Official Title of Study:

A Phase 1b/2 Study of BMS-986442 in Combination With Nivolumab or Nivolumab and Chemotherapies in Participants With Advanced Solid Tumors and Non-small Cell Lung Cancer

NCT Number: NCT05543629

Document Date (Date in which document was last revised): 12 January 2023

CLINICAL PROTOCOL CA115001

A Phase 1b/2 Study of BMS-986442 in Combination with Nivolumab or Nivolumab and Chemotherapies in Participants with Advanced Solid Tumors and Non-small Cell Lung Cancer

Brief Title:

A Phase 1b/2 Study of BMS-986442 with Nivolumab with or without Chemotherapy in Solid Tumors and Non-small Cell Lung Cancer

Protocol Amendment 02

Incorporates Administrative Letter 01

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IND: 160891
EudraCT/EU Trial Number: 2022-501676-26-00
UTN: U1111-1283-1243

DOCUMENT HISTORY

Document	Date of Issue	Summary of Change
Protocol Amendment 02	12-Jan-2023	The main purpose of this amendment is to update the classification of the chemotherapies planned for administration from Non-Investigational Medicinal Product (Non-IMP) to IMP. Additional updates include providing regulatory agency identifier numbers, allowing both serum and plasma for blood-based clinical safety labs, and adding clarity associated with palliative radiotherapy scenarios.
Administrative Letter 01	08-Aug-2022	This letter aligns the primary objective presented in the Protocol Summary Objective and Endpoints table with the primary objective presented in Section 4, Objectives and Endpoints (Table 4-1) of the protocol.
Protocol Amendment 01	27-Jul-2022	The main purpose of this amendment is to update the eligibility criteria to include all actionable mutations, adjust eligibility criteria for docetaxel, and adjust dosing modifications for nivolumab. In addition, staggered dosing for safety monitoring during dose escalation was utilized and stopping rules based on safety monitoring were specified [redacted].
Original Protocol	06-Jun-2022	Not applicable

OVERALL RATIONALE FOR PROTOCOL AMENDMENT 02:

The purpose of this amendment is to update the classification of the chemotherapies (docetaxel, carboplatin, pemetrexed, and paclitaxel) planned for administration from Non-Investigational Medicinal Product (Non-IMP) to IMP. Distribution of the chemotherapies is unchanged and will be supplied by the Sponsor in regions where it is not available through insurance. The protocol was also updated to include additional regulatory agency identifier numbers on the title page, allow both serum and plasma for blood-based clinical safety laboratory evaluations, add clarity associated with palliative radiotherapy scenarios, and correct typographical errors/document formatting issues.

The protocol summary has been updated to align with the changes/edits reported in the table below.

SUMMARY OF CHANGES FOR PROTOCOL AMENDMENT 02

Section Number & Title	Description of Change	Brief Rationale
Title Page	• Updated Clinical Scientist contact information. • Added European Union Drug Regulating Authorities Clinical Trials Database/European Union (EudraCT/EU) Trial Number and Universal Trial Number (UTN).	• Change in study personnel. • Updated per regulatory agency identifier number availability.
Section 2: Schedule of Activities Section 6.2: Exclusion Criteria Section 7.1.3: Part D: Nivolumab, BMS-986442, Pemetrexed, and Carboplatin Table 7.4.1-1: Adverse Event Criteria for Delay, Resume, and Discontinue of Nivolumab and BMS-986442 Section 9.2.7: Potential Drug-induced Liver Injury Table 9.4.4-1: Clinical	• Removed reference to serum chemistry procedures in Table 2-1: Screening Procedural Outline for All Parts (CA115001), Table 2-2: On-Treatment Procedural Outline for All Parts (CA115001), and Table 2-3: Follow-Up Procedural Outline for All Study Parts (CA115001). • Updated mention of serum creatinine, alkaline phosphatase, and urea assessments to refer to "serum/plasma" assessments.	• Updated to allow both serum and plasma samples when assessing study participant blood samples for safety purposes.

SUMMARY OF CHANGES FOR PROTOCOL AMENDMENT 02		
Section Number & Title	**Description of Change**	**Brief Rationale**
Laboratory Assessments		
Section 3.2.4: BMS-986442 Clinical Activity Section 3.2.4.1: Preliminary Safety Data of BMS-986442 Monotherapy Section 3.3.1: Risk Assessment Section 5.5: Justification for the BMS-986442 Dose	Updated reports of preliminary data from BMS-986442 studies.	Data associated with BMS-986442/AGEN1777 monotherapy study have been updated to align with Investigator Brochure v02 released on 21-Oct-2022.
Section 5.1.1: Screening	Information was added regarding reconsenting of participants who exceed the 28-day screening period due to study-related procedures.	Information provided for extending the screening period.
Section 7.1: Study Interventions Administered	Updated Table 7.1-1: Study Interventions for Parts A to C; updated Table 7.1-2: Study Interventions for Parts D and E.	The chemotherapy (docetaxel, carboplatin, pemetrexed, and paclitaxel) classifications have been updated to Investigational Medicinal Product (IMP) based on current regulatory guidance. Footnotes have been modified to reference chemotherapy subsection numbers.
Section 7.7.4: Palliative Local Therapy	Added new section.	Additional guidance for on-treatment palliative radiotherapy was added for clarity.
Table 9.4.4-1: Clinical Laboratory Assessments	Removed row indicating testing for drugs of abuse.	Correction of an inadvertent error.
All	Minor edits and formatting and typographical corrections.	Minor; therefore have not been summarized.

TABLE OF CONTENTS

1 PROTOCOL SUMMARY

Protocol Title:

A Phase 1b/2 Study of BMS-986442 in Combination with Nivolumab or Nivolumab and Chemotherapies in Participants with Advanced Solid Tumors and Non-small Cell Lung Cancer

Brief Title:

A Phase 1b/2 Study of BMS-986442 with Nivolumab with or without Chemotherapy in Solid Tumors and Non-small Cell Lung Cancer

Rationale:

BMS-986442 (AGEN1777) is a fragment crystallizable-engineered bispecific human immunoglobulin gamma 1 antibody that selectively binds to [redacted] and [redacted] on certain populations of T cells and natural killer (NK) cells. As a dual antagonist, BMS-986442 is designed to block [redacted] binding to their shared ligand ([redacted]) and facilitate T-cell and NK cell activation by relieving inhibitory signals and enabling [redacted] to bind to the stimulatory receptor CD226.

Recent preclinical evidence supports that the programmed cell death protein 1 (PD-1) pathway may directly inhibit CD226 signaling and that the blockade of [redacted] PD-1 pathways would be required for full restoration of CD226 co-stimulation and T-cell priming. Consistent with this, the combination of BMS-986442 with an anti-PD-1 antibody in human peripheral blood mononuclear cells stimulated with staphylococcal enterotoxin A peptide generated superior T-cell stimulation compared with BMS-986442, anti-PD-1, or the control antibodies alone. As chemotherapy increases tumor antigen delivery to antigen-presenting cells and subsequent T-cell priming, addition of chemotherapy to BMS-986442 and anti-PD-ligand(L)-1 treatment may further broaden the anti-tumor response and enhance therapeutic efficacy.

Taken together, these findings support the clinical rationale to combine BMS-986442 with a PD(L)-1 agent such as nivolumab (either alone or in combination with chemotherapy) to enhance anti-tumor efficacy in cancer patients.

Objectives and Endpoints:

Objectives	Endpoints
Primary	
• To characterize the safety and tolerability, and to establish the MTD, MAD, and/or RP2D of BMS-986442 in combination with nivolumab or with nivolumab and the following chemotherapies: docetaxel; carboplatin and pemetrexed; carboplatin and paclitaxel, in participants with advanced cancer including NSCLC.	• Incidence of AEs, SAEs, AEs meeting protocol-defined DLT criteria, AEs leading to discontinuation, and death (per CTCAE v5.0).

Objectives	Endpoints
Secondary	
• To characterize the PK of BMS-986442 administered in combination with nivolumab or in combination with nivolumab and chemotherapy.	• Summary measures of BMS-986442 PK parameters such as, but not limited to, Cmax, Tmax, and AUC (0-T), from serum concentration-time data for BMS-986442 when administered in combination with nivolumab or in combination with nivolumab and chemotherapy.
• To characterize the immunogenicity of BMS-986442 administered in combination with nivolumab or in combination with nivolumab and chemotherapy.	• Incidence of ADAs to BMS-986442 when BMS-986442 is administered in combination with nivolumab or in combination with nivolumab and chemotherapy.
• To assess the preliminary anti-tumor activity of BMS-986442 administered in combination with nivolumab or nivolumab and chemotherapy.	• ORR, DOR, DCR, and PFSR at 6 months and 12 months per RECIST v1.1 by Investigator.

Abbreviations: ADA, anti-drug antibody; AE, adverse event; AUC (0-T), area under the serum concentration-time curve from time zero to the time of the last quantifiable concentration; Cmax, maximum observed concentration; CTCAE, Common Terminology Criteria for Adverse Events; DCR, disease control rate; DLT, dose-limiting toxicity; DOR, duration of response; MAD, maximum administered dose; MTD, maximum tolerated dose; NSCLC, non-small cell lung cancer; ORR, overall response rate; PFSR, progression-free survival rate; PK, pharmacokinetics; RP2D, recommended Phase 2 dose(s); SAE, serious adverse event; Tmax, time of maximum observed concentration; v, version.

Overall Design:

CA115001 is a Phase 1b/2 multi-center, open-label study of BMS-986442 administered in combination with nivolumab or nivolumab with 1 of 3 standard chemotherapy regimens used in the treatment of advanced solid tumors and advanced or metastatic non-small cell lung cancer (NSCLC): docetaxel, carboplatin with pemetrexed, and carboplatin with paclitaxel. The study is composed of 6 parts. For all study parts nivolumab will be given at a fixed dose of 360 mg every 3 weeks (Q3W).

- Part A: Dose escalation of BMS-986442 in combination with nivolumab in participants with advanced solid tumors
- Part B: Dose expansions for BMS-986442 in combination with nivolumab
  - Part B1: Randomized dose expansions in 2L+ post-immuno-oncology (IO)/platinum-doublet NSCLC
  - Part B2: Dose expansions in post-IO gastric cancer/gastroesophageal junction and post-IO squamous cell carcinoma of the head and neck (SCCHN)
- Part C: Dose escalation of BMS-986442 in combination with nivolumab and docetaxel in 2L+ post-IO/platinum-doublet NSCLC
- Part D: Dose escalation of BMS-986442 in combination with nivolumab and carboplatin and pemetrexed in 1L non-squamous NSCLC
- Part E: Dose escalation of BMS-986442 in combination with nivolumab and carboplatin and paclitaxel in 1L squamous NSCLC

- Part F may include randomized cohorts to evaluate whether BMS-986442 (either as monotherapy or in combination) can produce clinical benefit in participants with advanced/metastatic NSCLC. The design of Part F will be reported in a future amendment.

All participants will be centrally assigned to treatment (Parts A, B2, C, D, and E) or randomized (Part B1 and Part F) using Interactive Response Technology.

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

Number of Participants:

The approximate total number of participants treated in Parts A to E will be 225.

Study Population:

Main Inclusion Criteria:

- Participants in all parts of the study must have measurable disease per Response Evaluation Criteria in Solid Tumors (RECIST) v1.1.
- Participants in Part A, advanced solid tumors, must meet all of the following:
  - Documented histologically or cytologically confirmed advanced unresectable/metastatic solid malignancy of any histology.
  - Have progressed on, are ineligible for, or intolerant of existing therapy(ies) known to provide clinical benefit for the condition of the participant.
  - Have experienced radiographically documented progressive disease on or after the most recent therapy.
- Participants in Part B2 gastric cancer/gastroesophageal junction (GEJ) expansion must meet all of the following:
  - Advanced or metastatic gastric or GEJ cancer and have progressed during or after, or been intolerant to, at least 1 standard treatment regimen in the advanced or metastatic setting (or have progressed within 6 months of adjuvant therapy).
  - Disease progression while on or after prior PD-(ligand[L])1 treatment as monotherapy or in combination with other modalities.
  - Participants with known human epidermal growth factor receptor 2 (HER2)-positive gastric cancer and must have received prior treatment with a HER2 inhibitor (eg, trastuzumab).
- Participants in Part B2 SCCHN expansion must meet all of the following:
  - Documented histologically confirmed, recurrent, or metastatic SCCHN (oral cavity, pharynx, larynx), and not amenable to local therapy with curative intent. Any other cancers of the head and neck, including nasopharyngeal cancer, salivary gland, and neuroendocrine tumors, are excluded.
  - Disease progression on or after, or been intolerant to, a platinum-containing regimen.
  - Prior focal palliative radiotherapy must have been completed at least 2 weeks before study drug administration.

  - Documented historical human papillomavirus (HPV) status for oropharyngeal cancers. HPV status should preferably be determined using p16 immunohistochemistry or HPV polymerase chain reaction (if available).
  - Disease progression while on or after prior PD-(L)1 treatment as monotherapy or in combination with other modalities, if available.
- Participants in Parts B1 and C, NSCLC, must meet all of the following:
  - Documented histologically or cytologically confirmed metastatic NSCLC of non-squamous or squamous histology with Stage IV A/B (as defined by the 8th International Association for the Study of Lung Cancer Classification) or recurrent disease following multi-modal therapy for locally advanced disease, measurable by RECIST v1.1
  - Recurrent or progressive disease during or after platinum-doublet chemotherapy (PDCT) for advanced or metastatic disease, OR must have recurrent or progressive disease within 6 months after completing PDCT for local disease.
  - Disease progression while on or after prior PD-(L)1 treatment as monotherapy or in combination with other modalities.
  - Prior definitive chemoradiation for locally advanced disease is permitted as long as the last administration of chemotherapy or radiotherapy (whichever was given last) occurred less than 6 months prior to enrollment.
  - Participants with disease having known actionable mutations in epidermal growth factor receptor (EGFR) including exon 20 insertion mutations, anaplastic lymphoma kinase (ALK), ROS proto-oncogene 1 (ROS1), rearranged during transfection (RET), neurotrophic tropomyosin-receptor kinase (NTRK), Kirsten rat sarcoma (KRAS) (G12C), MET exon 14 skipping mutations, or proto-oncogene B-Raf (BRAF) (V600E) must have progressed on, have been intolerant to, or not be a candidate for standard targeted therapy (as available per country/region standard-of-care practices).
  - Experienced radiographically documented progressive disease on or after the most recent therapy.
- [redacted]
- Participants in Parts D and E, NSCLC, must meet all of the following:
  - Documented histologically or cytologically confirmed metastatic NSCLC of non-squamous (Part D) or squamous (Part E) histology with Stage IVA/B (as defined by the 8th International Association for the Study of Lung Cancer Classification) or recurrent disease following multi-modal therapy for locally advanced disease, measurable by RECIST v1.1, who have not had systemic therapy for metastatic or recurrent disease.
  - Participants with disease having known genetic aberrations in EGFR including exon 20 insertion mutations, ALK, ROS1, KRAS (G12C), RET, NTRK, MET exon 14 skipping mutations, or BRAF (V600E) that are sensitive to targeted therapy (as available per country/region standard-of-care practices) will be excluded.

  - Prior definitive chemoradiation for locally advanced disease is permitted as long as the last administration of chemotherapy or radiotherapy (whichever was given last) occurred at least 6 months prior to enrollment.
  - Prior adjuvant or neoadjuvant chemotherapy for early-stage lung cancer is permitted if completed at least 6 months prior to initiating study treatment.
- Part F: Criteria for Part F will be similar to either Part C or Parts D/E, dependent on the population chosen (either post-PDCT and anti-PD-[L1] therapy or treatment-naive NSCLC), and will be added via a future amendment.

Main Exclusion Criteria:

- Untreated symptomatic central nervous system metastases or leptomeningeal metastases.
- Concurrent malignancy (present during screening) requiring treatment, or history of prior malignancy active within 2 years prior to randomization in study Part B1 or treatment assignment in all other study parts.
- Participants with an active, known, or suspected autoimmune disease.
- Participants with a condition requiring systemic treatment with either corticosteroids (> 10 mg daily prednisone equivalent) within 14 days or other immunosuppressive medications within 30 days of randomization in study Part B1 or treatment assignment in all other study parts.
- Previous severe acute respiratory syndrome coronavirus disease 2 infection within 10 days for mild or asymptomatic infections, or 20 days for severe/critical illness prior to C1D1.
- Radiation therapy within 2 weeks prior to first study treatment.
- Prior treatment with an anti-PD-1, anti-PD-L1, or anti-cytotoxic T-lymphocyte-associated antigen 4 antibody, or any other antibody or drug specifically targeting T-cell co-stimulation or checkpoint pathways for Parts D and E.
- Systemic anticancer therapies or biological therapies within 4 weeks or 5 half-lives (whichever is shorter) prior to the first administration of study treatment.
- Prior therapy with an anti-[redacted] or anti-[redacted] antibody.
- Part C: Prior docetaxel therapy is not permitted.
- Parts D, and E: Prior systemic therapy for advanced or metastatic NSCLC is not permitted.

Intervention Groups and Duration:

- The screening period will be up to 28 days and begins by establishing the participant's initial eligibility after signing the informed consent form. The treatment period will last a maximum of approximately 35 cycles (105 weeks) from the first dose of study treatment, even if the study is terminated and regardless of treatment delays. The follow-up period includes a safety follow-up and a survival follow-up that begin after the end of treatment visit or date of last dose (whichever occurs later). The safety follow-up period for all treatment groups is 100 days after the end-of-treatment visit or date of last dose (whichever occurs later), with visits to occur at 30, 60, and 100 (± 7) days. Survival follow-up for all parts will begin on the date of discontinuation of study treatment and last for a period of 2 years (approximately 105 weeks)

or until death, lost to follow-up, withdrawal of consent, conclusion of the study, or study termination, whichever comes first.

- Dosing regimens are as follows, dependent on treatment assignment or randomization:
  - Nivolumab and BMS-986442: Participants will receive nivolumab at a dose of 360 mg Q3W over an approximately 30-minute infusion. Participants will receive BMS-986442 (20 mg dose level up to and including 600 mg dose level) Q3W administered as a 60-minute infusion at the dose level indicated, dependent on treatment assignment or randomization. BMS-986442 at the 1200 mg dose level will be administered as an infusion over 90 minutes (Q3W). There will be no intra-subject dose escalations or reductions of BMS-986442 or nivolumab allowed. Doses of study drug(s) may be interrupted, delayed, or discontinued, depending on how well the participant tolerates the treatment.
  - Docetaxel: Participants will receive Q3W docetaxel infusion at a dose based on body weight, using body surface area formula per institution practice.
  - Pemetrexed: Participants will receive pemetrexed at a dose of 500 mg/m^2 as a 10-minute intravenous (IV) infusion on Day 1 of each cycle. Pemetrexed will be administered on Cycle 1 through Cycle 4. Participants who have SD or response are permitted to receive pemetrexed 500 mg/m^2 alone as maintenance therapy until disease progression or unacceptable toxicity.
  - Carboplatin: Carboplatin should be given following pemetrexed (Part D) or paclitaxel (Part E) on Day 1 of each cycle, and the carboplatin dose will be calculated using the Calvert formula. The dose of carboplatin may be capped per local standards. Carboplatin will be administered for up to 4 cycles.
  - Paclitaxel: Participants will receive paclitaxel 200 mg/m^2 as a 180-minute IV infusion with carboplatin at a dose of area under the serum concentration-time curve (AUC) 5 or AUC 6 for Part D or AUC 6 for Part E as a 30-minute IV infusion on Day 1 of a 3-week cycle, or at doses per the local prescribing information. The infusion time can follow local institutional standards. Paclitaxel will be administered for up to 4 cycles. Paclitaxel dosing calculations should be based on body surface area.

Study Intervention:

Study Intervention for CA115001		
Medication	**Potency**	**IMP/Non-IMP/AxMP**
BMS-986442	[redacted] mg/vial	IMP
Nivolumab	100 mg/vial	IMP
Docetaxel	Various strengths	IMP
Carboplatin	450 mg/vial/various strengths	IMP
Pemetrexed	500 mg/vial/various strengths	IMP
Paclitaxel	100 mg/vial/various strengths	IMP

Abbreviations: AxMP, auxiliary medicinal product; IMP, investigational medicinal product.

Statistical Methods

In Parts A, C, D, and E of the study, at least 3 participants will be enrolled per dose level, and dose escalation decisions will be guided by Bayesian optimal interval (BOIN) design to identify the maximum tolerated dose (MTD). The final recommended MTD/maximum administered dose (MAD)/recommended Phase 2 dose (RP2D) will be based on recommendation from the BOIN and overall clinical assessment of all available safety, pharmacokinetic, pharmacodynamic, and efficacy data. A Bayesian continuous monitoring framework will be utilized for continuous monitoring of toxicity for a safety-evaluation period of 28 days of treatment and to detect safety signals that may lead to changes in study conduct.

Interim analyses may be performed for administrative purposes or publications. No formal inferences requiring any adjustment to statistical significance level will be performed.

Statistical methods for the randomized expansion in Part F will be introduced via amendment when the patient population is determined.

Data Monitoring Committee:

A Data Monitoring Committee (DMC) will not be used in the study.

Other Committee: Yes

Although there is not a formal DMC for this study, BMS has developed a multi-layered process to ensure safety monitoring through close collaboration of study site Investigators, the BMS study team, and the BMS Worldwide Patient Safety (WWPS)-led Safety Management Team, which will be employed in this study. To support safety oversight, BMS has established ongoing processes for collection, review, analysis, and submission of individual adverse event reports and their aggregate analyses. Signal detection will be performed at least monthly and ad hoc throughout the study. Because this is an open-label study, WWPS, the BMS Medical Monitor, and the Investigators will have access to all data necessary for safety evaluation.

[redacted]

Brief Summary:

The purpose of this study is to characterize the safety and tolerability, and to establish the MTD, MAD, and/or RP2D of BMS-986442 in combination with nivolumab or with nivolumab and chemotherapy in participants with advanced cancer, including NSCLC. Study details include the following:

Study Duration: Maximum of 4 years (up to of 35 cycles [105 weeks] from first dose of study treatment and up to 2 years on follow-up).

Study Intervention Duration: Maximum of approximately 35 cycles (105 weeks) from the first dose of study treatment.

Study Visit Frequency: On-treatment monitoring will include planned clinic visits on Cycle 1 Days 1, 2, 8, and 15; Cycle 2 Days 1, 2, and 8; and Day 1 of Cycles 3 and beyond. The safety

follow-up visits will occur at 30, 60, and 100 (± 7) days after the end of treatment visit or date of last dose (whichever occurs later).

2 SCHEDULE OF ACTIVITIES

Table 2-1: Screening Procedural Outline for All Parts (CA115001)

Procedure	Screening Visit (Day -28 to -1)	Notes
Eligibility Assessments		
Informed Consent	X	Must be obtained prior to performing any screening procedures. A participant is considered enrolled only when a protocol-specific informed consent is signed. 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.
Contact IRT	X	Register in interactive response system to obtain participant number. See Section 7.2 (Method of Study Intervention Assignment).
Inclusion/Exclusion Criteria	X	Must be confirmed prior to cohort assignment (Parts A, B2, C, D, and E) or cohort randomization (Part B1 and Part F) in IRT.
Medical History	X	All medical history relevant to disease under study, including tobacco history and any clinically significant toxicities or allergies related to previous treatments.
HPV Status for SCCHN	X	HPV status for oropharyngeal cancers, preferably using p16 IHC or HPV PCR, if available.
HER2 Status for Gastric/GEJ	X	HER2-positive status, if available.
Mutation Status for NSCLC	X	EGFR (including exon 20 insertion mutations), ALK, ROS1, RET, NTRK, KRAS (G12C), MET exon 14 skipping mutations, and BRAF (V600E) status if available.
Prior Cancer Therapies	X	Includes all prior cancer treatment regimens including medications, surgery, and radiation.
Safety Assessments		
Physical Examination (PE) and Physical Measurements	X	Includes height, weight, and BMI. If the screening PE is performed within 3 days prior to dosing on Day 1, then a single exam may count as both the screening and predose evaluation.
ECOG PS	X	See Appendix 6.
Vital Signs and Oxygen Saturation	X	Includes body temperature, respiratory rate, seated blood pressure, and seated heart rate. Blood pressure and heart rate should be measured after the participant has been resting quietly for at least 5 minutes. Obtain Pulse oximetry at rest.

Table 2-1: Screening Procedural Outline for All Parts (CA115001)

Procedure	Screening Visit (Day -28 to -1)	Notes
ECG	X	Single ECG should be recorded after the participant has been supine for at least 5 minutes and prior to blood draws (see Section 9.4.3).
Clinical Laboratory Assessments (Hematology, Chemistry, and Urinalysis)	X	Includes blood and urine samples. Safety labs and urinalysis do not need to be repeated if performed within 3 days of C1D1. Refer to Section 9.4.4 and Table 9.4.4-1.
FSH	X	Women only, as needed to document postmenopausal status. See Appendix 4.
Pregnancy Test (WOCBP only)	X	Serum or urine pregnancy test (minimum sensitivity equivalent units 25 IU/L or equivalent units of hCG) to be done at screening visit and repeated within 24 hours prior to first dose of study treatment. If the pregnancy test at screening is taken within 24 hours of dosing (C1D1), a repeat pregnancy test within 24 hours prior to first dose of study treatment is not required. WOCBP must have a negative pregnancy test within 24 hours prior to the start of study intervention and results also must be evaluated prior to study intervention administration. An extension up to 3 days prior to the start of study intervention administration is permissible in situations where results cannot be obtained within standard 24-hour window.
Serology	X	See Section 9.4.4. For HIV: testing at sites where locally mandated.
Assessment of Signs and Symptoms	X	Collected from the date of participant's written consent until prior to C1D1.
AEs and SAE Assessment	X	All AEs (SAEs or non-serious AEs) associated with SARS-CoV-2 infection collected from time of consent. All SAEs must be collected from the date of participant's written consent and collection of AE should begin at initiation of study treatment. All AEs/SAEs must be graded using CTCAE v5.
Concomitant Medication Use	X	Within 14 days prior to cohort assignment (Parts A, B2, C, D, and E) or cohort randomization (Part B1 and Part F) in IRT. Vaccine use (including COVID-19) must be collected within 30 days prior to first dose of study drug See Section 6.2 (Exclusion Criteria).
Tumor Assessments (Baseline)		
Body Imaging	X	Contrast-enhanced CT of the chest, abdomen, pelvis, and all other known and/or suspected sites of disease. CT/MRI of the neck is required only for SCCHN participants. Refer to Imaging Assessment details in Section 9.1.1.

Table 2-1: Screening Procedural Outline for All Parts (CA115001)

Procedure	Screening Visit (Day -28 to -1)	Notes
Brain Imaging	X	MRI of the brain without and with contrast is required for participants with NSCLC and/or those without NSCLC that have known or suspected brain metastases, unless participant has completed an imaging study of the brain within 28 days prior to the date of first dose of study treatment. CT of the brain without and with contrast can be performed if MRI is contraindicated. See Section 9.1.1 for further details.
[redacted]		

Abbreviations: AE; adverse event; ALK, anaplastic lymphoma kinase; BMI; body mass index; BRAF, proto-oncogene B-Raf; C, cycle; COVID-19, coronavirus disease 2019; CT; computed tomography; CTCAE, Common Terminology Criteria for Adverse Events; D, Day; ECG, electrocardiogram; ECOG PS, Eastern Cooperative Oncology Group Performance Status; EGFR, epidermal growth factor receptor; FSH, follicle-stimulating hormone; GEJ, gastroesophageal junction; hCG, human chorionic gonadotropin; HER2, human epidermal growth factor receptor 2; HIV, human immunodeficiency virus; HPV, human papillomavirus; IHC, immunohistochemistry; IRT, Interactive Response Technology; IU, international units; KRAS, Kirsten rat sarcoma; MRI, magnetic resonance imaging; NSCLC, non-small cell lung cancer; NTRK, neurotrophic tropomyosin-receptor kinase; PCR, polymerase chain reaction; PE, physical examination; RET, rearranged during transfection; ROS1, ROS proto-oncogene 1; SARS-CoV-2, severe acute respiratory syndrome coronavirus disease 2; SAE, serious adverse event; SCCHN, squamous cell carcinoma of the head and neck; v, version; WOCBP, women of child-bearing potential.

Table 2-2: On-Treatment Procedural Outline for All Parts (CA115001)

Procedure[a] (1 Cycle = 3 Weeks)	Cycle 1				Cycle 2			Cycle 3 and Beyond	EOT[b]/Early Termination	Notes[c]
	D1	D2	D8	D15	D1	D2	D8	D1		After C1D1, the visit window is ± 3 days.
Safety Assessments										
Complete PE	X								X	If the screening PE is performed within 3 days prior to dosing on Day 1, then a single exam may count as both screening and predose evaluation.
Targeted Physical Examination (PE)			X	X	X		X	X		If there are any new or worsening clinically significant changes since the last examination, report changes on the appropriate non-serious or SAE CRF page.
ECOG PS	X				X			X	X	See Appendix 6.
Vital Signs, Physical Measurements, and Oxygen Saturation [d]	X		X	X	X		X	X	X	Includes body temperature, body weight and BMI, respiratory rate, seated blood pressure, and seated heart rate. BP and heart rate should be measured after the participant has been resting quietly for at least 5 minutes. Pulse oximetry at rest.
ECGs	X				X			X	X	ECGs should be recorded after the participant has been supine for at least 5 minutes, and prior to blood draws. A single 12-lead safety ECG to be done pre-dose on Day 1 of all treatment cycles (all study parts). See Section 9.4.3.

Table 2-2: On-Treatment Procedural Outline for All Parts (CA115001)

Procedure[a] (1 Cycle = 3 Weeks)	Cycle 1				Cycle 2			Cycle 3 and Beyond	EOT[b]/Early Termination	Notes[c]
	D1	D2	D8	D15	D1	D2	D8	D1		After C1D1, the visit window is ± 3 days.
Clinical Laboratory Assessments (Hematology and Chemistry)	X		X	X	X		X	X	X	Perform on site/local laboratory testing within 3 days prior to each dose. For the first treatment visit, labs need not be repeated if performed within 3 days and the results are available and have been reviewed for eligibility. If the participant has an IRR, draw additional blood for a cytokine panel to be performed on site/local laboratory. Refer to Section 9.4.4 for the list of laboratory tests to be conducted.
Thyroid Function Test (TSH)	X				X			X	X	If TSH is abnormal, reflexive fT3 and fT4 should be collected. See Section 9.4.4 and Table 9.4.4-1.
Urinalysis	X				X			X	X	Refer to Section 9.4.4.
Pregnancy Test (WOCBP)	X				X			X	X	Serum or urine pregnancy test (minimum sensitivity equivalent units 25 IU/L or equivalent units of hCG) within 24 h prior to first dose and then every 3 weeks. Sample should be drawn within 24 h of Day 1 of each cycle, and results must be available and reviewed prior to administration of study treatment on Day 1 of each cycle while on study treatment. An extension up to 3 days to the start of study treatment or Day 1 of Cycle 2 and beyond is permissible in situations where results cannot be obtained within standard 24-h window.

Table 2-2: On-Treatment Procedural Outline for All Parts (CA115001)

Procedure[a] (1 Cycle = 3 Weeks)	**Cycle 1**				**Cycle 2**			**Cycle 3 and Beyond**	**EOT[b]/Early Termination**	**Notes[c]**
	D1	**D2**	**D8**	**D15**	**D1**	**D2**	**D8**	**D1**		**After C1D1, the visit window is ± 3 days.**
Monitor for AEs and Serious Adverse Events (SAEs)	Record at each visit. All AEs (SAEs or nonserious AEs, including those associated with SARS-CoV-2 infection) must be collected continuously during the treatment period until 100 days post discontinuation of dosing. All SAEs must be collected from the date of participant's written consent until 100 days post discontinuation of dosing or participation in the study, if the last scheduled visit occurs at a later time. All AEs/SAEs must be graded using CTCAE v5.									
Concomitant Medication Use	Continuously; see notes									Record at each visit
PK and Immunogenicity Assessments										
PK/Immunogenicity (IMG) Serial Blood Sampling	There is an additional PK draw on Cycle 1 Day 5. Refer to PK/IMG Collection Table 9.5-1 for timing of collections									
[redacted]										

Table 2-2: On-Treatment Procedural Outline for All Parts (CA115001)

Procedure[a] (1 Cycle = 3 Weeks)	Cycle 1				Cycle 2			Cycle 3 and Beyond	EOT[b]/Early Termination	Notes[c]
	D1	D2	D8	D15	D1	D2	D8	D1		After C1D1, the visit window is ± 3 days.
Tumor Assessments[e]										
Body Imaging	Contrast-enhanced CT of the chest, abdomen, pelvis, and all other known and/or suspected sites of disease should occur every 6 weeks starting from date of first dose (± 7 days) for the first 48 weeks, then every 12 weeks (± 7 days) until withdrawal of consent, death, or initiation of another anti-cancer treatment, whichever occurs first. For participants with SCCHN, a CT or MRI of the neck is also required. See Section 9.1.1 for further details.									
Brain Imaging	Participants with NSCLC and/or a history of brain metastasis or symptoms should have a surveillance MRI (without and with contrast) per standard of care (approximately every 12 weeks), or sooner if clinically indicated. CT of the brain without and with contrast can be performed if MRI is contraindicated. See Section 9.1.1 for further details.									
Study Intervention[f]										
Nivolumab (All Parts)	X				X			X		Nivolumab 360 mg Q3W
BMS-986442 (All Parts)	X				X			X		BMS986442 Q3W
Docetaxel (Part C)	X				X			X		Docetaxel Q3W
Carboplatin (Parts D and E)	X				X			X		Carboplatin will be administered Cycle 1 through Cycle 4 (Q3W).
Pemetrexed (Part D)	X				X			X		Pemetrexed will be administered Cycle 1 through Cycle 4 (Q3W). Participants who have SD or response are permitted to receive pemetrexed 500 mg/m^2 as maintenance therapy until disease progression or unacceptable toxicity.
Paclitaxel (Part E)	X				X			X		Paclitaxel will be administered Cycle 1 through Cycle 4 (Q3W).

