Official Title of Study:

A Phase 1/2 Study of BMS-986315 as Monotherapy and in Combination With Nivolumab or Cetuximab in Participants With Advanced Solid Tumors

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CLINICAL PROTOCOL CA047004

A Phase 1/2 Study of BMS-986315 as Monotherapy and in Combination with Nivolumab or Cetuximab in Participants with Advanced Solid Tumors

Short Title: Phase 1/2 Study of BMS-986315 with and without Nivolumab or Cetuximab in Solid Tumors

Revised Protocol Number: 02

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to partners to which BMS has transferred obligations, eg, a Contract Research Organization (CRO).

DOCUMENT HISTORY

Document	Date of Issue	Summary of Change
Revised Protocol 02	11-Nov-2020	The main changes include clarifying that tumor tissue quality thresholds only apply to the pharmacodynamics cohorts, broadening prior therapy inclusion criteria for RCC and NSCLC, revising contraception requirements for both women of childbearing potential and males and their WOCBP partners, adding responses to the COVID-19 pandemic, and updating nivolumab program standards.
Revised Protocol 01	04-Mar-2020	The protocol was revised [redacted]. See Summary of Key changes document for details.
Original Protocol	13-Jan-2020	Not applicable

OVERALL RATIONALE FOR REVISED PROTOCOL 02:

This protocol was revised to update the contraception language for women of child-bearing potential (WOCBP) participants and male participants, and their WOCBP partners. In addition, the protocol was revised to clarify where tissue quality thresholds apply and to broaden prior therapy inclusion criteria for renal cell carcinoma (RCC) and non-small cell lung cancer (NSCLC). Lastly, the protocol was revised in response to the COVID-19 pandemic and to incorporate updates in the nivolumab program standards.

SUMMARY OF KEY CHANGES FOR REVISED PROTOCOL 02		
Section Number & Title	**Description of Change**	**Brief Rationale**
Synopsis, Overall Design 5.1 Overall Design 5.1.2.4 Pharmacodynamic Cohorts 5.4.4 Rationale for Prospective Biomarker Identification 9.8.1 Collection of Tumor Tissue Specimens	[redacted]	
Synopsis, Overall Design Table 2-1 Screening Procedural Outline 5.1.1 Screening Period 5.1.2.4 Pharmacodynamic Cohorts 6.1 Inclusion Criteria (2a) 9.8.1 Collection of Tumor Tissue Specimens	Changed the tumor tissue sample quality thresholds to only apply to the PD cohorts; clarified that only those participants who have met tissue quality thresholds and have evaluable CD8 and HLA-E can be assigned for treatment in PD cohorts.	Changed the tissue quality thresholds for enrollment for the PD cohorts.
Table 2-1 Screening Procedure Outline (CA047004) Table 2-2 On Treatment Procedural Outline (CA047004) Table 2-3 Follow-up Procedural Outline (CA047004)	Revised wording for collection of SAEs until 100 days after "last dose of study treatment" instead of "after discontinuation of dosing" or after "EOT" (end of treatment). Revised wording for collection of nonserious AEs in Table 2-3 to "from time of first dose."	For clarity since the date of discontinuation of dosing or EOT visit could be different from the date of last dose. For consistency through the document.

SUMMARY OF KEY CHANGES FOR REVISED PROTOCOL 02		
Section Number & Title	**Description of Change**	**Brief Rationale**
9.2.1 Time Period and Frequency for Collecting AE and SAE Information	Added description to 9.2.1 for collection of nonserious AE.	
Table 2-2 On Treatment Procedural Outline (CA047004) Table 2-3 Follow-up Procedural Outline (CA047004) 3.3 Benefit/Risk Assessment Table 4-1 Objectives and Endpoints 6.2 Exclusion Criteria 2 (p, q) 6.4.1 Retesting During Screening or Lead-In Period 7.4.1 Dose Delays Due to Toxicity 7.4.2 Criteria to Resume Treatment 7.7.1 Prohibited and/or Restricted Treatments 9.2.1 Time Period and Frequency for Collecting AE and SAE Information 9.2.3 Follow-up of AEs and SAEs Table 9.8-1 Biomarker Sampling Schedule for BMS-986315 for Part 1A, Part 1B, and Part 1C (CA047-004) 9.8.3.2 Serum Factors 10.3.7 Other Analyses	Changes were made throughout the protocol to allow for the collection of serum samples to be used for potential future measurements of anti-SARS-CoV-2 serology; the risks associated with SARS-CoV-2 infection and study participation; and the collection and following of adverse events and serious adverse events.	For consistency with BMS standards, in the face of the rapidly evolving COVID-19 pandemic.
Table 2-1 Screening Procedure Outline (CA047004) Table 2-2 On Treatment Procedural Outline (CA047004) 6.1 Inclusion Criteria (3a iv)	Added that an extension for pregnancy test during screening for 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.	Aligned with new nivolumab program standards.

SUMMARY OF KEY CHANGES FOR REVISED PROTOCOL 02		
Section Number & Title	**Description of Change**	**Brief Rationale**
6.2 Exclusion Criteria (2d and 2r) 6.2 Exclusion Criteria (2s)	Revised eligibility for patients with HIV infection. Added leptomeningeal metastases as an exclusion.	
Table 2-2 On Treatment Procedural Outline (CA047004)	For weight assessment, added footnote "h" that for Study Part 1C participants, weight collected on Day 1 of each cycle should be used for body surface calculation throughout each cycle.	To clarify that the dosing of cetuximab in Part 1C is to be based on the weight taken on Day 1 of each cycle.
Table 2-2 On Treatment Procedural Outline (CA047004)	In body imaging, clarified that both disease progression and treatment discontinuation must occur before imaging ends.	To ensure adequate imaging data collection.
5.1.2 Treatment Period	Added text that participants may be enrolled to backfill dose escalation cohorts in Part 1A, Part 1B, and Part 1C.	To ensure that sufficient evaluable pharmacokinetics, PD, and clinical data are available to inform dose selection.
5.5.1 Justification for Dose Selection and Dosing Schedule of BMS-986315	Revised FIH starting dose from 200 to 80 mg.	Corrected typographical error.
6.1 Inclusion Criteria (3) (3a ix [2]) (3b ii - viii) 9.2.5 Pregnancy Appendix 4 Women of Childbearing Potential Definitions and Methods of Contraception	For WOCBP, revised the required contraception window from 9 to 5 months from last dose of study treatment. For male participants, revised contraception requirements to "not applicable" (ii-vii) and added statement (viii) that no measures were needed.	Aligned contraception window for WOCBP to nivolumab program standards. Transmission of monoclonal antibodies in seminal fluids is below biologically relevant amounts to induce fetal toxicity and none of the antibodies in this protocol is genotoxic, thus the contraception

SUMMARY OF KEY CHANGES FOR REVISED PROTOCOL 02		
Section Number & Title	**Description of Change**	**Brief Rationale**
	Revised Appendix 4.	requirements for males are unnecessary. Revised the Appendix to align with current BMS standards and removed male contraception.
6.1 Inclusion Criteria (2f iii and 2f v) 6.1 Inclusion Criteria (2g iii and 2g v)	For participants with RCC, removed limit on the total number of prior systemic treatment regimens. For participants with NSCLC, broadened the language on prior chemotherapy.	Aligned study inclusion criteria with global standards of care for RCC and NSCLC.
9.2.1 Time Period and Frequency for Collecting AE and SAE Information	Removed "the Pre-Screen ICF for biopsy."	Pre-Screen ICFs for biopsy are not used.
Table 9.5-5 Pharmacokinetic and Immunogenicity Sampling Schedule for Part 1C (CA047-004)	Added 2 time points for cetuximab pharmacokinetic serum collection.	To characterize the maximum concentration of cetuximab.
Table 9.5-3 PK and Immunogenicity Sampling Schedule for Part 1A (CA047-004) Table 9.5-4 Pharmacokinetic and Immunogenicity Sampling Schedule for Part 1B (CA047-004) Table 9.5-5 Pharmacokinetic and Immunogenicity Sampling Schedule for Part 1C (CA047-004)	Updated the end of infusion (EOI) sample collection footnote.	To clarify the EOI sample collection practice.
Table 9.8-1 Biomarker Sampling Schedule for BMS-986315 for Part 1A, Part 1B, and Part 1C (CA047-004)	Removed some collection time points under Serum Biomarkers, Plasma (ctDNA), Whole Blood PBMC, Whole Blood Immunophenotyping, and NKG2A.	To reduce participant burden.

SUMMARY OF KEY CHANGES FOR REVISED PROTOCOL 02		
Section Number & Title	**Description of Change**	**Brief Rationale**
Appendix 5 Management Algorithms	Updated the nivolumab adverse event management algorithm from NCI CTCAE v4 to v5.	Aligned nivolumab AE management with the updated Nivolumab Investigator's Brochure.
ALL	Minor formatting and typographical corrections	Minor, therefore have not been summarized.

TABLE OF CONTENTS

1 SYNOPSIS

Protocol Title: A Phase 1/2 Study of BMS-986315 as Monotherapy and in Combination with Nivolumab or Cetuximab in Participants with Advanced Solid Tumors

Short Title:

Phase 1/2 Study of BMS-986315 with and without Nivolumab or Cetuximab in Solid Tumors

Study Phase: 1/2

Rationale:

Patients with metastatic or refractory solid tumors have a very poor prognosis.

Despite advances in multimodal therapy, increases in overall survival (OS) in this patient population have been limited. The unmet need resides in the lack of effective treatments to deliver long-term survival, hence the need to test compounds that have novel mechanisms of action in clinical studies.

Immuno-oncology cancer drugs are able to alter the unfavorable balance between positive (co-stimulatory) and negative (co-inhibitory) T-cell surface molecules exploited by the tumors to escape immune surveillance.

CD94/NKG2 is a family of C-type lectin receptors that may stimulate or inhibit cytotoxic activity of NK cells through recognition of nonclassical MHC glycoproteins class I (HLA-E in humans and Qa-1 molecules in the mouse). CD94/NKG2 family includes seven members: NKG2A, B, C, D, E, F and H. NKG2A is an inhibitory receptor that contains 2 ITIM domains that recruit SHP-1 and SHP-2, leading to dephosphorylation of tyrosine kinases substrates which results in inhibition of NK and T cell responses. NKG2A is expressed on effector/memory CD8+, NK, NKT and γδT cells. HLA-E is physiologically expressed in most human tissues at low levels; however, tumor cells upregulate HLA-E expression with IFN-γ level increase during immune responses HLA-E expression has been correlated to poor immune response or worse prognosis in several tumor types. In parallel, NKG2A expression is higher in NK cells found in breast cancer and NSCLC as compared to normal tissue. As for T cells, NKG2A expression has been correlated with worse survival in patients with colorectal cancer. $NKG2A^{null}$ NK cells had higher cytotoxicity against HLA-E expressing tumor cells compared to NKG2A+ cells, highlighting the inhibitory capacity of NKG2A. Furthermore, in vitro studies show that both T and NK cells are necessary for tumor growth control in Qa-1 knockout cells, suggesting that blockade of the NKG2A-HLA-E axis might help to restore both T and NK cell activity.

Thus, an antagonistic antibody such as BMS-986315 that blocks HLA-E mediated inhibitory NKG2A signals could have a unique advantage of restoring both T and NK cell responses. Moreover, based on recent emerging clinical evidence of improved responses with combination therapies, the combination of BMS-986315 with anti-PD-1 or cetuximab may be able to overcome anti-PD-1 resistance in participants with advanced solid tumors who express HLA-E.

Study Population:

Participants must be at least 18 years old and have histologic confirmation of a solid tumor that is advanced (metastatic, recurrent, and/or unresectable) with measurable disease per Response Evaluation Criteria in Solid Tumors (RECIST) v1.1 and, in addition, have at least 1 lesion accessible for biopsy. The tumor types to be evaluated in participants are non-small cell lung cancer (NSCLC), renal cell carcinoma (RCC), and squamous cell carcinoma of the head and neck (SCCHN). These indications were chosen based on prevalence of NKG2A and HLA-E expression on immune cells and tumor cells in the tumor microenvironment (internal data at BMS). All participants must have progressed on or after treatment with an anti-PD-(L)1 drug.

Objectives and Endpoints

Objectives	Endpoints
Primary	
• To assess the safety and tolerability, and determine the MTD or MAAD and RP2D of BMS-986315 administered as monotherapy, and in combination with nivolumab or cetuximab, in participants with select advanced solid tumors.	• Incidence of AEs, SAEs, AEs meeting protocol-defined DLT criteria, AEs leading to discontinuation, and death.
Secondary	
• To assess the preliminary anti-tumor activity of BMS-986315 as monotherapy and in combination with nivolumab or cetuximab in participants with select advanced solid tumors.	• ORR, DOR, and PFSR at 6, 9, and 12 months
• To explore the PK of BMS-986315 when administered intravenously as monotherapy and in combination with nivolumab or cetuximab, in participants with select advanced solid tumors.	• Summary measures of PK parameters of BMS-986315 after monotherapy and combination treatments.
• To characterize the immunogenicity of BMS-986315 when administered alone and in combination with nivolumab or cetuximab, in participants with select advanced solid tumors.	• Incidence of anti-drug antibodies to BMS-986315 when BMS-986315 is administered alone and in combination with nivolumab or cetuximab.

Abbreviations: AE = adverse event; DOR = duration of response; DLT = dose-limiting toxicity; MAAD = maximum administered dose; MTD = maximum tolerated dose; ORR = objective response rate; PFSR = progression-free survival rate; PK = pharmacokinetics; RP2D = recommended Phase 2 dose; SAE = serious adverse event

Overall Design:

This is a Phase 1/2, multicenter, open-label study of BMS-986315, administered as a single agent and in combination with nivolumab or cetuximab, in participants with select advanced solid tumors: SCCHN, RCC, and NSCLC. All participants will be evaluated for total HLA-E expression and CD8+ T cell infiltration in fresh tumor samples by immunohistochemistry (IHC). Participants will be classified as "biomarker-negative" or "biomarker-positive" according to the expression of total HLA-E and CD8 in the tumor samples; allocation to specific cohorts may be defined by these biomarkers. [redacted]

The study is composed of 3 parts: Part 1A (dose escalation of BMS-986315 monotherapy), Part 1B (dose escalation of BMS-986315 in combination with nivolumab), and Part 1C (dose escalation of

BMS-986315 in combination with cetuximab). Each Part will have, in addition to the escalation cohorts, additional cohorts focused on studying pharmacodynamics changes associated to study treatments, called pharmacodynamics cohorts or PD cohorts. Additional tumor types and study expansion Parts may be included through a protocol amendment.

Part 1A

The BMS-986315 monotherapy dose escalation (Part 1A) will escalate the dose of BMS-986315 to determine the monotherapy MTD/recommended Phase 2 dose (RP2D). Specifically, Part 1A dose escalation will evaluate different doses of BMS-986315 starting at 80 mg followed by 200 mg, 600 mg, 1200 mg, and 2400 mg (flat doses, initially Q4W). If it appears that a planned dose level is associated with an unacceptable frequency of toxicities, then intermediate dose levels or an alternative administration schedule may be evaluated. After preliminary evaluation of safety and PK data from these intermediate dose or alternative administration schedules, resuming enrollment at a previously evaluated higher dose level may be initiated. Part 1A will evaluate the safety and tolerability of BMS-986315 monotherapy based on dose-limiting toxicities (DLTs), using time-to-event Bayesian optimal interval (TITE-BOIN) design to guide escalation decisions (see Appendix 8 for details), and the overall assessment of available safety, PK, and pharmacodynamic data. One additional cohort of participants, the BMS-986315 monotherapy PD cohort, will be enrolled at a dose level previously cleared for safety. The PD cohort will be implemented in order to gather additional information on pharmacodynamic activity (such as tumor cytolytic activity), safety, tolerability, preliminary efficacy, and PK in a single indication, initially SCCHN participants treated with BMS-986315 monotherapy.

Part 1B

The dose escalation of BMS-986315 in combination with nivolumab (Part 1B) will evaluate the safety and tolerability of escalating doses of BMS-986315 in combination with nivolumab, to determine the combination MTD/RP2D. Treatment in Part 1B will be initiated in a staggered manner relative to the BMS-986315 Monotherapy Escalation (Part 1A). Specifically, Part 1B can be initiated upon the decision to escalate when at least 2 dose levels (the current and 1 higher) in Part 1A have been cleared for safety in accordance with dose escalation rules, after which dose escalation in Part 1A and Part 1B will proceed in parallel separated by 2 dose levels, as stated above. At no point will the dose of BMS-986315 administered in combination with nivolumab in Part 1B exceed the highest dose determined to be tolerated in Part 1A. In Part 1B, the dose of BMS-986315 will be escalated, whereas the dose of nivolumab will be fixed at 480 mg Q4W. However, if it appears that a planned dose level is associated with an unacceptable frequency of toxicities then intermediate dose levels, alternative BMS-986315 administration schedules, or lower doses of nivolumab may be evaluated.

The safety and tolerability of the BMS-986315 in combination with nivolumab will be evaluated using TITE-BOIN design, used to guide dose escalation decisions.

Additional cohorts of participants may be enrolled within up to 2 dose levels previously cleared for safety in monotherapy. These potential combination cohorts would be implemented in order to gather additional information on pharmacodynamic activity, safety, tolerability, preliminary

efficacy and PK in a single indication, initially SCCHN participants treated with BMS-986315 in combination with nivolumab.

Part 1C

The dose escalation of BMS-986315 in combination with cetuximab (Part 1C) will evaluate the safety and tolerability of escalating doses of BMS-986315 in combination with cetuximab, to determine the combination MTD/RP2D in SCCHN participants. Treatment in Part 1C will be initiated in a staggered manner relative to the BMS-986315 Monotherapy Escalation (Part 1A). Specifically, Part 1C can be initiated upon the decision to escalate when at least 2 BMS-986315 dose levels (the current and 1 higher) in Part 1A, have been cleared for safety in accordance with dose escalation rules, after which, dose escalation in Part 1A and Part 1C will proceed in parallel separated by 2 dose levels as indicated above. At no point will the dose of BMS-986315 administered in combination with cetuximab in Part 1C exceed the highest dose determined to be tolerated in Part 1A. In Part 1C, the dose of BMS-986315 will be escalated, whereas the dose of cetuximab will be fixed at 500mg/m^2 Q2W. However, if it appears that a planned dose level is associated with an unacceptable frequency of toxicities, then intermediate dose levels, alternative BMS-986315 administration schedules, or de-escalating doses of cetuximab may be evaluated. Specifically, if toxicity attributable solely to cetuximab is found to be in excess as compared to the known toxicity profile of the label dose of 400mg/m^2 followed by 250mg/m2 QW, then a decision may be made to change the cetuximab dosing regimen for all of Part 1C.

The safety and tolerability of BMS-986315 in combination with cetuximab will be evaluated using TITE-BOIN design also used to guide escalation decisions. Additional cohorts of participants will be enrolled in up to 2 dose levels previously cleared for safety. The BMS-986315 in combination with cetuximab PD cohorts, will be implemented in order to gather additional information on pharmacodynamic activity, safety, tolerability, preliminary efficacy and PK in SCCHN participants treated with BMS-986315 in combination with cetuximab.

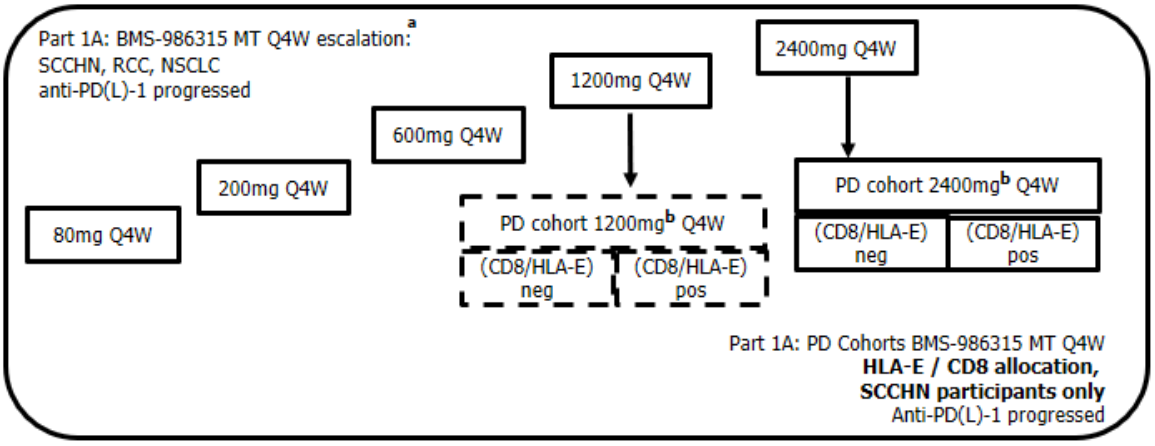
Pharmacodynamic Cohorts:

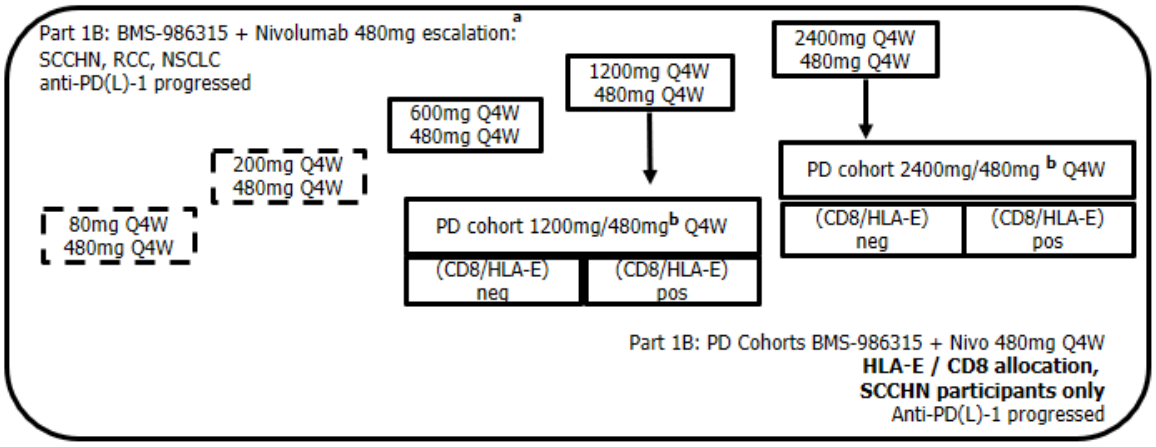
PD cohorts are included in Part 1A (one cohort) and Parts 1B and 1C (up to 2 cohorts) at different dose levels. Each of these PD cohorts will only be open once the dose level has been demonstrated to be tolerated. The objective of the PD cohorts is to obtain pharmacodynamic information, and additional data on safety, tolerability, preliminary efficacy, and PK, in participants with SCCHN. The goal of each PD cohort is to obtain approximately 10 paired biopsy samples of participants who are considered as “biomarker negative” and 20 paired biopsy samples of participants who are considered as “biomarker positive” which is consistent with the expected natural prevalence of these biomarkers in SCCHN. Therefore, up to approximately 40 participants are expected to be treated in each PD cohort in order to have 30 evaluable participants (with paired biopsies). A fresh screening tumor biopsy will be assessed for CD8 and total HLA-E using CLIA validated IHC assays. [redacted] Only those

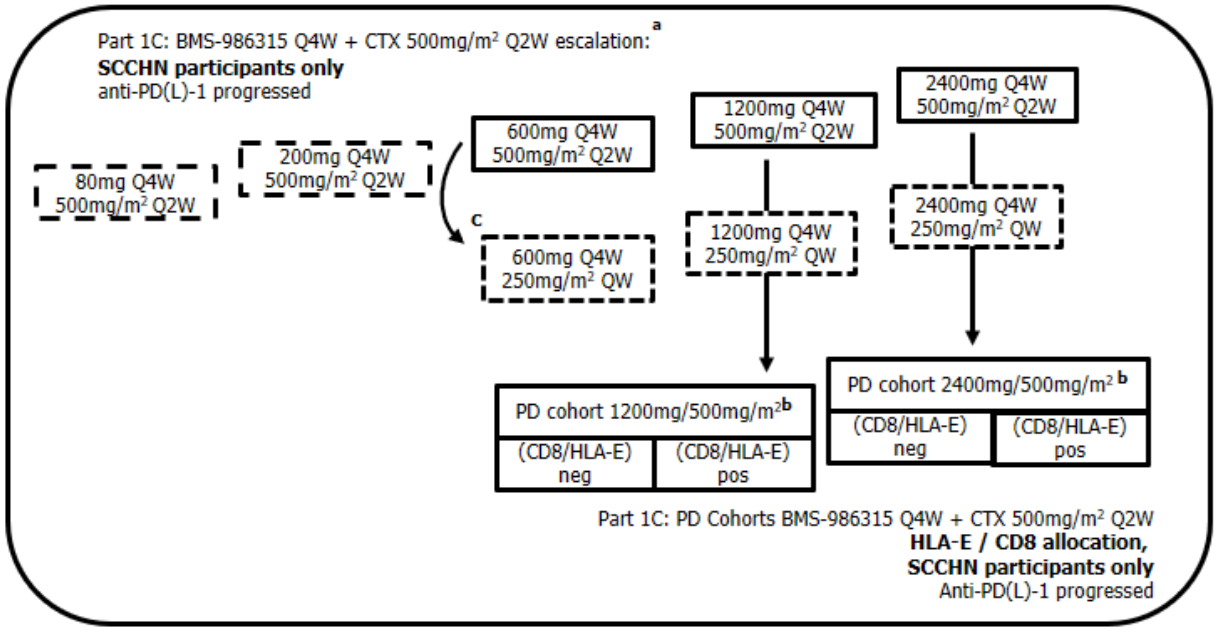
participants who have met tissue quality thresholds and have evaluable CD8 and HLA-E can be assigned for treatment in PD cohorts. All PD cohorts will enroll participants with SCCHN. Participants treated in the PD cohorts will be administered IV doses of BMS-986315 according to the dose defined for the PD cohort (e.g., 1200 mg or 2400 mg) Q4W once per cycle, for up to 26 cycles (104 weeks) of study therapy, unless criteria for study drug discontinuation are met earlier (see Section 8.1). In Part 1B, BMS-986315 will be combined with nivolumab 480mg Q4W. In Part 1C, BMS-986315 will be combined with cetuximab 500 mg/m^2 Q2W.

The study consists of 4 periods: Screening, Treatment, Safety Follow-up, and Survival Follow-up (up to 2 years following the EOT of study drug). The duration of the study will be approximately 4 years. The study design schematic and participant flow schematic are presented in Figure 1 and Figure 2 below.

Figure 1: Study Design Schematic







Abbreviations: CTX = cetuximab; neg = negative; pos = positive; NSCLC = non-small cell lung cancer; MT = monotherapy; PD L1 = Programmed death-ligand 1; PD = pharmacodynamic cohort; Q2W = every 2 weeks, Q4W = every 4 weeks

[a] Further expansion may be included as part of a protocol amendment

[b] Dose levels will be selected based on preliminary data from dose escalation

[c] The cetuximab dose may be changed to the approved dose for the entire program if excessive toxicity is observed, upon agreement between investigators and the Sponsor.

Figure 2: Study Period and Participant Flow Diagram

Abbreviation: Q4W: every 4 weeks; EOT: end of treatment

[a] Alternative dosing schedule may be used

[b] See Figure 1 for BMS-986315, nivolumab, and cetuximab dosing schedules

Number of Participants:

The approximate total number of participants treated will be up to 308 for Part 1 of Study CA047004, as shown below:

- Part 1A Monotherapy: (BMS-986315): The total sample size is up to approximately 76 participants including 36 participants for the dose escalation phase and up to approximately 40 participants in 1 PD cohort.

- Part 1B Combination Therapy: (BMS-986315 in combination with nivolumab): The total sample size is up to approximately 116 participants including 36 participants for the dose escalation phase and up to approximately 40 participants in each of the 2 PD cohorts.
- Part 1C Combination Therapy: (BMS-986315 in combination with cetuximab): The total sample size is up to approximately 116 participants including 36 participants for the dose escalation phase and up to approximately 40 participants in each of the 2 PD cohorts.

Treatment Arms and Duration:

Study treatment:

Study Drug for CA047004		
Medication	**Potency**	**IP/Non-IP**
BMS-986315	120 mg/mL	IP
Nivolumab	10 mg/mL	IP
Cetuximab	100 mg/50mL, 200 mg/100 mL, & various strengths	IP

Abbreviations: IP: Investigational Product

Data Monitoring Committee:

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). This collaborative process constitutes the safety monitoring plan for the 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. Because this is an open-label study, WWPS, the BMS medical monitor (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 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) and WWPS single case review physician, the study Medical Monitor (MM), the study biostatistician, and epidemiologist; 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 risk-benefit balance associated with the use of study treatment(s).

Central Image Collection

Images will be submitted to a central imaging vendor and may undergo blinded independent central review (BICR) at any time during the study. Prior to scanning, first participant sites should be qualified and understand the image acquisition guidelines and submission process as outlined in the CA047004 Imaging Manual provided by the central imaging vendor.

2 SCHEDULE OF ACTIVITIES

Study assessments and procedures are presented in Table 2-1 (Screening Procedural Outline), Table 2-2 (On-treatment Procedural Outline), and Table 2-3 (Follow-up Procedural Outline).

Table 2-1: Screening Procedural Outline (CA047004)

Procedure	Screening Visit (Days -35 to -1)	Notes
Eligibility Assessments		
Informed Consent	X	ICF prior to screening for study participation. If a participant is re-enrolled, the participant must be re-consented. Must be obtained prior to any study-related procedures. Consent for pretreatment and on treatment tumor biopsy samples are required for enrollment.
Collection of Fresh Biopsy/ Tumor Tissue Analysis	X	A fresh biopsy from a single, appropriately assessable lesion, is required for all participants to determine sufficient tumor content and CD8+ T-cell infiltration status by IHC analysis and HLA-E status by IHC analysis. For PD cohorts, in order to be treated the participant must have sufficient tumor tissue, an evaluable CD8 status, and an evaluable HLA-E status. Participants must have a lesion that can be biopsied at an acceptable clinical risk as judged by the investigator in order to be eligible for the study. (see Section 9.8)
IRT Participant Assignment	X	After the participants meet all eligibility criteria, sites will use IRT for participant number assignment. Subsequent visits will be registered into the IRT system for drug supply (see Section 7)
Inclusion/Exclusion Criteria	X	Must be confirmed prior to first dose. See Section 6 (Study Population).
Medical History	X	All medical history relevant to the disease under study, including tobacco history. Include any toxicities or allergy related to previous treatments.
Prior Cancer Therapies	X	
ECOG Performance Status Performance Status (PS)	X	See Appendix 6
Safety Assessments		
PE	X	If the screening PE is performed within 72 hours prior to dosing on Day 1, then a single examination may count as both the screening and predose evaluation.
Physical Measurements	X	Height and weight

Table 2-1: Screening Procedural Outline (CA047004)

Procedure	Screening Visit (Days -35 to -1)	Notes
Vital Signs	X	Includes body temperature, respiratory rate, and seated/supine blood pressure and heart rate. Blood pressure and heart rate should be measured after the participant has been resting quietly for at least 5 minutes.
Concomitant Medication Use	X	Must be collected within 14 days prior to first dose. Vaccine use must be collected within 30 days prior to first dose (See exclusion Criteria Section 6.2).
Oxygen Saturation	X	Pulse oximetry collected at rest.
MUGA/Echocardiogram (ECHO)	X	MUGA or echocardiogram done at screening to document LVEF.
ECG	X	ECGs should be recorded after the participant has been supine for at least 5 minutes and prior to blood draws. Screening ECG is to be collected as a single reading (see Section 9.4.3)
Laboratory Tests	X	See Section 9.4.4 for list of laboratory tests to conduct.
Urinalysis	X	Microscopic urine reflex only for urinalysis positive for blood/protein/leukocytes.
Serology	X	See Section 9.4.4
Pregnancy Test	X	For WOCBP only. WOCBP must have a negative pregnancy test within 24 hours prior to the start of study therapy and results also must be evaluated prior to study therapy administration. 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. Urine pregnancy test: minimum sensitivity 25 IU/L or equivalent units of hCG.
FSH	X	Women only, as needed to document postmenopausal status.
Tumor Assessments		
Body Imaging	X	Contrast enhanced CT of the chest, CT/MRI of the neck (required only for SCCHN participants), abdomen, pelvis, and all other known and/or suspected sites of disease, within 28 days prior to first dose. See Section 9.1 for further details.

Table 2-1: Screening Procedural Outline (CA047004)

Procedure	Screening Visit (Days -35 to -1)	Notes
Brain Imaging	X	MRI of the brain without and with contrast is required for participants with known or suspected brain metastases, unless participant has completed an imaging study of the brain within 28 days of study drug administration. CT of the brain without and with contrast can be performed if MRI is contraindicated. See Section 9.1 for further details.
Blood, Serum, and Plasma Pharmacodynamic Sampling	X	See Section 9.8 (Table 9.8-1).
Adverse Event Reporting		
Assessment of Signs, Symptoms and Clinical Complaints	X	Must be performed within 14 days prior to first dose.
Monitor for SAEs	X	All SAEs must be collected from the date of participant's written consent until 100 days after last dose of study treatment.

Abbreviations: CT = computed tomography; ECG = electrocardiogram; ECHO = echocardiogram; ECOG = Eastern Cooperative Oncology Group; FSH = follicle stimulating hormone; HCG = human chorionic gonadotropin; ICF = informed consent form; IHC = immunohistochemistry; IRT = interactive response technology; IU = international unit; L = liter; LVEF = left ventricle ejection fraction; MRI = magnetic resonance imaging; MUGA = multigated acquisition; PE = physical examination; PS = performance status; SAE = serious adverse event; SCCHN = squamous cell carcinoma of the head and neck; WOCBP = women of childbearing potential

Table 2-2: On Treatment Procedural Outline (CA047004)

Procedure[a]	Cycle 1 (28 days)				Cycle 2 (28 days)				Cycle 3 and Beyond (28 days)				EOT[b]	Notes
	D1	D8[c]	D15[c]	D22[c]	D1[c]	D8[c]	D15[c]	D22[c]	D1[c]	D8[c]	D15[c]	D22[c]		
Safety Assessments														
Physical Examination	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 serious adverse event CRF page.
Symptom Directed Physical Examination			X				X				X[g]			
Weight[h]	X				X				X				X	
Vital Signs[d]	X		X		X		X		X		X[g]		X	
Oxygen Saturation[d]	X		X		X		X		X		X[g]		X	
ECOG Performance Status	X				X				X				X	See Appendix 6
Concomitant Medication Use	X													Record at each visit
ECG	X				X				X				X	All ECGs should be recorded after the participant has been supine for at least 5 minutes and prior to blood draws. Safety ECGS are to be collected pre-dose on Day 1 of every cycle. ECGs to be performed in triplicate (Part 1A only) in association with PK sampling at pre-dose, EOI, and 4:00 hours on Day 1 of C1 and C4. (see Table 9.5-3). Single safety ECGs to be performed for all other time points.

Table 2-2: On Treatment Procedural Outline (CA047004)

Procedure[a]	Cycle 1 (28 days)				Cycle 2 (28 days)				Cycle 3 and Beyond (28 days)				EOT[b]	Notes
	D1	D8[c]	D15[c]	D22[c]	D1[c]	D8[c]	D15[c]	D22[c]	D1[c]	D8[c]	D15[c]	D22[c]		
Laboratory Tests	X		X		X		X		X				X	There will be a 72-hour window for collection of laboratory tests prior to dosing on C1D1. If screening laboratory tests are within 72 hours prior to C1D1, laboratory tests performed at screening can be used for C1D1. CBC with differential and serum chemistry panel are required to be completed Q2W for all participants during the first 2 study cycles, and Q4W after Cycle 3. See Section 9.4 and Table 9.4.4-1.
Electrolyte Monitoring (Sodium, Potassium, Chloride, Calcium, Phosphorus and Magnesium.)	X	X	X	X	X	X	X	X	X	X	X	X	X	For Part 1C only. Weekly assessments must continue for 8 weeks post last Cetuximab administration. See Follow up Table 2-3
Thyroid Function Test (TSH)	X				X				X				X	
Urinalysis	X				X				X				X	

Table 2-2: On Treatment Procedural Outline (CA047004)

Procedure[a]	Cycle 1 (28 days)				Cycle 2 (28 days)				Cycle 3 and Beyond (28 days)				EOT[b]	Notes
	D1	D8[c]	D15[c]	D22[c]	D1[c]	D8[c]	D15[c]	D22[c]	D1[c]	D8[c]	D15[c]	D22[c]		
Pregnancy Test	X				X				X				X	For WOCBP only. WOCBP must have a negative pregnancy test within 24 hours prior to the start of study therapy. If the screening pregnancy test is taken within 24 hours before dosing (C1D1), a further pregnancy test is not required. Urine pregnancy test: minimum sensitivity 25 IU/L or equivalent units of hCG. 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.
MUGA/ECHO	See notes													If clinically indicated.

