant Therapy

7.7.1 Prohibited and/or Restricted Treatments

Prohibited and/or restricted medications taken prior to study drug administration in the study are described below. Medications taken within 4 weeks (28 days) prior to study drug administration and up to 100 days during Safety Follow-up must be recorded on the eCRF.

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

- Immunosuppressive agents (including, but not limited to, calcineurin inhibitors, interleukin inhibitors, tumor necrosis factor alpha inhibitors).
- Immunosuppressive doses of systemic corticosteroids (except as stated in Section 7.7.3)
- Any concurrent systemic anti-neoplastic therapy (ie, chemotherapy, hormonal therapy, immunotherapy, or standard or investigational agents for treatment of SCLC)
- Any non-palliative radiation therapy. Radiation therapy administered with palliative intent (ie, for pain, bleeding, spinal cord compression, brain metastasis, new or impending pathologic fracture, superior vena-cava syndrome, or obstruction) is permitted.
- Any complementary medications (eg, herbal supplements or traditional Chinese medicines) intended to treat the disease under study. Such medications are permitted if they are used as supportive care.
- Any live/attenuated vaccine (eg, varicella, zoster, yellow fever, rotavirus, oral polio, and measles, mumps, rubella [MMR]) within 30 days of first treatment dose, during treatment, and until 100 days post last dose.
- Administration of investigational SARS-CoV-2 vaccines is not allowed during the study. Participants may receive authorized or approved SARS-CoV-2 vaccines while continuing on study treatment at the discretion of the Investigator.

- For carboplatin and etoposide prohibited and/or restricted medications, investigational sites should follow the locally approved labels and current institutional guidelines.

Any concomitant therapies must be recorded on the eCRF.

7.7.2 Other Restrictions and Precautions

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

7.7.2.1 Radiotherapy

At the discretion of the treating investigator, participants who achieve clinical benefit RECIST v1.1 criteria (see Appendix 6) during induction therapy in either arm may be offered prophylactic cranial irradiation if no brain metastases are observed on brain imaging. For participants with brain metastases at study entry that are stable upon completion of induction therapy, brain irradiation modalities (eg, whole brain radiation therapy, stereotactic radiosurgery, etc) may be offered at the discretion of the investigator.

Participants may also receive palliative radiation in nonmeasurable sites of disease as per local practices and investigators' discretion, after completion of the induction period, based on local practices and the investigator discretion.

During radiotherapy, participants should have BMS-986012 and/or nivolumab held. Radiation therapy should begin no sooner than 2 weeks after the most recent dose of BMS-986012 and/or nivolumab. Once all radiotherapy is completed, the next dose of BMS-986012 and/or nivolumab should be given no sooner than 2 weeks after the end of radiotherapy. Radiotherapy should be completed as quickly as possible, following institutional guidelines on safety, to avoid excessive delays in treatment of study agents.

7.7.2.2 Imaging Restriction and Precautions

It is the local imaging facility's responsibility to determine, based on participant attributes (eg, allergy history, diabetic history, and renal status), the appropriate imaging modality and contrast regimen per imaging study. Imaging contraindications and contrast risks are to be considered in this assessment. Participants with renal insufficiency are to be assessed as to whether or not they should receive contrast and if so, which contrast agent and dose is appropriate. Specific to MRI, participants with severe renal insufficiency (ie, estimated glomerular filtration rate < 30 mL/min/1.73 m^2) are at increased risk of nephrogenic systemic fibrosis; therefore, MRI contrast is contraindicated. In addition, participants may be excluded from MRI if they have tattoos, metallic implants, pacemakers, etc. This will be outlined in the image acquisition manual.

Gentle hydration before and after IV contrast should follow local standard of care. The ultimate decision to perform MRI in an individual participant in this study rests with the site radiologist, the investigator, and standards set by the local Ethics Committee.

7.7.3 Permitted Therapy

Participants are permitted the use of topical, ocular, intra-articular, intranasal, and inhalational corticosteroids (with minimal systemic absorption). Adrenal replacement steroid doses > 10 mg daily prednisone are permitted. A brief (less than 3 weeks) course of corticosteroids for prophylaxis (eg, contrast dye allergy) or for treatment of non-autoimmune conditions (eg, delayed-type hypersensitivity reaction caused by a contact allergen) is permitted. Steroids are also permitted as premedication for antiemetic purposes per institutional guidelines, as well as for the treatment of AEs as determined to be necessary by the investigator.

Prophylactic use of granulocyte-colony stimulating factor (G-CSF) is mandated starting from Cycle 1 and during the first 4 cycles of chemotherapy, ie, induction phase, for all participants aged >65 years and/or participants with additional risk factors as outlined in the NCCN guidelines, specifically persistent neutropenia and bone marrow involvement by tumor. Participants may also receive growth factors at any time during the whole treatment period (including granulocyte-colony stimulating factor and erythropoietin) at the discretion of the investigator per locally approved labels and institutional guidelines. Participants cannot receive growth factors prior to trial enrollment to meet protocol-specified inclusion and exclusion criteria, as noted under Inclusion Criteria 2, f, i.

Concomitant palliative and supportive care for disease-related symptoms (including bisphosphonates and receptor activator of nuclear factor kappa-B ligand inhibitors) are allowed.

Prior radiotherapy must have been completed before randomization and provided that Exclusion Criteria 1, e and f are met. See Section 7.7.2.1 for guidance on concomitant palliative radiotherapy.

Treatment of active SARS-CoV-2 infections or high-risk exposures, including use of investigational therapies, is allowed and should be discussed with the Medical Monitor.

7.7.4 BMS-986012 and Nivolumab Infusion-related Reactions

Since nivolumab and BMS-986012 contain only human immunoglobulin protein sequences, they are unlikely to be immunogenic and induce infusion or hypersensitivity reactions. However, if such a reaction were to occur, it might manifest with fever, chills, rigors, headache, rash, pruritus, arthralgias, hypotension, hypertension, bronchospasm, or other allergic-like reactions. All Grade 3 or 4 infusion reactions should be reported within 24 hours to the study Medical Monitor and reported as a serious AE (SAE) if it meets the criteria. Infusion reactions should be graded according to National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) v5.0 guidelines.

Pruritus as a sole manifestation should not be considered an infusion-related reaction. Specific treatment recommendations for pruritus management are listed in Section 7.7.5. Other general treatment recommendations are provided below and may be modified based on local treatment standards and guidelines, as appropriate:

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

- Remain at bedside and monitor participant until recovery from symptoms. The following prophylactic premedications are recommended for future infusions: diphenhydramine 50 mg (or equivalent) and/or acetaminophen/paracetamol 325 to 1,000 mg at least 30 minutes before additional nivolumab or BMS-986012 administrations.

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

- Stop the study drug infusion, begin an IV infusion of normal saline, and treat the participant with diphenhydramine 50 mg IV (or equivalent) and/or acetaminophen/paracetamol 325 to 1,000 mg; remain at bedside and monitor participant until resolution of symptoms. Corticosteroid and/or bronchodilator therapy may also be administered as appropriate. If the infusion is interrupted, then restart the infusion at 50% of the original infusion rate when symptoms resolve; if no further complications ensue after 30 minutes, the rate may be increased to 100% of the original infusion rate. Monitor participant closely. If symptoms recur, then no further study medication will be administered at that visit.

For future infusions, the following prophylactic premedications are recommended: diphenhydramine 50 mg (or equivalent) and/or acetaminophen/paracetamol 325 to 1,000 mg should be administered at least 30 minutes before nivolumab and/or BMS-986012 infusions. If necessary, corticosteroids (up to 25 mg of hydrocortisone or equivalent) may be used.

For Grade 3 or 4 symptoms (Grade 3: severe reaction, 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 study drug.
- Begin an IV infusion of normal saline and treat the participant as follows: Recommend bronchodilators, epinephrine 0.2 mg to 1 mg of a 1:1000 solution for intramuscular administration or 0.1 mg to 0.25 mg of a 1:10000 solution injected slowly for IV administration, and/or diphenhydramine 50 mg IV (or equivalent) with methylprednisolone 100 mg IV (or equivalent), as needed.
- Participant should be monitored until the investigator is comfortable that the symptoms will not recur.
- Investigators should follow their institutional guidelines for the treatment of anaphylaxis.
- Remain at bedside and monitor participant until recovery from symptoms.

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

Additional prophylactic medication to prevent future infusion reactions may be considered after discussion and agreement between investigator(s) and Sponsor/Medical Monitor.

7.7.5 Pruritus Management

Pruritus in participants treated with BMS-986012 is generally Grade 1 or 2, occurs during the first and second cycles on the day of infusion, and resolves after several days. The utility of antihistamines is unclear, and anecdotally steroids may be of use. Further work is being performed to understand the mechanism of action of pruritus, although this is a common AE in targeted therapy with an etiology that is often not understood. Approach to participant management should be in conjunction with a specialist, with various approaches such as antihistamines, topical corticosteroids, anesthetics, capsaicin, salicylic acid, and menthol.[42] Additional guidance in the management of pruritus and associated skin conditions of targeted therapies is available in Wu and Lacouture 2018.[43]

In addition, participants should be educated about this AE prior to receiving drug.

7.7.6 Management Algorithms for Nivolumab

I-O agents are associated with IMAEs that can differ in severity and duration from AEs caused by other therapeutic classes. Nivolumab is considered an I-O agent in this protocol. Early recognition and management of IMAEs associated with I-O agents may mitigate severe toxicity. Management algorithms have been developed from extensive experience with nivolumab to assist Investigators in assessing and managing the following groups of IMAEs:

- Gastrointestinal
- Renal
- Pulmonary
- Hepatic
- Endocrinopathies
- Skin
- Neurological
- Myocarditis

The algorithms recommended for the management of IMAEs in this protocol are in Appendix 5.

7.8 Treatment After the End of the Study

At the conclusion of the study, participants who continue to demonstrate clinical benefit will be eligible to receive BMS supplied study treatment for maximum treatment duration as specified in Section 7.1. Study treatment will be provided via an extension of the study, a rollover study

requiring approval by responsible health authority and ethics committee or through another mechanism at the discretion of BMS.

BMS reserves the right to terminate access to BMS supplied study treatment if any of the following occur: a) the study is terminated due to safety concerns; b) the development of the BMS-986012 is terminated for other reasons, including but not limited to lack of efficacy and/or not meeting the study objectives; c) the participant can obtain medication from a government sponsored or private health program. In all cases BMS will follow local regulations.

8 DISCONTINUATION CRITERIA

8.1 Discontinuation From Study Treatment

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

- Participant's request to stop study treatment. Participants who request to discontinue study treatment will remain in the study and must continue to be followed for protocol specified follow-up procedures. The only exception to this is when a participant specifically withdraws consent for any further contact with him/her or persons previously authorized by participant to provide this information
- Any clinical AE, laboratory abnormality or intercurrent illness which, in the opinion of the investigator, indicates that continued participation in the study is not in the best interest of the participant
- Termination of the study by Bristol-Myers Squibb (BMS)
- Loss of ability to freely provide consent through imprisonment or involuntarily incarceration for treatment of either a psychiatric or physical (eg, infectious disease) illness. (Note: Under specific circumstances and only in countries where local regulations permit, a participant who has been imprisoned may be permitted to continue as a participant. Strict conditions apply and BMS approval is required.)
- Documented radiographic progressive disease per RECIST v1.1 criteria, unless the participant meets criteria for treatment beyond progression.

Discontinuation of the study treatment for abnormal liver tests should be considered by the investigator when a participant meets 1 of the conditions outlined in Section 9.2.8 or if the investigator believes that it is in best interest of the participant.

If any of the study treatments is permanently discontinued for reasons other than disease progression, participants may continue with the remaining study treatments provided that no other dose-delay or discontinuation criteria are met and after consultation with the BMS Medical Monitor (or designee).

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

In the case of pregnancy, the investigator must immediately, within 24 hours of awareness of the pregnancy, notify the BMS Medical Monitor/designee of this event. In most cases, the study

treatment will be permanently discontinued in an appropriate manner (eg, dose tapering if necessary, for participant safety). Refer to Section 9.2.5 Pregnancy.

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

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

8.1.1 BMS-986012 Dose Discontinuation

BMS-986012 treatment should be permanently discontinued for the following:

- Grade ≥ 3 infusion-related reaction except for a Grade 3 infusion reaction that returns to Grade 1 in less than 6 hours (pruritus as a sole manifestation should not be considered an infusion-related reaction).
- Any drug-related Grade 4 nonhematologic toxicity AE or laboratory abnormality with the following exceptions:
  - Isolated Grade 4 electrolyte imbalances/abnormalities that are not associated with clinical sequelae and are corrected with supplementation/appropriate management within 72 hours of their onset
  - Grade 4 amylase or lipase elevations not associated with clinical or radiographic signs of pancreatitis
- Any drug-related liver function test abnormality that meets the following criteria require discontinuation:
  - AST or ALT > 5x ULN or T.bili > 3x ULN, regardless of baseline value*
  - Combination of AST or ALT and direct bilirubin meeting criteria for potential drug-induced liver injury (DILI; see Section 9.2.8)

*In most cases of AST or ALT > 5x ULN, study treatment will be permanently discontinued. If the investigator determines a possible favorable benefit-risk ratio that warrants continuation of study treatment, a discussion between the investigator and the BMS Medical Monitor/designee must occur and approval from Medical Monitor must be obtained prior to resuming therapy.

- Any dosing delay lasting > 6 weeks in induction period or > 8 weeks in maintenance period except:
  - Dosing interruptions to allow for prolonged steroid tapers to manage AEs for which no clear alternative cause is identified other than BMS-986012 are allowed.
  - Dosing interruptions > 6 weeks in induction period or > 8 weeks in maintenance period after last dose that occur for non-drug events for which a clear alternative cause is identified other than BMS-986012 may be allowed if approved by the BMS Medical Monitor.

  - Dose interruptions > 8 weeks to allow for completion radiotherapy as specified in Section 7.7.2.1. Tumor assessments should continue per protocol even if dosing is interrupted, and participants must otherwise meet the criteria for continued treatment at the time of re-initiation of study is considered.
- Any AE, laboratory abnormality, or intercurrent illness which presents a substantial clinical risk to the participant with continued BMS-986012 dosing, in the judgment of the investigator.

Any participant who develops > Grade 3 peripheral neuropathy attributed to BMS-986012 rather than carboplatin will require discontinuation of BMS-986012 if peripheral neuropathy does not return to Grade 1 or baseline upon adequate treatment.

8.1.2 Nivolumab Dose Discontinuation

Nivolumab treatment must be permanently discontinued per criteria in [redacted] in Section 7.4.

- Any event that leads to delay in dosing lasting > 6 weeks in induction period or > 8 weeks in maintenance period from the previous dose requires discontinuation, with the following exceptions:
  - Dosing delays to allow for prolonged steroid tapers to manage drug-related AEs are allowed.
  - Dosing delays lasting > 6 weeks in induction period or > 8 weeks in maintenance period from the previous dose that occur for non-drug-related reasons may be allowed if approved by the BMS Medical Monitor (or designee).

Prior to re-initiating treatment in a participant with a dosing delay lasting > 6 weeks in induction period or > 8 weeks in maintenance period, the BMS Medical Monitor (or designee) must be consulted. Tumor assessments should continue as per protocol even if dosing is delayed. Periodic study visits to assess safety and laboratory studies should also continue during such dosing delays.

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

8.1.3 Carboplatin or Etoposide Dose Discontinuation

Discontinuation of carboplatin and/or etoposide prior to administration of 4 cycles is permitted based on the investigator's assessment of the benefit and risk of continuing these therapies and on locally approved labels and institutional guidelines.

If both carboplatin and etoposide are discontinued for reasons other than disease progression, the following guidelines will apply:

- Discontinuation at Cycle 2: Participant will be taken off treatment and enter the safety and survival follow-up periods. Once in the Safety and Survival Follow-up, participants may receive additional therapies per the discretion of the investigator.
- Discontinuation at Cycles 3 or 4: If the first imaging evaluation shows clinical benefit (CR, PR, SD), participants may either continue to receive BMS-986012 and/or nivolumab and stop

carboplatin/etoposide treatment or can be taken off treatment and enter the safety and survival follow-up periods, at which time additional chemotherapy may be given at the discretion of the investigator. Participants who move into Safety and Survival Follow-up will no longer receive any study drug.

8.1.4 Treatment Beyond Disease Progression

Accumulating evidence indicates a minority of participants treated with immunotherapy may derive clinical benefit despite initial evidence of PD.[34,44,45,46]

Participants will be permitted to continue treatment beyond initial RECIST v1.1-defined progressive disease, assessed by the investigator up to a maximum of 24 months from date of first dose as long as they meet the following criteria:

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

Radiographic assessment/scan(s) should continue in accordance with the Section 2 Schedule of Activities until BICR-confirmed disease progression or treatment discontinuation, whichever occurs later, and should be submitted to the central imaging vendor.

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

For the participants who continue study therapy beyond progression, further progression is defined as an additional 10% increase in tumor burden with a minimum 5 mm absolute increase from time of initial disease progression. This includes an increase in the sum of diameters of all target lesions and/or the diameters of new measurable lesions compared to the time of initial disease progression. It is recommended that study treatment should be discontinued permanently upon documentation of further 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). Any new lesion considered non-measurable at the time of initial progression may become measurable and therefore included in the tumor burden if the longest diameter increases to at least 10 mm (except for pathological lymph nodes which must have a short axis of at least 15 mm). In situations where the relative increase in total tumor burden by 10% is solely due to inclusion of

new lesions which become measurable, these new lesions must demonstrate an absolute increase of at least 5 mm.