Abbreviations: AE; adverse event; BMI, body mass index; BMS, Bristol-Myers Squibb; BP, blood pressure; CRF, Case Report Form; CT, computed tomography; CTCAE, Common Terminology Criteria for Adverse Events; C, cycle; D, Day; ECG, electrocardiogram; ECOG PS, Eastern Cooperative Oncology Group Performance Status; EOI, end of infusion; EOT, end of treatment; fT3, free triiodothyronine; fT4, free thyroxine; h, hour; hCG, human chorionic gonadotropin; IMG, immunogenicity; IRR, infusion-related reaction; IU, international units; MRI, magnetic resonance imaging; NSCLC, non-small cell lung cancer; PE, physical

examination; PK, pharmacokinetic; Q3W, every 3 weeks; RECIST v1.1, response evaluation criteria in solid tumors version 1.1; SAE, serious adverse event; SARS-CoV-2, severe acute respiratory syndrome coronavirus disease 2; SCCHN, squamous cell carcinoma of the head and neck; SD, stable disease; TSH, thyroid-stimulating hormone; v, version; WOCBP, women of childbearing potential.

[a] If a dose is delayed, the procedures schedule for that same time point must also be delayed to coincide with when that time point's dosing actually occurs, with the exception of tumor assessments, which must occur as scheduled.

[b] EOT is defined as the time point where the decision is made to discontinue the participant from treatment. Evaluations will be performed prior to study discharge. For participants who complete all scheduled cycles of therapy, the EOT visit will be the same as the last scheduled and completed on-treatment visit as the start of the safety follow-up period. For participants who do not complete all scheduled cycles of therapy, the EOT visit will be the most recent on-treatment visit (with all available safety and response data); it does not need to be repeated and will be considered the start of the safety follow-up period.

[c] Some of the assessments referred to in this section may not be captured as data in the CRF. 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.

[d] Heart rate, BP, temperature, respiratory rate, and oxygen saturation will be obtained at the following timepoints (± 5 minutes for all timepoints):

- Nivolumab: At the start and EOI
- BMS-986442: At infusion start and every 30 minutes throughout 60-minute infusion and every 30 minutes for the next hour following EOI.
- Docetaxel: At infusion start and every 30 minutes throughout 60-minute infusion. 120-minute observation for first 2 cycles if participant does not experience any IRR, then they should be observed for at least 1 hour for all subsequent cycles (vitals every 30 minutes).
- Carboplatin: At infusion start and end. 120-minute observation for first 2 cycles if participant does not experience any IRR, then they should be observed for at least 1 hour for all subsequent cycles (vitals every 30 minutes).
- Pemetrexed: At infusion start.
- Paclitaxel: At infusion start and every 15 minutes for the first 30 minutes of infusion, subsequently every 30 minutes throughout 180-minute infusion.
- If any vital sign is abnormal (based upon clinical assessment) at the final check, the participant must be observed for an additional period of time, as clinically indicated.

[e] The same imaging modality is to be used for all assessments, per RECIST v1.1 (Appendix 5). If dosing is delayed, tumor assessments should continue on this imaging schedule. If the participant discontinues treatment, see Table 2-3.

[f] See Section 7 for study intervention and administration details. Participant must receive the first dose of study treatment within 3 calendar days from vial allocation.

Table 2-3: Follow-Up Procedural Outline for All Study Parts (CA115001)

Procedure	Follow-up Visit 1: 30 Days From Last Dose of Study Intervention (± 7 Days)[a]	Follow-up Visit 2: 60 Days From Last Dose of Study Intervention (± 7 Days)[a]	Follow-up Visit 3: 100 Days From Last Dose of Study Intervention (± 7 Days)[a]	Survival Follow-up (Assessed Every 12 Weeks ± 14 Days for 2 Years From Last Dose of Study Intervention)[b]	Notes[c]
Safety Assessments					
Targeted Physical Examination (PE)	X	X	X		If there are any new or worsening clinically significant changes since the last examination, report changes on the appropriate non-serious or SAE CRF page.
Vital Signs and Physical Measurements	X	X	X		Weight, seated BP, seated heart rate, body temperature, and respiratory rate. BP and heart rate should be measured after the participant has been resting quietly for at least 5 minutes.
ECOG PS	X	X	X		See Appendix 6.
Hematology, Chemistry, and Urinalysis	X	X	X		Refer to Section 9.4.4 Clinical Safety Laboratory Assessments for the list of laboratory tests and urinalysis.
Pregnancy Test (WOCBP)	X	X	X		Serum or urine (minimum sensitivity equivalent units 25 IU/L or equivalent units of hCG) pregnancy testing is required. If a urine test cannot be confirmed as negative (eg, an ambiguous result), a serum pregnancy test is required.

Table 2-3: Follow-Up Procedural Outline for All Study Parts (CA115001)

Procedure	Follow-up Visit 1: 30 Days From Last Dose of Study Intervention (± 7 Days)[a]	Follow-up Visit 2: 60 Days From Last Dose of Study Intervention (± 7 Days)[a]	Follow-up Visit 3: 100 Days From Last Dose of Study Intervention (± 7 Days)[a]	Survival Follow-up (Assessed Every 12 Weeks ± 14 Days for 2 Years From Last Dose of Study Intervention)[b]	Notes[c]
Adverse Event (AE) and Serious Adverse Events (SAE) Assessment	X	X	X	See notes.	Record at each visit. Collect continuously throughout the treatment period and for a minimum of 100 days following discontinuation of dosing. Beyond 100 days from the last dose of study therapy, participants will be followed for drug-related AEs/SAEs until resolution, returns to baseline, or is deemed irreversible, or until the participant is lost to follow-up or withdraws study consent. Participants will be followed for all AEs (SAEs and non-serious AEs) associated with confirmed or suspected SARS-CoV-2 infection (as defined in Section 9.2.3). All AEs/SAEs must be graded using CTCAE v5.
Concomitant Medications Review	X	X	X		Record at each visit.
Tumor Assessments					
Body Imaging	Participants without progressive disease at EOT will have contrast-enhanced CT of the chest, CT/MRI of the abdomen, pelvis, and all other known and/or suspected sites of disease every 6 weeks (± 7 days) starting from first dose up until Week 48, and then every 12 weeks (± 7 days) until withdrawal of consent, death, or initiation of another anti-cancer treatment, whichever occurs first. For participants with cancer of the head and neck, a CT or MRI of the neck is required.				
Brain Imaging	Participants with NSCLC and/or a history of brain metastasis or symptoms without progressive disease at EOT should have a surveillance MRI (without and with contrast) per standard of care (approximately every 12 weeks), or sooner if clinically indicated. CT of the brain without and with contrast can be performed if MRI is contraindicated. See Section 9.1.1. for further details.				

Table 2-3: Follow-Up Procedural Outline for All Study Parts (CA115001)

Procedure	Follow-up Visit 1: 30 Days From Last Dose of Study Intervention (± 7 Days)[a]	Follow-up Visit 2: 60 Days From Last Dose of Study Intervention (± 7 Days)[a]	Follow-up Visit 3: 100 Days From Last Dose of Study Intervention (± 7 Days)[a]	Survival Follow-up (Assessed Every 12 Weeks ± 14 Days for 2 Years From Last Dose of Study Intervention)[b]	Notes[c]
Pharmacokinetic (PK) and Immunogenicity Assessments					
PK/Immunogenicity (IMG) Serial Blood Sampling	Refer to Table 9.5-1 for timing of collections.				
Participant Status					
Assessment of Survival Status and Subsequent Cancer Therapy	X	X	X	X	During Safety Follow-Up and every 3 months (clinic visit or by telephone) during Survival Follow-up. Include documentation of subsequent cancer therapy (ie, systemic therapy, tumor-directed surgery, or radiation therapy).

Abbreviations: AE; adverse event; BMS, Bristol-Myers Squibb; BP, blood pressure; CRF, case report form; CT, computed tomography; CTCAE, Common Terminology Criteria for Adverse Events; ECOG PS, Eastern Cooperative Oncology Group Performance Status; EOT, end of treatment; hCG, human chorionic gonadotropin; IMG, immunogenicity; IU, international units; MRI, magnetic resonance imaging; NSCLC, non-small cell lung cancer; PE, physical examination; PK, pharmacokinetic; SAE, serious adverse event; SARS-CoV-2, severe acute respiratory syndrome coronavirus disease 2; v, version; WOCBP, women of childbearing potential.

[a] Participants must be followed for at least 100 days after last dose of study intervention. Follow-Up Visit 1 must occur 30 days from the last dose (± 7 days) or can be performed on the date of discontinuation if that date is greater than 30 days after last dose. Follow-up Visit 2 occurs approximately 60 days (± 7) from last dose of study intervention. Follow-up Visit 3 occurs approximately 100 days (± 7) from last dose of study intervention.

[b] Survival Follow-up visits to occur every 12 weeks (± 14 days) from Follow-Up Visit 3. Survival visit may be conducted in clinic or by telephone. BMS may request that survival data be collected on all treated participants outside of the 3-month specified window. At the time of this request, each participant will be contacted to determine their survival status unless the participant has withdrawn consent for all contact or is lost to follow-up.

[c] Some of the assessments referred to in this section may not be captured as data in the CRF. 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 regulation.

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

- Pharmacokinetic sampling
- Safety (electrocardiogram)
- Safety (clinical labs)

3 INTRODUCTION

CA115001 is a Phase 1b/2 study of BMS-986442 (AGEN1777), a fragment crystallizable (Fc)-engineered bispecific human immunoglobulin gamma 1 (IgG1) antibody that selectively blocks [redacted] and may enhance T and natural killer (NK) cell activation in combination with nivolumab or with nivolumab and chemotherapy.

The main goals of the study are to characterize the safety profile of BMS-986442 in combination with nivolumab or with nivolumab and chemotherapy, and to establish the recommended Phase 2 dose(s) (RP2D) for these combinations.

Additional goals include the [redacted] characterization of the pharmacokinetics (PK) for BMS-986442 and nivolumab, evaluation of the pharmacodynamic (PD) effects through analyses of several [redacted] aimed at establishing proof of mechanism, and evaluation of the preliminary anti-tumor activity.

A detailed description of the chemistry, pharmacology, efficacy, and safety of the study treatments is provided in the respective Investigator's Brochures (IBs) and package inserts.

3.1 Study Rationale

The development of immune checkpoint therapies has improved outcomes in patients with advanced malignancies.[1] However, despite the clinical success of agents targeting programmed cell death protein 1 (PD-1) or its ligand PD-L1, most patients fail to respond or experience a limited duration of response.[2]

[redacted] and [redacted] are expressed by subsets of T and NK cells where they function as suppressive co-inhibitory receptors, including within the tumor microenvironment (TME).[3] [redacted] and [redacted] bind to [redacted] which is expressed on myeloid cells such as antigen-presenting cells (APCs) and is overexpressed on tumor cells across several tumor indications.[4] [redacted] expression has also been associated with poor response to anti-PD-1 antibody therapy, suggesting that [redacted] blockade combined with PD(L)-1 pathway inhibition may help to overcome immune checkpoint-mediated immune suppression within the TME.[4] In preclinical models, blockade of [redacted] and [redacted] through a combination of monospecific antibodies has been shown to enhance anti-tumor efficacy compared with single agent treatments, and further enhanced efficacy has been observed with triple combination treatment including anti-PD-1.[5] Further supporting the rationale to combine BMS-986442 with PD-1 blockade, recent preclinical data support that the PD(L)-1 pathway may also inhibit CD226 signaling directly via phosphatase recruitment by the PD-1 intracellular domain.[6]

There is emerging evidence that Fcγ receptor (FcγR) co-engagement may contribute to anti-tumor efficacy in pre-clinical mouse models of immune checkpoint therapies, including [redacted] antagonists.[7] FcγRIIIA (CD16) co-engagement was shown to be required for optimal APC-mediated T-cell priming by a [redacted] antibody in human immune cell assays. Based on these

findings, BMS-986442 is engineered with increased affinity to FcγRIIIA to further enhance APC-mediated T-cell priming in the context of [redacted] and [redacted] inhibition.

Taken together, these findings support the rationale to evaluate BMS-986442 in combination with nivolumab (with or without chemotherapy) for its antitumor efficacy and benefit to patients.

3.1.1 Research Hypothesis

Blockade of [redacted] and [redacted] using BMS-986442 will enhance T and NK cell anti-tumor activity in the TME, broadening the therapeutic efficacy of anti-PD-1 based immunotherapy.

3.2 Background

3.2.1 Indication Background

Within the TME, the expression of co-inhibitory receptors such as [redacted] and [redacted] on immune cells correlates with a chronically exhausted, dysfunctional phenotype and is associated with limited response to immunotherapy.[8]

The Cancer Genome Atlas (TCGA) (across 33 types of indications) supports that [redacted] and [redacted] expression are correlated and highly expressed across a variety of cancer types as compared to healthy tissues. Non-small cell lung cancer (NSCLC) and gastric cancer show particularly high expression of [redacted] and [redacted] within the TCGA dataset. [redacted] the shared ligand of [redacted] and [redacted], is reportedly overexpressed across multiple tumor indications, including NSCLC, squamous cell carcinoma of the head and neck (SCCHN), melanoma, pancreatic cancer, colorectal carcinoma (CRC), and ovarian cancer.[9] Notably, the expression of [redacted] has been correlated with poor overall survival (OS).[10] Emerging clinical data support the rationale to target PD(L)-1 pathway blockade in the context of CD226 co-stimulatory signaling to further enhance T-cell responses and drive clinical efficacy.[11] The importance of the CD226 pathway has been explored in mouse preclinical models representing gastric cancers and SCCHN. Taken together, these observations support the evaluation of BMS-986442 in combination with nivolumab (with or without chemotherapy) in a range of solid tumors, NSCLC, gastric cancer, and SCCHN.[12,13]

3.2.2 BMS-986442 Mechanism of Action

BMS-986442 is a Fc-engineered bispecific human IgG1 antibody that selectively blocks [redacted] and [redacted] ligand interactions and enhances T and NK cell activation.

Selectivity of BMS-986442 for human [redacted] and [redacted] was evaluated by surface plasmon resonance (SPR) relative to monovalent and bivalent anti-[redacted] and anti-[redacted] control antibodies. Results demonstrated that BMS-986442 specifically binds to human [redacted] and [redacted], but not to human CD226, [redacted] CD111, or CD112. Anti-[redacted] and anti-[redacted] bivalent control antibodies bound to [redacted] and [redacted], respectively and uniquely, confirming the specific binding of BMS-986442 for [redacted] and [redacted].

BMS-986442 is designed to bind [redacted] and [redacted] with high affinity to block the interaction of these receptors and their cognate ligand [redacted] BMS-986442 binds to recombinant human [redacted] and [redacted] in a dose-dependent manner with estimated average affinities (K_D) of 0.14 nM and 22.9

nM, respectively, as measured by SPR. BMS-986442 binds cynomolgus monkey [redacted] with an estimated average K_D of 2.4 nM but does not bind cynomolgus monkey [redacted] or rodent [redacted].

In competitive cell-based binding assays, BMS-986442 exhibited concentration-dependent blockade of [redacted] binding to [redacted] or [redacted]-expressing cells. For BMS-986442, mean IC_{50} values of 0.07 µg/mL ([redacted]) and 1.77 µg/mL [redacted] were determined. In contrast, the bivalent isotype control did not disrupt [redacted] nor [redacted] interactions. The monovalent anti-[redacted] control blocked [redacted] interactions but did not disrupt [redacted] interactions. Likewise, the monovalent anti-[redacted] control blocked [redacted] interactions but did not disrupt [redacted] interactions. Consistent with the mechanism of action, these data demonstrate BMS-986442 is a potent ligand-blocking antagonist of [redacted] and [redacted].

The key biophysical and functional characteristics of BMS-986442 include a high affinity and selectivity for human [redacted] and [redacted], a capacity for simultaneous antigen binding, an ability to block [redacted] and [redacted] interactions to its shared ligand [redacted] enhanced T-cell responsiveness and NK cell activation, enhanced binding to FcγRIIA and FcγRIIIA receptors, activation of FcγRIIA and FcγRIIIA signaling, and enhanced T-cell effector function in combination with the anti-PD-1 balstilimab.

3.2.3 Nivolumab Mechanism of Action

Nivolumab (also referred to as BMS-936558, MDX1106, or ONO-4538) is a human monoclonal antibody (HuMAb; immunoglobulin G4 [IgG4]-S228P) that targets the PD-1-CD279 cell surface membrane receptor. PD-1 is a negative regulatory molecule expressed by activated T and B lymphocytes. Binding of PD-1 to its ligands, PD-L1 and 2 (PD-L2), results in the down-regulation of lymphocyte activation. Inhibition of the interaction between PD-1 and its ligands promotes immune responses and antigen-specific T-cell responses to both foreign antigens as well as self-antigens. Nivolumab is expressed in Chinese hamster ovary (CHO) cells and is produced using standard mammalian cell cultivation and chromatographic purification technologies. The clinical study product is a sterile solution for parenteral administration.

Nivolumab (OPDIVO^{TM}) is approved for the treatment of several types of cancer in multiple regions including the United States (US, Dec-2014), the European Union (EU, Jun-2015), and Japan (Jul-2014).

3.2.4 BMS-986442 Clinical Activity

BMS-986442 is currently being evaluated in Study C-1400-01 (NCT#05025085), which is a Phase 1 study to evaluate the safety and tolerability, PK, immunogenicity (IMG), and PD of BMS-986442 (AGEN1777) as a single agent and in combination with balstilimab in patients with advanced, metastatic, solid tumors. As of 24-Jun-2022, only the single-agent dose escalation component of the study has been initiated. Three participants were treated at each of the 2-, 6-, 20-, and 60-mg dose levels and 4 participants were treated at the 200-mg dose level, for a total of 16 patients. Overall, the safety profile of BMS-986442 has been manageable with no dose-limiting toxicities (DLTs) or treatment-related serious adverse events (SAEs) reported thus far. One patient

with ocular melanoma who received multiple prior lines of therapies, including immunotherapy, was treated at the 6-mg dose level and has received 10 cycles of study treatment and has stable disease, which is still ongoing. It is anticipated that the study will enroll up to approximately 75 evaluable patients with measurable advanced/metastatic solid tumors.

3.2.4.1 Preliminary Safety Data of BMS-986442 Monotherapy

Overall, based on preliminary data as of 24-Jun-2022, from study C-1400-01, the safety profile of BMS-986442 as monotherapy (n = 16) was manageable at the doses tested (up to 200 mg Q3W). There were no DLTs or adverse events (AEs) that led to treatment discontinuation. Thirteen of sixteen patients had treatment-related AEs (TRAEs), with the most frequently reported being chills (n = 5 each, 31.3%), rash (n = 5, 31.3%), nausea, fatigue, and pruritus (n = 2 each, 12.5%). All treatment-related AEs were Grade 1 to 2; no Grade 3 or higher TRAEs were reported. For all TRAEs, the dose of BMS-986442 was not changed.

Infusion-related treatment-emergent AEs (TEAEs) occurred in 7 (43.8%) patients. Before prophylaxis, 6 cases of infusion-related reactions (IRRs) from 8 infusions (75%) were reported. After prophylaxis implementation, 4 cases of IRRs from 73 infusions (5.5%) were reported as of 13-Oct-2022. The most frequently reported infusion-related TEAEs were chills (31.3%), rash (12.5%), IRRs (6.3%), and nausea (6.3%). On average, infusion-related TEAEs started 1 to 2 hours after the end of the infusion and resolved with symptomatic treatment (eg, diphenydramine, meperidine, ondansetron, hydromorphone). No infusion-related TEAEs were Grade ≥ 3 and no infusion-related TEAEs led to permanent drug withdrawal or resulted in death. The incidence of IRRs has been reduced since establishing an effective prophylactic regimen of diphenhydramine, acetaminophen, and extension of the infusion duration to 60 minutes.

3.2.5 Nivolumab Clinical Activity

Nivolumab has demonstrated durable responses exceeding 6 months as monotherapy in several tumor types, including NSCLC, melanoma, renal cell carcinoma (RCC), classical Hodgkin lymphoma (cHL), small-cell lung cancer (SCLC), gastric cancer, SCCHN, urothelial cancer, hepatocellular carcinoma (HCC), and CRC. In confirmatory trials, nivolumab as monotherapy demonstrated a statistically significant improvement in OS as compared with the current standard of care in patients with advanced or metastatic NSCLC, unresectable or metastatic melanoma, advanced RCC, or recurrent or metastatic SCCHN. Details of the clinical activity in these various malignancies are provided in the United States Prescribing Information (USPI) and Summary of Product Characteristics (SmPC).

3.3 Benefit/Risk Assessment

3.3.1 Risk Assessment

Study CA0115001 is designed to begin with a BMS-986442 and nivolumab safety dose escalation in Part A, before moving into the dose expansions in Part B and the dose escalations of BMS-986442 in combination with nivolumab and the designated chemotherapies occurring in Parts C to E.

BMS-986442 Risk Assessment:

Detailed information about the known and expected benefits, risks, and reasonably anticipated adverse events (AEs) of BMS-986442 may be found in the IB.

Consistent with its mechanism of action, BMS-986442 enhances T-cell responsiveness and interleukin (IL)-2 secretion in a primary T-cell stimulation assay in which peripheral blood mononuclear cells (PBMCs) from healthy human donors are stimulated with staphylococcal enterotoxin A (SEA) peptide and increasing concentrations of BMS-986442. However, BMS-986442 did not enhance cytokine secretion in the absence of SEA peptide and therefore does not pose a significant cytokine-mediated infusion reaction or cytokine release syndrome risk as assessed using whole blood or PBMCs from healthy volunteer donors in cytokine release assays.

BMS-986442 poses a low risk for immunogenicity (IMG) as assessed in an in vitro dendritic cell:T cell co-culture activation assay. Human PBMCs were obtained from healthy donors with HLA-DR class II alleles closely reflecting world population frequencies. The frequency of a positive response was 12.8%, 15.4%, and 61.5% for BMS-986442, Avastin (low IMG control), and ATR-107 (high IMG control), respectively.

In a tissue cross reactivity study, BMS-986442-positive staining was observed on hematopoietic cells, Kupffer cells, lymphocytes, and Hofbauer cells from human tissues. The staining is considered on-target binding since it was consistent with the distribution of [redacted] in the tissues. [redacted] binding could not be determined due to technical difficulties to develop appropriate immunohistochemistry (IHC) reagents.

Potential safety risks of BMS-986442 may be anticipated based on the clinical evaluation of other monospecific [redacted] antagonistic antibodies. Anti-[redacted] is currently being studied but there is no clinical data available at this time. A Phase 1 evaluation of a fully human monoclonal IgG1 [redacted] antibody, tiragolumab, was well tolerated up to 1200 mg when administered intravenous (IV) Q3W in participants with advanced solid tumors. No significant safety concerns were reported in participants administered with tiragolumab in combination with the anti-PD-L1 atezolizumab. In both the monotherapy and combination cohorts, Grade 3 or greater AEs were only reported in 4% of participants.[16] In the Phase 2 trial CITYSCAPE, tiragolumab in combination with atezolizumab in participants with advanced NSCLC demonstrated a safety profile similar to that of atezolizumab alone. Immune-related AEs were more frequent in participants treated with tiragolumab and atezolizumab combination but were primarily Grade 1 or 2 and manageable.[11]

BMS-986442 is currently being evaluated as monotherapy in advanced solid tumors (Protocol C-1400-01; NCT#05025085). As of 24-Jun-2022, the safety profile of BMS-986442 was manageable in 16 participants; 3 participants were treated at each of the 2-, 6-, 20-, and 60-mg dose levels, and four participants were treated at the 200-mg dose level (see Section 3.2.4.1).

In whole blood or PBMC cytokine release assay, BMS-986442, both in soluble or dry format, did not induce a dose-dependent increase in cytokine levels for IL-2, IL-4, IL-6, IL-8, IL-10, TNF-α, or IFN-γ, relative to untreated conditions or the isotype control antibody. These data support the conclusion that BMS-986442 does not present a significant risk for cytokine release or IRR.

Nivolumab Risk Assessment:

Extensive details on the safety profile of nivolumab are available in the IB and will not be repeated herein.

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

A pattern of immune-related AE has been defined, for which management algorithms have been developed; these are provided in Appendix 7. Most high-grade events were manageable with the use of corticosteroids or hormone replacement therapy (endocrinopathies) as instructed in these algorithms.

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

The frequency of these immune-related AEs may increase for BMS-986442 and nivolumab combination therapy with/without chemotherapy.

Nivolumab in Combination with Chemotherapy Risk Assessment:

Nivolumab in combination with chemotherapy has been assessed in a variety of studies and has demonstrated an acceptable safety profile. In part 2 of the Phase 3 Study CA209227,[14] the overall safety profile of nivolumab plus histology-based platinum-doublet chemotherapy (PDCT) in all treated participants with chemotherapy-naive Stage IV or recurrent NSCLC was consistent with the established safety profile of each component of the regimen. No new safety signals or toxicities were identified relative to previous experience with nivolumab monotherapy or with chemotherapy. Grade 3-4 TRAEs were reported in 44.8% and 35.3% of all participants treated with nivolumab plus PDCT and PDCT, respectively. Any grade TRAEs were reported in 84.8% and 78.4% participants treated with nivolumab plus PDCT and PDCT, respectively. In addition, in the Phase 3 Study CA2099LA, the combination of 2 immunotherapy agents, nivolumab and ipilimumab plus chemotherapy in treatment-naive NSCLC also demonstrated an acceptable safety profile and is now an approved regimen in some countries. In both CA209227 and CA2099LA, across all AE categories (serious AEs [SAEs], AEs leading to discontinuation of study drug, AEs), all causality and drug-related AEs were higher with the immunotherapy plus chemotherapy treatment combination when compared to chemotherapy treatment alone.

Although safety data from nivolumab in combination with docetaxel in NSCLC is not available, a non-randomized, multicohort, global Phase II CheckMate 9KD trial of 84 patients with chemotherapy-naive metastatic castration-resistant prostate cancer and ongoing androgen deprivation therapy received nivolumab in combination with docetaxel and prednisone for up to 10 cycles followed by nivolumab maintenance for up to 2 years. Overall, safety was consistent with the individual treatments. The most common any-grade TRAE reported was fatigue (39.3%) and the most common Grade 3-4 TRAE reported was neutropenia (16.7%). Three treatment-

related deaths were reported (1 pneumonitis related to nivolumab and 2 pneumonias related to docetaxel).[15]

SARS-CoV-2 Infection Risk Assessment:

Immunocompromised patient populations such as those with advanced solid tumors may be more susceptible to infections, including severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infections. In addition, the potential impact of BMS-986442 or BMS-986442 in combination with nivolumab with/without chemotherapy administration on the frequency or severity of SARS-CoV-2 infections in participants with advanced solid tumors are currently unknown. Participants with recent or acute infections will be excluded or delay the start of treatment as defined in Section 7.4. 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 7.4.2.

3.3.2 Benefit Assessment

Functional blockade of the [redacted] and [redacted] pathways is anticipated to enhance T and NK cell effector function and provide increased anti-tumor immunity either alone or in combination with PD-1/PD-L1 blockade. BMS-986442 is a Fc-engineered bispecific human IgG1 antibody, designed to bind [redacted] and [redacted] with high affinity, block the interaction of these receptors and their cognate ligand [redacted] and enhance NK cell activation and T-cell responsiveness. Furthermore, the BMS-986442 Fc region was engineered to enhance binding to FcγR to further improve its ability to enhance T-cell effector function and anti-tumor immunity, consistent with the requirement of Fc-FcγR co-engagement between T cells and APCs to promote optimal modulation of [redacted] antibodies.[7] Approximately 40% of patients express a low affinity allele of FcγRIIIA due to genetic polymorphism. FcγRIIIA polymorphism has been demonstrated to contribute to clinical activity of anti-cytotoxic T-lymphocyte-associated antigen 4 (CTLA4) therapy.[4] BMS-986442 demonstrates improved binding to both the high- and low-affinity FcγR and hence has the potential for similar clinical activity in participants with both the low- and high-affinity FcγR.

The combination of BMS-986442 and the anti-PD-1 antibody balstilimab generated superior T-cell stimulation, as measured by IL-2 cytokine secretion, in comparison with BMS-986442, balstilimab, or the bivalent isotype control antibodies alone, in healthy donor human PBMCs stimulated with SEA peptide. These data support the potential benefit of BMS-986442 with anti-PD-1 antibody such as nivolumab compared to either therapy alone to further augment tumor antigen recognition and T-cell responsiveness.

The investigation of [redacted] antibodies in human subjects has revealed promising anti-cancer effects. Two [redacted] antibodies, tiragolumab (IgG1; Roche) and vibostolimab (IgG1; Merck), demonstrated acceptable safety and tolerability profiles alone and in combination with atezolizumab (anti-PD-L1 antibody) or pembrolizumab (anti-PD-1 antibody), respectively, in patients with advanced solid tumors.[16,17] Notably, in the Phase 2 (CITYSCAPE) trial, tiragolumab in combination with atezolizumab in advanced NSCLC patients with high levels of PD-L1 (> 50% expression) showed an overall response rate (ORR) of 66%, as compared to 24% for atezolizumab

therapy alone.[11] Similarly, vibostolimab in combination with pembrolizumab demonstrated promising clinical efficacy in patients with metastatic NSCLC.[18]

Nivolumab plus PDCT clinical activity in chemotherapy-naive NSCLC has been demonstrated in 2 clinical studies. In CA209012, a multi-arm Phase 1 safety study of nivolumab in chemotherapy-naive NSCLC, 56 subjects were administered nivolumab in combination with cisplatin/gemcitabine, cisplatin/pemetrexed, or carboplatin/paclitaxel. ORR with the different combinations ranged from 42% to 50%. Nivolumab in combination with histology-based PDCT was studied in Part 2 of the Phase 3 trial CA209227.[7] In this trial, due to the hierarchical nature of the statistical design and because the primary end point of OS in the non-squamous population was not statistically significant, additional endpoints were purely descriptive. However, it is important to note that ORR, progression-free survival (PFS), and OS all demonstrated trends towards improved efficacy with the nivolumab plus chemotherapy combination versus chemotherapy alone after a minimum follow-up of 19.5 months for OS and 18.4 months for all other data. The OS hazard ratio (HR) in all randomized subjects was 0.81 (95.62% confidence interval [CI]: 0.67,0.97). The median PFS and OS were numerically higher in participants who received nivolumab plus chemotherapy, with a median OS of 18.27 months versus 14.72 months in the chemotherapy group, and a median PFS of 8.38 months with the nivolumab plus chemotherapy group versus 5.52 months in the chemotherapy group. In addition, ORR was higher with nivolumab plus chemotherapy when compared with chemotherapy alone in the all randomized population, as well as in the non-squamous (48.1% vs 25.7%) and the squamous (59.8% vs 32.4%) patient sub-groups.

3.3.3 Overall Benefit/Risk Conclusion

Overall, treatment with BMS-986442 in combination with nivolumab with/without chemotherapy in participants with advanced solid tumors, including NSCLC, gastric/gastroesophageal junction (GEJ) cancer, and SCCHN, is expected to be tolerable, and toxicities of the treatments are expected to be manageable. Immune-mediated adverse event (IMAE)-related toxicities may require the use of immunosuppressive agents. For management algorithms of AEs related to immuno-oncology (IO) agents, refer to Appendix 7.

Taking into account the measures taken to minimize risk to participants in this study, the potential risks identified in association with BMS-986442 in combination with nivolumab with/without chemotherapy are justified by the anticipated benefits that may be afforded to participants with advanced solid tumors, including NSCLC, gastric/GEJ cancer, and SCCHN. In addition, first-line therapy of BMS-986442 in combination with nivolumab and PDCT has the potential to improve efficacy compared to PDCT in combination with anti-PD-1 therapy.

The Sponsor will evaluate the benefit/risk profile of the study on an ongoing basis. This evaluation will be based on all available data, with particular attention to (i) AEs or other safety trends in this or any other clinical study of BMS-986442 whose character, severity, and/or frequency suggest that participants would be exposed to an unreasonable and significant risk of illness or injury; (ii) new nonclinical data suggesting an unreasonable and significant risk of illness or injury.

If such evaluation suggests that the benefit/risk profile of the study has become unfavorable, the Sponsor will pause enrollment and/or treatment until further evaluation of data and until interaction with the appropriate Health Authority(ies) can take place regarding potential actions. Such actions may include (but are not limited to) study continuation, substantial amendment, or termination of the study.

4 OBJECTIVES AND ENDPOINTS

Table 4-1: Objectives and Endpoints

Objectives	Endpoints
Primary	**Primary**
• To characterize the safety and tolerability, and to establish the MTD, MAD, and/or RP2D of BMS-986442 in combination with nivolumab or with nivolumab and the following chemotherapies: docetaxel; carboplatin and pemetrexed; carboplatin and paclitaxel, in participants with advanced cancer including NSCLC.	• Incidence of AEs, SAEs, AEs meeting protocol-defined DLT criteria, AEs leading to discontinuation, and death (per CTCAE v5.0).
Secondary	**Secondary**
• To characterize the PK of BMS-986442 administered in combination with nivolumab or in combination with nivolumab and chemotherapy.	• Summary measures of BMS-986442 PK parameters, such as, but not limited to, Cmax, Tmax, and AUC (0-T), from serum concentration-time data for BMS-986442 when administered in combination with nivolumab or in combination with nivolumab and chemotherapy.
• To characterize the immunogenicity of BMS-986442 administered in combination with nivolumab or in combination with nivolumab and chemotherapy.	• Incidence of ADAs to BMS-986442 when BMS-986442 is administered in combination with nivolumab or in combination with nivolumab and chemotherapy.
• To assess the preliminary anti-tumor activity of BMS-986442 administered in combination with nivolumab or nivolumab and chemotherapy.	• ORR, DOR, DCR, and PFSR at 6 months and 12 months per RECIST v1.1 by Investigator.
[redacted]	

Table 4-1: Objectives and Endpoints

Objectives	Endpoints
[redacted]	

Abbreviations: ADA, anti-drug antibody; AE, adverse event; AUC (0-T), area under the serum concentration-time curve from time zero to the time of the last quantifiable concentration; [redacted] Cmax, maximum observed concentration; CTCAE, Common Terminology Criteria for Adverse Events; [redacted] DCR, disease control rate; DLT, dose-limiting toxicity; DOR, duration of response; [redacted] MAD, maximum administered dose; MTD, maximum tolerated dose; NSCLC, non-small cell lung cancer; ORR, overall response rate; [redacted] PFSR, progression-free survival rate; PK, pharmacokinetics; [redacted] RECIST, Response Evaluation Criteria in Solid Tumors; [redacted] RP2D, recommended Phase 2 dose(s); SAE, serious adverse event; [redacted] Tmax, time of maximum observed concentration; v, version.

5 STUDY DESIGN

5.1 Overall Design

CA115001 is a Phase 1b/2, multi-center, open-label study of BMS-986442 administered in combination with nivolumab or nivolumab with 1 of 3 standard chemotherapy regimens used in the treatment of advanced solid tumors and advanced or metastatic NSCLC: docetaxel, carboplatin with pemetrexed, and carboplatin with paclitaxel. The primary objectives of the proposed study are to characterize the safety and tolerability and to establish the RP2Ds and MTDs or evaluate the maximum administered dose (MAD) for these combinations. Secondary objectives of the study are to characterize the PK and IMG profile and to assess the preliminary antitumor activity of BMS-986442 when administered in combination with nivolumab or in combination with nivolumab and the designated chemotherapy regimens.