Table 2-2: On Treatment Procedural Outline (CA047004)

Procedure[a]	Cycle 1 (28 days)				Cycle 2 (28 days)				Cycle 3 and Beyond (28 days)				EOT[b]	Notes
	D1	D8[c]	D15[c]	D22[c]	D1[c]	D8[c]	D15[c]	D22[c]	D1[c]	D8[c]	D15[c]	D22[c]		
Adverse Event Reporting														
Monitor for Adverse Events (AEs)	X													Nonserious AEs will be collected starting with the first dose of study drug and through 100 days after last dose of study treatment. All AEs (SAEs or nonserious AEs) including those associated with SARS-CoV-2 infection must be collected continuously during the treatment period.
Monitor for Serious Adverse Events (SAEs)	X													All SAEs must be collected from the date of participant's written consent until 100 days after last dose of study treatment. SAEs should be approved in the BMS EDC tool within 5 business days of entry. All AEs (SAEs or nonserious AEs) including those associated with SARS-CoV-2 infection must be collected continuously during the treatment period.
Pharmacokinetic (PK) Assessments														
Serial Blood Sampling	See Section 9.5, Table 9.5-3, Table 9.5-4, and Table 9.5-5 for the PK sampling schedule													
Immunogenicity (IMG) Assessments	See Section 9.5, Table 9.5-3, Table 9.5-4, and Table 9.5-5 for the Immunogenicity sampling schedule													

Table 2-2: On Treatment Procedural Outline (CA047004)

Procedure[a]	Cycle 1 (28 days)				Cycle 2 (28 days)				Cycle 3 and Beyond (28 days)				EOT[b]	Notes
	D1	D8[c]	D15[c]	D22[c]	D1[c]	D8[c]	D15[c]	D22[c]	D1[c]	D8[c]	D15[c]	D22[c]		
Biomarker Assessments														
Tumor Biopsy[e]	See Section 9.8 and Table 9.8-1													On treatment biopsy should be performed on C1D22 (plus or minus 5 days)
Blood, Serum, and Plasma Pharmacodynamic Sampling, and SARS-CoV-2 Serology	See Section 9.8 and Table 9.8-1													SARS-CoV-2 serum will be collected predose at C1D1 and collected approximately every 6 months during study treatment to be used for potential future measurements of anti-SARS-CoV-2 serology (anti-SARS-CoV-2 total or IgG). SARS-CoV-2 serum should also be collected approximately 4 weeks after a documented or suspected anti-SARS-CoV-2 infection.
Imaging Assessments[f]														
Body Imaging	See Notes													Contrast enhanced CT of the chest, CT/MRI of the neck (required for SCCHN participants), abdomen, pelvis, and all other known and/or suspected sites of disease will occur every 8 weeks starting 8 weeks from date of first dose (± 7 days) until disease progression and treatment discontinuation, whichever occurs

Table 2-2: On Treatment Procedural Outline (CA047004)

Procedure[a]	Cycle 1 (28 days)				Cycle 2 (28 days)				Cycle 3 and Beyond (28 days)				EOT[b]	Notes
	D1	D8[c]	D15[c]	D22[c]	D1[c]	D8[c]	D15[c]	D22[c]	D1[c]	D8[c]	D15[c]	D22[c]		
														later. See Section 9.1.1.1 for further details.
Brain Imaging	See Notes													Participants with a history of brain metastasis or symptoms should have a surveillance MRI study per standard of care (approximately every 12 weeks), or sooner if clinically indicated. CT of the brain without and with contrast can be performed if MRI is contraindicated. See Section 9.1.1.1 for further details
Study Treatment														
BMS-986315 Administration (Part 1A, 1B and Part 1C)	X				X				X					If a dose is delayed, the procedures scheduled for that same timepoint should also be delayed to coincide with when that timepoint's dosing actually occurs.
Nivolumab Administration (Part 1B only)	X				X				X					
Cetuximab Administration (Part 1C only)	X		X		X		X		X		X			

Abbreviations: AE = adverse event; BSA = body surface area; C = cycle; CBC = complete blood count; CRF = case report form; CT = computed tomography; D = day; ECG = electrocardiogram; ECHO = echocardiogram; ECOG = Eastern Cooperative Oncology Group; EDC = electronic data capture; EOI = end of infusion; EOT = end of treatment; ; hCG = human chorionic gonadotropin; IMG = immunogenicity; ; MRI = magnetic resonance imaging; MUGA = multigated acquisition scan; PK = pharmacokinetic; Q2W = administered every 2 weeks; Q4W = administered every 4 weeks; SAE = serious adverse event; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2; SCCHN = squamous cell carcinoma of the head and neck; TSH = thyroid stimulating hormone; WOCBP = women of childbearing potential

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

[b] EOT is defined as the visit where the decision is made to discontinue the participant from treatment. 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 and 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 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 as the start of the safety follow-up period.

[c] A ± 2 day window is allowed.

[d] Study Part 1A (dose escalation cohort): At C1D1 only, vital signs will be obtained before the infusion,every 15 minutes (± 5 minutes) until the 2 hours post infusion completion, and then every 30 minutes from the 2 hours post infusion completion to the 4 hours post infusion timepoint.Vital signs will be obtained before the infusion and then every 15 minutes (± 5 minutes) until 60 minutes post infusion completion on C2D1. Oxygen saturation also to be performed in conjunction with vital signs monitoring on these days.

Study Part 1A (pharmcodynamic cohorts), 1B, and 1C: Vital signs will be obtained before the infusion and then every 15 minutes (± 5 minutes) until 60 minutes post infusion completion for first 2 doses of study treatment on C1D1 and C2D1. Oxygen saturation also to be performed in conjunction with vital signs monitoring on these days

All Study Parts: For all subsequent cycles beginning with Cycle 3, vital signs and oxygen saturation are to be taken before the infusion and at the end of infusion. If any vital sign is abnormal (based upon medical assessment) at the final check or if the participant has had an infusion reaction during dosing (based upon clinician assessment), the participant must be observed further for a period of time, as clinically indicated. Vitals taken may be taken more frequently than specified during dosing based on medical judgment.

[e] Tumor biopsy to be performed at C1D22 ± 5 days. Tumor specimens must be collected within 5 days to the time point and must be obtained prior to C2D1 of study treatments. End of treatment/Upon progression biopsy is optional, but strongly encouraged at time of disease progression. Bone lesion biopsies are unacceptable for submission. See Section 9.8.

[f] The same imaging modality is to be used for all assessments, per RECIST v1.1 (Appendix 7). Tumor assessment to be performed prior to initiating next cycle of treatment.

[g] Participants in study Part 1C are required to have symptom directed PE, vital signs and oxygen saturation collected on Day 15 of Cycle 3 and Day 15 of all subsequent study cycles.

[h] For participants in Part 1C, weight collected on Day 1 of each cycle should be used for body surface area (BSA) calculation for cetuximab dosing.

Table 2-3: Follow-Up Procedural Outline (CA047-004)

Procedure[b]	Safety Follow-up[a]			Survival Follow-up[c]	Notes
	Follow-up 1 30 Days (± 7 Days)	Follow-up 2 60 Days (± 7 Days)	Follow-up 3 100 Days (± 7 Days)		
Safety Assessments					
Targeted PE, Measurements, Vital Signs, and ECOG PS	X	X	X		Weight, BP, HR, temperature and ECOG PS
Monitor for AEs	Continuously				Record at each visit. Collect all AEs continuously from time of first dose and throughout the treatment period and for a minimum of 100 days following last dose of study treatment. Participants will be followed for all SAEs, and all AEs (SAEs and non-serious AEs) associated with confirmed or suspected SARS-CoV-2 infection until resolution, the condition stabilizes, the event is otherwise explained, the event is deemed irreversible, the participant is lost to follow-up (as defined in Section 8.3), or for suspected cases, until SARS-CoV-2 infection is ruled-out.
Monitor for SAEs	Continuously				Record at each visit. Collect all SAEs continuously throughout the treatment period and for a minimum of 100 days following last dose of study treatment. Participants will be followed for all SAEs and all AEs (SAEs and non-serious AEs) associated with confirmed or suspected SARS-CoV-2 infection until resolution, the condition stabilizes, the event is otherwise explained, the event is deemed irreversible, the participant is lost to follow-up (as defined in Section 8.3) or for suspected cases, until SARS-CoV-2 infection is ruled-out.
Concomitant Medication Assessment	Continuously				Record at each visit
Subsequent Cancer Treatment	X	X	X	X	

Table 2-3: Follow-Up Procedural Outline (CA047-004)

Procedure[b]	Safety Follow-up[a]			Survival Follow-up[c]	Notes
	Follow-up 1 30 Days (± 7 Days)	Follow-up 2 60 Days (± 7 Days)	Follow-up 3 100 Days (± 7 Days)		
Laboratory Tests	X	X	X		CBC with differential and serum chemistry panel. See Section 9.4.4 and Table 9.4.4-1 (Clinical Safety Laboratory Assessments).
Electrolyte Monitoring (Sodium, Potassium, Chloride, Calcium, Phosphorus and Magnesium)	X	X			For Part 1C only. Assessments must be weekly for 8 weeks post last cetuximab administration. ± 7 day window does NOT apply. A ± 1 day window DOES apply.
Urinalysis	X	X	X		
Pregnancy Test (WOCBP only)	X	X	X		
Efficacy Assessments					
Body Imaging	Participants with SD/PR/CR will have imaging assessments completed every 12 weeks (± 7 days) from the date of EOT. Contrast enhanced CT of the chest, CT/MRI of the neck (required for SCCHN participants), abdomen, pelvis, and all other known and/or suspected sites of disease should be completed. See Section 9.1.1.1 for further details.				
Brain Imaging	Participants with a history of brain metastasis or symptoms should have surveillance MRIs per standard of care (approximately every 12 weeks) or sooner if clinically indicated. CT of the brain without and with contrast can be performed if MRI is contraindicated. See Section 9.1.1.1 for further details.				

Table 2-3: Follow-Up Procedural Outline (CA047-004)

Procedure[b]	Safety Follow-up[a]			Survival Follow-up[c]	Notes
	Follow-up 1 30 Days (± 7 Days)	Follow-up 2 60 Days (± 7 Days)	Follow-up 3 100 Days (± 7 Days)		
Assessment of Participant Survival Status	X	X	X	X	During safety follow-up and every 3 months (clinic visit or by telephone) during survival phase. Include documentation of subsequent chemotherapy.
PK and IMG Assessments	See Section 9.5 for the immunogenicity sampling schedule.				
SARS-CoV-2 Serology	X				Serum collection to be used for potential future measurements of anti-SARS serology (anti-SARS-CoV2 total or IgG). See Table 9.8-1.

Abbreviations: AE = adverse event; BP = blood pressure; CBC = complete blood count; CR = complete response; CT = computed tomography; ECOG PS = Eastern Cooperative Oncology Group Performance Status; eCRF = electronic case report form; HR = heart rate; IgG = immunoglobulin G; IMG = immunogenicity; MRI = magnetic resonance imaging; PE = physical examination; PK = pharmacokinetic; PR = partial response; SAE = serious adverse event; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2; SCCHN = squamous cell carcinoma of the head and neck; SD = stable disease; WOCBP = women of childbearing potential

[a] Participants must be followed for at least 100 days after last dose of study treatment. Follow-up visits at Days 30 (± 7 days), 60 (± 7 days), and 100 (± 7 days) should occur relative to the last dose of study treatment or date of discontinuation, whichever is later. Follow-up visits should be conducted in person.

[b] 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.

[c] Survival Follow-up visits to occur every 3 months (± 14 days) from Follow-up Visit #3. Survival visit may be conducted in person 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.

Note: In the event multiple procedures are required at a single time point, the ECG may be obtained up to 15 minutes earlier, vital signs may be obtained up to 10 minutes earlier or later, and clinical laboratory sample may be obtained up to 5 minutes earlier than the nominal time point, ensuring the PK samples can be collected on time.

3 INTRODUCTION

NKG2A is an inhibitory receptor that is expressed on NK and T cells and contributes to tumor resistance to immune cells, mediated by expression of its ligand HLA-E in tumor cells. BMS-986315 is an antagonistic antibody to NKG2A and its use as monotherapy or in combination with nivolumab or cetuximab will be explored in the CA047004 study, a Phase 1/2, first-in-human (FIH), ascending multiple-dose study, in participants with select advanced/metastatic solid tumors including non-small cell lung cancer (NSCLC), renal cell carcinoma (RCC) and squamous cell carcinoma of the head and neck (SCCHN). This study will evaluate the safety profile, tolerability, pharmacokinetics (PK), pharmacodynamics (PD) of intravenous (IV) doses of BMS-986315 administered every 4 weeks (Q4W) as monotherapy and in combination with nivolumab or cetuximab in participants with advanced solid tumors and is expected to determine the maximum tolerated dose (MTD)/maximum administered dose (MAAD) or an alternate dose(s) of BMS-986315 to be used in future expansions or trials.

3.1 Study Rationale

Patients with metastatic or refractory solid tumors have a very poor prognosis.[1]

Despite advances in multimodal therapy, increases in overall survival (OS) in this patient population have been limited. The unmet need resides in the lack of effective treatments to deliver long-term survival, hence the need to test compounds that have novel mechanisms of action in clinical studies.

Immuno-oncology (I-O) cancer drugs are able to alter the unfavorable balance between positive (co-stimulatory) and negative (co-inhibitory) T-cell surface molecules exploited by the tumors to escape immune surveillance.[2]

The most extensively studied immune-modulating molecules are agents blocking checkpoint molecules, such as programmed cell death 1 [PD-1] and cytotoxic T lymphocyte–associated antigen 4 [CTLA-4]). Inhibition of these negative regulatory receptors, referred to as immune checkpoint blockade, results in the enhanced activation of T-cell responses and potent antitumor activity in preclinical models. Trials with CTLA-4 blockade provided the first clinical evidence of improvement in OS with immune modulatory anticancer therapy in patients with metastatic melanoma.[3,4] Shortly after that, objective responses were obtained for NSCLC, melanoma, and RCC with anti-PD-1 antibody therapy.[5] Moreover, metastatic melanoma patients treated with the combination of ipilimumab and an anti-PD-1 antibody (nivolumab) achieved an unprecedented 53% response rate and prolonged responses,[6] which demonstrated the potential of combination therapy. The benefit of combination therapy was also demonstrated in RCC.[7]

CD94/NKG2 is a family of C-type lectin receptors that may stimulate or inhibit cytotoxic activity of NK cells through recognition of nonclassical MHC glycoproteins class I (HLA-E in humans and Qa-1 molecules in the mouse).[8] CD94/NKG2 family includes seven members: NKG2A, B, C, D, E, F and H. NKG2A, an inhibitory receptor, and NKG2C, an activating receptor, exist as heterodimers, commonly linked with CD94 NKG2A signals through 2 ITIM domains that recruit SHP-1 and SHP-2, leading to dephosphorylation of tyrosine kinases substrates which results in

inhibition of NK and T cell responses.[9] NKG2A is expressed on effector/memory CD8+, NK, NKT and γδT cells. HLA-E is physiologically expressed in most human tissues at low levels;[10] however, tumor cells upregulate HLA-E expression with IFN-γ level increase during immune responses.[11] HLA-E expression has been correlated to poor immune response or worse prognosis in several tumor types.[12,13,14] In parallel, NKG2A expression is higher in NK cells found in breast cancer and NSCLC as compared to normal tissue.[15,16] As for T cells, NKG2A expression has been correlated with worse survival in patients with colorectal cancer.[17] $NKG2A^{null}$ NK cells had higher cytotoxicity against HLA-E expressing tumor cells compared to $NKG2A^{+}$ cells, highlighting the inhibitory capacity of NKG2A.[18] Furthermore, in vitro studies show that both T and NK cells are necessary for tumor growth control in Qa-1 knockout cells,[8] suggesting that blockade of the NKG2A-HLA-E axis might help to restore both T and NK cell activity.

Cetuximab is an anti-epidermal growth factor receptor (EGFR) monoclonal antibody that is approved for the treatment of locally or regionally advanced SCCHN in combination with radiation therapy, and recurrent or metastatic SCCHN in combination with or progressing after platinum-based therapy. Cetuximab can mediate antibody-dependent cellular cytotoxicity (ADCC) in in vitro studies,[8,19] and therefore a combination with BMS-986315 could further increase NK cell activity.

Thus, an antagonistic antibody such as BMS-986315 that blocks HLA-E mediated inhibitory NKG2A signal could have a unique advantage of restoring both T and NK cell responses. Moreover, based on recent emerging clinical evidence of improved responses with combination therapies, the combination of BMS-986315 with nivolumab or cetuximab may be able to overcome anti-PD-1 resistance in participants with advanced solid tumors that express HLA-E.

3.1.1 Research Hypothesis

It is anticipated that BMS-986315 as monotherapy, and in combination with nivolumab or cetuximab, will demonstrate adequate safety and tolerability at pharmacologically relevant doses in participants with solid tumors with resistance to prior anti-PD-1 therapy, so as to permit further clinical development. Furthermore, it is anticipated that expression of CD8 (surrogate marker for NKG2A) and HLA-E, will enrich for pharmacodynamic activity and clinical response related to anti-NKG2A combined with anti-PD-1 or cetuximab.

3.2 Background

A detailed description of the chemistry, pharmacology, efficacy, and safety of BMS-986315 is provided in the BMS-986315 Investigator's Brochure (IB) and information for nivolumab is provided in the nivolumab IB.[20,21] For prescribing information and administration instructions on cetuximab, please refer to the current label and package insert that is applicable for your geographic region.[22]

3.2.1 BMS-986315

3.2.1.1 BMS-986315 Nonclinical Pharmacology

BMS-986315 binds to human NKG2A with EC50 value of 0.36 nM and with a Kd of 0.42 nM by Scatchard analysis. BMS-986315 blocks human and cynomolgus NKG2A and HLA-E interaction (IC50 0.33 nM), but does not block interaction between HLA-E and activating receptor NKG2C. This suggests that anti-NKG2A antibody will block NKG2A mediated inhibitory signaling without affecting potential positive signaling induced by NKG2C and HLA-E interaction.

BMS-986315 enhances NK and CD8+ T cell effector function (e.g. cytotoxicity and cytokine production) in functional assays using primary NK and CD8+ T cells isolated from healthy human peripheral blood mononuclear cell (PBMC) and human tumors. Furthermore, co-blockade of NKG2A: HLA-E and PD-1:PD-L1 further increases tumor-infiltrating CD8+ T cell functional activity. BMS-986315 does not induce cytokine release over background level in whole blood from human donors.

BMS-986315 was developed with an inert Fc (IgG1.3) to prevent FcγR binding. Since NKG2A is an inhibitory receptor expressed on CD8+ T and NK cells, avoiding agonism or depletion of NKG2A expressing CD8+ T or NK cells is necessary. Thus, blockade of NKG2A:HLA E interaction must be accomplished with an antibody unable to interact with human FcγRs.

BMS-986315 binds to human NKG2A, with a Kd of 0.42 nM and cynomolgus NKG2A with a Kd of 0.99 nM, but not to mouse NKG2A. Thus, to evaluate the effect of NKG2A blockade in mouse tumor models, an anti-mNKG2A monoclonal antibody (mAb) equipotent to BMS-986315 was generated. Treatment with anti-mNKG2A mAb as a single agent, given every 3 or 4 days for 5 doses via the intraperitoneal (IP) route, led to reduced tumor growth in several syngeneic mouse tumor models. Importantly, near maximum antitumor efficacy was observed in the CT26 and 1956 tumor models when the systemic drug concentrations prior to the next dose (or at trough) were greater than 18 nM, with the corresponding tumor NKG2A receptor occupancy (RO) estimated to be 92%-96%. Antitumor activity of anti NKG2A mAb was further enhanced when it was combined with other checkpoint inhibitors: anti PD-1, anti CTLA-4 or anti-LAG3. In anti-mNKG2A and anti-PD 1 combination studies specifically, complete tumor growth inhibition (TGI) was observed in the anti-mNKG2A+anti-PD-1 group (both anti-mNKG2A and anti-PD-1 dosed at 10 mg/kg IP every 3-4 days) compared to the isotype control group and was associated with an increase in NK and tumor specific CD8+ T cell cytotoxicity and IFNγ levels.

Enhanced tumor growth inhibition was also observed when anti-mNKG2A antibody was combined with anti-mCTLA4 in the 1956 syngeneic mouse tumor model. Antibodies were administered IP every 3-4 days beginning at Day 6 post implantation for a total of 3 doses. When anti-mNKG2A mAb dosed at 10 mg/kg was combined anti-mCTLA-4 dosed at 0.1 mg/kg, enhanced antitumor activity was observed compared to monotherapy with a mean TGI of 93.1% relative to isotype control.

Combinations of anti-NKG2A with either anti-PD-1 or anti-PD-1 and anti-LAG3 were also tested in the A20 lymphoma model. Antibodies were administered IP every 3 days beginning at Day 4 post implantation for a total of 5 doses. Anti-mNKG2A combined with either anti-PD-1 or

anti-LAG-3 (at 10 mg/kg) extended survival of mice over single agent alone with a survival of 50% and 70%, respectively. The triple combination of anti-mNKG2A/anti-mPD-1/anti-mLAG-3 provided the greatest benefit in this model with a survival of 80% at the end of the study.

Thus, BMS-986315 alone or in combination with anti-PD-1 or other checkpoint inhibitors may reverse the inhibitory pathways among CD8+ T and NK cells, providing therapeutic benefit beyond anti-PD-1 monotherapy. Additional details are provided in the BMS-986315 IB.[20]

3.2.1.2 BMS-986315 Nonclinical Pharmacokinetics

The PK and PD of BMS-986315 were characterized in mice (using the mouse surrogate antibody [anti-mNKG2A]) and cynomolgus monkeys. Additional details are provided in the IB.[20]

Following IV administration of BMS-986315 to monkeys, the total body clearance (CLTp) at doses of 0.5, 10, and 50 mg/kg was 3.1, 2.4, and 2.5 mL/day/kg, respectively. The steady state volume of distribution (Vss) ranged from 53 to 77 mL/kg, with the terminal half-life (T-HALF) of 14-23 days. Furthermore, PK/PD modeling of the NKG2A RO data in monkey whole blood revealed that the BMS-986315 effective concentration required to achieve 50% of the maximum RO (EC50) was 20 ± 5.4 nM, consistent with the in vitro data (31 ± 5.4 nM).

To facilitate the evaluation of PK/PD/efficacy relationships in mouse syngeneic models, the PK of the mouse surrogate antibody was evaluated in C57BL6 mice (used for 1956 tumor model) and BALB/c mice (used for CT26 tumor model). After an IV bolus dose to C57BL6 mice, the CLTp of anti-mNKG2A at doses of 0.3, 1 and 10 mg/kg was 31, 21, and 10 mL/day/kg, respectively, suggesting non-linear PK. The Vss was dose dependent, ranging from 127 to 159 mL/kg. with a corresponding terminal T-half was 4.6, 6.2, and 11 days, respectively. Following subcutaneous (SC) administration of 0.3, 3, and 10 mg/kg to BALB/c mice, the area under the curve (AUC) values of anti-mNKG2A were 2.6- to 4.7-fold higher than those after IV dosing at the same dose (0.3 and 10 mg/kg), which may be due to the difference in mouse strain. Consequently, the SC bioavailability was >100%. Similar to IV administration, anti-mNKG2A demonstrated some degree of non-linear PK after SC dosing.

The tumor-to-serum AUC(0-14d) ratio of the mouse surrogate antibody anti-mNKG2A was 0.09 in the CT26 tumor model, with a concentration-time profile in tumors largely parallel to that in serum. PK/PD modeling of the NKG2A RO data in mouse whole blood and CT26 tumors showed good in vitro-to-in vivo correlation between the serum and tumor RO EC50. Moreover, the in vivo tumor RO EC50 (0.19 ± 0.04 nM) was about 10-fold higher than that (0.02 ± 0.01 nM) in serum.

Based on these results, the extent of the tumor NKG2A RO at trough was estimated based on the systemic drug concentrations obtained from mouse efficacy studies in the mouse 1956 and CT26 tumor models. Near maximum antitumor efficacy was observed when the systemic drug concentrations prior to the next dose (or at trough) were greater than 18 nM, with the corresponding tumor NKG2A RO estimated to be 92%-96%.

Prediction of Human Pharmacokinetic and Efficacious Dose Projection for BMS-986315

Using the PK model established in monkeys, the human PK of BMS-986315 was predicted by assuming that human PK is linear at doses ≥ 0.5 mg/kg and the same as that in monkeys. The predicted human T-HALF is 16 days. If NKG2A expression is high in some patients or the dose is lower than 0.5 mg/kg, the human T-HALF may be shorter than predicted.

The human efficacious dose of BMS-986315 was projected by targeting 95% tumor NKG2A RO at trough. This was based on an integrated analysis of PK/RO/antitumor efficacy data in mouse syngeneic models as described above, where near maximum antitumor efficacy was observed when the tumor NKG2A RO at trough was 92%-96%. Using the predicted human serum PK, the tumor drug levels in humans were predicted using a tumor-to-serum concentration ratio of 0.10 determined in mice. To predict human tumor RO, an in vitro human whole blood RO EC50 of 0.05 ± 0.01 nM was scaled by 10-fold, based on the findings from the mouse CT26 model, to obtain the tumor RO EC50 of 0.5 nM. Together with the predicted human tumor drug levels and tumor RO EC50, the human efficacious IV dose, given every 4 weeks, is projected to be 2.5 mg/kg. (200 mg for an 80-kg subject). At this dose, the maximum plasma concentration and AUC0-tau at steady state is predicted to be 665 nM (or 100 µg /mL) and 6,100 nM•day (or 915 µg•day/mL), respectively.

3.2.1.3 BMS-986315 Nonclinical Toxicology

The nonclinical safety of BMS-986315 was evaluated in an in vitro tissue cross-reactivity study in human and monkey tissues, an in vitro immunogenicity study with human monocytes, cytokine release assessments in human whole blood, and a 1-month toxicity study in cynomolgus monkeys. BMS-986315 is pharmacologically active in monkeys but does not bind to rodent NKG2A.

As an NKG2A antagonist, BMS-986315 has low risk for cytokine release and did not induce cytokine release in vitro, in human whole blood at a concentration of 10 µg/mL.[23]

In a non-GLP tissue-cross reactivity study in normal human tissues, fluorescently-tagged BMS-986315 labeled small subsets of mononuclear cells in lymphoid organs (spleen, tonsil, thymus), lymphoid-rich tissue (colon, small intestine), as well as in uterus, liver, and lung.[24] Similar labeling was seen in normal cynomolgus monkey tissues. No unexpected tissue cross-reactivity was observed.

In an in vitro non-GLP immunogenicity study using human monocytes, the proliferative CD4 response was low, indicative of a low potential for immunogenicity in humans.[25]

In a pivotal 1-month toxicity study in monkeys (0, 10, or 100 mg/kg SC or 1 mg/kg slow bolus IV, QW×5 doses), BMS-986315 was clinically well tolerated at all doses with no effects on clinical observations, body weight, visual food consumption estimates, cardiovascular, neurological, respiratory, ophthalmologic, clinical pathology, or histopathologic parameters, and no BMS-986315-related changes in total T, helper, cytotoxic, B or NK cell numbers, or activation of NK cell enriched peripheral blood cell populations.[26] No significant irritation or local tolerance issues were observed at the injection sites. Evidence of robust target engagement (receptor occupancy and reduced receptor expression) was observed at all doses. Based on the clinical

tolerability and lack of anatomic or clinical pathology findings, the no-observed-adverse-effect level (NOAEL) was considered to be 100 mg/kg (AUC[0-168h]=425,000 µg●h/mL).

Overall, the nonclinical toxicology assessment of BMS-986315 has demonstrated an acceptable safety profile, supporting clinical use in oncology patients. Additional details are provided in the BMS-986315 IB.[20]

3.2.2 Nivolumab

3.2.2.1 Nivolumab Mechanism of Action

Cancer immunotherapy rests on the premise that tumors can be recognized as foreign rather than as self and can be effectively attacked by an activated immune system. An effective immune response in this setting is thought to rely on immune surveillance of tumor antigens expressed on cancer cells that ultimately results in an adaptive immune response and cancer cell death. Meanwhile, tumor progression may depend upon acquisition of traits that allow cancer cells to evade immunosurveillance and escape effective innate and adaptive immune responses.[27],[28],[29] Current immunotherapy efforts attempt to break the apparent tolerance of the immune system to tumor cells and antigens by either introducing cancer antigens by therapeutic vaccination or by modulating regulatory checkpoints of the immune system. T-cell stimulation is a complex process involving the integration of numerous positive as well as negative co-stimulatory signals in addition to antigen recognition by the T-cell receptor (TCR).[30] Collectively, these signals govern the balance between T-cell activation and tolerance.

PD-1 is a member of the CD28 family of T-cell co-stimulatory receptors that also includes CD28, CTLA4, ICOS, and BTLA.[31] PD-1 signaling has been shown to inhibit CD-28-mediated upregulation of IL-2, IL-10, IL-13, IFN-γ, and Bcl-xL. PD-1 expression also been noted to inhibit T-cell activation, and expansion of previously activated cells. Evidence for a negative regulatory role of PD-1 comes from studies of PD-1 deficient mice, which develop a variety of autoimmune phenotypes.[32] .These results suggest that PD-1 blockade has the potential to activate anti-self T-cell responses, but these responses are variable and dependent upon various host genetic factors. Thus, PD-1 deficiency or inhibition is not accompanied by a universal loss of tolerance to self-antigens.

In vitro, nivolumab (BMS-936558) binds to PD-1 with high affinity (EC50 0.39-2.62 nM), and inhibits the binding of PD-1 to its ligands PD-L1 and PD-L2 (IC50 ± 1 nM). Nivolumab binds specifically to PD-1 and not to related members of the CD28 family such as CD28, ICOS, CTLA-4 and BTLA. Blockade of the PD-1 pathway by nivolumab results in a reproducible enhancement of both proliferation and IFN-γ release in the mixed lymphocyte reaction (MLR). Using a cytomegalovirus (CMV) re-stimulation assay with human PBMC, the effect of nivolumab on antigen specific recall response indicates that nivolumab augmented IFN-γ secretion from CMV specific memory T-cells in a dose-dependent manner versus isotype-matched control. In vivo blockade of PD-1 by a murine analog of nivolumab enhances the anti-tumor immune response and result in tumor rejection in several immunocompetent mouse tumor models (MC38, SA1/N, and PAN02).[33]

A detailed description of the chemistry, pharmacology, efficacy, and safety of nivolumab is provided in the current IB.[34]

3.2.2.2 Nivolumab Clinical Experience

The overall clinical safety experience with nivolumab, as either monotherapy or in combination with other therapeutics, is based on experience in approximately 20,200 participants treated to date.[21]

For monotherapy, the safety profile is similar across tumor types. In Phase 3 controlled studies, the safety profile of nivolumab monotherapy is acceptable in the context of the observed clinical efficacy, and manageable using established safety guidelines. Clinically relevant adverse events (AEs) typical of stimulation of the immune system were infrequent and manageable by delaying or stopping nivolumab treatment and timely immunosuppressive therapy or other supportive care.

In several ongoing clinical trials, the safety of nivolumab in combination with other therapeutics such as ipilimumab, cytotoxic chemotherapy, anti-angiogenics, and targeted therapies is being explored. Most studies are ongoing and, as such, the safety profile of nivolumab combinations continues to evolve.

Details on the clinical safety and PK profile of nivolumab, including results from other clinical studies, are summarized in the nivolumab IB. [34]

3.2.2.3 Nivolumab Clinical Pharmacology Summary

The PK of nivolumab was studied in participants over a dose range of 0.1 to 10 mg/kg administered as a single dose or as multiple doses of nivolumab every 2 or 3 weeks. The geometric mean (% CV%) clearance (CL) was 9.5 mL/h (49.7%), geometric mean volume of distribution at steady state (Vss) was 8.0 L (30.4%), and geometric mean elimination half-life (t1/2) was 26.7 days (101%). Steady-state concentrations of nivolumab were reached by 12 weeks when administered at 3 mg/kg every 2 weeks (Q2W), and systemic accumulation was approximately 3 fold. The exposure to nivolumab increased dose proportionally over the dose range of 0.1 to 10 mg/kg administered every 2 weeks. The clearance of nivolumab increased with increasing body weight. The population PK (PPK) analysis suggested that the following factors had no clinically important effect on the CL of nivolumab: age (29 to 87 years), gender, race, baseline LDH, PD-L1. Also the PPK analysis suggested no difference in CL of nivolumab based on age, gender, race, tumor type, baseline tumor size, and hepatic impairment.

Although ECOG status, baseline glomerular filtration rate (GFR), albumin and body weight had an effect on nivolumab CL, the effect was not clinically meaningful. When nivolumab is administered in combination with ipilimumab, the CL of nivolumab was increased by 24%, whereas there was no effect on the clearance of ipilimumab.

Using the same PPK model, nivolumab exposures for flat (mg) dosing regimens (ie, 240 mg Q2W, 360 mg Q3W, and 480 mg Q4W) were simulated and evaluated against exposure data for nivolumab 3 mg/kg Q2W and 10 mg/kg Q2W doses. At these flat doses, simulated median (90% prediction interval [PI]) average steady-state concentrations (Cavgss) were predicted to be similar

(< 10% difference) to the median (90% PI) Cavgss for nivolumab 3 mg/kg Q2W in participants weighing 80 kg, which is the approximate median body weight of participants included in the PPK analyses described above. Full details on the clinical pharmacology aspects of nivolumab can be found in the IB. [34]

3.2.2.4 Nivolumab Safety Profile

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

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

Additional details on the safety profile of nivolumab, including results from other clinical studies, are available in the nivolumab IB.[34]

3.2.3 Cetuximab

EGFR represents an important therapeutic target in SCCHN. Cetuximab (C225), a chimerized monoclonal antibody of IgG1 subclass, was originally derived from a mouse myeloma cell line. The chimerization process resulted in an antibody which bound to EGFR with a relative affinity 5-fold greater than the murine monoclonal antibody. Cetuximab blocks binding of EGF and TGFα to EGFR, inhibiting ligand-induced activation of the receptor and stimulating EGFR internalization.[35] EGFR is overexpressed in >90% of SCCHN with co-expression of ligands, predominantly transforming growth factor-α and amphiregulin.[36,37] Inhibition of EGFR activation results in inhibition of cellular proliferation and invasion and induction of apoptosis. Cetuximab has been licensed for the treatment of locally or regionally advanced squamous cell carcinoma of the head and neck, but the objective tumor response is limited to approximately 13% of patients.[38] Cetuximab is also able to increase IFN-γ production by natural killer cells through antibody-dependent cellular cytotoxicity.[39] Therefore, a regimen combining BMS-986315 and cetuximab may be able to restore NK cell cytotoxicity while simultaneously stimulating ADCC.

Extensive clinical experience with the use of cetuximab exists and is summarized in the prescribing and use sections of the current drug label.[22] Cetuximab is approved for the treatment of locally or regionally advanced squamous cell carcinoma of the head and neck in combination with radiation therapy, recurrent locoregional disease or metastatic squamous cell carcinoma of the head and neck in combination with platinum based therapy with fluorouracil, and recurrent or metastatic squamous cell carcinoma of the head and neck progressing after platinum-based therapy. As per the approved dose regimen, cetuximab is administered as an IV infusion at 400 mg/m^2 initial loading dose followed by weekly maintenance doses at 250 mg/m^2. An alternative off label dosing

regimen of 500mg/m^2 every 2 weeks is supported by multiple trials in both SCCHN and colorectal cancer indications, with data suggesting that safety and efficacy both as monotherapy or combined to different chemotherapy regimens is similar between the 2 dosing regimens.[40,41,42,43,44] As included in the cetuximab prescribing information, the most commonly reported adverse reactions (incidence ≥ 25%) among patients treated with cetuximab include cutaneous adverse reactions (including rash, pruritus, and nail changes), headache, diarrhea, and infection. Serious adverse reactions (Grades 3 and 4) include infusion reactions (in 2-5% of cases), cardiopulmonary arrest (2%), pulmonary toxicity (<0.5%), and dermatologic toxicity (1-17% of cases). Close monitoring and guidelines for appropriate medical care per the current label should be followed to ensure participant safety. Please refer to Sections 7.4.2.1, 7.4.2.2, and 7.4.2.3 for recommendations on prevention and management of cetuximab-induced adverse events.