8.1.5 Post Study Treatment Study Follow-up

In this study, PFS is a key endpoint of the study. Post study follow-up is of critical importance and is essential to preserving participant safety and the integrity of the study. Participants who discontinue study treatment must continue to be followed (in this study or a rollover study) 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.

BMS may request that survival data be collected on all treated/randomized participants outside of the protocol defined window (Table 2-3). At the time of this request, each participant will be contacted to determine their survival status unless the participant has withdrawn consent for all contacts or is lost to follow-up.

8.2 Discontinuation From the Study

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

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

8.3 Lost to Follow-up

- All reasonable efforts must be made to locate participants to determine and report their ongoing status. This includes follow-up with persons authorized by the participant.
- Lost to follow-up is defined by the inability to reach the participant after a minimum of **three** documented phone calls, faxes, or emails as well as lack of response by participant to one registered mail letter. All attempts should be documented in the participant's medical records.
- If it is determined that the participant has died, the site will use permissible local methods to obtain date and cause of death.
- If investigator's use of third-party representative to assist in the follow-up portion of the study has been included in the participant's informed consent, then the investigator may use a

Sponsor retained third-party representative to assist site staff with obtaining participant's contact information or other public vital status data necessary to complete the follow-up portion of the study.

- The site staff and representative will consult publicly available sources, such as public health registries and databases, in order to obtain updated contact information.
- If after all attempts, the participant remains lost to follow-up, then the last known alive date as determined by the investigator should be reported and documented in the participant's medical records.

9 STUDY ASSESSMENTS AND PROCEDURES

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

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

If a participant shows pulmonary-related signs (hypoxia, fever) or symptoms (eg, dyspnea, cough, fever) consistent with possible pulmonary AEs, the participant should be immediately evaluated to rule out pulmonary toxicity, according to the suspected pulmonary toxicity management algorithm in Appendix 5.

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

9.1 Efficacy Assessments

Efficacy assessments for the anti-tumor activity of both arms will be based on tumor measurements, using RECIST v1.1.

9.1.1 Imaging Assessment for the Study

Central Image Collection and Full Read Analysis

Images will be submitted to a central imaging vendor for BICR at any time during the study. Prior to scanning the first participant, sites should be qualified and understand the image acquisition guidelines and submission process as outlined in the Imaging Manual provided by the central imaging vendor.

Screening and on-study images should be acquired as outlined in Section 2 Schedule of Activities.

Tumor assessments at other time points may be performed if clinically indicated and should be submitted to the central imaging vendor as soon as possible. Unscheduled CT/MRI should be submitted to the central imaging vendor. X-rays and bone scans that clearly demonstrate interval progression of disease, for example most commonly as unequivocal lesions that are unmistakably new since the prior CT/MRI, should be submitted to central imaging vendor. Otherwise, they do not need to be submitted centrally.

Methods of Measurement

Contrast-enhanced CT of the chest, abdomen, pelvis, and all other known and/or suspected sites of disease should be performed for tumor assessments. Images should be acquired with slice thickness of 5 mm or less with no intervening gap (contiguous). Every attempt should be made to image each participant using an identical acquisition protocol on the same scanner for all imaging time points. Tumor measurements should be made by the same investigator or radiologist for each assessment, whenever possible. Change in tumor measurements and tumor response to guide ongoing study treatment decisions will be assessed by the investigator using the RECIST v1.1 criteria.

If a participant has a contraindication for CT IV contrast, then a noncontrast CT of the chest and a contrast-enhanced MRI of the abdomen, pelvis, and other known/suspected sites of disease should be obtained.

If a participant has a contraindication for both MRI and CT IV contrasts, then a non-contrast CT of the chest and a non-contrast MRI of the abdomen, pelvis, and other known/suspected sites of disease should be obtained.

If a participant has a contraindication for MRI (eg, incompatible pacemaker) in addition to contraindication to CT IV contrast, then a noncontrast CT of the chest, abdomen, pelvis, and other known/suspected sites of disease is acceptable.

Use of CT component of a PET-CT scanner: Combined modality scanning such as with positron emission tomography (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 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 v1.1 measurements. However, if a site can document that the CT performed as part of a PET-CT is of identical diagnostic quality to a diagnostic CT (with IV and oral contrast), then the CT portion of the PET-CT can be used for RECIST v1.1 measurements. Note, however, that the PET portion of the CT introduces additional data which may bias an investigator if it is not routinely or serially performed.

Bone scan or PET scan are not adequate for assessment of RECIST v1.1 response in target lesions. In selected circumstances where such modalities are the sole modality used to assess certain non-target organs, those nontarget organs may be evaluated less frequently. For example, bone scans may need to be repeated only when complete response is identified in target disease or when progression in bone is suspected.

Bone scans may be collected per local standards, as clinically indicated.

MRI of brain (without and with contrast) should be acquired as outlined in Section 2 (Schedule of Activities). MRI is the preferred method of brain imaging but CT of the brain (without and with contrast) can be performed if MRI is contraindicated or unavailable.

9.1.1.1 Imaging and Clinical Assessment

Tumor assessments should continue even if dosing is delayed or discontinued; sites should not change the schedule of imaging due to a dose delay. Changes in tumor measurements and tumor responses will be assessed by the same investigator or designee using RECIST v1.1 criteria. Investigators will report the number and size of new lesions that appear while on study. The time point of tumor assessments will be reported on the eCRF based on the investigator's assessment using RECIST v 1.1 criteria (see Appendix 6 for specifics of RECIST v1.1 criteria to be used in this study). Assessments of PR and CR must be confirmed at least 4 weeks (28 days) after initial response. A BOR of SD requires a minimum of 35 days on study from randomization to the date of the first imaging assessment.

9.1.1.2 BICR Confirmation of Progression or Recurrence

Sites should submit all scans to the central imaging vendor on a rolling basis, throughout the duration of the study. BICR of scans will occur on a rolling basis, blinded to treatment arm, clinical data, and investigator assessment of submitted scans. When progression per RECIST v1.1 criteria is assessed by the investigator, the site will inform the central imaging vendor, in order for BICR assessment of progression to be performed. The BICR will be completed and the results provided to the site as specified in the imaging vendor documents, provided there are no pending imaging queries to the site. All details on the timelines and associated process requirements will be outlined in the Imaging Manual.

Participants whose progression is not confirmed by the BICR will be required to continue tumor assessments (if clinically feasible) according to the protocol-specified schedule, or sooner if clinically indicated. Also, if participants discontinue treatment without radiographic progression,

tumor assessments will continue according to the protocol-specified schedule, as noted in Section 2 (Schedule of Activities), until progression has been confirmed by BICR.

All study treatment decisions will be based on the investigator's assessment of tumor images and not on the BICR assessment.

9.1.2 Patient-reported Outcomes

The evaluation of patient-reported outcomes (PROs) is an increasingly important aspect of clinical efficacy in oncology trials. Such data provide an understanding of the impact of treatment from the participant's perspective and offer insights into participant experience that may not be captured through physician reporting.

Participants will be asked to complete the Lung Cancer Symptom Scale (LCSS), a single-item from the Functional Assessment of Chronic Therapy – General (FACIT GP5 item), the Patient Global Impression of Severity (PGIS), and the Patient Global Impression of Change (PGIC) at designated study visits. When possible, participants should complete the PRO measures prior to any other assessments or study procedures when they are being administered during study visits.

If exceptional circumstances preclude the continued administration of measures using planned modalities, then alternate administration methods may be required, after consultation with Sponsor or the Sponsor's representative.

9.1.2.1 Lung Cancer Symptom Scale

The LCSS is a measure of disease-related symptoms and quality of life suited to use in patients suffering from lung cancer.[47] It includes 6 items measuring loss of appetite, fatigue, coughing, shortness of breath, hemoptysis, and pain. Three additional items measure overall symptom burden, disease-related functional limitations, and quality of life. The questionnaire uses a 24-hour recall period, and responses for each item are captured using a 100-mm visual analog scale (VAS). Scores for individual items ranging from 0 (no symptomatology or highest quality of life) to 100 (worst symptomatology or quality of life) are derived by dividing the length of the line drawn from the lowest possible response to the participant's response by the length of the VAS and multiplying the resulting quotient by 100. An Average Symptom Burden Index (ASBI) score can be derived as the average of scores for the 6 symptom-related items, with a clinically meaningful change in ASBI score being defined as 10 points. Accordingly, a meaningful deterioration in symptoms as measured by the ASBI is reflected in a mean post-baseline score change ≥10 points.

9.1.2.2 FACIT GP5

The FACIT GP5 will be administered to assess the extent of perceived bother due to symptomatic AEs. Evidence exists for the validity of this item and its usefulness as an overall summary measure of burden due to symptomatic treatment toxicities.[48]

9.1.2.3 Patient Global Impression of Severity and Change

The PGIS and PGIC will be included as additional exploratory endpoints and will be used as anchor measures for assessing thresholds for meaningful change in score for the LCSS. The PGIS is a single item that assesses participants' perceptions of overall severity of cancer symptoms for

the past 7 days with a 5-level categorical scale with response options ranging from “none” to “very severe.” The PGIC assesses participants’ perceptions of overall change in symptom severity since before treatment and assesses whether or not participants feel such a change is meaningful. The PGIC uses a 7-item bidirectional Likert-type scale with response options ranging from “much worse” to “much improved.” Completion of the PGIC will begin with Cycle 2.

9.2 Adverse Events

The definitions of an AE or SAE can be found in Appendix 3.

AEs will be reported by the participant (or, when appropriate, by a caregiver or a surrogate).

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

Contacts for SAE reporting specified in Appendix 3.

9.2.1 Time Period and Frequency for Collecting AE and SAE Information

Appendix 1 in the IB represents the Reference Safety Information to determine expectedness of serious AEs for expedited reporting.

The collection of non-serious AEs (with the exception of non-serious AEs related to SARS-CoV-2 infection) should begin at initiation of study treatment.

All SAEs must be collected from the time of signing the consent, including those thought to be associated with protocol-specified procedures and within 100 days of discontinuation of dosing, except in cases where a study participant has started a new anti-neoplastic therapy. However, any SAE occurring after the start of a new treatment that is suspected to be related to study treatment by the investigator will be reported. For participants randomized and never treated with study drug, SAEs should be collected for 30 days from the date of randomization.

All SAEs and all AEs (SAEs and non-serious AEs) associated with confirmed or suspected SARS-CoV-2 infection must be collected from the date of the participant’s written consent until 100 days following discontinuation of dosing.

The investigator must report any SAE that occurs after these time periods and that is believed to be related to study drug or protocol-specified procedure, (eg, a follow-up [redacted]).

- Medical occurrences that begin before the start of study treatment but after obtaining informed consent will be recorded on the appropriate section of the CRF module.
- All SAEs will be recorded and reported to Sponsor or designee within 24 hours, as indicated in Appendix 3.
- The investigator will submit any updated SAE data to the sponsor or designee within 24 hours of updated information being available.

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

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

9.2.2 Method of Detecting AEs and SAEs

Adverse events can be spontaneously reported or elicited during open-ended questioning, examination, or evaluation of a participant. Care should be taken not to introduce bias when collecting AE and/or SAEs. Inquiry about specific AEs should be guided by clinical judgement in the context of known AEs, when appropriate for the program or protocol.

All nonserious AEs (not only those deemed to be treatment-related) should be collected continuously during the treatment period and for a minimum of 100 days following discontinuation of study treatment, except in cases where a study participant has started a new anti-neoplastic therapy. However, any AE occurring after the start of a new treatment that is suspected to be related to study treatment by the investigator will be reported.

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

9.2.3 Follow-up of AEs and SAEs

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

After the initial AE/SAE report, the investigator is required to proactively follow each participant at subsequent visits/contacts. All SAEs, and non-serious AEs of special interest (as defined in Section 9.2), and AEs (SAEs and non-serious AEs) associated with confirmed or suspected SARS-CoV-2 infection will be followed until resolution, until the condition stabilizes, until the event is otherwise explained, or until the participant is lost to follow-up (as defined in Section 8.3).

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

9.2.4 Regulatory Reporting Requirements for SAEs

- Prompt notification by the investigator to the Sponsor of SAEs is essential so that legal obligations and ethical responsibilities towards the safety of participants and the safety of a product under clinical investigation are met.

- An investigator who receives an investigator safety report describing SAEs or other specific safety information (eg, summary or listing of SAEs) from the Sponsor will file it along with the Investigator's Brochure and will notify the IRB/IEC, if appropriate according to local requirements.

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

9.2.5 Pregnancy

If, following initiation of the study treatment, it is subsequently discovered that a participant is pregnant or may have been pregnant at the time of study exposure, including during at least for 6 months after study product administration, the investigator must immediately notify the BMS Medical Monitor/designee of this event and complete and forward a Pregnancy Surveillance Form to BMS Designee within 24 hours of awareness of the event and in accordance with SAE reporting procedures described in Appendix 3.

If the investigator determines a possible favorable benefit/risk ratio that warrants continuation of study treatment, or re-initiation of study treatment, a discussion between the investigator and the BMS Medical Monitor/designee must occur.

Protocol-required procedures for study discontinuation and follow-up must be performed on the participant.

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

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

If any sexual activity (eg, vaginal, anal, oral) has occurred between a male participant and a pregnant partner(s) without the use of a condom during and at least for 6 months after the last dose of chemotherapy (ie, carboplatin and etoposide), the information should be reported to the Sponsor or designee, even if the male participant has undergone a successful vasectomy.

In order for Sponsor or designee to collect any pregnancy surveillance information from the female partner, the female partner(s) must sign an informed consent form for disclosure of this information. Information on the pregnancy will be collected on the Pregnancy Surveillance Form.

9.2.6 Laboratory Test Result Abnormalities

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

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

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

9.2.7 Immune-mediated Adverse Events

IMAEs 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 participant's case report form.

9.2.8 Potential Drug-induced Liver Injury

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

Potential drug induced liver injury is defined as:

1) AT (ALT or AST) elevation > 3 times ULN

AND

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

AND

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

9.2.9 Other Safety Considerations

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

9.3 Overdose

For this study, any dose of BMS-986012 or nivolumab greater than 420 mg or 360 mg Q3W during induction therapy or any dose of BMS-986012 or nivolumab greater than 560 mg or 480 mg Q4W in maintenance therapy, respectively, within a 24-hour time period will be considered an overdose.

In the event of an overdose, the investigator should:

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

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

9.4 Safety

Planned time points for all safety assessments are listed in the Schedule of Activities.

Safety assessments will be based on reported AEs and the measurement results of vital signs, ECG, physical examinations, and clinical laboratory tests. A local laboratory will perform the clinical laboratory tests and will provide reference ranges for these tests. Both AEs and laboratory tests will be graded using the NCI CTCAE v5.0.

In case study participants may not be able to come to the investigational site for the assessment of vital signs, ECG, physical examinations and clinical laboratory tests due to public health emergency (eg, Covid-19 pandemic), alternative locations for local assessments would be permitted.

9.4.1 Physical Examinations

Refer to the Schedule of Activities (Section 2).

9.4.2 Vital Signs

Refer to the Schedule of Activities (Section 2).

9.4.3 Electrocardiograms

Refer to the Schedule of Activities (Section 2) for timing of ECG assessments for safety. The investigators will review the 12-lead ECGs using their site's standard ECG machines throughout the study.

9.4.4 Clinical Safety Laboratory Assessments

- Investigators must document their review of each laboratory safety report.
- All clinical safety laboratory assessments will be performed locally per the Schedule of Activities (Section 2)

Results of clinical laboratory tests performed on Day -1 must be available prior to dosing.

Table 9.4.4-1: Clinical Laboratory Assessments

Hematology - Complete Blood Count	
Hemoglobin	
Hematocrit	
Total leukocyte count, including differential	
Platelet count	
CD4 count (at screening and as clinically indicated for known HIV-positive participants)	
Chemistry	
Aspartate aminotransferase Alanine aminotransferase Total bilirubin Direct bilirubin (reflex if total bilirubin is abnormal) Alkaline phosphatase Lactate dehydrogenase Creatinine Blood urea nitrogen or serum urea Uric acid Fasting glucose Amylase (screening and as clinically indicated) Lipase (screening and as clinically indicated)	Total protein Albumin - screening only Sodium Potassium Chloride Calcium Phosphorus Magnesium Creatine kinase Creatinine clearance - screening only Thyroid-stimulating hormone (TSH), free T3 and free T4 - screening TSH, with reflexive free T3 and freeT4 if TSH is abnormal - on treatment
Urinalysis	
Protein	
Glucose	
Blood	
Leukocyte esterase	
Specific gravity	
pH	
Microscopic examination of the sediment if blood, protein, or leukocytes esterase are positive on the dipstick	
Serology	
Hepatitis B/C (hepatitis B surface antigen, hepatitis C virus (HCV) antibody, or HCV ribonucleic acid) at screening only. Human immunodeficiency virus (HIV)-1 and HIV-2 antibody (at screening, if mandated by local requirement [see Appendix 8])	
Other Analyses	
Pregnancy test (women of childbearing potential only; minimum sensitivity 25 IU/L or equivalent units of human chorionic gonadotropin)	
Follicle stimulating hormone screening - only required to confirm menopause in women < age 55)	

9.4.5 Imaging Safety Assessment

Not applicable.