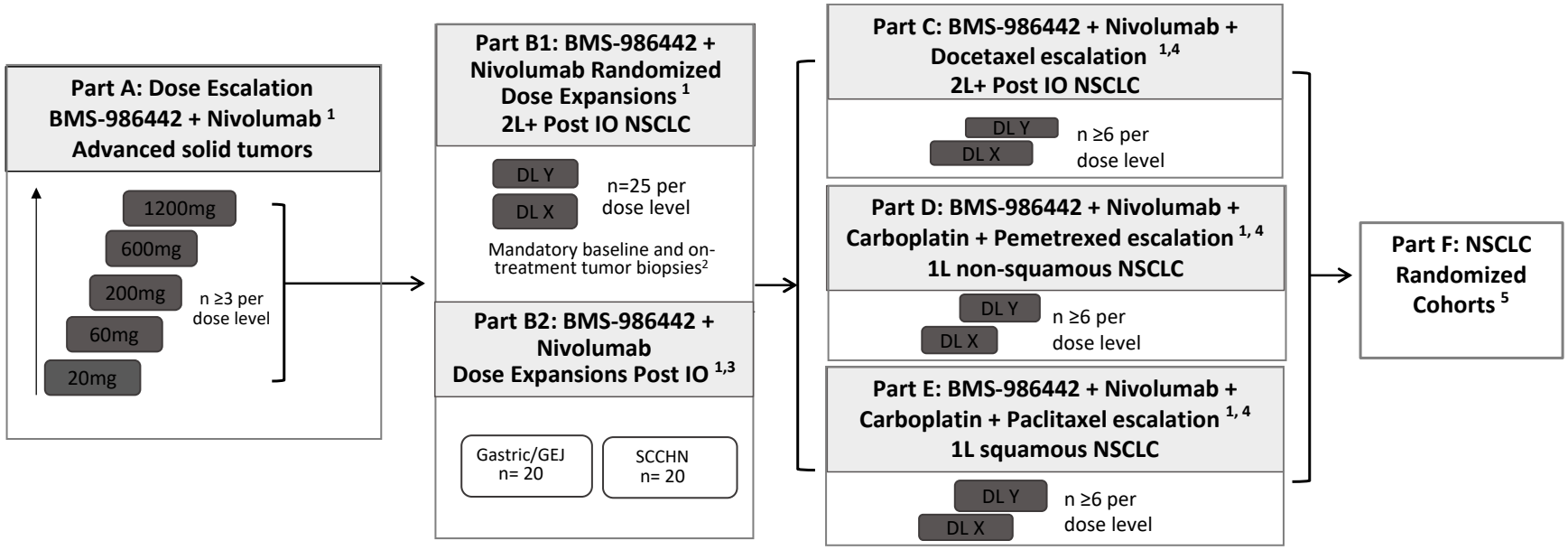
The study is composed of 6 parts, with the dose escalation of BMS-986442 in combination with a fixed dose of nivolumab occurring in Part A, the dose expansions for BMS-986442 and nivolumab

occurring in Part B, and the dose escalations of BMS-986442 in combination with nivolumab and the designated chemotherapies occurring in Parts C to E: docetaxel (Part C), carboplatin and pemetrexed (Part D), and carboplatin and paclitaxel (Part E). Part F may include randomized cohorts to evaluate whether BMS-986442 (either as monotherapy or in combination) can produce clinical benefit in participants with advanced/metastatic NSCLC. The design of Part F will be reported in a future amendment.

See Section 6.1 (Inclusion Criteria) [redacted] for specifications.

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

Figure 5.1-1: Study Design Schema



Abbreviations: 1L, first line; 2L, second line; C, Cycle; D, Day; DLX, dose level X; DLY, dose level Y; IO, immuno-oncology; IV, intravenous; GEJ, gastroesophageal junction; NSCLC, non-small cell lung cancer; Q3W, every 3 weeks; SCCHN, squamous cell carcinoma of the head and neck.

[1] BMS-986442 (IV Q3W) in combination with a fixed dose of nivolumab (360 mg IV Q3W). Intermediate dose levels may be added after discussion and agreement between the Sponsor and the Investigators.

[2] [redacted]

[3] Up to 2 tumor-specific expansion cohorts may evaluate one selected dose level that is in the range of tolerable dose levels evaluated in Part A.

[4] Parts C, D, and E may be opened after the initial safety evaluation of the first 10 participants in each dose level of Part B1. Each cohort in Parts C, D, and E have an optional backfill up to a total of 15 participants per dose level.

[5] Part F will be described in a future amendment.

5.1.1 Screening

The screening period will be up to 28 days and begins by establishing the participant's initial eligibility after signing the informed consent form (ICF). The informed consent may be obtained electronically using an electronic consent form where allowed by applicable laws, regulations, and Institutional Review Boards (IRBs)/Independent Ethics Committees (IECs). Participants are able to opt out of this use and consent on a paper consent if necessary. Participants will be enrolled using Interactive Response Technology (IRT). See the Schedule of Activities (Section 2) for study procedures conducted during screening.

If a participant exceeds the 28-day screening period due to a study-related procedure (eg, scheduling of a tumor biopsy or waiting for a study-related laboratory value) or a SARS-CoV-2 infection, the participant must be reconsented, but does not require a new participant identification number (see Section 6.4.1). In this situation, the Medical Monitor should be notified, and the fewest number of procedures from the initial screening should be repeated to qualify the participant, while maintaining participant safety and eligibility.

5.1.2 Treatment Period

The treatment period will last a maximum of approximately 35 cycles (105 weeks) from the first dose of study treatment, regardless of treatment delays. For all parts, the DLT evaluation period will be 4 weeks or 1 full cycle and 1 week into the second cycle.

Treatment arms are illustrated in Figure 5.1-1. On-treatment monitoring will include planned clinic visits, physical examinations, vital sign measurements, 12-lead ECG, and clinical laboratory evaluations that will be performed at selected times throughout the dosing interval (see Section 2). Imaging for tumor assessment will utilize Response Evaluation Criteria in Solid Tumors (RECIST) v1.1 and will occur every 6 weeks during the first 48 months of treatment, followed by every 12 weeks during the remainder of treatment. Participants will be closely monitored for AEs throughout the study. Samples will be collected before and after study drug administration for PK analysis and pharmacodynamic parameter measurements (see Section 9.5 for further details).

5.1.2.1 Part A: Dose Escalation of BMS-986442 with Nivolumab

Part A will evaluate increasing doses of BMS-986442 in combination with nivolumab (360 mg IV Q3W). Both agents will be administered IV on a Q3W schedule, and the Bayesian optimal interval (BOIN) method will be utilized to guide the dose escalation with approximately 3 to 9 DLT-evaluable participants per dose level. Five dose levels of BMS-986442 are planned to be evaluated, with a starting dose level of 20 mg. The starting dose level of BMS-986442 in combination with nivolumab was selected based on results from the ongoing study (C-1400-01, NCT05025085) sponsored by Agenus, evaluating BMS-986442 monotherapy that has declared all dose levels up to 60 mg safe and tolerable (see Section 5.5 for further information). The C-1400-01 study is evaluating dose levels of BMS-986442 of 2, 6, 20, 60, 200, and 1200 mg, given to participants with advanced solid tumors IV on a Q3W schedule.

The proposed escalation will start at BMS-986442 20 mg Q3W and escalate up to, but not exceed, the MTD from the monotherapy escalation in the C-1400-01 study, if the MTD is determined. For

the situation that the MTD is not determined in the C-1400-01 study, the highest dose of BMS-986442 that may be tested in the Part A escalation of the current study will not exceed the maximum dose of BMS-986442 that was evaluated in the C-1400-01 study and that passed DLT review. The planned dose levels to be evaluated in the Part A combination escalation may also be modified, or intermediate dose levels may be added after discussion and agreement between the Sponsor and the Investigators.

The Part A decisions for escalation, de-escalation, or continuing evaluation at the same dose level will be guided by the BOIN escalation design framework (Table 5.1.2.1-1) with a target DLT rate of 30% (24%, 36%). Up to 9 DLT-evaluable participants may be treated at each dose level, depending on the number of observed DLTs. The DLT evaluation period will be 28 days (4 weeks) from Cycle 1 Day 1 (C1D1). Dose escalation/de-escalation decisions or decisions to continue enrollment at the current dose will be made by the Sponsor in collaboration with Investigators and take into consideration all available safety, and if available, PK and PD data.

A staggered dosing (sentinel participant) approach will be used. The first participant in each cohort will be observed for at least 7 days after their initial exposure to the combination of BMS-986422 and nivolumab before additional participants in that cohort are dosed. Subsequently, the remaining participants in each dose cohort must be observed for at least 24 hours after their initial exposure to the combination regimen before additional participants are exposed.

Initially, the first 3 participants treated in Part A will be evaluated for DLTs. If no DLT is observed in the first 3 DLT-evaluable participants, the current dose level will be considered safe, and another 3 participants will be enrolled at the higher BMS-986442 dose level. If 1 DLT is observed out of 3 DLT-evaluable participants, an additional 3 to 4 participants will be enrolled at the same BMS-986442 dose level. If ≤ 1 DLTs are observed out of 6 DLT-evaluable participants, the dose level will be considered safe.

Although the maximum number of DLT-evaluable participants at each dose level is 9, if 3 DLTs are observed out of 9 DLT-evaluable participants, the design recommends staying at the same dose level (Table 5.1.2.1-1). After considering the totality of available data, including safety and PK/PD from all treated participants, the dose may be considered safe based on discussion between the Investigator and Sponsor/Medical Monitor (MM). De-escalation may be considered if the safety and tolerability profile for the selected BMS-986442 dose is evaluated as not acceptable, after discussion between the Investigator(s) and the Sponsor/MM. Once a tolerable dose level has been determined for BMS-986442 in combination with nivolumab in Part A, enrollment in Parts B1 and B2 may begin.

Table 5.1.2.1-1: Safety Evaluation Guidance for DLT-related Decisions by BOIN Design Framework

Actions Based on Number of DLTs	Number of DLT-evaluable Participants Treated at the Current Dose									
	3	4	5	6	7	8	9	10	11	12
Escalate if # of DLT ≤	0	0	1	1	1	1	2	2	2	2

Table 5.1.2.1-1: Safety Evaluation Guidance for DLT-related Decisions by BOIN Design Framework

Actions Based on Number of DLTs	Number of DLT-evaluable Participants Treated at the Current Dose									
	3	4	5	6	7	8	9	10	11	12
Stay if # of DLT =	1	1	NA	2	2	2	3	3	3	3, 4
De-escalate if # of DLT ≥	2	2	2	3	3	3	4	4	4	5
Eliminate if # of DLT ≥	3	3	4	4	5	5	5	6	6	7

Abbreviations: BOIN, Bayesian optimal interval; DLT, dose-limiting toxicity; NA, not applicable.

5.1.2.2 Part B: Dose Expansions Evaluating the Combination of BMS-986442 and Nivolumab

Part B will be made up of 2 subparts:

- Part B1 will involve randomized dose expansions to compare 2 tolerable dose levels in participants with 2L+ post-IO/platinum doublet NSCLC.
- Part B2 will involve evaluation of 1 selected dose level in 2 additional tumor types: gastric cancer/GEJ and SCCHN.

Part B1: Randomized Dose Expansions in Post-IO/Platinum-Doublet NSCLC Participants

Part B1 is designed to further characterize 2 different dose levels of BMS-986442 in combination with nivolumab (360 mg IV Q3W) in participants with advanced or metastatic NSCLC who have been treated with a platinum-doublet standard of care chemotherapy and have also progressed while on a prior PD-(L)1 agent as a monotherapy or in combination. The 2 dose levels for Part B1 will be selected based on the totality of the available data from the Part A dose escalation, including safety, tolerability, PK, IMG, [redacted] results. Participants will be randomized to 1 of the 2 dose levels and each dose level will treat up to 25 participants.

Participants in Part B1 will undergo mandatory attempted screening biopsy (see Section 9.8.2). The goal of Part B1 is to evaluate 2 dose levels of BMS-986442 for evidence of PD modulation in the tumor, for additional safety and tolerability evaluation and to evaluate preliminary anti-tumor efficacy in participants with NSCLC who have progressed on prior PD-(L)1 treatment. The available data from Part B will be utilized to identify the RP2D for the doublet combination.

There will be a planned safety review after the first 10 participants in each of the 2 dose levels in Part B1 have completed the first 2 cycles of study treatment. The results of this safety review, along with PK and PD data (as available), will be required to initiate Parts C, D, and E. Enrollment into Part B1 will not be paused for this safety review.

Part B2: BMS-986442 + Nivolumab, Dose Expansion in post IO Gastric Cancer/Gastroesophageal Junction and Post-IO SCCHN

Gastric cancer/GEJ and SCCHN are among the solid tumors with highest expression of [redacted] and [redacted] and therefore have the potential to benefit from treatment with BMS-986442 and nivolumab. Part B2 includes 2 expansion cohorts in post IO gastric cancer/GEJ and post IO SCCHN with approximately 20 response evaluable participants in each. The main objective of these expansion cohorts is to further evaluate the safety and preliminary efficacy at a tolerated dose level. Part B2 may start once Part A has completed enrollment and the available data are reviewed for safety and tolerability. The dose of BMS-986442 selected will be based on the totality of the data available (eg, safety, PK, PD) and will not exceed the highest dose determined to be safe and tolerable in Part A.

5.1.2.3 Parts C, D, and E: Dose Escalation of BMS-986442 in Combination with Nivolumab and Chemotherapy in NSCLC

Parts C, D, and E are combination dose escalation cohorts that will evaluate BMS-986442 in combination with nivolumab and chemotherapy in NSCLC. They will open after the planned safety review of the first 10 participants in each dose level is completed in Part B1. For Parts C, D, and E, dose escalation will be guided by the BOIN method and approximately 6 to 12 DLT-evaluable participants will be treated at each dose level to enable DLT review and dose escalation decisions. The subsequent decisions will be based on the BOIN design framework as shown in Table 5.1.2.1-1. Additional participants (for a maximum of 15 per dose level) may be treated at or below the MTD for further evaluation of safety, PK, IMG, and PD parameters. Each part may treat approximately 30 participants over 2 dose levels.

Part C: Dose Escalation for BMS-986442 in Combination with Nivolumab and Docetaxel

Part C will evaluate up to 2 different dose levels of BMS-986442 in combination with nivolumab (360 mg IV Q3W) and docetaxel (75 mg/m^2 IV Q3W) for this triplet combination in participants with advanced or metastatic NSCLC who have been treated with 2L+ platinum-doublet standard of care chemotherapy and progressed while on prior PD-(L)1 treatment.

Part D: Dose Escalation for BMS-986442 in Combination with Nivolumab, Carboplatin, and Pemetrexed

Part D will evaluate up to 2 different dose levels of BMS-986442 in combination with nivolumab, carboplatin, and pemetrexed in participants with advanced/metastatic non-squamous NSCLC who have not had systemic therapy for advanced/metastatic disease.

Part E: Dose Escalation for BMS-986442 in Combination with Nivolumab, Carboplatin, and Paclitaxel

Part E is designed to evaluate the safety of up to 2 different dose levels of BMS-986442 in combination with nivolumab, carboplatin, and paclitaxel in participants with advanced/metastatic squamous NSCLC who have not had systemic therapy for advanced/metastatic disease.

5.1.2.4 Part F: Randomized Cohorts in NSCLC

Phase 2 randomized cohorts may be introduced following a substantial amendment that will fully define Part F. The intent of Part F, if proposed, would be to evaluate whether BMS-986442 either alone or in combination with nivolumab with/without chemotherapy may provide additional clinical benefit over standard-of-care treatment in participants with metastatic NSCLC for frontline treatment or subsequent to PDCT and anti-PD-(L)1 therapy. The rationale for the indication chosen, the randomized treatment arms, and the dose of BMS-986442 will be based on the safety/tolerability, PK/PD, and preliminary efficacy data from Parts A, B1, C, D, and E.

5.1.3 Follow-up Period

The follow-up period includes a safety follow-up and a survival follow-up, which begin after the end of treatment visit or date of last dose (whichever occurs later). The safety follow-up period for all treatment groups, even if the study is terminated, is 100 days after the end-of-treatment visit or date of last dose (whichever occurs later), with visits to occur at 30, 60, and 100 (± 7) days. Survival follow-up for all parts will occur every 12 weeks (± 14 days) from Follow-up Visit 3 and last for a period of 2 years from the date of discontinuation of study treatment or until death, lost to follow-up, withdrawal of consent, conclusion of the study, or study termination, whichever comes first.

5.1.4 Data Monitoring Committee and Other Committees

A Data Monitoring Committee (DMC) will not be used in the study.

Although there is not a formal DMC for this study, BMS has developed a multi-layered process to ensure safety monitoring through close collaboration of study site Investigators, the BMS study team, and the BMS Worldwide Patient Safety (WWPS)-led Safety Management Team (SMT), which will be employed in this study. To support safety oversight, BMS has established ongoing processes for collection, review, analysis, and submission of individual AE reports and their aggregate analyses. Because this is an open-label study, WWPS, the BMS MM, and the Investigators will have access to all data necessary for safety evaluation.

BMS WWPS is an internal group that operates independently from the clinical team to monitor safety across all BMS protocols and to analyze all data in an unblinded fashion. Within BMS, an SMT is established for investigational therapies under clinical development, and a member of WWPS chairs this team. In addition, 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 (Chair of the SMT), MM, Global Regulatory lead, and Pharmacovigilance Scientist; all of whom analyze the data in an unblinded fashion. Furthermore, the SMT routinely monitors for actual or potential issues related to participant safety that could result in a change in the medical benefit/risk balance associated with the use of study treatment(s).

If there is any treatment-related Grade ≥ 4 toxicity or death as assessed by the Sponsor, enrollment in that arm will be placed on hold and an ad-hoc SMT meeting will be convened. Additionally, a Bayesian continuous monitoring framework will be utilized for continuous monitoring of toxicity in the study. If at any time during the study, the posterior probability of the DLT rate exceeding 33% is greater than 0.85, that will also trigger enrollment in that arm being placed on hold and an

ad-hoc SMT meeting being convened. The SMT will re-evaluate the benefit-risk profile of the drug combination in context of the totality of the data, and assess whether termination or resumption of the cohort/study is appropriate.

5.2 Number of Participants

The approximate total number of participants treated in Parts A to E will be 225.

- Part A: Approximately 45 participants for the dose escalation.
- Part B: Approximately 90 participants total, across both subparts B1 and B2.
  - Part B1: Approximately 50 participants, 25 per dose level.
  - Part B2: Approximately 40 participants, 20 per tumor type.
- Parts C, D, and E: Approximately 30 participants for each part, or 15 participants per dose level for up to 2 dose levels, for a total of approximately 90 participants.
- Part F: Varies depending on whether randomized participants are in post-IO or 1L NSCLC; will be clarified via a future amendment.

5.3 End of Study Definition

The start of the trial is defined as the first participant first visit.

End of trial is defined as the last participant last visit or scheduled procedure shown in the Schedule of Activities for the last participant.

Study completion is defined as the final date on which data for the primary endpoint were or are expected to be collected, if this is not the same.

A participant is considered to have completed the study if he/she has completed the last visit or the last procedure shown in the Schedule of Activities.

5.4 Scientific Rationale for Study Design

BMS-986442 is being investigated in participants with advanced solid tumors or NSCLC in combination with nivolumab or nivolumab and chemotherapy. The study design includes the following:

- A 28-day screening period
- A treatment period that can last up to 2 calendar years (approximately 105 weeks) for BMS-986442 (Q3W) and/or nivolumab (Q3W)
- Dose escalation portion (Part A), advanced solid tumors
- Randomized dose expansion (Part B1)
- Tumor-specific expansion in gastric and SCCHN (Part B2)
- Combinations with chemotherapy (Parts C, D, and E)
- Safety follow-up (100 days over 3 visits)
- Survival follow-up (up to 2 years after last dose)

5.4.1 Rationale for Combining BMS-986442 with Nivolumab

[redacted] and [redacted] are expressed on subsets of T and NK cells and function as negative regulators of T and NK cell effector function in the TME.[3] [redacted] and [redacted] bind to a shared ligand, [redacted] which is expressed on APCs and overexpressed on some tumor cells and functions to suppress anti-tumor T-cell and NK cell function. [redacted] expression has been associated with poor response to anti-PD-1 therapy, suggesting that blockade of both [redacted] and [redacted] are needed to achieve full reversal of checkpoint suppression.[4] In preclinical models, blockade of [redacted] and [redacted] through a combination of monospecific antibodies has been shown to enhance anti-tumor efficacy compared with single agent treatments, and triple combination with anti-PD-1 to further enhance efficacy.[5] Further supporting the rationale to combine [redacted] and [redacted] blockade with PD-1 blockade, recent preclinical data support that the PD(L)-1 pathway may also inhibit CD226 signaling directly.[6] Retrospective expression analysis showed that high levels of [redacted] were associated with limited response to antibodies targeting the PD(L)-1 pathway, particularly in patients with high PD-L1-expressing tumors.[19]

Taken together, these findings support the rationale to evaluate BMS-986442 in combination with nivolumab (with or without chemotherapy) to increase antitumor efficacy and provide clinical benefit to patients.

5.4.2 Rationale for Combining BMS-986442 with Nivolumab and Chemotherapy

The interaction of a tumor with the immune system is complex. Tumors and the TME 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, PD-L1, transforming growth factor [TGF]-beta). In addition, some tumor-derived factors are able to enhance immune system counter-regulatory systems, such as increased T-regulatory cells. Finally, suboptimal tumor antigen delivery and presentation has been postulated as another mechanism by which tumors can successfully evade immune system recognition.

Cancer therapeutics such as chemotherapy may modulate tumor/immune system interactions in favor of the immune system. Chemotherapy can result in tumor cell death with a resultant increase in tumor antigen delivery to antigen-presenting cells, and tumor cell death may also lead to a reduction in soluble and membrane-bound factors inhibiting tumor-infiltrating T cells. Chemotherapy may also disrupt immune system regulatory networks by decreasing numbers of T-regulatory cells.

Despite recent innovations in cancer treatment, alternative therapies are needed for participants with advanced NSCLC. The recent Food and Drug Administration approvals of pembrolizumab in combination with PDCT and nivolumab in combination with ipilimumab and PDCT in first-line NSCLC increase the armamentarium of immunotherapy combinations and have improved the prognosis in this population. However, less than 50% of patients are expected to benefit from anti-PD-1/PD-L1 combination therapy, highlighting the need for further investigation into other strategies such as simultaneous inhibition of multiple immune checkpoints in combination with

chemotherapy. The rationale for combining BMS-986442 and nivolumab (Section 5.4.1) and the clinical data from trials studying nivolumab in combination with chemotherapy suggest a potential for increasing benefit by combining these agents and targeting their non-overlapping mechanisms of action (see Section 3.2.2 and Section 3.2.3). The safety profile of nivolumab in combination with chemotherapy has been manageable. Therefore, it is expected that once the safety profile of BMS-986442 and nivolumab is evaluated in Part A and is on-going in Part B1 in this study, addition of BMS-986442 to nivolumab and chemotherapy will provide an acceptable benefit/risk ratio for further evaluation in Parts C, D, and E.

5.4.3 Rationale for Two Year Duration of Treatment

The optimal duration of immunotherapy is an important question and continues to be investigated. Clinical trials across different tumor types in the nivolumab and ipilimumab development program indicate that most of the responses occur early, with a median time to response of 2-4 months, and emerging data suggests that benefit can be maintained in the absence of continued treatment. A retrospective pooled analysis of 2 melanoma studies suggests that the majority of patients who discontinue nivolumab and/or ipilimumab for toxicity maintain disease control in the absence of further treatment.[20]

Accumulating data suggest that 2 years of PD-1 checkpoint inhibitor treatment may be sufficient for long-term benefit. CA209003, a dose-escalation cohort expansion trial evaluating the safety and clinical activity of nivolumab in patients with previously treated advanced solid tumors (including 129 patients with NSCLC), specified a maximum treatment duration of 2 years. Among 16 patients with NSCLC who discontinued nivolumab after completing 2 years of treatment, 12 patients were alive > 5 years and remained progression-free without any subsequent therapy. In the CA209003 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.[21] 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).[22]

In contrast, a shorter duration of nivolumab of only 1 year was associated with increased risk of progression in previously-treated patients with NSCLC, suggesting that treatment beyond 1 year is likely needed. In CA209153, patients with previously-treated advanced NSCLC who completed 1 year of nivolumab therapy were randomized to either continue or stop treatment, with the option of retreatment upon progression. Among 163 patients still on treatment at 1 year and without progression, those who were randomized to continue nivolumab had significant improvement in PFS compared to those who were randomized to stop treatment, with median PFS (post-randomization) not reached vs 10.3 months, respectively; HR = 0.42 (95% CI, 0.25 to 0.71). 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.

Collectively, these data suggest that there is minimal if any benefit derived from continuing IO treatment beyond 2 years in advanced tumors. Even though immunotherapy is well tolerated,

patients will be at risk for additional toxicity with longer-term treatment. Therefore, in this study, treatment will be given for a maximum of 2 years from the start of study treatment.

5.4.4 Rationale for Treatment Beyond Progression

Immunotherapeutic agents produce atypical clinical response patterns that are not usually observed with conventional chemotherapy. Accumulating clinical evidence indicates that some participants treated with immune system-stimulating agents may develop disease progression by the conventional response criteria before demonstrating clinical objective responses and/or stable disease (SD). Two distinct non-conventional patterns have been reported: 1) a reduction in target tumor burden despite the appearance of new lesion(s), and 2) a transient increase in target tumor burden in an initial phase, followed by subsequent tumor shrinkage. These phenomena were observed in a BMS Phase 2 study of nivolumab in patients with solid tumors. Two hypotheses potentially explain these phenomena. First, enhanced inflammation within tumors could lead to an increase in tumor size, which would appear as enlarged target lesions and as newly visible small non-target lesions. Over time, both the malignant and inflammatory portions of the mass may then decrease, leading to overt signs of clinical improvement. Alternatively, in some individuals, the kinetics of tumor growth may initially outpace anti-tumor immune activity. With sufficient time, the anti-tumor activity will dominate and become clinically apparent. Therefore, it is important to avoid premature discontinuation of the study treatment that might induce a non-conventional response pattern in some patients.

5.5 Justification for the BMS-986442 Dose

CA115001 is the first study combining BMS-986442 plus nivolumab with and without chemotherapy. The BMS-986442 starting dose of 20 mg IV Q3W was selected based on the totality of available preclinical and clinical data from the ongoing Agenus C-1400-01 Phase 1 study.

Based on preclinical data, a Q3W-dosing interval for BMS-986442 is supported by estimated human PK parameters. The serum terminal half-life of BMS-986442 was calculated to be [redacted] days in a single-dose non-Good Laboratory Practice cynomolgus monkey toxicokinetic study. The predicted serum BMS-986442 terminal half-life in humans was estimated to be ~[redacted] days.

Agenus C-1400-01 is an ongoing Phase 1 study that is evaluating the safety, tolerability, PK, IMG, and PD of BMS-986442 (AGEN1777) as a single agent in participants with advanced, metastatic solid tumors. As of 24-Jun-2022, 16 participants have been treated Q3W with 2 mg (n = 3), 6 mg (n = 3), 20 mg (n = 3), 60 mg (n = 3), and 200 mg (n = 4) BMS-986442. There have been no reported DLTs, all dose levels tested were declared tolerable, and the monotherapy MTD/MAD has not yet been determined (Section 3.2.4.1).

The starting dose of BMS-986442 (20 mg IV Q3W) in study CA115001 is below the 60-mg dose of BMS-986442 that has cleared the DLT evaluation in the ongoing C-1400-01 study.

5.5.1 Nivolumab

The nivolumab dose of 360 mg IV Q3W was selected based on clinical data and modeling and simulation approaches using population PK (PPK) and exposure-response (E-R) analyses of data

from studies in multiple tumor types (melanoma, NSCLC, and RCC) where body weight normalized dosing (mg/kg) was used.

Nivolumab PK has been extensively studied in multiple tumor types, including melanoma, NSCLC, RCC, cHL, SCCHN, CRC, and urothelial carcinoma, and has been safely administered at doses up to 10 mg/kg IV Q2W. Nivolumab monotherapy was originally approved as a body-weight based dose of 3 mg/kg IV Q2W, and was updated to 240 mg IV Q2W or 480 mg IV Q4W in multiple indications.[23,24] Nivolumab 360 mg IV Q3W is also under evaluation in monotherapy and in combination therapy studies. Less frequent 360 mg IV Q3W and 480 mg IV 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 IV Q2W, 360 mg IV Q3W, and 480 mg IV Q4W are predicted to be comparable to 3 mg/kg IV 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 IV Q2W, 360 mg IV Q3W, and 480 mg IV Q4W. The simulated average serum concentration at steady state (Cavgss) following administration of nivolumab 360 mg IV Q3W and 480 mg IV Q4W are predicted to be similar to those following administration of nivolumab 240 mg IV Q2W and nivolumab 3 mg/kg IV Q2W administered to patients over a wide body weight range (34-180 kg) across tumor types.

Extensive E-R analyses of multiple PK measures (maximum serum concentration [Cmax] at Day 1, average serum concentration [Cavg] at Day 28, and trough serum concentration [Cmin] at Day 28) and efficacy and safety endpoints indicated that the efficacy of the flat-dose 480 mg IV Q4W regimen is similar to that of the 3 mg/kg IV Q2W regimen. In E-R efficacy analyses for OS and ORR conducted in melanoma, RCC, and NSCLC using Cavgd28 as the exposure measure, probabilities of achieving a response and survival probabilities at 1 year and 2 years for 480 mg IV Q4W were similar to those of 3 mg/kg IV Q2W. In E-R safety analyses, it was demonstrated that the exposure margins for safety are maintained following nivolumab 480 mg IV Q4W, and that the predicted risks of discontinuations due to AEs or death, AE Grade 3+, and IMAEs Grade 2+ are similar following nivolumab 480 mg IV Q4W relative to nivolumab 3 mg/kg IV Q2W across tumor types. In addition, nivolumab exposures with 240 mg IV Q2W, 360 mg IV Q3W, and 480 mg IV Q4W flat-dose regimens across tumor types are maintained well below the corresponding exposures observed with the well-tolerated 10 mg/kg IV Q2W regimen.

Additional details on nivolumab posologies and benefit/risk can be found in the IB.

5.6 Clinical Pharmacology Summary of Nivolumab

Nivolumab PK was assessed using a PPK approach for single-agent nivolumab.

Nivolumab as a single agent: The PK of single-agent nivolumab was studied in patients over a dose range of 0.1 to 20 mg/kg administered as a single dose or as multiple doses of nivolumab as a 60-minute IV infusion every 2 or 3 weeks. Nivolumab clearance (CL) decreases over time, with a mean maximal reduction (% coefficient of variation [CV%]) from baseline values of 24.5% (47.6%) resulting in a geometric mean steady-state clearance (CLss) (CV%) of 8.2 mL/h (53.9%) in patients with metastatic tumors; the decrease in CLss is not considered clinically relevant. Nivolumab CL does not decrease over time in patients with completely resected melanoma, as the geometric mean population CL is 24% lower in this patient population compared with patients with metastatic melanoma at steady state. The geometric mean volume of distribution at steady state (Vss) (CV%) is 6.8 L (27.3%), and geometric mean elimination half-life (t1/2) is 25 days (77.5%). Steady-state concentrations of nivolumab were reached by 12 weeks when administered at 3 mg/kg IV every 2 weeks, and systemic accumulation was 3.7-fold. The exposure to nivolumab increases dose proportionally over the dose range of 0.1 to 10 mg/kg administered IV every 2 weeks. The predicted exposure (Cavg and Cmax) of nivolumab after a 30-minute infusion is comparable to that observed with a 60-minute infusion.

Specific Populations: The PPK analysis suggested that the following factors had no clinically important effect on the CL of nivolumab: age (29 to 87 years), weight (35 to 160 kg), gender, race, baseline lactate dehydrogenase (LDH), PD-L1 expression, solid tumor type, tumor size, renal impairment, and mild hepatic impairment.

Renal Impairment: The effect of renal impairment on the CL of nivolumab was evaluated by a PPK analysis in patients with mild (estimated glomerular filtration rate [eGFR] 60 to 89 mL/min/1.73 m^2), moderate (eGFR 30 to 59 mL/min/1.73 m^2), or severe (eGFR 15 to 29 mL/min/1.73 m^2) renal impairment. No clinically important differences in the CL of nivolumab were found between patients with renal impairment and patients with normal renal function.

Hepatic Impairment: The effect of hepatic impairment on the CL of nivolumab was evaluated by PPK analyses in patients with HCC and in patients with other tumors with mild hepatic impairment (total bilirubin [T. bili] less than or equal to the upper limit of normal [ULN] and aspartate aminotransferase [AST] greater than ULN or T. bili greater than 1 to 1.5 times ULN and any AST) and in HCC patients with moderate hepatic impairment (T. bili greater than 1.5 to 3 times ULN and any AST). No clinically important differences in the CL of nivolumab were found between patients with mild/moderate hepatic impairment.

Full details on the clinical pharmacology aspects of nivolumab can be found in the IB and product label.

Nivolumab 360 mg IV Q3W is approved in combination with ipilimumab 1 mg/kg IV Q6W in patients with malignant pleural mesothelioma, in combination with ipilimumab 1 mg/kg Q6W and 2 cycles of platinum-doublet chemotherapy in patients with metastatic NSCLC, and in combination with fluoropyrimidine- and platinum-containing chemotherapy in patients with gastric cancer, GEJ cancer, and esophageal adenocarcinoma. Nivolumab 360 mg IV Q3W will be the dosing regimen used in combination with BMS-986442 with or without chemotherapy in this study.

6 STUDY POPULATION

This study permits the re-enrollment of a participant that has discontinued the study as a pretreatment failure. If re-enrolled, the participant must be re-consented and meet all inclusion/exclusion criteria.

Prospective approval of protocol deviations to recruitment and enrollment criteria, also known as protocol waivers or exemptions, is not permitted.

6.1 Inclusion Criteria

Participants are eligible to be included in the study only if all of the following criteria apply:

1) Signed Written Informed Consent

a) 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 patient care.