3.2.3.1 Cetuximab Clinical Pharmacology Summary

The PK of cetuximab administered as monotherapy or in combination with concomitant chemotherapy or radiation therapy exhibits nonlinear PK over a dose range of 20 to 200 mg/m^2. The AUC increased in a greater than dose proportional manner while clearance of cetuximab decreased from 0.08 to 0.02 L/h/m^2. At doses above 200 mg/m^2, clearance of cetuximab appeared to plateau. The volume of distribution for cetuximab appeared to be independent of dose and approximated the vascular space for 2-3 L/m^2.[22]

Following the recommended dose regimen (400 mg/m^2 initial dose; 250 mg/m^2 weekly dose), cetuximab concentration reached steady-state by the third weekly infusion with mean peak and trough concentrations ranging from 160 to 235 and 41 to 85 µg/mL, respectively. The mean half-life of cetuximab was approximately 112 hours (63-230 hours).[22]

Cetuximab PK was similar in patients with approved indications including colorectal cancer (CRC) and SCCHN. PPK analysis was performed to investigate the potential effects of selected covariates including hepatic and renal function, race, weight, body surface area (BSA), and age on cetuximab PK. None appeared to have statistically significant effect on cetuximab PK. Small difference in CL was observed between males and females in CRC and SCCHN, with females exhibiting a lower maximal CL. However gender differences do not appear to necessitate any dose modification because of a similar safety profile.[22]

3.3 Benefit/Risk Assessment

Patients who have advanced solid tumors have a poor prognosis and few curative options. There is no prior human experience with BMS-986315; therefore, clinical benefit in participants with advanced solid tumors has not been established. However, checkpoint inhibitors are important immunotherapy agents that are improving patient outcomes across several types of solid and hematological malignancies. Additionally, 1 other NKG2A inhibitor, monalizumab from Innate Pharma/Astra-Zeneca, has entered human trials, both as monotherapy and in combination with an anti-PD-L1 drug or with cetuximab. Safety data has been presented for monalizumab, showing safe dose escalation up to 10 mg/kg in participants with solid tumors and very mild AEs in doses up to 10 mg/kg every 2 weeks.[45] An ongoing phase II study is evaluating the combination of

monalizumab and cetuximab in 40 platinum-progressed SCCHN participants, with toxicity comparable to that of cetuximab alone. The Objective Response Rate (ORR) of 27.5% median Progression Free Survival (mPFS) of 5 months, and mOS of 10.3 months suggest that efficacy is superior to historical data for cetuximab monotherapy[8], which strongly suggests a role for monalizumab in the observed response rate.

There is no prior human experience with BMS-986315. Therefore, at this moment the benefit-risk for participants with advanced solid tumors has not been assessed. However participants in the current study should have exhausted treatment options proven to provide benefit. In addition to the safety data reported by Innate Pharma/Astra-Zeneca that demonstrated a safe profile in doses up to 10 mg/kg Q2W, the evaluation of risk for this study is based on information from in vitro studies on human cells and from nonclinical in vivo studies in monkeys.

Whether BMS-986315, nivolumab, or cetuximab administration increases the risk for contracting severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection or increases the severity or duration of symptoms is currently unknown. This unknown risk must be considered when enrolling a participant.

No additional safety monitoring or routine screening tests will be required due to the SARS-CoV-2 pandemic. Participants with recent or acute infections will be excluded or delay start of treatment as defined in Section 6.2 Exclusion Criteria. 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. An exploratory analysis of the impact of SARS-CoV-2 serologic status on subjects receiving BMS-986315 may be performed.

4 OBJECTIVES AND ENDPOINTS

Table 4-1: Objectives and Endpoints

Objectives	Endpoints
Primary	
• To assess the safety and tolerability, and determine the MTD or MAAD and RP2D of BMS-986315 administered as monotherapy, and in combination with nivolumab or cetuximab, in participants with select advanced solid tumors.	• Incidence of AEs, SAEs, AEs meeting protocol-defined DLT criteria, AEs leading to discontinuation, and death.
Secondary	
• To assess the preliminary anti-tumor activity of BMS-986315 as monotherapy and in combination with nivolumab or cetuximab in participants with select advanced solid tumors.	• ORR, DOR, and PFSR at 6, 9, and 12 months
• To explore the PK of BMS-986315 when administered intravenously as monotherapy and in combination with nivolumab or cetuximab, in participants with select advanced solid tumors.	• Summary measures of PK parameters of BMS-986315 after monotherapy and combination treatment.
• To characterize the immunogenicity of BMS-986315 when administered alone and in combination with nivolumab or cetuximab, in participants with select advanced solid tumors.	• Incidence of anti-drug antibodies to BMS-986315 when BMS-986315 is administered alone and in combination with nivolumab or cetuximab.

Table 4-1: Objectives and Endpoints

Objectives	Endpoints
Exploratory	
• To explore changes in biomarkers such as tumor inflammation, cytolytic activity, levels of intratumoral TILs (CD8), and other pharmacodynamic parameters and associations with anti-tumor activity, when BMS-986315 is administered alone and in combination with nivolumab or cetuximab.	• Summary changes in biomarkers of interest eg CD8, immune-related markers and measures of association of baseline levels, and of changes in these markers with anti-tumor activity measures.
• To characterize the PK and immunogenicity of nivolumab and cetuximab when administered in combination with BMS-986315.	• Summary measure of trough nivolumab and cetuximab concentration and the incidence of anti-drug antibodies to nivolumab and cetuximab when administered in combination with BMS-986315.
• To assess the potential dose-related and exposure-related effect of BMS-986315 when administered as monotherapy, on the QTc interval.	• Summary measures of changes in QTc after monotherapy treatment from baseline by dose and association measures of QTc changes with BMS-986315 PK exposure.
• To explore OS up to 2 years following monotherapy and combination treatments.	• OSR at 1 year and up to 2 years
• To explore impact of SARS-CoV-2 serologic status on participants with RCC, SCCHN, and NSCLC receiving BMS-986315 as monotherapy or combined with nivolumab or cetuximab in advanced solid tumors.	• Incidence of participants with positive SARS-CoV-2 serologic status and associations of measures of positive SARS-CoV-2 status with select safety and PD biomarkers.

Abbreviations: AE = adverse event; DOR = duration of response; DLT = dose-limiting toxicity; MAAD = maximum administered dose; MTD = maximum tolerated dose; NSCLC = non-small cell lung cancer; ORR = objective response rate; OS = overall survival; OSR = overall survival rate; PD = pharmacodynamics; PFSR = progression-free survival rate; PK = pharmacokinetics; QTc = interval corrected for heart rate using Frederica's formula; RCC = renal cell carcinoma; RP2D = recommended Phase 2 dose; SAE = serious adverse event; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2; SCCHN = squamous cell carcinoma of the head and neck;TIL = tumor-infiltrating lymphocytes.

5 STUDY DESIGN

5.1 Overall Design

This is a Phase 1/2, multicenter, open-label study of BMS-986315, administered as a single agent and in combination with nivolumab or cetuximab, in participants with select advanced solid tumors: SCCHN, RCC, and NSCLC. All participants will be evaluated for total HLA-E expression and CD8+ T cell infiltration in fresh tumor samples by immunohistochemistry (IHC). [redacted] The study is composed of 3 parts: Part 1A (dose escalation of BMS-986315 monotherapy), Part 1B (dose escalation of BMS-986315 in combination with nivolumab), and Part 1C (dose escalation of

BMS-986315 in combination with cetuximab). Each Part will have, in addition to the escalation cohorts, additional cohorts focused on studying pharmacodynamics changes associated to study treatments, called pharmacodynamics cohorts or PD cohorts. Additional tumor types and study expansion parts may be included through a protocol amendment.

Part 1A

BMS-986315 monotherapy dose escalation (Part 1A) will escalate the dose of BMS-986315 to determine the monotherapy MTD/recommended Phase 2 dose (RP2D). Specifically, Part 1A dose escalation will evaluate different doses of BMS-986315 starting at 80 mg followed by 200 mg, 600 mg, 1200 mg, and 2400 mg (flat doses, initially Q4W). If it appears that a planned dose level is associated with an unacceptable frequency of toxicities, then intermediate dose levels or an alternative administration schedule may be evaluated. Part 1A will evaluate the safety and tolerability of BMS-986315 monotherapy based on dose-limiting toxicities (DLTs), using time-to-event Bayesian optimal interval (TITE-BOIN) design to guide escalation decisions (see Appendix 8 for details), and the overall assessment of available safety, PK, and pharmacodynamic data. One additional cohort of participants, the BMS-986315 monotherapy PD cohort, will be enrolled at a dose level previously cleared for safety. The PD cohort will be implemented in order to gather additional information on pharmacodynamic activity (such as tumor cytolytic activity), safety, tolerability, preliminary efficacy, and PK in a single indication, initially SCCHN participants treated with BMS-986315 monotherapy. Please refer to Section 5.1.2.4 for additional information on the PD cohorts.

Part 1B

The dose escalation of BMS-986315 in combination with nivolumab (Part 1B) will evaluate the safety and tolerability of escalating doses of BMS-986315 in combination with nivolumab, to determine the combination MTD/RP2D. Treatment in Part 1B will be initiated in a staggered manner relative to the BMS-986315 Monotherapy Escalation (Part 1A). Specifically, Part 1B can be initiated upon the decision to escalate when at least 2 dose levels (the current and 1 higher) in Part 1A have been cleared for safety in accordance with dose escalation rules, after which dose escalation in Part 1A and Part 1B will proceed in parallel separated by 2 dose levels as stated above, (see Section 7.2). At no point will the dose of BMS-986315 administered in combination with nivolumab in Part 1B exceed the highest dose determined to be tolerated in Part 1A. In Part 1B, the dose of BMS-986315 will be escalated, whereas the dose of nivolumab will be fixed at 480 mg Q4W. However, if it appears that a planned dose level is associated with an unacceptable frequency of toxicities then intermediate dose levels, alternative BMS-986315 administration schedules, or lower doses of nivolumab may be evaluated.

The safety and tolerability of the BMS-986315 in combination with nivolumab will be evaluated using TITE-BOIN design, used to guide dose escalation decisions.

Additional cohorts of participants may be enrolled within up to 2 dose levels previously cleared for safety in monotherapy. These potential combination cohorts would be implemented in order to gather additional information on pharmacodynamic activity, safety, tolerability, preliminary efficacy and PK in a single indication, initially SCCHN participants treated with BMS-986315 in

combination with nivolumab. Please refer to Section 5.1.2.4 for additional information on the PD cohorts.

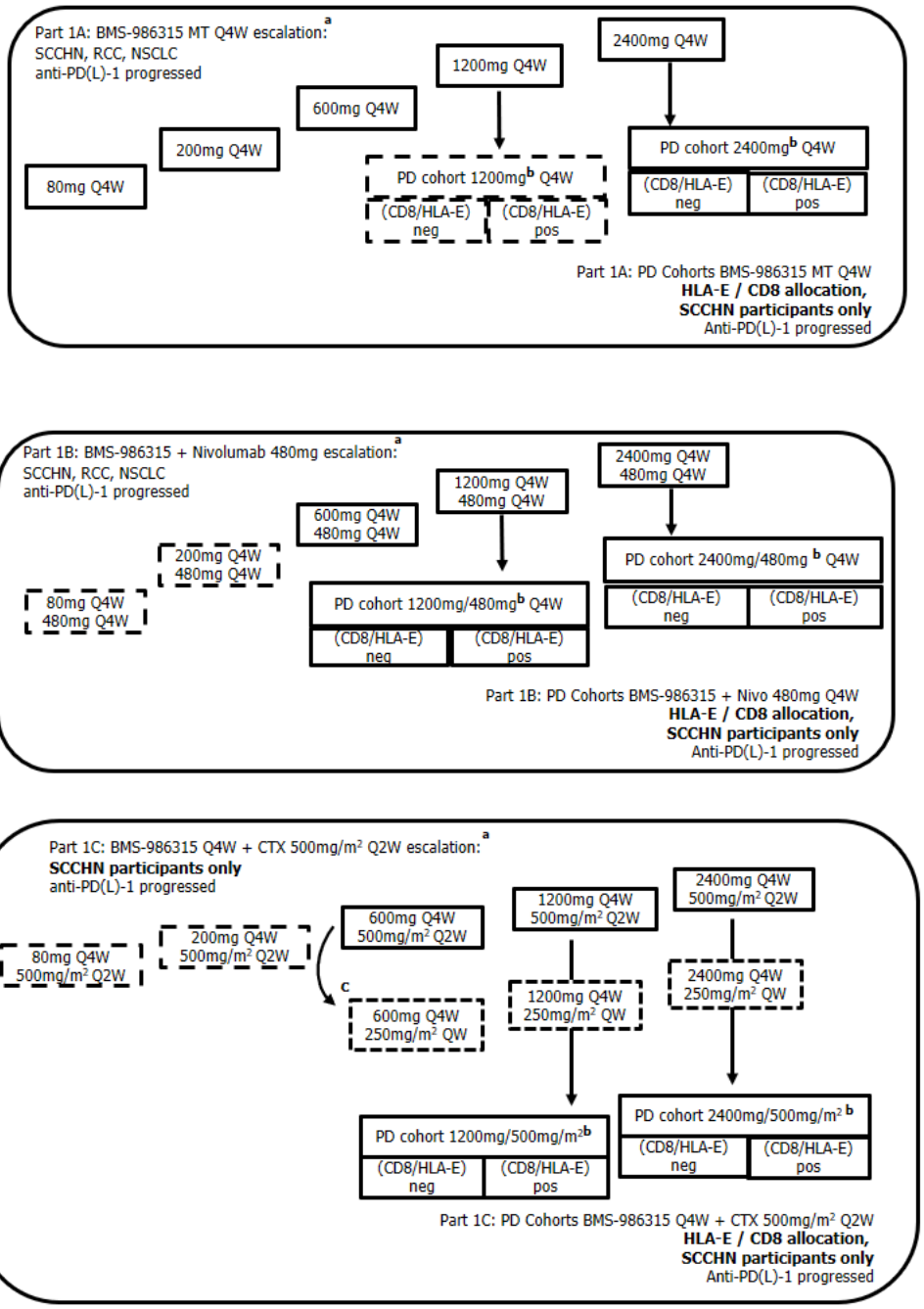
Part 1C

The dose escalation of BMS-986315 in combination with cetuximab (Part 1C) will evaluate the safety and tolerability of escalating doses of BMS-986315 in combination with cetuximab, to determine the combination MTD/RP2D in SCCHN participants. Treatment in Part 1C will be initiated in a staggered manner relative to the BMS-986315 Monotherapy Escalation (Part 1A). Specifically, Part 1C can be initiated upon the decision to escalate when at least 2 BMS-986315 dose levels (the current and 1 higher) in Part 1A have been cleared for safety in accordance with dose escalation rules, after which, dose escalation in Part 1A and Part 1C will proceed in parallel separated by 2 dose levels as indicated above, (see Section 7.2). At no point will the dose of BMS-986315 administered in combination with cetuximab in Part 1C exceed the highest dose determined to be tolerated in Part 1A. In Part 1C, the dose of BMS-986315 will be escalated, whereas the dose of cetuximab will be fixed at 500mg/m^2 Q2W. However, if it appears that a planned dose level is associated with an unacceptable frequency of toxicities, then intermediate dose levels, alternative BMS-986315 administration schedules, or de-escalating doses of cetuximab may be evaluated. Specifically, if toxicity attributable solely to cetuximab is found to be in excess as compared to the known toxicity profile of the label dose of 400mg/m^2 followed by 250mg/m^2 QW, then a decision may be made to change the cetuximab dosing regimen for all of Part 1C.

The safety and tolerability of BMS-986315 in combination with cetuximab will be evaluated using TITE-BOIN design also used to guide escalation decisions. Additional cohorts of participants will be enrolled in up to 2 dose levels previously cleared for safety. The BMS-986315 in combination with cetuximab PD cohorts, will be implemented in order to gather additional information on pharmacodynamic activity, safety, tolerability, preliminary efficacy and PK in SCCHN participants treated with BMS-986315 in combination with cetuximab. Please refer to Section 5.1.2.4 for additional information on the PD cohorts.

The study consists of 4 periods: Screening, Treatment, Safety Follow-up, and Survival Follow-up (up to 2 years following the EOT of study drug). The duration of the study will be approximately 4 years. The study design schematic is presented in Figure 5.1-1. A detailed schematic for study period and participant flow is presented in Figure 5.1-2.

Figure 5.1-1: Study Design Schematic



Abbreviations: CTX = cetuximab; MT = monotherapy; neg = negative, NSCLC = non-small cell lung cancer; PD = pharmacodynamic cohort; PD-L1 = Programmed death-ligand 1; Q2W = every 2 weeks, Q4W = every 4 weeks

[a] Further expansion may be included as part of a protocol amendment

[b] Dose levels will be selected based on preliminary data from dose escalation

[c] The cetuximab dose may be changed to the approved dose for the entire program if excessive toxicity is observed, upon agreement between investigators and the Sponsor.

Figure 5.1-2: Study Period and Participant Flow Diagram

Abbreviation: Q4W: every 4 weeks; EOT: end of treatment

[a] Alternative dosing schedule may be used

b See Figure 5.1-1 for BMS-986315, nivolumab, and cetuximab dosing schedules

5.1.1 Screening Period

The screening period will be up to 35 days, and begins when the participant signs the main informed consent form (ICF). During the screening period, participants will submit a fresh biopsy which will be evaluated for adequate and evaluable tumor tissue by the central laboratory. Only those participants who have met tissue quality thresholds and have evaluable CD8 and HLA-E can be assigned for treatment in PD cohorts. Please refer to the laboratory manual for additional details. Participants will be allocated in the PD cohorts according to CD8 and HLA-E expression. Participants must have a lesion that can be biopsied at an acceptable clinical risk as judged by the investigator in order to be eligible for the study; see Table 2-1. Participants will be enrolled using an Interactive Response Technology (IRT). The screening assessments are shown in Table 2-1. If a participant exceeds the 35-day screening period due to a study-related procedure (eg, scheduling of a tumor biopsy or waiting for a study-related laboratory value), the participant must be re-consented, but does not require a new participant identification number. In this situation, safety laboratory tests should be repeated and the Bristol Myers Squibb (BMS) Medical Monitor or designee should be notified. Any additional procedures and tests should only be repeated if needed to maintain participant safety and confirm eligibility after discussion with the BMS Medical Monitor or designee.

5.1.2 Treatment Period

The dosing regimen of BMS-986315 is Q4W. Refer to Section 5.1 Overall Design. All participants will be treated for up to 104 weeks. The treatment period will consist of up to 26 treatment cycles (each cycle is 4 weeks in length). Continuous safety evaluation and tumor assessment (every 8 weeks [Q8W]) will guide the decision to treat a participant with additional cycles of study therapy if the participant has confirmed clinical benefit (up to a maximum of 104 weeks) for all study parts.

Study visits in Part 1A (BMS-986315 Monotherapy Dose Escalation) will be performed every 2 weeks for the first 8 weeks following the first dose of study treatment. BMS-986315 will be administered every 4 weeks (Q4W) and will be infused over approximately 60 minutes for the first 2 cycles and then approximately 30 minutes for cycles 3 and beyond. BMS-986315 will require a 4 hour observation period following the completion of the infusion for the first dose in the escalation cohort and 60 minutes observation for the second dose for each participant. For the pharmacodynamic cohorts, the observation period is 60 minutes for the first 2 doses. See Table 2-

2. Please refer to the pharmacy manual for dose-specific infusion times and administration details for BMS-986315.

In Part 1B (BMS-986315 in Combination with Nivolumab Dose Escalation) nivolumab will be administered Q4W and will be infused over 30 minutes. Nivolumab will be given first, followed by a 30-minute observation period. After that, BMS-986315 will be infused over approximately 60 minutes for the first 2 cycles and then over approximately 30 minutes for cycles 3 and beyond. BMS-986315 infusions will require a 60-minute observation period following the completion of the infusion for the first 2 doses for each participant. Please refer to the pharmacy manual for dose-specific infusion times and administration details for nivolumab and BMS-986315.

In Part 1C (BMS-986315 in Combination with Cetuximab Dose Escalation) cetuximab will be administered Q2W and will be infused over 150 minutes for the first dose, and 120 minutes for subsequent doses. Cetuximab will be given first, followed by a 60-minute observation period. After that, BMS-986315 will be infused over approximately 60 minutes for the first 2 cycles and then over approximately 30 minutes for cycles 3 and beyond. BMS-986315 infusions will require a 60-minute observation period following the completion of the infusion for the first 2 doses for each participant. Please refer to the pharmacy manual for dose specific infusion times and administration details for cetuximab and BMS-986315.

All eligible participants will be initially assigned to Part 1A (dose escalation of BMS-986315 monotherapy). Treatment in Part 1B and Part 1C will be initiated in a staggered manner relative to the dose escalation of BMS-986315 (Part 1A). Specifically, Part 1B and Part 1C can be initiated when at least 2 dose levels (the current and 1 one higher) in Part 1A have cleared the DLT period in accordance with dose escalation rules, after which dose escalation in Part 1A, Part 1B, and Part 1C will proceed in parallel. At no point will the dose of BMS-986315 administered in combination with nivolumab in Part 1B or cetuximab in Part 1C exceed the highest safe dose in ongoing monotherapy dose escalation in Part 1A, or the highest dose determined to be tolerated in Part 1A.

The monotherapy and combination dose escalation cohorts will be kept separated by 2 dose levels (the current and 1 higher) until dose escalation in monotherapy is completed. Initially, 3 participants will be enrolled at the start of each cohort via staggered dosing (see Sentinel Participant below). Additional information on DLTs can be found in Section 5.1.3.

Participants may be enrolled to backfill dose escalation cohorts in Part 1A, Part 1B, or Part 1C. Any available PD, PK, and clinical data obtained from backfill participants will be utilized among the totality of data considered for dose selection. Backfill will not result in treatment of participants exceeding maximum participant numbers planned for the study. Enrollment of backfill participants requires prior consultation with the medical monitor.

Sentinel Participant:
During the dose escalation phase in Parts 1A, 1B, and 1C, a staggered dosing (sentinel participant) approach, will be used. In Part 1A the first participant to be dosed at C1D1 of the first dose level will be observed for 5 days, before additional participants (ie, Participant 2 onward in that cohort) receive study treatments in the same dose level. In Parts 1B and 1C, the first participant to be dosed

at C1D1 of each dose level will be observed for 5 days, before additional participants (ie, Participant 2 onward in each cohort) receive study treatments in the same dose level.

5.1.2.1 BMS-986315 Monotherapy Dose Escalation Design (Part 1A)

Approximately 36 participants are expected to be treated during the BMS-986315 Monotherapy Dose Escalation (Part 1A) of the study guided by TITE-BOIN design (Figure 5.1.2.1-1, TITE BOIN Appendix 8) for the primary objective. Additionally, up to approximately 40 participants are expected to be treated in the SCCHN PD cohort in monotherapy (in order to have 30 evaluable).

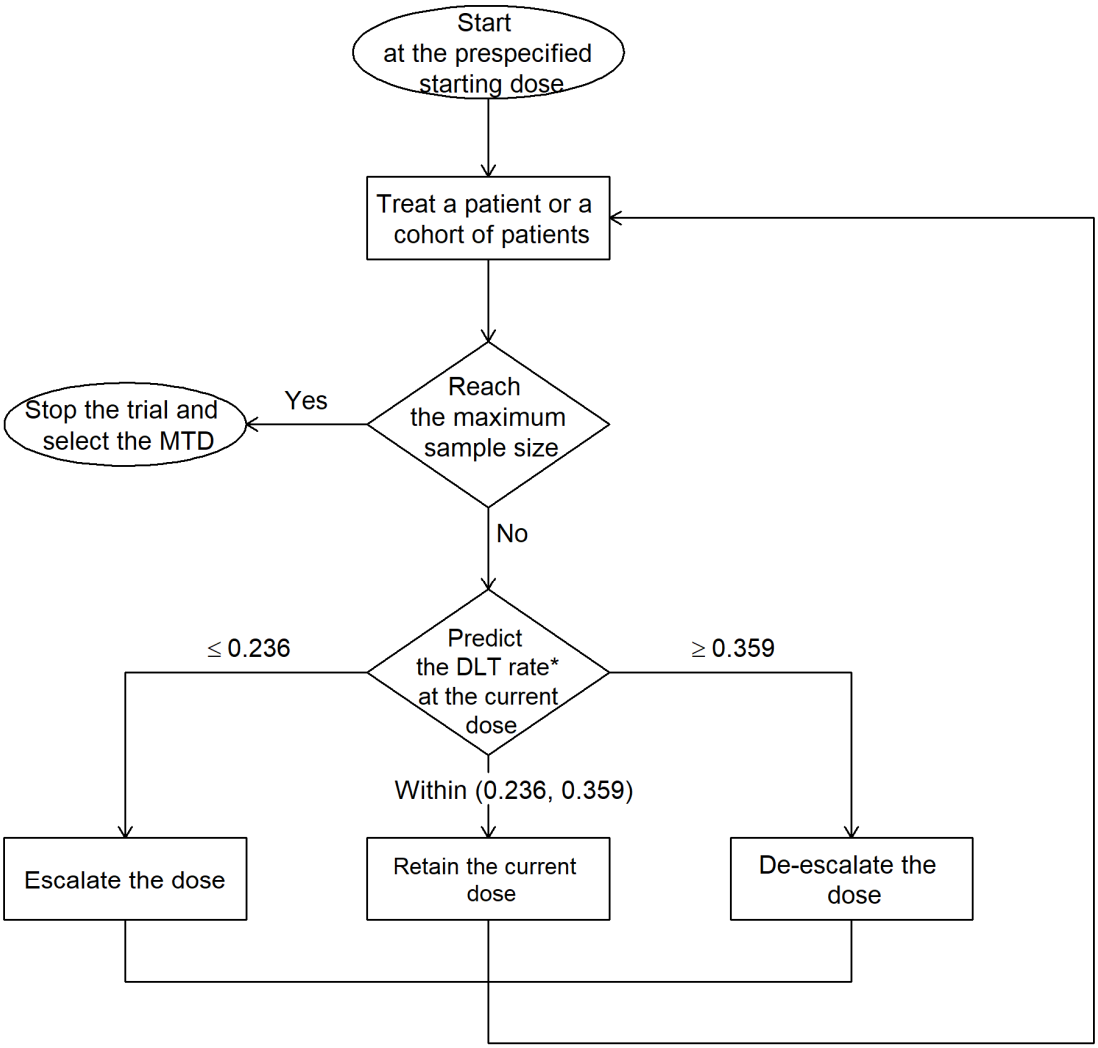
In dose escalation, each participant will be administered IV doses of BMS-986315 in planned dose levels of 80 mg followed by 200 mg, 600 mg, 1200 mg, and 2400 mg Q4W once per cycle, for up to 26 cycles (104 weeks) of study therapy, unless criteria for study drug discontinuation are met earlier (see Section 8).

Prior to declaring the MTD, and in consultation with investigators, the Sponsor has the option to investigate dose levels intermediate to those defined in the protocol. Planned dose levels may be modified based upon the DLT data in the evaluated doses and clinical evaluation of all available safety and PK/pharmacodynamic data. Once the tolerability (during the DLT evaluation) of a dose level has been established, additional participants may be added at that dose level to better characterize the safety, PK, and pharmacodynamic profiles.

The BMS-986315 Monotherapy Dose Escalation (Part 1A) phase of the study will evaluate the safety and tolerability of BMS-986315, based on DLTs, guided by the TITE-BOIN design. During the monotherapy dose escalation phase, approximately 3 participants will be treated at each dose level, allowing at least 2 participants for a decision at the lower dose levels. In order to allow for any unforeseen discontinuations (such as disease progression) before the 4-week DLT period (28 days) is completed, an extra participant may be enrolled in each dose escalation cohort after the 2 initial dose levels. Therefore, there may be a total of 4 participants (3 + 1) at the start of a cohort. Cohort tolerability assessment and subsequent dose recommendation will occur when at least 2 out of 3 or 3 out of 4 participants within a cohort have completed the 4-week (28 day) DLT period or have been followed sufficiently based on the TITE-BOIN design to make an escalation decision. Any toxicities that occur beyond the DLT period will be considered in making dose level decisions and/or dose level modifications. Additional information on DLTs can be found in Section 5.1.3.

If the potential DLT occurring in the third evaluable participant regarding any specific dose level does not influence the dose recommendation by TITE-BOIN, the next dose level may proceed without waiting for the third participant to complete the corresponding DLT-observation period, after discussion and agreement between the Sponsor and investigators. Continuous reassessment of dose recommendation, by TITE-BOIN in the BMS-986315 Monotherapy Escalation (Part 1A) will be carried out for each dose level. Planned dose levels for dose escalation are provided in Section 5.1 Overall Design.

Figure 5.1.2.1-1: Flowchart Using the TITE-BOIN Design



Abbreviations: DLT = dose-limiting toxicity; MTD = maximum tolerated dose.

5.1.2.2 BMS-986315 in Combination with Nivolumab Dose Escalation Design (Part 1B)

Approximately 36 participants are expected to be treated during the BMS-986315 Combination with Nivolumab Dose Escalation (Part 1B) of the study guided by TITE-BOIN for the primary objective. Additionally, up to approximately 80 participants are expected to be treated across 2 SCCHN PD cohorts in combination with nivolumab.

Based on preliminary safety, PK, and pharmacodynamic data from Part 1A, the starting dose of BMS-986315 in Part 1B may be higher than the starting dose from Part 1A. Each dose level in

Part 1B, including the starting dose, will only be opened after at least that dose and one higher dose level in Part 1A have demonstrated tolerability during the DLT observation period. Additional cohorts in Parts 1A and 1B may proceed in parallel and will be separated by at least 2 dose levels (the current and 1 higher cleared in Part 1A). Each participant will be administered IV doses of BMS-986315 (in doses based on Part 1A data) combined with 480 mg of nivolumab Q4W (once per cycle), for up to 26 cycles of study therapy (104 weeks) unless criteria for study drug discontinuation are met earlier (see Section 8).

The combination dose escalation phase (Part 1B) of the study will evaluate the safety and tolerability of BMS-986315, given in combination with nivolumab, based on DLTs, using a TITE-BOIN. During the combination dose escalation phase, approximately 3 participants will be treated at each dose level. However, to allow for any unforeseen discontinuations (such as disease progression) before the 4-week DLT period (28 days) is completed, an extra participant may be enrolled in each dose escalation cohort. Therefore, there may be a total of 4 participants (3 + 1) at the start of each cohort, provided that the fourth participant is able to start dosing within approximately 1 week of the third participant in the same dose escalation cohort. Cohort tolerability assessment and subsequent dose recommendation will occur when at least 3 evaluable participants within a cohort have completed a 4 week DLT period or have been sufficiently followed, based on the TITE-BOIN design, to make an escalation decision depending on the number of DLTs so far. Any toxicities that occur beyond the DLT period will be considered in making dose level decisions and/or dose level modifications. Additional information on DLTs can be found in Section 5.1.3.

If the potential DLT occurring in the third-evaluable participant regarding any specific dose level does not influence the dose recommendation by TITE-BOIN, the next dose level may proceed without waiting for the third participant to complete the corresponding DLT-observation period, after discussion and agreement between the Sponsor and investigators. Continuous reassessment of dose recommendation, by TITE-BOIN in the BMS-986315 in Combination with Nivolumab Dose Escalation (Part 1B) will be carried out for each dose level. Planned dose levels for dose escalation are provided in Section 5.1.

Planned dose levels may be modified based upon the DLT data in the evaluated doses and clinical evaluation of all available safety and PK/pharmacodynamic data. Once the tolerability (during the DLT evaluation) of a dose level has been established, additional participants may be added at that dose level to better characterize the safety, PK, and pharmacodynamic profiles.

5.1.2.3 BMS-986315 in Combination with Cetuximab Dose Escalation Design (Part 1C)

Approximately 36 participants are expected to be treated during the BMS-986315 combination with cetuximab dose escalation (Part 1C) of the study guided by TITE-BOIN for the primary objective. Additionally, up to approximately 80 participants are expected to be treated in the SCCHN PD cohorts in combination with cetuximab.

Based on preliminary safety, PK, and pharmacodynamic data from Part 1A, the starting dose of BMS 986315 in Part 1C may be higher than the starting dose from Part 1A. Each dose level in Part

1C, including the starting dose, will only be opened after at least that dose and 1 higher dose level in Part 1A have demonstrated tolerability during the DLT observation period. Additional cohorts in Parts 1A and 1C may proceed in parallel and will be separated by at least 2 dose levels (as indicted above). Each participant will be administered Q4W IV doses of BMS-986315 (in doses based on Part 1A data) combined with 500mg/m^2 of cetuximab Q2W for up to 26 cycles of study therapy (104 weeks) unless criteria for study drug discontinuation are met earlier (see Section 8).

The combination dose escalation phase (Part 1C) of the study will evaluate the safety and tolerability of BMS-986315, given in combination with cetuximab, based on DLTs, using a TITE-BOIN. During the combination dose escalation phase, approximately 3 participants will be treated at each dose level. However, to allow for any unforeseen discontinuations (such as disease progression) before the 4 week DLT period (28 days) is completed, an extra participant may be enrolled in each dose escalation cohort. Therefore, there may be a total of 4 participants (3 + 1) at the start of each cohort, provided that the fourth participant is able to start dosing within approximately 1 week of the third participant in the same dose escalation cohort. Cohort tolerability assessment and subsequent dose recommendation will occur when at least 3 evaluable participants within a cohort have completed a 4 week DLT period or have been sufficiently followed, based on the TITE-BOIN design to make an escalation decision depending on the number of DLTs so far. Any toxicities that occur beyond the DLT period will be considered in making dose level decisions and/or dose level modifications. Additional information on DLTs can be found in Section 5.1.3.

If the potential DLT occurring in the third-evaluable participant regarding any specific dose level does not influence the dose recommendation by TITE-BOIN, the next dose level may proceed without waiting for the third participant to complete the corresponding DLT-observation period, after discussion and agreement between the Sponsor and investigators. Continuous reassessment of dose recommendation, by TITE-BOIN in the BMS-986315 in combination with cetuximab dose escalation (Part 1C) will be carried out for each dose level. Planned dose levels for dose escalation are provided in Section 5.1.

Planned dose levels may be modified based upon the DLT data in the evaluated doses and clinical evaluation of all available safety and PK/pharmacodynamic data. Once the tolerability (during the DLT evaluation) of a dose level has been established, additional participants may be added at that dose level to better characterize the safety, PK, and pharmacodynamic profiles.

5.1.2.4 Pharmacodynamic Cohorts

As introduced in previous sections, PD cohorts are included in Part 1A (1 cohort) and Parts 1B and 1C (up to 2 cohorts) at different dose levels. Each of these PD cohorts will only be open once the dose level has been demonstrated to be tolerated. The objective of the PD cohorts is to obtain pharmacodynamic information, and additional data on safety, tolerability, preliminary efficacy, and PK, in participants with SCCHN. The goal of each PD cohort is to obtain approximately 10 paired biopsy samples of participants who are considered as “biomarker negative” and 20 paired biopsy samples of participants who are considered as “biomarker positive” which is consistent with the expected natural prevalence of these biomarkers in SCCHN. Therefore, up to

approximately 40 participants are expected to be treated in each PD cohort in order to have 30 evaluable participants (with paired biopsies). A fresh screening tumor biopsy will be assessed for CD8 and total HLA-E using CLIA validated IHC assays. [redacted]. All PD cohorts will enroll participants with SCCHN. Participants treated in the PD cohorts will be administered IV doses of BMS-986315 according to the dose defined for the PD cohort (e.g., 1200 mg or 2400 mg) Q4W once per cycle, for up to 26 cycles (104 weeks) of study therapy, unless criteria for study drug discontinuation are met earlier (see Section 8.1). In Part 1B, BMS-986315 will be combined with nivolumab 480mg Q4W. In Part 1C, BMS-986315 will be combined with cetuximab 500 mg/m^2 Q2W.

5.1.3 Dose Limiting Toxicities

For the purpose of guiding decisions regarding dose escalation in Parts 1A, 1B, and 1C, DLTs will be defined based on the incidence, intensity, and duration of AEs excluding toxicities clearly related to disease progression or intercurrent illness. The DLT period will start on the first day of cycle 1 and end at day 28 (therefore, 4 weeks) in Parts 1A, 1B and 1C. The severity of AEs will be graded according to National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) v5.0.

For the purpose of participant management, DLTs that occur at any time during treatment (not limited to DLT observation period) will result in study drug being held pending evaluation of the event being related to study drug, in accordance with Section 7.4. A participant is considered DLT evaluable if receiving 1 dose of BMS-986315 in Part 1A, 1 dose of BMS-986315 and nivolumab (480mg) in Part 1B, or 1 dose of BMS-986315 and cetuximab (500 mg/m^2) in Part 1C, and completing the DLT observation period.

Participants who withdraw from the study during the 4 week DLT evaluation period for reasons other than a DLT may be replaced with a new participant at the same dose level. The incidence of DLT(s) during the 4 week DLT evaluation period will be used in dose escalation decisions and to define the MTD/RP2D in monotherapy and in combination with nivolumab or cetuximab. AEs occurring after the 4-week DLT period will be considered for the purposes of defining the RP2D upon agreement between the Sponsor and Investigators. Participants experiencing a DLT will not be retreated with study drug (except for Grade 3 or 4 acneiform rash in Part 1C), and will enter the safety follow-up period of the study.

5.1.3.1 Hepatic Dose Limiting Toxicity

Any 1 of the following events, excluding toxicities clearly related to disease progression or intercurrent illness, will be considered a hepatic DLT:

- Grade 4 elevations in serum transaminases (AST, ALT), alkaline phosphatase (ALP) or total bilirubin, in the absence of cholestasis.
- Grade 3 elevations in serum transaminases (AST, ALT) or alkaline phosphatase (ALP) in the absence of cholestasis, lasting longer than 5 days.
- Grade 2 elevations in AST or ALT with symptomatic liver inflammation (e.g., right upper quadrant tenderness, jaundice, and pruritus).
- AST or ALT > 3 x ULN and concurrent total bilirubin > 2 x ULN without initial findings of cholestasis (elevated ALP, eg, findings consistent with Hy's law or FDA definition of potential drug-induced liver injury [pDILI]). Note that this specific category of DLT uses ULN rather than CTCAE grade for definition.