9.5 Pharmacokinetics

PK of BMS-986012 and nivolumab will be derived from serum concentration versus time data. Table 9.5-1 provides a detailed sampling schedule for PK and immunogenicity measurements for BMS-986012 and nivolumab for participants in Arm A. Table 9.5-2 provides a detailed sampling schedule for PK and immunogenicity measurements for nivolumab for participants in Arm B. All on-treatment PK time points are intended to align with days on which study drug is administered. Further details of sample collection, processing, and shipment will be provided in the Laboratory Manual.

Serum concentration analysis for BMS-986012 and nivolumab will be performed by validated bioanalytical methods. Bioanalytical samples designated for assessments (eg, immunogenicity, PK, or biomarker) from the same collection time point may be used interchangeably for analyses, if required (including, but not limited to, insufficient volume for complement assessment, to follow-up on suspected immunogenicity-related AE, etc).

Additionally, residual bioanalytical samples will be archived and may be used for potential exploratory bioanalysis (including, but not limited to, analysis of drug-ADA immune complexes, metabolite analyses, etc) and/or for additional method purposes (including, but not limited to, cross-validation, ADA/PK selectivity, cut point, etc).

In case study participants may not be able to come to the investigational site for PK and immunogenicity sample collection due to public health emergency (eg, Covid-19 pandemic), the Sponsor Medical Monitor should be contacted to discuss the best course of action.

Table 9.5-1: Pharmacokinetic and Immunogenicity Sampling Schedule for Arm A

Study Day of Sample Collection (1 cycle = 21 days for first 4 cycles and 1 cycle = 28 days from Cycle 5 onward)	Event	Time Relative to BMS-986012 Dose (hr:min)	BMS-986012 PK Serum Sample	BMS-986012 IMG Serum Sample	Nivolumab PK Serum Sample	Nivolumab IMG Serum Sample
Cycle 1 Day 1	Predose[a]	0:00	X	X	X	X
	EOI[b]	[b]	X		X	
Cycle 1 Day 8		168:00	X		X	
Cycle 1 Day 15		336:00	X		X	
Cycle 2 Day 1	Predose[a]	0:00	X	X	X	X
Cycle 3 Day 1	Predose[a]	0:00	X		X	
Cycle 4 Day 1	Predose[a]	0:00	X	X	X	X
Cycle 5 Day 1	Predose[a]	0:00	X		X	
	EOI[b]	[b]	X		X	
Every 4 cycles starting at Cycle 6 Day 1 until Cycle 26 Day 1	Predose[a]	0:00	X	X	X	X
Follow-up Period[c]						
Follow-up 30 day	FU1		X	X	X	X
Follow-up 60 day	FU2		X	X	X	X
Follow-up 100 day	FU3		X	X	X	X

Abbreviations: PK = pharmacokinetic; IMG = immunogenicity; EOI = end of infusion; FU = follow-up.

[a] Predose samples should be collected just before the administration of the first study drug (chemotherapy for induction treatment and BMS-986012 for maintenance treatment) on that day (preferably within 30 minutes). If it is known that a dose is going to be delayed, then the predose sample should be collected just prior to the delayed dose. However, if a predose sample is collected but the dose is subsequently delayed, an additional predose sample should not be collected.

[b] EOI = end of infusion, PK samples for both BMS-986012 and nivolumab should be taken immediately prior to nivolumab EOI, preferably within 2 minutes prior to EOI. The EOI occurs when the entire nivolumab dose in the infusion bag is administered to the patient. If diluent is used to flush the dose remaining in the infusion line, then the EOI will occur when there is no dose is remaining in the infusion line after a flush. If the EOI is delayed beyond the nominal infusion duration (30 minutes), the collection of this sample should also be delayed accordingly. EOI samples may not be collected from the same IV access as the drug was administered.

[c] If a participant discontinues study drug treatment during the treatment/sampling period, they will move to sampling at the follow-up visits.

Table 9.5-2: Pharmacokinetic and Immunogenicity Sampling Schedule for Arm B

Study Day of Sample Collection (1 cycle = 21 days for first 4 cycles and 1 cycle = 28 days from Cycle 5 onward)	Event	Time Relative to Nivolumab Dose (hr:min)	Nivolumab PK Serum Sample	Nivolumab IMG Serum Sample
Cycle 1 Day 1	Predose[a]	0:00	X	X
	EOI[b]	[b]	X	
Cycle 1 Day 8		168:00	X	
Cycle 1 Day 15		336:00	X	
Cycle 2 Day 1	Predose[a]	0:00	X	X
Cycle 3 Day 1	Predose[a]	0:00	X	
Cycle 4 Day 1	Predose[a]	0:00	X	X
Cycle 5 Day 1	Predose[a]	0:00	X	
	EOI[b]	[b]	X	
Every 4 cycles starting at Cycle 6 Day 1 until Cycle 26 Day 1	Predose[a]	0:00	X	X
Follow Up Period[c]				
Follow-up 30 day	FU1		X	X
Follow-up 60 day	FU2		X	X
Follow-up 100 day	FU3		X	X

Abbreviations: PK = pharmacokinetic; IMG = immunogenicity; EOI = end of infusion; FU = follow-up.

[a] Predose samples should be collected just before the administration of the first study drug (chemotherapy for induction treatment and nivolumab for maintenance treatment) on that day (preferably within 30 minutes). If it is known that a dose is going to be delayed, then the predose sample should be collected just prior to the delayed dose. However, if a predose sample is collected but the dose is subsequently delayed, an additional predose sample should not be collected.

[b] EOI = end of infusion, a PK sample should be taken immediately prior to the EOI, preferably within 2 minutes prior to the EOI. The EOI occurs when the entire nivolumab dose in the infusion bag is administered to the patient. If diluent is used to flush the dose remaining in the infusion line, then the EOI will occur when there is no dose is remaining in the infusion line after a flush. If the EOI is delayed beyond the nominal infusion duration (30 minutes), the collection of this sample should also be delayed accordingly. EOI samples may not be collected from the same IV access as the drug was administered.

[c] If a participant discontinues study drug treatment during the treatment/sampling period, they will move to sampling at the follow-up visits.

9.6 Pharmacodynamics

Pharmacodynamic measures will be based on select biomarker samples collected as described in Section 9.8 (in the form of biomarker assessments) and may be assessed for associations with clinical outcomes. There will be 4 types of specimens obtained for biomarker testing: [redacted]. The sample subtypes and testing plans associated with each are described in Section 9.8. Complete instructions on the collection, processing, handling, and shipment of all samples described herein will be provided in a separate Laboratory Manual.

Exploratory analysis of these biomarkers will assess pharmacodynamic changes following treatment. For more details about biomarkers, please see Section 9.8 (Biomarkers).

9.7 Pharmacogenomics

Pharmacogenomics assessments include [redacted] and [redacted] analysis, as described in Section 9.8 (Biomarkers). The final disposition of samples will be conducted per local regulations.

9.7.1 ADME Sampling

Not applicable.

9.8 Biomarkers

Biomarkers are increasingly playing a key role in the development of cancer therapeutics. By evaluating treatment-induced changes in molecular markers measured in [redacted], the activity of experimental agents may be assessed, and the details of their mechanisms of action may be elucidated. To explore potential predictive markers for clinical response to BMS-986012, 3 types of specimens may be obtained from all participants for biomarker testing: [redacted] In this study, [redacted] samples may be collected at baseline, whereas [redacted] samples will be collected at baseline and on-treatment to identify markers associated with clinical activity and MOA of BMS-986012 in combination with chemotherapy plus nivolumab. The pharmacodynamic changes between baseline and on-treatment measures will also be monitored and evaluated for associations with PK data and AEs.

The biomarker sampling schedule is provided in Table 9.8-1. Further details of sample collection, processing, and shipment will be provided in the Laboratory Manual. Biomarker assessments may be shared with the Investigators at the end of study and/or during Investigator meetings in a summarized fashion.

[redacted] and biomarkers collections (Table 9.8.4-1) may be retained for additional research purposes. See Section 9.8.4 (Additional Research Collection).

In case study participants may not be able to come to the investigational site for Biomarkers sample collection due to public health emergency (eg, Covid-19 pandemic), the Sponsor Medical Monitor should be contacted to discuss the best course of action.

Table 9.8-1: Biomarker Sampling Schedule for Arms A and B

Study Day of Sample Collection[a] (1 cycle = 21 days for first 4 cycles and 1 cycle = 28 days from Cycle 5 onward)	**Event**	[redacted]				
Screening		X[b]	X	X	X	X
Cycle 1 Day 1	Predose[c]		X	X	X	X
Cycle 1 Day 8			X		X	X
Cycle 1 Day 15			X		X	X
Cycle 2 Day 1	Predose[c]		X		X	X
Cycle 3 Day 1	Predose[c]		X		X	X
Cycle 4 Day 1	Predose[c]		X		X	X
Cycle 5 Day 1	Predose[c]		X		X	X
Every 4 cycles starting at Cycle 6 Day 1 until Cycle 26 Day 1	Predose[c]		X		X	X
Upon progression[d]		X[e]	X		X	X
Follow Up Period[f]						
Follow-up 30 day	FU1		X		X	X
Follow-up 60 day	FU2		X		X	X
Follow-up 100 day	FU3		X		X	X

Abbreviations: [redacted]; FU = follow-up; Ig = immunoglobulins.

[a] Detailed instructions for the collection, processing, and shipping of each sample will be provided in the Laboratory Manual.

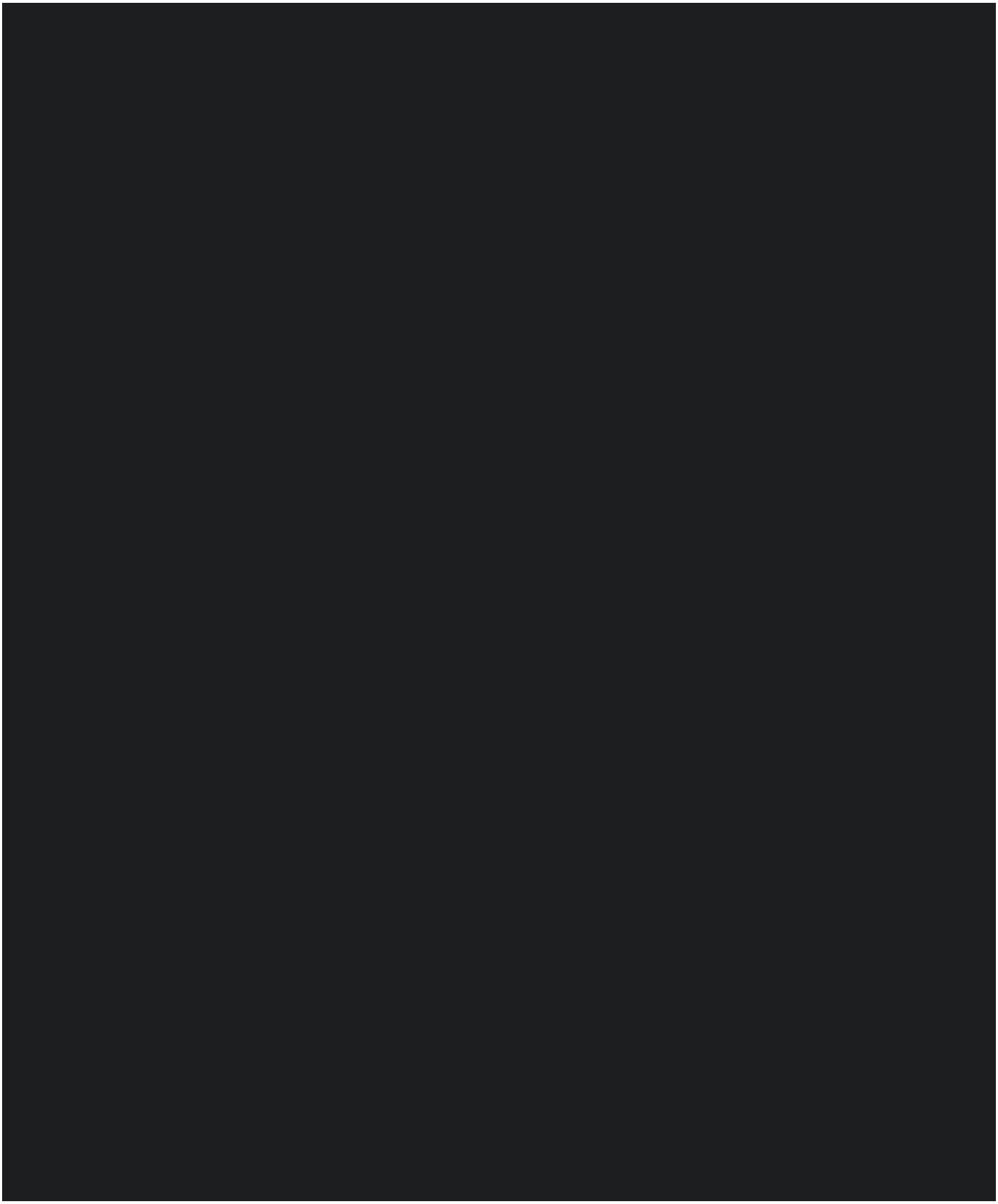
[b] Optional screening [redacted] for all participants except for those participating in the separate PET tracer sub-study, where [redacted] is mandatory. [redacted] sample submission is mandatory for all participants except those participating in the separate PET tracer sub-study where it is optional.

[c] Predose samples must be collected (within 30 minutes) prior to the administration of the first study drug (chemotherapy for induction treatment and BMS-986012 [Part A] or nivolumab [Part B] for maintenance treatment).

[d] Upon-progression samples should be collected within 30 days of documented disease progression unless they are already collected in another visit that falls under the defined window (eg, Follow-up 30 day or a prior scheduled visit).

[e] Upon-progression [redacted] is optional, but strongly encouraged, at time of disease progression.

[f] If a participant discontinues study drug treatment during the treatment/sampling period, the participant will move to sampling at the follow-up visits.



[redacted]

[redacted]

9.8.4 Additional Research Collection

This protocol will include residual sample storage for additional research (AR).

For All US sites:

Additional research is required for all study participants, except where prohibited by IRBs/ethics committees, or academic/institutional requirements. Where one or more of these exceptions occurs, participation in the additional research should be encouraged but will not be a condition of overall study participation.

- If the IRB/ethics committees and site agree to the mandatory additional research retention and/or collection, then the study participant must agree to the mandatory additional research as a requirement for inclusion in the study.
- If optional participation is permitted and approved, then the study participants may opt out of the additional research retention and/or collection.

For non-US Sites

Additional research is optional for all study participants, except where retention and/or collection is prohibited by local laws or regulations, ethics committees, or institutional requirements.

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

Sample Collection and Storage

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

- Residual samples from PK, immunogenicity, biomarker, [redacted] (see Table 9.8.4-1) will also be retained for additional research purposes.

Samples kept for future research will be stored at the BMS Biorepository in [redacted]

The manager of these samples will ensure they are properly used throughout their usable life and will destroy the samples at the end of the scheduled storage period, no longer than fifteen (15) years after the end of the study or the maximum allowed by applicable law.

Transfers of samples by research sponsor to third parties will be subject to the recipient's agreement to establish similar storage procedures.

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

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

Table 9.8.4-1: Residual Sample Retention for Additional Research Schedule

Sample Type	Timepoints for Which Residual Samples Will Be Retained
Pharmacokinetic	*All*
Immunogenicity	*All*
[redacted] biomarker samples	*All*
[redacted]	*All*

9.8.5 Immunogenicity Assessments

Samples will be collected from all participants as indicated in Table 9.5-1 and Table 9.5-2.

Immunogenicity samples will be analyzed for anti-BMS-986012 and anti-nivolumab antibodies by validated immunogenicity assays. Bioanalytical samples designated for assessments (eg, immunogenicity, PK, or biomarker) from the same collection time point may be used interchangeably for analyses, if required (including, but not limited to, insufficient volume for complement assessment, to follow-up on suspected immunogenicity related AE, etc). Additionally, residual bioanalytical samples will be archived and may be used for potential exploratory bioanalysis (including, but not limited to, analysis of drug-ADA immune complexes,

metabolite analyses, etc) and/or for additional method purposes (including, but not limited to, cross-validation, ADA/PK selectivity, cut point, etc).

9.8.6 Other Assessments

Not applicable.

9.9 Health Economics OR Medical Resource Utilization and Health Economics

Health economics/medical resource utilization and health economics parameters will not be evaluated in this study.

10 STATISTICAL CONSIDERATIONS

10.1 Sample Size Determination

The sample size of the study is based on assessing the primary efficacy objective. Based on the information observed in studies (IMpower133 and EA5161 studies), a piecewise exponential distribution is assumed in each treatment arm with a constant HR of 0.55 and control arm PFS rates of 35% and 14% at 6 and 12 months, respectively, for the sample size calculation. A total of 120 participants are planned to be randomized at 1:1 ratio into this study. Given an enrollment period of 18 months, minimum follow-up of 12 months, and 5% annual dropout rate, this can provide approximately 85% power with a 2-sided alpha of 0.05 when 102 PFS events have been observed. An interim analysis will be conducted when approximately 75% information (ie, 77 PFS events) is available. The stopping boundaries at the interim and final analyses will be based on the actual number of PFS events at the time of the analysis using Lan-DeMets alpha spending function with O'Brien-Fleming boundaries.