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

2) Type of Participant and Target Disease Characteristics

a) Participants in all parts of the study must have measurable disease per RECIST v1.1 (Appendix 5).

b) Participants must have an Eastern Cooperative Oncology Group Performance Status of 0 or 1 (Appendix 6).

c) Participants must have a life expectancy of at least 3 months at the time of first dose.

d) Participants in Part A advanced solid tumors must meet all of the following:

i) Documented histologically or cytologically confirmed advanced unresectable/metastatic solid malignancy of any histology.

ii) Have progressed on, are ineligible for, or intolerant of existing therapy(ies) known to provide clinical benefit for the condition of the participant.

iii) Have experienced radiographically documented progressive disease on or after the most recent therapy.

e) Participants in Part B2 gastric cancer/GEJ expansion must meet all of the following:

i) Advanced or metastatic gastric or GEJ cancer and have progressed during or after, or been intolerant to, at least 1 standard treatment regimen in the advanced or metastatic setting (or have progressed within 6 months of adjuvant therapy).

ii) Disease progression while on or after prior PD-(L)1 treatment as monotherapy or in combination with other modalities.

iii) Participants with known human epidermal growth factor receptor 2 (HER2)-positive gastric cancer must have received prior treatment with a HER2 inhibitor (eg, trastuzumab).

f) Participants in Part B2 SCCHN expansion must meet all of the following:

i) Documented histologically confirmed, recurrent, or metastatic SCCHN (oral cavity, pharynx, larynx), and not amenable to local therapy with curative intent. Any other

cancers of the head and neck, including nasopharyngeal cancer, salivary gland, and neuroendocrine tumors are excluded.

ii) Disease progression on or after, or been intolerant to, a platinum-containing regimen.

iii) Prior focal palliative radiotherapy must have been completed at least 2 weeks before study drug administration.

iv) Documented historical human papillomavirus (HPV) status for oropharyngeal cancers. HPV status should preferably be determined using p16 IHC or HPV polymerase chain reaction (PCR) (if available).

v) Disease progression while on or after prior PD-(L)1 treatment as monotherapy or in combination with other modalities, if available.

g) Participants in Parts B1 and C, NSCLC, must meet all of the following:

i) Documented histologically or cytologically confirmed metastatic NSCLC of non-squamous or squamous histology with Stage IV A/B (as defined by the 8th International Association for the Study of Lung Cancer Classification) or recurrent disease following multi-modal therapy for locally advanced disease, measurable by RECIST v1.1.

ii) Recurrent or progressive disease during or after PDCT for advanced or metastatic disease OR must have recurrent or progressive disease within 6 months after completing PDCT for local disease.

iii) Disease progression while on or after prior PD-(L)1 treatment as monotherapy or in combination with other modalities.

iv) Prior definitive chemoradiation for locally advanced disease is permitted as long as the last administration of chemotherapy or radiotherapy (whichever was given last) occurred less than 6 months prior to enrollment.

v) Participants with disease having known actionable mutations in epidermal growth factor receptor (EGFR) including exon 20 insertion mutations, anaplastic lymphoma kinase (ALK), ROS proto-oncogene 1 (ROS1), rearranged during transfection (RET), neurotrophic tropomyosin-receptor kinase (NTRK), Kirsten rat sarcoma (KRAS) (G12C), MET exon 14 skipping mutations, or proto-oncogene B-Raf (BRAF) (V600E) must have progressed on, have been intolerant to, or not be a candidate for standard targeted therapy (as available per country/region standard-of-care practices).

vi) Experienced radiographically documented progressive disease on or after the most recent therapy.

h) [redacted]

i) Participants in Parts D and E, NSCLC, must meet all of the following:

i) Documented histologically or cytologically confirmed metastatic NSCLC of non-squamous (Part D) or squamous (Part E) histology with Stage IV A/B (as defined by the 8th International Association for the Study of Lung Cancer Classification) or recurrent disease following multi-modal therapy for locally advanced disease,

measurable by RECIST v1.1, who have not had systemic therapy for metastatic or recurrent disease.

ii) Participants with disease having known genetic aberrations in EGFR including exon 20 insertion mutations, ALK, ROS1, KRAS (G12C), RET, NTRK, MET exon 14 skipping mutations or BRAF (V600E) that are sensitive to targeted therapy (as available per country/region standard-of-care practices) will be excluded.

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

iv) Prior adjuvant or neoadjuvant chemotherapy for early-stage lung cancer is permitted if completed at least 6 months prior to initiating study treatment.

j) Part F: Criteria for Part F will be similar to either Part C or Parts D/E, dependent on the population chosen (either post-PDCT and anti-PD-[L1] therapy or treatment-naive NSCLC), and will be added via a future amendment.

3) Age of Participant

Participant must be ≥ 18 years of age or local age of majority at the time of signing the informed consent.

4) Reproductive Status

Investigators shall counsel women of childbearing potential (WOCBP), and male participants who are sexually active with WOCBP, on the importance of pregnancy prevention, the implications of an unexpected pregnancy, and the potential of fetal toxicity occurring due to transmission of study intervention, 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 age of majority, or older at time of consent.

ii) Female participants who are not of childbearing potential must have documented proof that they are not of childbearing potential.

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

iv) WOCBP must have a negative serum or urine pregnancy test (minimum sensitivity 25 IU/L or equivalent units of human chorionic gonadotropin [hCG]) 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.

- 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.

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

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

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

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

(a) Is not a WOCBP

OR

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

(i) All participants: 6 months after last dose.

b) Male Participants:

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

i) Azoospermic male participants enrolled in Parts A, B1, or B2 are exempt from contraceptive requirements. However, azoospermic male participants enrolled in Parts C, D, or E 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.

ii) Male participants enrolled in Parts C, D, or E are required to use a condom during the intervention period and for at least 3 months after the last dose of study intervention.

iii) Female partners of males enrolled in Parts C, D, or E in the study should be advised to use highly effective methods of contraception during the study intervention period and for at least 3 months after the last dose of the male participant's study intervention.

iv) Male participants enrolled in Parts C, D, or E 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 3 months after the last dose of study intervention.

v) Male participants enrolled in Parts C, D, or E must refrain from donating sperm during the intervention period and for at least 3 months after the last dose of study intervention.

vi) 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.

vii) No additional contraceptive measures are required to be used for male participants enrolled in Parts A, B1, or B2.

6.2 Exclusion Criteria

Participants are excluded from the study if any of the following criteria apply:

1) Medical Conditions

a) Untreated symptomatic central nervous system (CNS) metastases. Participants are eligible if CNS metastases have been treated and participants have neurologically returned to baseline (except for residual signs or symptoms related to the CNS treatment). In addition, participants must have been 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 in study Part B1, or treatment assignment in all other study parts. Imaging performed within 28 days prior to first study treatment in study Part B1 or treatment assignment in all other study parts must document radiographic stability of CNS lesions and be performed after completion of any CNS directed therapy.

b) Leptomeningeal metastases.

c) Concurrent malignancy (present during screening) requiring treatment or history of prior malignancy active within 2 years prior to randomization in study Part B1 or treatment assignment in all other study parts (ie, participants with a history of prior malignancy are eligible if treatment was completed at least 2 years before randomization/ treatment assignment and the patient 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.

d) Participants with an active, known, or suspected autoimmune disease. Participants with type 1 diabetes mellitus, hypothyroidism only requiring hormone replacement, skin disorders (such as vitiligo, psoriasis, or alopecia) not requiring systemic treatment, or conditions not expected to recur in the absence of an external trigger are permitted to enroll.

e) Participants with a condition requiring systemic treatment with either corticosteroids (> 10 mg daily prednisone equivalent) within 14 days or other immunosuppressive medications within 30 days of randomization in study Part B1 or treatment assignment in all other study parts. Inhaled or topical steroids, and adrenal replacement steroid doses > 10 mg daily prednisone equivalent, are permitted in the absence of active autoimmune disease.

f) Prior organ or tissue allograft.

g) Toxicity (except for alopecia) related to prior anti-cancer therapy and/or surgery, unless the toxicity is either resolved, returned to baseline or Grade 1, or deemed irreversible.

h) History of life-threatening toxicity related to prior T-cell agonist or checkpoint inhibitor 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 other immune checkpoint pathways), except those that are unlikely to re-occur with standard countermeasures (eg, hormone replacement after adrenal crisis).

i) History of or with active interstitial lung disease or pulmonary fibrosis.

j) Evidence of active infection that requires systemic antibacterial, antiviral, or antifungal therapy ≤ 7 days prior to the first dose of study treatment.

k) Known human immunodeficiency virus (HIV) positive with an acquired immune deficiency syndrome (AIDS)-defining opportunistic infection within the last year, or a current CD4 count < 350 cells/µL. Participants with HIV are eligible if:
   i) They have received antiretroviral therapy for at least 4 weeks prior to randomization in study Part B1 or Part F or treatment assignment in all other study parts, as clinically indicated, while enrolled on study.
   ii) They have a documented HIV viral load of less than 400 copies/mL within 4 weeks prior to the first dose of study treatment.
   iii) They continue on antiretroviral therapy as clinically indicated while enrolled on study.
   iv) 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.

l) Participants with serious or uncontrolled medical disorders.

m) Subject has any condition, including active or uncontrolled infection, or the presence of laboratory abnormalities, which places the subject at unacceptable risk if he/she were to participate in the study.

n) Previous SARS-CoV-2 infection within 10 days for mild or asymptomatic infections, or 20 days for severe/critical illness, prior to C1D1.
   i) Acute symptoms must have resolved and based on Investigator assessment in consultation with the MM, there are no sequelae that would place the participant at a higher risk of receiving study treatment.

o) Uncontrolled or significant cardiovascular disease including, but not limited to, any of the following:
   i) Myocardial infarction or stroke/transient ischemic attack within the past 12 months.
   ii) Uncontrolled angina within the past 3 months.
   iii) History of aortic aneurysm.
   iv) Any history of clinically significant arrhythmias (such as ventricular tachycardia, ventricular fibrillation, or Torsades de Pointes).
   v) History of other clinically significant heart disease (eg, cardiomyopathy, congestive heart failure with New York Heart Association functional classification III to IV, pericarditis, or significant pericardial effusion).
   vi) Cardiovascular disease-related requirement for daily supplemental oxygen therapy.
   vii) QT interval corrected for heart rate using Fridericia's formula (QTcF) prolongation > 480 msec, except for right bundle branch block.
   viii) History of myocarditis, regardless of etiology.

2) Reproductive Status

a) Woman who are pregnant.

b) Women who are breastfeeding.

3) Prior/Concomitant Therapy

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

b) 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.

c) Radiation therapy within 2 weeks prior to first study treatment. Participants must have recovered (ie, Grade ≤ 1 or at baseline) from radiation-related toxicities prior to first study treatment.

d) Prior treatment with an anti-PD-1, anti-PD-L1, or anti-CTLA-4 antibody, or any other antibody or drug specifically targeting T-cell co-stimulation or checkpoint pathways for Parts D and E.

e) Systemic anticancer therapies or biological therapies within 4 weeks or 5 half-lives (whichever is shorter) prior to the first administration of study treatment.

f) Participation in a study of an investigational agent and received study therapy or used an investigational device within 28 days or 5 half-lives (whichever is shorter).

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

h) Previous SARS-CoV-2 vaccine within 7 days of C1D1. For vaccines requiring more than 1 dose, the full series (eg, both doses of a 2-dose series) should be completed prior to C1D1 when feasible and when a delay in C1D1 would not put the study participant at risk.

i) Part C: Prior docetaxel therapy is not permitted.

j) Parts D and E: Prior systemic therapy for advanced or metastatic NSCLC is not permitted.

k) Prior therapy with an anti-[redacted] or anti-[redacted] antibody.

4) Allergies and Adverse Drug Reaction

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

b) Part C: History of hypersensitivity to docetaxel or polysorbate 80.

c) Part D: Hypersensitivity to pemetrexed, carboplatin, or any of the excipients.

d) Part E: Hypersensitivity to paclitaxel, carboplatin, or any of the excipients.

5) Physical and Laboratory Test Findings

a) White blood cells < 2000/µL.

b) Neutrophils < 1500/µL (stable off any growth factor within 4 weeks of first study treatment administration).

c) Platelets < 100 x 10^3/µL (transfusion to achieve this level is not permitted within 2 weeks of first study treatment administration).

d) Hemoglobin < 9.0 g/dL (transfusion to achieve this level is not permitted within 2 weeks of first study treatment administration).

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

f) Aspartate aminotransferase (AST)/alanine aminotransferase (ALT): > 3.0 x ULN. Participants in Part C only: AST and/or ALT > 1.5 x ULN concomitant with alkaline phosphatase > 2.5 x ULN.

g) All participants, except Part C: Total bilirubin > 1.5 x ULN (except participants with Gilbert Syndrome who must have a total bilirubin level of < 3.0 x ULN).

Participants in Part C only: Total bilirubin > ULN.

h) Any positive test result for hepatitis B virus (HBV) indicating presence of virus, eg, Hepatitis B surface antigen (sAG, Australia antigen) positive.

i) Any positive test result for hepatitis C virus (HCV) indicating presence of active viral replication (detectable HCV-ribonucleic acid [RNA]). Note: Participants with positive HCV antibody and an undetectable HCV RNA are eligible to enroll.

j) Participants with ≥ Grade 2 peripheral neuropathy for Parts C, D, and E.

6) Other Exclusion Criteria

a) Prisoners or participants who are involuntarily incarcerated. (Note: Under certain specific circumstances and only in countries where local regulations permit, a person who has been imprisoned may be included or permitted to continue 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.

c) Inability to comply with restrictions as listed in Section 6.3 for participants in Part C.

d) Any major surgery within 4 weeks of study drug administration. Participants must have recovered from the effects of major surgery or significant traumatic injury at least 14 days before the first dose of study treatment.

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

Participants receiving docetaxel should be advised to use appropriate sun protection due to the potential risk of photosensitivity which may cause sunburn with minimal sun exposure.

6.4 Screen Failures

Screen failures are defined as participants who consent to participate in the clinical study but who are not subsequently entered 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 SAEs.

6.4.1 Retesting During Screening or Lead-in Period

Participant Re-enrollment: This study permits the re-enrollment of a participant who has discontinued the study as a pretreatment 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 administration of study intervention is the value by which study inclusion will be assessed, because 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 MM may be needed to identify whether repeat testing of any particular parameter is clinically relevant.

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, participants 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 MM 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 MM (eg, safety labs, SpO2, chest CT scan) should be repeated.

7 STUDY INTERVENTION(S) AND CONCOMITANT THERAPY

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

Study intervention includes both Investigational [Medicinal] Product (IP/IMP) and Non-investigational/Auxiliary [Medicinal] Product (Non-IP/Non-IMP/AxMP) as indicated in Table 7.1-1 and Table 7.1-2.

An IP, also known as IMP 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 from 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-IPs/AxMPs.

7.1 Study Interventions Administered

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

Table 7.1-1: Study Interventions for Parts A to C

Part	Part A	Part B1 & B2	Part C
Intervention Name	BMS-986442 + nivolumab	BMS-986442 + nivolumab	BMS-986442 + nivolumab + docetaxel[a]
Type	Biologic + Biologic	Biologic + Biologic	Biologic + Biologic + Drug
Dose Formulation	Solutions in a single-use vial	Solutions in a single-use vial	Solutions in a single-use vial
Unit Dose Strength(s)	[redacted] mg/vial + 100 mg/vial or [redacted] mg/vial + 100 mg/vial	[redacted] mg/vial + 100 mg/vial or [redacted] mg/vial + 100 mg/vial	[redacted] mg/vial + 100 mg/vial + various strengths or [redacted] mg/vial + 100 mg/vial + various strengths
Dosage Level(s)	BMS-986442: 20, 60, 200, 600, 1200 mg Q3W Nivolumab 360 mg Q3W	BMS-986442: Doses Q3W TBD Nivolumab 360 mg Q3W	BMS-986442: Doses Q3W TBD Nivolumab 360 mg Q3W Docetaxel 75 mg/m^2 Q3W
Route of Administration	IV infusions	IV infusions	IV infusions
Use	Experimental	Experimental	Experimental + SOC
IMP and Non-IMP/AxMP	IMP + IMP	IMP + IMP	IMP + IMP + IMP
Sourcing	Provided centrally by the Sponsor	Provided centrally by the Sponsor	Provided locally by the trial site (docetaxel)[b] + provided centrally by the Sponsor (BMS-986442 + Nivolumab)
Packaging and Labeling	Study interventions will be provided in vials. Each vial will be labeled as required per country requirement.	Study interventions will be provided in vials. Each vial will be labeled as required per country requirement.	Study interventions will be provided in vials. Each vial will be labeled as required per country requirement.
Current/Former Name(s) or Alias(es)	TIGIT bispecific antibody (BMS-986442) Anti-PD-1 (nivolumab) or BMS-936558 or MDX1106 or Ono-4538	TIGIT bispecific antibody (BMS-986442) Anti-PD-1 (nivolumab) or BMS-936558 or MDX1106 or Ono-4538	TIGIT bispecific antibody (BMS-986442) Anti-PD-1 (nivolumab) or BMS-936558 or MDX1106 or Ono-4538 Taxane/Taxotere chemotherapy (docetaxel)

Abbreviations: AxMP, auxiliary medicinal product; BID, twice daily; IMP, investigational medicinal product; IV, intravenous; PD-1, programmed cell death protein 1; Q3W, every 3 weeks; SmPC, Summary of Product Characteristics; SOC, standard of care; TBD, to be determined; TIGIT, T cell immunoreceptor with Ig and ITIM domains.

[a] Premedication consists of an oral corticosteroid, such as dexamethasone 16 mg per day (eg, 8 mg BID) for 3 days starting 1 day prior to docetaxel administration (see Section 7.1.2).

[b] Sponsor may provide docetaxel in regions where it is not available through insurance or as part of SOC.

Table 7.1-2: Study Interventions for Parts D and E

ARM Name	Part D	Part E
Intervention Name	4 cycles of BMS-986442 + nivolumab + carboplatin + pemetrexed,[a] followed by BMS-986442 + nivolumab + pemetrexed maintenance	4 cycles of BMS-986442 + nivolumab + carboplatin + paclitaxel,[b] followed by BMS-986442 + nivolumab maintenance
Type	Biologic + Biologic + Drug + Drug	Biologic + Biologic + Drug + Drug
Dose Formulation	Solutions in a single-use vial	Solutions in a single-use vial
Unit Dose Strength(s)	[redacted] mg/vial or [redacted] mg/vial + 100 mg/vial + 450 mg/vial /various strengths + 500 mg/vial/various strengths	[redacted] mg/vial or [redacted] mg/vial + 100 mg/vial + 450 mg/vial /various strengths + 100 mg/vial/various strengths
Dosage Level(s)	BMS-986442: Dose TBD Q3W Nivolumab 360 mg Q3W Carboplatin AUC 5 or AUC 6 Q3W[c] Pemetrexed 500 mg/m^2 Q3W	BMS-986442: Dose TBD Q3W Nivolumab 360 mg Q3W Carboplatin AUC 6 Q3W Paclitaxel 200 mg/m^2 Q3W
Route of Administration	IV Infusions	IV Infusions
Use	Experimental (BMS-986442 + nivolumab) + SOC	Experimental (BMS-986442 + nivolumab) + SOC
IMP and Non-IMP/AxMP	IMP + IMP + IMP + IMP	IMP + IMP + IMP + IMP
Sourcing	Provided locally by the trial site (carboplatin, pemetrexed, and paclitaxel)[d] + provided centrally by the Sponsor (BMS-986442 + Nivolumab)	Provided locally by the trial site (carboplatin, pemetrexed, and paclitaxel)[d] + provided centrally by the Sponsor (BMS-986442 + Nivolumab)
Packaging and Labeling	Study interventions will be provided in vials. Each vial will be labeled as required per country requirement.	Study interventions will be provided in vials. Each vial will be labeled as required per country requirement.
Current/Former Name(s) or Alias(es)	TIGIT bispecific antibody (BMS-986442) Anti-PD-1 (nivolumab) or BMS-936558 or MDX1106 or Ono-4538 Platinum chemotherapy (carboplatin) Folate analog metabolic inhibitor (pemetrexed)	TIGIT bispecific antibody (BMS-986442) Anti-PD-1 (nivolumab) or BMS-936558 or MDX1106 or Ono-4538 Platinum chemotherapy (carboplatin) Taxane chemotherapy (paclitaxel)

Abbreviations: AUC, area under the serum concentration-time curve; AxMP, auxiliary medicinal product; IMP, investigational medicinal product; IV, intravenous; PD-1, programmed cell death protein 1; Q3W, every 3 weeks; SOC, standard of care; TBD, to be determined; TIGIT, T cell immunoreceptor with Ig and ITIM domains.

[a] Premedications for use with pemetrexed include corticosteroids, folic acid, vitamin B12, and antiemetic treatments (see Section 7.1.3).

[b] Premedications for use with paclitaxel include corticosteroids and histamine H2-receptor blockers (see Section 7.1.4).

[c] Dose selected per local SOC.

[d] Sponsor may provide carboplatin, pemetrexed, and paclitaxel in regions where it is not available through insurance or as part of SOC.

During the treatment phase, participants will receive 1 of the treatment regimens by arm described in Table 7.1-1 and Table 7.1-2.

7.1.1 Part A and Part B: Nivolumab and BMS-986442

Nivolumab will be administered as the first infusion. Participants will receive nivolumab at a dose of 360 mg over an approximately 30-minute infusion each treatment cycle followed by an observation period of at least 30 minutes. If needed, flush the IV line with an appropriate amount of diluent (eg, 0.9% Sodium Chloride or 5% Dextrose in water) to ensure that the complete dose is administered over approximately 30 minutes. Begin study treatment within 3 calendar days of randomization in study Part B1 or treatment assignment in all other study parts.

Participants will receive BMS-986442 at the dose level indicated dependent on treatment assignment or randomization. BMS-986442 (20 mg dose level up to and including 600 mg dose level) will be administered as an infusion over 60 minutes (Q3W) followed by a 60-minute observation period. BMS-986442 at the 1200 mg dose level will be administered as an infusion over 90 minutes (Q3W), followed by a 60-minute observation period.

There will be no intra-subject dose escalations or reductions of BMS-986442 or nivolumab allowed. For Q3W dosing cycles, participants may be dosed no less than 19 days from the previous dose. Premedications are not recommended for the first dose of nivolumab. Participants should receive prophylaxis with IV diphenhydramine 25 mg (or equivalent) 30 minutes prior to dosing of BMS-986442 with or without acetaminophen 325 to 1000 mg administered 30 to 60 minutes before the first 3 study drug administrations of BMS-986442. If pre-dosed premedicated participants experience no infusion-related reactions (IRRs), potential cessation of premedication beyond dose 3 may be discussed with the MM.

Monitor participants carefully for infusion reactions during nivolumab and BMS-986442 administration. If an acute infusion reaction is noted, manage participants according to Section 7.4.

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

Please refer to the current IB and/or Pharmacy Manual for further details regarding storage, preparation, and administration of nivolumab and BMS-986442.

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

Use separate infusion bags and filters when administering nivolumab and BMS-986442 and/or chemotherapies mentioned in Table 7.1-1 on the same day.

Parts A and B: BMS-986442 and nivolumab study treatment will continue until progression, unacceptable toxicity, withdrawal of consent, completion of 2 years of treatment (approximately 105 weeks), or the study ends, whichever occurs first.

7.1.2 Part C: Nivolumab, BMS-986442, and Docetaxel

Follow the instructions in Part A and Part B above for administration of nivolumab and BMS-986442. After the BMS-986442 infusion, there is a 60-minute delay before the start of the docetaxel infusion to monitor the participant for signs of possible infusion reactions and to differentiate any such reaction from one related to the subsequent docetaxel infusion. Dosing of nivolumab, BMS-986442, and docetaxel will be continued for a maximum of 24 months Q3W (± 3 days), until progression, unacceptable toxicity, withdrawal of consent, or the study ends, whichever occurs first. For docetaxel, the recommended premedication regimen is oral dexamethasone 16 mg per day (eg, 8 mg twice daily) (or equivalent dose of another corticosteroid) for 3 days starting 1 day prior to docetaxel administration; however, other corticosteroids and/or schedules and routes of administration are also acceptable according to local standards. Antiemetic premedication will be administered according to local standards.

Dosing calculations of docetaxel should be based on the body weight assessed at baseline using body surface area formula per institution practice. Docetaxel should be infused over 60 minutes. The dose may remain the same if the participant's weight is within 10% of the baseline weight or prior dose weight. All doses should be rounded up or to the nearest milligram per institutional standard.

Participants who experience an event related to docetaxel necessitating discontinuation of chemotherapy may continue to receive other study treatments (Section 7.4.4). Study treatment can continue for up to 2 years (approximately 105 weeks), or until treatment discontinuation criteria are met.

7.1.3 Part D: Nivolumab, BMS-986442, Pemetrexed, and Carboplatin

Follow the instructions in Part A and Part B above for administration of nivolumab and BMS-986442. After the BMS-986442 infusion, there is a 60-minute delay before the start of the pemetrexed infusion to monitor the participant for signs of possible infusion reactions and to differentiate any such reaction from one related to the subsequent chemotherapy infusion.

Pemetrexed dosing calculations should be based on the body surface area calculation. The dose may remain the same if the participant's weight is within 10% of the weight used to calculate the previous dose.

Premedications for use with pemetrexed include the following:

- Oral or IV corticosteroid should be given according to local standards at a dose equivalent to dexamethasone 4 mg twice daily on the day prior to, the day of, and the day after the administration of pemetrexed.
- Oral folic acid 350 to 1000 µg daily (dosed in accordance with local prescribing information) should be given starting 1 week prior to the first dose of pemetrexed, with at least 5 doses of folic acid administered in the 7 days prior to the first dose. Oral folic acid should be continued

daily throughout the treatment with pemetrexed and for 21 days after the last dose of pemetrexed.

- Intramuscular injection of vitamin B12 1000 µg should be given approximately 1 week prior to the first dose of pemetrexed and repeated every 3 cycles thereafter during pemetrexed treatment. Subsequent injections of vitamin B12 may be given on the same day as pemetrexed (participant with non-squamous histology may begin folic acid and vitamin B12 prior to treatment assignment, in anticipation of pemetrexed).
- Antiemetic premedication will be administered according to local standards. Recommended antiemetic treatments are dexamethasone (dosing according to local standards; an equivalent dose of another corticosteroid may be substituted) and a 5-HT3 receptor antagonist (type per Investigator discretion and local standards of care). Additional use of antiemetic premedication may be employed at the discretion of the Investigator.

Participants will receive pemetrexed at a dose of 500 mg/m^2 as a 10-minute IV infusion on Day 1 of each cycle.

Carboplatin should be given following pemetrexed on Day 1 of each cycle, and the carboplatin dose (area under the serum concentration-time curve [AUC] 5 or 6) will be calculated using the Calvert formula as follows:

> Carboplatin dose (mg) = target area under the serum concentration-time curve (AUC) × (CrCl [mL/min] + 25)

CrCl calculation is based on the Cockcroft-Gault formula and should include the most recent serum/plasma creatinine and most recent weight. NOTE: If calculation of the CrCl by the Cockcroft-Gault formula yields a result of > 125 mL/min, then a CrCl should be calculated by an alternative formula per institutional standards or capped at 125 mL/min.

The dose of carboplatin may be capped per local standards and should be administered intravenously for 15 minutes or longer.

After Cycle 4 of carboplatin and pemetrexed, participants in Part D who have SD or response are permitted to receive pemetrexed 500 mg/m^2 alone as maintenance therapy until treatment discontinuation criteria are met or approximately 2 years (approximately 105 weeks) of total treatment have been received.

7.1.4 Part E: Nivolumab, BMS-986442, Paclitaxel, and Carboplatin

Follow the instructions in Part A and Part B above for administration of nivolumab and BMS-986442. After the BMS-986442 infusion, there is a 60-minute delay before the start of the paclitaxel infusion to monitor the participant for signs of possible infusion reactions and to differentiate any such reaction from one related to the subsequent chemotherapy infusion.

Participants will receive paclitaxel 200 mg/m^2 as a 180-minute IV infusion with carboplatin at a dose of AUC 5 or AUC 6 for Part D and AUC 6 for Part E as a 30-minute IV infusion on Day 1 of a 3-week cycle, or at doses per the local prescribing information. The infusion time can follow local institutional standards.

Paclitaxel dosing calculations should be based on the body surface area calculation. The dose may remain the same if the participant's weight is within 10% of the baseline weight or prior dose weight.

Premedications for use with paclitaxel include the following:

- Oral or IV corticosteroid should be given according to local standard at a dose equivalent to dexamethasone 20 mg, 12 hours and 6 hours prior to paclitaxel administration.
- Histamine H2-receptor blocker (per local standard of care) should be administered 30 to 60 minutes prior to paclitaxel infusion.
- Doses of paclitaxel and/or carboplatin may be interrupted, delayed, reduced, or discontinued depending on how well the participant tolerates the treatment.

Follow the instructions in Part D for administering carboplatin following paclitaxel.

Participants who complete the first 4 cycles of study treatment without evidence of disease progression will continue with maintenance treatment of BMS-986442 and nivolumab.

7.1.5 Observation Time for All Study Parts

Participants should be observed for 2 hours after all infusions are completed for the first 2 cycles, and if they do not experience any IRR, then they should be observed for at least 1 hour after completion of all infusions for all subsequent cycles.

7.2 Method of Study Intervention Assignment

Study using IRT: All participants will be centrally assigned to treatment (Parts A, B2, C, D, and E) or randomized (Parts B1 and F) using IRT. Before the study is initiated, each user will receive log-in information and directions on how to access the IRT.

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

Participants in Part B1 will be randomized to receive 1 of 2 interventions (Q3W). Randomization will be done according to a computer-generated randomization scheme prepared by a Randomization coordinator within the Drug Supply Management Department of BMS Research and Development.

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] (eg, [redacted]). The patient identification number (PID) will ultimately comprise 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 assign treatment (Parts A, B2, C, D, and E) or randomize the participant into the open dose panel (Part B1).

7.3 Blinding

This is an open-label study; participants in Parts A, B2, C, D, and E will be assigned to treatment and participants in Parts B1 and F will be randomized to treatment. It has been determined that blinding could negatively impact participant safety management, therefore blinding procedures are not applicable. The specific treatment to be taken by a participant will be assigned using IRT. The site will contact the Interactive Response System prior to the start of study intervention administration for each participant. The site will record the treatment assignment on the applicable case report form (CRF), if required.

7.4 Dosage Modification

Dosing for all study treatment drugs should initially be delayed if any criteria in Table 7.4.1-1 (for BMS-986442 and/or nivolumab) or Table 7.4.3-1 (for docetaxel) or Section 7.4.5 (chemotherapy for Parts D and E) are met. That is, immunotherapy should also be delayed if criteria for delay of chemotherapy are met, and chemotherapy should also be delayed if criteria for immunotherapy are met.

Intra-subject dose escalation or dose reductions will not be permitted for BMS-986442 or nivolumab, in order to allow better evaluation of the safety and efficacy at individual dose levels and schedules, except as described for cohort level dose de-escalations for BMS-986442. Assessments of study interventions will be used in considering criteria for dose delay, resumption, and discontinuation (see Section 7.4.1, Section 7.4.2, and Section 8.2.1).

Parts C to E: Dose reductions for chemotherapy may be required and will be performed according to the following guidance (see Section 7.4.3 through Section 7.4.6.3). In Parts D and E, the dose reductions for each agent in the chemotherapy regimen are not linked and may be adjusted independently. If criteria for discontinuation of the chemotherapy regimen are met, immunotherapy (BMS-986442 and nivolumab) may continue until the criteria for treatment discontinuation are met. If criteria for discontinuation of BMS-986442 and nivolumab are met, chemotherapy may continue if the participant meets the criteria to continue chemotherapy treatment.

7.4.1 Dose Modification Criteria for Nivolumab and BMS-986442

Dose delay criteria apply for all drug-related AEs. Delay administration of nivolumab and BMS-986442 if any of the delay criteria in Table 7.4.1-1 are met. Delay nivolumab and BMS-986442 dosing for any AE, laboratory abnormality, or intercurrent illness which, in the judgment of the Investigator, warrants delaying the dose of study medication.

For participants who require delay of nivolumab and BMS-986442, re-evaluate weekly, or more frequently if clinically indicated, and resume dosing when criteria to resume treatment are met (see Section 7.4.2). Continue tumor assessments per protocol even if dosing is delayed. See Section 8.2 for further information regarding permanent discontinuation of study interventions.

Table 7.4.1-1: Adverse Event Criteria for Delay, Resume, and Discontinue of Nivolumab and BMS-986442

Drug-Related Adverse Event (AE) per CTCAE V5	Severity	Action Taken	Clarifications, Exceptions, and Resume Criteria
Gastrointestinal			
Colitis or Diarrhea	Grade 2	Delay dose	Dosing may resume when AE resolves to baseline.
	Grade 3	Nivolumab monotherapy: Delay dose	Dosing may resume when AE resolves to baseline.
	Grade 4	Permanently discontinue	
Renal			
Serum/Plasma Creatinine Increased	Grade 2 or 3	Delay dose	Dosing may resume when AE resolves to Grade ≤ 1 or baseline value.
	Grade 4	Permanently discontinue	
Pulmonary			
Pneumonitis	Grade 2	Delay dose	Dosing may resume after pneumonitis has resolved to ≤ Grade 1.
	Grade 3 or 4	Permanently discontinue	
Hepatic			
AST, ALT, or T.bili increased	AST or ALT > 3x and ≤ 5x ULN or T.bili > 1.5x and ≤ 3x ULN, regardless of baseline value	Delay dose	Dosing may resume when laboratory values return to baseline.
	AST or ALT > 5 x ULN, regardless of baseline value	Delay dose or permanently discontinue	In most cases of AST or ALT > 5 x 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 MM/designee must occur and approval from the MM be received prior to resuming therapy.

Table 7.4.1-1: Adverse Event Criteria for Delay, Resume, and Discontinue of Nivolumab and BMS-986442

Drug-Related Adverse Event (AE) per CTCAE V5	Severity	Action Taken	Clarifications, Exceptions, and Resume Criteria
	Concurrent AST or ALT > 3 x ULN and T.bili > 2 x ULN, regardless of baseline value, or T. bili > 3 x ULN, or AST or ALT > 8 x ULN with no tumor involvement of the liver, or AST or ALT > 10 x ULN with tumor involvement of the liver	Permanently discontinue	
Endocrinopathy			
Adrenal Insufficiency	Grade 2 adrenal insufficiency	Delay dose	Dosing may resume after adequately controlled with hormone replacement.
	Grade 3 or 4 adrenal insufficiency or adrenal crisis	Delay dose or permanently discontinue	Mandatory discussion with and approval from the MM needed prior to resuming therapy. If adrenal insufficiency resolves or is adequately controlled with physiologic hormone replacement, participant may not require discontinuation of study drug.
Hyperglycemia	Hyperglycemia requiring initiation or change in daily management (Grade 2 or 3)	Delay dose	Dosing may resume if hyperglycemia resolves to Grade ≤ 1 or baseline value, or is adequately controlled with glucose-controlling agents.
	Grade 4	Delay dose or permanently discontinue	Mandatory discussion with and approval from the MM needed prior to resuming therapy. If hyperglycemia resolves, or is adequately controlled with glucose-controlling agents, participant may not require discontinuation of study drug.