5.1.3.2 Hematologic Dose Limiting Toxicity

Any of the following events will be considered a DLT:

- Grade 4 neutropenia
- Grade 4 thrombocytopenia
- Grade 4 anemia
- Grade 3 thrombocytopenia with clinically significant bleeding, or any requirement for platelet transfusion.
- Febrile neutropenia
- Grade ≥ 3 hemolysis (i.e., requiring transfusion or medical intervention such as steroids).

5.1.3.3 Dermatologic Dose Limiting Toxicity

Any of the following events will be considered a DLT:

- Grade 4 skin toxicity of any duration
- Grade 4 rash
- Grade 3 rash if no improvement (i.e., resolution to ≤ Grade 2) after a 1 to 2 week infusion delay. Topical steroid treatment is allowed for symptom control.

5.1.3.4 Other Dose Limiting Toxicities

Any of the following events will be considered a DLT:

- Grade 2 drug-related uveitis, episcleritis, iritis eye pain or blurred vision that does not respond to topical therapy and does not improve to Grade 1 severity within 2 weeks OR requires systemic treatment.
- Grade 2 pneumonitis that does not respond to dose delay and systemic steroids within 14 days.
- Grade ≥ 3 drug-related uveitis, episcleritis, iritis, pneumonitis, bronchospasm or neurologic toxicity.
- Grade 4 hypersensitivity/infusion reaction, or Grade 3 that does not resolve to Grade 1 in < 6 hours.

- Grade 4 colitis
- Grade 3 colitis that does not respond within 48 hours of systemic steroid treatment.
- Any death not clearly due to the underlying disease or extraneous causes.

Other ≥ Grade 3 toxicity events, excluding toxicities clearly related to disease progression or intercurrent illness, will be considered a DLT, with the exception of the following Grade 3 events which will NOT be considered DLTs:

- Grade 3 electrolyte abnormalities that are not complicated by associated clinical adverse experiences, last less than 72 hours and either resolve spontaneously or respond to conventional medical intervention.
- Grade 3 nausea, vomiting, or diarrhea that lasts less than 48 hours, and either resolves spontaneously or responds to conventional medical intervention.
- Grade 3 elevation of amylase or lipase not associated with clinical or radiographic evidence of pancreatitis.
- Grade 3 fever not associated with hemodynamic compromise (e.g., hypotension, clinical or laboratory evidence of impaired end-organ perfusion).
- Grade 3 endocrinopathy that is well controlled by hormone replacement.
- Grade 3 tumor flare (defined as pain, irritation, or rash that localizes to sites of known or suspected tumor).
- Grade 3 fatigue that lasts ≤ 7 days.
- Grade 3 infusion reaction that returns to Grade 1 in < 6 hours.

5.1.3.5 Dose Limiting Toxicities Specific to Part 1C

In addition to all DLTs described in Sections 5.1.3.1, 5.1.3.2, 5.1.3.3, and 5.1.3.4, in Part 1C the following adverse events will be considered DLTs:

- Grade 3 or 4 infusion reaction of any duration
- Grade 4 cetuximab-related rash
- Grade 3 cetuximab-related rash that does not improve by at least 1 Grade in ≤ 2 weeks despite interruption of study therapy and maximal medical intervention.
- Please refer to Section 7.4.2.1 for management of cetuximab-induced acneiform rash.

5.1.4 Follow Up

5.1.4.1 Safety Follow-up

Upon completion of study therapy, or once the decision is made to discontinue the participant from treatment, i.e., at end of treatment (EOT), all participants will enter a safety follow-up period.

For participants who complete all scheduled cycles of therapy, the EOT visit will be the same visit as the last scheduled and completed on-treatment visit, and will be 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), and will not need to be repeated. Accordingly, for these participants, this visit will be considered the start of the safety follow-up period.

After the EOT visit, all participants will be evaluated for any new AEs for at least 100 days after the last dose of study treatment. Follow-up visits should occur at Days 30, 60 and 100 (+/- 7 days for all study visits) after the last dose, or the date of discontinuation (+/- 7 days). All participants will be required to complete the 3 clinical safety follow-up visits, regardless of whether new anti-cancer therapy is started, except those participants who withdraw consent for study participation.

5.1.4.2 Progression and Survival Follow-up

Follow up for progression and survival of participants who stop study therapy before having completed 2 years of study therapy should be attempted through phone calls or other means deemed appropriate by the study center approximately every 3 months (12 weeks) for 2 years from the start of study therapy or from the start of treatment with nivolumab whichever is later.

The safety follow-up period and survival follow-up period will occur simultaneously following the EOT visit. After the safety follow-up period ends, all participants will continue in the survival follow-up period. Participants will be followed-up by telephone Q12W (from Follow-Up visit #3) for up to 2 years or until death, loss to follow-up, withdrawal of consent, or conclusion of the study, whichever comes first. Participants with stable disease (SD), partial response (PR), or complete response (CR) at the time of EOT visit should undergo tumor assessment via computed tomography (CT)/magnetic resonance imaging (MRI) scans every 12 weeks during the follow-up periods until progression. The duration of this follow-up is up to 2 years following the last dose of study treatment, although a longer follow-up period could be considered in selected cases if an efficacy signal is apparent. Tumor assessment scans, for participants who have ongoing clinical benefit beyond the 2 year period following the end of treatment, may continue to be collected as part of standard-of-care treatment upon agreement between the Sponsor and Investigator. Subsequent therapies will also be recorded in this survival follow-up period.

5.1.5 Treatment Beyond Disease Progression

Participants will be permitted to continue treatment beyond initial RECIST 1.1 defined progressive disease, as assessed by the investigator, as long as the following criteria are considered:

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

Radiographic assessment/scan(s) should continue in accordance with the Section 2 Schedule of Activities for the duration of the treatment beyond progression and should be submitted to the central imaging vendor.

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

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 PD. This includes an increase in the sum of diameters of all target lesions and/ or the diameters of new measurable lesions compared to the time of initial PD. It is recommended that study treatment should be discontinued permanently upon documentation of further progression.

New lesions are considered measureable at the time of initial progression if the longest diameter is at least 10 mm (except for pathological lymph nodes which must have a short axis of at least 15 mm). Any new lesion considered non-measureable at the time of initial progression may become measureable and therefore included in the tumor burden if the longest diameter increases to at least 10 mm (except for pathological lymph nodes which must have a short axis of at least 15 mm). In situations where the relative increase in total tumor burden by 10% is solely due to inclusion of new lesions which become measurable, these new lesions must demonstrate an absolute increase of at least 5 mm.

5.1.6 Data Monitoring Committee and Other External Committees

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). This collaborative process constitutes the safety monitoring plan for the 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. Because this is an open-label study, WWPS, the BMS medical monitor (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 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) and WWPS single case review physician, the study Medical Monitor (MM), the study biostatistician, and epidemiologist; 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 risk-benefit balance associated with the use of study treatment(s).

5.2 Number of Participants

The approximate total number of participants treated will be up to 308 for Part 1 of Study CA047004, as shown below:

- Part 1A Monotherapy: (BMS-986315): The total sample size is up to approximately 76 participants including 36 participants for the dose escalation phase and up to approximately 40 participants in 1 PD cohort.
- Part 1B Combination Therapy: (BMS-986315 in combination with nivolumab): The total sample size is up to approximately 116 participants including 36 participants for the dose escalation phase and up to approximately 40 participants in each of the 2 PD cohorts.
- Part 1C Combination Therapy: (BMS-986315 in combination with cetuximab): The total sample size is up to approximately 116 participants including 36 participants for the dose escalation phase and up to approximately 40 participants in each of the 2 PD cohorts.

5.3 End of Study Definition

The start of the study is defined as the first visit for the first participant screened. Similarly, the end of the study is defined as the last visit or scheduled procedure shown in the Schedule of Activities (see Section 2) for the last participant. Primary study completion is defined as the final date on which data for the primary endpoint are expected to be collected.

5.4 Scientific Rationale for Study Design

BMS-986315 will be evaluated in participants with RCC, NSCLC and SCCHN who have progressed on or after treatment with anti-PD-(L)1 drugs. These indications were chosen based on prevalence of NKG2A and HLA-E expression on immune cells and tumor cells in the tumor microenvironment (internal data at BMS). Participants in the SCCHN PD cohorts of Parts 1A, 1B, and 1C may be allocated according to CD8+ T-cell infiltration (measured by CD8 IHC), as well as HLA-E expression (measured by total HLA-E IHC) in fresh tumor biopsy samples obtained during the screening period. Background information for biomarker analysis is included in Section 9.8.1. The study design includes the following:

- 35-day Screening period
- Treatment period of up to twenty-six 4-week cycles, totaling 104 weeks;
- Dose escalation phases in monotherapy and combination with nivolumab or cetuximab;
- Safety follow-up period of 100 days;
- Survival follow-up period of up to 2 years.

The rationale for the individual elements of the study design are given below.

5.4.1 Rationale for Dose-Escalation Design

The TITE-BOIN design[46] is used to guide escalation decisions and the MTD selection. Unlike the majority of existing phase I designs, which require suspending the accrual after treating each

cohort of patients, the TITE-BOIN design allows the option for real-time dose assignment decisions for new patients while some enrolled patients' toxicity data are still pending. This may shorten the trial duration and reduce the logistic difficulties caused by repeatedly suspending accrual. The TITE-BOIN works by predicting the DLT outcome for patients whose DLT data are pending based on their follow-up time. It is implemented in a simple way similar to the traditional 3+3 design, but is more flexible and possesses superior operating characteristics that are comparable to those of mTPI2 and the more complex model-based designs, such as the time-to-event continual reassessment method (TITE-CRM).

5.4.2 Rationale for the Combination of BMS-986315 with Nivolumab

I-O represented a paradigm shift in cancer treatment. Unprecedented increase in response rates were obtained, especially through the use of checkpoint inhibitors. In particular, mAbs directed against the PD-1 (programmed-cell death protein 1)/PD-L1 (programmed -cell death ligand 1) axis (PDx) in monotherapy and in combination with anti-CTLA-4, which have been approved for the treatment of several indications, including metastatic melanoma, NSCLC, RCC, bladder cancer, Hodgkin lymphoma, and CRC with microsatellite instability-high or mismatched repair-deficient.[47,48,49,50,51]

PD-1 is a member of the CD28 family of T-cell co-stimulatory receptors that also includes CD28, CTLA-4, ICOS, and BTLA. [52] PD-1 signaling has been shown to inhibit CD28-mediated upregulation of IL-2, IL-10, IL-13, IFN-γ and Bcl-xL. PD-1 expression has also been noted to inhibit T cell activation, and expansion of previously activated cells. Evidence for a negative regulatory role of PD-1 comes from studies of PD-1 deficient mice, which develop a variety of autoimmune phenotypes.[53] These results suggest that PD-1 blockade has the potential to activate anti-self T-cell responses, but these responses are variable and dependent upon various host genetic factors. Thus, PD-1 deficiency or inhibition is not accompanied by a universal loss of tolerance to self-antigens.

In vitro, nivolumab (BMS-936558) binds to PD-1 with high affinity (EC50 0.39-2.62 nM), and inhibits the binding of PD-1 to its ligands PD-L1 and PD-L2 (IC50 ± 1 nM). Nivolumab binds specifically to PD-1 and not to related members of the CD28 family such as CD28, ICOS, CTLA-4 and BTLA. Blockade of the PD-1 pathway by nivolumab results in a reproducible enhancement of both proliferation and IFN-γ release in the mixed lymphocyte reaction (MLR). Using a cytomegalovirus (CMV) re-stimulation assay with PBMC, the effect of nivolumab on antigen specific recall response indicates that nivolumab augmented IFN-γ secretion from CMV specific memory T cells in a dose-dependent manner versus isotype-matched control. In vivo blockade of PD-1 by a murine analog of nivolumab enhances the anti-tumor immune response and result in tumor rejection in several immunocompetent mouse tumor models (MC38, SA1/N, and PAN02).[54]

However, only a fraction of the patients benefit from treatment with specific PD-1 or PD-L1 antibodies; moreover, many will develop secondary resistance after initially responding. One of the major hurdles in immune-oncology is understanding the mechanisms of primary resistance, as well as what leads to loss of response. In this sense, the identification of novel molecular targets and development of combined therapies is crucial. Blocking additional inhibitory pathways of

effector lymphocytes may lead to superior response and make it possible to overcome resistance. Moreover, targeting receptors that may have an effect on tumor infiltrating immune cells beyond T cells may be an attractive strategy. Since NKG2A is expressed on effector/memory CD8+, but also on NK, NKT and γδ-T cells, and both NKG2A and HLA-E expression have been linked to worse prognostic features in solid and hematologic malignancies, the combination of nivolumab and BMS-986315 may potentiate responses in participants with inflamed tumors that express HLA-E.

BMS-986315 enhances NK and CD8+ T cell effector function (e.g. cytotoxicity and cytokine production) in functional assays using primary NK and CD8+ T cells isolated from healthy human PBMC). Furthermore, co-blockade of NKG2A:HLA-E and PD-1:PD-L1 further increases tumor infiltrating CD8+ T cell functional activity in vitro. Anti NKG2A mouse surrogate antibody (anti-mNKG2A) alone or in combination with anti mPD 1 reduces tumor growth in multiple mouse tumor models. Treatment with anti mNKG2A mAb as a single agent led to reduced tumor growth in the CT26 and 1956 syngeneic mouse tumor models. The combination of anti-mNKG2A and anti-mPD-1 mAbs demonstrated further enhancement in antitumor activity that was associated with an increase in NK and tumor specific CD8 T-cell cytotoxicity and IFN γ levels. Anti-mNKG2A combined with anti mPD-1 extended survival of mice over single agents versus each agent alone in the A20 lymphoma model. Together, BMS 986315 in combination with anti-PD-1 may reverse the inhibitory pathways among CD8+ T cells and NK cells, providing therapeutic benefit beyond anti PD-1 monotherapy.

The power of combining immune-oncology drugs to broaden responses has been demonstrated in metastatic melanoma and RCC.[55,56] Prior experience with the combination of nivolumab and ipilimumab, and the pre-clinical data utilizing the combination of BMS-986315, and anti-PD-1 support the investigation of this combination in the clinic.

5.4.3 Rationale for the Combination of BMS-986315 with Cetuximab

The anti-EGFR monoclonal antibody, cetuximab acts by inducing Fcγ receptor-mediated ADCC. In in vitro studies using human cells, cetuximab has been shown to enhance NK cell killing of primary colon tumors through ADCC. Specifically, cetuximab enhanced the cytotoxic activity of NK cells on EGFR+ tumor cells in a CD16 dependent manner.[19]

In addition, NKG2A blockade with monalizumab has been shown to enhance cetuximab-mediated ADCC (CD137 and CD107 used as a readout) in a dose dependent manner using co-cultures of PBMC from healthy volunteers with head and neck tumor cell lines that express HLA-E and EGFR.[57] Taken together, combination of monalizumab and cetuximab may provide greater antitumor activity than either agent alone.

One other NKG2A inhibitor has been tested in combination with cetuximab, monalizumab from Innate Pharma/Astra-Zeneca. A phase II study evaluated the combination of monalizumab and cetuximab in 40 platinum-progressed SCCHN participants, with toxicity comparable to that of cetuximab alone. An ORR of 27.5%, mPFS of 5 months and mOS of 10.3 months, although not directly compared to cetuximab monotherapy in this study, are superior to historical data for

cetuximab monotherapy[58] which strongly suggests a role for monalizumab in the observed response rate.

Based on the scientific rationale for the combination and the precedent data for monalizumab, BMS-986315 will be tested in combination with cetuximab in SCCHN participants in Part 1C in this study.

5.4.4 Rationale for Prospective Biomarker Identification

BMS-986315 will be developed in participants with NSCLC, RCC and SCCHN. These indications were chosen based on expression of the target (NKG2A) and the ligand (HLA-E) for BMS-986315 which may increase efficacy. The PD cohorts will include only participants with SCCHN to allow for a more robust measurement of pharmacodynamic readouts, while participants with SCCHN, NSCLC, and RCC will be enrolled in escalation cohorts. All participants in the PD cohorts will be allocated to "biomarker negative" or "biomarker positive" groups according to IHC analysis of CD8 and HLA-E expression in a fresh tumor biopsy obtained during the screening period. Participants in escalation cohorts will be evaluated for CD8 and HLA-E expression retrospectively. The goal of each PD cohort is to obtain approximately 10 paired biopsy samples of participants who are considered as "biomarker negative" and 20 paired biopsy samples of participants who are considered as "biomarker positive", which is consistent with the expected natural prevalence of these biomarkers in SCCHN. [redacted] Responses to PD-1 and PD-L1 therapies have been enriched in patients with increases in inflamed tumor microenvironments. These tumors are also more likely to respond to other immune checkpoint blockade, including anti-NKG2A therapy. [redacted] will enrich for participants who have CD8 T cells present and are more likely to respond checkpoint blockade. The presence of the HLA-E ligand is necessary for response to NKG2A blockade. [redacted] enriches for the presence of HLA-E and increases the likelihood that it is expressed on the membrane.

Internal data suggest that a correlation exists between CD8 and NKG2A expression based on analysis of a set of tumor samples including NSCLC, RCC and SCCHN. Enrolling both biomarker-negative and biomarker-positive participants will provide a better understanding of the impact of HLA-E and CD8 expression on pharmacodynamic activity and potentially clinical activity. Further details on the assessment of CD8 and HLA-E expression in patient tumor samples can be found in Section 9.8.1.

Investigators and staff will follow local institutional guidelines for the safe performance of biopsies and procedures that require general anesthesia should not be performed to obtain a biopsy specimen. Prior to the biopsy procedure, the investigators should consult with the radiology staff to evaluate the degree of risk associated with the procedure. This evaluation must find the biopsy procedure clinically acceptable.

5.4.5 Rationale for Two Year Duration of Treatment with Nivolumab

The optimal duration of immunotherapy is an important question and continues to be investigated. Clinical trials across different tumors types in the nivolumab and ipilimumab development program indicate that most of the responses occur early, with a median time to response of 2-4 months[59,60,61,62,63] and emerging data suggests that benefit can be maintained in the absence of continued treatment. A recent analysis in a melanoma study suggests the majority of patients who discontinue nivolumab for toxicity maintain disease control in the absence of further treatment.[64] Furthermore, a limited duration of ipilimumab, including only 4 induction doses, resulted in long term survival in patients with metastatic melanoma, with a sustained plateau in survival starting around 2 years after the start of treatment.[65]

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 participants with previously treated advanced solid tumors (including 129 participants with NSCLC), specified a maximum treatment duration of 2 years. Among 16 participants with NSCLC who discontinued nivolumab after completing 2 years of treatment, 12 participants were alive >5 years later 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.[66] 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).[67]

Similar results have been reported in clinical studies of pembrolizumab, another PD-1 inhibitor. Keynote-010 was a randomized phase 3 trial of pembrolizumab (at either 2 mg/kg or 10 mg/kg every 3 weeks) versus docetaxel in participants with previously treated, PD-L1-positive, advanced NSCLC which specified a maximum treatment duration of 2 years for pembrolizumab. OS was significantly longer with both pembrolizumab 2 mg/kg (HR 0.72, $p = 0.00017$) and pembrolizumab 10 mg/kg (HR 0.60, $p < 0.00001$) compared to docetaxel, with an OS plateau developing beyond 2 years in both pembrolizumab arms. Among 690 patients who received pembrolizumab, 47 patients completed 2 years of pembrolizumab and stopped treatment. Most were able to maintain their response, including those with SD, with only 2 patients (4%) having confirmed progression after stopping at 2 years.[68]

Keynote-006 was a randomized phase 3 study of pembrolizumab versus ipilimumab in patients with advanced melanoma, which also specified a maximum 2 year duration of pembrolizumab treatment. 104 (19%) of 556 patients randomized to pembrolizumab completed 2 years of treatment. With a median follow-up of 9 months after completion of pembrolizumab, the estimated risk of progression or death was 9% in these patients.[69]

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

In contrast, a shorter duration of nivolumab of only 1 year was associated with increased risk of progression in previously treated participants with NSCLC, suggesting that treatment beyond 1 year is likely needed. In CA209153, participants with previously treated advanced NSCLC who completed 1 year of nivolumab therapy were randomized to either continue or stop treatment, with the option of retreatment upon progression. Among 163 participants still on treatment at 1 year and without progression, those who were randomized to continue nivolumab had significant improvement in PFS compared to those who were randomized to stop treatment, with median PFS (post-randomization) not reached vs 10.3 months, respectively; HR=0.42 (95% CI, 0.25 to 0.71). With a median follow-up of 14.9 months post-randomization, there also was a trend for participants on continued treatment to live longer (OS HR = 0.63 [95% CI: 0.33, 1.20]). Of note, the PFS curves in both groups plateau approximately 1 year after randomization (i.e., 2 years after treatment initiation), suggesting that there may be minimal benefit in extending treatment beyond a total of 2 years[70].

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

5.5 Justification for Dose

5.5.1 Justification for Dose selection and Dosing Schedule of BMS-986315

The FIH starting dose of BMS-986315 is selected to be 80 mg flat dose administered Q4W. This is determined by taking into consideration the totality of nonclinical pharmacology and toxicology data for BMS-986315, as well as the available clinical experience for the same target with monalizumab. The toxicology-based approach for the starting dose selection utilizes the highest nonseverely toxic dose (HNSTD) identified from a 1-month repeat-dose toxicity study in cynomolgus monkeys. The human starting dose of BMS-986315 is projected by targeting < 90% tumor NKG2A RO at trough. In addition, the emerging clinical safety and PK data on monalizumab, another monoclonal antibody targeting NKG2A, under clinical development are used to inform the starting dose selection after detailed comparisons of in vitro activities between monalizumab and BMS-986315 conducted by BMS.

The HNSTD of BMS-986315 from a GLP 1-month repeat-dose toxicity study in monkeys was determined to be 100 mg/kg. BMS-986315 is well tolerated at doses up to the highest dose tested of 100 mg/kg in monkeys. Using the standard body weight (BW) conversion to the human equivalent dose and applying a safety factor of 6 fold, the maximum recommended human starting dose is calculated to be 16.7 mg/kg (or 1336 mg for a BW of 80 kg). In addition, the exposure-based method for starting dose calculation is used. At the HNSTD, the antibody drug exposure (AUC[0-168h]) observed after the 4th dose was 425,000 µg•h/mL. Assuming that the drug exposure in monkeys was at steady state, the FIH starting dose after applying a safety factor of 6-fold is estimated to be 8.1 mg/kg (or 650 mg for the BW of 80 kg), using the predicted human clearance of 2.75 mL/d/kg.

The human starting dose of BMS-986315 is projected by targeting < 90% tumor NKG2A RO at trough. The maximum antitumor efficacy was demonstrated in the 1956 and CT26 mouse syngeneic models at a dose of 1 mg/kg, using an anti-mNKG2A mouse surrogate antibody that had binding affinity and functional activity comparable to BMS-986315. The minimal antitumor effect was observed at doses ≤ 0.3 mg/kg with the trough intratumor NKG2A RO of ≤ 65%. In contrast, the intratumor NKG2A RO at the maximum eficacious dose of 1 mg/kg were estimated to be 92-96% at trough. PK/pharmacodynamic modeling of mouse blood and tumor RO data with the surrogate antibody revealed that the tumor NKG2A RO EC50 was about 10-fold higher than that in blood. Agreements in the RO EC50 values between in vitro and in vivo were also observed in both mice (blood and tumor) and monkeys (blood). Together with 10% tumor penetration results observed in mice, the predicted human PK data, and the human in vitro whole blood RO EC50 of 0.05 nM, at the human starting IV dose of 1 mg/kg given Q4W (80 mg for a 80-kg subject), the projected intratumor RO at trough is < 90%.

Clinical safety experience of monalizumab that is currently under Phase 2 trials is leveraged to support the starting dose selection of BMS-986315. Monalizumab is a humanized (IgG4S241P) antibody with a high binding affinity for the NKG2A receptor and inert FcγR binding that is the similar to BMS-986315. In-house side-by-side experiments showed comparable RO EC50 values in blood samples obtained from healthy participants and cancer patients (N = 24), with the RO EC50 of BMS-986315 being 2-fold more potent than that (0.11 nM) of monalizumab. Using the same prediction methodology as BMS-986315, the intratumor RO for monalizumab at its Phase II dose of 10 mg/kg Q2W is predicted to be > 95% at trough.

Considering the totality of preclinical pharmacology and toxicology data along with prior clinical safety experience for the same target, the FIH starting dose of BMS-986315 is selected to be 80 mg flat dose administered Q4W. The dosing schedule of Q4W is selected based on projected human T1/2 of BMS-986315 at ~16 days. The proposed FIH starting dose represents the intent of ensuring adequate patient safety while limiting the number of cancer patients receiving sub-therapeutic doses.

5.5.2 Justification for Dose of Nivolumab

The nivolumab dose of 480 mg Q4W was selected for this study based on clinical data and modeling and simulation approaches using population PK (PPK) and exposure-response (ER) analyses examining relationships between nivolumab exposures and efficacy (eg, OS and OR) and safety responses, using data from studies in multiple tumor types (melanoma, NSCLC, and RCC) with body weight-normalized dosing (mg/kg). A flat dose is expected to reduce prescription dosing errors, shorten pharmacy preparation time, and improve ease of administration. Extending the dosing interval to 4 weeks provides numerous benefits to patients, as they would have increased flexibility between clinical visits. The PPK analyses have shown that exposure to nivolumab increased dose proportionally over the dose range of 0.1 mg/kg to 10 mg/kg administered Q2W, and no clinically meaningful differences in PK across ethnicities and tumor types were observed.

Nivolumab clearance and volume of distribution were found to increase as body weight increases but less than proportionally with increasing weight, indicating that milligram-per-kilogram dosing

represents an over-adjustment for the effect of body weight on nivolumab PK. Using the PPK and ER models, nivolumab exposures and probabilities of efficacy responses and risks of AEs were predicted following nivolumab 480 mg Q4W and were comparable to those following nivolumab 3 mg/kg Q2W. The overall distributions of average nivolumab steady-state exposures (Cavgss) were comparable following administration with either nivolumab 3 mg/kg Q2W or nivolumab 480 mg Q4W over a wide range of body-weight ranges. Nivolumab 480 mg Q4W is predicted to result in approximately 43% greater steady-state peak concentrations (Cmaxss) compared to nivolumab 3 mg/kg Q2W; however, these exposures are predicted to be lower than the exposure ranges observed at doses up to nivolumab 10 mg/kg Q2W used in the nivolumab clinical program. Although the Cmaxss of nivolumab is expected to be greater following nivolumab 480 mg Q4W compared to nivolumab 3 mg/kg Q2W, the predicted Cmaxss following nivolumab 480 mg Q4W is well below the median Cmaxss achieved following administration of nivolumab 10 mg/kg Q2W, a safe and tolerable dose level.

Exposure-safety analysis demonstrated that the exposure margins for safety are maintained following nivolumab 480 mg Q4W, and the predicted risks of discontinuations due to AEs or death, Grade 3+ AEs, and Grade 2+ immune-mediated AEs (IMAEs) are predicted to be similar following nivolumab 480 mg Q4W relative to nivolumab 3 mg/kg Q2W across tumor types. Safety analyses using available data following nivolumab 3 mg/kg Q2W and 10 mg/kg Q2W administration indicated that there were no differences in AE profiles across body-weight groups. Finally, initial evidence demonstrates that, following administration of nivolumab 480 mg Q4W, nivolumab has been well tolerated.

Nivolumab 480 mg Q4W is predicted to have approximately 16% lower steady-state trough concentrations (Cminss) compared to nivolumab 3 mg/kg Q2W. While these exposures are predicted to be lower, they are on the flat part of the ER curves and are not predicted to affect efficacy. Exposure-efficacy analyses of multiple PK measures and efficacy endpoints (e.g., OS and OR) indicated that, following administration of nivolumab 480 mg Q4W, efficacy is predicted to be similar to that following administration of nivolumab 3 mg/kg Q2W across multiple tumor types. Based on these data, nivolumab 480 mg Q4W is expected to have similar efficacy and safety profiles to nivolumab 240 mg Q2W or nivolumab 3 mg/kg Q2W.

5.5.3 Justification for dose of Cetuximab

Cetuximab will be used in this study at an alternative dose and schedule of 500 mg/m^2 Q2W. The selected dosing regimen for cetuximab at 500 mg/m^2 every 2 weeks suggested moderately lower trough concentration and comparable AUC at steady-state (35.2 ± 13.8 µg/mL and 34953 µg/mL·h over 2 weeks) as compared to the approved dosing regimen (47.0 ± 37.3 µg/mL and 17278 µg/mL·h over 1 week)[71], while peak concentration at steady-state is higher (306 ± 63 µg/mL) compared to that of the approved dosing regimen (210 ± 54 µg/mL).[42]

This dose and schedule is supported by several studies in which participants with SCCHN and colorectal cancer were treated with cetuximab monotherapy or in combination with varied chemotherapy regimens. [40,41,42,43,44] In these reports, safety and efficacy were comparable to the

approved dose of 400 mg/m^2 followed by 250 mg/m^2 QW. The choice for the Q2W schedule aims at alleviating the treatment burden for participants, who will be spared from weekly clinical visits and infusion time. The schedule for BMS-986315 will be Q4W in Part 1C.

Rigorous safety monitoring directed at known cetuximab-associated adverse events will be applied to all participants enrolled in Part 1C. Cetuximab dose may be changed to the approved dose (400mg/m^2 followed by 250mg/m^2 QW) for the entire program, at any time, after discussion and agreement between the Investigators and the Sponsor.

6 STUDY POPULATION

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

6.1 Inclusion Criteria

1) Signed Written Informed Consent

a) Participants or legally authorized representative (see Appendix 2), must have signed and dated an Institutional Review Board (IRB)/Independent Ethics Committee (IEC) approved written informed consent form in accordance with regulatory and institutional guidelines. This must be obtained before the performance of any protocol related procedures that are not part of normal patient care.

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

c) The participant must sign the consent for screening/pre-treatment and on-treatment tumor biopsy samples at an acceptable clinical risk, as judged by the investigator. Therefore, the participant must have a suitable tumor lesion for the biopsy procedure, as judged by the investigator, in order to be eligible for the study (See Section 9.8.1 for details).

2) Type of Participant and Target Disease Characteristics

a) A fresh pre-treatment tumor biopsy from an unresectable or metastatic site of disease must be provided for biomarker analyses, and to the analytical laboratory for inclusion. The fresh biopsy will be evaluated for adequate and evaluable tumor tissue. Only those participants who have met tissue quality thresholds and have evaluable CD8 and HLA-E can be assigned for treatment in PD cohorts. Please refer to the laboratory manual for additional details. Participants with an unevaluable CD8 or HLA-E results will not be permitted to enter the PD cohorts of the study. The biopsy must be a core biopsy, a punch biopsy, an excisional biopsy, or a surgical specimen. Fine needle aspiration is unacceptable for submission.

b) Participants must have histologic confirmation of 1 of the 3 tumors described below (metastatic, recurrent and/or unresectable), with measurable disease per RECIST v1.1 (Appendix 7) and, in addition, have at least 1 lesion accessible for biopsy.

c) Eastern Cooperative Oncology Group Performance Status of 0 or 1 (Appendix 6).

d) Participants with controlled brain metastases are eligible. Controlled brain metastases are defined as no radiographic progression for at least 4 weeks following radiation and/or surgical treatment (or 4 weeks of observation if no intervention is clinically indicated), and no longer taking steroids for at least 2 weeks prior to first dose of study treatment, and with no new or progressive neurological signs and symptoms.

e) Study participants will be expected to have received standard of care therapies, including an available PD-(L)1 inhibitor known to be effective in the tumor type for which they are being evaluated.

f) Participants with RCC
   i) Advanced or metastatic RCC with clear cell component
   ii) Participants must have received at least 1 but not more than 2 prior anti-angiogenic therapy regimens (including but not limited to sunitinib, sorafenib, pazopanib, axitinib, tivozanib, and bevacizumab) in the advanced or metastatic setting. Prior cytokine therapy (e.g., IL-2 IFN-g), vaccine therapy, or treatment with cytotoxics is allowed.
   iii) **Not applicable per revised protocol 02**: Participants must have received no more than 3 total prior systemic treatment regimens in the advanced or metastatic setting and must have evidence of progression on or after the last treatment regimen received and within 6 months prior to study enrollment.
   iv) For enrollment in escalation cohorts, participants must have received and progressed on or after anti-PD-(L)1 therapy, if available.
   v) Participants must have received prior systemic treatment regimens in the advanced or metastatic setting and must have evidence of progression on or after the last treatment regimen received and within 6 months prior to study enrollment.

g) Participants with NSCLC
   i) Histologically confirmed NSCLC meeting stage criteria for stage IIIB, stage IV, or recurrent disease.
   ii) Participants must have recurrent or progressive disease during or after platinum doublet-based chemotherapy or at least two prior lines of systemic therapy for advanced or metastatic disease. OR Must have recurrent or progressive disease within 6 months after completing platinum-based chemotherapy for local disease.
   iii) **Not applicable per revised protocol 02:** Participants must have known EGFR status, anaplastic lymphoma kinase (ALK) status, and ROS1 receptor tyrosine kinase mutational status.
      (a) Participants with an activating EGFR mutation must have received an EGFR tyrosine kinase inhibitor
      (b) Participants with an ALK translocation or ROS1 mutational status must have received the correspondent targeted therapy
   iv) For enrollment in escalation cohorts, participants must have received and progressed on or after anti-PD-(L)1 therapy, if available.
   v) Status for actionable mutations (eg, EGFR, ALK, ROS1, RET, etc.) must be known (when testing is available as per country/region standard of care practices); participants with actionable mutations must have received and progressed on, have been intolerant to, or not be a candidate for, standard tyrosine kinase inhibitors (as available per country/region standard of care practices).

h) Participants with SCCHN
   i) Histologically confirmed, recurrent, or metastatic squamous cell carcinoma of the head and neck (oral cavity, pharynx, larynx), and not amenable to local therapy with curative intent.

ii) Participants who progressed on or after, or were intolerant to, a platinum-containing regimen.

iii) Prior curative radiation therapy must have been completed at least 4 weeks prior to first study drug administration. Prior focal palliative radiotherapy must have been completed at least 2 weeks before study drug administration.

iv) Documentation of p16 is sufficient to determine human papillomavirus (HPV) status of tumor for SCCHN of the oropharynx. Note: If results are not available, then a sample (tissue on microscopic slides, tissue block or a fresh tissue biopsy in formalin) should be sent to the central laboratory for analysis.

v) For enrollment in escalation cohorts, participants must have received and progressed on or after anti-PD-(L)1 therapy, if available.

vi) For enrollment in the PD cohorts only, participants must have received and been resistant to anti-PD-(L)1 therapy. Refer to inclusion criteria 2 i) for the definition of anti-PD-(L)1 resistance.

i) Participants with SCCHN in the PD cohorts must have received prior anti-PD-1/PD-L1 therapy and have radiologically or clinically documented disease progression or recurring disease on or within 3 months following last dose of anti-PD-1/PD-L1 therapy for their advanced (metastatic and/or unresectable) cancer, and have been considered for all other potentially efficacious therapies prior to enrollment.

(1) One intervening systemic therapy is allowed between anti-PD-(L)1 therapy and enrollment

(2) Anti-PD-(L)1 therapies may have been received in sequential or combination regimens

(3) Required documentation includes start and stop dates of prior anti-PD(L)1 therapy and a progression date no more than 3 months after the last dose of anti-PD-(L)1 therapy. If only clinical progression was captured from prior therapy, radiologic progression is to be documented via pre-treatment scan prior to treatment assignment by IRT. Investigators will be required to confirm progression on follow-up imaging in cases of equivocal progression.

(4) All available scans on the prior anti-PD-(L)1 containing regimen, including the baseline scan (prior to starting anti-PD-(L)1 and scans after the last dose of anti-PD-(L)1 but before the start of any intervening therapy will be submitted to the imaging vendor and may undergo BICR at the Sponsor's discretion.

3) Age and Reproductive Status

Investigators shall counsel women of childbearing potential (WOCBP) participants, and male participants who are sexually active with WOCBP, on the importance of pregnancy prevention and the implications of an unexpected pregnancy.

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

a) **Female Participants**

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

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

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

iv) WOCBP must have a negative highly sensitive pregnancy test (if urine: minimum sensitivity 25 IU/L or equivalent units of 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.

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

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

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

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

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

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

(1) Is not a WOCBP
OR

(2) Is a WOCBP and using a contraceptive method that is highly effective (with a failure rate of <1% per year), with low user dependency, as described in Appendix 4 during the treatment period and for at least 5 months from the last dose of study treatment. WOCBP agree not to donate eggs (ova, oocytes) for the purpose of reproduction for the same time period as contraception requirements listed above.

b) Male Participants

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

ii) **Not applicable per protocol revision 02**: Males who are sexually active with WOCBP must agree to follow instructions for method(s) of contraception defined in Appendix 4 and as described below.

iii) **Not applicable per protocol revision 02:** Azoospermic males are not exempt from contraceptive requirements and will be required to always use a latex or other synthetic condom during any sexual activity (eg, vaginal, anal, oral) with WOCBP even if the participant has undergone a successful vasectomy or if the partner is pregnant.

iv) **Not applicable per protocol revision 02:** 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. Males should continue to use a condom during the treatment period and for at least 6 months if receiving BMS-986315 monotherapy or in combination with cetuximab or 7 months if receiving nivolumab in combination with BMS-986315 after the last dose of study treatment.

v) **Not applicable per protocol revision 02:** Female partners of males participating in the study should be advised to use highly effective methods of contraception during the treatment period and for at least 6 months if receiving BMS-986315 monotherapy or in combination with cetuximab or 7 months if receiving nivolumab in combination with BMS-986315 after the last dose of study treatment.

vi) **Not applicable per protocol revision 02:** Male participants must refrain from donating sperm during the treatment period and for at least 6 months if receiving BMS-986315 monotherapy or in combination with cetuximab or 7 months if receiving nivolumab in combination with BMS-986315 after the last dose of study treatment.

vii) **Not applicable per protocol revision 02:** 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.

viii) No additional contraceptive measures are required to be used.