With 12 participants per arm for initial evaluation of safety, there will be above 80% probability to observe at least 1 occurrence of the safety event if the incident rate in the population is 13%. Considering participants might not complete the 8-week period, with 9 safety evaluable participants per arm there will be above 80% probability to observe at least 1 occurrence of the safety event if the incident rate in the population is 17%.

10.2 Populations for Analyses

For purposes of analysis, the following populations are defined:

Population	Description
Enrolled	All participants who sign informed consent and are registered into the Interactive Response Technology.
Randomized	All participants who were randomized to either treatment arm.
Treated	All participants who received at least 1 dose of any study medication.
Response-evaluable	All randomized participants with measurable disease at baseline and 1 of the following: (1) at least 1 post-baseline tumor assessment, (2) clinical progression, or (3) death.
Pharmacokinetic	All treated participants who have evaluable concentration-time data.

Population	Description
Immunogenicity	All treated participants who have baseline and at least 1 post-baseline immunogenicity assessment.
Biomarker	All treated participants with available biomarker data.

10.3 Statistical Analyses

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

A description of the participant population will be included in a statistical output report, including subgroups of age, gender, and race.

10.3.1 Efficacy Analyses

Endpoint	Statistical Analysis Methods
Primary	
The primary efficacy endpoint is progression free survival (PFS) by blinded independent central review (BICR), defined as the time from randomization to the date of the first documented tumor progression by BICR or death from any cause.	The PFS curve will be estimated using the Kaplan-Meier product-limit method. A log-rank test stratified by the presence of liver metastases and ECOG PS 0 or 1 will be used to compare PFS based on RECIST v1.1 by BICR between the 2 treatment arms. Hazard ratio and corresponding 2-sided 95% confidence intervals (CI) will be estimated using a Cox proportional hazard model, with treatment group as a single covariate, stratified by above factors to assist in interpretation of the PFS analysis.

Endpoint	Statistical Analysis Methods
Secondary	
PFS by investigator, defined as the time from randomization to the date of the first documented tumor progression by investigator or death from any cause.	Analysis of PFS based on investigator will be performed as above.
Objective response rate (ORR) is defined as the proportion of participants with a confirmed best overall response of complete response (CR) or partial response (PR) by Response Evaluation Criteria in Solid Tumors (RECIST) v1.1. Duration of response (DOR) is defined for participants who have a confirmed CR or PR as the date from first documented CR or PR per RECIST v1.1 to the date of the documentation of disease progression or death due to any cause, whichever is earlier. Time to response (TTR) is defined for participants who had a confirmed CR or PR as the time from the date of randomization to date of first documented CR or PR per RECIST v1.1. ORR, DOR, and TTR will be assessed per RECIST v1.1 both by BICR and by investigator assessment.	The ORR and its corresponding 95% exact CI will be calculated by Clopper-Pearson method for each arm. The median DOR will be estimated using the Kaplan-Meier method with corresponding 95% CI. Descriptive statistics and summaries will be presented for TTR.
Overall Survival (OS) is defined as the time from randomization to the time of death due to any cause.	OS will be estimated using the Kaplan-Meier techniques. A 2-sided 95% CI for median OS in each treatment group will be computed via the log-log transformation method.
Progression free survival rate (PFSR) by BICR and by investigator at 6 and 12 months, defined as the proportion of participants progression free at 6 and 12 months. Overall Survival Rate (OSR) at 12 and 24 months, defined as the proportion of participants surviving at 12 and 24 months.	PFSR and OSR will be calculated by the Kaplan-Meier method and corresponding 95% CI will be derived based on Greenwood formula by treatment.
Exploratory	
Will be described in the Statistical Analysis Plan finalized before database lock.	

Abbreviations: BICR = blinded independent central review; CI = confidence interval; CR = complete response; DOR = duration of response; ORR = objective response rate; OS = overall survival; OSR = overall survival rate; PFS = progression-free survival; PFSR = progression-free survival rate; PR = partial response; RECIST v1.1 = Response Evaluation Criteria in Solid Tumors version 1.1; TTR = time to response.

10.3.2 Safety Analyses

All safety analyses will be performed on the treated population.

Endpoint	Statistical Analysis Methods
Primary	
The primary safety endpoint of this study is the incidence of adverse events (AEs) at worst grade, serious adverse events (SAEs) at worst grade, AEs leading to discontinuation, and deaths.	Descriptive statistics of safety will be presented using National Cancer Institute Common Terminology Criteria for Adverse Events version 5.0 (NCI CTCAE v5.0). On-study AEs, treatment-emergent AEs, SAEs, and treatment-related SAEs will be tabulated using worst grade per NCI CTCAE v5.0 criteria by System Organ Class and Preferred Term.
Secondary	
Not applicable.	
Exploratory	
Will be described in the Statistical Analysis Plan finalized before database lock.	

Abbreviations: AE = adverse event; NCI CTCAE v5.0 = National Cancer Institute Common Terminology Criteria for Adverse Events version 5.0; SAE = serious adverse event.

10.3.3 Other Analyses

PK, pharmacodynamic, and biomarker exploratory analyses will be described in the SAP finalized before database lock. The PPK analysis will be presented separately from the main clinical study report.

Endpoint	Statistical Analysis Methods for Biomarkers
Primary	
Not applicable.	
Secondary	
The immunogenicity of BMS-986012 will be measured by assessment of the presence or absence of specific anti-drug antibodies (ADAs) to BMS-986012. The incidence of positive ADAs will be calculated.	Frequency distribution of baseline ADA-positive participants and ADA-positive participants after initiation of the treatment will be presented.
Exploratory	
Will be described in the statistical analysis plan finalized before database lock	

Abbreviation: ADA = antidrug antibody.

10.3.4 Interim Analyses

10.3.4.1 Interim Analysis for Efficacy

One interim analysis is planned for PFS, which is expected to occur when approximately 75% of the information (ie, 77 PFS events) is available. This is expected at approximately 19 months after the start of enrollment assuming 18 months of enrollment. This analysis will use a prespecified HR cutoff provided by the Sponsor to determine the initial efficacy signal by an independent DMC. The hypothesis will be tested to ensure trial-wide overall control of Type-I error at 5%. Demonstration of superiority will not stop the trial as further follow-up is needed to test the primary

objective and explore additional hypotheses. There is no analysis for futility at this interim analysis.

The Statistical Analysis Plan will further describe the planned interim analyses.

10.3.4.2 Bayesian Continuous Monitoring for Safety

A Bayesian continuous monitoring framework[49] will be utilized to detect safety signals that occur during the study that may lead to any change in the study conduct. Incidence rates of TRAEs of Grade 3 to 4 as assessed by the Investigator within an 8-week safety follow-up period will also be evaluated in reference to a potential 60% TRAEs of Grade 3 to 4, which is close to the incidence rate observed in atezolizumab and durvalumab studies.[6,11]

For aggregate safety data for both arms, the Bayesian safety monitoring boundaries are established using a noninformative prior, Beta(0.5, 0.5). The posterior distribution is Beta(0.5+n, 0.5+(m-n)), where n and m are the number of TRAEs observed out of the total number of evaluable participants. A participant is considered evaluable if they have either experienced an event or was followed for 8 weeks without an event. The stopping criterion function is defined as the posterior probability of (TRAEs > 60%|data) > 0.75. This criterion is not binding; however, it may be used to pause enrollment in this arm when there is greater than a 75% probability that the toxicity rate is over 60%, corresponding to a final boundary (at or above) of 17 out of 24 total participants. The boundaries are shown in Table 10.3.4.2-1 below.

Table 10.3.4.2-1: Safety Monitoring Boundary

Number of Evaluable Participants (Cumulative)	Safety Boundary (Number with Treatment-related Adverse Events Observed)
4-5	4
6	5
7-8	6
9	7
10-11	8
12	9
13-14	10
15-16	11
17	12
18-19	13
20	14
21-22	15
23	16
24	17

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12 APPENDICES

APPENDIX 1 ABBREVIATIONS AND TRADEMARKS

Term	Definition
ADA	anti-drug antibody
ADCC	antibody-dependent cellular cytotoxicity
ADCP	antibody-dependent cellular phagocytosis
AE	adverse event
AIDS	Acquired Immune Deficiency Syndrome
ALT	alanine aminotransferase
anti-fuic-GM1	anti-fucosyl-GM1
ART	antiretroviral therapy
ASBI	Average Symptom Burden Index
AST	aspartate aminotransferase
AUC	area under the curve
Bcl-xL	B-cell lymphoma-extra large
BICR	blinded independent central review
BMS	Bristol-Myers Squibb
BOR	best overall response
BSA	body surface area
BTLA	B and T-lymphocyte attenuator
Cavg	average serum concentration
Cavgss	average serum concentration at steady state
CD28	Cluster of Differentiation 28
CDC	complement-dependent cytotoxicity
cHL	classical Hodgkin lymphoma
CHO	Chinese hamster ovary
CI	confidence interval
Cmax	maximum serum concentration
Cmin	trough serum concentration
CMV	cytomegalovirus
CNS	central nervous system
CPS	combined positive score

Term	Definition
CR	complete response
CT	computed tomography
CTC	circulating tumor cel
CTCAE	Common Terminology Criteria for Adverse Events
ctDNA	circulating tumor deoxyribonucleic acid
CTLA-4	cytotoxic T-lymphocyte-associated protein 4
D	day
DILI	drug-induced liver injury
DLT	dose-limiting toxicity
DMC	Data Monitoring Committee
DNA	deoxyribonucleic acid
DOR	duration of response
EC50	half maximal effective concentration
ECG	electrocardiogram
ECGs	electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	electronic case report form.
EOI	end of infusion
EORTC QLQ-C30	European Organization for Research and Treatment of Cancer Quality-of-life Questionnaire Core 30
EOT	end of treatment
EQ-5D-5L	Euroqol questionnaire - 5 Dimensions - 5 Levels
E-R	exposure-response
ESMO	European Society of Medical Oncology
ES-SCLC	extensive-stage small cell lung cancer
FACIT GP5	A single item from the Functional Assessment of Chronic Therapy – General
Fc	fragment crystallizable
[redacted]	
FDA	Food and Drug Administration
FFPE	formalin fixed paraffin embedded

Term	Definition
FIH	first-in-human
FSH	follicle Stimulating Hormone
FU	follow-up
fuc-GM1	Fucosyl-GM1
HBsAg	Hepatitis B surface antigen
HBV	hepatitis B virus
hCG	human chorionic gonadotropin
HCV	hepatits C virus
HIV	human immunodeficiency virus
HR	hazard ratio
IB	Investigator Brochures
IC50	half maximal inhibitory concentration
ICF	informed consent form
ICOS	inducible costimulatory molecule
IEC	independent ethics committee
IFN	interferon
IgG1	immunoglobulin G1
[redacted]	
IL	interleukin
IMAE	immune-mediated adverse event
IMG	immunogenicity
I-O	immuno-oncology
IP/IMP	Investigational [Medicinal] Product
IRB	Institutional Review Board
IRT	interactive response technology
IV	intravenous/intravenously
LCSS	Lung Cancer Symptom Scale
mAb	monoclonal antibody
MMR	measles, mumps, rubella
MRI	magnetic resonance imaging

Term	Definition
NCCN	National Comprehensive Cancer Network
NCI	National Cancer Institute
NK	natural killer
NSCLC	non-small cell lung cancer
ORR	<overall/objective> response rate
OS	overall survival
OSR	overall survival rate
PBCM	peripheral blood mononuclear cells
PBMC	peripheral blood mononuclear cells
PCI	prophylactic cranial irradiation
PD	progressive disease
PD-1	programmed cell death 1
PD-L1	programmed cell death ligand 1
PE	Physical Examination
PET	positron emission tomography
PFS	progression-free survival
PFSR	progression-free survival rate
PGIC	Patient Global Impression of Change
PGIS	Patient Global Impression of Severity
PID	participant indentification number
PK	pharmacokinetic
PPK	population PK
PR	partial response
PRO	patient-reported outcome
PS	performance status
Q2W	every 2 weeks
Q3W	every 3 weeks
Q4W	every 4 weeks
R&D	research& development
RCC	renal cell carcinoma

Term	Definition
RECIST	Response Evaluation Criteria in Solid Tumors
RNA	riboneucleic acid
RT-PCR	reverse transcriptase polymerase chain reaction
SAE	serious adverse event
SCCHN	squamous cell carcinoma of the head and neck
SCLC	small cell lung cancer
SD	stable disease
SMT	Safety Medical Team
SUV	standardized uptake value
TCR	T-cell receptor
[redacted]	
ULN	upper limit of normal
US	United Sates
VAS	visual analog scale
WOCBP	women of childbearing potential
WS	Worldwide Patient Safety

APPENDIX 2 STUDY GOVERNANCE CONSIDERATIONS

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

REGULATORY AND ETHICAL CONSIDERATIONS

GOOD CLINICAL PRACTICE

This study will be conducted in accordance with:

- Consensus ethical principles derived from international guidelines including the Declaration of Helsinki and Council for International Organizations of Medical Sciences (CIOMS) International Ethical Guidelines Good Clinical Practice (GCP),
- as defined by the International Council on Harmonisation (ICH)
- in accordance with the ethical principles underlying European Union Directive 2001/20/EC
- United States Code of Federal Regulations, Title 21, Part 50 (21CFR50)
- applicable local requirements.

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

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

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

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

INSTITUTIONAL REVIEW BOARD/INDEPENDENT ETHICS COMMITTEE

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

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

COMPLIANCE WITH THE PROTOCOL AND PROTOCOL REVISIONS

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

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

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

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

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

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

FINANCIAL DISCLOSURE

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

INFORMED CONSENT PROCESS

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

The Sponsor or designee will provide the investigator with an appropriate sample ICF, which will include all elements required by ICH, GCP and applicable regulatory requirements. The sample ICF will adhere to the ethical principles that have their origin in the Declaration of Helsinki.

The investigator or his/her representative must:

- Obtain the IRB/IEC's written approval/favorable opinion of the written ICF and any other information to be provided to the participants, prior to the beginning of the study, and after any revisions are completed for new information.
- Provide a copy of the ICF and written information about the study in the language in which the participant is most proficient prior to clinical study participation. The language must be non-technical and easily understood.
- Explain the nature of the study to the participant and answer all questions regarding the study.
- Inform participant that his/her participation is voluntary. Participant will be required to sign a statement of informed consent that meets the requirements of 21 CFR 50, local regulations, ICH guidelines, Health Insurance Portability and Accountability Act (HIPAA) requirements, where applicable, and the IRB/IEC or study center.
- Allow time necessary for participant to inquire about the details of the study.
- Obtain an informed consent signed and personally dated by the participant and by the person who conducted the informed consent discussion.
- Include a statement in participant's medical record that written informed consent was obtained before participant was enrolled in the study and the date the written consent was obtained. The authorized person obtaining the informed consent must also sign the ICF.
- Re-consent participant to the most current version of the ICF(s) during his/her participation in the study, as applicable.

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

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

The ICF must also include a statement that BMS and local and foreign regulatory authorities have direct access to participant records.

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

BMS COMMITMENT TO DIVERSITY IN CLINICAL TRIALS

The mission of BMS is to transform patients' lives through science by discovering, developing, and delivering innovative medicines that help them prevail over serious diseases.

BMS is committed to doing its part to ensure that patients have a fair and just opportunity to achieve optimal health outcomes.

BMS is working to improve the recruitment of a diverse participant population with the goal that the clinical trial becomes more reflective of the real-world population and the people impacted by the diseases studied.

DATA PROTECTION, DATA PRIVACY, AND DATA SECURITY

BMS collects and processes personal data of study participants, patients, health care providers, and researchers for biopharmaceutical research and development to advance innovative, high-quality medicines that address the medical needs of patients. BMS ensures the privacy, protection, and confidentiality of such personal data to comply with applicable laws. To achieve these goals, BMS has internal policies that indicate measures and controls for processing personal data. BMS adheres to these standards to ensure that collection and processing of personal data are limited and proportionate to the purpose for which BMS collects such personal data. This purpose is clearly and unambiguously notified to the individual at the time of collection of personal data. In the true spirit of science, BMS is dedicated to sharing clinical trial information and data with participants, medical/research communities, the media, policy makers, and the general public. This is done in a manner that safeguards participant privacy and informed consent while respecting the integrity of national regulatory systems. Clinical trial data, health-related research, and pharmacovigilance activities on key-coded health data transferred by BMS across national borders is done in compliance with the relevant data protection laws in the country and GCP requirements.

BMS protects Personal Information with adequate and appropriate security controls as indicated under the data protection laws. To align with the recommended security standards, BMS has adopted internal security standards and policies to protect personal data at every stage of its processing.

To supplement these standards, BMS enters into Clinical Trial Agreements (CTAgs) with confidentiality obligations to ensure proper handling and protection of personal data by third parties accessing and handling personal data.

BMS takes unauthorized access and disclosure of Personal Information very seriously. BMS has adopted the security standards that include National Institute of Standards and Technology Cybersecurity Framework for studies in the US. BMS aligns with these standards to continuously assess and improve its ability to protect, detect, and respond to cyber attacks and other unauthorized attempts to access personal data. These standards also aid in mitigating possible adverse effects. Furthermore, BMS Information Technology has defined 6 principles to protect our digital resources and information:

1) Responsibilities of IT Personnel
2) Securing the BMS Digital Infrastructure
3) Identity and Access Management
4) External Partner Connections
5) Cyber Threat Detection and Response
6) Internal Cyber Incident Investigation

SOURCE DOCUMENTS

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

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

STUDY TREATMENT RECORDS

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

If	Then
Supplied by BMS (or its vendors):	Records or logs must comply with applicable regulations and guidelines and should include: • 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 participant, including unique participant 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/biocomparability, if applicable • dates and initials of person responsible for Investigational Product dispensing/accountability, as per the Delegation of Authority Form.
Sourced by site, and not supplied by BMS or its vendors (examples include IP sourced from the sites stock or commercial supply, or a specialty pharmacy)	The investigator or designee accepts responsibility for documenting traceability and study treatment integrity in accordance with requirements applicable under law and the SOPs/standards of the sourcing pharmacy.