Table 7.4.1-1: Adverse Event Criteria for Delay, Resume, and Discontinue of Nivolumab and BMS-986442

Drug-Related Adverse Event (AE) per CTCAE V5	Severity	Action Taken	Clarifications, Exceptions, and Resume Criteria
Hypophysitis/Hypopituitarism	Symptomatic Grade 1-3 that is also associated with corresponding abnormal lab and/or pituitary scan	Delay dose	Dosing may resume if endocrinopathy resolves to be asymptomatic or is adequately controlled with only physiologic hormone replacement.
	Grade 4	Delay dose or permanently discontinue	Mandatory discussion with and approval from the MM needed prior to resuming therapy. If endocrinopathy resolves or is adequately controlled with physiologic hormone replacement, participant may not require discontinuation of study drug.
Hyperthyroidism or Hypothyroidism	Grade 2 or 3	Delay dose	Dosing may resume if endocrinopathy resolves to be asymptomatic or is adequately controlled with only physiologic hormone replacement or other medical management.
	Grade 4	Delay dose or permanently discontinue	Mandatory discussion with and approval from the MM needed prior to resuming therapy. If endocrinopathy resolves or is adequately controlled with physiologic hormone replacement or other medical management, participant may not require discontinuation of study drug.
Skin			
Rash	Grade 2 rash covering > 30% body surface area or Grade 3 rash	Delay dose	Dosing may resume when rash reduces to ≤ 10% body surface area
	Suspected Stevens-Johnson syndrome (SJS), toxic epidermal necrolysis (TEN), or drug reaction with eosinophilia and systemic symptoms (DRESS)	Delay dose	Dosing may resume if SJS, TEN, or DRESS is ruled out and rash reduces to ≤ 10% body surface area.
	Grade 4 rash or confirmed SJS,TEN, or DRESS	Permanently discontinue	

Table 7.4.1-1: Adverse Event Criteria for Delay, Resume, and Discontinue of Nivolumab and BMS-986442

Drug-Related Adverse Event (AE) per CTCAE V5	Severity	Action Taken	Clarifications, Exceptions, and Resume Criteria
Neurological			
Guillain-Barre Syndrome (GBS)	Any Grade	Permanently discontinue	
Myasthenia Gravis (MG)	Any Grade	Permanently discontinue	
Encephalitis	Any Grade encephalitis	Delay dose	After workup for differential diagnosis, (ie, infection, tumor-related), if encephalitis is not drug-related, then dosing may resume when AE resolves.
	Any Grade drug-related encephalitis	Permanently discontinue	
Myelitis	Any Grade myelitis	Delay dose	After workup for differential diagnosis, (ie, infection, tumor-related), if myelitis is not drug-related, then dosing may resume when AE resolves.
	Any Grade drug-related myelitis	Permanently discontinue	
Neurological (other than GBS, MG, encephalitis, or myelitis)	Grade 2	Delay dose	Dosing may resume when AE resolves to baseline.
	Grade 3 or 4	Permanently discontinue	
Myocarditis			
Myocarditis	Symptoms induced from mild to moderate activity or exertion	Delay dose	Dosing may resume after myocarditis has resolved.
	Severe or life-threatening, with symptoms at rest or with minimal activity or exertion, and/or where intervention indicated.	Permanently discontinue	

Table 7.4.1-1: Adverse Event Criteria for Delay, Resume, and Discontinue of Nivolumab and BMS-986442

Drug-Related Adverse Event (AE) per CTCAE V5	Severity	Action Taken	Clarifications, Exceptions, and Resume Criteria
Other Clinical AE			
Pancreatitis: Amylase or Lipase increased	Grade 3 with symptoms	Delay dose	Note: Grade 3 increased amylase or lipase without signs or symptoms of pancreatitis does not require dose delay. Dosing may resume when participant becomes asymptomatic.
	Grade 4	Permanently discontinue	
Uveitis	Grade 2 uveitis	Delay dose	Dosing may resume if uveitis responds to topical therapy (eye drops) and after uveitis resolves to Grade ≤ 1 or baseline. If participant requires oral steroids for uveitis, then permanently discontinue study drug.
	Grade 3 or 4 uveitis	Permanently discontinue	
Other Drug-Related AE **(not listed above)**	Grade 2 non-skin AE, except fatigue	Delay dose	Dosing may resume when AE resolves to Grade ≤ 1 or baseline value.
	Grade 3 AE - first occurrence lasting ≤ 7 days	Delay dose	Dosing may resume when AE resolves to Grade ≤ 1 or baseline value.
	Grade 3 AE - first occurrence lasting > 7 days	Permanently discontinue	
	Recurrence of Grade 3 AE of any duration	Permanently discontinue	
	Grade 4 or life-threatening adverse reaction	Permanently discontinue	

Table 7.4.1-1: Adverse Event Criteria for Delay, Resume, and Discontinue of Nivolumab and BMS-986442

Drug-Related Adverse Event (AE) per CTCAE V5	Severity	Action Taken	Clarifications, Exceptions, and Resume Criteria
Other Lab abnormalities			
Other Drug-Related lab abnormality **(not listed above)**	Grade 3	Delay dose	Exceptions: No delay required for: Grade 3 lymphopenia Permanent discontinuation for: Grade 3 thrombocytopenia > 7 days or associated with bleeding.
	Grade 4	Permanently discontinue	Exceptions: The following events do not require discontinuation of study drug: Grade 4 neutropenia ≤ 7 days. Grade 4 lymphopenia or leukopenia. Grade 4 isolated electrolyte imbalances/abnormalities that are not associated with clinical sequelae and are responding to supplementation/appropriate management within 72 hours of their onset.
Infusion Reactions (manifested by fever, chills, rigors, headache, rash, pruritus, arthralgia, hypotension, hypertension, bronchospasm, or other allergic-like reactions.)			
Hypersensitivity reaction or infusion reaction	Grade 3 or 4	Permanently discontinue	Refer to Section 7.4.9 on Treatment of Related Infusion Reactions.

Abbreviations: AE, adverse event; ALT, alanine aminotransferase; AST, aspartate aminotransferase; CTCAE, Common Terminology Criteria for Adverse Events; DRESS, drug reaction with eosinophilia and systemic symptoms; GBS, Guillain-Barre syndrome; MG, myasthenia gravis; MM, medical monitor; SJS, Stevens-Johnson syndrome; T.bili, total bilirubin; TEN, toxic epidermal necrolysis; ULN, upper limit of normal; V, version.

7.4.2 Criteria to Resume Treatment of Nivolumab and BMS-986442

Participants may resume treatment with study drug if they have completed AE management (ie, corticosteroid taper) or are on ≤ 10 mg prednisone or equivalent and meet the requirements per Table 7.4.1-1.

Prior to re-initiating treatment in a participant with a dosing delay lasting > 8 weeks, the MM (or designee) must be consulted. Continue tumor assessments per protocol even if dosing is delayed. Continue periodic study visits to assess safety and laboratory studies weekly or more frequently if clinically indicated during such dosing delays.

Dose delay is required for participants with confirmed SARS-CoV-2 infection. 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 MM. 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 on-study treatment in a participant with a dosing delay lasting 8 weeks or greater due to SARS-CoV-2 infection, the MM/designee must be consulted.

7.4.3 Dose Modification Criteria for Docetaxel

The criteria for dose delay, resumption, and discontinuation in Table 7.4.3-1 apply to docetaxel. In addition, delay docetaxel for any AE, laboratory abnormality, or intercurrent illness that in the judgment of the Investigator, warrants delaying the dose of study medication.

For participants who require delay of docetaxel, re-evaluate weekly or more frequently if clinically indicated, and resume dosing when criteria to resume treatment are met (see Section 7.4.4). Continue tumor assessments per protocol even if dosing is delayed. Dose modifications of docetaxel are permissible.

Table 7.4.3-1: Adverse Event Criteria for Delay, Resume, and Discontinue of Docetaxel

Drug-related AE per CTCAE V5	Severity	Action Taken for Docetaxel	Clarifications, Exceptions, and Resume Criteria
Hematological			
Neutropenia	Grade 2	Delay dose/reduce dose[a]	If not recovered on the day of administration, delay next infusion until neutrophil count ≥ 1.5×10^9/L. 1st episode: No dose reduction is required. 2nd episode: Consider dose reduction by 1 dose level.[a] G-CSF may be administered at the discretion of the Investigator and following local guidelines.
	Grade 3 or 4	Delay dose/reduce dose[a] or permanently discontinue	Delay next infusion until neutrophil count ≥ 1.5×10^9/L. No dose reduction if isolated and duration ≤ 7 days and recovered by Day 22 to ≤ Grade 1. If duration > 7 days or not recovered on Day 22 to ≤ Grade 1: 1st episode: Consider prophylactic G-CSF in subsequent cycles. 2nd episode or 1st episode despite prophylactic G-CSF: Reduce dose by 1 dose level.[a] 3rd episode or 2nd episode despite prophylactic G-CSF: Permanently discontinue.
Febrile neutropenia or neutropenic infection	Grade 3 or 4	Delay dose/reduce dose[a] or permanently discontinue	Delay next infusion until neutrophil count ≥ 1.5×10^9/L. 1st episode: Reduce the dose[a] and consider prophylactic G-CSF in subsequent cycles. 2nd episode: Permanently discontinue.
Thrombocytopenia	Grade 2	Delay dose	Dosing may resume when AE resolves to Grade ≤ 1 or baseline.
	Grade 3 or 4	Delay dose/reduce dose[a] or permanently discontinue	Dosing may resume when AE resolves to Grade ≤ 1 or baseline. If Grade 3 without delay, no dose reduction required. If Grade 4 or Grade 3 with delay: 1st episode: Reduce dose by 1 dose level.[a] 2nd episode: Permanently discontinue. Permanent discontinuation for: Grade 3 thrombocytopenia > 7 days or associated with bleeding.

Table 7.4.3-1: Adverse Event Criteria for Delay, Resume, and Discontinue of Docetaxel

Drug-related AE per CTCAE V5	Severity	Action Taken for Docetaxel	Clarifications, Exceptions, and Resume Criteria
Gastrointestinal			
Diarrhea	Grade 2	Delay dose	Dosing may resume when AE resolves to baseline.
	Grade 3	Delay dose/reduce dose[a] or permanently discontinue	1st episode: Reduce dose by 1 dose level.[a] 2nd episode: Permanently discontinue.
	Grade 4	Permanently discontinue	
Colitis or enterocolitis	Grade 2	Delay dose	Dosing may resume when AE resolves to baseline.
	Grade 3 or 4	Delay dose/reduce dose[a] or permanently discontinue	Dosing may resume when AE resolves to Grade ≤ 1 or baseline. 1st episode: Reduce dose by 1 dose level.[a] 2nd episode: Permanently discontinue.
Skin			
Rash	Grade 2 rash covering < 30% of body surface	Delay dose	Dosing may resume when AE resolves to Grade ≤ 1 or baseline. Dosing may resume when rash reduces to ≤ 10% body surface area.
	Grade 2 rash covering > 30% body surface area or Grade 3 rash	Delay dose/reduce dose,[a] or permanently discontinue	Dosing may resume when AE resolves to Grade ≤ 1 or baseline. 1st episode: Reduce dose by 1 dose level.[a] 2nd episode: Permanently discontinue.
	Grade 4	Permanently discontinue	
Neurological			
Peripheral neuropathy	Grade 2	Reduce dose[a]	Reduce dose by 1 dose level.[a]
	Grade 3 or 4	Permanently discontinue	

Table 7.4.3-1: Adverse Event Criteria for Delay, Resume, and Discontinue of Docetaxel

Drug-related AE per CTCAE V5	Severity	Action Taken for Docetaxel	Clarifications, Exceptions, and Resume Criteria
Hepatic			
AST, ALT, or T.bili[b] increased with or without alkaline phosphatase increase	AST or ALT > 3× and ≤ 5× ULN or T.bili > 1.5× and ≤ 3× ULN, regardless of baseline value, or T.bili > ULN and/or AST/ALT > 1.5× ULN associated with alkaline phosphatase > 2.5× ULN (in the absence of bone metastasis)	Delay dose/reduce dose[a]	Dose reduction may be considered at the discretion of the Investigator and following local guidelines.[a] Dosing may resume when laboratory values return to baseline.
	AST or ALT > 5× ULN or T.bili > 3× ULN, regardless of baseline value, or concurrent AST or ALT > 3× ULN and T.bili > 2× ULN or INR > 1.5, regardless of baseline value	Permanently discontinue	
Infusion Reactions (manifested by fever, chills, rigors, headache, rash, pruritus, arthralgia, hypotension, hypertension, bronchospasm, or other allergic-like reactions)			
Hypersensitivity reaction or infusion reaction	Grade 3 or 4	Permanently discontinue	Refer to Section 7.4.10.

Table 7.4.3-1: Adverse Event Criteria for Delay, Resume, and Discontinue of Docetaxel

Drug-related AE per CTCAE V5	Severity	Action Taken for Docetaxel	Clarifications, Exceptions, and Resume Criteria
Other Clinical AE			
CME diagnosed by ophthalmologic examination	Any grade	Permanently discontinue	CME has been reported in participants treated with docetaxel. Participants with impaired vision should undergo a prompt and complete ophthalmologic examination. In case CME is diagnosed, docetaxel treatment should be discontinued, and appropriate treatment initiated.
Other drug-related AE (not listed above)	Grade 2 non-skin AE, except fatigue	Delay dose	Dosing may resume when AE resolves to Grade ≤ 1 or baseline value.
	Grade 3	Delay dose/reduce dose[a] or permanently discontinue	Dosing may resume when AE resolves to Grade ≤ 1 or baseline value. 1st episode: Dose reduction may be considered at the discretion of the Investigator.[a] 2nd episode: Permanently discontinue.
	Grade 4 or life-threatening adverse reaction	Permanently discontinue	
Other Laboratory Abnormalities			
Other drug-related lab abnormality (not listed above)	Grade 3	Delay dose/reduce dose[a]	Dose reduction may be considered at the discretion of the Investigator and following local guidelines.[a] Exceptions: No delay required for: Grade 3 lymphopenia.
	Grade 4	Permanently discontinue	Exceptions: The following events do not require discontinuation of study drug: Grade 4 lymphopenia or leukopenia. Grade 4 isolated electrolyte imbalances/abnormalities that are not associated with clinical sequelae and are responding to supplementation/appropriate management within 72 hours of their onset.
SARS-CoV-2 Infection Either Confirmed or Suspected		Delay dose	Participants with SARS-CoV-2 infection (either confirmed or suspected) may resume treatment after 1) at least 10 days (20 days for severe/critical illness) have passed since symptoms first appeared or positive test result (eg, RT-PCR or viral antigen), 2) resolution of acute symptoms (including at least 24 hours has passed since last fever without fever-reducing medications), 3) evaluation by the

Table 7.4.3-1: Adverse Event Criteria for Delay, Resume, and Discontinue of Docetaxel

Drug-related AE per CTCAE V5	Severity	Action Taken for Docetaxel	Clarifications, Exceptions, and Resume Criteria
			Investigator with confirmation that there are no sequelae that would place the participant at a higher risk of receiving investigational treatment, and 4) consultation with the BMS MM. For suspected cases, treatment may also resume if SARS-CoV-2 infection is ruled-out as per institutional policy for testing of SARS-CoV-2 and other criteria to resume treatment are met.

Abbreviations: AE, adverse event; ALT, alanine aminotransferase; AST, aspartate aminotransferase; BMS, Bristol Myers Squibb; CME, cystoid macular edema; CTCAE, Common Terminology Criteria for Adverse Events; G-CSF, granulocyte colony-stimulating factor; INR, international normalized ratio; MM, medical monitor; RT-PCR, reverse transcriptase polymerase chain reaction; SARS-CoV-2, severe acute respiratory syndrome coronavirus disease 2; T.bili, total bilirubin; ULN, upper limit of normal; V, version.

[a] See Section 7.4.4 for instructions on docetaxel dose reduction.

[b] For participants with Gilbert's syndrome, direct bilirubin should be monitored and utilized in place of T.bili for toxicity assessments.

7.4.4 Docetaxel Dose Reduction and Criteria to Resume Treatment

The docetaxel dose can be reduced when necessary, as described in Table 7.4.4-1. The dose that has been reduced for toxicity must not be re-escalated. Up to a maximum of 1 dose reduction will be allowed per participant. If a second dose reduction is required per the modifications above, the participant should discontinue study treatment. Participants who experience an event related to docetaxel necessitating discontinuation of chemotherapy may continue to receive other study treatments. See Table 7.4.3-1 for criteria on resuming docetaxel treatment after a dose delay.

Table 7.4.4-1: Dose Reductions for Docetaxel

Dose Level	Docetaxel
Starting dose	75 mg/m^2
First dose reduction	60 mg/m^2
Second dose reduction	Discontinue docetaxel

7.4.5 Dose Delay Criteria for Chemotherapies in Part D and Part E

Chemotherapy drugs in Parts D and E should be delayed for any of the following on Day 1 of each cycle:

- Absolute neutrophil count (ANC) < 1500/µL (SI units: < 1.5 × 10^9/L)
- Platelets < 100 x 10^3/µL (SI units: < 0.1 × 10^9/L)
- Any Grade ≥2 non-skin, non-hematologic, drug-related AE (excluding Grade 2 alopecia, Grade 2 fatigue, and Grade 2 laboratory abnormalities)
- Any Grade ≥3 skin, drug-related AE
- Any Grade ≥3 drug-related laboratory abnormality, with the following exceptions for lymphopenia, AST, ALT, or T. bili:
  - Grade 3 lymphopenia does not require dose delay.
  - If a participant has a baseline AST, ALT, or T. bili that is within normal limits, delay dosing for drug-related Grade ≥ 2 toxicity.
  - If a participant has baseline AST, ALT, or T. bili within the Grade 1 toxicity range, delay dosing for drug-related Grade ≥ 3 toxicity.
- Any AE, laboratory abnormality, or intercurrent illness that, in the judgment of the investigator, warrants delaying the dose of study medication. Investigators should consult local labeling for the chemotherapy drugs being administered to any given participant for additional guidance on dose delays.

Participants should be re-evaluated weekly or more frequently if clinically indicated until re-treatment criteria are met (as per Section 7.4.6.3).

7.4.6 Dose Reduction and Criteria to Resume Treatment for Chemotherapies in Part D and Part E

Dose reductions for chemotherapy may be required and will be performed according to Table 7.4.6-1 or per institutional guidelines. Chemotherapy dose reductions are permanent; once the dose of any chemotherapy agent is reduced, it may not be re-escalated in subsequent cycles, except as noted when starting pemetrexed maintenance therapy. The dose reductions for each agent in the PDCT regimen are not linked and may be adjusted independently as summarized below.

Table 7.4.6-1: Dose Reductions for Chemotherapy (Parts D and E)

Dose Level	Carboplatin	Pemetrexed	Paclitaxel
Starting Dose	AUC6 or AUC5	500 mg/m^2	200 mg/m^2
1st dose reduction	AUC5 (if starting dose was AUC6) or AUC4 (if starting dose was AUC5)	375 mg/m^2	150 mg/m^2
2nd dose reduction	AUC4 (if starting dose was AUC6) or AUC3 (if starting dose was AUC5)	250 mg/m^2	100 mg/m^2
3rd dose reduction	Discontinue	Discontinue	Discontinue

Abbreviation: AUC, area under the serum concentration-time curve.

Dose modifications listed are specific to USPI. Variations may apply per local label.

Any participants with 2 prior dose reductions for 1 agent who experience a toxicity that would cause a third dose reduction must be discontinued from that agent.

7.4.6.1 Dose Reductions for Hematologic Toxicity for Chemotherapies in Part D and Part E

Dose modifications for hematologic toxicities (according to Common Terminology Criteria for Adverse Events [CTCAE] v5) are summarized in Table 7.4.6.1-1. Dose adjustments are based on nadir blood counts (assessed as per local standards) since the preceding drug administration. Dose level adjustments for PDCT are relative to that of the preceding administration. Generally, both chemotherapy agents in the PDCT regimen should be dose-reduced together for hematologic toxicity. Participants receiving chemotherapy may receive growth factors (including granulocyte colony-stimulating factor [G-CSF] and erythropoietin) after completion of the first cycle at the discretion of the Investigator and following local guidelines. Additionally, prophylactic antibiotics may be used according to local standards of care. Please report any antibiotic or growth factor use on the electronic case report form (eCRF). Dose modifications listed are specific to USPI. Variations may apply per local label.

Table 7.4.6.1-1: Dose Modifications for Hematologic Toxicity (Based on Nadir Counts)

Toxicity	Carboplatin	Paclitaxel	Pemetrexed
Neutrophil Count Decrease			
Grade 4 (< 500/mm^3 or < 0.5 × 109/L)	Reduce 1 dose level	Reduce 1 dose level	Reduce 1 dose level
Platelet Count Decrease			
Grade 3 (25,000 < 50,000/mm^3; 25.0 < 50.0 × 109/L)	Reduce 1 dose level	Reduce 1 dose level	Reduce 1 dose level
Grade 4 (< 25,000/mm^3; < 25.0 × 109/L)	Reduce 1 dose level	Reduce 1 dose level	Reduce 1 dose level

7.4.6.2 Dose Reductions for Non-hematologic Toxicities for Chemotherapies in Part D and Part E

Chemotherapy dosing guidelines use CTCAE v5. All dose reductions should be made based on the worst-grade toxicity. Participants experiencing any of the toxicities during the previous cycle should have their chemotherapy delayed until retreatment criteria are met and then reduced for all subsequent cycles by 1 dose level or discontinued as appropriate. Dose levels for the 2 drugs in the PDCT regimen are not linked and may be reduced independently, as summarized in Table 7.4.6.2-1.

Table 7.4.6.2-1: Dose Modifications for Non-Hematologic Toxicity for Chemotherapies (Parts D and E)

Toxicity	Carboplatin	Paclitaxel	Pemetrexed
Febrile neutropenia Grade ≥ 3	Reduce 1 dose level	Reduce 1 dose level	Reduce 1 dose level
Diarrhea Grade ≥ 3	No change	Reduce 1 dose level	Reduce 1 dose level
Allergic reaction[a] **Grade ≥ 3**	Discontinue	Discontinue	Discontinue
Neuropathy Grade 2	Reduce 1 dose level	No change	No change
Neuropathy Grade 3-4	Discontinue	Discontinue	Discontinue
CrCl < 50 mL/min	No change	Discontinue if CrCl < 20 mL/ min	No change
Other Grade ≥ 3 toxicity (except for fatigue and transient arthralgia and myalgia)	Adjust as medically indicated	Adjust as medically indicated	Adjust as medically indicated

Abbreviations: CrCl, creatinine clearance.

[a] Only the drug(s) causing the hypersensitivity reaction or acute infusion reaction (Grade ≥ 3) require(s) discontinuation. All other drugs may be continued.

7.4.6.3 Criteria to Resume Chemotherapy Treatment for Part D and Part E

Participants may resume treatment with chemotherapy when the absolute neutrophil count returns to 1500/μL (SI units: $< 1.5 \times 10^9$/L), the platelet count returns to $<100 \times 10^3$/μL (SI units: $< 0.1 \times 10^9$/L), and all other drug-related toxicities have returned to baseline or Grade 1 (or Grade 2 for alopecia and fatigue). If a participant fails to meet criteria for re-treatment, then re-treatment should be delayed, and the participant should be re-evaluated weekly or more frequently as clinically indicated. Any participant who fails to recover from toxicity attributable to chemotherapy to baseline or Grade 1 (except Grade 2 alopecia and fatigue) within 6 weeks from the last dose given should discontinue the drug(s) that caused the delay. When resuming chemotherapy treatment, please follow the dose-reduction recommendations in Section 7.4.5.

7.4.7 Dose-limiting Toxicities

The DLT evaluation period is 28 days for Parts A, B, C, D, and E. Participants in all parts will be considered DLT evaluable if they receive all specified study treatments (Cycle 1 and Cycle 2) and did not have a DLT event occur at any time before completion of the DLT period. In addition, participants who experienced a DLT after receiving a minimum of a partial dose of BMS-986442 will be DLT evaluable. Participants who receive a partial or full dose of BMS-986442 but do not meet DLT evaluable criteria will be included in the overall safety evaluation.

For the purpose of guiding decisions regarding dose escalation in Parts A, C, D, and E, DLTs will be defined based on the incidence, intensity, and duration of the AEs for which no clear alternative cause is identified and will exclude events clearly related to disease progression or intercurrent illness. The DLT evaluation period will begin on the first day of Cycle 1 and end on Day 28 (ie, 4 weeks). Any toxicities that occur beyond the DLT period will be accounted for in making final dose level decisions. Participants who have discontinued due to a DLT or received all specified study treatments during the 4-week DLT period will be considered as DLT evaluable. Participants who withdraw from the study during the DLT evaluation period, or have received less than the specified number of study treatments for reasons other than a DLT during the DLT evaluation period, will not be considered as DLT-evaluable participants and may be replaced with a new participant at the same dose level. Participants who are dose delayed during the DLT evaluation period for reasons other than a DLT will be considered as DLT-evaluable participants if they received at least 1 cycle of study treatment.

Any AE that is not clearly due to disease progression or extraneous causes that occurs within the 28-day DLT evaluation window and meets criteria for permanent discontinuation as listed in Table 7.4.1-1, Table 7.4.3-1 and Table 7.4.6.2-1, will be considered a DLT. In addition, the following AEs will be DLTs, except for those that are clearly due to disease progression or extraneous causes.

- Any death that is not clearly due to the underlying disease or extraneous causes within the 28-day DLT period.

Non-hematological toxicity:

- Any Grade ≥ 3 non-hematological toxicity. Exceptions will be made for:
  - Grade 3 nausea, diarrhea, or vomiting that resolves to baseline within 72 hours after holding study treatment and implementing optimal medical management.
  - Grade 3 fatigue that resolves to ≤ Grade 2 within 7 days.
  - Grade 3 increases in amylase or lipase that are not associated with symptoms or clinical manifestations of pancreatitis.
  - Grade 3 rash that reduces to ≤ Grade 1 within 14 days.
  - Grade 3 or 4 isolated electrolyte imbalances/abnormalities that are not associated with clinical sequelae and are responding to supplementation/appropriate management within 72 hours.
- AST/ALT > 3× and ≤ 5× ULN or T.bili > 1.5× and ≤ 3× ULN that is associated with new clinical signs/symptoms of liver inflammation or any case that meets Hy's Law criteria.
- Any AST/ALT > 5× ULN or T.bili > 3× ULN, irrespective of baseline values.
- Any Grade myocarditis.
- Any Grade myelitis, encephalitis, myasthenia gravis, or Guillain-Barre syndrome.
- Grade ≥ 2 uveitis, episcleritis, iritis eye pain, or blurred vision.
- Any Grade confirmed Stevens-Johnson syndrome (SJS), toxic epidermal necrolysis (TEN), or drug reaction with eosinophilia and systemic symptoms (DRESS).

Hematological toxicity:

- Grade 4 neutropenia of > 7 days duration.
- Grade 4 thrombocytopenia.
- Grade 3 thrombocytopenia with clinically significant bleeding.
- Febrile neutropenia.

Toxicity for Parts C to E Only :

- Any AE resulting in a > 2-week delay in the cycle of chemotherapy during the first 2 cycles (Parts C-E only) will be a DLT.

DLT Exception:

- Infusion reactions attributed to chemotherapy will not be considered DLTs.

Note: For participants who experience a DLT, further treatment will be based on Table 7.4.3-1, and the criteria to resume treatment in Section 7.4.2 and Section 7.4.6.

7.4.8 Management Algorithms for Immuno-oncology Agents

IO agents are associated with AEs that can differ in severity and duration from AEs caused by other therapeutic classes. Nivolumab and BMS-986442 are considered IO agents and the management algorithms in Appendix 7 provide guidance on assessing and managing the following groups of AEs:

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

7.4.9 Treatment of Related Infusion Reactions

Since nivolumab contains only human immunoglobulin protein sequences, it is unlikely to be immunogenic and induce infusion or hypersensitivity reactions. However, if such a reaction were to occur, it might manifest with fever, chills, rigors, headache, rash, pruritus, arthralgias, hypotension, hypertension, bronchospasm, or other allergic-like reactions. Report all Grade 3 or 4 infusion reactions within 24 hours as an SAE if it meets the criteria.

Treatment recommendations are provided below based on CTCAE v5 grading definitions and may be modified based on local treatment standards and guidelines, as appropriate:

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

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

For Grade 2 symptoms: (Therapy or infusion interruption indicated but responds promptly to symptomatic treatment (eg, antihistamines, nonsteroidal anti-inflammatory drugs (NSAIDs), narcotics, IV fluids); prophylactic medications indicated for ≤ 24 hrs):

- 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 1000 mg; remain at bedside and monitor participant until resolution of symptoms. Corticosteroid and/or bronchodilator therapy may also be administered as appropriate. If the infusion is interrupted, then restart the infusion at 50% of the original infusion rate when symptoms resolve; if no further complications ensue after 30 minutes, the rate may be increased to 100% of the original infusion rate. Monitor participant closely. If symptoms recur, then no further 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 1000 mg administered at least 30 minutes before nivolumab and/or ipilimumab infusions. If necessary, corticosteroids (up to 25 mg of hydrocortisone or equivalent) may be used.

For Grade 3 or 4 symptoms: (severe reaction, Grade 3: Prolonged (eg, not rapidly responsive to symptomatic medication and/or brief interruption of infusion); recurrence of symptoms following initial improvement; hospitalization indicated for clinical sequelae. Grade 4: Life-threatening consequences; urgent intervention 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 to 1 mg of a 1:1000 solution for subcutaneous administration or 0.1 to 0.25 mg of a 1:10,000 solution injected slowly for IV administration, and/or diphenhydramine 50 mg IV with methylprednisolone 100 mg IV (or equivalent), as needed. Monitor participant until the Investigator judges that the symptoms will not recur. Study drug will be permanently discontinued. Follow institutional guidelines for the treatment of anaphylaxis. Remain at bedside and monitor participant until recovery of the symptoms.

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

7.4.10 Docetaxel-related Hypersensitivity Reactions

Participants should be observed closely for hypersensitivity reactions especially during the first and second infusions. Hypersensitivity reactions may occur within a few minutes following the initiation of the infusion of docetaxel, thus facilities for the treatment of hypotension and bronchospasm should be available. If hypersensitivity reactions occur, minor symptoms such as flushing or localized cutaneous reactions do not require interruption of therapy. However, severe reactions (≥ Grade 3), such as severe hypotension, bronchospasm, or generalized rash/erythema require immediate discontinuation of docetaxel and appropriate therapy. Participants who have developed severe hypersensitivity reactions should not be re-challenged with docetaxel. Participants who have previously experienced a hypersensitivity reaction to paclitaxel may be at risk to develop a hypersensitivity reaction to docetaxel, including a more severe hypersensitivity reaction. These participants should be closely monitored during initiation of docetaxel therapy.

7.5 Preparation/Handling/Storage/Accountability

The IMP/Non-IMP/AxMP must be stored in a secure area according to local regulations. It is the responsibility of the Investigator, or designee where permitted, to ensure that IMP/Non-IMP/AxMP is only dispensed to study participants. The IMP/Non-IMP/AxMP must be dispensed only from official study sites by authorized personnel according to local regulations.

The product storage manager should ensure that the study intervention 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 intervention arise, the study intervention should not be dispensed, and BMS should be contacted immediately.

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

IMP/Non-IMP/AxMP documentation (whether supplied by BMS or not) must be maintained and must include all processes required to ensure the 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).

- The Investigator or designee must confirm appropriate temperature conditions have been maintained during transit for all study intervention received and any discrepancies are reported and resolved before use of the study intervention.
- The Investigator, institution, or head of the medical institution (where applicable) is responsible for study intervention accountability, reconciliation, and record maintenance (ie, receipt, reconciliation, and final disposition of records).
- Further guidance and information for the final disposition of unused study interventions are provided in Appendix 2.
- Further preparation/administration and handling instruction will be provided in the Pharmacy Manual.

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

7.6 Treatment Compliance

Not applicable.

7.7 Concomitant Therapy

7.7.1 Prohibited and/or Restricted Treatments

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

- Immunosuppressive agents.
- Immunosuppressive doses of systemic corticosteroids. 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.
- Any concurrent systemic anti-neoplastic therapy (ie, chemotherapy, hormonal therapy, immunotherapy, or standard or investigational agents for treatment of NSCLC, SCCHN, gastric cancer)
- 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]) during treatment and until 100 days post last dose.
- Administration of investigational SARS-CoV-2 vaccines is not allowed during the study.

7.7.2 Other Restrictions and Precautions

Strong cytochrome P450 3A4 (CYP3A4) inhibitors and inducers should be avoided during the treatment with docetaxel (Part C). Please refer to Appendix 8 for a list of common strong CYP3A4 inhibitors and inducers.

7.7.3 Permitted Therapy

Participants are permitted the use of the following treatments:

- In the absence of active autoimmune disease, ocular, intra-articular, intra-nasal, inhaled or topical steroids, and adrenal replacement steroid doses > 10 mg daily prednisone equivalent 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).
- Participants receiving chemotherapy may receive growth factors (including granulocyte colony-stimulating factor [G-CSF] and erythropoietin) after completion of the first cycle at the discretion of the Investigator and following local guidelines.
- Prior palliative radiotherapy must have been completed at least 2 weeks prior to treatment.
- Participants may receive authorized or approved SARS-CoV-2 vaccines while continuing on study treatment at the discretion of the Investigator.
- Treatment of active SARS-CoV-2 infections or high-risk exposures, including use of investigational therapies, is allowed and should be discussed with the MM.
- Participants may receive authorized or approved non-vaccine pre-exposure prophylaxis against SARS-CoV-2 infection, such as the combination tixagevimab co-packaged with cilgavimab. Washout periods for monoclonal antibodies and experimental agents do not apply to said prophylactic medications. If SARS-CoV-2 pre-exposure prophylaxis is being used, the site should consistently document its use in the Prior and Concomitant Medication CRF (especially the date of administration). It may be unclear how non-vaccine pre-exposure prophylactic agents against SARS-CoV-2 infection affects central lab assessment of SARS-CoV-2 serology. Certain agents in this class may have long elimination half-lives (and durations of effect), which may impact subsequent plans for vaccination against SARS-CoV-2.