6.2 Exclusion Criteria

1) Medical Conditions

a) Women who are breastfeeding

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

2) Medical History and Concurrent Diseases

a) For Part 1C only, participants who experienced Grade 3 or above infusion-related reactions from prior EGFR inhibiting therapy.

b) Participants with active, known or suspected autoimmune disease.

(1) Participants with atopic dermatitis, well controlled asthma and/or mild allergic rhinitis (seasonal allergies) are eligible

(2) Participants with the following disease conditions are also eligible:

(a) Vitiligo

(b) Type 1 diabetes mellitus on stable conditions under insulin treatment

(c) Residual hypothyroidism due to autoimmune condition only requiring hormone replacement

(d) Euthyroid participants with a history of Graves' disease (participants with suspected autoimmune thyroid disorders must be negative for thyroglobulin and thyroid peroxidase antibodies and thyroid stimulating Ig prior to the first dose of study drug(s).

(3) The pathogenesis of psoriasis has been linked to the activity of NK cells and therefore participants with psoriasis with any degree of severity are excluded from this study.

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

d) **Not applicable per protocol revision 02**: Known history of positive test for human immunodeficiency virus (HIV) or known acquired immunodeficiency syndrome (AIDS). NOTE: Testing for HIV must be performed at sites where mandated locally.

e) Participants with concomitant second malignancies (except adequately treated nomelanomatous skin cancers or in situ bladder, breast, or cervical cancers) are excluded unless a complete remission was achieved at least 2 years prior to study entry, and no additional therapy is required or anticipated to be required during the study period. However, participants with concomitant malignancies that do not require treatment and are clinically stable and anticipated to be followed in an active surveillance manner for the next 12 months may be eligible, upon agreement with the medical monitor. Treatment should not be required at timing of consent and not be expected to be needed not only for the concurrent malignancy, but also for complications caused by it. The investigator should inform the participant that the study treatment is not intended and not expected to be considered as treatment for the concurrent malignancy.

f) Participants with serious or uncontrolled medical disorders.

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

h) Prior organ or tissue allograft

i) 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 6 months

ii) Uncontrolled angina within the past 3 months

iii) Any history of clinically significant arrhythmias (such as ventricular tachycardia, ventricular fibrillation, or torsades de pointes)

iv) History of other clinically significant heart disease (e.g., cardiomyopathy, congestive heart failure with New York Heart Association functional classification III to IV (Appendix 9).

v) Cardiovascular disease-related requirement for daily supplemental oxygen therapy

vi) QT interval corrected for heart rate using Fridericia's formula (QTcF) prolongation > 480 msec, except for right bundle branch block

vii) History of myocarditis regardless of etiology

j) History of or with active interstitial lung disease or pulmonary fibrosis

k) History of chronic hepatitis as evidenced by the following:
   (a) Positive test for hepatitis B surface antigen
   (b) Positive test for qualitative hepatitis C viral load by PCR
   (c) Participants with positive hepatitis C antibody and negative quantitative hepatitis C by PCR are eligible. History of resolved hepatitis A virus infection is not an exclusion criterion.
   (d) Additional testing or substitute testing per institutional guidelines to rule out infection is permitted

l) Evidence of active infection that requires systemic antibacterial, antiviral, or antifungal therapy ≤7 days prior to the first dose of study drug (except for viral infections that are presumed to be associated with the underlying tumor type required for study entry).

m) Receipt of non-oncology vaccines containing live virus for prevention of infectious diseases within 30 days prior to first dose of study drug.

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

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

p) 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 medical monitor, there are no sequelae that would place the participant at a higher risk of receiving study treatment.

q) Previous SARS-CoV-2 vaccine within 14 days of C1D1.

r) Known HIV positive with an AIDS defining opportunistic infection within the last year or a current CD4 count < 350 cells/µL. Participants with HIV are eligible if:
   - they have received antiretroviral therapy (ART) for at least 4 weeks prior to treatment assignment as clinically indicated while enrolled on study
   - they continue on ART as clinically indicated while enrolled on study
   - 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.

s) Leptomeningeal metastases

3) Prior/Concomitant Therapy

a) Cytotoxic agents, unless at least 4 weeks have elapsed from last dose of prior anti-cancer therapy and initiation of study therapy.

b) Non-cytotoxic agents, unless at least 4 weeks or 5 half-lives (whichever is shorter) have elapsed from the last dose of prior anti-cancer therapy and the initiation of study therapy. agents.

c) Prior immune therapy treatments, unless at least 4 weeks or 5 half-lives (whichever is shorter) have elapsed from the last dose of immune therapy and initiation of study therapy.

d) Prior participation in anti-NKG2A clinical study

e) Treatment with botanical preparations (eg herbal supplements or traditional Chinese medicines) intended for general health support or to treat the disease under study within 2 weeks prior to randomization/treatment. Refer to Section 7.7.1 for prohibited therapies.

f) SCCHN participants to be enrolled in Part 1C:

i) Previous treatment with cetuximab, unless it was received in the locally advanced setting and did not have progressive disease for at least 4 months of treatment. Use of cetuximab in the R/M setting is an exclusion criteria, regardless of response.

ii) Prior Grade 3 or 4 cetuximab related IRR

iii) Active severe acne or skin infection

iv) Allergy to galactose-alpha-1 and 3-galactose (alpha-gal)

v) Hypomagnesemia, unless imbalance is corrected and a follow up test demonstrates normal magnesium levels

4) Physical and Laboratory Test Findings

a) WBC < 2,000/μL

b) Neutrophils < 1500/μL

c) Platelets < 100×10^3/μL

d) Hemoglobin < 9.0 g/dL

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

f) AST/ALT: > 3.0 × ULN

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

5) Allergies and Adverse Drug Reaction

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

b) History of allergy or hypersensitivity to study drug components

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 Bristol Myers Squibb approval is required.

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

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

6.3 Lifestyle Restrictions

Participants in Part 1C should be advised to avoid sun exposure. Participants should wear sunscreen and hats and limit sun exposure during treatment and for 2 months after the last dose of cetuximab.

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 serious AEs.

6.4.1 Retesting During Screening or Lead-In Period

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

Retesting of laboratory parameters and/or other assessments during the extended screening period will be permitted (in addition to any parameters that require a confirmatory value).The most current result prior to treatment assignment is the value by which study inclusion will be assessed, as it represents the participant's most current, clinical state.

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

Testing for asymptomatic SARS-CoV-2 infection by RT-PCR or viral antigen is not required. However, some participants may develop suspected or confirmed symptomatic SARS-CoV-2 infection, or be discovered to have asymptomatic SARS-CoV-2 infection during the screening period. In such cases, subjects may be considered eligible for the study after meeting all inclusion/exclusion criteria related to active infection, and after meeting the following criteria:

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

screening tests already performed which could potentially be affected by the SARS-CoV-2 infection or its complications on an individual basis and agreed upon with the Medical Monitor (eg, safety labs, oxygen saturation, chest CT scan) should be repeated.

7 TREATMENT

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

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

- BMS-986315
- Nivolumab
- Cetuximab

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

Drugs used in this open-label study qualify as IPs. Their description and storage information are described in Table 7-1. Please refer to the Pharmacy Manual for additional information.

Table 7-1: Study treatments for CA047004

Product Description / Class and Dosage Form	Potency	IP/Non-IMP	Blinded or Open Label	Packaging / Appearance	Storage Conditions (per label)
BMS-986315	120mg/mL	IP	Open Label	Kit	Refer to Product Label
Nivolumab	10 mg/mL	IP	Open Label	Kit	Refer to Product Label
Cetuximab	100 mg/50mL, 200 mg/100 mL & various strengths	IP	Open Label	Kit	Refer to Product Label

Abbreviations: IP: Investigational Product

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

7.1 Treatments Administered

The dosing schedule for each IP is detailed below in Table 7.1-1 for all study parts. Planned dose levels may be modified (eg, change in administration schedule) based upon evaluation of all available safety, PK, and pharmacodynamic data.

All participants will be monitored continuously for AEs while on study treatment. Treatment modifications (eg, dose delay, reduction, re-treatment, or discontinuation) will be based on specific laboratory and AE criteria, as described in Section 7.4. All participants treated in Part 1C should receive pre-medication as described in Section 7.4.2.3.

Table 7.1-1: Selection and Timing of Dose[a]

Study Treatment	Unit dose strength(s)/Dosage level(s)	Dosage formulation Frequency of Administration	Route of Administration
BMS-986315	80, 200, 600, 1200, and 2400 mg	Q4W	IV
Nivolumab	480mg	Q4W	IV
Cetuximab	500mg/m^2	Q2W	IV

Abbreviations: Q4W = every 4 weeks; Q2W = every 2 weeks; IV = intravenous

[a]Additional doses may be explored.

7.2 Method of Treatment Assignment

During the screening visit, the investigative site will call into the enrollment option of the Interactive Response Technology (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 00001, (e.g., 00001, 00002, 00003....00010). The patient identification number (PID) will ultimately be comprised of the site number and participant number. For example, the first participant screened (i.e., enrolled) at site number 1, will have a PID of 0001 00001. Once it is determined that the participant meets the eligibility criteria following the screening visit, the investigative site will call the IRT to assign the participant into the open dose panel.

Participants will not be replaced if they are discontinued from the study secondary to an adverse event unless the adverse event can be determined to be unrelated to treatment. All eligible participants will be initially assigned to Part 1A (dose escalation of BMS-986315 monotherapy) until the decision is made to escalate to the third dose cohort. Subsequently, treatment in Part 1B and Part 1C can be initiated, and dose escalation in the 3 parts will occur in parallel. That is, Part 1B and Part 1C can be initiated when at least 2 dose levels (the current and 1 higher) in Part 1A have cleared the DLT period in accordance with dose escalation rules, after which dose escalation in Part 1A, Part 1B, and Part 1C will proceed in parallel. Treatment assignments will alternate between all open study parts, with consecutively treated participants assigned to different parts, through IRT, based on cohort availability and inclusion criteria.

In addition, participants enrolled in monotherapy or combination pharmacodynamic cohorts will be assigned to dose levels that are already established as safe based on data coming from the

corresponding dose escalation cohort (see Section 5.1). PD cohort enrollment will take place in Part 1A, Part 1B, and Part 1C. Within each PD cohort, participants will be further assigned to either a CD8/HLA-E positive sub-cohort (biomarker positive), or a CD8/HLA-E negative sub-cohort (biomarker negative) based on the results of biomarker expression analysis.

7.3 Blinding

This is a non-randomized open-label study. The specific treatment to be taken by a participant will be assigned using an Interactive Response Technology (IRT). The site will contact the Interactive Response System prior to the start of study treatment administration for each participant. The site will record the treatment assignment on the applicable case report form, if required.

Designated staff of Bristol Myers Squibb Research & Development may obtain the treatment codes prior to database lock to facilitate the bioanalytical analysis of PK samples and immunogenicity. A bioanalytical scientist in the Bioanalytical Sciences department of Bristol Myers Squibb Research & Development (or a designee in the external central bioanalytical laboratory) will have access to the treatment assignments in order to minimize unnecessary bioanalytical analysis of samples.

7.4 Dosage Modification

Intra-participant dose escalation/reduction of BMS-986315 or nivolumab is not permitted in this study in order to allow better evaluation of the safety and efficacy at individual dose levels and schedules. No dose reductions of BMS-986315 or nivolumab will be allowed. Cetuximab dose may be reduced due to toxicity as described below.

7.4.1 Dose Delays Due to Toxicity

Participants who experience the following must have all study drug(s) withheld:

- Potential DLTs, until DLT relatedness is defined.
- Select AEs and laboratory abnormalities:
  - ≥ Grade 1 pneumonitis
  - ≥ Grade 2 abnormality in AST, ALT or total bilirubin
  - ≥ Grade 2 creatinine increased
  - ≥ Grade 2 diarrhea or colitis
  - ≥ Grade 2 neurological AE
  - Grade 2 myocarditis
  - AE, laboratory abnormality, or concurrent illness that, in the judgment of the Investigator, warrants delaying study drug administration.
  - For SCCHN participants in Part 1C: Grade 3 or 4 acneiform rash
  - Confirmed SARS-CoV-2 infection

Criteria for participants who are required to permanently discontinue both study drugs is listed in Section 8. Participants not meeting guidelines for permanent discontinuation will be permitted to

resume therapy based on the criteria specified below in Section 7.4.2. Participants eligible to resume study therapy will resume study therapy at the nominal treatment visit following their last received study medication dose.

The end of cycle tumor assessments, such as computed tomography (CT), magnetic resonance imaging (MRI), or positron emission tomography (PET), will continue on a Q8W schedule relative to the participant's first dose, regardless of any treatment delay incurred

7.4.2 Criteria to Resume Treatment

Subsequent dosing with study therapy may resume once drug-related non DLT AEs resolve to Grade 1 or baseline. Participants experiencing AEs not meeting criteria for permanent discontinuation as outlined in Section 8 may resume treatment with study medication under the following criteria:

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

- Participants may resume treatment in the presence of Grade 2 fatigue
- Participants who have not experienced a Grade 3 drug-related skin AE may resume treatment in the presence of Grade 2 skin toxicity
- Participants with Grade 2 uveitis, episcleritis, iritis, eye pain or blurred vision not meeting DLT criteria (Section 5.1.3) must resolve to baseline prior to resuming study therapy
- For participants with Grade 2 AST, ALT, or total bilirubin elevations, dosing may resume when laboratory values return to baseline, and management with corticosteroids, if needed, is complete
- Participants with combined AST/ALT and total bilirubin values meeting DLT criteria (Section 5.1.3) should have treatment permanently discontinued.
- Drug-related pulmonary toxicity, diarrhea or colitis must have resolved to baseline before treatment is resumed. Participants with persistent Grade 1 pneumonitis after completion of a steroid taper over at least 1 month may be eligible for retreatment if discussed with and approved by BMS Medical Monitor (or designee).
- Participants with SCCHN in Part 1C may resume treatment in the presence of Grade 2 cetuximab-induced acneiform rash. Please see Section 7.4.2.1 for management and dose reduction guidelines.
- 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-PRC test result, or positive RT-PCR viral antigen test result, 2) resolution of acute symptoms (including at least 24 hours has passed since last fever without fever-reducing medications), 3) evaluation by the Investigator with confirmation that there are no sequelae that would place the participant at a higher risk of receiving investigational treatment, and 4) consultation by the medical monitor. For suspected cases, treatment may also resume if SARS-CoV-2 infection is ruled-out and other criteria to resume treatment are met.
  - Prior to re-initiating on-study treatment in a participant with a dosing delay lasting 8 weeks due to SARS-CoV-2 infection, the medical monitor/designee must be consulted

Participants with drug-related endocrinopathies adequately controlled with only physiologic hormone replacement may resume treatment after consultation with the BMS Medical Monitor (or designee).

7.4.2.1 Management of Cetuximab-Induced Acneiform Rash

Participants with SCCHN in Part 1C must have treatment withheld if diagnosed with Grade 3 or 4 dermatologic toxicity or acneiform rash. Treatment may be resumed when the event has improved to Grade 2, with dose management as described below. If Grade ≥ 3 rash does not resolve to Grade ≤ 2 within 14 days of interruption of cetuximab treatment and despite optimal supportive care, the patient should not receive any further treatment with cetuximab. BMS-986315 treatment may be continued upon discussion between the investigator and the sponsor.

The recommendations for management are as follows:

General/Prevention:

- Grade 1 rash: mild rash may not need treatment. However, if treatment is considered necessary, topical hydrocortisone (1% or 2.5%) cream and/or clindamycin 1% gel can be used.
- Grade 2 rash: relief from major symptoms caused by Grade 2 skin-related adverse events should be achieved by a combination of local and systemic therapies including systemic antibiotics (e.g., doxycycline or minocycline), topical treatment (e.g., hydrocortisone 2.5% cream, clindamycin 1% gel, pimecrolimus 1% cream), antihistamines (e.g., diphenhydramine). Oral corticosteroids will not be allowed for the management of Grade 1 and 2 rash.
- Grade 3 (or greater) rash: may be treated in a manner similar to Grade 2 rash. In the event of Grade ≥ 3 rash, treatment with cetuximab should be paused until recovery Grade ≤ 2. Treatment should be resumed at a reduced dose (see below). If Grade ≥ 3 rash does not resolve to Grade ≤ 2 within 14 days of stopping cetuximab treatment and despite optimal supportive care, the patient should not receive any further treatment with cetuximab.

Grade 3 or 4 dermatologic toxicities and infectious sequelae (e.g., acneiform rash, mucocutaneous disease etc):

- 1st occurrence, Grade 3/4: delay infusion 1 to 2 weeks; if condition improves, continue at 500mg/m^2 Q2W. If no improvement, discontinue cetuximab.
- 2nd occurrence, Grade 3/4: delay infusion 1 to 2 weeks; if condition improves, resume treatment at 400mg/m^2 Q2W. If no improvement, discontinue cetuximab.
- 3rd occurrence, Grade 3/4: delay infusion 1 to 2 weeks; if condition improves, resume treatment at 300mg/m^2 Q2W. If no improvement, discontinue cetuximab.
- 4th occurrence, Grade 3/4: discontinue cetuximab.
- These recommendations were adapted from the cetuximab label "Recommended Dosage Modifications for Adverse Reactions" table. Management should be individualized according to guidelines used at each participating institution and to the clinical judgement of the Investigator.

7.4.2.2 Management of Drug-related Infusion Reactions in Parts 1A and 1B

Since nivolumab and BMS-986315 contain only human immunoglobulin protein sequences, they are unlikely to be immunogenic and induce infusion or hypersensitivity reactions. However, if such a reaction were to occur, it might manifest with fever, chills, rigors, headache, rash, pruritus, arthralgias, hypotension, hypertension, bronchospasm, or other allergic-like reactions. All Grade 3 or 4 infusion reactions should be reported within 24 hours to the study medical monitor and reported as an SAE if it meets the criteria. Infusion reactions should be graded according to NCI CTCAE (Version 5.0) guidelines.

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

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

- Remain at bedside and monitor participant until recovery from symptoms. The following prophylactic premedications are recommended for future infusions: diphenhydramine 50 mg (or equivalent) and/or acetaminophen/paracetamol 325 to 1000 mg at least 30 minutes before additional nivolumab or BMS-986315 administrations.

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

- Stop the study drug infusion, begin an IV infusion of normal saline, and treat the participant with diphenhydramine 50 mg IV (or equivalent) and/or acetaminophen/paracetamol 325 to 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 should be administered at least 30 minutes before nivolumab and/or BMS-986315 infusions. If necessary, corticosteroids (up to 25 mg of hydrocortisone or equivalent) may be used.

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

- Immediately discontinue infusion of study drug. Begin an IV infusion of normal saline and treat the participant as follows: recommend bronchodilators, epinephrine 0.2 to 1 mg of a 1:1000 solution for subcutaneous administration or 0.1 to 0.25 mg of a 1:10,000 solution injected slowly for IV administration, and/or diphenhydramine 50 mg IV with methylprednisolone 100 mg IV (or equivalent), as needed. Participant should be monitored until the Investigator is comfortable that the symptoms will not recur. Study drug will be permanently discontinued except for a Grade 3 infusion reaction that returns to Grade 1 in less than 6 hours. Investigators should follow their institutional guidelines for the treatment of anaphylaxis. Remain at bedside and monitor participant until recovery of the symptoms.
- In case of late-occurring hypersensitivity symptoms (e.g., appearance of a localized or generalized pruritus within 1 week after treatment), symptomatic treatment may be given (e.g., oral antihistamine or corticosteroids).

7.4.2.3 Prevention and Management of Drug-related Infusion Reactions in Part 1C

Cetuximab is known to cause serious and fatal infusion reactions. Among 1373 patients who received cetuximab across clinical trials, any grade infusion-related reactions (IRR) occurred in 8.4% and Grade 3/4 in 2.2% of patients.[22] IRRs might manifest with fever, chills, rigors, headache, rash, pruritus, arthralgia, hypotension, hypertension, bronchospasm, rapid onset of airway obstruction, shock, loss of consciousness, myocardial infarctions and/or cardiac arrest. Approximately 90% of severe IRR to cetuximab occur in the first infusion despite premedication with antihistamines. Infusions should be performed in a setting with resuscitation equipment and other agents necessary to treat anaphylaxis.

All Grade 3 or 4 infusion reactions should be reported within 24 hours to the study medical monitor or designee and reported as an SAE if it meets the criteria. Infusion reactions should be graded according to NCI CTCAE (Version 5.0) guidelines. All Grade 3 or 4 infusion reactions to cetuximab will be considered as DLT and will incur in immediate discontinuation of cetuximab treatment. Participants may continue to receive treatment with BMS-986315 upon discussion between investigator and the Sponsor.

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

For treatment with cetuximab, all recommendations described in Section 7.4.2.2 apply. In addition:

- Premedicate with a histamine-1 (H1) receptor antagonist intravenously 30–60 minutes prior to the first dose or subsequent doses as deemed necessary
- For Grade 1 or 2 infusion reactions: interrupt the infusion and upon recovery, resume the infusion at 50% of the infusion rate.
- For Grade 3 or 4 infusion reactions: immediately and permanently discontinue cetuximab.

7.5 Preparation/Handling/Storage/Accountability

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

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

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

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

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

Please refer to current version of the Investigator Brochures and/or pharmacy manual for complete preparation, storage, and handling information.

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

7.5.1 Retained Samples for Bioavailability / Bioequivalence / Biocomparability

Not applicable.

7.6 Treatment Compliance

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

7.7 Concomitant Therapy

Concomitant medications are recorded at baseline and throughout study treatment and safety follow-up in the appropriate section of the eCRF.

All medications (prescription and over-the-counter [OTC]), vitamin and mineral supplements, and/or herbs taken by the participant from Screening through the Follow-up period will be documented and recorded, including start and stop date, dose and route of administration, frequency, and indication. Medications taken for a procedure (eg, biopsy) should also be included.

Any premedication use should be documented on the appropriate eCRF.

Anti-hypertensive medication usage should be documented on the appropriate eCRF. If anti-hypertensive medication is being periodically withheld, the exact dosing dates should be documented on the eCRF.

Prior anti-cancer treatments will be recorded during Screening and documented on the appropriate eCRF. Any subsequent anti-cancer therapy will be recorded until end of study or death, in the appropriate section of the eCRF.

Supportive medications for the management of acneiform rash for participants in Part 1C, as described in Section 7.4.2.1, should be documented on the appropriate eCRF.

7.7.1 Prohibited and/or Restricted Treatments

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

- 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.
- Immunosuppressive agents
- Immunosuppressive doses of systemic corticosteroids (except as stated in Section 6)
- Any concurrent anti-neoplastic therapy (ie, chemotherapy, hormonal therapy, immunotherapy, extensive, non-palliative radiation therapy)
- Any botanical preparation (eg, herbal supplements or traditional Chinese medicines) intended to treat the disease under study or provide supportive care. Use of marijuana and its derivatives for treatment of symptoms related to cancer or cancer treatment are permitted if obtained by medical prescription or if its use (even without a medical prescription) has been legalized locally.
- Administration of investigational SARS-CoV-2 vaccines is not allowed during the study. Participants may receive 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 medical monitor.

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

7.7.2 Other Restrictions and Precautions

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

For participants who need to undergo elective surgery (not tumor-related) during the study, it is recommended to hold study drug(s) for at least 2 weeks before and 2 weeks after surgery, or until

the participant recovers from the procedure, whichever is longer. Prior to resuming study drug treatment, surgically-related AEs should resolve to ≤ Grade 1 or baseline and participant must meet relevant eligibility criteria as determined by the BMS Medical Monitor in discussion with the Investigator. The BMS Medical Monitor must be consulted prior to re-initiating treatment in a participant with a dosing interruption lasting > 8 weeks after the last dose.

7.7.2.1 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 MRI, participants with severe renal insufficiency (ie, estimated glomerular filtration rate (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 acquisition manual.

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

7.7.3 Permitted Therapy

Participants are permitted the use of:

- Topical, ocular, intra-articular, intranasal, and inhalational corticosteroids (with minimal systemic absorption).
- Adrenal replacement steroid doses > 10 mg daily prednisone are permitted.
- A brief (less than 1 week) 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.
- Supportive therapy for the management of acneiform rash as described in Section 7.4.2.1.

7.7.3.1 Radiotherapy

Palliative and supportive care for disease-related symptoms may be offered to all participants on the trial; however, Investigators should consult with the BMS Medical Monitor prior to initiating palliative radiation in participants who have not yet completed the DLT evaluation interval (Parts 1A, 1B, and 1C).

The potential for overlapping toxicities with radiotherapy and BMS-986315 administered as monotherapy or in combination with nivolumab or cetuximab is currently not known. Therefore, palliative radiotherapy is not recommended while receiving any of these drugs, alone or in combination. If palliative radiotherapy in short courses and for isolated fields is required to control symptoms not clearly related to disease progression, then drug administration should be withheld,

if possible, for at least 1 week before radiation and for at least 1 week after its completion. Participants should be closely monitored for any potential toxicity during and after receiving radiotherapy. Prior to resuming study drug treatment, radiotherapy-related AEs should resolve to ≤ Grade 1 or baseline and participants must meet relevant eligibility criteria as determined by the BMS Medical Monitor in discussion with the Investigator. The BMS Medical Monitor must be consulted prior to re-initiating treatment in a participant with a dosing interruption lasting > 8 weeks after the last dose.

Details of palliative radiotherapy should be documented in the source records and eCRF. Details in the source records should include: dates of treatment, anatomical site, dose administered and fractionation schedule, and AEs. Symptoms requiring palliative radiotherapy should be evaluated for objective evidence of disease progression. Participants receiving palliative radiation of target lesions will have the evaluation of BOR just prior to radiotherapy but such participants will no longer be evaluable for determination of response subsequent to the date palliative radiation occurs.

7.8 Treatment After the End of the Study

At the conclusion of the study, participants who continue to demonstrate clinical benefit will be eligible to receive BMS supplied study treatment up to the maximum duration of 26 cycles. Study treatment will be provided via an extension of the study, a rollover study requiring approval by responsible health authority and ethics committee or through another mechanism at the discretion of BMS.

BMS reserves the right to terminate access to BMS supplied study treatment if any of the following occur: a) The study is terminated due to safety concerns; b) The development of BMS-986315 is terminated for other reasons, including but not limited to lack of efficacy and/or not meeting the study objectives; c) The participant can obtain medication from a government sponsored or private health program. In all cases BMS will follow local regulations.

8 DISCONTINUATION CRITERIA

8.1 Discontinuation from Study Treatment

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

- Participant's request to stop study treatment. Participants who request to discontinue study treatment will remain in the study and must continue to be followed for protocol specified follow-up procedures. The only exception to this is when a participant specifically withdraws consent for any further contact with him/her or persons previously authorized by participant to provide this information
- Any clinical AE, laboratory abnormality or intercurrent illness which, in the opinion of the investigator, indicates that continued participation in the study is not in the best interest of the participant
- Documented disease progression as defined by RECIST v1.1 (Appendix 7) unless participants meet criteria for treatment beyond progression (Section 5.1.5).

- Clinical deterioration while receiving active study therapy that, in the opinion of the Investigator, indicates that continued participation in the study is not in the best interest of the participant.
- Any drug-related AE occurring at any time that meets DLT criteria as outlined in Section 5.1.3 will require permanent discontinuation.
- Inability to comply with protocol.
- Discretion of the investigator.
- Pregnancy.
- Termination of the study by Bristol Myers Squibb (BMS)
- Loss of ability to freely provide consent through imprisonment or involuntarily incarceration for treatment of either a psychiatric or physical (eg, infectious disease) illness. (Note: Under specific circumstances and only in countries where local regulations permit, a participant who has been imprisoned may be permitted to continue as a participant. Strict conditions apply and BMS approval is required.)
- Individual participants with confirmed CR will be given the option to discontinue study therapy on a case by case basis after specific consultation and agreement between the investigator and BMS Medical Monitor in settings where benefit/risk justifies discontinuation of study therapy.
- Any event that leads to delay in dosing lasting > 8 weeks from the previous dose requires discontinuation, with the following exceptions:
  - Dosing delays to allow for prolonged steroid tapers to manage drug-related adverse events are allowed.
  - Dosing delays that occur for non-drug-related reasons may be allowed if approved by the BMS Medical Monitor (or designee).

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

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

The assessment for discontinuation of nivolumab should be made separately from the assessment made for discontinuation of BMS-986315. Although there is overlap among the discontinuation criteria, if a participant in any of the combination arms meets criteria for discontinuation and investigator is unable to determine whether the event is related to both or 1 study drug, the participant should discontinue both nivolumab and BMS-986315 and be taken off the treatment phase of the study. An exception to the discontinuation of BMS-986315 can be made in the case of a nivolumab-related hypersensitivity or infusion reaction.

Specifically for hypersensitivity or infusion related reactions, because nivolumab or cetuximab are administered first, if a participant presents with a reaction before the administration of

BMS-986315 has started, treatment with BMS-986315 may continue after the hypersensitivity or infusion related reactions have been resolved. For other immune-mediated AEs, when signs or symptoms have developed after administration of both study drugs, if discontinuation criteria are met, both study drugs should be discontinued. Refer to the Schedule of Activities for data to be collected at the time of treatment discontinuation and follow-up and for any further evaluations that can be completed.

In the case of pregnancy, the investigator must immediately, within 24 hours of awareness of the pregnancy, notify the BMS Medical Monitor/designee of this event. In the event a female participant becomes pregnant during a clinical trial, the study treatment must be discontinued immediately. If the investigator determines a possible favorable benefit/risk ratio that warrants continuation of study treatment, a discussion between the investigator and the BMS Medical monitor/designee must occur. In the event a partner of a male participant becomes pregnant, the investigator must immediately notify the BMS Medical Monitor/designee of this event. Refer to Section 9.2.5 Pregnancy.

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

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

8.1.1 Post Study Treatment Study Follow-up

In this study, safety and efficacy are key endpoints of the study. Post study follow-up is of critical importance and is essential to preserving participant safety and the integrity of the study. Participants who discontinue study treatment must continue to be followed (in this study or a rollover study) for collection of outcome and/or survival follow-up data as required and in line with Section 5 until death or the conclusion of the study.

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

8.2 Discontinuation from the Study

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

- Participants should notify the investigator of the decision to withdraw consent from future follow-up **in writing**, whenever possible.

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

8.3 Lost to Follow-Up

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

9 STUDY ASSESSMENTS AND PROCEDURES

Study procedures and timing are summarized in the Schedule of Activities. Protocol waivers or exemptions are not allowed.

All immediate safety concerns must be discussed with the Sponsor immediately upon occurrence or awareness to determine if the participant should continue or discontinue treatment.

Adherence to the study design requirements, including those specified in the Schedule of Activities, is essential and required for study conduct.

All screening evaluations must be completed and reviewed to confirm that potential participants meet all eligibility criteria before study treatment assignment. The investigator will maintain a screening log to record details of all participants screened and to confirm eligibility or record reasons for screening failure, as applicable.

Procedures conducted as part of the participant's routine clinical management (eg, blood count) and obtained before signing of informed consent may be utilized for screening or baseline purposes provided the procedure meets the protocol-defined criteria and has been performed within the timeframe defined in the Schedule of Activities Section 2).

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

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

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

9.1 Efficacy Assessments

Efficacy assessments for the anti-tumor activity of BMS-986315, alone and in combination with nivolumab or cetuximab, will be based on tumor measurements, using RECIST v1.1.

Only data for the procedures and assessments specified in this protocol should be submitted to the Sponsor or Designee on a CRF. Additional procedures and assessments may be performed as part of standard of care. However, data for these assessments should remain in the participant's medical record and should not be provided to the Sponsor or Designee, unless specifically requested from BMS or Designee.

9.1.1 Imaging Assessment for the Study

Images will be submitted to a central imaging vendor and may undergo blinded independent central review (BICR) at any time during the study. Prior to scanning first participant, sites should be qualified and understand the image acquisition guidelines and submission process as outlined in the CA047-004 Imaging Manual provided by the central imaging vendor.

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

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

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 timepoints. Tumor measurements should be made by the same investigator or radiologist for each assessment, whenever possible. Change in tumor measurements and tumor response to guide ongoing study treatment decisions will be assessed by the investigator using the RECIST 1.1 criteria.

If a participant has a contraindication for CT intravenous 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 intravenous 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 intravenous 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 which may bias an investigator if it is not routinely or serially performed.

Bone scan or PET scan are not adequate for assessment of RECIST 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 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.

9.1.1.2 Imaging and Clinical Assessment

Tumor assessments should continue even if dosing is delayed or discontinued. Changes in tumor measurements and tumor responses will be assessed by the same investigator using RECIST 1.1 criteria. Investigators will report the number and size of new lesions that appear while on study.

The timepoint of tumor assessments will be reported on the eCRF based on the investigator's assessment using RECIST 1.1 criteria (See Appendix 7 for specifics of RECIST 1.1 criteria to be used in this study)

Assessments of PR and CR must be confirmed at least 4 weeks after initial response☐🅰 Best Overall Response (BOR) of SD requires a minimum of 49 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 serious adverse event (SAE) can be found in Appendix 3.

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

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

Contacts for SAE reporting specified in Appendix 3

9.2.1 Time Period and Frequency for Collecting AE and SAE Information

After the participant signs the consent form, all SAEs related to the biopsy must be collected and followed until resolution or stabilization. After the participant signs the main ICF to participate in the study, all SAEs, whether related or not related to study drug, must be collected, including those thought to be associated with protocol-specified procedures.

<u>After the Main ICF is signed:</u>

- All SAEs, must be collected from the time of signing the consent, including those thought to be associated with protocol-specified procedures and within 100 days of last dose of study treatment except in cases where a study participant has started a new anti-neoplastic therapy. Any SAE occurring after the start of a new anti-neoplastic therapy that is suspected to be related to study treatment by the investigator will be reported.
- The investigator must report any SAE that occurs after these time periods and that is believed to be related to study drug or protocol-specified procedure (eg follow-up).
- Medical occurrences that begin before the start of study treatment but after obtaining informed consent will be recorded on the appropriate section of the eCRF section.
- All SAEs will be recorded and reported to Sponsor or designee within 24 hours, as indicated in Appendix 3.
- The investigator will submit any updated SAE data to the sponsor or designee within 24 hours of updated information being available.

- 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 last dose of study treatment.
- With the exception of nonserious AEs related to SARS infection, all nonserious AE (not only those deemed to be treatment-related) should be collected from the time of first dose and continuously during the treatment period and for a minimum of 100 days following last dose of study treatment.

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

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

9.2.2 Method of Detecting AEs and SAEs

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

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

9.2.3 Follow-up of AEs and SAEs

- Nonserious AEs should be followed to resolution or stabilization, or reported as SAEs if they become serious (see Section Appendix 3).
- Follow-up is also required for nonserious AEs that cause interruption or discontinuation of study treatment and for those present at the end of study treatment as appropriate.
- All identified nonserious AEs must be recorded and described on the nonserious AE page of the CRF (paper or electronic). Completion of supplemental CRFs may be requested for AEs and/or laboratory abnormalities that are reported/identified during the course of the study.
- After the initial AE/SAE report, the investigator is required to proactively follow each participant at subsequent visits/contacts. All SAEs and AEs (SAEs and non-serious AEs) including ones associated with confirmed or suspected SARS-CoV-2 infection will be followed until resolution, until the condition stabilizes, until the event is otherwise explained, the event is deemed irreversible, or until 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.

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

9.2.4 Regulatory Reporting Requirements for SAEs

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

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

9.2.5 Pregnancy

If, following initiation of the study treatment, it is subsequently discovered that a participant is pregnant or may have been pregnant at the time of study exposure, (including for at least 5 months after last dose of study treatment), the investigator must discontinue study treatment. The investigator must immediately notify the BMS Medical Monitor/designee of this event and complete and forward a Pregnancy Surveillance Form to BMS Designee within 24 hours of awareness of the event and in accordance with SAE reporting procedures described in Appendix 3.

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

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

Any pregnancy that occurs in a female partner of a male study participant should be reported to Sponsor or designee.

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

9.2.6 Laboratory Test Result Abnormalities

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

- Any laboratory test result that is clinically significant or meets the definition of an SAE

- Any laboratory test result abnormality that required the participant to have study treatment discontinued or interrupted
- Any laboratory test result abnormality that required the participant to receive specific corrective therapy

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

9.2.7 Immune-Mediated Adverse Events

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

9.2.8 Potential Drug Induced Liver Injury (DILI)

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

Potential drug induced liver injury is defined as:

- Aminotransferases (ATs, ALT or AST elevation > 3 times upper limit of normal [ULN]) AND
- Total bilirubin > 2 times ULN, without initial findings of cholestasis (elevated serum ALP), 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.