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

CASE REPORT FORMS

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

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

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

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

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

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

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

MONITORING

Monitoring details describing strategy, including definition of study critical data items and processes (eg, risk-based initiatives in operations and quality such as risk management and mitigation strategies and analytical risk-based monitoring), methods, responsibilities, and requirements, including handling of noncompliance issues and monitoring techniques (central, remote, or on-site monitoring) are provided in the monitoring plan.

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

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

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

RECORDS RETENTION

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

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

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

RETURN OF STUDY TREATMENT

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

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

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

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

- Accountability and disposal records are complete, up-to-date, and available for the Monitor to review throughout the clinical trial period.

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

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

DISSEMINATION OF CLINICAL STUDY DATA

In order to benefit potential study participants, patients, healthcare providers and researchers, and to help BMS honor its commitments to study participants, BMS will make information about clinical research studies and a summary of their results available to the public as per regulatory and BMS requirements. BMS will post study information on local, national or regional databases in compliance with national and international standards for disclosure. BMS may also voluntarily disclose information to applicable databases.

CLINICAL STUDY REPORT

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

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

- Participant recruitment (eg, among the top quartile of enrollers)
- Involvement in trial design
- Other criteria (as determined by the study team)

SCIENTIFIC PUBLICATIONS

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

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

Authorship of publications at BMS is aligned with the criteria of the International Committee of Medical Journal Editors (ICMJE, www.icmje.org). Authorship selection is based upon significant

contributions to the study (ie, ICMJE criterion #1). Authors must meet all 4 ICMJE criteria for authorship:

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

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

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

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

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

ADVERSE EVENTS

Adverse Event Definition:

An Adverse Event (AE) is defined as any new untoward medical occurrence or worsening of a preexisting medical condition in a clinical investigation participant administered study treatment and that does not necessarily have a causal relationship with this treatment.

An AE can therefore be any unfavorable and unintended sign (such as an abnormal laboratory finding), symptom, or disease temporally associated with the use of study treatment, whether or not considered related to the study treatment.

Events Meeting the AE Definition

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

Events NOT Meeting the AE Definition

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

DEFINITION OF SAE

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

SERIOUS ADVERSE EVENTS

Serious Adverse Event (SAE) is defined as any untoward medical occurrence that, at any dose:
Results in death
Is life-threatening (defined as an event in which the participant was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe)
Requires inpatient hospitalization or causes prolongation of existing hospitalization (see NOTE below) 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 (e.g., 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 (e.g., lack of housing, economic inadequacy, caregiver respite, family circumstances, administrative reason) • admission for administration of anticancer therapy in the absence of any other SAEs (applies to oncology protocols)
Results in persistent or significant disability/incapacity
Is a congenital anomaly/birth defect
Is an important medical event (defined as a medical event(s) that may not be immediately life-threatening or result in death or hospitalization but, based upon appropriate medical and scientific judgment, may jeopardize the participant or may require intervention [e.g., medical, surgical] to prevent one of the other serious outcomes listed in the definition above.) Examples of such events include, but are not limited to, intensive treatment in an emergency room or at home for allergic bronchospasm; blood dyscrasias or convulsions that do not result in hospitalization.) Potential drug induced liver injury (DILI) is also considered an important medical event. (See Section 9.2.7 for the definition of potential DILI.)

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

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

EVALUATING AES AND SAES

Assessment of Causality

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

Follow-up of AEs and SAEs

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

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

All SAEs must be followed to resolution or stabilization.

REPORTING OF SAES TO SPONSOR OR DESIGNEE

- SAEs, whether related or not related to study treatment, and pregnancies must be reported to BMS (or designee) immediately within 24 hours of awareness of the event.

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

SAE Email Address: Refer to Contact Information list.

SAE Facsimile Number: Refer to Contact Information list.

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

APPENDIX 4 WOMEN OF CHILDBEARING POTENTIAL DEFINITIONS AND METHODS OF CONTRACEPTION

DEFINITIONS

Woman of Childbearing Potential (WOCBP)

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

Women in the following categories are not considered WOCBP

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

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

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

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.

End of Relevant Systemic Exposure

- End of relevant systemic exposure is the time point where the IMP or any active major metabolites has decreased to a concentration that is no longer considered to be relevant for

human teratogenicity or fetotoxicity. This should be evaluated in context of safety margins from the no-observed adverse effect level (NOAEL) or the time required for 5 half-lives of the IMP to pass.

METHODS OF CONTRACEPTION

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

Highly Effective Contraceptive Methods That Are <u>User Dependent</u> *Failure rate of <1% per year when used consistently and correctly.*[a]
• Combined (estrogen- and progestogen-containing) hormonal contraception associated with inhibition of ovulation and/or implantation (This method of contraception can only be used by WOCBP participants in studies where hormonal contraception is permitted by the study protocol)[b] – oral (birth control pills) – intravaginal (vaginal birth control suppositories, rings, creams, gels) – transdermal • Combined (estrogen-and progestogen-containing) hormonal contraception must begin at least 30 days prior to initiation of study therapy
• Progestogen-only hormonal contraception associated with inhibition of ovulation (This method of contraception can only be used by WOCBP participants in studies where hormonal contraception is permitted by the study protocol)[b] – oral – injectable • Progestogen-only hormonal contraception must begin at least 30 days prior to initiation of study therapy
Highly Effective Methods That Are User Independent
• Implantable progestogen-only hormonal contraception associated with inhibition of ovulation and/or implantation (This method of contraception can only be used by WOCBP participants in studies where hormonal contraception is permitted by the study protocol)[b] • Intrauterine device (IUD) • Intrauterine hormone-releasing system (IUS) (This method of contraception can only be used by WOCBP participants in studies where hormonal contraception is permitted by the study protocol) [b,c] • Bilateral tubal occlusion
• Vasectomized partner Having 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.

Male participants will be required to always use a latex or other synthetic condom during any sexual activity (eg, vaginal, anal, oral) with WOCBP; even if the participants have undergone a successful vasectomy or if their partner is already pregnant or breastfeeding.
• Sexual abstinence *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 treatment. 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.* • Continuous abstinence must begin at least 30 days prior to initiation of study therapy • It is not necessary to use any other method of contraception when complete abstinence is elected. • WOCBP participants who choose complete abstinence must continue to have pregnancy tests, as specified in Section 2. • Acceptable alternate methods of highly effective contraception must be discussed in the event that the WOCBP participants chooses to forego complete abstinence • Periodic abstinence (including but not limited to calendar, symptothermal, post-ovulation methods), withdrawal (coitus interruptus), spermicides only, and lactational amenorrhoea method (LAM) are not acceptable methods of contraception for this study.
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 treatment, 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 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

Less Than Highly Effective Contraceptive Methods That Are User Dependent *Failure rate of >1% per year when used consistently and correctly.*
• Male or female condom with or without spermicide. Male and female condoms cannot be used simultaneously • Diaphragm with spermicide • Cervical cap with spermicide • Vaginal Sponge with spermicide • Progestogen-only oral hormonal contraception, where inhibition of ovulation is not the primary mechanism of action (This method of contraception cannot be used by WOCBP participants in studies where hormonal contraception is prohibited)

Unacceptable Methods of Contraception
• Periodic abstinence (calendar, symptothermal, post-ovulation methods) • Withdrawal(coitus interruptus). • Spermicide only • Lactation amenorrhea method (LAM)

COLLECTION OF PREGNANCY INFORMATION

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

APPENDIX 5 MANAGEMENT ALGORITHMS FOR STUDIES UNDER CTCAE VERSION 5.0

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

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

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

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

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

GI Adverse Event Management Algorithm

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

Grade of Diarrhea/ Colitis (NCI CTCAE v5)	Management	Follow-up
Grade 1 Diarrhea: < 4 stools/day over baseline Colitis: asymptomatic	• Continue I-O therapy per protocol • Symptomatic treatment	• Close monitoring for worsening symptoms • Educate patient to report worsening immediately If worsens: • Treat as Grade 2 or Grade 3-4
Grade 2 Diarrhea: 4-6 stools per day over baseline; IV fluids indicated < 24 hrs; Limiting instrumental ADL Colitis: abdominal pain; blood in stool	• Delay I-O therapy per protocol • Symptomatic treatment	If improves to Grade 1: • Resume I-O therapy per protocol If persists > 5-7 days or recurs: • 0.5-1 mg/kg/day methylprednisolone or oral equivalent • When symptoms improve to Grade 1, taper steroids over at least 1 month, consider prophylactic antibiotics for opportunistic infections, and resume I-O therapy per protocol. If worsens or persists > 3-5 days with oral steroids: • Treat as Grade 3-4
Grade 3-4 Diarrhea (G3): ≥ 7 stools per day over baseline; IV fluids ≥24 hrs; limiting self care ADL Colitis (G3): severe abdominal pain, peritoneal signs G4: life-threatening, perforation	• Discontinue or delay I-O therapy per protocol* • 1 to 2 mg/kg/day methylprednisolone IV or IV equivalent • Add prophylactic antibiotics for opportunistic infections • Consider lower endoscopy	If improves: • Continue steroids until grade 1, then taper over at least 1 month If persists > 3-5 days, or recurs after improvement: • Add infliximab 5 mg/kg (if no contraindication) or other immunosuppressants. • Consider testing CMV for steroid refractory colitis Note: Infliximab should not be used in cases of perforation or sepsis

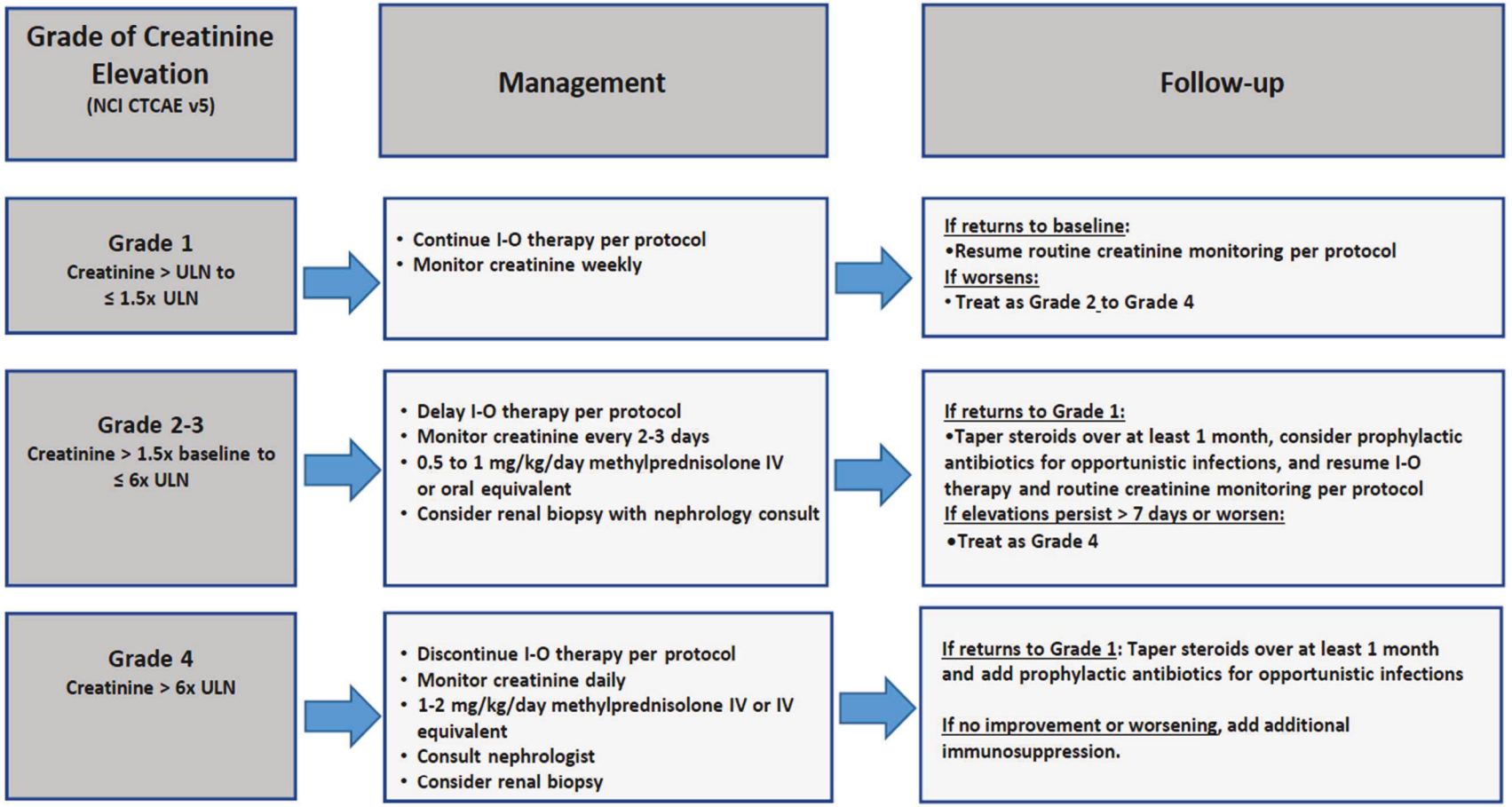
Patients on IV steroids may be switched to an equivalent dose of oral corticosteroids (eg, prednisone) at start of tapering or earlier, after sustained clinical improvement is observed. Lower bioavailability of oral corticosteroids should be taken into account when switching to the equivalent dose of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

* Discontinue for Grade 4 diarrhea or colitis. For Grade 3 diarrhea or colitis, 1) Nivolumab monotherapy: Nivolumab can be delayed. 2) Nivolumab+ Ipilimumab combination: Ipilimumab should be discontinued while nivolumab can be delayed. Nivolumab monotherapy can be resumed when symptoms improve to Grade 1. Please refer to protocol for dose delay and discontinue criteria for other combinations.

28-Sep-2020

Renal Adverse Event Management Algorithm

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

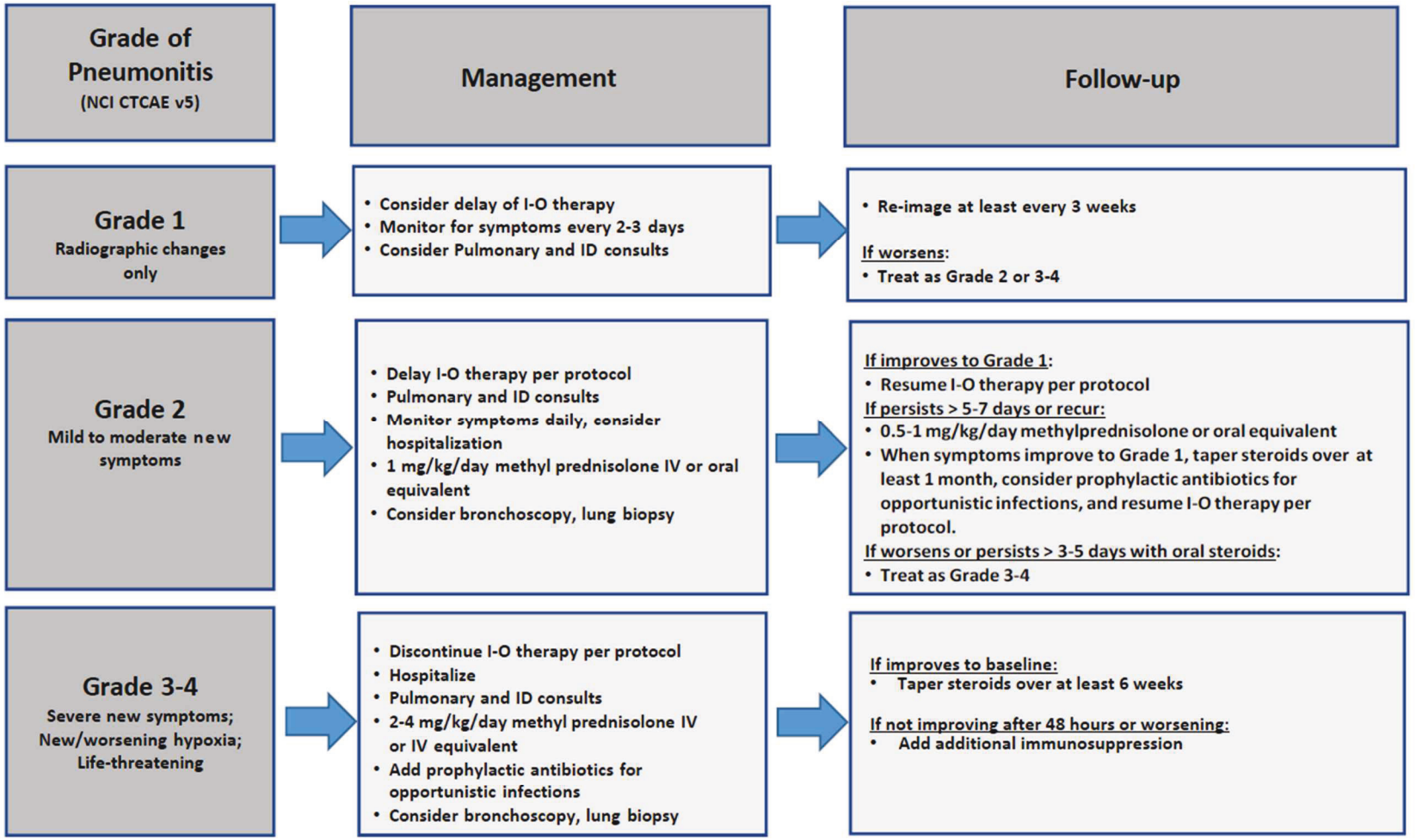


Patients on IV steroids may be switched to an equivalent dose of oral corticosteroids (eg, prednisone) at start of tapering or earlier, after sustained clinical improvement is observed. Lower bioavailability of oral corticosteroids should be taken into account when switching to the equivalent dose of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

28-Sep-2020

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.