7.7.4 Palliative Local Therapy

Palliative local therapy, including palliative radiation therapy and palliative surgical resection, to symptomatic non-target bone lesions, skin lesions, or CNS lesions is permitted prior to discontinuation of study intervention for participants who do not have evidence of overall clinical

or radiographic progression per RECIST v1.1. Palliative local therapy to lesions causing hemoptysis may also be permitted prior to discontinuation of study intervention in participants who do not have evidence of overall clinical or radiographic progression per RECIST v1.1, provided that the lesions undergoing palliative local therapy are not the only sites of measurable disease and the case is discussed with and approved by the Sponsor/Medical Monitor (or designee).

Participants requiring palliative local therapy should be evaluated for objective evidence of disease progression prior to the initiation of such therapy, particularly if the most recent tumor assessment was more than 4 weeks prior to the start of local therapy. If progression per RECIST v1.1 is identified on any tumor assessments prior to the initiation of palliative local therapy, then participants must either discontinue study intervention or they must meet criteria to continue treatment beyond progression (Section 8.1.1) in order to resume immunotherapy after palliative local therapy. The potential for overlapping toxicities with radiotherapy and immunotherapy currently is not known; however, anecdotal data suggest that it is tolerable. As concurrent radiotherapy and the immunotherapy regimens evaluated in this study have not been formally evaluated, whenever palliative radiotherapy is required for a tumor lesion, then immunotherapy should be withheld for at least 1 week before, during, and 1 week after radiation. Participants should be closely monitored for any potential toxicity during and after receiving radiotherapy and AEs should resolve to Grade ≤ 1 prior to resuming immunotherapy.

7.7.5 Surgery

Participants undergoing major surgery for any reason while on study should have BMS-986442, nivolumab, and/or chemotherapy held for at least 3 weeks after surgery, and these study treatments should not be resumed until wound healing has occurred and it is considered safe to do so in the assessment of the Investigator. Wound healing must be evaluated by the surgeon prior to resuming study treatment. Prior to resuming study treatment, surgically related AEs should resolve to Grade 1 or baseline, and participants must meet relevant eligibility criteria as determined by the BMS MM (or designee) in discussion with the Investigator.

7.7.5.1 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 magnetic resonance imaging (MRI), participants with severe renal insufficiency (ie, eGFR < 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 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.

7.8 Continued Access to Study Intervention After the End of the Study

At the end of the study, BMS will not continue to provide BMS-supplied study intervention to participants/Investigators unless BMS chooses to extend the study. The Investigator should ensure that the participant receives appropriate standard of care to treat the condition under study.

BMS reserves the right to terminate access to BMS-supplied study intervention if any of the following occur: a) the study is terminated due to safety concerns; b) the development of BMS-986442 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 other health program. In all cases, BMS will follow local regulations.

8 DISCONTINUATION CRITERIA

8.1 Discontinuation From Study Intervention

Participants MUST discontinue IP (and Non-IP/AxMP at the discretion of the Investigator) for any of the following reasons:

- Participant's request to stop study intervention. Participants who request to discontinue study intervention 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 the 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 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.)
- Pregnancy (refer to Section 9.2.5).
- Significant noncompliance with protocol (eg, procedures, assessments, medications, etc). The Investigator should discuss such issues with the MM.
- Investigators may consider the discontinuation of investigational treatment for participants, after discussion with the MM, for the following:
  - Radiographic progression of disease per RECIST 1.1 criteria; however, participants who meet criteria for treatment beyond progression may continue to receive study intervention.
  - Clinical deterioration attributed to disease progression, without radiographic progression per RECIST 1.1, that in the judgment of the Investigator makes it unsafe for the participant to continue with study intervention.

Nivolumab and BMS-986442 treatment must be permanently discontinued per criteria in Table 7.4.1-1 in Section 7.4.1. Discontinue nivolumab and BMS-986442 for 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.

Any event that leads to a delay in dosing lasting > 8 weeks from the previous dose requires discontinuation of study drug, with the following exceptions:

- Dosing delays to allow for prolonged steroid tapers to manage drug-related AEs are allowed.
- Dosing delays lasting > 8 weeks from the previous dose that occur for non-drug-related reasons may be allowed if approved by the MM (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.

All participants who discontinue study intervention 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 (eg, is imprisoned or involuntarily incarcerated for the treatment of either a psychiatric or physical illness).

If study intervention 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 per local regulatory requirements in each region/country and entered on the appropriate CRF page.

For all participants, global deterioration of health status requiring discontinuation of treatment without objective evidence of disease progression at that time should be reported as "symptomatic deterioration" in the source data and in the eCRF.

8.1.1 Nivolumab and BMS-986442 Treatment Beyond Disease Progression

Accumulating evidence indicates a minority of participants treated with immunotherapy may derive clinical benefit despite initial evidence of PD.[25]

Participants treated with BMS-986442 and nivolumab will be permitted to continue with their assigned treatment beyond initial RECIST 1.1-defined PD, 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 nivolumab treatment. All other elements of the main consent, including description of reasonably foreseeable risks or discomforts, or other alternative treatment options, will still apply.

Treatment beyond progression may be administered during or after localized interventions (surgery/radiation therapy).

Radiographic assessment/scan(s) should continue in accordance with the Section 2 Schedule of Activities for the duration of the treatment beyond progression and should be submitted to the central imaging vendor. Balance the assessment of clinical benefit with clinical judgment as to whether the participant is clinically deteriorating and unlikely to receive any benefit from continued treatment with nivolumab and BMS-986442.

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. Upon documentation of further progression, permanently discontinue study treatment unless the clinical judgement of the Investigator is that continuing treatment is in the patient's best interest.

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 be 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.

8.1.2 Post-study Intervention Study Follow-up

In this study, [redacted] 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 intervention 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.

If progression has not occurred before treatment discontinuation, tumor assessments should continue according to the Schedule of Activities.

Participants should undergo 100 days of safety follow-up post last dose of study intervention (follow-up Day 30, 60, and 100), even if the study is terminated. All participants who received study interventions will also be followed for survival data.

Participants who discontinue study intervention may continue to be followed.

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 contact or is lost to follow-up.

8.2 Discontinuation From the Study

Participants who request to discontinue study intervention 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.
- 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 intervention only or also from study procedures and/or post-treatment study follow-up, and entered on the appropriate CRF page.
- In the event that vital status (whether the participant is alive or dead) is being measured, publicly available information should be used to determine vital status only as appropriately directed in accordance with local law.
- If the participant withdraws consent for disclosure of future information, the Sponsor may retain and continue to use any data collected before such a withdrawal of consent.

8.2.1 Individual Discontinuation Criteria

- A participant may withdraw completely from the study at any time at his/her own request, or may be withdrawn at any time at the discretion of the Investigator for safety, behavioral, compliance, or administrative reasons. This is expected to be uncommon. Stopping study intervention is not considered withdrawal from the study.
- At the time of discontinuing from the study, if possible, an early termination visit should be conducted, as shown in the Schedule of Activities. See the Schedule of Activities for data to be collected at the time of study discontinuation and follow-up and for any further evaluations that need to be completed.
- The participant will be permanently discontinued both from the study intervention and from the study at that time.
- 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

The following actions must be taken if a participant fails to return to the clinic for a required study visit:

- 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 (3)** documented phone calls, faxes, or emails, as well as lack of response by participant to one (1) 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 the 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 the participant's contact information or other public vital status data necessary to complete the follow-up portion of the study.

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

9 STUDY ASSESSMENTS AND PROCEDURES

- Study procedures and timing are summarized in the Schedule of Activities (Section 2).
- Protocol waivers or exemptions are not allowed.
- All immediate safety concerns must be discussed with the Sponsor immediately upon occurrence or awareness to determine if the participant should continue or discontinue treatment.
- Adherence to the study design requirements, including those specified in the Schedule of Activities, is essential and required for study conduct.
- All screening evaluations must be completed and reviewed to confirm that potential participants meet all eligibility criteria before treatment assignment (Parts A, B2, C, D, and E) and randomization (Parts B1 and F). 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.

[redacted]

- Repeat or unscheduled samples may be taken for safety reasons or for technical issues with the samples.
- Perform additional measures, including non-study required laboratory tests, 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.
- Evaluate participant immediately to rule out cardiac or pulmonary toxicity if participant shows cardiac or pulmonary-related signs (hypoxia, abnormal heart rate, or changes from baseline) or symptoms (eg, dyspnea, cough, chest pain, fatigue, palpitations).
- 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

9.1.1 Imaging Assessment for the Study

[redacted] 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. Participants in Parts A, B2, C, D and E will be assessed locally by the investigator or designee using the RECIST 1.1 criteria (see Appendix 5).

Collect any additional imaging that may demonstrate tumor response or progression (including scans performed at unscheduled time points and/or at an outside institution) for RECIST 1.1 tumor assessment. 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 the central imaging vendor. Otherwise, they do not need to be submitted centrally.

9.1.1.1 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. For participants with SCCHN, CT or MRI of the neck is also required. 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. Changes in tumor measurements and tumor response to guide ongoing study treatment decisions will be assessed by the Investigator using RECIST 1.1 criteria (refer to Appendix 5).

If a participant has a contraindication for CT IV contrast, then a non-contrast CT of the chest and a contrast-enhanced MRI of the neck (required for SCCHN participants), 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 neck (required for SCCHN participants), 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 non-contrast CT of the neck (required for SCCHN participants), 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 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 1.1 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 1.1 measurements. Note, however, that the PET portion of the CT introduces additional data that may bias an Investigator if it is not routinely or serially performed.

Bone scan or PET scan are not adequate for assessment of RECIST 1.1 response in target lesions. In selected circumstances where such modalities are the sole modality used to assess certain non-target organs, those non-target organs may be evaluated less frequently. For example, bone scans may need to be repeated only when complete response (CR) 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 the brain (without and with contrast) should be acquired as outlined in Section 2 (Schedule of Activities). CT of the brain (without and with contrast) can be performed if MRI is contraindicated. MRI of the brain without and with contrast is required at screening for participants with NSCLC and/or those without NSCLC that have known or suspected brain metastases, unless participant has completed an imaging study of the brain within 28 days prior to the date of first dose of study treatment. Participants with NSCLC and/or a history of brain metastasis or symptoms without progressive disease at EOT should have a surveillance MRI (without and with contrast) per standard of care (approximately every 12 weeks), or sooner if clinically indicated.

9.1.1.2 Imaging and Clinical Assessment

Tumor assessments should continue on the protocol-defined imaging schedule, regardless if dosing is delayed or discontinued. Changes in tumor measurements and tumor responses will be assessed by the same Investigator or designee (ie, radiologist or sub-investigator), using RECIST 1.1 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 1.1 criteria (see Appendix 5 for specifics of RECIST 1.1 criteria to be used in this study). Assessments of partial response (PR) and complete response (CR) must be confirmed at least 4 weeks (28 days) after initial response. A best overall response of SD requires a minimum of 35 days on study from date of first dose to the date of the first imaging assessment.

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

Refer to Appendix 3 for SAE reporting.

Use CTCAE v5 definitions and grading for safety reporting of all AEs and SAEs on the CRF.

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 CRF.

9.2.1 Time Period and Frequency for Collecting AE and SAE Information

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 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 intervention or a protocol-specified procedure (eg, a follow-up skin biopsy).

- Medical occurrences that begin before the start of study intervention but after obtaining informed consent will be recorded on the appropriate section of the CRF module.
- All SAEs will be recorded and reported to the 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 intervention 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.

For participants randomized (Parts B1 and Part F) or assigned (Parts A, B2, C, D, and E) to treatment and never treated with study drug, collect SAEs for 30 days from the date of randomization or treatment assignment.

Collect all non-serious AEs (not only those deemed to be treatment-related) continuously during the treatment period and for a minimum of 100 days following discontinuation of study treatment.

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, 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.

9.2.2 Method of Detecting AEs and SAEs

AEs 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 AEs 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.

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

- Non-serious 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 non-serious AEs that cause interruption or discontinuation of study intervention and for those present at the end of study intervention, as appropriate.
- All identified non-serious AEs must be recorded and described on the non-serious 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 nonserious AEs of special interest (as defined in Section 9.2) will be followed until resolution, until the condition stabilizes, until the event is otherwise explained, or until the participant is lost to follow-up (as defined in Section 8.3). All SAEs, and AEs (SAEs and non-serious AEs) associated with confirmed or suspected SARS-CoV-2 infection will be followed 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.

All SAEs 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 toward 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 IB and will notify the IRB/IEC, if appropriate, according to local requirements.

The Sponsor or designee must report AEs to regulatory authorities and ethics committees according to local applicable laws and regulations. A SUSAR (suspected, unexpected serious adverse reaction) is a subset of SAEs and must 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 intervention, it is subsequently discovered that a participant is pregnant or may have been pregnant at the time of study exposure, including during at least 6 months after study treatment administration, the Investigator must immediately notify the BMS

MM/Designee of this event and complete and forward a Pregnancy Surveillance Form to the BMS designee within 24 hours of awareness of the event and in accordance with SAE reporting procedures described in Appendix 3.

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

Any pregnancy that occurs in a female partner of a male study participant during and at least for 3 months after study treatment administration, enrolled in Parts C, D, or E should be reported to the Sponsor or designee. In order for the Sponsor or designee to collect any pregnancy surveillance information from the female partner, the female partner must sign an ICF for disclosure of this information. Information on this pregnancy will be collected on the Pregnancy Surveillance Form. Any pregnancy that occurs in a female partner of a male study participant enrolled in Parts A, B1, or B2 is not required to be reported to the Sponsor or designee.

If any sexual activity involving penile intercourse (eg, vaginal, anal, oral) has occurred between a male participant enrolled in Parts C, D, or E and a pregnant partner(s) without the use of a condom during and at least for 3 months after study product administration, the information should be reported to the Sponsor or designee, even if the male participant has undergone a successful vasectomy. Reporting is not required for any sexual activity involving penile intercourse (eg, vaginal, anal, oral) that has occurred between a male participant enrolled in Parts A, B1, or B2 and a pregnant partner(s) without the use of a condom.

9.2.6 Laboratory Test Result Abnormalities

The following laboratory test result abnormalities should be captured on the non-serious AE CRF page or SAE eCRF, 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 intervention 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 vs low hemoglobin value).

9.2.7 Potential Drug-induced Liver Injury

Specific criteria for identifying a potential drug-induced liver injury (DILI) have not been identified for this protocol. Standard medical practice in identifying and monitoring hepatic issues should be followed.

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 DILI is defined as:

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

9.2.8 Other Safety Considerations

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

9.3 Overdose

An overdose is defined as the accidental or intentional administration of any dose of a product that is considered both excessive and medically important. Overdoses that meet the regulatory definition of SAE will be reported as an SAE (see Appendix 3).

In the event of an overdose, the treating physician should do the following:

- Contact the MM immediately.
- Closely monitor the participant for AEs/SAEs and laboratory abnormalities until at least 5 times the projected elimination half-life of BMS-986442 (5 × 9.01 days ~ 46 days), of nivolumab (5 × 25 days = 125 days), of docetaxel (5 × 11.1 hours ~ 2.5 days), of carboplatin (5 × 5.9 hours ~ 1.5 days), paclitaxel (5 × 27 hours ~ 6 days), and pemetrexed (5 × 3.5 hours ~ 18 hours).
- Obtain a plasma sample for PK analysis if requested by the MM (determined on a case-by-case basis).
- Document the quantity of the excess dose as well as the duration of the overdosing in the CRF.

There are a few reports of docetaxel overdose. There is no known antidote for docetaxel overdose. In case of overdose, the participant should be kept in a specialized unit and vital functions closely monitored. Exacerbation of AEs may be expected. The primary anticipated complications of overdose would consist of bone marrow suppression, peripheral neurotoxicity, and mucositis.

Participants should receive therapeutic G-CSF as soon as possible after discovery of overdose. Other appropriate symptomatic measures should be taken, as needed.

There is no known antidote for paclitaxel overdosage. The primary anticipated complications of overdosage would consist of bone marrow suppression, peripheral neurotoxicity, and mucositis.

There is no known antidote for carboplatin overdosage. The anticipated complications of overdosage would be secondary to bone marrow suppression and/or hepatic toxicity.

No drugs are approved for the treatment of pemetrexed overdose. Based on animal studies, administration of leucovorin may mitigate the toxicities of pemetrexed overdosage. It is not known whether pemetrexed is dialyzable.

Decisions regarding dose interruptions or modifications will be made by the Investigator in consultation with the MM 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.

9.4.1 Physical Examinations

Refer to Schedule of Activities.

9.4.2 Vital Signs

Refer to Schedule of Activities.

9.4.3 Electrocardiograms

Refer to the Schedule of Activities for timing of assessments in Table 2-1 and Table 2-2.

To monitor participant safety throughout the study, the Investigators will review the 12-lead ECGs collected using their site's standard ECG machines. In both scenarios, Fridericia's Correction Formula (QTcF) will be the QT interval correction method applied to each ECG reading.

9.4.4 Clinical Safety Laboratory Assessments

- Investigators must document their review of each laboratory safety report.
- A local laboratory will perform the analyses and will provide reference ranges for these tests.
- 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
Prothrombin time, activated partial thromboplastin time, and international normalized ratio - screening only

Table 9.4.4-1: Clinical Laboratory Assessments

Chemistry	
Aspartate aminotransferase (AST) Alanine aminotransferase (ALT) Total bilirubin Direct bilirubin (reflex if total bilirubin is abnormal) Gamma-glutamyl transferase (reflex if liver function is abnormal) Alkaline phosphatase (ALP) Lactate dehydrogenase (LDH) Creatinine Blood urea nitrogen (BUN) or serum/plasma urea Uric acid Glucose (fasting glucose at screening) Amylase Lipase Troponin C-reactive protein	Total protein Albumin - screening only Sodium Potassium Chloride Calcium Phosphorus Magnesium Creatine kinase/Creatine phosphokinase Creatinine clearance - screening only TSH, free T3 and free T4 - screening (total T3 may be allowed if collection of fT3 is not feasible. TSH, with reflexive fT3 and fT4 if TSH is abnormal - on treatment (total T3 may be allowed if collection of fT3 is not feasible) Cytokine panel: if the participant has an IRR, draw additional blood and preform analysis locally
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, (HBV sAG, HCV antibody or HCV RNA) - screening only	
HIV-1 and -2 antibody (HIV RNA if HIV-positive) - screening only, and as mandated by local requirement	
Other Analyses	
Pregnancy test (WOCBP only: minimum sensitivity 25 IU/L or equivalent units of hCG).	
FSH screening - only required to confirm menopause in women < age 55	

Abbreviations: ALP, alkaline phosphatase; ALT, alanine aminotransferase; AST, aspartate aminotransferase; BUN, blood urea nitrogen; FSH, follicle-stimulating hormone; fT3, free triiodothyronine; fT4, free thyroxine; HBV, hepatitis B virus; hCG, human chorionic gonadotropin; HCV, hepatitis C virus; HIV, human immunodeficiency virus; IRR, infusion-related reaction; IU, international units; LDH, lactate dehydrogenase; RNA, ribonucleic acid; sAG, surface antigen; T3, triiodothyronine; T4, thyroxine; TSH, thyroid-stimulating hormone; WOCBP, women of childbearing potential.

9.4.5 Imaging Safety Assessment

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

9.5 Pharmacokinetics

The PK of BMS-986442 will be derived from serum concentration versus time data when appropriate. The PK parameters to be assessed following intensive PK collections include the following:

Cmax	Maximum observed serum concentration
Tmax	Time of maximum observed serum concentration
AUC(0-T)	Area under the serum concentration-time curve from time zero to time of last quantifiable concentration
AUC(TAU)	Area under the serum concentration-time curve in 1 dosing interval
Parameters that may potentially be assessed following dose administration in Cycle 4	
Ctau	Serum concentration observed at the end of a dosing interval
CLT	Total body clearance
Css-avg	Average concentration over a dosing interval (AUC[TAU]/tau)
AI_AUC	AUC Accumulation Index; ratio of AUC(TAU) at steady-state to AUC(TAU) after the first dose
T-HALFeff	Effective elimination half-life that explains the degree of accumulation observed for a specific exposure measure (exposure measure includes AUC[TAU])
Parameter to be reported separately	
[redacted]	

Individual participant PK parameter values will be derived by noncompartmental methods using a validated PK analysis program. Actual times will be used for the analyses.

Table 9.5-1 lists the sampling schedule to be followed for the assessment of PK and IMG. Further details of blood collection and processing will be provided to the site in the Laboratory Manual.

All predose samples should preferably be taken within 30 minutes before the start of any dose infusion. Predose serum nivolumab concentrations will be collected for the assessment of [redacted] when administered in combination with BMS-986442.

End-of-infusion (EOI) PK samples for BMS-986442 and nivolumab should be taken immediately following the last drug infusion (preferably within 5 minutes after the end of the infusion) on the contralateral arm (ie, the arm not used for the infusion). Because the EOI PK sample is drawn with the intent of accurately estimating the Cmax of the drug, draw the EOI PK sample after all the study drug has been infused. If the site infuses the drug without a flush, then collect the EOI PK sample within approximately 5 minutes after the end of the infusion. If a flush is administered to clear the IV lines of the drug and to ensure delivery of the entire drug dose, then draw the EOI sample within approximately 5 minutes after end of the flush. Do not draw EOI samples from the same IV access that the drug was administered. On-treatment PK samples are intended to be drawn relative to actual dosing days. For Parts A to F, EOI PK samples should be taken following the instructions noted in Table 9.5-1.

If a dose occurs on a different day within the cycle due to delays or minor schedule adjustments, PK and ADA samples should be adjusted accordingly. If it is known that a dose is going to be delayed, then the predose sample should be collected just prior to the delayed dose. However, if a

predose sample is collected but the dose is subsequently delayed, an additional predose sample should not be collected. Further details of sample collection, processing, and shipment will be provided in the Laboratory Manual.

Table 9.5-1: Pharmacokinetic and Immunogenicity Sampling Schedule for Parts A-E (All participants)

Study Day of Sample Collection (1 Cycle = 3 weeks)	Event	Time (Relative to Start of Infusion) (hr:min)	BMS-986442 PK Serum Sample	[redacted]	BMS-986442 ADA Serum Sample	[redacted]
Cycle 1 Day 1	Predose[a]	0:00	X		X	
	EOI[b]	See note[b]	X			
		4:00	X			
Cycle 1 Day 2		24:00	X			
Cycle 1 Day 5		96:00[c]	X			
Cycle 1 Day 8		168:00[d]	X			
Cycle 1 Day 15		336:00	X			
Cycle 2 Day 1	Predose[a]	0:00	X		X	
	EOI[b]	See note[b]	X			
Cycle 3 Day 1	Predose[a]	0:00	X		X	
	EOI[b]	See note[b]	X			
Cycle 4 Day 1	Predose[a]	0:00	X		X	
	EOI[b]	See note[b]	X			
		4:00	X			
		24:00	X			
		96:00[c]	X			
		168:00[d]	X			
		336:00	X			
Cycle 5 Day 1	Predose[a]	0:00	X		X	
Cycle 9 Day 1 and every 5 cycles thereafter until EOT	Predose[a]	0:00	X		X	
EOT			X		X	
Follow-up Period						

Table 9.5-1: Pharmacokinetic and Immunogenicity Sampling Schedule for Parts A-E (All participants)

Study Day of Sample Collection (1 Cycle = 3 weeks)	Event	Time (Relative to Start of Infusion) (hr:min)	BMS-986442 PK Serum Sample	[redacted]	BMS-986442 ADA Serum Sample	[redacted]
Follow-up 30 Day			X		X	
Follow-up 100 Day			X		X	

Abbreviations: ADA, anti-drug antibody; Cmax, maximum observed concentration; EOI, end of infusion; EOT, end of treatment; PK, pharmacokinetics.

[a] Predose: All predose samples should be taken within 30 minutes before the start of the study drug infusion.

[b] Since the end of infusion PK (EOI) sample is drawn with the intent of accurately estimating the maximum concentration (Cmax) of the drug, draw the EOI when all the study drug has been infused. If the site infuses drug without a flush, then collect the EOI sample within approximately 5 minutes after end of infusion. If a flush is administered to clear the IV lines of the drug and to ensure delivery of the entire drug dose, then draw the EOI sample within approximately 5 minutes after end of the flush. Do not draw EOI samples from the same IV access that the drug was administered.

[c] The 96:00 hour sample may be taken between 72:00 and 120:00 hours post dose.

[d] The 168:00 hour sample may be taken between 144:00 and 192:00 hours post dose.

Treatment assignments will be released to the bioanalytical laboratory in order to minimize unnecessary analysis and/or reanalysis of PK/ADA samples.

Serum concentration analyses for BMS-986442 and nivolumab will be performed by validated bioanalytical method(s).

Bioanalytical samples designated for assessments (eg, IMG, PK, [redacted]) 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 IMG-related AE, etc).

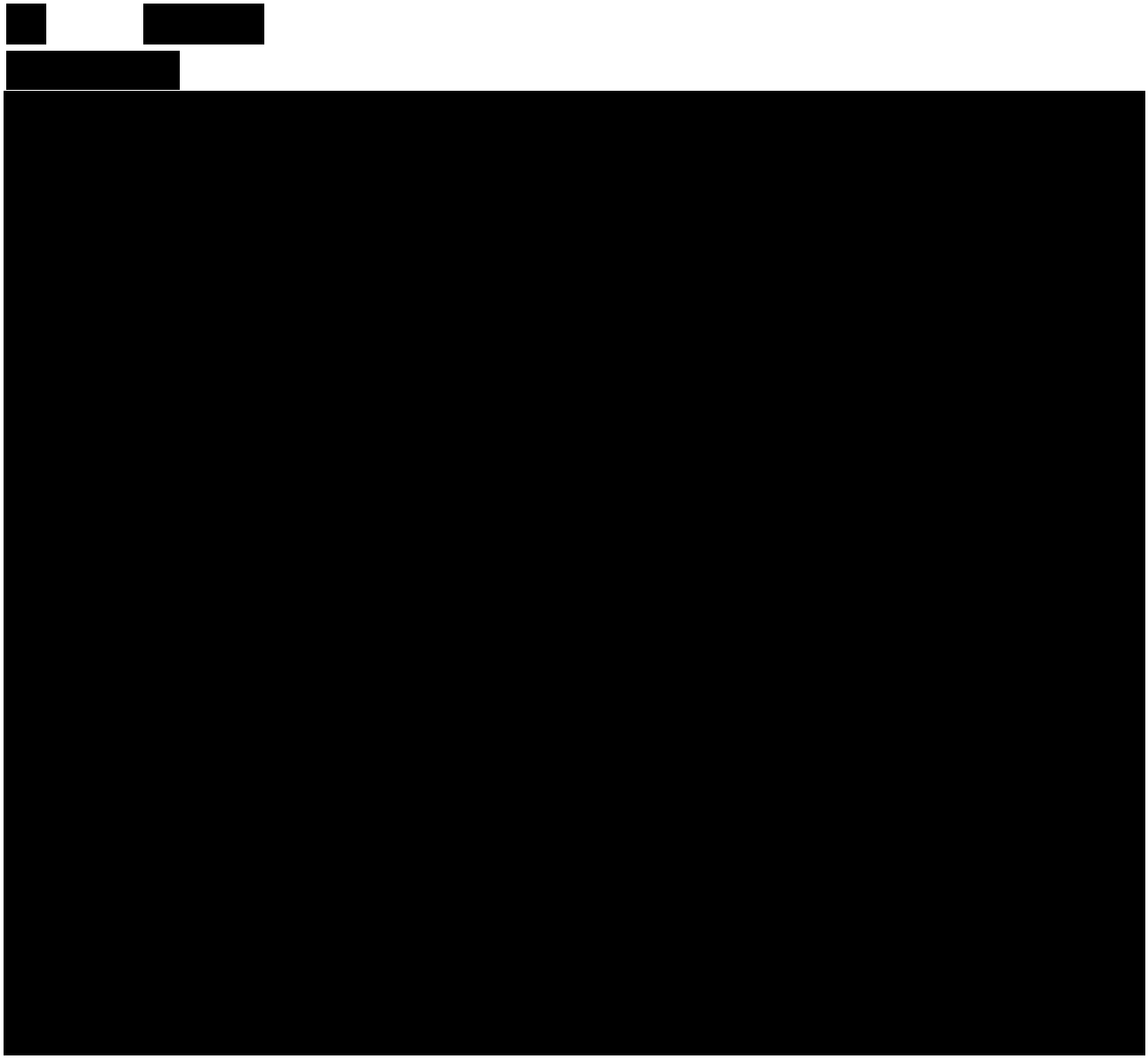
Additionally, residual bioanalytical samples will be archived and may be used for potential [redacted] bioanalysis (including, but not limited to, analysis of drug-ADA immune complexes, metabolite analyses, etc) and/or for additional method purposes (including, but not limited to, cross-validation, ADA/PK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

9.6 Immunogenicity Assessments

Antibodies to BMS-986442 and nivolumab will be evaluated in serum samples collected from all participants according to the collection schedule in Table 9.5-1. Additionally, serum samples should also be collected at the final visit from participants who discontinued study intervention or were withdrawn from the study. These samples will be tested by the Sponsor/designee.

Serum samples will be screened for antibodies binding to BMS-986442 and nivolumab, and the titer of confirmed positive samples will be reported. Other analyses may be performed to further characterize the IMG of BMS-986442 and nivolumab.

The detection and characterization of antibodies to BMS-986442 and nivolumab will be performed using validated method(s) by or under the supervision of the Sponsor. All samples collected for detection of antibodies to study intervention will also be evaluated for serum concentration to enable interpretation of the antibody data. Antibodies may be further characterized and/or evaluated for their ability to neutralize the activity of the study intervention(s). Samples may be stored for a maximum of 15 years (or according to local regulations) following the last participant's last visit for the study at a facility selected by the Sponsor to enable further analysis of immune responses to BMS-986442 and nivolumab.



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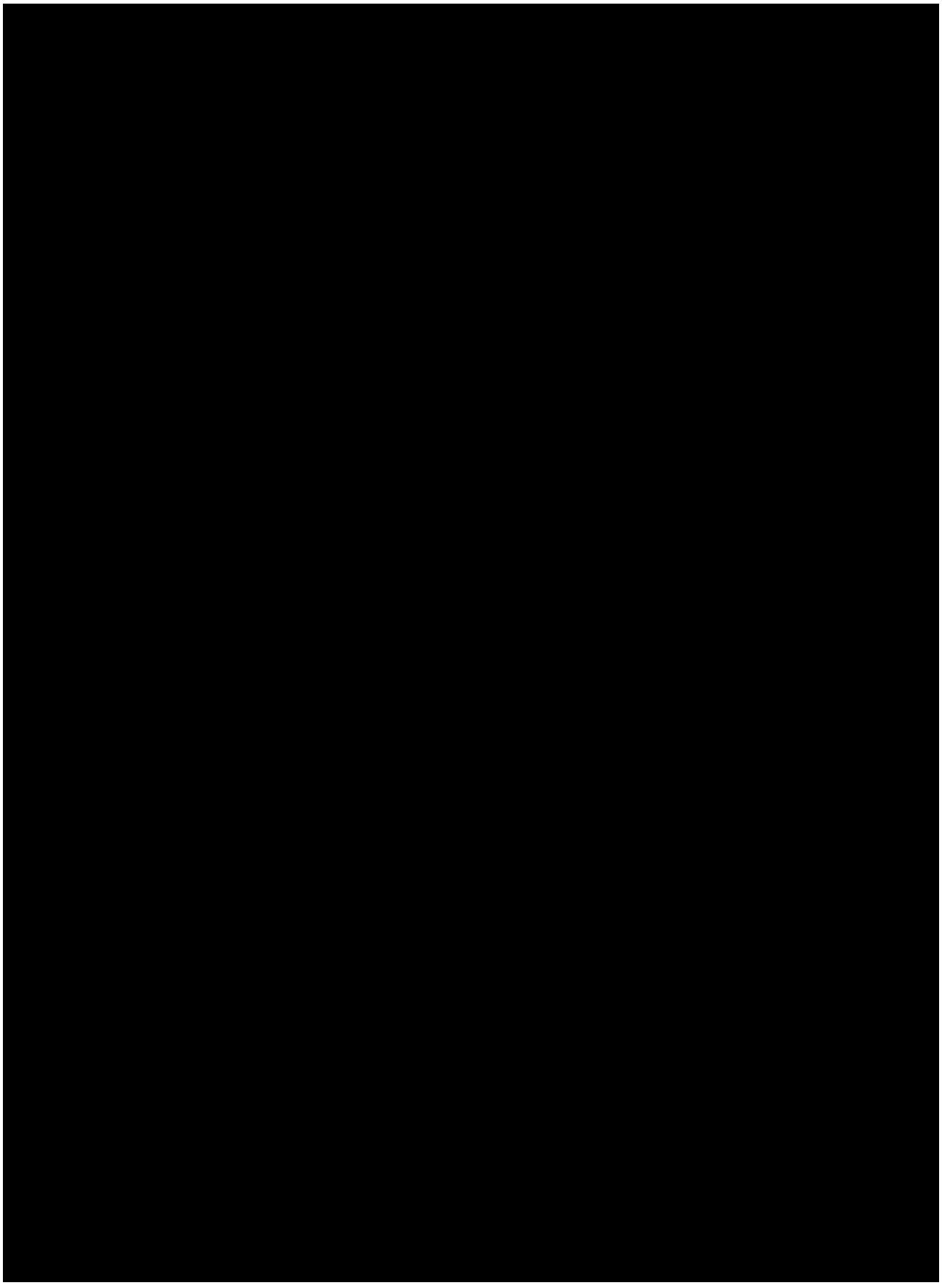

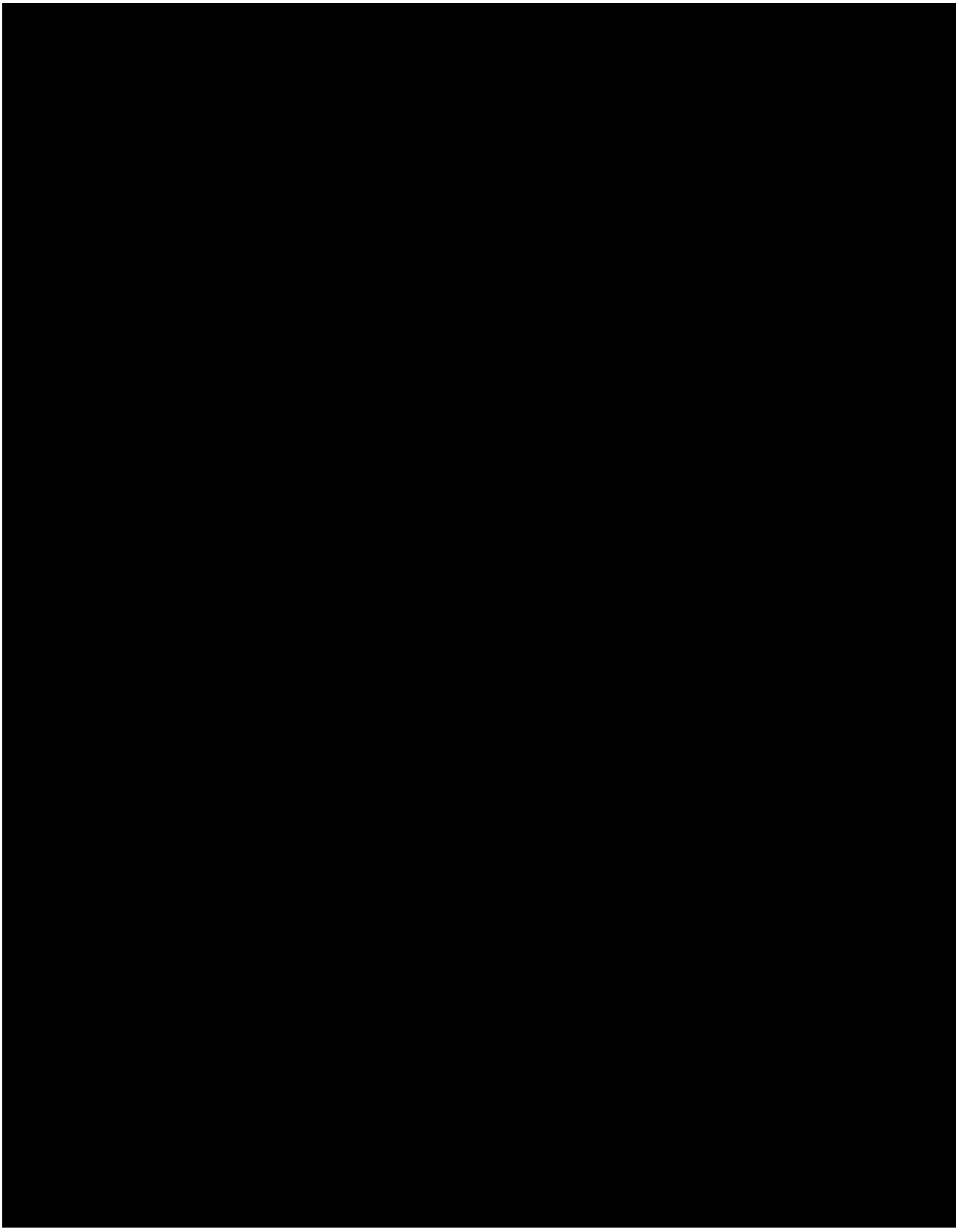

[redacted]

9.9 Additional Research

This protocol will include residual sample storage for additional research.