The key responsibilities for Investigators during p-DILI assessment include: (i) Early detection, medical evaluation (including the exclusion of other potential causes) and rapid laboratory confirmation of liver-related abnormalities; and (ii) BMS notification of p-DILI cases via SAE forms. Following the gathering and assessment of relevant clinical information, BMS is responsible for: (i) Timely evaluation and triaging of p-DILI cases; (ii) Expedited reporting of p-DILI cases; and (iii) Expanded review of p-DILI cases including a detailed assessment of all available clinical information, investigations, and biochemical data.

Investigators are expected to monitor ongoing routine and ad hoc hepatic laboratory test results to rapidly determine whether a participant meets p-DILI criteria. They are expected to promptly notify BMS of all p-DILI cases. p-DILI cases may be identified by abnormal liver biochemistry values, whether or not they are accompanied by liver-related signs and/or symptoms. In both cases, expedited confirmation with repeat laboratory testing should occur within 3 business days using a

Hepatic Laboratory Panel (ALT, AST, total bilirubin, ALP). Any participant with an abnormal Hepatic Laboratory Panel that meets p-DILI criteria is a candidate for study treatment discontinuation. Any confirmed p-DILI events must be reported (along with a description of the clinical findings) to BMS as an SAE within 24 hours of confirmation.

An extensive clinical history, examination and appropriate investigations should be obtained to exclude cholestatic and other apparent causes that may explain the observed abnormalities in liver function and/or hepatic signs and symptoms. Other apparent causes include, non-exhaustively and by way of example only, the following: infectious diseases (such as active hepatitis A, B, and C), congenital diseases (such as Gilbert's syndrome), neoplastic diseases, autoimmune diseases (such as primary biliary cirrhosis), and the use of concomitant hepatotoxic medications (such as antibiotics, the oral contraceptive pill and herbal medicines). All investigations to exclude potential causes of liver function abnormalities or hepatic signs and/or symptoms should be guided by relevant factors such as the participant's age, gender, clinical history, and signs and symptoms.

9.2.9 Other Safety Considerations

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

9.2.10 Management Algorithms for Nivolumab

IO agents are associated with imAEs that can differ in severity and duration from AEs caused by other therapeutic classes. Nivolumab and BMS-986315 are considered IO agents in this protocol. Early recognition and management of imAEs associated with IO agents may mitigate severe toxicity. Management algorithms have been developed from extensive experience with ipilimumab and nivolumab to assist Investigators in assessing and managing the following groups of imAEs:

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

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

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 (refer to Appendix 3). All instances of accidental overdose and/or dosing errors should be reported on the Dosage Administration Record eCRF.

In the event of an overdose the investigator should:

- Contact the Medical Monitor immediately
- Closely monitor the participant for AEs/SAEs and laboratory abnormalities
- Obtain a plasma sample for PK analysis if requested by the Medical Monitor (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.

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

9.4 Safety

Safety assessments will be based on reported AEs and the measurement results of vital signs, ECG, PEs, and clinical laboratory tests. AEs will be coded using the most current version of Medical Dictionary for Regulatory Activities (MedDRA) and the incidence of observed AEs will be tabulated and reviewed for potential significance and clinical importance. AEs will be assessed continuously during the study and for 100 days after the last dose of BMS-986315 in the case of monotherapy, and the last dose of BMS-986315 and nivolumab or cetuximab for combination therapy. In addition, electrolytes will be monitored for 8 weeks after EOT visit for participants in Part 1C. Local laboratory will perform the clinical laboratory tests and will provide reference ranges for these tests. Both AEs and laboratory tests will be graded using the NCI CTCAE v5.0.

Planned time points for all safety assessments are listed in the Schedule of Activities (Section 2).

9.4.1 Physical Examinations

Refer to Schedule of Activities (Section 2).

9.4.2 Vital signs

Refer to Schedule of Activities (Section 2).

9.4.3 Electrocardiograms

Refer to the Schedule of Activities for timing of ECG assessments for safety in Table 2-2. The investigators will review the 12-lead ECGs using their site's standard ECG machines throughout the study. The QTc will be applied to each ECG reading.

Refer to the Schedule of ECG collection for effect of BMS-986315 on the QTc interval in Table 9.5-3. Electrocardiogram recording should be obtained prior to PK samples at each timepoint as indicated in Table 9.5-3. The ECGs will be assessed by an independent core laboratory. A separate manual will include additional details and instructions. All ECG tests will be performed in triplicate for Cycles 1 and 4 (ie, 1 ECG test equals 3 consecutive individual 12 lead ECGs performed 1-5 minutes apart). Special Restrictions: Subjects should refrain from strenuous

physical activity and use of (methyl) xanthenes (eg, coffee, tea, cola, chocolate) or alcohol on the days when ECG measurements will be obtained.

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.
- The laboratory tests that will be performed for study participants are shown in Table 9.4.4-1.
- Results of all laboratory tests required by this protocol must be provided to the Sponsor, recorded either on the laboratory pages of the CRF or by another mechanism as agreed upon between the Investigator and BMS (eg, provided electronically). If the units of a test result differ from those printed on the CRF, the recorded laboratory values must specify the correct units. Any abnormal laboratory test result considered clinically significant by the Investigator must be recorded on the appropriate AE page of the CRF.

Table 9.4.4-1: Clinical Safety Laboratory Assessments

Hematology - CBC	
Hemoglobin	
Hematocrit	
Total leukocyte count, including differential	
Platelet count	
Prothrombin time, activated partial thromboplastin time and *international normalized ratio* (at screening only)	
Chemistry	
Aspartate aminotransferase (AST) Alanine aminotransferase (ALT) Total bilirubin Direct Bilirubin (reflex if total bilirubin is abnormal) Alkaline phosphatase (ALP) Lactate dehydrogenase (LDH) Creatinine Creatine kinase/Creatine phosphokinase C-reactive protein Blood Urea Nitrogen (BUN) or serum UREA Fasting glucose Lipase Amylase Total Protein Troponin	Gamma-glutamyl transferase (reflex if liver function is abnormal) Albumin Sodium Potassium Chloride Calcium Phosphorus Magnesium Creatinine clearance (Cockcroft-Gault method) (screening only) Free T4 (screening and reflex only) TSH, with reflexive fT4 if TSH is abnormal (on-treatment)

Table 9.4.4-1: Clinical Safety Laboratory Assessments
Serology
Hepatitis B/C, (HBV sAG, HCV antibody or HCV RNA), HIV-1 and HIV-2 Ab- (at screening and as mandated by local requirement)
Other Analyses
Pregnancy test (WOCBP only). Minimum sensitivity for urine test: 25 IU/L or equivalent units of HCG).
FSH screening (only required to confirm menopause in women < age 55)
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

Abbreviations: CBC = complete blood count; FSH = follicle stimulating hormone; HBV sAG = hepatitis B surface antigen; HCG = human chorionic gonadotropin; HCV = hepatitis C virus; HIV = human immunodeficiency virus; IU = international unit; L = liter; RNA = ribonucleic acid; 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 and Immunogenicity

Pharmacokinetic and immunogenicity (IMG) assessment data for BMS-986315 in Part 1A and BMS-986315 in combination with nivolumab and cetuximab in Part 1B and Part 1C will be collected from study participants assigned to the study at the time points indicated in Table 9.5-3, Table 9.5-4, and Table 9.5-5. All time points are relative to the start of BMS-986315 administration. All on-treatment time points are intended to align with days on which study drug is administered; if dosing occurs on a different day, the PK and IMG sampling 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. All predose samples should be collected within 30 minutes before the start of first drug infusion.

Pharmacokinetic parameters of BMS-986315 will be derived, if feasible, from serum concentration versus time data following Cycle 1 Day 1 and Cycle 4 Day 1. Trough concentrations of nivolumab and cetuximab will be summarized. PK parameters that will be assessed are shown below:

Table 9.5-1: PK Parameters	
BMS-986315	
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; may be calculated if concentrations are not quantifiable up to TAU across a treatment group
AUC(TAU)	Area under the serum concentration-time curve in 1 dosing interval
Ctau	Observed serum concentration at the end of a dosing interval
Ctrough	Trough observed serum concentrations (this includes pre-dose concentrations [C0] and Ctau)
Nivolumab	
Ctrough	Trough observed serum concentrations (this includes pre-dose concentrations [C0] and Ctau)
Cetuximab	
Ctrough	Trough observed serum concentrations (this includes pre-dose concentrations [C0] and Ctau

Table 9.5-2: PK Parameters of BMS-986315 that May be Assessed Following the Dose Administration in Cycle 4 Day 1	
Css-avg	Average serum concentration over a dosing interval (AUC[TAU]/tau) at steady state
AI_AUC	AUC Accumulation Index; ratio of AUC(TAU) at steady-state to AUC(TAU) after the first dose.
DF	Degree of fluctuation or fluctuation index (to be calculated at steady state)
T-HALFeff AUC	Effective elimination half-life that explains the degree of AUC accumulation observed

Individual participant PK parameter values will be derived by non-compartmental methods using a validated PK analysis program. Actual times will be used for all formal analyses.

Sparse nivolumab concentration-time data will be collected and may be used in an integrated PPK or exposure response analysis along with data from other nivolumab studies, which will be the subject of a separate report. Sparse cetuximab concentration-time data will be collected and may be used in an integrated PPK analysis along with data from previous cetuximab monotherapy studies, which will be the subject of a separate report. Separate samples will be collected for PK and IMG assessments.

Table 9.5-3: PK and Immunogenicity Sampling Schedule for Part 1A (CA047-004)					
Study Day of Sample Collection[a] (1 Cycle = 4 weeks)	**Event**	**Time Relative to BMS-986315 Dose (hr:min)**	**BMS-986315 PK Serum Sample**	**BMS-986315 IMG Serum Sample**	**ECG[b]**
Cycle 1 Day 1	Predose[c]	00:00	X	X	X
	EOI	See note[d]	X		X
		04:00	X		X
Cycle 1 Day 2		24:00	X		
Cycle 1 Day 4 (± 1 Day)		72:00	X		
Cycle 1 Day 8		168:00	X		
Cycle 1 Day 15		336:00	X		
Cycle 1 Day 22		504:00	X		
Cycle 2 Day 1	Predose[c]	00:00	X	X	
	EOI	See note[d]	X		
Cycle 3 Day 1	Predose[c]	00:00	X	X	
	EOI	See note[d]	X		
Cycle 4 Day 1	Predose[c]	00:00	X	X	X
	EOI	See note[d]	X		X
		04:00	X		X
Cycle 4 Day 2		24:00	X		
Cycle 4 Day 4 (± 1 Day)		72:00	X		
Cycle 4 Day 8		168:00	X		

Table 9.5-3: PK and Immunogenicity Sampling Schedule for Part 1A (CA047-004)					
Study Day of Sample Collection[a] (1 Cycle = 4 weeks)	**Event**	**Time Relative to BMS-986315 Dose (hr:min)**	**BMS-986315 PK Serum Sample**	**BMS-986315 IMG Serum Sample**	**ECG[b]**
Cycle 4 Day 15		336:00	X		
Cycle 4 Day 22		504:00	X		
Cycle 5 Day 1	Predose[c]	00:00	X	X	
Cycle 8 Day 1	Predose[c]	00:00	X	X	
Cycle 12 Day 1	Predose[c]	00:00	X	X	
Cycle 16 Day 1	Predose[c]	00:00	X	X	
Cycle 20 Day 1	Predose[c]	00:00	X	X	
Cycle 26 Day 1	Predose[c]	00:00	X	X	
Follow Up Period					
Follow Up 30 Day			X	X	
Follow Up 100 Day			X	X	

Abbreviations: ECG = electrocardiogram;; EOI = End of infusion; IMG = immunogenicity; PK = pharmacokinetic

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

[b] ECGs will be collected in triplicate and evaluated by a central reader during on Cycle 1 Day 1 and Cycle 4 Day 1 only. ECGs should be done prior to the Pharmacokinetic sample. For ECGs collection at End of infusion, ECGs should be done prior to End of infusion.

[c] All predose samples should be collected within 30 minutes before the start of the first drug infusion.

[d] EOI=End of infusion: Since the end of infusion-PK (EOI-PK) sample is drawn with the intent of accurately estimating the maximum concentration (Cmax) of the drug, draw the EOI-PK when all the study drug has been infused. If the site infuses drug without a flush, then collect the EOI-PK 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-PK 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. If the end of infusion is delayed to beyond the nominal infusion duration, the collection of this sample should also be delayed accordingly. Nominal sampling time will vary depending on dose and infusion time.

Table 9.5-4: Pharmacokinetic and Immunogenicity Sampling Schedule for Part 1B (CA047-004)

Study Day of Sample Collection[a] (1 Cycle = 4 weeks)	Event	Time Relative to BMS-986315 Dose (hr:min)	BMS-986315 PK Serum Sample	Nivolumab PK Serum Sample	BMS-986315 IMG Serum Sample	Nivolumab IMG Serum Sample
Cycle 1 Day 1	Predose[b]	00:00	X	X	X	X
	EOI	See note[c]	X			
		04:00	X			
Cycle 1 Day 2		24:00	X			
Cycle 1 Day 4 (± 1 Day)		72:00	X			
Cycle 1 Day 8		168:00	X			
Cycle 1 Day 15		336:00	X			
Cycle 1 Day 22		504:00	X			
Cycle 2 Day 1	Predose[b]	00:00	X	X	X	X
	EOI	See note[c]	X			
Cycle 3 Day 1	Predose[b]	00:00	X	X	X	X
	EOI	See note[c]	X			
Cycle 4 Day 1	Predose[b]	00:00	X	X	X	X
	EOI	See note[c]	X			
		04:00	X			
Cycle 4 Day 2		24:00	X			
Cycle 4 Day 4 (± 1 Day)		72:00	X			
Cycle 4 Day 8		168:00	X			

Table 9.5-4: Pharmacokinetic and Immunogenicity Sampling Schedule for Part 1B (CA047-004)

Study Day of Sample Collection[a] (1 Cycle = 4 weeks)	Event	Time Relative to BMS-986315 Dose (hr:min)	BMS-986315 PK Serum Sample	Nivolumab PK Serum Sample	BMS-986315 IMG Serum Sample	Nivolumab IMG Serum Sample
Cycle 4 Day 15		336:00	X			
Cycle 4 Day 22		504:00	X			
Cycle 5 Day 1	Predose[b]	00:00	X	X	X	X
Cycle 8 Day 1	Predose[b]	00:00	X	X	X	X
Cycle 12 Day 1	Predose[b]	00:00	X	X	X	X
Cycle 16 Day 1	Predose[b]	00:00	X	X	X	X
Cycle 20 Day 1	Predose[b]	00:00	X	X	X	X
Cycle 26 Day 1	Predose[b]	00:00	X	X	X	X
Follow Up Period						
Follow Up 30 Day			X	X	X	X
Follow Up 100 Day			X	X	X	X

Abbreviations:EOI = End of infusion; IMG = immunogenicity; PK = pharmacokinetic

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

[b] All predose samples should be collected within 30 minutes before the start of the first drug infusion

[c] EOI=End of infusion: Since the end of infusion-PK (EOI-PK) sample is drawn with the intent of accurately estimating the maximum concentration (Cmax) of the drug, draw the EOI-PK when all the study drug has been infused. If the site infuses drug without a flush, then collect the EOI-PK 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-PK 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. If the end of infusion is delayed to beyond the nominal infusion duration, the collection of this sample should also be delayed accordingly. Nominal sampling time will vary depending on dose and infusion time.

Table 9.5-5: Pharmacokinetic and Immunogenicity Sampling Schedule for Part 1C (CA047-004)

Study Day of Sample Collection[a] (1 Cycle = 4 weeks)	Event	Time Relative to BMS-986315 Dose (hr:min)	BMS-986315 PK Serum Sample	Cetuximab PK Serum Sample	BMS-986315 IMG Serum Sample	Cetuximab IMG Serum Sample
Cycle 1 Day 1	Predose[b]	00:00	X	X	X	X
	EOI	See note[c]	X	X		
		04:00	X			
Cycle 1 Day 2		24:00	X			
Cycle 1 Day 4 (± 1 Day)		72:00	X			
Cycle 1 Day 8		168:00	X			
Cycle 1 Day 15		336:00	X			
Cycle 1 Day 22		504:00	X			
Cycle 2 Day 1	Predose[b]	00:00	X	X	X	X
	EOI	See note[c]	X			
Cycle 3 Day 1	Predose[b]	00:00	X	X	X	X
	EOI	See note[c]	X			
Cycle 4 Day 1	Predose[b]	00:00	X	X	X	X
	EOI	See note[c]	X	X		
		04:00	X			
Cycle 4 Day 2		24:00	X			
Cycle 4 Day 4 (± 1 Day)		72:00	X			

Table 9.5-5: Pharmacokinetic and Immunogenicity Sampling Schedule for Part 1C (CA047-004)

Study Day of Sample Collection[a] (1 Cycle = 4 weeks)	Event	Time Relative to BMS-986315 Dose (hr:min)	BMS-986315 PK Serum Sample	Cetuximab PK Serum Sample	BMS-986315 IMG Serum Sample	Cetuximab IMG Serum Sample
Cycle 4 Day 8		168:00	X			
Cycle 4 Day 15		336:00	X			
Cycle 4 Day 22		504:00	X			
Cycle 5 Day 1	Predose[b]	00:00	X	X	X	X
Cycle 8 Day 1	Predose[b]	00:00	X	X	X	X
Cycle 12 Day 1	Predose[b]	00:00	X	X	X	X
Cycle 16 Day 1	Predose[b]	00:00	X	X	X	X
Cycle 20 Day 1	Predose[b]	00:00	X	X	X	X
Cycle 26 Day 1	Predose[b]	00:00	X	X	X	X
Follow Up Period						
Follow Up 30 Day			X	X	X	X
Follow Up 100 Day			X	X	X	X

Abbreviations: EOI = End of infusion; IMG = immunogenicity; PK = pharmacokinetic

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

[b] All predose samples should be collected within 30 minutes before the start of the first drug infusion.

[c] EOI=End of infusion: Since the end of infusion-PK (EOI-PK) sample is drawn with the intent of accurately estimating the maximum concentration (Cmax) of the drug, draw the EOI-PK when all the study drug has been infused. If the site infuses drug without a flush, then collect the EOI-PK 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-PK 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. If the end of infusion is delayed to beyond the nominal infusion duration, the collection of this sample should also be delayed accordingly. Nominal sampling time will vary depending on dose and infusion time.

Further details of sample collection, processing, and shipment will be provided in the laboratory procedures manual. Serum PK samples will be analyzed for BMS-986315, nivolumab, and cetuximab by validated ligand binding assays.

Immunogenicity samples will be analyzed for anti-nivolumab/anti-cetuximab/anti-BMS-986315 antibodies by validated immunogenicity assays. Bioanalytical samples designated for assessments (e.g. immunogenicity, PK, or biomarker) from the same collection time point may be used interchangeably for analyses, if required (including but not limited to insufficient volume for complement assessment, to follow-up on suspected immunogenicity related AE, etc.). Additionally, residual bioanalytical samples will be archived and may be used for potential exploratory bioanalysis (including but not limited to: analysis of drug-anti-drug antibodies immune complexes, metabolite analyses, etc.) and or for additional method purposes (including but not limited to cross-validation, anti-drug antibody/PK selectivity, cut point, etc.).

For all PK and immunogenicity serum samples, the date and actual time collected must be recorded. Blood samples should be drawn from a site other than the infusion site (ie, contralateral arm) on days of infusion. If the infusion was interrupted, the interruption details will also be documented on the CRF. Further details of sample collection, processing, and shipment will be provided in the laboratory/procedure manual.

9.6 Pharmacodynamics

Pharmacodynamic measures will be based on select biomarker samples collected as described in Section 9.8 (in the form of biomarker assessments) may be assessed for associations with clinical outcomes. There will be four types of specimens obtained for biomarker testing: (i) whole blood, (ii) serum, (iii) plasma, and (iv) tumor tissue. The sample subtypes and testing plans associated with each are described in Section 9.8. Complete instructions on the collection, processing, handling, and shipment of all samples described herein will be provided in a separate Laboratory Procedures Manual.

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

9.7 Pharmacogenomics

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

9.7.1 ADME Sampling

Not applicable.

9.8 Biomarkers

Biomarkers are increasingly playing a key role in the development of cancer therapeutics. By evaluating treatment-induced changes in molecular markers measured in tissue and body fluids, the activity of experimental agents may be assessed and the details of their mechanisms of action may be elucidated. To explore potential predictive markers for clinical response to BMS-986315 and identify appropriate doses and treatment schedules, 4 types of specimens will be obtained from all participants for biomarker testing: (i) whole blood, (ii) serum, (iii) plasma, and (iv) tumor tissue.

Blood and tumor tissue samples will be collected in this study at baseline and on treatment to identify markers associated with clinical activity and mechanism of action of BMS-986315 monotherapy or in combination with nivolumab or cetuximab. The pharmacodynamic changes between baseline and on treatment measures will also be monitored and evaluated for associations with PK data and adverse events (AEs).

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

Residual blood (or blood derivatives such as serum, plasma, plasma circulating tumor DNA [ctDNA], PBMCs, and extracted RNA/deoxyribonucleic acid [DNA]) or tumor tissue (fresh biopsy and extracted RNA/DNA) from tumor biopsy and biomarkers collections (Table 9.8.3.6-1) may be retained for additional research purposes. See Section 9.8.3.6 (Additional Research Collection)

Table 9.8-1: Biomarker Sampling Schedule for BMS-986315 for Part 1A, Part 1B, and Part 1C (CA047-004)

Study Day of Sample Collection[a] (1 Cycle = 4 weeks)	Event	Tumor Biopsy[b]	Serum Biomarkers	Plasma (ctDNA)	Whole Blood DNA	Whole Blood Gene Expression	Whole Blood PBMC	Whole Blood Immuno-phenotyping	NKG2A RO	Anti-SARS-CoV-2 Serology
Screening		X	X	X	X	X	X			
Cycle 1 Day 1	Predose[c]		X	X		X	X	X	X	X
Cycle 1 Day 8			X					X	X	
Cycle 1 Day 15			X						X	
Cycle 1 Day 22		X	X	X		X	X	X	X	
Cycle 2 Day 1	Predose[c]		X					X	X	
Cycle 3 Day 1	Predose[c]		X				X		X	
Cycle 4 Day 1	Predose[c]		X	X					X	
Every 6 Cycles Starting at Cycle 7 Day 1 Until Cycle 25 (C7D1; C13D1; C19D1; C25D1)	Predose[c]			X						X
Approximately 4 Weeks After Confirmed or Suspected SARS-CoV-2 Infection										X
End of treatment/ Upon progression		X	X	X		X	X			
Follow-up Visit 1										X

Abbreviations: ctDNA = circulating tumor deoxyribonucleic acid; C = cycle; D = day; DNA = deoxyribonucleic acid; PBMC = peripheral blood mononuclear cell; RO = receptor occupancy

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

[b] Mandatory pre- and on-treatment biopsies for all subjects. On-treatment tumor biopsies to be performed at Cycle 1 Day 22 (± 5days). On-treatment tumor specimens may be collected within 5 days of the time point and must be obtained prior to administration of study treatments. End of treatment/Upon progression

biopsy is optional, but strongly encouraged, at time of disease progression. Subjects obtaining biopsies should have adequate tissue collected as outlined in the laboratory manual.

[c] Predose samples must be collected prior to the start of the first drug infusion.

9.8.1 Collection of Tumor Tissue Specimens

Tumor tissue will be collected to examine the effects of BMS-986315 administration in the tumor tissue itself. Understanding the effects of BMS-986315 at the tumor site is an important aspect of this study and requires the collection of tumor biopsies prior to and during treatment. Fresh pre- and on-treatment biopsy specimens are mandatory, therefore participants must have a lesion that can be biopsied at an acceptable clinical risk as judged by the investigator in order to be eligible for the study. Tumor biopsies are to be collected at screening and on treatment; see Table 9.8-1 for the tumor collection schedule time points. Additional biopsies are optional but strongly encouraged at time of EOT/progressive disease. On treatment tumor specimens may be collected within 5 days to the time point (C1D22 ± 5 days) and must be obtained prior to administration of study treatments. Sufficient tumor specimens must be obtained from consenting participants at baseline and on-treatment to determine CD8 and HLA-E status and for exploratory biomarker analysis (detailed in Section 9.8.2 [Tumor-based Biomarkers]).

Biomarker assessments may include but are not limited to DNA sequencing, gene expression analysis, IHC assessment of number and functionality of infiltrating immune cells, and mass-spectrometry sample analyses for intratumoral receptor occupancy.

Note 1: Investigators and staff will follow local institutional guidelines for the safe performance of biopsies and that procedures that require general anesthesia should not be performed to obtain a biopsy specimen. Prior to the biopsy procedure the investigators should consult with the radiology staff to evaluate the degree of risk associated with the procedure. This evaluation must find the biopsy procedure clinically acceptable.

Note 2: Biopsies must be excisional, incisional, core-needle, or punch biopsy. Fine-needle biopsies and biopsies of bone lesions that do not have a soft-tissue component are not acceptable. Incisional or excisional biopsies are strongly encouraged where feasible. Immediate confirmation for presence of viable tumor cells from collected tissue samples is strongly recommended. If adequate tissue is not obtained following initial passages of the needle, repeat passages may be completed.

Note 3: Collection procedures at baseline and on study treatment (and at surgical resection or progression if progression occurs before completing the study treatment) should be completed on a single, appropriately assessable lesion, when applicable. In case the lesion sampled at baseline is no longer accessible or within acceptable clinical risk to re-biopsy during the study, tissue from alternative lesion(s) may be obtained; this should be documented.

Refer to the Laboratory Manual for detailed instructions.

CD8 and HLA-E Expression

Enrollment into the PD cohorts is limited to SCCHN participants with fresh pre-treatment tumor biopsies evaluable for CD8 and HLA-E. Biopsies will be assessed for both CD8 and total HLA-E expression in the tumor microenvironment which will be measured using CLIA analytically validated IHC assays. [redacted]

[redacted]

9.8.2 Tumor-based Biomarkers

9.8.2.1 Protein Expression

Tumor tissue samples are subject to IHC assays to determine the abundance of TILs and expression of immunoregulatory proteins by the tumor cell, TILs or surrounding stroma cells. Analytes may include, but are not limited to, NKG2A, HLA-E, PD-L1, PD-1, CD3, CD8, and GzmB. Pharmacodynamic changes in TIL prevalence and the presence (and/or abundance) of immunoregulatory and other proteins may be examined. Baseline and pharmacodynamic measures may also be correlated to clinical outcomes.

Tumor tissue may also be used to investigate NKG2A RO and for proteomic analysis or other exploratory analysis of protein expression and characterization.

9.8.2.2 Gene Expression and Mutation Analyses

Sample analyses of mRNA (or micro RNA miRNA) may be completed using RNA isolated from tumor tissue. Targeted or whole transcriptome RNA-sequence, or similar methodologies may be used to assess gene expression signatures, such as, but not limited to, those associated with immune-related signaling, for potential association with clinical outcomes. Focus may be given to monitoring a battery of immunoregulatory genes associated with tumor-infiltrating immune cells. Examples include immunoregulatory genes associated with T cells, NK cells, IFN-γ signaling, and cytolytic activity.

Total DNA will also be isolated from the tumor tissue sample. Whole genome or whole exome sequencing may be performed using this DNA material to investigate potential associations between somatic mutations and copy number variation with efficacy measures. TMB refers to the total number of nonsynonymous somatic mutations that exist within a tumor's genome. High TMB has been hypothesized to correlate with improved efficacy in patients treated with IO therapies. This hypothesis has been supported in multiple publications across IO therapies, tumor types, and lines of treatment.

9.8.3 Blood-based Biomarkers

A variety of biomarkers that may be associated with the treatment efficacy with BMS-986315 will be investigated in peripheral blood specimens taken from all participants prior to and during treatment. Blood samples will be collected prior to and during treatment with BMS-986315 alone or in combination with nivolumab or cetuximab. These blood samples may be assessed for changes in quantity or phenotype of immune cell subsets, changes in soluble factors such as cytokines and chemokines, changes in immune cell functionality, changes in soluble HLA-E, NKG2A RO, changes in NKG2A cell surface expression, changes in gene expression, tumor mutational burden (TMB), or changes in TCR and BCR repertoires. These biomarkers may be used to assess pharmacodynamic changes by dose, and potential associations with efficacy measures, e.g.

objective response. Several sample analyses will be completed and are described briefly below. Additional biomarker assessments may also be performed if samples are available.

9.8.3.1 Whole Blood for Immunophenotyping

Flow cytometry will be used to assess baseline and serial on-treatment alterations in composition/activation status of immune-cell subsets present in the whole blood samples obtained from all participants in each treatment arm. Lymphocyte subsets to be assayed may include, but not be limited to, CD8+ and CD4+ T-cell subsets, NK cells and populations of those cells as defined by the expression of activation, exhaustion, or signaling markers, such as Ki67, human-leukocyte antigen-antigen D-related, cytolytic markers, and/or PD-1. Monocytes/macrophages and dendritic cell populations may also be monitored in a similar fashion, with a focus on characterizing subsets defined by the expression of lineage-specific markers.

9.8.3.2 Serum Factors

To understand the level of soluble circulating proteins and the impact they may have on the clinical activity of the study treatments, the protein concentrations of a panel of cytokines, chemokines, and other relevant immunomodulatory, soluble factors may be investigated by enzyme-linked immunosorbent assay (ELISA) or other relevant immunoassay methods. Examples of specific analytes to be assessed may include, but are not limited to, factors induced by IFN-γ signaling (eg, T-cell chemoattractants CXCL9 and CXCL10), cytolytic markers (eg, granzyme A/B, perforin), SARS-CoV-2 serologic status, and soluble HLA-E.

9.8.3.3 Whole Blood DNA

Whole blood collected from participants prior to study treatment initiation may be used to generate genomic DNA for the understanding of genetic variation analyses. These analyses will focus on genetic variations within genes associated with or affecting immunoregulatory signaling to explore if natural variation within those genes is associated with a response to each component of the combination treatment.

Additionally, genomic DNA from whole blood may be used as a comparator for participants with tumors examined by whole-exome or genome-mutation analysis. Whole-exome or whole-genome sequencing methods may be used for this analysis. Lastly, genomic DNA from whole blood may be used for TCR sequencing.

9.8.3.4 Plasma for Circulating Tumor DNA

Plasma samples may be collected at the time points indicated in Table 9.8-1. Plasma ctDNA may be assessed for association with tumor mutational burden (TMB).

9.8.3.5 Peripheral Blood Mononuclear Cells

Whole-blood samples may be collected for isolation and cryopreservation of PBMCs. These cryopreserved samples may be used for functional activation tests, for additional assays if new biology suggests analysis beyond the immunophenotyping described above, and for TCR sequencing if needed.

9.8.3.6 Additional Research Collection

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

For All US sites:

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

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

For non-US Sites

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

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

Sample Collection and Storage

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

Residual samples from PK, IMG, biomarker, and tumor biopsy collections (see Table 9.8.3.6-1) will also be retained for additional research purposes.

Samples kept for future research will be stored at the BMS Biorepository [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 research sponsor to third parties will be subject to the recipient's agreement to establish similar storage procedures.

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

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

Table 9.8.3.6-1: Residual Sample Retention for Additional Research Schedule

Sample Type	Timepoints for which residual samples will be retained
PK	All
Tumor Biopsy	All
Blood Biomarker Samples	All

9.9 Health Economics OR Medical Resource Utilization and Health Economics

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

10 STATISTICAL CONSIDERATIONS

10.1 Sample Size Determination

The approximate total number of participants treated will be up to 308 for Part 1 as shown below:

- In Part 1A, approximately 36 participants will be treated in dose escalation phase, and up to 40 participants will be treated in SCCHN PD cohort, for a total of up to approximately 36+40=76 participants.
- In Part 1B, with 2 SCCHN PD cohorts, up to approximately 36+40+40=116 participants will be treated, with 36 participants in dose escalation phase, and 40 participants in each SCCHN PD cohort.
- In Part 1C, similar to part 1B, up to approximately 36+40+40=116 participants will be treated.

10.1.1 Part 1 Dose Escalation

The maximum number of participants treated in dose escalation phase of Part 1A, Part 1B, and Part 1C will be approximately 36 each, totaling approximately 108 participants.

The study will enroll 2-3 participants at each of the 2 lower doses in Part 1A to balance collecting DLT data and limiting exposure to potentially sub-therapeutic doses during dose escalation. Otherwise, 3-4 participants are expected to be treated at each dose level in Parts 1A, 1B, and 1C, and dose escalation decisions will be guided by the TITE-BOIN design. The BOIN design takes a very simple form, rendering it easy to implement in practice. It is more straightforward and transparent than other model-based and model-assisted method. 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. This allows generation of

a decision table that guides dose selection depending on the number of participants treated and observed DLTs. The BOIN design also has improved over-dosing control and generally a higher probability of correctly selecting the MTD, compared with previous model-assisted methods. As an extension to the standard BOIN, TITE-BOIN further allows real-time dose assignment decisions while some patients' toxicity data are still pending, thus provides a practical design to accelerate early phase drug development. When there is no pending data, the TITE-BOIN will seamlessly reduce to the BOIN design. A TITE-BOIN dose-escalation decision table for this study with a selected target DLT rate of 30%, an escalation boundary of 23.6%, and de-escalation boundary of 35.9% is presented in Appendix 8.

Dose escalation may be stopped prior to reaching an MTD based on review of available safety, PK, and pharmacodynamic data and discussions between sponsor and investigators. While the TITE-BOIN will use DLT and safety information only, clinical assessment will take into consideration of the totality of available data including PK/pharmacodynamics from all treated participants, in assigning the next dose level. The final MTD/MAAD/recommended Phase 2 dose will be based on the recommendation from the TITE-BOIN and overall clinical assessment of all available safety, PK, PD, and preliminary efficacy data if available.

10.1.2 Part 1 PD Cohorts

Sizing of PD cohort in each of Parts 1A, 1B, and 1C is based on getting a reasonable estimate of the PD signal difference between biomarker negative and positive population. The PD signal of primary interest to be assessed is tumor cytolytic activity. Assuming natural prevalence of biomarker positive (~70%) in SCCHN population, we expect to enroll biomarker positive participants to biomarker negative participants in the ratio of 2:1. With a total sample size of 30 participants (20 biomarker positive and 10 biomarker negative), the two-sided 80% confidence interval for the difference in the pharmacodynamic signal between the biomarker positive and biomarker negative is (14%, 46%). This assumes a 5% probability of tumor cytolytic activity in the biomarker negative and 35% probability of cytolytic activity in the biomarker positive subgroups, respectively.

In order to account for 25% non-evaluable biopsy samples or lack of repeat biopsy due to early dropouts, about 10 more participants would be needed. That is in order to have 30 evaluable participants, up to approximately 40 will need to be treated per dose level of the SCCHN PD cohorts in monotherapy and combination therapy.

10.2 Populations for Analyses

For purposes of analysis, the following populations are defined in Table 10.2-1 below:

Table 10.2-1: Populations for Analysis

Population	Description
All Enrolled	All participants who signed an ICF and were registered into the IRT.
All Treated	All enrolled participants who receive at least 1 dose of study drug.

Table 10.2-1: Populations for Analysis	
Population	**Description**
Response-evaluable	All treated participants with measurable disease at baseline and 1 of the following: (a) at least 1 post baseline tumor assessment, (b) radiologic progression, (c) death.
PK	All treated participants that have available serum concentration data that allow for computation of PK parameter values.
Immunogenicity	All Treated participants with baseline and at least 1 pre-infusion immunogenicity assessment.
Biomarker	All Treated participants who have available biomarker data.

Abbreviations: ICF = informed consent form; IRT = Interactive Response Technology; PK = pharmacokinetics.

10.3 Statistical Analyses

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

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

10.3.1 Efficacy Analyses

The main efficacy analyses (Table 10.3.1-1) will be performed on the treated population, presented separately by study part. Efficacy analyses based on the response-evaluable population may be performed for interim analyses when the minimum follow-up period is less than sufficient to warrant adequate interpretation of the result.

Table 10.3.1-1: Efficacy Statistical Analysis	
Endpoint	**Statistical Analysis Methods**
ORR is defined as the proportion of population of interest whose BOR is either CR or PR per RECIST v1.1 BOR for a population of participants will be assessed per RECIST v1.1.	Estimate of ORR and corresponding 2-sided exact 95% CI using the Clopper-Pearson method by treatment for each tumor type
Median DOR DOR for a participant with a BOR of CR or PR is defined as the time between the date of first response and the date of the first objectively documented tumor progression per RECIST v1.1 or death, whichever occurs first.	Median duration of response using the Kaplan-Meier method and corresponding 2-sided 95% CI using Brookmeyer and Crowley methodology (using log-log transformation) by treatment for each tumor type Analysis is dependent on the number of responders
PFSR at 6, 9, and 12 months PFS for a participant is defined as the time from the first dosing date to the date of first objectively documented disease progression or death due to any cause, whichever occurs first.	Estimate by the Kaplan-Meier method and corresponding 95% CI will be derived based on Greenwood formula by treatment for each tumor type.