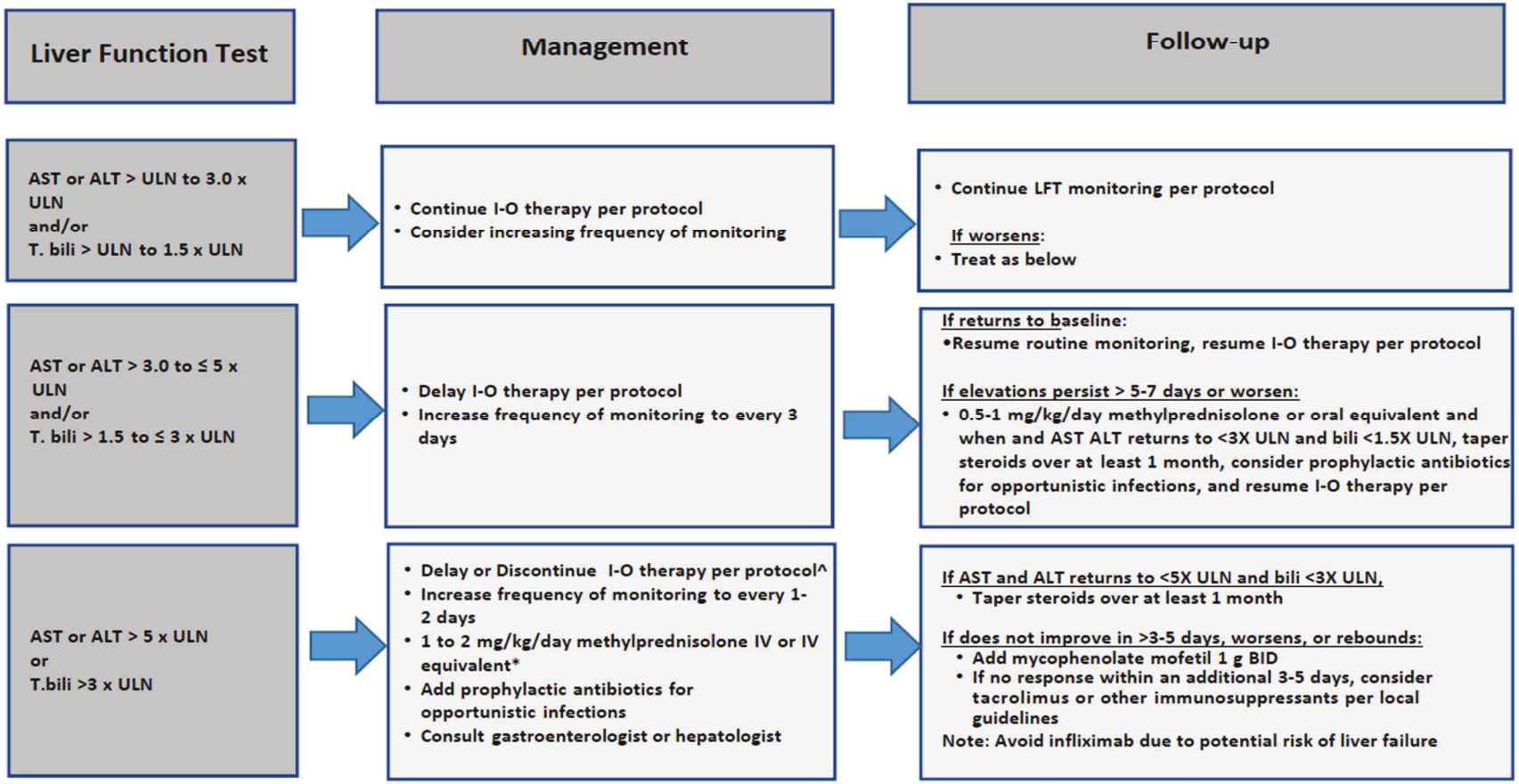


Patients on IV steroids may be switched to an equivalent dose of oral corticosteroids (eg, prednisone) at start of tapering or earlier, after sustained clinical improvement is observed. Lower bioavailability of oral corticosteroids should be taken into account when switching to the equivalent dose of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

28-Sep-2020

Hepatic Adverse Event Management Algorithm

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

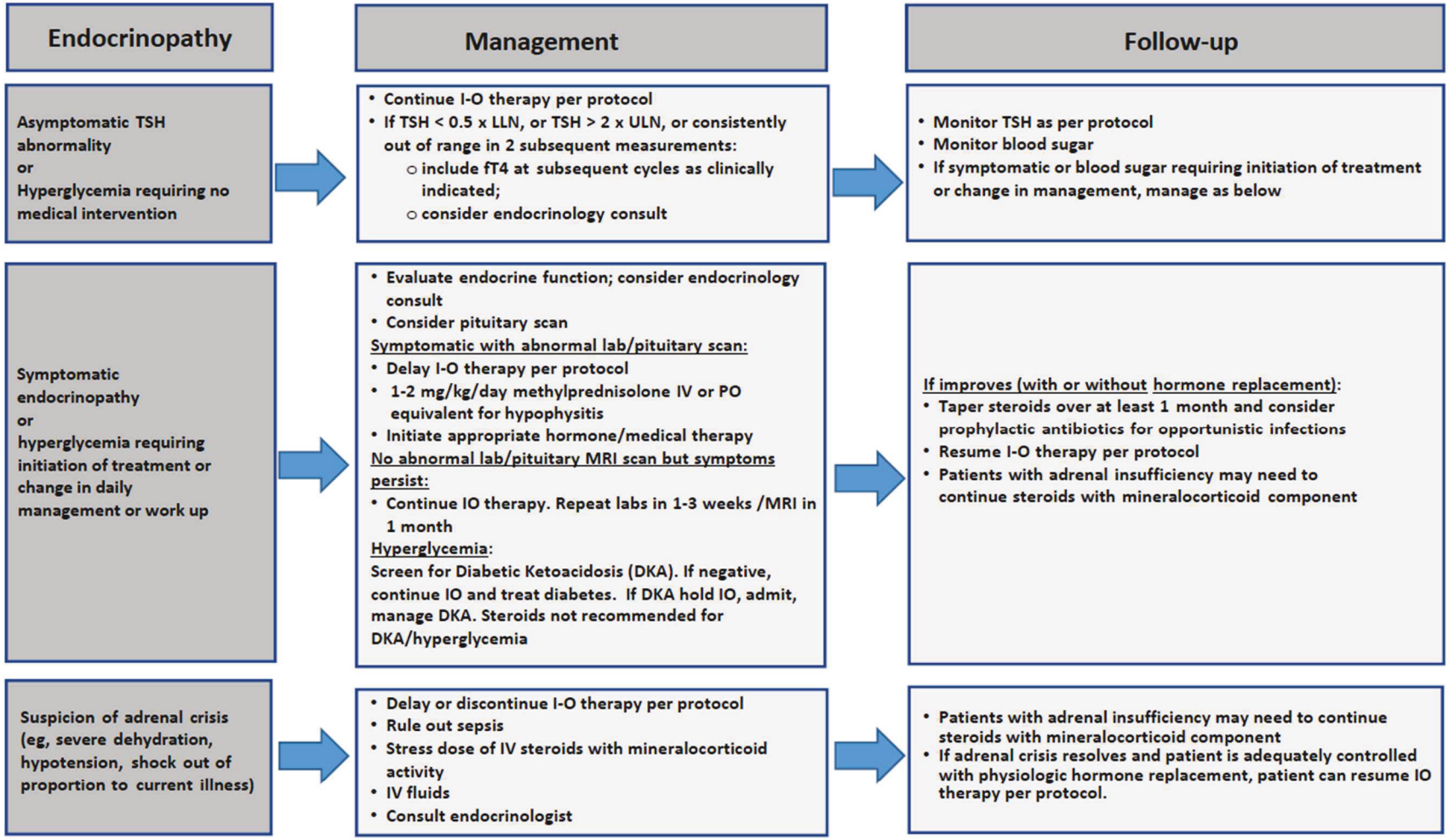


Patients on IV steroids may be switched to an equivalent dose of oral corticosteroids (e.g. prednisone) at start of tapering or earlier, after sustained clinical improvement is observed. Lower bioavailability of oral corticosteroids should be taken into account when switching to the equivalent dose of oral corticosteroids.
^ Please refer to protocol dose delay and discontinue criteria for specific details.
*The recommended starting dose for AST or ALT > 20 x ULN or bilirubin >10 x ULN is 2 mg/kg/day methylprednisolone IV.

28-Sep-2020

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.

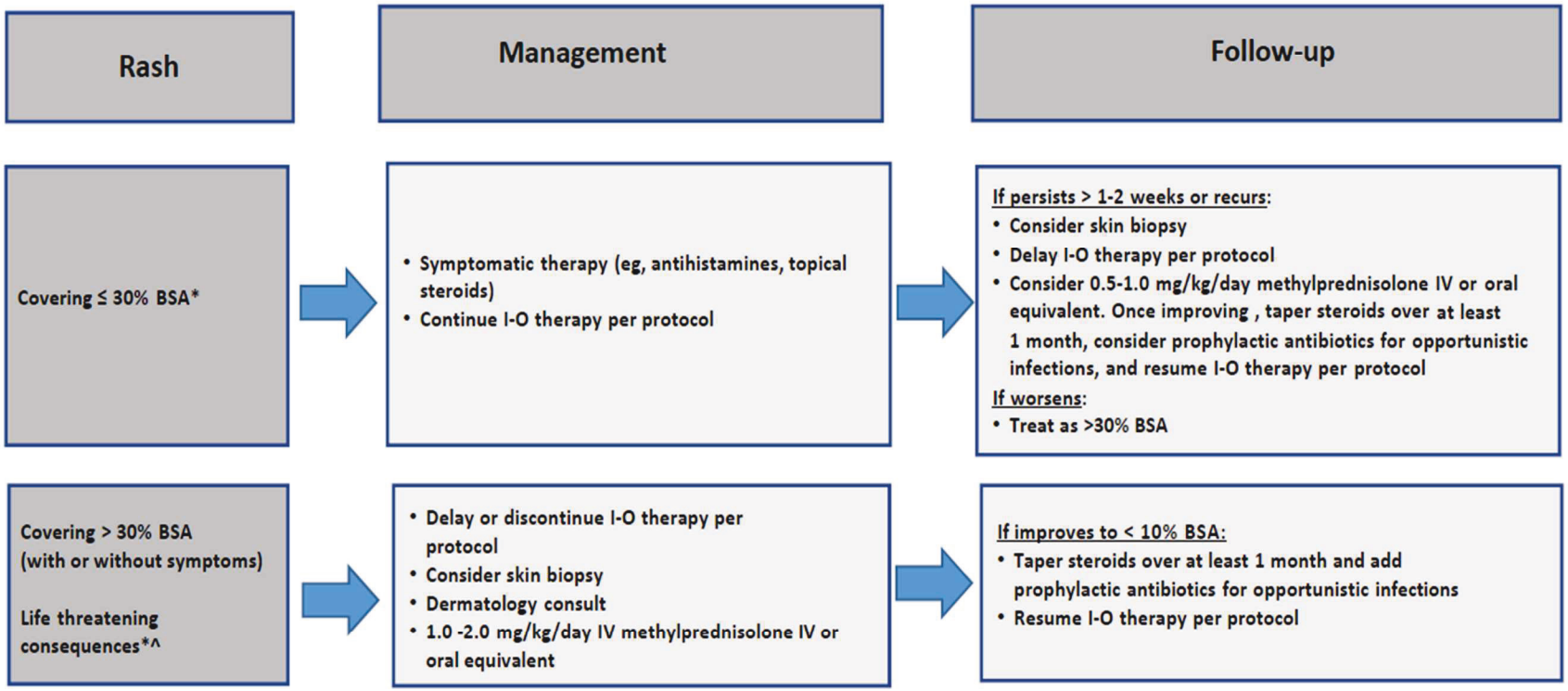


Patients on IV steroids may be switched to an equivalent dose of oral corticosteroids (eg, prednisone) at start of tapering or earlier, after sustained clinical improvement is observed. Lower bioavailability of oral corticosteroids should be taken into account when switching to the equivalent dose of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

28-Sep-2020

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, after sustained clinical improvement is observed. Lower bioavailability of oral corticosteroids should be taken into account when switching to the equivalent dose of oral corticosteroids.

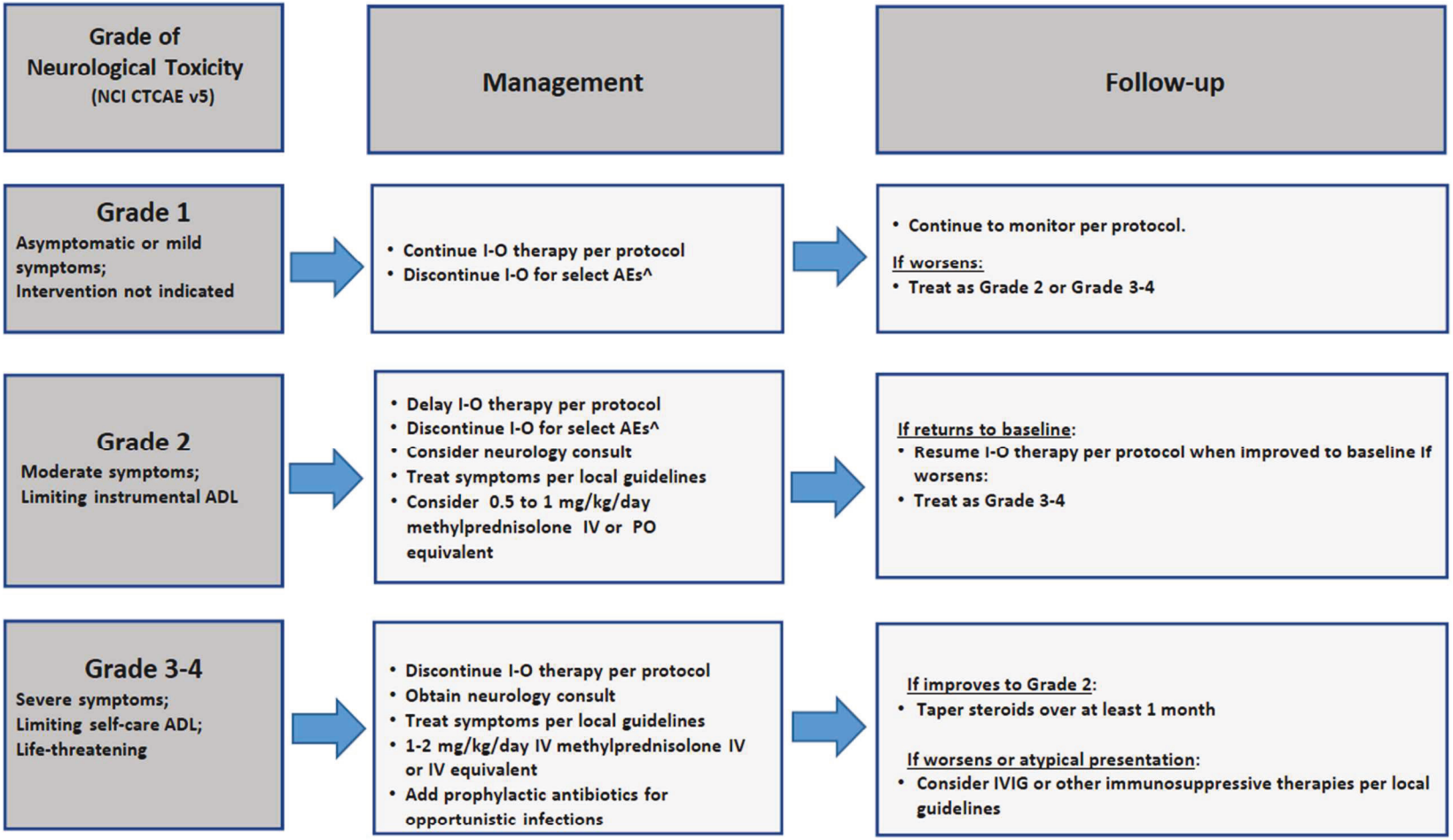
*Refer to NCI CTCAE v5 for term-specific grading criteria.

^If Steven-Johnson Syndrome (SJS),toxic epidermal necrosis (TEN), Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS) is suspected, withhold I-O therapy and refer patient for specialized care for assessment and treatment. If SJS, TEN, or DRESS is diagnosed, permanently discontinue I-O therapy.