For All sites:

Additional research is required for all study participants, except where prohibited by IRBs/ethics committees, local laws or regulations, or academic/institutional requirements. Where 1 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.

Additional research is intended to expand the 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. This may also include genetic/genomic exploration aimed at exploring disease pathways, progression, and response to treatment etc.

Sample Collection and Storage

Residual samples (see Table 9.9-1) will also be retained for additional research purposes.

Samples kept for future research will be stored at the BMS Biorepository in [redacted] or an independent, BMS-approved storage vendor.

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 the 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 laboratory procedure manual.

Table 9.9-1: Residual Sample Retention for Additional Research Schedule

Sample Type	Time points for Which Residual Samples Will be Retained
Serum/Plasma	All
PBMC	All
Tumor Biopsy	All

Abbreviation: PBMC, peripheral blood mononuclear cell.

9.10 Other Assessments

Whole blood, serum and plasma samples will be collected at the times indicated in [redacted] for the measurement of DNA, RNA, [redacted].

9.11 Health Economics OR Medical Resource Utilization and Health Economics

Not applicable.

10 STATISTICAL CONSIDERATIONS

10.1 Statistical Hypotheses

There is no formal primary research hypothesis for this study to be statistically tested.

10.2 Sample Size Determination

Sample Size Justification for Dose Escalation (Parts A and C to E)

It is expected that at least 3 DLT-evaluable participants will be treated in Part A of the study in each dose level. Though the exact number will depend on the number of participants with a DLT, up to approximately 9 DLT-evaluable participants may be treated to enable DLT review. Assuming a DLT target of 30% (24%, 36%), the BOIN design framework will be used to guide decisions in this setting, including potential de-escalation to a lower dose of BMS-986442 in combination with nivolumab.

Similarly, in Parts C, D, and E, approximately 6 to 12 DLT-evaluable participants will be treated at each dose level to enable DLT review and dose escalation decisions guided by the BOIN method. Additional participants (for a maximum of 15 per dose level) may be treated at any dose level at or below the estimated MTD for further evaluation of safety, PK, IMG, and PD parameters, as required.

Sample Size Justification for Indication-specific Cohorts (Part B)

Parts B1 and B2 will be indication-specific cohorts of BMS-986442 in combination with nivolumab. Part B1 will involve randomized dose expansions to compare 2 tolerable dose levels in participants with 2L+ post-IO/platinum doublet NSCLC, and Part B2 will involve evaluation of 1 selected dose level in 2 additional tumor types: gastric cancer/GEJ and SCCHN.

The sample sizes for Parts B1 and B2 are based on assessing an initial anti-tumor activity signal as estimated by the ORR following treatment of BMS-986442 in combination with nivolumab and to provide additional information for the safety profile in the NSCLC and gastric cancer/GEJ and SCCHN populations, respectively.

Approximately 50 participants will be treated with BMS-986442 in combination with nivolumab in Part B1 and an additional 40 participants may be treated with the same treatment in Part B2.

In addition to the above, Table 10.2-1 summarizes the 80% exact CI for various ORRs for combination therapy with sample sizes of 20, 25, and 30. For example, 4 responders will need to be observed in 25 evaluable participants (an observed ORR = 16%) for the lower bound of the 80% CI to exclude a 5% ORR. Similarly, 6 responders will need to be observed in 20 evaluable participants (an observed ORR = 30%) for the lower bound of the 80% CI to exclude a 15% ORR.

Table 10.2-1: Potential ORR and Exact 80% CI

Sample Size	Number of Responders	ORR	80% Exact CI
20	2	0.10	[0.027, 0.245]
	3	0.15	[0.056, 0.304]
	5	0.25	[0.127, 0.415]
	6	0.30	[0.166, 0.467]
25	3	0.12	[0.045, 0.248]
	4	0.16	[0.072, 0.295]
	6	0.24	[0.131, 0.383]
	8	0.32	[0.196, 0.467]
30	3	0.10	[0.037, 0.209]
	5	0.17	[0.083, 0.287]
	7	0.23	[0.135, 0.361]
	10	0.33	[0.218, 0.466]

Abbreviations: CI, confidence interval; ORR, overall response rate.

10.3 Analysis Sets

For the purposes of analysis, the following populations are defined:

Population	Description
Enrolled	All participants who signed informed consent (and are registered into the IRT, if applicable)
Treated	All participants who received at least 1 dose of study intervention
Randomized (Part B1 only)	All participants who were randomized using IRT
Response- Evaluable	All participants who received at least 1 dose of study intervention, had a baseline tumor assessment with measurable disease, and 1 of the following: 1) at least 1 evaluable on-treatment tumor assessment, 2) clinical progression, or 3) death prior to the first on-treatment tumor evaluation
PK	All treated participants who have evaluable concentration-time data
PK Evaluable	All participants who have adequate PK profiles or have at least 1 evaluable PK parameter.
IMG	All participants who received BMS-986442 or nivolumab who have baseline and at least 1 post-baseline measurement
[redacted]	

Abbreviations: IMG, immunogenicity; IRT, Interactive Response Technology; PK, pharmacokinetics.

10.4 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 the clinical study report, including subgroups of age, gender, race, and other study-specific populations and demographic characteristics.

10.4.1 General Considerations

In Parts A, C, D, and E of the study, at least 3 participants will be enrolled per dose level and dose escalation decisions will be guided by BOIN design to identify the MTD. The BOIN design takes a very simple form, rendering it easy to implement in practice. The dose escalation and de-escalation in the BOIN design is determined by comparing the observed DLT rate at the current dose with a pair of fixed dose escalation and de-escalation boundaries, which allows generation of a decision table that guides dose selection depending on the number of participants treated and observed DLTs. A BOIN dose-escalation decision table with a selected target DLT rate of 30%, an escalation boundary of 24%, and de-escalation boundary of 36% will be used in this study.

Dose escalation may be stopped prior to reaching an MTD based on review of available safety, PK, and PD data, and on discussions between the sponsor and Investigators. While the BOIN will use DLT and safety information only, clinical assessment will take into consideration the totality of available data including PK/PD from all treated participants, in assigning the next dose level. The final recommended MTD/MAD/RP2D will be based on the recommendation from the BOIN and overall clinical assessment of all available safety, PK, PD, and efficacy data.

10.4.2 Primary Endpoint

Table 10.4.2-1: Primary Endpoint

Primary Endpoint	Statistical Analysis Methods
Incidence of AEs, SAEs, AEs meeting protocol-defined DLT criteria, AEs leading to discontinuation, and death.	DLT rate by dose level, frequency distribution of treated participants with AEs using the worst CTCAE grade. Participants will only be counted (1) once at the preferred term level, (2) once at the system organ class level, and (3) once in the "total participant" row at their worst CTCAE grade, regardless of system organ class or preferred term.

Abbreviations: AE, adverse event; CTCAE, Common Terminology Criteria for Adverse Events; DLT, dose-limiting toxicity; SAE, serious adverse event.

10.4.3 Secondary Endpoints

Table 10.4.3-1: Secondary Endpoints

Secondary Endpoint	Statistical Analysis Methods
Summary measures of BMS-986442 PK parameters, such as but not limited to, Cmax, Tmax, AUC(0-T) from serum concentration-time data during BMS-986442 when administered in combination with nivolumab or in combination with nivolumab and chemotherapy.	Summary statistics tabulations by dose: geometric means and CVs (medians and ranges for Tmax). Scatter plots vs dose for each cycle measured; dose proportionality based on a power model and a CI around the power coefficient.
Incidence of ADAs to BMS-986442 when BMS-986442 is administered in combination with nivolumab or in combination with nivolumab and chemotherapy.	Frequency distribution of baseline ADA-positive participants and ADA-positive participants after initiation of the treatment for each of BMS-986442 and nivolumab.
ORR, DOR, DCR, PFSR at 6 and 12 months.	The ORR and its corresponding 95% exact CI will be calculated by Clopper-Pearson method. Median DOR and its corresponding 95% CI will be estimated using KM product-limit method. The DCR and its corresponding 95% exact CI will be calculated by Clopper-Pearson method. The PFSR at 6 and 12 months will be estimated by the KM method and corresponding 95% CI will be derived based on the Greenwood formula by treatment for each tumor type.

Abbreviations: ADA, anti-drug antibody; AUC(0-T), area under the serum concentration-time curve from time zero to the time of the last quantifiable concentration; CI, confidence interval; Cmax, maximum observed concentration; DCR, disease control rate; DOR, duration of response; KM, Kaplan-Meier; ORR, overall response rate; PFSR, progression-free survival rate; PK, pharmacokinetic; Tmax, time of maximum observed concentration.

[redacted]

10.4.5 Other Safety Analysis

10.4.5.1 Continuous Safety Monitoring

A Bayesian continuous monitoring framework will be utilized for continuous monitoring of toxicity in the study to detect safety signals that may lead to changes in study conduct.[26]

For this type of monitoring, the proportion of DLTs is used to provide formal monitoring boundaries. These boundaries were established using a non-informative prior, Beta (0.5, 0.5). The posterior distribution is Beta (0.5+n, 0.5+(m-n)), where n is the number of participants observed with DLT, and m is the total number of treated participants.

The monitoring function for toxicity is defined as the posterior probability of (DLT rate > 33% | cumulative data) > 0.85. This criterion implies that there is a greater than 85% posterior probability

that the aggregate DLT rate across arms is larger than 33%. It will be applied after at least 3 participants per arm in the study are treated and can be performed on a continuous basis afterwards. The resulting boundaries are presented in Table 10.4.5.1-1.

If any time during the study, this DLT rate reaches the pre-specified threshold for toxicity in any treatment arm, then, taking into account all available safety information, the dose level may be re-evaluated and, based on the totality of data, an additional lower dose level may be administered to the remaining participants. Therefore, this criterion implies that the study may terminate enrollment toward an arm when there is greater than 85% probability that the DLT rate is over 33%.

Table 10.4.5.1-1: Safety Continuous Monitoring Boundary

Number of Safety-evaluable Participants (per Arm)[a]	Aggregate Toxicity Boundary (# Evaluable Participants with Event) for > 85% Probability of DLT > 33%
3	2
4-5	3
6-7	4
8-10	5
11-12	6
13-15	7
16-17	8
18-20	9
21-23	10
24-25	11

Abbreviation: DLT, dose-limiting toxicity.

[a] Additional thresholds for the monitoring of > 25 participants per arm if needed will be calculated by the statistician.

10.4.6 Other Analyses

Other analyses may include analyses of assessments, which are not defined as endpoints, that need to be prespecified and not necessarily be reported in the clinical study report, such as, but not limited to, [redacted] PPK, health care utilization endpoints, and health technology assessment-related endpoints.

[redacted] will be described in the SAP finalized before database lock. PPK analysis and E-R analyses, if conducted, would be reported in a separate pharmacometrics report. Pharmacodynamic analyses will be presented separately from the main clinical study report.

10.5 Interim Analyses

Interim analyses may be performed for administrative purposes or publications. No formal inferences requiring any adjustment to statistical significance level will be performed.

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12 APPENDICES

APPENDIX 1 ABBREVIATIONS AND TRADEMARKS

Term	Definition
ADA	anti-drug antibody
AE	adverse event
AIDS	acquired immune deficiency syndrome
ALK	anaplastic lymphoma kinase
ALP	alkaline phosphatase
ALT	alanine aminotransferase
APC	antigen-presenting cell
AST	aspartate aminotransferase
AUC	area under the serum concentration-time curve
AUC(0-T)	area under the serum concentration-time curve from time zero to the time of the last quantifiable concentration
AUC(TAU)	area under the concentration-time curve in 1 dosing interval
AxMP	auxiliary medicinal product
[redacted]	
BMI	body mass index
BMS	Bristol-Myers Squibb
BOIN	Bayesian optimal interval
BP	blood pressure
BRAF	proto-oncogene B-Raf
BUN	blood urea nitrogen
Cavg	average serum concentration
Cavg28	average serum concentration at Day 28
Cavgss	average serum concentration at steady state
CD	cluster of differentiation
cHL	classical Hodgkin lymphoma
CI	confidence interval
CL	clearance
CLss	steady-state clearance
CLT	total body clearance
Cmax	maximum observed concentration
Cmin	minimum observed concentration
CME	cystoid macular edema

Term	Definition
CNS	central nervous system
CONSORT	Consolidated Standards of Reporting Trials
COVID-19	coronavirus disease 2019
CR	complete response
CRC	colorectal carcinoma
CrCl	creatinine clearance
CRF	case report form, paper or electronic
CRO	contract research organization
CSR	clinical study report
Css-avg	average concentration over a dosing interval
CT	computed tomography
CTAg	clinical trial agreement
Ctau	serum concentration observed at the end of a dosing interval
CTCAE	Common Terminology Criteria for Adverse Events
[redacted]	
CTLA-4	cytotoxic T-lymphocyte-associated antigen 4
[redacted]	
CV	coefficient of variation
CYP3A4	cytochrome P450 3A4
DCR	disease control rate
DILI	drug-induced liver injury
dL	deciliter
DLT	dose-limiting toxicity
DMC	Data Monitoring Committee
DNA	deoxyribonucleic acid
DOR	duration of response
DRESS	drug reaction with eosinophilia and systemic symptoms
ECG	electrocardiogram
eCRF	electronic Case Report Form
ECOG PS	Eastern Cooperative Oncology Group Performance Status
EDC	electronic data capture
eGFR	estimated glomerular filtration rate
EGFR	epidermal growth factor receptor

Term	Definition
EOI	end-of-infusion
EOT	end of treatment
E-R	exposure-response
EU	European Union
Fc	fragment crystallizable
FcγR	Fcγ receptor
[redacted]	
FSH	follicle-stimulating hormone
fT4	free thyroxine
GBS	Guillain-Barre syndrome
G-CSF	granulocyte colony stimulating factor
GEJ	gastroesophageal junction
h	hour
HBsAg	hepatitis B surface antigen
HBV	hepatitis B virus
HCC	hepatocellular carcinoma
hCG	human chorionic gonadotropin
HCV	hepatitis C virus
HER2	human epidermal growth factor receptor 2
HIV	human immunodeficiency virus
HPV	human papillomavirus
HR	hazard ratio
HRT	hormone replacement therapy
IB	Investigator's Brochure
ICF	informed consent form
ICMJE	International Committee of Medical Journal Editors
IEC	Independent Ethics Committee
IFN-γ	interferon-γ
IgG1	immunoglobulin gamma 1
IHC	immunohistochemistry
IL	interleukin
IMAE	immune-mediated adverse event
IMG	immunogenicity

Term	Definition
IMP	Investigational Medicinal Product
INR	international normalized ratio
IO	immuno-oncology
IP	Investigational Product
IRB	Institutional Review Board
[redacted]	
IRR	infusion-related reactions
IRT	Interactive Response Technology
ITIM	immunoreceptor tyrosine-based inhibitory motif
IU	international unit
IV	intravenous
KRAS	Kirsten rat sarcoma
LAM	lactational amenorrhea method
LDH	lactate dehydrogenase
MAD	maximum administered dose
MG	Myasthenia Gravis
min	minute
mL	milliliter
MM	Medical Monitor
MMR	measles, mumps, rubella
MRI	magnetic resonance imaging
MTD	maximum tolerated dose
µg	microgram
N	number of participants or observations
N/A	not applicable
NK	natural killer
Non-IMP	non-investigational medicinal product
NRAS	N-ras oncogene
NSAID	non-steroidal anti-inflammatory drug
NSCLC	non-small cell lung cancer
NTRK	neurotrophic tropomyosin-receptor kinase
ORR	overall response rate
OS	overall survival

Term	Definition
PBMC	peripheral blood mononuclear cell
PCR	polymerase chain reaction
PD	pharmacodynamic
PD-1	programmed cell death protein 1
PD-L1	programmed cell death ligand 1
PDCT	platinum-doublet chemotherapy
PE	physical examination
PFS	progression-free survival
PFSR	progression-free survival rate
PID	patient identification number
PK	pharmacokinetic
PPK	population pharmacokinetics
PR	partial response
[redacted]	
QTcF	QT interval corrected for heart rate using Fridericia's formula
Q2W	every 2 weeks
Q3W	every 3 weeks
Q4W	every 4 weeks
Q6W	every 6 weeks
RCC	renal cell carcinoma
RECIST	Response Evaluation Criteria in Solid Tumors
RET	rearranged during transfection
RNA	ribonucleic acid
[redacted]	
ROS1	ROS proto-oncogene 1
RP2D	recommended Phase 2 dose(s)
RT-PCR	reverse transcriptase polymerase chain reaction
SAE	serious adverse event
SAP	Statistical Analysis Plan
SARS-CoV-2	severe acute respiratory syndrome coronavirus disease 2
SCCHN	squamous cell carcinoma of the head and neck
SCLC	small-cell lung cancer
SD	stable disease

Term	Definition
SEA	staphylococcal enterotoxin A
SI	international system of units
SJS	Stevens-Johnson syndrome
SmPC	Summary of Product Characteristics
SMT	Safety Management Team
[redacted]	
SOC	standard of care
SPR	surface plasmon resonance
SUSAR	suspected, unexpected serious adverse reaction
T. bili	total bilirubin
TBD	to be determined
TCGA	The Cancer Genome Atlas
[redacted]	
TEN	toxic epidermal necrolysis
TGF	transforming growth factor
T-HALFeff	effective elimination half-life that explains the degree of accumulation observed for a specific exposure measure
TIGIT	T-cell immunoreceptor with Ig and ITIM domains
Tmax	time of maximum observed concentration
TME	tumor microenvironment
TNF-α	tumor necrosis factor α
TRAE	treatment-related adverse event
Treg	regulatory T cell
TSH	thyroid-stimulating hormone
ULN	upper limit of normal
USPI	United States Prescribing Information
v	version
Vss	geometric mean volume of distribution at steady state
WNOCBP	women not of childbearing potential
WOCBP	women of childbearing potential
WWPS	Worldwide Patient Safety

APPENDIX 2 STUDY GOVERNANCE CONSIDERATIONS

The terms "participant" and "subject" refer to a person who has consented to participate in the clinical research study. Typically, the term "participant" is used in the protocol and the term "subject" is used in the Case Report Form (CRF).

REGULATORY AND ETHICAL CONSIDERATIONS

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
- Applicable International Council for Harmonisation (ICH) Good Clinical Practice (GCP) Guidelines
- Applicable laws, regulations, and requirements

The study will be conducted in compliance with the protocol. The protocol, any revisions/amendments, and the participant informed consent form (ICF) will receive approval/favorable opinion by the Institutional Review Board/Independent Ethics Committee (IRB/IEC), and regulatory authorities according to applicable 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) that is likely to affect, to a significant degree, 1 or more of the following: (1) the rights, physical safety, or mental integrity of 1 or more participants; (2) the scientific value of the clinical 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, Investigator's Brochure, product labeling information, ICF, participant recruitment materials (eg, advertisements), and any other written information to be provided to participants.

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

The investigator is responsible for providing oversight of the conduct of the study at the site and adherence to requirements of the following where applicable:

ICH guidelines
United States (US) Code of Federal Regulations, Title 21, Part 50 (21CFR50)
European Union (EU) Directive 2001/20/EC
European Regulation 536/2014 for clinical studies (if applicable)
European Medical Device Regulation 2017/745 for clinical device research (if applicable)
the IRB/IEC
all other applicable local regulations

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, by the local Health Authority), except where necessary to eliminate an immediate hazard(s) to study 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 the following:

- IRB/IEC
- Regulatory authority(ies), if applicable according to 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, by the local Health Authority, must be sent to Bristol-Myers Squibb Company (BMS).

If an amendment substantially alters the study design or increases the potential risk to the participant: (1) the ICF 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 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 participants prior to enrollment.

FINANCIAL DISCLOSURE

Investigators and sub-investigators will provide the Sponsor with sufficient, accurate financial information, in accordance with 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 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 the 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 IRB/IEC written approval/favorable opinion of the written ICF and any other information to be provided to the participant 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 proficient prior to clinical study participation. The language must be nontechnical and easily understood.
- Explain the nature of the study to the participant and answer all questions regarding the study.
- Inform the participant that his/her participation is voluntary. The participant will be required to sign a statement of informed consent that meets the requirements of 21 CFR Part 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 the participant to inquire about the details of the study.

Obtain an ICF signed and personally dated by participant and by the person who conducted the informed consent discussion.

- Include a statement in the participant's medical record that written informed consent was obtained before the 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 the participant to the most current version of the ICF(s) during his/her participation.

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 participant's signed ICF, and, in the US, the participant's signed HIPAA Authorization.

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

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

Source documents provide evidence for the existence of the participant and substantiate the integrity of the data collected. Source documents are filed at the investigator's site.

Data reported on the CRF or entered in the electronic Case Report Form (eCRF) that are transcribed from source documents must be consistent with the source documents or the discrepancies must be explained.

- The investigator may need to request previous medical records or transfer records, depending on the study. Also, current medical records must be available.
- Definition of what constitutes source data and its origin can be found in the source data location list/map or equivalent document.

The investigator is responsible for ensuring that the source data are accurate, legible, contemporaneous, original, and attributable, whether the data are handwritten 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 records/electronic health records, adverse event (AE) tracking/reporting, protocol-required assessments, and/or drug accountability records.

When paper records from such systems are used in place of an 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 INTERVENTION RECORDS

Records for study intervention (whether supplied by BMS, its vendors, or the site) must substantiate study intervention 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 the following: • 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 • non-study 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 per the Delegation of Authority Form
Sourced by site and not supplied by BMS or its vendors (examples include Investigational Product sourced from the site's stock or commercial supply or a specialty pharmacy)	The investigator or designee accepts responsibility for documenting traceability and study intervention integrity in accordance with requirements applicable under law and the standard operating procedures/standards of the sourcing pharmacy

BMS or its 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 test result abnormalities that are reported or identified during the study.

For sites using the Sponsor or designee electronic data capture (EDC) tool, eCRFs will be prepared for all data collection fields except for fields specific to serious adverse events (SAEs) and pregnancy, which will be reported on the electronic SAE form and Pregnancy Surveillance Form, respectively. If the electronic SAE form is not available, a paper SAE form can be used.

The confidentiality of records that could identify 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 and SAE/pregnancy CRFs must be promptly reviewed, signed, and dated by the investigator or qualified physician who is a sub-investigator and who is delegated this task on the Delegation of Authority Form. Sub-investigators 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 eCRFs must meet Sponsor or designee training requirements and must only access the BMS EDC tool using the unique user account provided by the 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 non-compliance 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 source documents.

In addition, the study may be evaluated by the 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 the 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 its 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 its 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 its designee.

RETURN OF STUDY INTERVENTION

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

If	Then
Study interventions supplied by BMS (including its vendors)	Any unused study interventions supplied by BMS can only be destroyed after being inspected and reconciled by the responsible Study Monitor, unless study intervention containers must be immediately destroyed as required for safety or to meet local regulations (eg, cytotoxic or biologic agents). Partially used study interventions and/or empty containers may be destroyed after proper reconciliation and documentation. However, unused Investigational Medicinal Product must be reconciled by the site monitor/Clinical Research Associate prior to destruction. If study interventions will be returned, the return will be arranged by the responsible Study Monitor.
Study interventions sourced by site, not supplied by BMS (or its vendors; eg, study interventions sourced from the site's 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 of study interventions, 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 standard operating procedures 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 (eg, 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 Study 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 interventions provided by BMS (or its vendors). Destruction of non-study interventions sourced by the site, not supplied by BMS, is solely the responsibility of the investigator or designee.

STUDY AND SITE CLOSURE

The Sponsor/designee reserves the right to close the study site or to terminate the study at any time for any reason at the sole discretion of the Sponsor. Study sites will be closed upon study completion. A study site is considered closed when all required documents and study supplies have been collected and a study-site closure visit has been performed.

The investigator may initiate study-site closure at any time, provided there is reasonable cause and sufficient notice is given in advance of the intended termination.

Reasons for the early closure of a study site by the Sponsor or investigator may include, but are not limited to the following:

For study termination

Discontinuation of further study intervention development

For site termination:

- Failure of the investigator to comply with the protocol, the requirements of the IRB/IEC or local Health Authorities, the Sponsor's procedures, or GCP guidelines
- Inadequate or no recruitment (evaluated after a reasonable amount of time) of participants by the investigator

If the study is prematurely terminated or suspended, the Sponsor shall promptly inform the investigators, the IECs/IRBs, the regulatory authorities, and any contract research organization(s) used in the study of the reason for termination or suspension, as specified by the applicable

regulatory requirements. The investigator shall promptly inform the participant and should ensure appropriate participant therapy and/or follow-up.

DISSEMINATION OF CLINICAL STUDY DATA

To benefit potential study participants, patients, health care 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 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.

In the European Union (EU), the summary of results and summary for laypersons will be submitted within 1 year of the end of trial in the EU/European Economic Area and third countries.

CLINICAL STUDY REPORT

A Signatory Investigator must be selected to sign the Clinical Study Report (CSR).

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 and interpretation

SCIENTIFIC PUBLICATIONS

The data collected during this study are confidential and proprietary to the 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 the Sponsor or designee at the earliest practicable time prior to submission or presentation and otherwise within the 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 the Sponsor is aligned with the criteria of the International Committee of Medical Journal Editors (ICMJE; www.icmje.org). Authorship selection is based on 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 participants with quality data), analysis, or interpretation of data for the work (eg, problem solving, advice, evaluation, insights, and conclusion)
2) Drafting the work or revising it critically for important intellectual content

3) Final approval of the version to be published
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 the Sponsor 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 pre-existing medical condition in a clinical investigation participant administered study treatment 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, electrocardiograms, 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/serious adverse event (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

A 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 Bristol-Myers Squibb (BMS) clinical studies: • A visit to the emergency room or other hospital department < 24 hours that does not result in admission (unless considered an important medical or life-threatening event). • Elective surgery, planned prior to signing consent. • Admissions as per protocol for a planned medical/surgical procedure. • Routine health assessment requiring admission for baseline/trending of health status (eg, routine colonoscopy). • Medical/surgical admission other than to remedy ill health and planned prior to entry into the study. Appropriate documentation is required in these cases. • Admission encountered for another life circumstance that carries no bearing on health status and requires no medical/surgical intervention (eg, lack of housing, economic inadequacy, caregiver respite, family circumstances, administrative reason). • Admission for administration of 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 [eg, medical, surgical] to prevent one of the other serious outcomes listed in the definition above). Examples of such events include, but are not limited to, intensive treatment in an emergency room or at home for allergic bronchospasm and 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 DILI must follow the same transmission timing and processes to BMS as used for SAEs. (See Section 9.2.5 for reporting pregnancies.)

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 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 the 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 the Sponsor.

The investigator may change his/her opinion of causality in light of follow-up information and send an SAE follow-up report with the updated causality assessment.

The causality assessment is one of the criteria used when determining regulatory reporting requirements.

- **Assessment of Intensity**

For the reporting of all AEs, including intensity or severity, on case report forms, please follow the definitions in National Cancer Institute Common Terminology Criteria for Adverse Events version 5 (NCI CTCAE v5).

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 electronic case report form (eCRF).
  - The paper SAE Report Form is intended only as a back-up option when the electronic data capture 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 transmission.
    - When paper forms are used, the original paper forms are to remain on site.
- Pregnancies must be recorded on paper Pregnancy Surveillance Forms and transmitted via email or confirmed facsimile transmission.

SAE Email Address: [redacted]

SAE Facsimile Number: *Will be provided by local site monitor.*

SAE Telephone Contact (required for SAE and pregnancy reporting): *Will be provided by local site monitor.*

APPENDIX 4 WOMEN OF CHILDBEARING POTENTIAL DEFINITIONS AND METHODS OF CONTRACEPTION

Appendix 4 provides general information and definitions related to Woman of Childbearing Potential and methods of contraception that can be applied to most clinical trials. For information specific to this study regarding acceptable contraception requirements for female and male participants, refer to Section 6.1 of the protocol. Only the contraception methods as described in Section 6.1 are acceptable for this study.

DEFINITIONS

Woman of Childbearing Potential (WOCBP)

A woman is considered fertile following menarche and until becoming postmenopausal 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. Suggested guidelines for the duration of the washout periods for HRT types are presented below. 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 timepoint where the Investigational Medicinal Product (IMP) or any active major metabolites have 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 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 (rings) – 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.

• 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 participant chooses to forego complete abstinence. • Periodic abstinence (including, but not limited to, calendar, symptothermal, postovulation methods), withdrawal (coitus interruptus), spermicides only, and lactational amenorrhea method (LAM) are not acceptable methods of contraception for this study.
NOTES: [a] Typical use failure rates may differ from failure rates when contraceptive methods are used consistently and correctly. Use should be consistent with local regulations regarding the use of contraceptive methods for participants 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. For information specific to this study regarding permissibility of hormonal contraception, refer to Sections 6.1 INCLUSION CRITERIA and 7.7.1 PROHIBITED AND/OR RESTRICTED TREATMENTS of the protocol. [c] IUSs are acceptable methods of contraception in the absence of definitive drug interaction studies when hormone exposures from intrauterine devices do not alter contraception effectiveness. For information specific

to this study regarding permissibility of hormonal contraception, refer to Sections 6.1 INCLUSION CRITERIA and 7.7.1 PROHIBITED AND/OR RESTRICTED TREATMENTS of the protocol.

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, postovulation methods). • Withdrawal (coitus interruptus). • Spermicide only. • 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 Appendix 3.

APPENDIX 5 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 < 10 mm or pathological lymph nodes with ≥ 10 to < 15 mm short axis) as well as truly non-measurable lesions. Lesions considered truly non-measurable include: leptomeningeal disease, 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 (< 10 mm 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

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; NE, not evaluable.

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; NE, not evaluable.

[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

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	PD	SD provided minimum criteria for SD duration met, otherwise, PD
CR	NE	SD provided minimum criteria for SD duration met, otherwise, NE
PR	CR	PR
PR	PR	PR
PR	SD	SD
PR	PD	SD provided minimum criteria for SD duration met, otherwise, PD
PR	NE	SD provided minimum criteria for SD duration met, otherwise, NE
NE	NE	NE

CR, complete response; PR, partial response; SD, stable disease; PD, progressive disease; NE, not evaluable.

[a] If a CR is truly met at first time point, then any disease seen at a subsequent time point, even disease meeting PR criteria relative to baseline, makes the disease PD at that point (since disease must have reappeared after CR). Best response would depend on whether minimum duration for SD was met. However, sometimes 'CR' may be claimed when subsequent scans suggest small lesions were likely still present and in fact the 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 6 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 7 MANAGEMENT ALGORITHMS FOR STUDIES UNDER CTCAE VERSION 5

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. Noninflammatory etiologies should be considered and appropriately treated.