Abbreviations: BOR, best overall response; CI, confidence interval; CR, complete response; DOR, duration of response; ORR, overall response rate; PFS, progression free survival; PFSR, progression free survival rate; PR partial response; RECIST, Response Evaluation Criteria In Solid Tumors

Overall survival rate (OSR) at 1 year and 2 years will be analyzed similarly to PFSR. Details of the censoring scheme on time-to-event endpoints such as DOR, PFS, and OSR will be described in the Statistical Analysis Plan.

10.3.2 Safety Analyses

All safety analyses will be performed on the treated population. Statistical analyses for Safety are shown in Table 10.3.2-1.

Table 10.3.2-1: Safety Statistical Analysis

Endpoint	Statistical Analysis Methods
Incidence of AEs, SAEs, AEs meeting protocol defined DLT criteria, AEs leading to discontinuation, and death; AEs will be graded according to CTCAE v5.0.	DLT rate by dose level, frequency distribution of treated participants with AE using the worst CTC grade. Participants will only be counted (1) once at the PT level, (2) once at the system organ class level, and (3) once in the 'total participant' row at their worst CTC grade, regardless of system organ class or PT.
Laboratory abnormalities Laboratory values will be graded according to CTCAE v5.0.	Laboratory shift table using the worst CTC grade on treatment per participant

Abbreviations: AE, adverse event; CTC, common terminology criteria; CTCAE, common terminology criteria for adverse events; DLTs, dose-limiting toxicities; PT, preferred term; SAE, serious adverse event.

10.3.3 PK Analyses for BMS-986315, Nivolumab, and Cetuximab

Table 10.3.3-1: PK Statistical Analyses

Endpoint	Statistical Analysis Methods
BMS-986315	
Cmax, AUC(0-T), AUC(TAU), Ctau, Ctrough, Css-avg, AI_AUC, DF, and T-HALFeff_AUC	Summary statistics: geometric means and coefficients of variation
Cmax, AUC(0-T), AUC(TAU)	Scatter plots vs dose for each cycle measured; dose proportionality based on a power model and a CI around the power coefficient
Tmax	Summary statistics: medians and ranges
Ctrough	geometric mean plots vs time (e.g. day or cycle)
Nivolumab	
Ctrough	Summary statistics: geometric means and coefficients of variation, plots vs time (e.g. day or cycle)

Table 10.3.3-1: PK Statistical Analyses

Endpoint	Statistical Analysis Methods
Cetuximab	
Ctrough	Summary statistics: geometric means and coefficients of variation, plots vs time (e.g. day or cycle)

Abbreviations: AI_AUC, accumulation index ratio of AUC(TAU) at steady state to AUC (TAU) after the first dose; AUC(0-T), area under the concentration-time curve from time zero to the time of the last quantifiable concentration; AUC(TAU), area under the concentration-time curve in one dosing interval; CI, confidence interval; Cmax, maximum observed concentration; Css-avg, average concentration over a dosing interval (AUC(TAU)/tau); Ctau, observed concentration at the end of a dosing interval; Ctrough, trough observed serum concentration; DF, Degree of fluctuation or fluctuation index; Tmax, time of maximum observed concentration; T-HALFeff_AUC, mean effective half-life accumulation index ratio area under the curve T-HALFeff_AUC, mean effective half-life accumulation index ratio area under the curve T-HALFeff_AUC, mean effective half-life accumulation index ratio area under the curve

Summary statistics will be tabulated for each PK parameter, if feasible, and wherever applicable, by treatment and dosing regimen. PK time-concentration data of nivolumab and cetuximab may be pooled with data from other studies for population PK analysis, which will be presented in a separate report.

10.3.4 Immunogenicity Analyses

Endpoint	Statistical Analysis Methods
• Incidence of anti-drug antibodies to BMS-986315 • Incidence of anti-drug antibodies to nivolumab, with combination treatment • Incidence of anti-drug antibodies to cetuximab with combination treatment Baseline anti-drug antibody-positive participant is defined as a participant who has an anti-drug antibody-detected sample at baseline[a] anti-drug antibody-positive participant is a participant with at least 1 anti-drug antibody-positive sample relative to baseline after initiation of the treatment.	Frequency distribution baseline anti-drug antibody-positive participants and anti-drug antibody-positive participants after initiation of the monotherapy and combination treatment. Frequency distribution of nivolumab baseline anti-drug antibody-positive participants and anti-drug antibody-positive participants after initiation of the combination treatment. Frequency distribution of cetuximab baseline anti-drug antibody-positive participants and anti-drug antibody-positive participants after initiation of the combination treatment.

[a] Baseline sample is the last sample before initiation of the treatment

10.3.5 Exploratory Biomarker Analyses

Endpoint	Statistical Analysis Methods
• Summary measures of change (or % change) from baseline in various biomarkers (e.g. by IHC) in the tumor and peripheral blood. • Association measures of baseline biomarker levels and biomarker changes with tumor response measures.	Summary statistics/plots by planned study day and dose in each arm. Plots of the time course of biomarkers Plots and summaries of baseline biomarker levels and biomarker changes by tumor response outcome.

10.3.6 ECG Analyses

Endpoint	Statistical Analysis Methods
Summary measures of changes in QTc from baseline by dose and association measures of QTc changes with BMS-986315 PK exposure, following monotherapy treatment.	Summary changes in the QTc by dose and study day. Frequency distributions of max QTc values in pre-specified categories by dose. Modeling of concentration-response effect of BMS-986315 on QTc by linear mixed effect regression model stratified by study day as well as pooled across days.

10.3.7 Other Analyses

Additional biomarker exploratory analyses will be described in the statistical analysis plan finalized before database lock. Any population PK analyses will be presented separately from the main clinical study report. All SARS-CoV-2-related AEs (if any) will be listed.

10.3.8 Interim Analysis

Interim analyses will be performed prior to the end of the study, e.g. at the completion of a study part such as the end of the escalation phase (in 1A, 1B or 1C), or at the completion of a PD cohort, for evaluation of the available data in that study part. 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
ADCC	antibody-dependent cellular cytotoxicity
AE	adverse event
AI	accumulation index
AI_AUC	accumulation index ratio of AUC at steady state to that after the first dose
AI_TAU	Ratio of AUC[TAU] at steady state to that after the first dose
ALK	anaplastic lymphoma kinase
ALT	alanine aminotransferase
AUC	area under the concentration-time curve
AUC(INF)	area under the concentration-time curve from time zero extrapolated to infinite time
AUC(0-T)	area under the concentration-time curve from time zero to the time of the last quantifiable concentration
AUC(TAU)	area under the concentration-time curve in one dosing interval
AST	aspartate aminotransferase
AT	aminotransaminases
A-V	atrioventricular
β-HCG	beta-human chorionic gonadotrophin
BICR	blinded independent central review
BID, bid	bis in die, twice daily
BMS	Bristol Myers Squibb
BOR	best overall response
BP	blood pressure
BUN	blood urea nitrogen
BW	body weight
C	Celsius
Cavgss	average steady state concentration
CBC	complete blood count
CD8	Cluster of differentiation 8
CFR	Code of Federal Regulations

Term	Definition
CI	confidence interval
CL	clearance
CLTp	total body clearance
cm	centimeter
Cmax, CMAX	maximum observed concentration
Cmaxss	steady state peak concentration
CMV	cytomegalovirus
CNS	Central nervous system
CR	Complete response
CRC	Colorectal cancer
CRF	Case Report Form, paper or electronic
CRO	Contract Research Organization
Ctau	Concentration in a dosing interval (eg, concentration at 24 hours, concentration at 12 hours, etc.)
CTCAE	Common Terminology Criteria for Adverse Events
CTLA-4	cytotoxic T lymphocyte-associated antigen 4
Ctrough	Trough observed plasma concentration
CV	coefficient of variation
CYP	cytochrome p-450
CT	Computed tomography
D/C	discontinue
DF	Degree of fluctuation or fluctuation index (to be calculated at steady state)
DLT	Dose limiting toxicity
DMC	Data monitoring committee
DOR	Duration of response
DSM IV	Diagnostic and Statistical Manual of Mental Disorders (4^{th} Edition)
ECOG	Eastern Cooperative Oncology Group
ECOG-PS	Eastern Cooperative Oncology Group Performance Status
ECG	electrocardiogram
EGFR	epidermal growth factor receptor

Term	Definition
ECHO	echocardiogram
eCRF	Electronic Case Report Form
EDC	Electronic Data Capture
eg	exempli gratia (for example)
EOI	end of infusion
EOT	End of treatment
ER	exposure response
ESR	Expedited Safety Report
F	bioavailability
FDA	Food and Drug Administration
FIH	First in human
FSH	follicle stimulating hormone
g	gram
GCP	Good Clinical Practice
GGT	gamma-glutamyl transferase
GFR	glomerular filtration rate
h	hour
HBsAg	hepatitis B surface antigen
HBV	hepatitis B virus
HCG	human chorionic gonadotropin
HCV	hepatitis C virus
HIV	Human Immunodeficiency Virus
HLA-E	histocompatibility antigen, alpha chain E
HNSTD	highest nonseverely toxic dose
HPV	human papillomavirus
HR	heart rate
IB	Investigator's brochure
ICF	Informed consent form
ICH	International Conference on Harmonisation
IgG	immunoglobulin G

Term	Definition
IHC	immunohistochemistry
IMG	immunogenicity
IEC	Independent Ethics Committee
IND	Investigational New Drug Exemption
IMAE	immune-mediated adverse event
I-O	immuno-oncology
IP	intraperitoneal
IRB	Institutional Review Board
IRR	infusion-related reactions
IRT	Interactive Response Technology
IU	International Unit
IV	intravenous
kg	kilogram
L	liter
LAM	Lactation amenorrhea method
LDH	lactate dehydrogenase
ln	natural logarithm
LVEF	left ventricle ejection fraction
MAAD	Maximum administered dose
mAb	monoclonal antibody
mg	milligram
min	minute
mL	milliliter
MLR	mixed lymphocyte reaction
MM	Medical monitor
mmHg	millimeters of mercury
MOA	Mechanism of action
mPFS	median Progression Free Survival
MRI	Magnetic resonance imaging
MTD	maximum tolerated dose

Term	Definition
MUGA	multigated acquisition
μg	microgram
N	number of subjects or observations
NCI	National Cancer Institute
NK	Natural killer
NKG2A	natural killer cell receptor
N/A	not applicable
NOAEL	no-observed-adverse-effect level
NSAID	nonsteroidal anti-inflammatory drug
NSCLC	Non-small cell lung cancer
ORR	Objective response rate
OS	Overall survival
OSR	overall survival rate
PBMC	peripheral blood mononuclear cell
PD	pharmacodynamic
PD cohort	pharmacodynamics cohort
PD-1	programmed cell death 1
pDILI	potential drug-induced liver injury
PE	Physical exam
PFSR	progression-free survival rate
PI	prediction interval
PID	patient identification number
PK	pharmacokinetics
PPK	population pharmacokinetics
PR	partial response
PS	Performance status
Q2W	administered every 2 weeks
Q4W	administered every 4 weeks
Q8W	administered every 8 weeks
QC	quality control

Term	Definition
QD, qd	quaque die, once daily
QTc	interval corrected for heart rate using Frederica's formula
RBC	red blood cell
RCC	Renal cell carcinoma
RO	Receptor occupancy
RP2D	Recommended phase 2 dose
RT-PCR	reverse-transcription polymerase chain reaction
SAE	serious adverse event
SAR-CoV-2	severe acute respiratory syndrome coronavirus 2;
SC	subcutaneous
SCCHN	Squamous cell carcinoma of the head and neck
SD	standard deviation
SMT	Safety Management Team
SOP	Standard Operating Procedures
t	temperature
T	time
TAO	Trial Access Online, the BMS implementation of an EDC capability
TCR	T-cell receptor
TGI	tumor growth inhibition
T-HALF	Half life
TITE-BOIN	time-to-event Bayesian optimal interval
TITE-CRM	time-to-event continual reassessment method
TIL	Tumor infiltrating lymphocyte
TID, tid	ter in die, three times a day
Tmax, TMAX	time of maximum observed concentration
TSH	thyroid stimulating hormone
ULN	upper limit of normal
Vss	Volume of distribution
WBC	white blood cell
WHO	World Health Organization
WOCBP	women of childbearing potential

Term	Definition
WNOCBP	women **not** of childbearing potential
WWPS	Worldwide Patient Safety

APPENDIX 2 STUDY GOVERNANCE CONSIDERATIONS

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

REGULATORY AND ETHICAL CONSIDERATIONS

GOOD CLINICAL PRACTICE

This study will be conducted in accordance with:

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

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

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

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

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

INSTITUTIONAL REVIEW BOARD/INDEPENDENT ETHICS COMMITTEE

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

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

COMPLIANCE WITH THE PROTOCOL AND PROTOCOL REVISIONS

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

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

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

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

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

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

FINANCIAL DISCLOSURE

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

INFORMED CONSENT PROCESS

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

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

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

Investigators must:

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

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

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

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

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

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

SOURCE DOCUMENTS

The Investigator is responsible for ensuring that the source data are accurate, legible, contemporaneous, original and attributable, whether the data are hand-written on paper or entered electronically. If source data are created (first entered), modified, maintained, archived, retrieved, or transmitted electronically via computerized systems (and/or any other kind of electronic

devices) as part of regulated clinical trial activities, such systems must be compliant with all applicable laws and regulations governing use of electronic records and/or electronic signatures. Such systems may include, but are not limited to, electronic medical/health records (EMRs/EHRs), adverse event tracking/reporting, protocol required assessments, and/or drug accountability records).

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

STUDY TREATMENT RECORDS

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

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

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

CASE REPORT FORMS

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

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

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

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

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

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

MONITORING

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

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

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

RECORDS RETENTION

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

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

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

RETURN OF STUDY TREATMENT

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

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

It is the investigator's or designee's responsibility to arrange for disposal, provided that procedures for proper disposal have been established according to applicable federal, state, local, and

institutional guidelines and procedures, and provided that appropriate records of disposal are kept. The following minimal standards must be met:

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

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

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

CLINICAL STUDY REPORT

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

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

- Participant recruitment (eg, among the top quartile of enrollers)
- Involvement in trial design
- Regional representation (eg, among top quartile of enrollers from a specified region or country)

SCIENTIFIC PUBLICATIONS

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

Scientific Publications (such as abstracts, congress podium presentations and posters, and manuscripts) of the study results will be a collaborative effort between the study Sponsor and the external authors. No public presentation or publication of any interim results may be made by any

principal investigator, sub-investigator or any other member of the study staff without the prior written consent of the Sponsor.

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

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

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

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

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

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

ADVERSE EVENTS

Adverse Event Definition:

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

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

Events Meeting the AE Definition

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

Events NOT Meeting the AE Definition

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

DEFINITION OF SAE

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

SERIOUS ADVERSE EVENTS

Serious Adverse Event (SAE) is defined as any untoward medical occurrence that, at any dose:
Results in death
Is life-threatening (defined as an event in which the participant was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe)
Requires inpatient hospitalization or causes prolongation of existing hospitalization (see NOTE below) NOTE: The following hospitalizations are not considered SAEs in BMS clinical studies: • a visit to the emergency room or other hospital department < 24 hours, that does not result in admission (unless considered an important medical or life-threatening event) • elective surgery, planned prior to signing consent • admissions as per protocol for a planned medical/surgical procedure • routine health assessment requiring admission for baseline/trending of health status (e.g., routine colonoscopy) • medical/surgical admission other than to remedy ill health and planned prior to entry into the study. Appropriate documentation is required in these cases • admission encountered for another life circumstance that carries no bearing on health status and requires no medical/surgical intervention (e.g., lack of housing, economic inadequacy, caregiver respite, family circumstances, administrative reason) • admission for administration of anticancer therapy in the absence of any other SAEs (applies to oncology protocols)
Results in persistent or significant disability/incapacity
Is a congenital anomaly/birth defect
Is an important medical event (defined as a medical event(s) that may not be immediately life-threatening or result in death or hospitalization but, based upon appropriate medical and scientific judgment, may jeopardize the participant or may require intervention [e.g., medical, surgical] to prevent one of the other serious outcomes listed in the definition above.) Examples of such events include, but are not limited to, intensive treatment in an emergency room or at home for allergic bronchospasm; blood dyscrasias or convulsions that do not result in hospitalization.) Potential drug induced liver injury (DILI) is also considered an important medical event. (See Section 9.2.7 for the definition of potential DILI.)

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

EVALUATING AES AND SAES

Assessment of Causality

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

Follow-up of AEs and SAEs

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

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

All SAEs must be followed to resolution or stabilization.

REPORTING OF SAES TO SPONSOR OR DESIGNEE

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

SAE Email Address: Refer to Contact Information list.

SAE Facsimile Number: Refer to Contact Information list.

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

APPENDIX 4 WOMEN OF CHILDBEARING POTENTIAL DEFINITIONS AND METHODS OF CONTRACEPTION

DEFINITIONS

Woman of Childbearing Potential (WOCBP)

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

Women in the following categories are not considered WOCBP

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

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

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

Note: Females treated with hormone replacement therapy, (HRT) are likely to have artificially suppressed FSH levels and may require a washout period in order to obtain a physiologic FSH level. The duration of the washout period is a function of the type of HRT used. The duration of the washout period below are suggested guidelines and the investigators should use their judgment in checking serum FSH levels.

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

Other parenteral products may require washout periods as long as 6 months. If the serum FSH level is > 40 mIU/ml at any time during the washout period, the woman can be considered postmenopausal.

End of Relevant Systemic Exposure

- End of relevant systemic exposure is the time point where the IMP or any active major metabolites has decreased to a concentration that is no longer considered to be relevant for human teratogenicity or fetotoxicity. This should be evaluated in context of safety margins from the no-observed adverse effect level (NOAEL) or the time required for 5 half-lives of the IMP to pass.

METHODS OF CONTRACEPTION

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

Highly Effective Contraceptive Methods That Are User Dependent *Failure rate of <1% per year when used consistently and correctly.*[a]
• Combined (estrogen- and progestogen-containing) hormonal contraception associated with inhibition of ovulation and/or implantation. (This method of contraception can only be used by WOCBP participants in studies where hormonal contraception is permitted by the study protocol)[b] – oral (birth control pills) – intravaginal (vaginal birth control suppositories, rings, creams, gel) – 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 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] • Intrauterine device (IUD) • 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.

Sexual abstinence

Sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the study treatment. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the study and the preferred and usual lifestyle of the participant.

- Continuous abstinence must begin at least 30 days prior to initiation of study therapy
- It is not necessary to use any other method of contraception when complete abstinence is elected.
- WOCBP participants who choose complete abstinence must continue to have pregnancy tests, as specified in Section 2.
- Acceptable alternate methods of highly effective contraception must be discussed in the event that the WOCBP participants chooses to forego complete abstinence
- Periodic abstinence (including but not limited to calendar, symptothermal, post-ovulation methods), withdrawal (coitus interruptus), spermicides only, and lactational amenorrhoea method (LAM) are not acceptable methods of contraception for this study.

NOTES:

[a] Typical use failure rates may differ from those when used consistently and correctly. Use should be consistent with local regulations regarding the use of contraceptive methods for participants participating in clinical studies.

[b] Hormonal contraception may be susceptible to interaction with the study treatmentg, which may reduce the efficacy of the contraceptive method. Hormonal contraception is permissible only when there is sufficient evidence that the IMP and other study medications will not alter hormonal exposures such that contraception would be ineffective or result in increased exposures that could be potentially hazardous. In this case, alternative methods of contraception should be utilized.

[c] Intrauterine hormone releasing systems are acceptable methods of contraception in the absence of definitive drug interaction studies when hormone exposures from intrauterine devices do not alter contraception effectiveness

Less Than Highly Effective Contraceptive Methods That Are User Dependent

Failure rate of >1% per year when used consistently and correctly.

- Male or female condom with or without spermicide. Male and female condoms cannot be used simultaneously
- Diaphragm with spermicide
- Cervical cap with spermicide
- Vaginal Sponge with spermicide
- Progestogen-only oral hormonal contraception, where inhibition of ovulation is not the primary mechanism of action (This method of contraception cannot be used by WOCBP participants in studies where hormonal contraception is prohibited)

Unacceptable Methods of Contraception

- Periodic abstinence (calendar, symptothermal, post-ovulation methods)

- Withdrawal (coitus interruptus)
- Spermicide only
- Lactation amenorrhea method (LAM)

COLLECTION OF PREGNANCY INFORMATION

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

APPENDIX 5 MANAGEMENT ALGORITHMS FOR STUDIES UNDER CTCAE VERSION 5.0

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

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

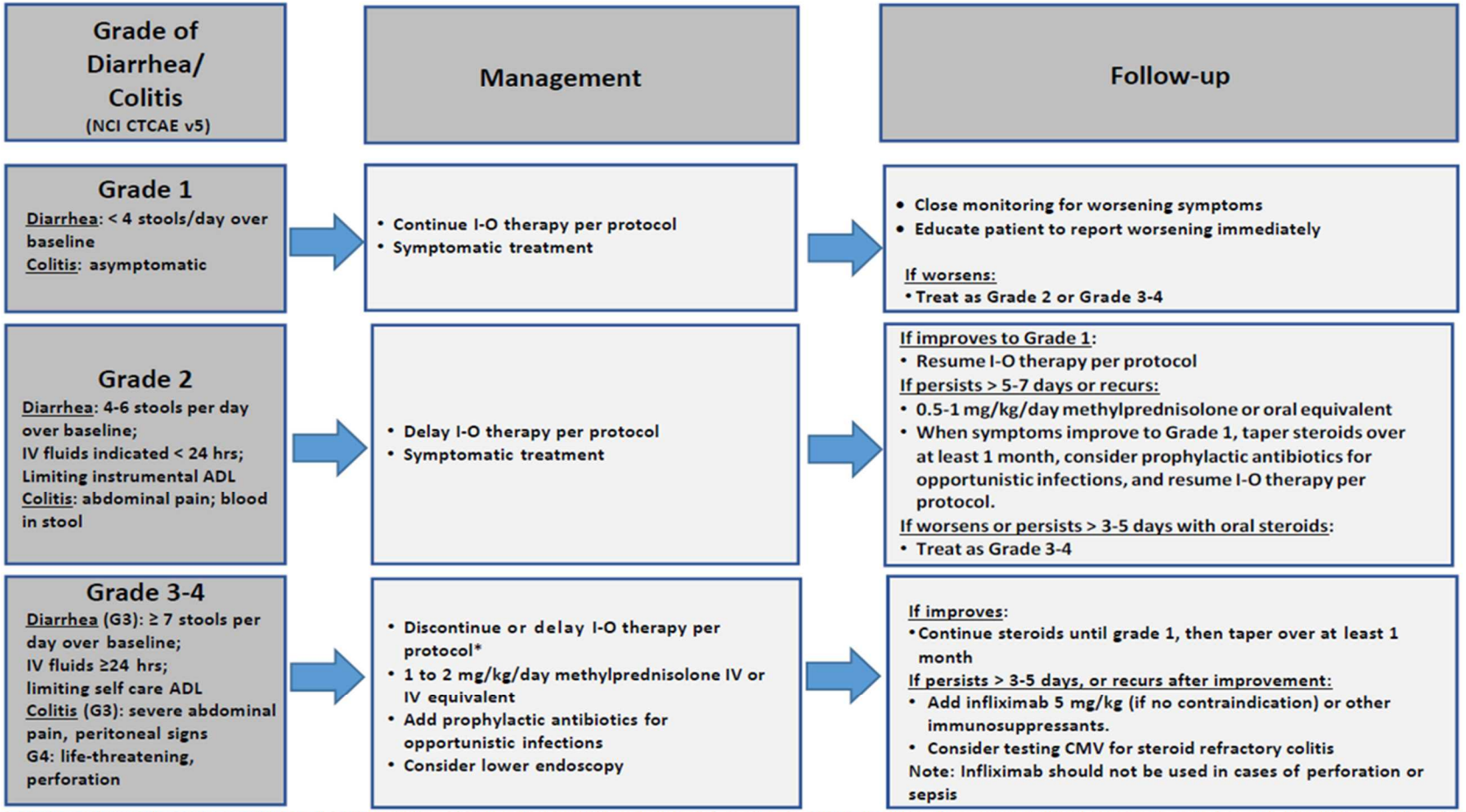
Corticosteroids are a primary therapy for immuno-oncology drug-related adverse events. The oral equivalent of the recommended IV doses may be considered for ambulatory patients with low grade toxicity. The lower bioavailability of oral corticosteroids should be taken into account when switching to the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

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



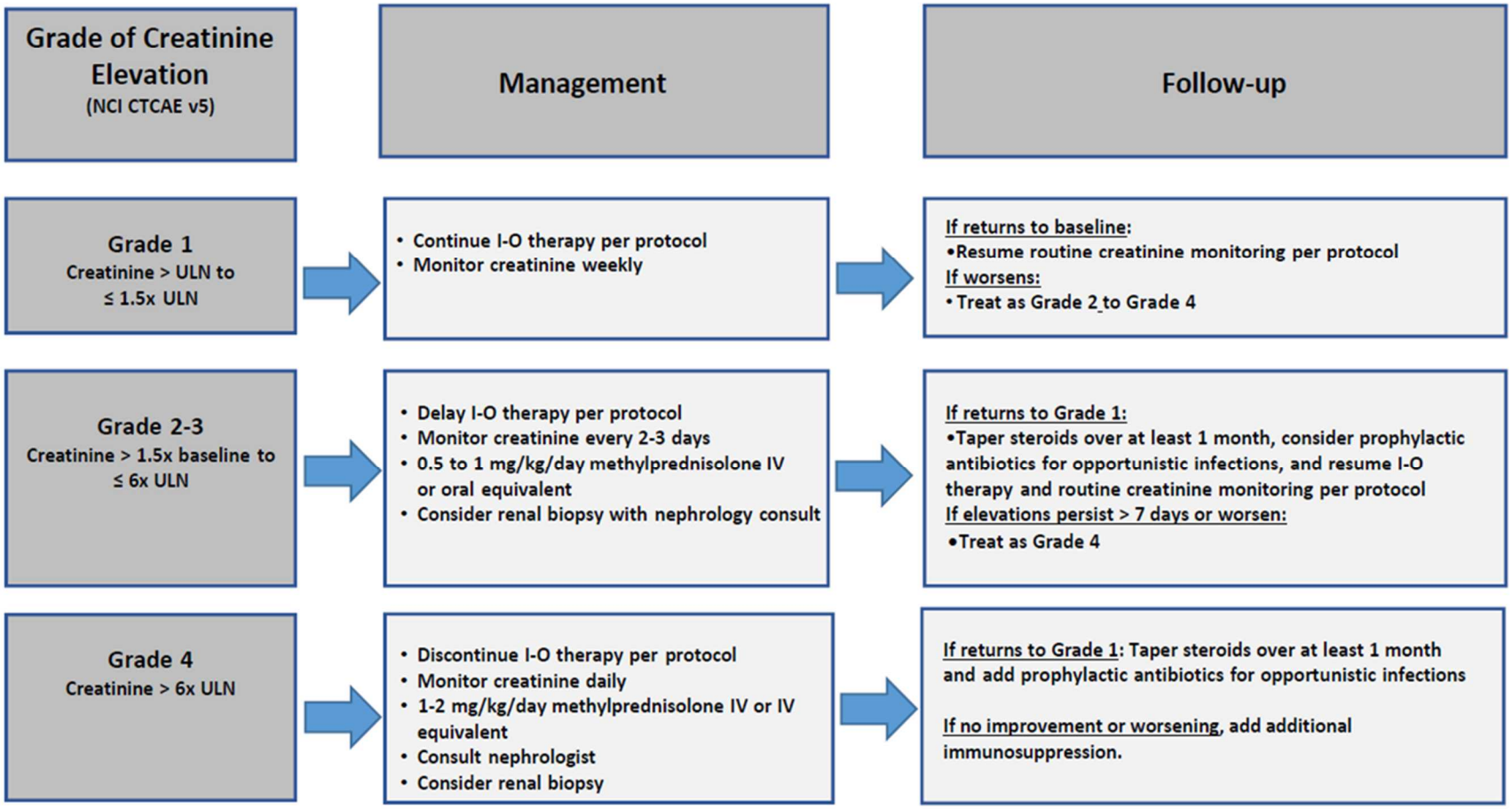
Patients on IV steroids may be switched to an equivalent dose of oral corticosteroids (eg, prednisone) at start of tapering or earlier, after sustained clinical improvement is observed. Lower bioavailability of oral corticosteroids should be taken into account when switching to the equivalent dose of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

6HS

Renal Adverse Event Management Algorithm

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

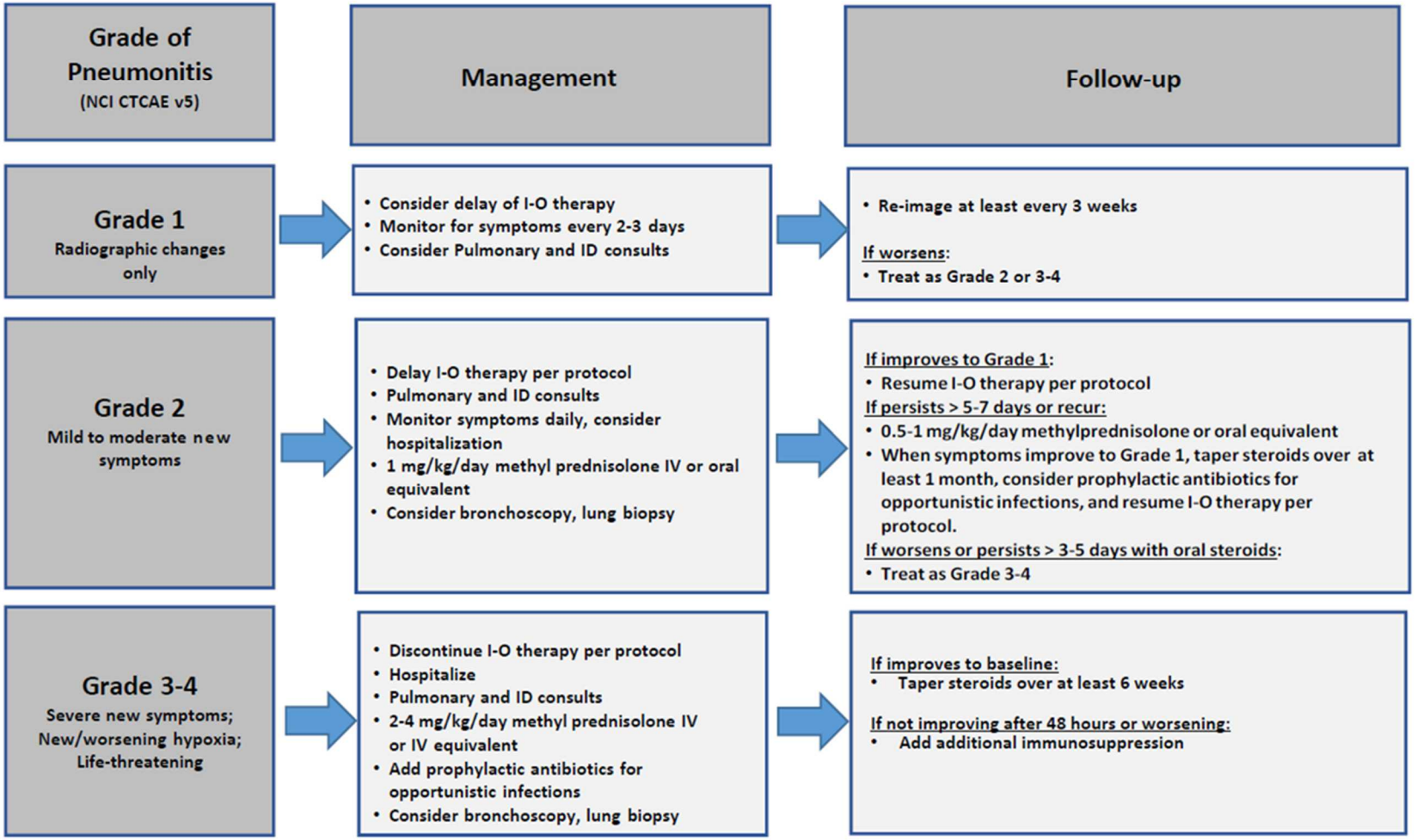


Patients on IV steroids may be switched to an equivalent dose of oral corticosteroids (eg, prednisone) at start of tapering or earlier, after sustained clinical improvement is observed. Lower bioavailability of oral corticosteroids should be taken into account when switching to the equivalent dose of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

6HS

Pulmonary Adverse Event Management Algorithm

Rule out non-inflammatory causes. If non-inflammatory cause, treat accordingly and continue I-O therapy.
Evaluate with imaging and pulmonary consultation.

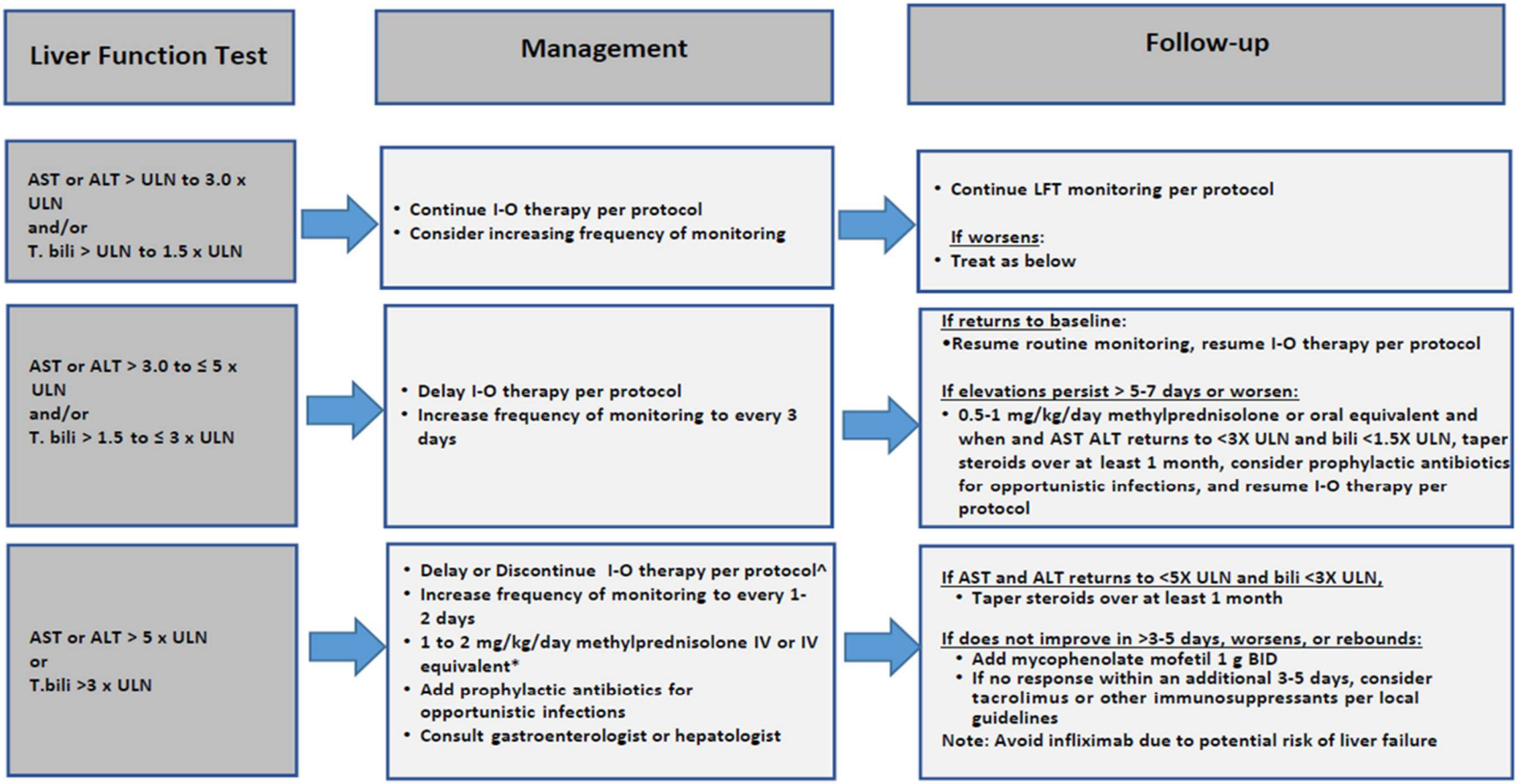


Patients on IV steroids may be switched to an equivalent dose of oral corticosteroids (eg, prednisone) at start of tapering or earlier, after sustained clinical improvement is observed. Lower bioavailability of oral corticosteroids should be taken into account when switching to the equivalent dose of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

6HS

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.

6HS

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.