28-Sep-2020

Neurological Adverse Event Management Algorithm

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



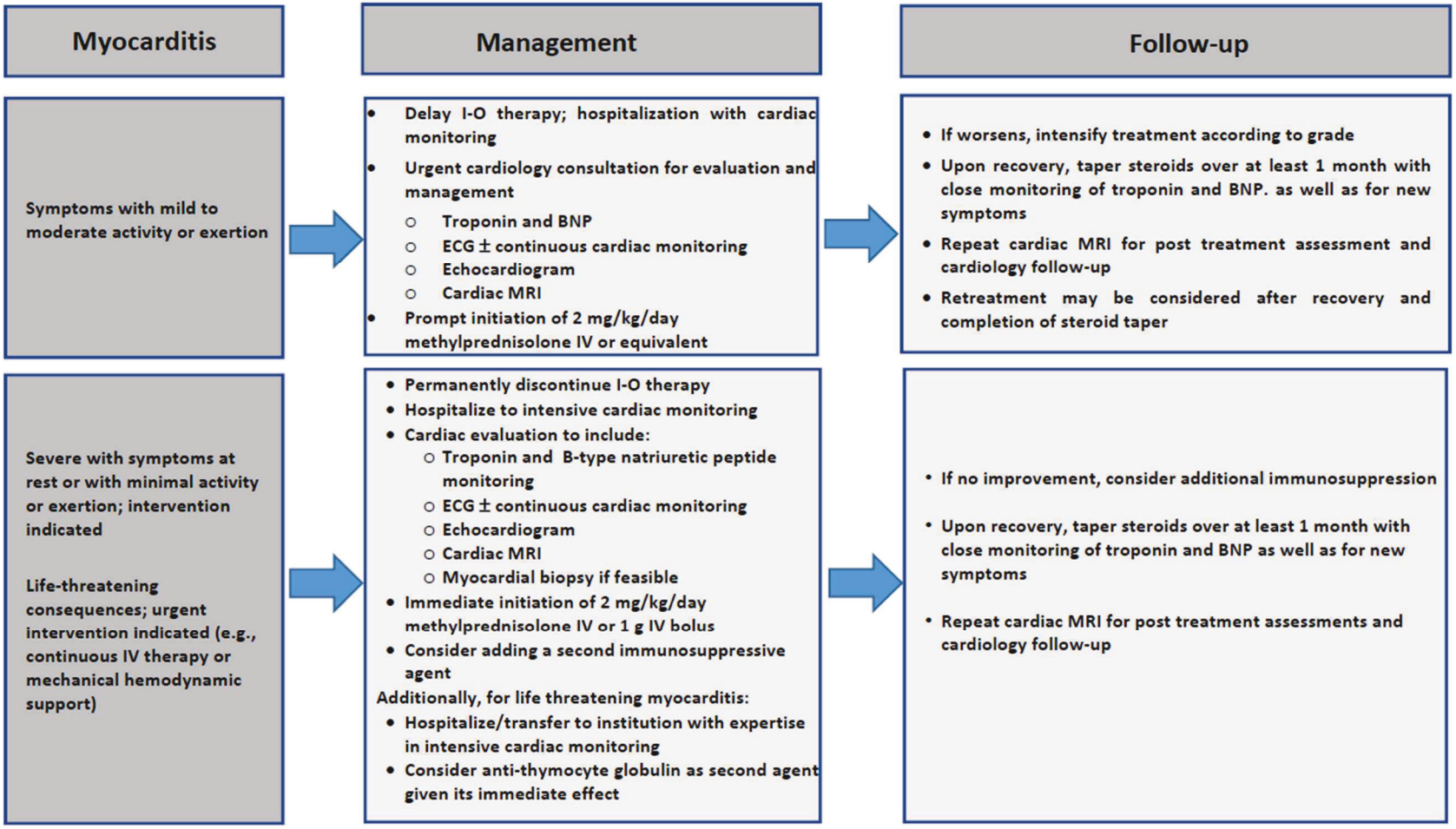
Patients on IV steroids may be switched to an equivalent dose of oral corticosteroids (eg. prednisone) at start of tapering or earlier, after sustained clinical improvement is observed. Lower bioavailability of oral corticosteroids should be taken into account when switching to the equivalent dose of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

^Discontinue for any grade myasthenia gravis, Guillain-Barre syndrome, treatment-related myelitis, or encephalitis.

28-Sep-2020

Myocarditis 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 (eg, prednisone) at start of tapering or earlier, after 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.

28-Sep-2020

APPENDIX 6 RESPONSE EVALUATION CRITERIA IN SOLID TUMORS GUIDELINES (VERSION 1.1) WITH BMS MODIFICATIONS

1 EVALUATION OF LESIONS

Solid tumors will be evaluated using Response Evaluation Criteria In Solid Tumors version 1.1 (RECIST 1.1) guideline with BMS modifications.[1]

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

1.1 Measurable

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

- 10 mm by CT/MRI scan (scan slice thickness no greater than 5 mm), or ≥2x slice thickness if greater than 5mm.

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

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

Note: Lesions on X-Ray are not to be selected as Target or Non-Target Lesions.

1.2 Non-Measurable

All other lesions are considered non-measurable, including small lesions (longest diameter < 10mm or pathological lymph nodes with ≥ 10 to < 15 mm short axis) as well as truly non-measurable lesions. Lesions considered truly non-measurable include: leptomeningeal disease, inflammatory breast disease, lymphangitic involvement of skin or lung, abdominal masses/abdominal organomegaly identified by physical exam that is not measurable by reproducible imaging techniques.

Note: Lesions on X-Ray are not to be selected as Target or Non-Target Lesions.

1.3 Special considerations regarding lesion measurability

1.3.1 Bone lesions

- Bone scan, PET scan and 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.

1.4 Baseline Documentation Of 'Target' And 'Non-Target' Lesions

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

Note: A maximum of two lesions can be selected per organ system. For example, a maximum of two lung lesions can be selected (selected from one lung or one lesion from each). A maximum of two lymph nodes can be selected at baseline, as the lymphatic system is considered one organ.

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

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

All other lesions (or sites of disease) including pathological lymph nodes should be identified as non-target lesions and should also be recorded at baseline. Measurements are not required and these lesions should be followed as 'present', 'absent', or in rare cases 'unequivocal progression' (more details to follow). In addition, it is possible to record multiple 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').

2 RESPONSE CRITERIA

2.1 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.
- **Not Evaluable (NE):** If one or more target lesions cannot be measured or adequately assessed as either fully resolved or too small to measure (due to missing or poor quality images), and the sum of diameters of the remaining measured target lesions (if any) has not increased sufficiently to meet Progressive Disease as defined above.

2.1.1 Special Notes on the Assessment of Target Lesions

2.1.1.1 Lymph nodes

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

2.1.1.2 Target lesions that become 'too small to measure'

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

2.1.1.3 Lesions that split or coalesce on treatment

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

2.2 Evaluation of Non-Target Lesions

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

- **Complete Response (CR):** Disappearance of all non-target lesions. All lymph nodes must be non-pathological in size (< 10mm short axis).
- **Non-CR/Non-PD:** Persistence of one or more non-target lesion(s)
- **Progressive Disease (PD):** Unequivocal progression of existing non-target lesions.

2.2.1 Special Notes on Assessment of Progression of Non-Target Disease

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

2.2.1.1 When the patient also has measurable disease

In this setting, to achieve 'unequivocal progression' on the basis of the non-target disease, there must be an overall level of substantial worsening in non-target disease such that, even in presence of SD or PR in target disease, the overall tumor burden has increased sufficiently to merit discontinuation of therapy A modest 'increase' in the size of one or more non-target lesions is usually not sufficient to qualify for unequivocal progression status. Pleural effusions, pericardial effusions and ascites will not be followed as target or non-target lesions and will not contribute to response or progression. The designation of overall progression solely on the basis of change in non-target disease in the face of SD or PR of target disease will therefore be extremely rare.

2.2.1.2 When the patient has only non-measurable disease

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

patient should be considered to have had overall PD at that point. While it would be ideal to have objective criteria to apply to non-measurable disease, the very nature of that disease makes it impossible to do so; therefore the increase must be substantial.

2.2.2 New Lesions

The appearance of new malignant lesions denotes disease progression; therefore, some comments on detection of new lesions are important. There are no specific criteria for the identification of new radiographic lesions; however, the finding of a new lesion should be unequivocal: ie, not attributable to differences in scanning technique, change in imaging modality or findings thought to represent something other than tumor (for example, some 'new' bone lesions may be simply healing or flare of pre-existing lesions). This is particularly important when the patient's baseline lesions show partial or complete response. For example, necrosis of a liver lesion may be reported on a CT scan report as a 'new' cystic lesion, which it is not.

NOTE: Fluid collections (pleural effusions, pericardial effusions, and ascites) will not be considered new lesions and will not contribute to response or progression. In the event a new fluid collection is seen on a post-baseline imaging exam, a comment may be made, but the appearance of a new fluid collection alone should not result in an assessment of Progressive Disease (PD). A lesion identified on a follow-up study in an anatomical location that was not scanned at baseline is considered a new lesion and will indicate disease progression. An example of this is the patient who has visceral disease at baseline and while on study has a CT or MRI brain ordered which reveals metastases. The patient's brain metastases are considered to be evidence of PD even if he/she did not have brain imaging at baseline. A lesion identified on Chest X-Ray that was not present in prior CT can be considered a new lesion and will result in Progressive Disease (PD).

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

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

2.3 Response Assessment

2.3.1 Evaluation of Best Overall Response

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

2.3.2 Time Point Response

At each protocol specified time point, a response assessment occurs. Table 2.3.2-1 provides a summary of the overall response status calculation at each time point for patients who have measurable disease at baseline. When patients have non-measurable (therefore non-target) disease only, Table 2.3.2-2 is to be used.

Table 2.3.2-1: Time Point Response: Patients With Target (± Non-Target) Disease

Target Lesions	Non-Target Lesions	New Lesions	Overall Response
CR	CR	No	CR
CR	Non-CR/non-PD	No	PR
CR	Not evaluated	No	PR
PR	Non-PD or not all evaluated	No	PR
SD	Non-PD or not all evaluated	No	SD
Not all evaluated	Non-PD	No	NE
PD	Any	Yes or No	PD
Any	PD	Yes or No	PD
Any	Any	Yes	PD

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

Table 2.3.2-2: Time Point Response: Patients with Non-target Disease Only		
Non-Target Lesions	**New Lesions**	**Overall Response**
CR	No	CR
Non-CR/non-PD	No	Non-CR/non-PD[a]
Not all evaluated	No	NE
Unequivocal PD	Yes or No	PD
Any	Yes	PD
CR = complete response, PD = progressive disease and NE = inevaluable		

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

2.3.3 Best Overall Response

Best response determination of complete or partial response requires confirmation: Complete or partial responses may be claimed only if the criteria for each are met at a subsequent time point of ≥ 4 weeks (28 days) later. In this circumstance, the best overall response can be interpreted as in Table 2.3.3-1. When SD is believed to be best response, it must meet the protocol specified minimum time from the date of first treatment or randomization date.

For example, if the first scheduled follow-up imaging visit is Week 6 (± 7 days) for a particular protocol, a Best Response of SD can only be made after the subject is on-study for a minimum of 6 weeks (42 days) minus 7 days, for an absolute minimum time on-study of 35 days from the reference start date (reference date is considered Day 1 on study). If the subject is not on-study for at least this amount of time, any tumor assessment indicating stable disease before this time period will have a Best Response of NE unless PD is identified.

Special note on response assessment: When nodal disease is included in the sum of target lesions and the nodes decrease to 'normal' size (< 10 mm), they may still have a measurement reported on scans. This measurement should be recorded even though the nodes are normal in order not to overstate progression should it be based on increase in size of the nodes. As noted earlier, this means that patients with CR may not have a total sum of 'zero' on the case report form (CRF).

Table 2.3.3-1: Best Overall Response (Confirmation of CR and PR Required)		
Overall Response First Time Point	**Overall Response Subsequent Time Point**	**Best Overall Response**
CR	CR	CR
CR	PR	SD, PD OR PR[a]
CR	SD	SD provided minimum criteria for SD duration met, otherwise, PD
CR	PD	SD provided minimum criteria for SD duration met, otherwise, PD

Table 2.3.3-1: Best Overall Response (Confirmation of CR and PR Required)		
Overall Response First Time Point	**Overall Response Subsequent Time Point**	**Best Overall Response**
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, 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.

2.3.4 Confirmation Scans

Verification of Response: To be assigned a status of CR or PR, changes in tumor measurements must be confirmed by consecutive or subsequent repeat assessments that should be performed no less than 28 days after the criteria for response are first met. Subsequent documentation of a CR may provide confirmation of a previously identified CR even with an intervening NE or PR (eg, CR NE CR or CR PR CR). Subsequent documentation of a PR may provide confirmation of a previously identified PR even with an intervening NE or SD (eg, PR NE PR or PR SD PR). However, only one (1) intervening time point will be allowed between PR/CRs for confirmation.

Verification of Progression: Progression of disease should be verified in cases where progression is equivocal. If repeat scans confirm PD, then progression should be declared using the date of the initial scan. If repeat scans do not confirm PD, then the subject is considered to not have progressive disease.

REFERENCES

1. Eisenhauer EA, Therasse P, Bogaerts J, et al. New response evaluation criteria in solid tumors: revised RECIST guideline (version 1.1). Eur J Cancer 2009; 45: 228-47.

APPENDIX 7 EASTERN COOPERATIVE ONCOLOGY GROUP (ECOG) PERFORMANCE STATUS

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

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

APPENDIX 8 COUNTRY SPECIFIC REQUIREMENTS

Argentina, Czech Republic, France, Germany, Spain, Peru, and Any Other Countries Where Exclusion of HIV Positive Participants Is Locally Mandated

Protocol Section	Country-specific language
Section 2 Flow Chart/Time and Events Schedule, Table 2-1: Screening Assessments- Laboratory Tests	Add "HIV" to the list of laboratory tests
Section 6.2 Exclusion Criterion 1) Medical Conditions, t), i), ii) and iii)	"Known human immunodeficiency virus (HIV) positive with an acquired immunodeficiency syndrome (AIDS)-defining opportunistic infection within the last year or a current CD4 count < 350 cells/uL. Participants with HIV are eligible if: i) They have received antiretroviral therapy (ART) for at least 4 weeks prior to randomization as clinically indicated while enrolled on study. ii) They continue on ART as clinically indicated while enrolled on study. iii) CD4 counts and viral load are monitored per standard of care by a local health care provider. NOTE: Testing for HIV must be performed at sites where mandated locally. HIV-positive participants must be excluded where mandated locally." to be replaced with "Positive test for HIV."

APPENDIX 9 PROTOCOL AMENDMENT SUMMARY OF CHANGE HISTORY

Overall Rationale for Protocol Amendment 02, 22-Jul-2022

The primary reasons for this protocol amendment are to:

- Add mandatory use of prophylactic growth factors starting from Cycle 1 and during the first 4 cycles of chemotherapy treatment period, ie, induction phase for all participants aged >65 years and/or participants with additional risk factors, as per National Comprehensive Cancer Network (NCCN) guidelines.

[redacted]

The Synopsis was also updated to reflect changes made in the body.

SUMMARY OF KEY CHANGES FOR PROTOCOL AMENDMENT 02		
Section Number & Title	**Description of Change**	**Brief Rationale**
Table 2-1: Screening Procedural Outline Section 5.1.1: Screening Section 6.1: Inclusion Criteria Section 9.8: Biomarkers	Screening [redacted] mandatory requirement changed to optional for all participants except for those participating in the separate PET tracer sub-study. [redacted]	Given the non-standard of care approach with the requirement of the [redacted], and the knowledge that the majority of patients likely [redacted], the mandatory [redacted] has been removed from the protocol via this amendment for all participants except those taking part in the PET tracer sub-study. Participants will be able to enter the study with their standard of care [redacted] and provide only this [redacted] for entry, in addition to

SUMMARY OF KEY CHANGES FOR PROTOCOL AMENDMENT 02		
Section Number & Title	**Description of Change**	**Brief Rationale**
		meeting all other Inclusion/Exclusion criteria. The protocol will continue to ask for an optional [redacted] should investigators determine this will not provide additional risk to their patients.
Table 2-2: On-treatment Procedural Outline (CA001050)	Hematology assessments were added on Days 8 and 15 of Cycles 1 and 2. A note was added to clarify that only hematology is required at those time points.	Additional blood count monitoring will now be mandated within the first two cycles to create a more standard approach of monitoring hematological toxicities within the study
Table 2-2: On-treatment Procedural Outline (CA001050) Section 7.7.3 Permitted therapy	Prophylactic use of growth factors is mandatory starting from Cycle 1 and during the first 4 cycles of chemotherapy treatment period, ie, induction phase for all participants aged >65 years and/or participants with additional risk factors.	Prophylactic G-CSF is being added as per NCCN guidelines for this patient population who are at intermediate risk for developing neutropenia and with additional risk factors for developing more serious complications.
Table 4-1: Objectives and Endpoints Section 10.3.3: Other Analyses	Objectives to assess associations of [redacted] in pretreatment [redacted] assessed using [redacted] and [redacted] assays with anti-tumor activity measures and to assess associations of [redacted] (combined positive score [CPS]) in pretreatment [redacted] with anti-tumor activity measures have been moved from secondary to tertiary/exploratory.	The fit-for-purpose validation of these assays may not be adequate to generate data for reporting to health authorities.