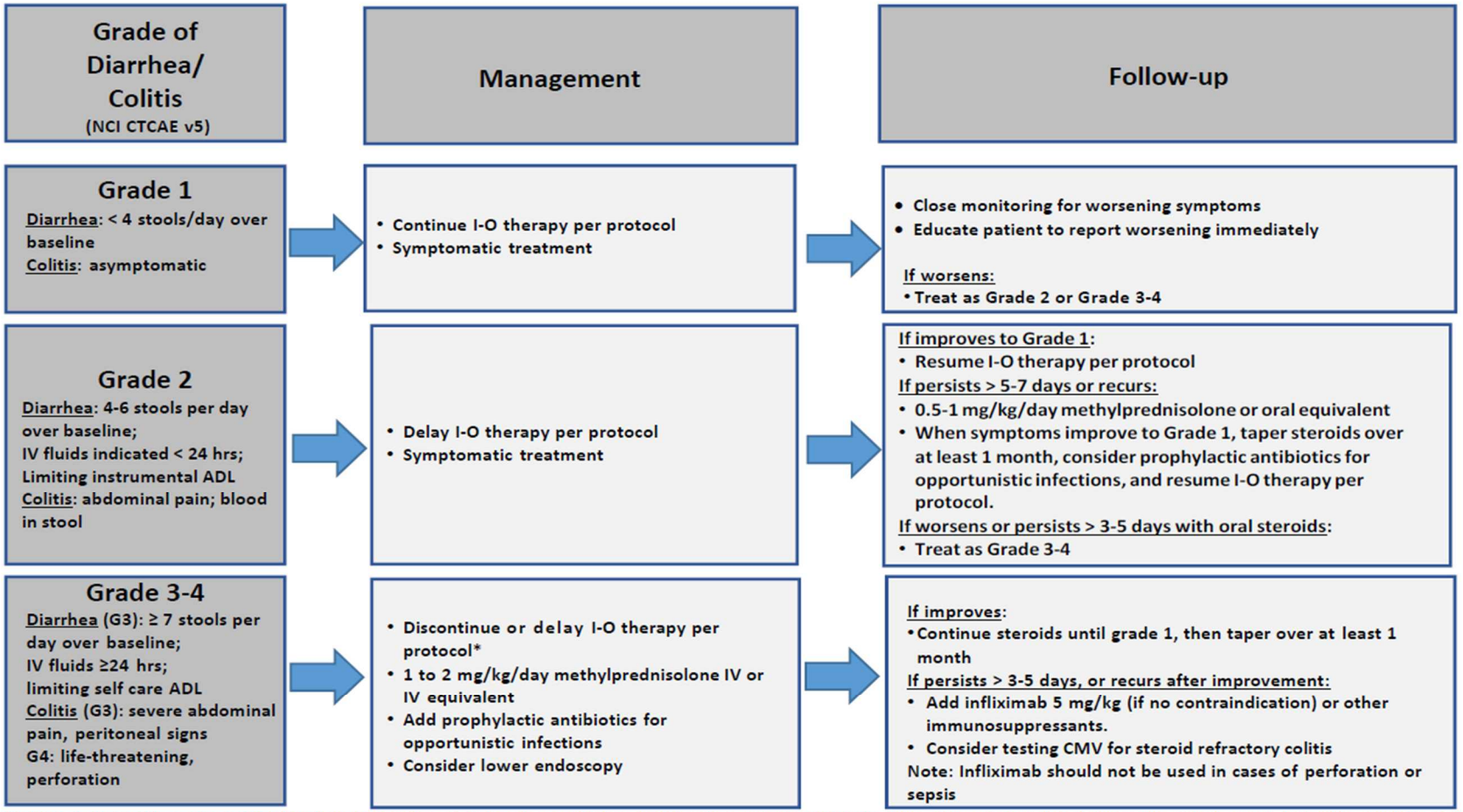
Corticosteroids are a primary therapy for immuno-oncology drug-related adverse events. The oral equivalent of the recommended IV doses may be considered for ambulatory patients with low-grade toxicity. The lower bioavailability of oral corticosteroids should be taken into account when switching to the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

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

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

GI Adverse Event Management Algorithm

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



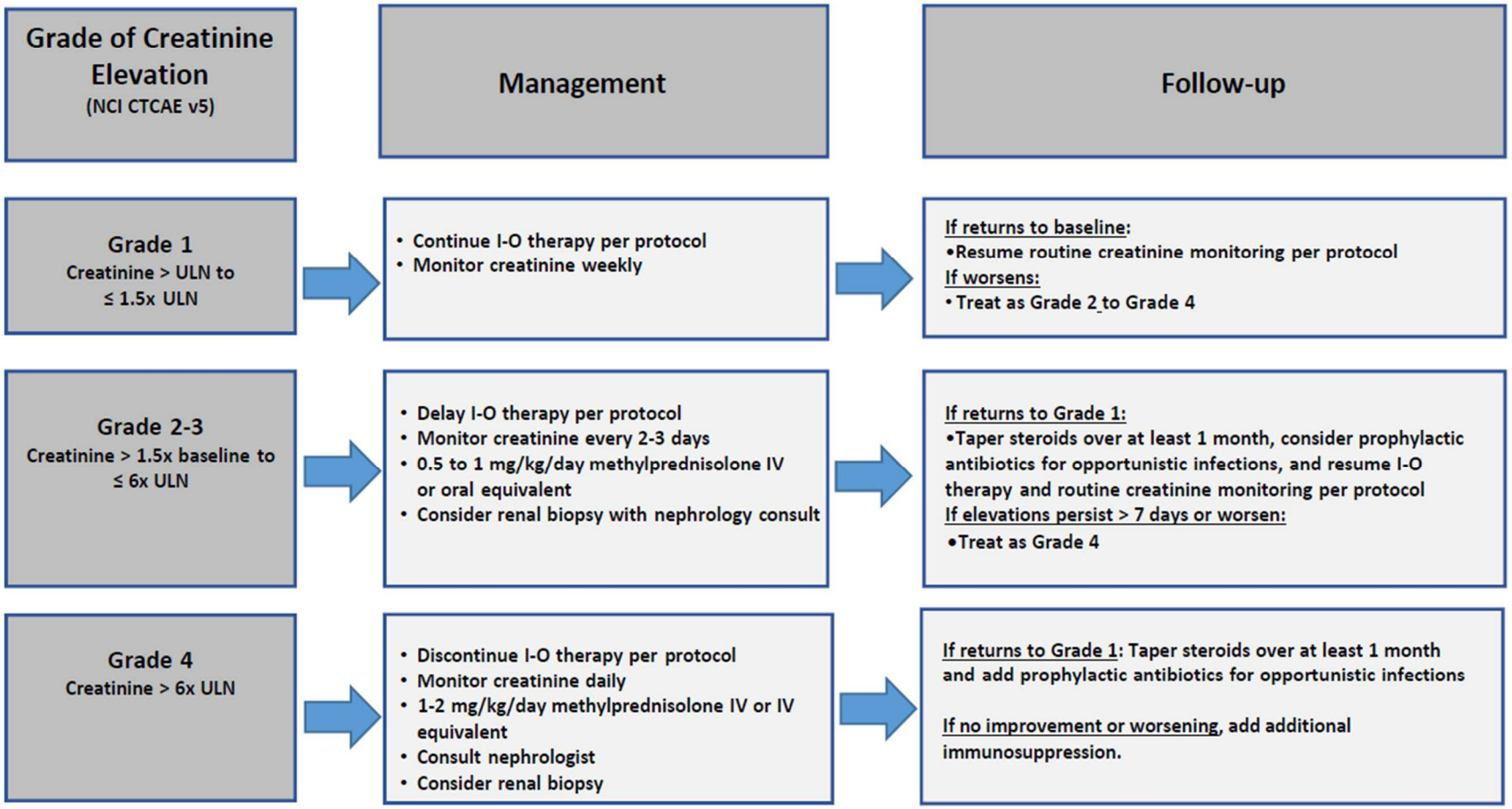
Patients on IV steroids may be switched to an equivalent dose of oral corticosteroids (eg, prednisone) at start of tapering or earlier, after sustained clinical improvement is observed. Lower bioavailability of oral corticosteroids should be taken into account when switching to the equivalent dose of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

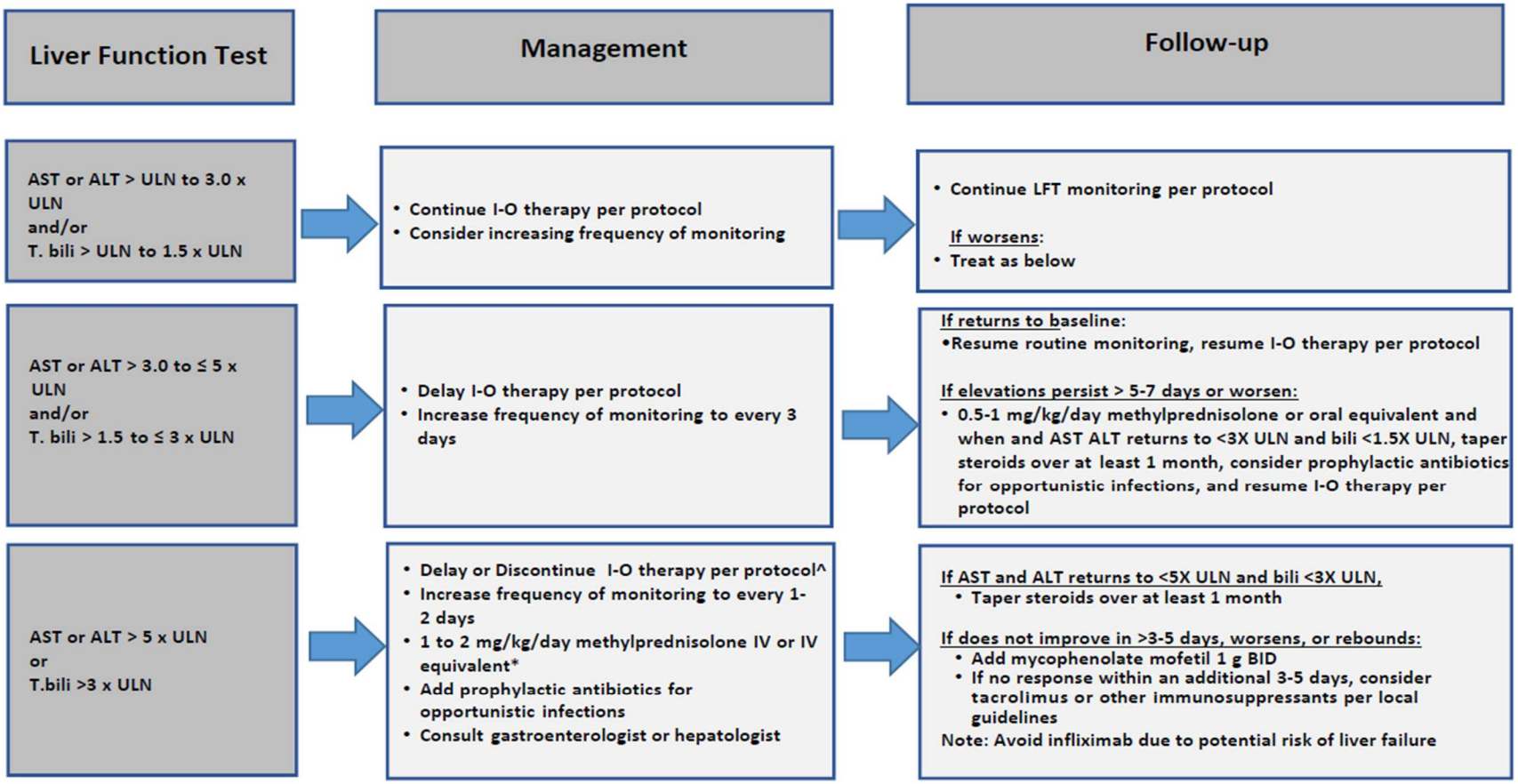
Grade of Pneumonitis (NCI CTCAE v5)	Management	Follow-up
Grade 1 Radiographic changes only	• Consider delay of I-O therapy • Monitor for symptoms every 2-3 days • Consider Pulmonary and ID consults	• Re-image at least every 3 weeks If worsens: • Treat as Grade 2 or 3-4
Grade 2 Mild to moderate new symptoms	• Delay I-O therapy per protocol • Pulmonary and ID consults • Monitor symptoms daily, consider hospitalization • 1 mg/kg/day methyl prednisolone IV or oral equivalent • Consider bronchoscopy, lung biopsy	If improves to Grade 1: • Resume I-O therapy per protocol If persists > 5-7 days or recur: • 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 Severe new symptoms; New/worsening hypoxia; Life-threatening	• Discontinue I-O therapy per protocol • Hospitalize • Pulmonary and ID consults • 2-4 mg/kg/day methyl prednisolone IV or IV equivalent • Add prophylactic antibiotics for opportunistic infections • Consider bronchoscopy, lung biopsy	If improves to baseline: • Taper steroids over at least 6 weeks If not improving after 48 hours or worsening: • Add additional immunosuppression

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.

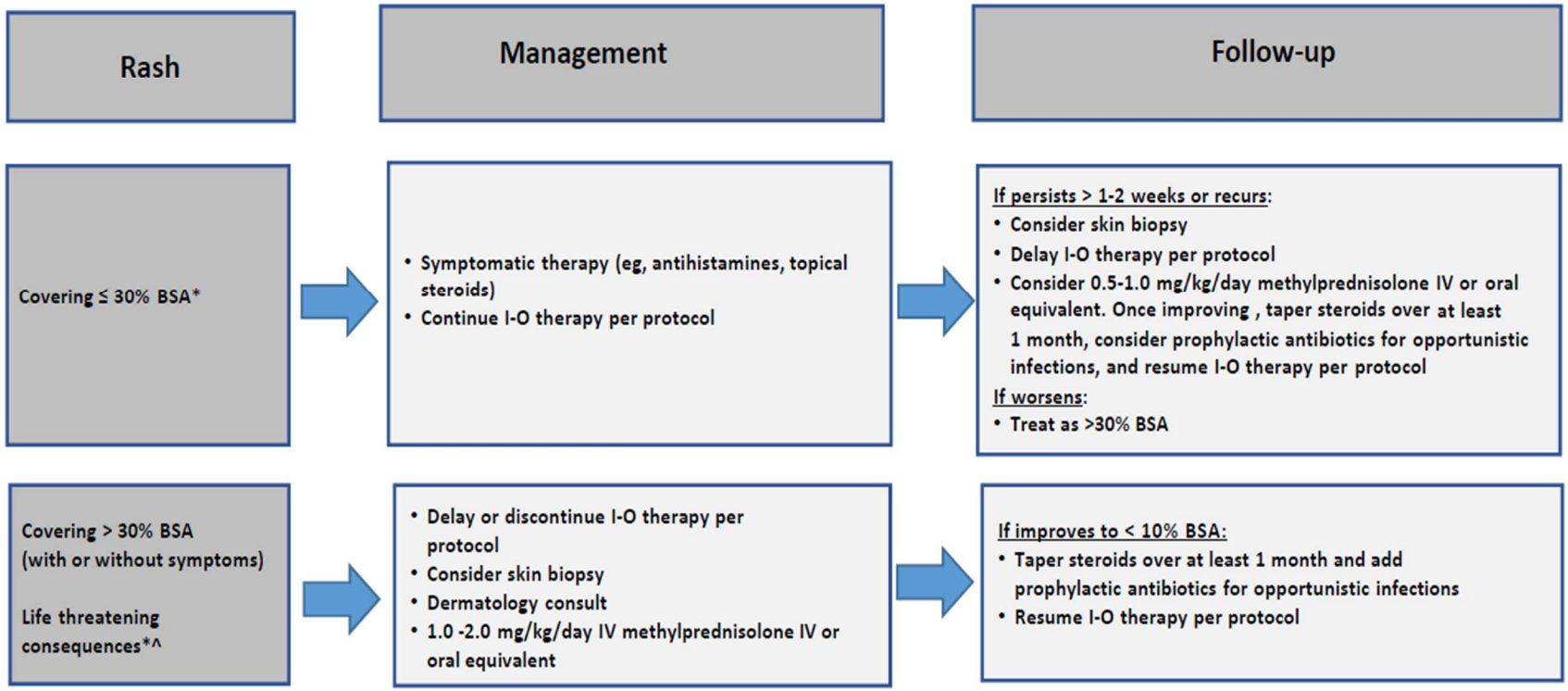
Endocrinopathy	Management	Follow-up
Asymptomatic TSH abnormality or Hyperglycemia requiring no medical intervention	• Continue I-O therapy per protocol • If TSH < 0.5 x LLN, or TSH > 2 x ULN, or consistently out of range in 2 subsequent measurements: ○ include fT4 at subsequent cycles as clinically indicated; ○ consider endocrinology consult	• Monitor TSH as per protocol • Monitor blood sugar • If symptomatic or blood sugar requiring initiation of treatment or change in management, manage as below
Symptomatic endocrinopathy or hyperglycemia requiring initiation of treatment or change in daily management or work up	• Evaluate endocrine function; consider endocrinology consult • Consider pituitary scan Symptomatic with abnormal lab/pituitary scan: • Delay I-O therapy per protocol • 1-2 mg/kg/day methylprednisolone IV or PO equivalent for hypophysitis • Initiate appropriate hormone/medical therapy No abnormal lab/pituitary MRI scan but symptoms persist: • Continue IO therapy. Repeat labs in 1-3 weeks /MRI in 1 month Hyperglycemia: Screen for Diabetic Ketoacidosis (DKA). If negative, continue IO and treat diabetes. If DKA hold IO, admit, manage DKA. Steroids not recommended for DKA/hyperglycemia	If improves (with or without hormone replacement): • Taper steroids over at least 1 month and consider prophylactic antibiotics for opportunistic infections • Resume I-O therapy per protocol • Patients with adrenal insufficiency may need to continue steroids with mineralocorticoid component
Suspicion of adrenal crisis (eg, severe dehydration, hypotension, shock out of proportion to current illness)	• Delay or discontinue I-O therapy per protocol • Rule out sepsis • Stress dose of IV steroids with mineralocorticoid activity • IV fluids • Consult endocrinologist	• Patients with adrenal insufficiency may need to continue steroids with mineralocorticoid component • If adrenal crisis resolves and patient is adequately controlled with physiologic hormone replacement, patient can resume IO therapy per protocol.

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.

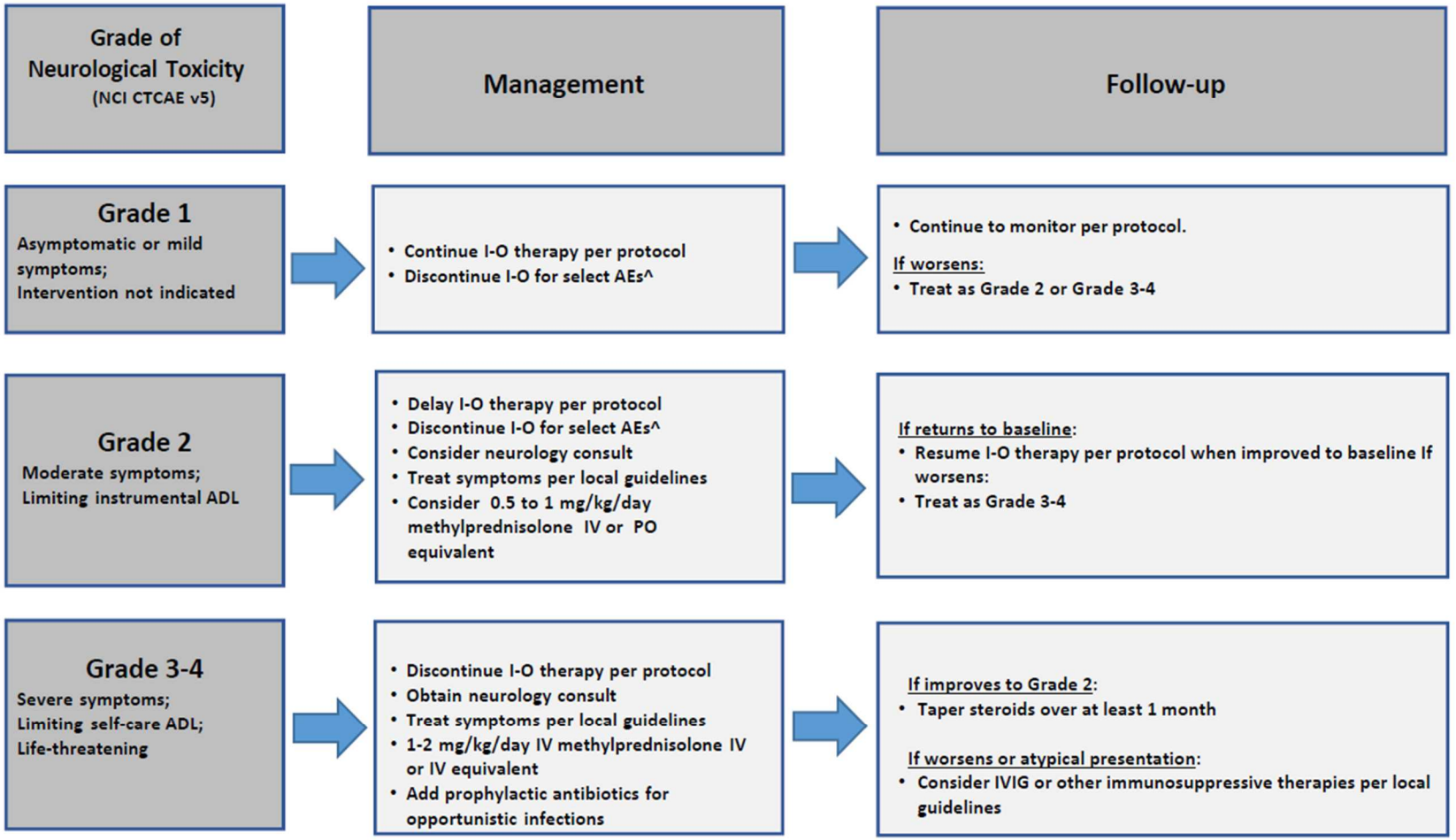
*Refer to NCI CTCAE v5 for term-specific grading criteria.

^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.



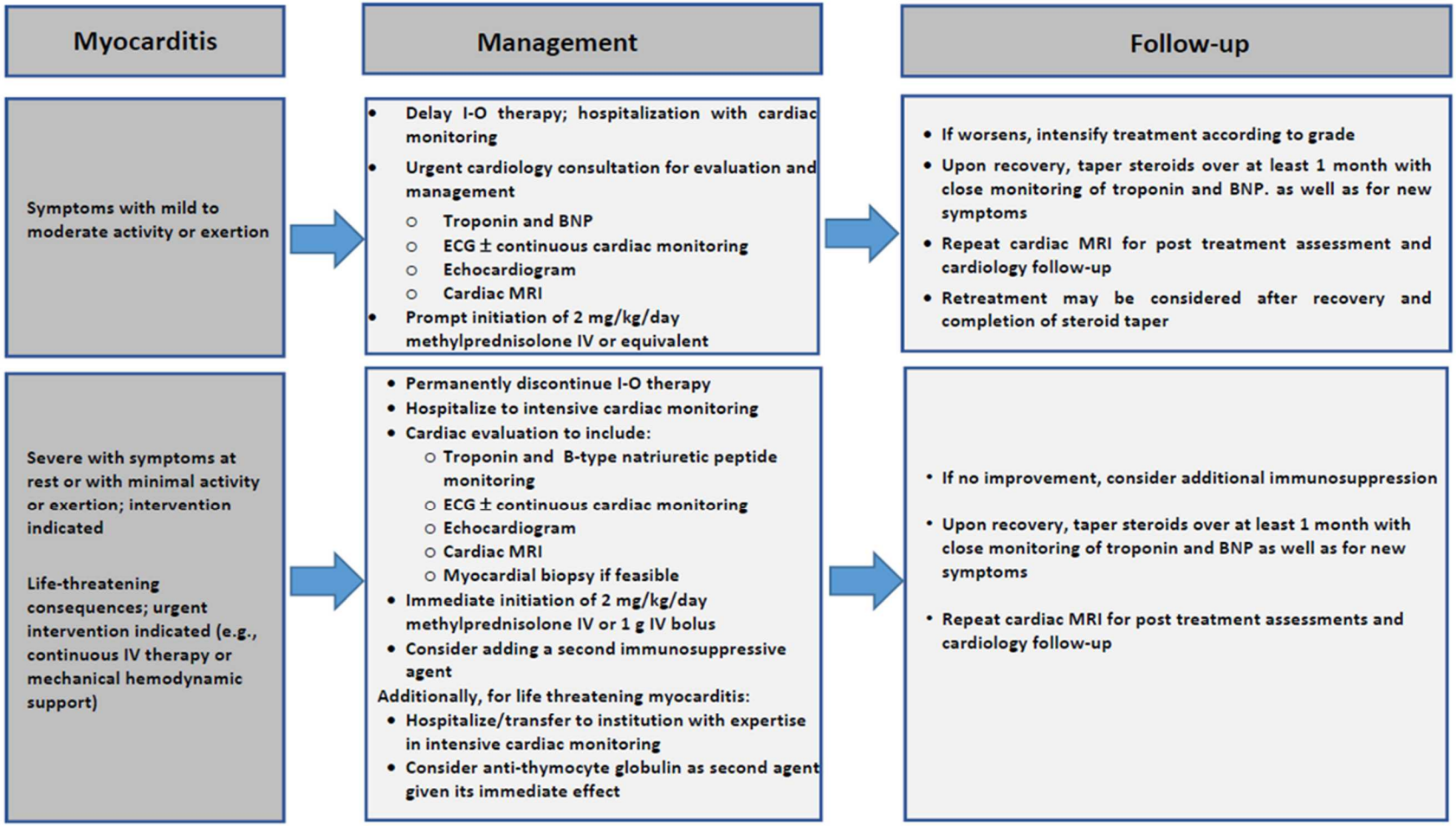
Patients on IV steroids may be switched to an equivalent dose of oral corticosteroids (eg. prednisone) at start of tapering or earlier, after sustained clinical improvement is observed. Lower bioavailability of oral corticosteroids should be taken into account when switching to the equivalent dose of 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 8 CYP3A4 STRONG INHIBITOR AND INDUCER GUIDANCE

The lists below are not meant to be all inclusive. Please consult individual drug labels for further information. Additional information is also available at:

http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/DrugInteractionsLabeling/ucm093664.htm

Representative Examples of Drugs that are Strong CYP3A4 Inhibitors or Inducers

CYP Enzyme	Strong Inhibitors[a] ≥ 5 fold Increase in AUC Or > 80% Decrease in CL	Strong Inducers ≥ 80% Decrease in AUC
CYP3A	Boceprevir, clarithromycin, conivaptan, grapefruit juice[b], indinavir, itraconazole, ketoconazole, lopinavir/ritonavir, mibefradil[c], nefazodone, nelfinavir, posaconazole, ritonavir, saquinavir, telaprevir, telithromycin, voriconazole	Avasimibe[d], carbamazepine, phenytoin, rifampin, St. Johns Wort[e]

Abbreviations: AUC, area under the concentration time curve; CL, clearance; CYP, cytochrome P450.

[a] A strong inhibitor for a specific CYP is defined as an inhibitor that increases the AUC of a substrate for that CYP by equal or more than 5-fold.

[b] The effect of grapefruit juice varies widely among brands and is concentration, dose, and preparation dependent. Studies have shown that it can be classified as a "strong CYP3A inhibitor" when a certain preparation was used (eg, high dose, double strength) or as a "moderate CYP3A inhibitor" when another preparation was used (eg, low dose, single strength).

[c] Withdrawn from the United States market because of safety reasons.

[d] Not a marketed drug.

[e] The effect of St John's Wort varies widely and is preparation dependent.

APPENDIX 9 PROTOCOL AMENDMENT SUMMARY OF CHANGE HISTORY

Overall Rationale for Protocol Amendment 01, 27-Jun-2022:

The purpose of this amendment is [redacted] to update the eligibility criteria to include all actionable mutations, adjust eligibility criteria for docetaxel, and adjust dosing modifications for nivolumab. In addition, the protocol was updated to utilize staggered dosing for safety monitoring during dose escalation and specify stopping rules for the study based on safety monitoring [redacted]. In addition [redacted] the dosing instructions were updated and additional information provided regarding the [redacted] plan.

SUMMARY OF CHANGES FOR PROTOCOL AMENDMENT 01		
Section Number & Title	**Description of Change**	**Brief Rationale**
Section 2: Schedule of Activities Table 2-1: Screening Procedural Outline for All Parts (CA115001)	MET exon 14 skipping mutation status and EGFR exon 20 insertion mutation status were added to the eligibility assessments.	To align with updated eligibility criteria [redacted].
Section 5.1.2.1: Part A: Dose Escalation of BMS-986442 with Nivolumab	The following language was added to this section: "A staggered dosing (sentinel participant) approach will be used. The first participant in each cohort will be observed for at least 7 days after their initial exposure to the combination of BMS-986422 and nivolumab before additional participants in that cohort are dosed. Subsequently, the remaining participants in each dose cohort must be observed for at least 24 hours after their initial exposure to the combination	Added additional enrollment guidelines and safety monitoring for dose escalation (Part A) [redacted].

SUMMARY OF CHANGES FOR PROTOCOL AMENDMENT 01		
Section Number & Title	**Description of Change**	**Brief Rationale**
	regimen before additional participants are exposed.	
Section 5.1.3: Follow-up Period	A clarification was added that is applicable to the safety follow-up period. The words "even if the study is terminated" were added to the following language in this section: "The safety follow-up period for all treatment groups, even if the study is terminated, is 100 days after the end-of-treatment visit or date of last dose (whichever occurs later), with visits to occur at 30, 60, and 100 (± 7) days.	Updated for clarification [redacted].
Section 5.1.4: Data Monitoring Committee and Other Committees	The following language was added to this section: "If there is any treatment-related Grade ≥ 4 toxicity or death as assessed by the Sponsor, enrollment in that arm will be placed on hold and an ad-hoc SMT meeting will be convened. Additionally, a Bayesian continuous monitoring framework will be utilized for continuous monitoring of toxicity in the study. If at any time during the study, the posterior probability of the DLT rate exceeding 33% is greater than 0.85, that will also trigger enrollment in that arm being placed on hold and an ad-hoc SMT meeting being convened. The SMT will re-evaluate the benefit-risk profile of the drug combination in context of the totality of the data, and assess whether termination or	Specified stopping rules based on safety [redacted].

SUMMARY OF CHANGES FOR PROTOCOL AMENDMENT 01		
Section Number & Title	**Description of Change**	**Brief Rationale**
	resumption of the cohort/study is appropriate."	
Section 6.1: Inclusion Criteria	Inclusion criterion 2-g-v was updated to specify epidermal growth factor receptor (EGFR) mutations include exon 20 insertion mutations, as well as updated to add MET exon 14 skipping mutations, and include abbreviations for rearranged during transfection and neurotrophic tropomyosin-receptor kinase. The updated criterion is as follows: "Participants with disease having known actionable mutations in epidermal growth factor receptor (EGFR) including exon 20 insertion mutations, anaplastic lymphoma kinase (ALK), ROS proto-oncogene 1 (ROS1), rearranged during transfection (RET), neurotrophic tropomyosin-receptor kinase (NTRK), Kirsten rat sarcoma (KRAS) (G12C), MET exon 14 skipping mutations, or proto-oncogene B-Raf (BRAF) (V600E) must have progressed on, have been intolerant to, or not be a candidate for standard targeted therapy (as available per country/region standard-of-care practices)." Inclusion criterion 2-i-ii was updated to specify EGFR mutations include exon 20 insertion mutations, as well as updated to add MET exon 14	Updated and clarified eligibility criteria to include known actionable mutations (as per regional standard of care) [redacted].

SUMMARY OF CHANGES FOR PROTOCOL AMENDMENT 01		
Section Number & Title	**Description of Change**	**Brief Rationale**
	skipping mutations, RET, and NTRK. The updated criterion is as follows: "Participants with disease having known genetic aberrations in EGFR including exon 20 insertion mutations, ALK, ROS1, KRAS (G12C), RET, NTRK, MET exon 14 skipping mutations, or BRAF (V600E) that are sensitive to targeted therapy (as available per country/region standard-of-care practices) will be excluded."	
Section 6.2: Exclusion Criteria	Exclusion criterion 5-f was updated to add specific requirements for participants in study Part C. The additional criterion that was added and applicable to study Part C is as follows: "Participants in Part C only: AST and/or ALT > 1.5 x ULN concomitant with alkaline phosphatase > 2.5 x ULN." Exclusion criterion 5-g was updated to add specific requirements for participants in study Part C. The additional criterion that was added and applicable to study Part C is as follows: "All participants, except Part C: Total bilirubin > 1.5 x ULN (except participants with Gilbert Syndrome who must have a total bilirubin level of < 3.0 x ULN). Participants in Part C only: Total bilirubin > ULN."	To implement more stringent exclusion criteria and align with the docetaxel US Prescribing Information (USPI) [redacted].

SUMMARY OF CHANGES FOR PROTOCOL AMENDMENT 01		
Section Number & Title	**Description of Change**	**Brief Rationale**
Section 7.1.1: Part A and Part B: Nivolumab and BMS-986442	This section was updated to include separate infusion time guidance (90 minutes) for the BMS-986442 dose level of 1200 mg. The updated BMS-986442 infusion time guidance displayed in this section is as follows: "BMS-986442 (20 mg dose level up to and including 600 mg dose level) will be administered as an infusion over 60 minutes (Q3W) followed by a 60-minute observation period. BMS-986442 at the 1200 mg dose level will be administered as an infusion over 90 minutes (Q3W), followed by a 60-minute observation period."	To align with dosing recommendations based on endotoxin exposure at 1200 mg dose.
Section 7.1.3: Part D: Nivolumab, BMS-986442, Pemetrexed, and Carboplatin	This section was updated to include "dosed in accordance with local prescribing information," which was added to the guidance for oral folic acid administration. The updated language is as follows: "Oral folic acid 350 to 1000 µg daily (dosed in accordance with local prescribing information) should be given starting 1 week prior to the first dose of pemetrexed, with at least 5 doses of folic acid administered in the 7 days prior to the first dose."	To align with regional dosing variations of folic acid in conjunction with pemetrexed [redacted].
Section 7.4.1: Dose Modification Criteria for Nivolumab and BMS-986442	The hepatic severity criterion within table 7.4.1-1 was updated to include the following additional criteria for permanent discontinuation of nivolumab and BMS-986442 (additional criteria in underline):	Updated dose modification guidelines for hepatic adverse events to align with the current USPI for nivolumab [redacted].

SUMMARY OF CHANGES FOR PROTOCOL AMENDMENT 01		
Section Number & Title	**Description of Change**	**Brief Rationale**
Table 7.4.1-1: Adverse Event Criteria for Delay, Resume, and Discontinue of Nivolumab and BMS-986442	"Concurrent AST or ALT > 3 x ULN and T.bili > 2 x ULN, regardless of baseline value, or T. bili > 3 x ULN, or AST or ALT > 8 x ULN with no tumor involvement of the liver, or AST or ALT > 10 x ULN with tumor involvement of the liver"	
[redacted]		

SUMMARY OF CHANGES FOR PROTOCOL AMENDMENT 01		
Section Number & Title	**Description of Change**	**Brief Rationale**
[redacted]		
Section 10.4.5.1: Continuous Safety Monitoring Table 10.4.5.1-1: Safety Continuous Monitoring Boundary	This section and table content were updated in order to expand the participant population to all treated participants. Part B specifics were replaced with treated participants in all study parts. The previously specified time period of 28 days was removed, as the safety monitoring time period will be expanded and encompass the full study length (through all participants' safety follow-up).	This section and table were updated in parallel with the updates made within Section 5.1.4 (specified stopping rules based on safety [redacted]).
All	Minor formatting and typographical corrections.	Because these errors are minor, they have not been summarized.