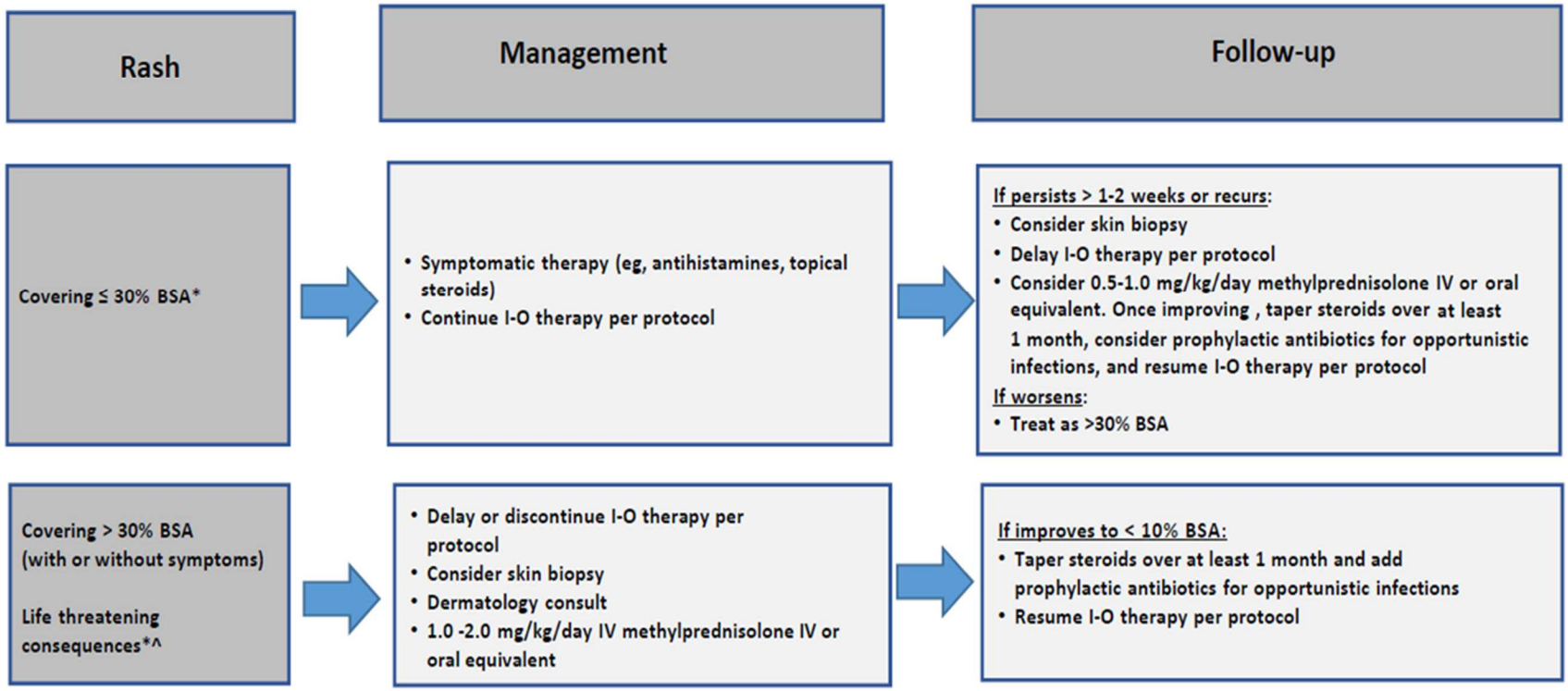
Endocrinopathy	Management	Follow-up
Asymptomatic TSH abnormality or Hyperglycemia requiring no medical intervention	• Continue I-O therapy per protocol • If TSH < 0.5 x LLN, or TSH > 2 x ULN, or consistently out of range in 2 subsequent measurements: ○ include fT4 at subsequent cycles as clinically indicated; ○ 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.

6HS

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.

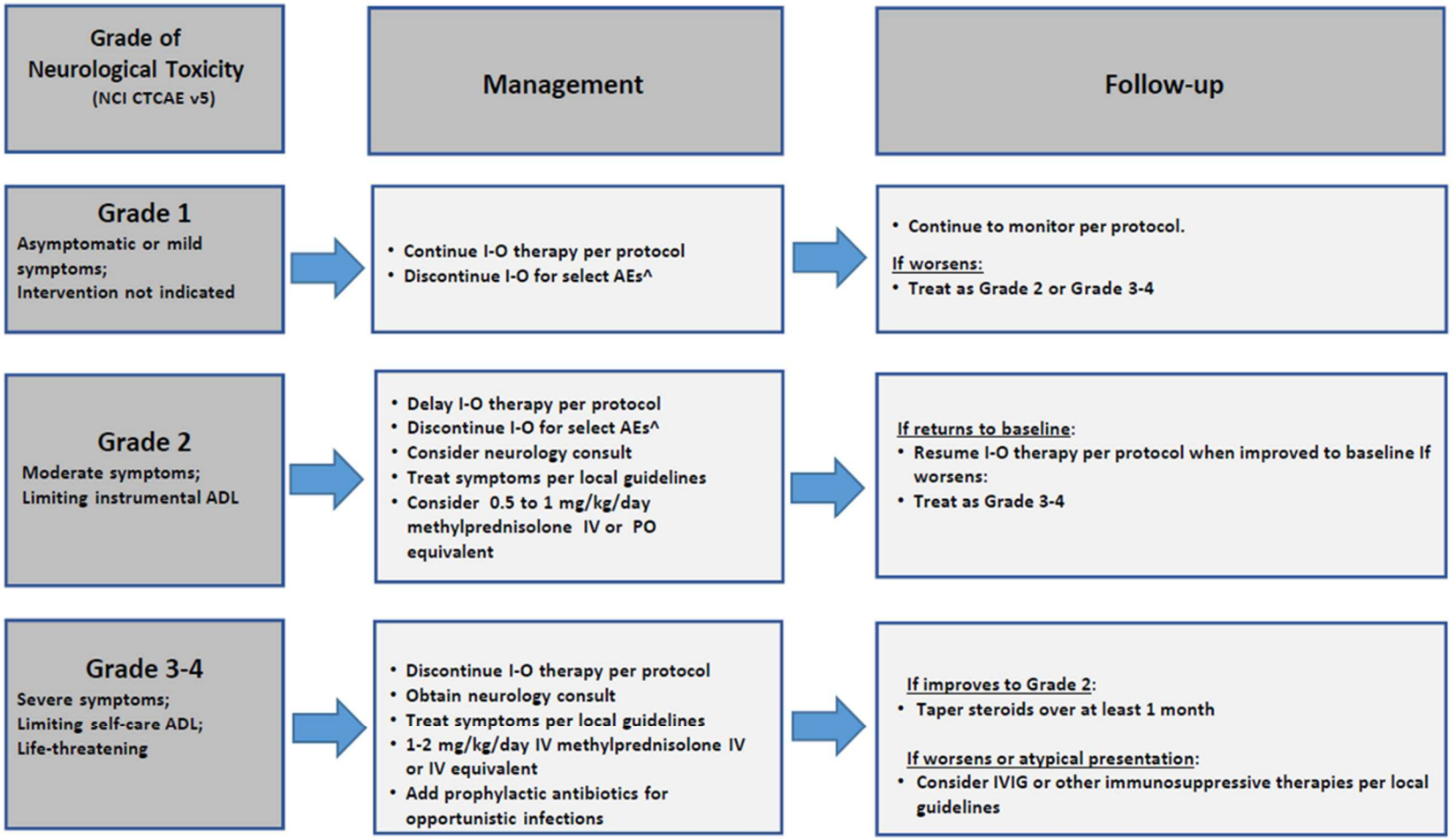
*Refer to NCI CTCAE v5 for term-specific grading criteria.

^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.

6HS

Neurological Adverse Event Management Algorithm

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



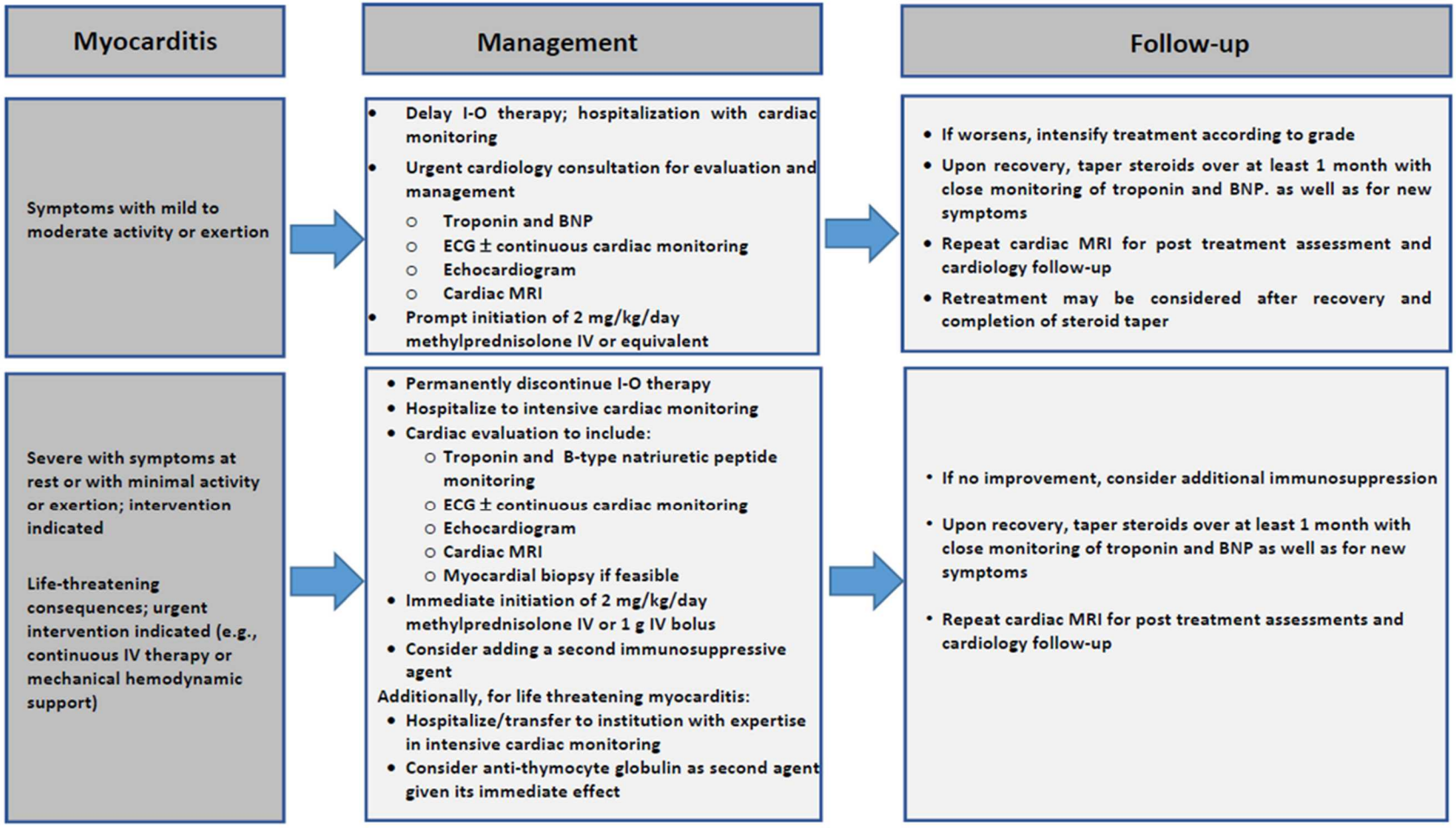
Patients on IV steroids may be switched to an equivalent dose of oral corticosteroids (eg. prednisone) at start of tapering or earlier, after sustained clinical improvement is observed. Lower bioavailability of oral corticosteroids should be taken into account when switching to the equivalent dose of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

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

6HS

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.

6HS

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, et al. Toxicity and Response Criteria of the Eastern Cooperative Oncology Group. Am J Clin Oncol 1982; 5: 649-655.

APPENDIX 7 RESPONSE EVALUATION CRITERIA IN SOLID TUMORS GUIDELINES (VERSION 1.1) WITH BMS MODIFICATIONS

1 EVALUATION OF LESIONS

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

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

1.1 Measurable

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

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

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

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

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

1.2 Non-Measurable

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

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

1.3 Special Considerations Regarding Lesion Measurability

1.3.1 Bone Lesions

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

1.4 Baseline Documentation of 'Target' and 'Non-Target' Lesions

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

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

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

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

All other lesions (or sites of disease) including pathological lymph nodes should be identified as non-target lesions and should also be recorded at baseline. Measurements are not required and these lesions should be followed as 'present', 'absent', or in rare cases 'unequivocal progression' (more details to follow). In addition, it is possible to record multiple non-target lesions involving the same organ as a single item on the case record form (eg, 'multiple enlarged pelvic lymph nodes' or 'multiple liver metastases').

2 RESPONSE CRITERIA

2.1 Evaluation of Target Lesions

- **Complete Response (CR):** Disappearance of all target lesions. Any pathological lymph nodes (whether target or non-target) must have reduction in short axis to < 10 mm.
- **Partial Response (PR):** At least a 30% decrease in the sum of diameters of target lesions, taking as reference the baseline sum diameters.
- **Progressive Disease (PD):** At least a 20% increase in the sum of diameters of target lesions, taking as reference the smallest sum on study (this includes the baseline sum if that is the smallest on study). In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 5 mm. (Note: the appearance of one or more new lesions is also considered progression).
- **Stable Disease (SD):** Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as reference the smallest sum diameters while on study.
- **Not Evaluable (NE):** If one or more target lesions cannot be measured or adequately assessed as either fully resolved or too small to measure (due to missing or poor quality images), and the sum of diameters of the remaining measured target lesions (if any) has not increased sufficiently to meet Progressive Disease as defined above.

2.1.1 Special Notes on the Assessment of Target Lesions

2.1.1.1 Lymph nodes

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

2.1.1.2 Target lesions that become 'too small to measure'

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

default value is derived from the 5 mm CT slice thickness (but should not be changed with varying CT slice thickness). The measurement of these lesions is potentially non-reproducible, therefore providing this default value will prevent false responses or progressions based upon measurement error. To reiterate, however, if the radiologist is able to provide an actual measure, that should be recorded, even if it is below 5 mm.

2.1.1.3 Lesions that split or coalesce on treatment

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

2.2 Evaluation of Non-Target Lesions

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

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

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

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

2.2.1.1 When the patient also has measurable disease

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

2.2.1.2 When the patient has only non-measurable disease

This circumstance arises in some trials when it is not a criterion of study entry to have measurable disease. The same general concepts apply here as noted above, however, in this instance there is no measurable disease assessment to factor into the interpretation of an increase in non-measurable disease burden. Because worsening in non-target disease cannot be easily quantified (by definition: if all lesions are truly non-measurable) a useful test that can be applied when assessing patients for

unequivocal progression is to consider if the increase in overall disease burden based on the change in non-measurable disease is comparable in magnitude to the increase that would be required to declare PD for measurable disease: ie, an increase in tumor burden representing an additional 73% increase in 'volume' (which is equivalent to a 20% increase diameter in a measurable lesion). Examples include, an increase in lymphangitic disease from localized to widespread, or may be described as 'sufficient to require a change in therapy'. If 'unequivocal progression' is seen, the patient should be considered to have had overall PD at that point. While it would be ideal to have objective criteria to apply to non-measurable disease, the very nature of that disease makes it impossible to do so; therefore the increase must be substantial.

2.2.2 New Lesions

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

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

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

1. Negative FDG-PET at baseline, with a positive FDG-PET at follow-up is a sign of PD based on a new lesion.
2. No FDG-PET at baseline and a positive FDG-PET at follow-up: If the positive FDG-PET at follow-up corresponds to a new site of disease confirmed by CT, this is PD. If the positive FDG-PET at follow-up is not confirmed as a new site of disease on CT, additional follow-up CT scans are needed to determine if there is truly progression occurring at that site (if so, the

date of PD will be the date of the initial abnormal FDG-PET scan). If the positive FDG-PET at follow-up corresponds to a pre-existing site of disease on CT that is not progressing on the basis of the anatomic images, this is not PD.

2.3 Response Assessment

2.3.1 Evaluation of Best Overall Response

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

2.3.2 Time Point Response

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

Table 2.3.2-1: Time Point Response

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

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

Table 2.3.2-2: Time Point Response

Non-Target Lesions	New Lesions	Overall Response
CR	No	CR
Non-CR/non-PD	No	Non-CR/non-PD[a]

Table 2.3.2-2: Time Point Response		
Non-Target Lesions	**New Lesions**	**Overall Response**
Not all evaluated	No	NE
Unequivocal PD	Yes or No	PD
Any	Yes	PD
CR = complete response, PD = progressive disease and NE = inevaluable		

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

2.3.3 Best Overall Response

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

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

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

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

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**
PR	CR	PR
PR	PR	PR
PR	SD	SD
PR	PD	SD provided minimum criteria for SD duration met, otherwise, PD
PR	NE	SD provided minimum criteria for SD duration met, otherwise, NE
NE	NE	NE
CR = complete response, PR = partial response, SD = stable disease, PD = progressive disease, and NE = inevaluable		

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

2.3.4 Confirmation Scans

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

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

REFERENCES

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

APPENDIX 8 TITE-BOIN DECISION TABLE

The time-to-event Bayesian optimal interval (TITE-BOIN) design (Yuan et al., 2018) will be used to guide the maximum tolerated dose (MTD) selection.

The target toxicity rate for the MTD is $\phi = 0.3$ and the maximum sample size is 36. We will enroll and treat patients in cohorts of initial size 2-3 at the two lower dose levels and 3-4 at the subsequent doses. The DLT assessment window is T=28 days. The trial design is illustrated in Figure 1 and described through the following three steps:

1. Patients in the first cohort are treated at dose level 1.
2. To assign a dose to the next cohort of patients, count the number of patients ("No. treated"), the number of patients who experienced DLT ("No. DLTs"), and the number of pending patients ("No. data pending") and their standardized total follow-up time ("STFT") at the current dose, and then make the dose escalation/de-escalation decision according to the rule displayed in Table 1, which minimizes the probability of incorrect dose assignment.

   The STFT is defined as

   $$\text{STFT} = \frac{\text{sum of the followup time for pending patients at the current dose}}{\text{length of the DLT assessment window}}$$

   When using Table 1, please note the following:
   a. "Y&Elim" means de-escalating to the next lower dose and eliminating the current and higher doses from the trial to prevent treating any future patients at these doses because they are overly toxic. When the lowest dose is eliminated, stop the trial for safety. In this case, no dose should be selected as the MTD.
   b. If the current dose is the lowest dose and the decision table indicates dose de-escalation but no elimination, treat the new patients at the lowest dose.
   c. If the current dose is the highest dose and the rule indicates dose escalation, treat the new patients at the highest dose.
   d. For patient safety, if at the current dose, more than 50% of the patients' DLT outcomes are pending, suspend the accrual to wait for more data to become available. This rule corresponds to "Suspend" in Table 1.
3. Repeat step 2 until the maximum sample size of 36 is reached or stop the trial if the number of patients treated at the current dose reaches at least 12 or up to 15.

Table 1: TITE-BOIN Decision Table

No. Patients Treated	No. DLTs observed	No. Pending patients	STFT		
			Escalation	Stay	De-escalation
2	0	≤1	Y		
2	0	2	Suspend	Suspend	Suspend
2	≥1	≤1			Y
3	0	≤1	Y		
3	0	≥2	Suspend	Suspend	Suspend
3	1	0		Y	

Table 1: TITE-BOIN Decision Table

No. Patients Treated	No. DLTs observed	No. Pending patients	STFT		
			Escalation	Stay	De-escalation
3	1	1		>0.88	≤0.88
3	1	≥2	Suspend	Suspend	Suspend
3	2	≤1			Y
3	3	0			Y&Elim
4	0	≤2	Y		
4	0	≥3	Suspend	Suspend	Suspend
4	1	≤2		Y	
4	1	≥3	Suspend	Suspend	Suspend
4	2	≤2			Y
4	≥3	≤1			Y&Elim
5	0	≤2	Y		
5	0	≥3	Suspend	Suspend	Suspend
5	1	0	Y		
5	1	1	≥0.39	<0.39	
5	1	2	≥1.55	<1.55	
5	1	≥3	Suspend	Suspend	Suspend
5	2, 3	≤3			Y
5	≥4	≤1			Y&Elim
6	0	≤3	Y		
6	0	≥4	Suspend	Suspend	Suspend
6	1	≤1	Y		
6	1	2	≥0.6	<0.6	
6	1	3	≥1.96	<1.96	
6	1	≥4	Suspend	Suspend	Suspend
6	2	0		Y	
6	2	1		>0.73	≤0.73
6	2	2		>1.8	≤1.8
6	2	3		>2.87	≤2.87
6	2	≥4	Suspend	Suspend	Suspend
6	3	≤3			Y
6	≥4	≤2			Y&Elim

Table 1: TITE-BOIN Decision Table

No. Patients Treated	No. DLTs observed	No. Pending patients	STFT		
			Escalation	Stay	De-escalation
7	0	≤3	Y		
7	0	≥4	Suspend	Suspend	Suspend
7	1	≤2	Y		
7	1	3	≥0.81	<0.81	
7	1	≥4	Suspend	Suspend	Suspend
7	2	≤3		Y	
7	2	≥4	Suspend	Suspend	Suspend
7	3, 4	≤4			Y
7	≥5	≤2			Y&Elim
8	0	≤4	Y		
8	0	≥5	Suspend	Suspend	Suspend
8	1	≤3	Y		
8	1	4	≥1.01	<1.01	
8	1	≥5	Suspend	Suspend	Suspend
8	2	≤4		Y	
8	2	≥5	Suspend	Suspend	Suspend
8	3, 4	≤5			Y
8	≥5	≤3			Y&Elim
9	0	≤4	Y		
9	0	≥5	Suspend	Suspend	Suspend
9	1	≤4	Y		
9	1	≥5	Suspend	Suspend	Suspend
9	2	0	Y		
9	2	1	≥0.59	<0.59	
9	2	2	≥1.65	<1.65	
9	2	3	≥2.71	<2.71	
9	2	4	≥3.77	<3.77	
9	2	≥5	Suspend	Suspend	Suspend
9	3	0		Y	
9	3	1		>0.58	≤0.58
9	3	2		>1.65	≤1.65

Table 1: TITE-BOIN Decision Table

No. Patients Treated	No. DLTs observed	No. Pending patients	STFT		
			Escalation	Stay	De-escalation
9	3	3		>2.72	≤2.72
9	3	4		>3.79	≤3.79
9	3	≥5	Suspend	Suspend	Suspend
9	4	≤5			Y
9	≥5	≤4			Y&Elim
10	0	≤5	Y		
10	0	≥6	Suspend	Suspend	Suspend
10	1	≤5	Y		
10	1	≥6	Suspend	Suspend	Suspend
10	2	≤1	Y		
10	2	2	≥0.84	<0.84	
10	2	3	≥2.01	<2.01	
10	2	4	≥3.18	<3.18	
10	2	5	≥4.35	<4.35	
10	2	≥6	Suspend	Suspend	Suspend
10	3	≤1		Y	
10	3	2		>0.91	≤0.91
10	3	3		>2.1	≤2.1
10	3	4		>3.28	≤3.28
10	3	5		>4.47	≤4.47
10	3	≥6	Suspend	Suspend	Suspend
10	4, 5	≤6			Y
10	≥6	≤4			Y&Elim
11	0	≤5	Y		
11	0	≥6	Suspend	Suspend	Suspend
11	1	≤5	Y		
11	1	≥6	Suspend	Suspend	Suspend
11	2	≤2	Y		
11	2	3	≥1.08	<1.08	
11	2	4	≥2.36	<2.36	
11	2	5	≥3.64	<3.64	

Table 1: TITE-BOIN Decision Table

No. Patients Treated	No. DLTs observed	No. Pending patients	STFT		
			Escalation	Stay	De-escalation
11	2	≥6	Suspend	Suspend	Suspend
11	3	≤5		Y	
11	3	≥6	Suspend	Suspend	Suspend
11	4, 5	≤7			Y
11	≥6	≤5			Y&Elim
12	0	≤6	Y		
12	0	≥7	Suspend	Suspend	Suspend
12	1	≤6	Y		
12	1	≥7	Suspend	Suspend	Suspend
12	2	≤3	Y		
12	2	4	≥1.33	<1.33	
12	2	5	≥2.72	<2.72	
12	2	6	≥4.11	<4.11	
12	2	≥7	Suspend	Suspend	Suspend
12	3	≤6		Y	
12	3	≥7	Suspend	Suspend	Suspend
12	4	0		Y	
12	4	1		>0.43	≤0.43
12	4	2		>1.5	≤1.5
12	4	3		>2.57	≤2.57
12	4	4		>3.65	≤3.65
12	4	5		>4.72	≤4.72
12	4	6		>5.79	≤5.79
12	4	≥7	Suspend	Suspend	Suspend
12	5, 6	≤7			Y
12	≥7	≤5			Y&Elim
13	0	≤6	Y		
13	0	≥7	Suspend	Suspend	Suspend
13	1	≤6	Y		
13	1	≥7	Suspend	Suspend	Suspend
13	2	≤3	Y		

Table 1: TITE-BOIN Decision Table

No. Patients Treated	No. DLTs observed	No. Pending patients	STFT		
			Escalation	Stay	De-escalation
13	2	4	≥0.08	<0.08	
13	2	5	≥1.58	<1.58	
13	2	6	≥3.08	<3.08	
13	2	≥7	Suspend	Suspend	Suspend
13	3	0	Y		
13	3	1	≥0.77	<0.77	
13	3	2	≥1.79	<1.79	
13	3	3	≥2.81	<2.81	
13	3	4	≥3.84	<3.84	
13	3	5	≥4.86	<4.86	
13	3	6	≥5.89	<5.89	
13	3	≥7	Suspend	Suspend	Suspend
13	4	≤1		Y	
13	4	2		>0.75	≤0.75
13	4	3		>1.91	≤1.91
13	4	4		>3.07	≤3.07
13	4	5		>4.23	≤4.23
13	4	6		>5.39	≤5.39
13	4	≥7	Suspend	Suspend	Suspend
13	5, 6	≤8			Y
13	≥7	≤6			Y&Elim
14	0	≤7	Y		
14	0	≥8	Suspend	Suspend	Suspend
14	1	≤7	Y		
14	1	≥8	Suspend	Suspend	Suspend
14	2	≤4	Y		
14	2	5	≥0.21	<0.21	
14	2	6	≥1.82	<1.82	
14	2	7	≥3.43	<3.43	
14	2	≥8	Suspend	Suspend	Suspend
14	3	≤1	Y		

Table 1: TITE-BOIN Decision Table

No. Patients Treated	No. DLTs observed	No. Pending patients	STFT		
			Escalation	Stay	De-escalation
14	3	2	≥1.03	<1.03	
14	3	3	≥2.13	<2.13	
14	3	4	≥3.23	<3.23	
14	3	5	≥4.32	<4.32	
14	3	6	≥5.42	<5.42	
14	3	7	≥6.52	<6.52	
14	3	≥8	Suspend	Suspend	Suspend
14	4	≤7		Y	
14	4	≥8	Suspend	Suspend	Suspend
14	5	0		Y	
14	5	1		>0.97	≤0.97
14	5	2		>1.97	≤1.97
14	5	3		>2.97	≤2.97
14	5	4		>3.98	≤3.98
14	5	5		>4.98	≤4.98
14	5	6		>5.99	≤5.99
14	5	7		>6.99	≤6.99
14	5	≥8	Suspend	Suspend	Suspend
14	6, 7	≤8			Y
14	≥8	≤6			Y&Elim
15	0	≤7	Y		
15	0	≥8	Suspend	Suspend	Suspend
15	1	≤7	Y		
15	1	≥8	Suspend	Suspend	Suspend
15	2	≤5	Y		
15	2	6	≥0.35	<0.35	
15	2	7	≥2.07	<2.07	
15	2	≥8	Suspend	Suspend	Suspend
15	3	≤1	Y		
15	3	2	≥0.11	<0.11	
15	3	3	≥1.29	<1.29	

Table 1: TITE-BOIN Decision Table

No. Patients Treated	No. DLTs observed	No. Pending patients	STFT		
			Escalation	Stay	De-escalation
15	3	4	≥2.46	<2.46	
15	3	5	≥3.64	<3.64	
15	3	6	≥4.81	<4.81	
15	3	7	≥5.98	<5.98	
15	3	≥8	Suspend	Suspend	Suspend
15	4	≤7		Y	
15	4	≥8	Suspend	Suspend	Suspend
15	5	0		Y	
15	5	1		>0.28	≤0.28
15	5	2		>1.35	≤1.35
15	5	3		>2.42	≤2.42
15	5	4		>3.5	≤3.5
15	5	5		>4.57	≤4.57
15	5	6		>5.64	≤5.64
15	5	7		>6.72	≤6.72
15	5	≥8	Suspend	Suspend	Suspend
15	6, 7	≤9			Y
15	≥8	≤7			Y&Elim

Note: "No. Patients Treated" is the total number of patients treated at the current dose level, "No. DLTs observed" is the number of patients who experienced DLT at the current dose level, "No. Pending patients" denotes the number of patients whose DLT data are pending at the current dose level, "STFT" is the standardized total follow-up time for the patients with data pending. "Y" represents "Yes", and "Y&Elim" represents "Yes and Eliminate". When a dose is eliminated, all higher doses should also be eliminated.

After the trial is completed, select the MTD based on isotonic regression as specified in Yuan et al. (2018). This computation is implemented by the "Estimate MTD" tab of the BOIN Design Desktop Program (Venier et al., 2018). Specifically, select as the MTD the dose for which the isotonic estimate of the toxicity rate is closest to the target toxicity rate. If there are ties, select the higher dose level when the isotonic estimate is lower than the target toxicity rate and select the lower dose level when the isotonic estimate is greater than or equal to the target toxicity rate.

Operating characteristics

Table 2 shows the operating characteristics of the trial design based on 1000 simulations of the trial using the BOIN Design Desktop Program (Venier et al., 2018). The time to toxicity is simulated from a uniform distribution Unif(0,T), and the patient accrual follows a Poisson process at the rate of 3 patients per month. The operating characteristics show that the design selects the true MTD, if any, with high probability and allocates more patients to the dose levels with the DLT rate closest to the target of 0.3.

Table 2: Operating Characteristics of the TITE-BOIN design.

	Dose Level					Number of Patients	% Early Stopping	Duration (months)
	1	2	3	4	5			
Scenario 1								
True DLT Rate	0.30	0.47	0.53	0.58	0.64			
Selection %	64.7	16.8	2.6	0.5	0.0		15.4	10.3
# Pts Treated	11.4	5.8	2.4	0.9	0.3	20.84		
Scenario 2								
True DLT Rate	0.01	0.11	0.30	0.45	0.67			
Selection %	0.5	21.1	59.7	18.4	0.3		0.0	12.4
# Pts Treated	1.8	7.0	10.9	6.3	1.8	27.84		
Scenario 3								
True DLT Rate	0.02	0.07	0.13	0.30	0.47			
Selection %	0.1	2.0	24.6	57.7	15.6		0.0	12.9
# Pts Treated	1.5	2.5	7.1	10.8	5.9	27.84		
Scenario 4								
True DLT Rate	0.05	0.08	0.12	0.15	0.30			
Selection %	0.3	1.2	3.7	23.6	71.2		0.0	12.5
# Pts Treated	1.7	2.1	3.0	6.9	12.0	25.64		

References

Yuan, Y., Lin, R., Li, D., Nie, L. and Warren, K.E. (2018). Time-to-event Bayesian Optimal Interval Design to Accelerate Phase I Trials. *Clinical Cancer Research*, DOI: 10.1158/1078-0432.CCR-18-0246.

Venier, J., Herrick, R., Norris, C., Liu, S., Zhang, L., Yuan, Y., Lin, R., & Zhou, H. (2018). Bayesian Optimal Interval (BOIN) Phase I Design (PID-862): Version 1.0.7, Houston, Texas: The University of Texas MD Anderson Cancer Center
Available at: https://biostatistics.mdanderson.org/SoftwareDownload/

APPENDIX 9 NEW YORK HEART ASSOCIATION FUNCTIONAL CLASSIFICATION

Heart failure is usually classified according to the severity of the patient's symptoms. The table below describes the most commonly used classification system, the New York Heart Association (NYHA) functional classification. It places patients in 1 of 4 categories based on how much they are limited during physical activity.

Class	Patient Symptoms
I	No limitation of physical activity. Ordinary physical activity does not cause undue fatigue, palpitation, or dyspnea (shortness of breath).
II	Slight limitation of physical activity. Comfortable at rest. Ordinary physical activity results in fatigue, palpitation, or dyspnea (shortness of breath).
III	Marked limitation of physical activity. Comfortable at rest. Less than ordinary activity causes fatigue, palpitation, or dyspnea.
IV	Unable to carry on any physical activity without discomfort. Symptoms of heart failure at rest. If any physical activity is undertaken, discomfort increases.

Class	Objective Assessment
A	No objective evidence of cardiovascular disease. No symptoms and no limitation in ordinary physical activity.
B	Objective evidence of minimal cardiovascular disease. Mild symptoms and slight limitation during ordinary activity. Comfortable at rest.
C	Objective evidence of moderately severe cardiovascular disease. Marked limitation in activity due to symptoms, even during less-than-ordinary activity. Comfortable only at rest.
D	Objective evidence of severe cardiovascular disease. Severe limitations. Experiences symptoms even while at rest.

APPENDIX 10 REVISED PROTOCOL SUMMARY OF CHANGE HISTORY

Overall Rationale for the Revised Protocol 01, 04-Mar-2020

The protocol was revised [redacted].The revised protocol applies to all participants.

SUMMARY OF KEY CHANGES FOR REVISED PROTOCOL 01		
Section Number & Title	**Description of Change**	**Brief Rationale**
Synopsis	All changes listed below have been applied to the synopsis as applicable	N/A
Title Page	Updated the Medical Monitor and contact information	New medical monitor assignment
Table 2-2 On Treatment Procedural Outline (CA047004)	Revised table note 'd' to increase the monitoring time to 4 hours post the first dose of BMS-986315 for patients treated in the BMS-986315 monotherapy dose escalation in Part 1A Added table note 'g' to Symptom Directed Physical Exam on Day 15. Edited Table note 'g' as follows: Participants in study Part 1C are required to have <u>symptom directed PE,</u> vital signs and oxygen saturation collected on Day 15 of Cycle 3 and Day 15 of all subsequent study cycles	[redacted] To correct an omission in the original revised protocol.
Section 5.1 Study Design, Overall Design, Figure 5.1-1 Study Design Schematics, Section 5.1.2.1 BMS-986315 Monotherapy Dose Escalation Design (Part 1A), Section 5.1.2.4 Pharmacodynamic Cohorts, Table 7.1-1	Starting dose was changed from 200 mg Q4W to 80 mg Q4W and subsequent doses in the Part 1 are 200, 600, 1200, and 2400 mg Q4W	[redacted]

SUMMARY OF KEY CHANGES FOR REVISED PROTOCOL 01		
Section Number & Title	**Description of Change**	**Brief Rationale**
Section 5.1 Study Design Figure 5.1-2 Study Period and Participant Flow Diagram-	Screening period was corrected to 35 days. Previously was 28 days in the schematic.	Typographical error corrected to reflect the correct screening window throughout the protocol.
Section 5.1.3 Dose Limiting Toxicities, including 5.1.3.1 Hepatic Dose Limiting Toxicity and 5.1.3.4 Other Dose Limiting Toxicities,	The text: "for which no clear alternative cause is identified" is replaced with: "excluding toxicities clearly related to disease progression or intercurrent illness"	[redacted]
Section 5.1.3.2, Hematologic Dose Limiting Toxicity	Revised DLT criteria: Previous version: Grade 4 neutropenia > 7 days in duration Revised version: Grade 4 neutropenia Previous version: N/A Revised version: Grade 4 anemia Previous version: Grade 3 hemolysis (i.e. requiring transfusion or medical intervention such as steroids) Revised version: Grade ≥ 3 hemolysis (i.e. requiring transfusion or medical intervention such as steroids)	
Section 5.1.3.4, Other Dose Limiting Toxicities,	Previous version: Grade 3 drug-related uveitis, episcleritis, iritis, pneumonitis, bronchospasm or neurologic toxicity Revised version: Grade ≥ 3 drug-related uveitis, episcleritis, iritis, pneumonitis, bronchospasm or neurologic toxicity	

SUMMARY OF KEY CHANGES FOR REVISED PROTOCOL 01		
Section Number & Title	**Description of Change**	**Brief Rationale**
	Previous version: Grade ≥ 3 colitis that does not respond within 48 hours of systemic steroid treatment Revised version: Grade 4 colitis Grade 3 colitis that does not respond within 48 hours of systemic steroid treatment	[redacted]
Section 5.1.3.4 Other Dose Limiting Toxicities	Previous version: Grade 3 or grade 4 elevation of amylase or lipase not associated with clinical or radiographic evidence of pancreatitis. Revised version: Grade 3 elevation of amylase or lipase not associated with clinical or radiographic evidence of pancreatitis The preceding paragraph introducing the list of exceptions is revised to remove mention of Grade 4 events as follows "...with the exception of the following Grade 3 or 4 events which will NOT be considered DLTs" Previous version: Grade 3 fatigue Revised version: Grade 3 fatigue that lasts ≤ 7 days	
Section 5.5.1 Justification for Dose selection and Dosing Schedule of BMS-986315	Section updated based on revised starting dose	Starting dose was selected based on totality of nonclinical pharmacology and toxicology data for BMS-986315, plus clinical experience for monalizumab (which has the same target). Dosing schedule (Q4W) was not changed in the revised protocol

SUMMARY OF KEY CHANGES FOR REVISED PROTOCOL 01		
Section Number & Title	**Description of Change**	**Brief Rationale**
Section 9.8 Biomarkers Table 9.8-1	Revised the title to include "1" i.e. Part 1A, 1B, 1C	For clarification that A, B, C refer to Part 1