SUMMARY OF KEY CHANGES FOR PROTOCOL AMENDMENT 02		
Section Number & Title	**Description of Change**	**Brief Rationale**
Section 6.2: Exclusion Criteria	Criterion 1) e) is no longer applicable. Criterion 1) w) has been added to clarify that previously treated limited stage SCLC (LS-SCLC) participants are excluded.	Clarification that previously treated limited stage SCLC (LS-SCLC) are excluded.
Section 8.1.4: Treatment Beyond Disease Progression	Addition of new references of accumulating evidence that minority of participants treated with immunotherapy may derive clinical benefit despite initial evidence of progressive disease.	Provide more recent published references.
Appendix 2	Added new section: Bristol-Myers Squibb Company (BMS) Commitment to Diversity in Clinical Trials. Added new section: Data Protection, Data Privacy, Data Security.	To align with BMS commitment to diversity in clinical trials. To align with BMS practice and comply with European Union Clinical Trials Regulation requirement.

Overall Rationale for Protocol Amendment 01; 02-Jul-2021

The primary reasons for these changes are to:

- Align dose modification criteria and immuno-oncology (IO) agent management algorithms with the current Common Terminology Criteria for Adverse Event (CTCAE) version 5.0 (v5.0).
- Provide additional guidance on the management of coronavirus 2 (SARS-CoV-2) infection prior to entering the study and during the study and add additional serologic testing for severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) status.
- Incorporate additional updates to improve alignment across protocol sections and/or clarify expectations for eligibility, assessments, sample collections, treatment administration, and country-specific requirements.

This protocol amendment applies to future participants enrolled in the study and, where applicable, to all participants currently enrolled.

Summary of Key Changes for Protocol Amendment 01		
Section Number & Title	**Description of Change**	**Brief Rationale**
All	Minor formatting and typographical corrections	Minor, therefore have not been summarized
Global	References to "intervention period" or "combination therapy" have been changed to "induction period" or "therapy" in certain instances	Clarified references to first 4 cycles where participants are receiving chemotherapy.
Synopsis	Updated text	To align with the protocol changes in Sections 2 through 9.
Section 2 Schedule of Activities Table 2-1 Screening Procedural Outline Table 2-2 On-treatment Procedural Outline Table 2-3 Follow-up Procedural Outline Section 9.1.1 Imaging Assessment for the Study	Brain imaging row in Section 2 tables and in Imaging section: updated text to indicate that MRI is the preferred imaging method, but CT can be used if MRI is unavailable.	Updated based on site feedback to add flexibility to the protocol for a population that needs immediate treatment.

Summary of Key Changes for Protocol Amendment 01		
Section Number & Title	**Description of Change**	**Brief Rationale**
Section 2 Schedule of Activities Table 2-1 Screening Procedural Outline Table 2-2 On-treatment Procedural Outline Table 2-3 Follow-up Procedural Outline Section 9.2.1 Time Period and Frequency for Collecting AE and SAE Information Section 9.2.3 Follow-up of AEs and SAEs	Added text for the collection of adverse events (AEs) and serious adverse events (SAEs) for SARS-CoV-2. Added/updated rows for SARS-CoV-2 serology in Section 2 tables.	To allow for the evaluation of the impact of SARS-CoV-2 infection.
Section 2 Schedule of Activities Table 2-1 Screening Procedural Outline Section 5.1.1 Screening	1. Informed consent row and Section 5.1.1: re-enrollment text added. 2. Medical history: added recording of SARS-CoV-2 vaccination received more than 30 days prior to randomization. 3. Serology row: updated text for human immunodeficiency virus (HIV) testing. 4. SARS-CoV-2 serology row: serum collection will not be used to determine eligibility. 5. Added footnote b. 6. Added footnote c.	1. To be consistent with Section 6.4.1. 2. Ensure SARS-CoV-2 vaccination received more than 30 days prior to randomization are recorded. 3. Clarify that HIV testing is only required if locally mandated. 4. Clarify that serum collection for SARS-CoV-2 measures is not an eligibility requirement. 5. Added to be consistent with text in Section 5.1.1. 6. Added to be consistent with newly added criterion 2) h) in Section 6.1.
Section 2 Schedule of Activities Table 2-2 On-treatment Procedural Outline	1. [redacted] Pharmacodynamic Sampling row: updated notes. 2. Randomize row: updated notes.	1. Clarify samples will include samples upon disease progression. 2. Clarify timing between first dose and randomization.

Summary of Key Changes for Protocol Amendment 01		
Section Number & Title	**Description of Change**	**Brief Rationale**
Section 2 Schedule of Activities Table 2-3 Follow-up Procedural Outline	Review of Subsequent Cancer Therapy row: updated notes.	Clarify types of subsequent therapy.
Section 3.2.2 BMS-986012 Mechanism of Action Section 3.2.3 Nivolumab Mechanism of Action	Updated with text indicating BMS-986012 and nivolumab was produced in Chinese hamster ovary cells using recombinant DNA technology.	To align with [redacted]. Clarified production of BMS-986012 and nivolumab.
Section 3.3 Benefit/Risk Assessment	1. Added language to address the possible impact of study treatment on the risk of contracting SARS-CoV-2 or increasing severity of symptoms. 2. Added language about the concomitant use of SARS-CoV-2 vaccines during the study.	1. Provide guidance about balancing individual benefit risk when enrolling a participant in the study with added challenges due to the SARS-CoV-2 pandemic. 2. Risk assessment for concomitant use of SARS-CoV-2 vaccines during the study.
Section 4 Objectives and Endpoints Table 4-1 Objectives and Endpoints 9.8 Biomarkers	Updated exploratory objective for SARS-CoV-2 serologic status. Added "specific time" points to text in Section 9.8. anti-SARS-CoV-2 "IgM" became "total."	Clarify that assessment is for all study treatments and at specified time points beyond baseline. Clarify possible measurements of SARS-CoV-2 Serology.
Section 5.1.2 Treatment Section 7.1 Treatments Administered	Updated text describing order of administration when study drugs are administered on the same day.	Clarify order of treatment for both induction and maintenance phase.
Section 5.1.4 Data Monitoring Committee and Other External Committees	Removed sentence regarding adjudicated events.	This study will not have adjudication documentation to submit to the Data Monitoring Committee.

Summary of Key Changes for Protocol Amendment 01		
Section Number & Title	**Description of Change**	**Brief Rationale**
Section 6.1 Inclusion Criteria 1) Signed Written Informed Consent Section 9.2 Adverse Events	Criterion 1) a) is not applicable (N/A) per this revision and replaced with 1) c). Removed reference to legally authorized representative (LAR). Removed reference to LAR in Adverse Events section.	The study will not include participants who are incapable of giving informed consent to protect more vulnerable populations per Good Clinical Practice
Section 6.1 Inclusion Criteria 2) Type of Participant and Target Disease Characteristics	1. Criterion 2) a) is N/A per this revision and replaced with 2) g). Updated to American Joint Committee on Cancer 8th edition. 2. Criterion 2) b) is N/A per this revision and replaced with 2) h). Updated to collect sample from any disease site and added a note for when sample cannot be collected for safety issues.	1. Update follows most recent guidance and will not alter the enrolled population. 2. To allow the eligibility of participants who may be unable to provide a sample from the primary site or unable to provide a sample for safety reasons.
Section 6.1 Inclusion Criteria 3) Age and Reproductive Status	1. Criterion 3) a) iv), including sub bullet (1) is N/A per this revision and replaced with 3) a) x) with sub bullet (1). Added text extending pregnancy testing window prior to dosing. 2. Criteria 3) b) iv) through vii) is N/A per this revision and replaced with 3) b) ix) through xii). Updated to reflect male contraception requirements based on chemotherapy.	1. To allow flexibility in timing of test when results cannot be obtained within the standard window. 2. BMS-986012 and nivolumab are not considered genotoxic and there is no expected transmission of a biologically relevant amount to women of childbearing potential (WOCBP) partner.

Summary of Key Changes for Protocol Amendment 01		
Section Number & Title	**Description of Change**	**Brief Rationale**
Section 6.2 Exclusion Criteria 1) Medical Conditions	1. Criterion 1) a) is N/A per this revision and replaced with 1) r). Added requirement for Japan only. 2. Criterion 1) f) is N/A per this revision and replaced with 1) s). Added text for asymptomatic central nervous system (CNS) metastases. 3. Criterion 1) k) is N/A per this revision and replaced with 1) t) and sub bullets i) through iii) with a note. Updated eligibility text for participants with HIV. 4. Criterion 1) o) is N/A per this revision and replaced with 1) u). Updated text for participants with concurrent and prior malignancy. 5. Criterion 1) q) is N/A per this revision and replaced with 1) v), including sub bullet i). Updated timing for previous SARS-CoV-2 infection (asymptomatic and severe) prior to first dose.	1. Added per local requirements. 2. Clarify that asymptomatic CNS metastases do not require immediate treatment to be eligible. 3. Update includes more specific requirements for eligibility of participants with HIV. 4. Allow for participants with prior cancers whose natural history or treatment does not have the potential to interfere with the safety or efficacy assessment of study drugs. 5. Exclusion of or delay of study start for participants with recent SARS-CoV-2 infection.

Summary of Key Changes for Protocol Amendment 01		
Section Number & Title	**Description of Change**	**Brief Rationale**
Section 6.2 Exclusion Criteria 2) Prior/Concomitant Therapy	1. Criterion 2) b) is N/A per this revision and replaced with 2) c). Updated text for complementary medications/botanical preparations. 2. Added criterion d) for live/attenuated vaccine. 3. Added criterion e) for SARs-CoV-2 vaccine.	1. To permit complementary medications if they do not have proven anti-cancer effects and if they are being used as supportive care. 2) To align with Section 7.7.1. 2) To mitigate unexpected drug interaction prior to start of study treatments.
Section 6.4.1 Retesting During Screening or Lead-in Period	Criteria added for the retesting of participants who may have suspected or confirmed symptomatic SARS-CoV-2 during the screening period.	To allow for participants who meet all eligibility criteria and symptoms have resolved to enroll in the study.
Section 7.1.1 BMS-986012 Dosing	Added "approximately" before 60-minute infusion.	To allow for variations of this timing.
Section 7.1.2 Nivolumab Dosing	1. Updated text to include "approximately" before the 30-min intravenous (IV) infusion. 2. Added language for the appropriate length of time between nivolumab dosing and premedication. 3. Added language about assuring sterility of the solution.	1. To allow for variations of this timing. 2. To align with windows allowed for nivolumab Q3W dosing. 3. To clarify drug handling requirements.
Section 7.4 Dosage Modification Section 8.1 Discontinuation From Study Treatment	Removed paragraph referencing using CTCAE v4 for management and dose modification and CTCAE v5.0 for reporting of AEs.	Per this amendment, CTCAE v5.0 should be used for management, dose modification, and reporting of all AEs.
Section 7.4.1 Nivolumab Dose Delay Criteria	Dose delay criteria moved to a tabular format [redacted] and discontinuation and criteria to resume treatment were included.	To be aligned with CTCAE v5.0 definitions and inclusion of SARS-CoV-2 criteria and new terms. Tabular format added for ease of use.

Summary of Key Changes for Protocol Amendment 01		
Section Number & Title	**Description of Change**	**Brief Rationale**
Section 7.4.2 BMS-986012 Dose Delay Criteria	Updated ALT/AST and Total bilirubin criteria. Added SARS-CoV-2 infection. Updated amylase and/or lipase to say, "without signs or symptoms of pancreatitis" instead of "that are asymptomatic."	To align with current standards and CTCAE v5.0.
Section 7.4.3 Carboplatin/Etoposide Dose Delay	Add text that delays > 6 weeks are not permitted unless discussed and approved by the Medical Monitor.	To allow for more flexibility in case all study treatments are delayed.
Section 7.4.4 Criteria to Resume Treatment with Nivolumab	Removed specific criteria to resume treatment for nivolumab listed in this section. Section title was updated to remove BMS986012, which was moved to its own section.	Criteria to resume treatment for nivolumab was moved to [redacted]. Section title was updated and criteria to resume for BMS-986012 was moved to a new section, Section 7.4.5.
Section 7.4.5 Criteria to Resume Treatment with BMS-986012	New section added, includes new criteria to resume treatment for participants who develop confirmed or suspected SARS-CoV-2 infection during study treatment.	New section added now that criteria to resume treatment for nivolumab has been moved to [redacted] SARS-CoV-2 language added to address participants who develop infection during study treatment.

Summary of Key Changes for Protocol Amendment 01		
Section Number & Title	**Description of Change**	**Brief Rationale**
Section 7.7.1 Prohibited and/or Restricted Treatments	1. Updated concurrent "anti-neoplastic therapy" to "systemic anti-neoplastic therapy" and made non-palliative radiation therapy its own bullet. 2. Complementary medications/botanical preparation bullet was updated. 3. Vaccine listing was updated, and a bullet for SARS-CoV-2 vaccine was added. 4. Added bullet for chemotherapy prohibited and/or restricted medications.	1. Clarify the terminology. 2. To allow complementary medications if they do not have proven anti-cancer effects and if they are being used as supportive care. 3. Clarify vaccine management. 4. Added per local requirements.
Section 7.7.3 Permitted Therapy	Added that treatment for active SARS-CoV-2 infection is allowed and should be discussed with the Medical Monitor.	Clarify SARS-CoV-2 infection management.
Section 8.1.1 BMS-986012 Dose Discontinuation	Updated liver function text abnormality criteria for discontinuation. Added text for approval from Medical Monitor to resume therapy in specific cases of ALT or AST elevations.	To be consistent with CTCAE v5.0.
Section 8.1.2 Nivolumab Dose Discontinuation	Removed specific discontinuation criteria listed in this section and referenced new location in [redacted].	Discontinuation criteria was moved to [redacted]
Section 8.1.3 Carboplatin or Etoposide Dose Discontinuation	Removed text for participant replacement.	Potential early discontinuations have been taken into consideration when determining the sample size.
Section 9.1.2 Patient-reported Outcomes	Replaced the last paragraph in this section with new text	To allow for greater flexibility of alternative

Summary of Key Changes for Protocol Amendment 01		
Section Number & Title	**Description of Change**	**Brief Rationale**
	about alternate administration in exceptional circumstances.	administration methods in exceptional circumstances.
Section 9.2.5 Pregnancy	Male contraception use during and after study treatment updated to reflect the length of time required for chemotherapy only.	BMS-986012 and nivolumab are not considered genotoxic and there is no expected transmission of a biologically relevant amount to WOCBP partner.
Section 9.4.4 Clinical Safety Laboratory Assessments	Added a table title and updated table text for hepatitis to indicate it is at screening only and HIV to indicate it is at screening if locally mandated.	For consistency with Table 2-1 Screening Procedural Outline and Section 6.2 Exclusion Criteria.
Section 9.5 Pharmacokinetics Table 9.5-1 Pharmacokinetic and Immunogenicity Sampling Schedule for Arm A Table 9.5-2 Pharmacokinetic and Immunogenicity Sampling Schedule for Arm B	Defined first study drug in footnote a.	Clarify that the predose sample should be taken prior to chemotherapy for the induction phase.
Section 9.7 Pharmacogenomics	Deleted last sentence.	Removal of repeated sentence.

Summary of Key Changes for Protocol Amendment 01		
Section Number & Title	**Description of Change**	**Brief Rationale**
Section 9.8 Biomarkers Table 9.8-1 Biomarker Sampling Schedule for Arms A and B	1. Updated the title of Serum Biomarkers column to Anti-SARS-CoV-2 Serology and added additional collection time points. Deleted footnote c as this is now in the table. 2. Updated footnote b. 3. Footnote c (previously footnote d) was updated to indicate it is within 30 min of the first study drug. 4. Defined first study drug in footnote c (previously footnote d).	1. Additional samples to be collected to better understand the impact of SARS-CoV-2 serologic status on participants with extensive-stage small cell lung cancer (ES-SCLC) receiving study treatments. 2. Updated to be consistent with newly added criterion 2) h) in Section 6.1. 3. Clarify timing of the predose sample collection. 4. Clarify that the predose sample should be taken prior to chemotherapy for the induction phase.
[redacted]		
Section 9.8.3.6 Anti-SARS-CoV-2 Serology	Title was updated (previously Serum Biomarkers). Updated text to remove mention of possible objectives for serum collection for measurements of SARS-CoV-2 serology and align with Table 9.8-1.	Additional samples to be collected to better understand the impact of SARS-CoV-2 serologic status on participants with ES-SCLC receiving study treatments.

Summary of Key Changes for Protocol Amendment 01		
Section Number & Title	**Description of Change**	**Brief Rationale**
Appendix 2 Study Governance Considerations	1. Updated text under Informed Consent Process to remove legally acceptable representative and updated investigator responsibilities. 2. Removed text under Case Report Forms. 3. Updated text under Monitoring. 4. Added Dissemination of Clinical Study Data	1. The study will not include participants who are incapable of giving informed consent to protect more vulnerable populations per Good Clinical Practice. 2. Text is not applicable based on Electronic Data Capture system utilized for this study. 3. To allow for alternative monitoring plan to be defined when on-site monitoring is not available. 4. To clarify disclosure of study results.
Appendix 5 Management Algorithms for Studies Under CTCAE Version 5.0	Updated title of appendix and management algorithms.	Updated to be consistent with CTCAE v5.0 and addendum 01 of Nivolumab Investigator's Brochure version 19.
Appendix 8 Country Specific Requirements	Removed Italy from list of countries. Updated HIV text.	Requirement not applicable to Italy. HIV text updated to reflect changes in Section 6.2.