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Clinical Protocol CA024001

A Phase 1/2a Study of BMS-986242 Administered in Combination with Nivolumab (BMS-936558, Anti-PD-1) in Advanced Malignant Tumors

Revised Protocol: 01

Study Director/Medical Monitor
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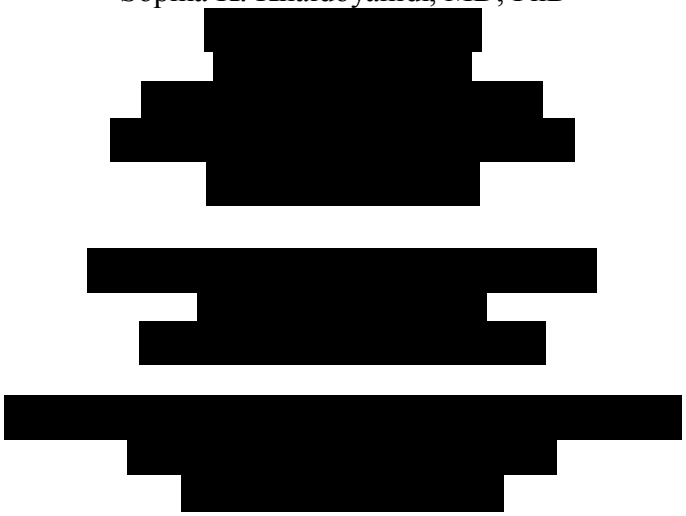

Replace all previous version(s) of the protocol with this revised protocol and please provide a copy of this revised protocol to all study personnel under your supervision, and archive the previous versions.

DOCUMENT HISTORY

Document	Date of Issue	Summary of Change
Revised Protocol 01	31-Oct-2017	Reduced starting dose based on FDA feedback. Added exclusion criterion for participants with current or recent gastrointestinal disease
Original Protocol	19-Sep-2017	Not Applicable

OVERALL RATIONALE FOR REVISED PROTOCOL 01:

Changes were made to the protocol to address FDA feedback.

The Revised Protocol applies to all participants.

SUMMARY OF KEY CHANGES FOR REVISED PROTOCOL 01		
Section Number & Title	**Description of Change**	**Brief Rationale**
Table 2-1	Removed cervical cancer participants from the Mutational and Viral Status	Correction of error. No cervical cancer participants are in this study
Section 5.1 Overall Design	Revised starting dose to 12.5 mg	Reduced starting dose based on FDA feedback
Section 5.1.2.1 Part 1 Dose Escalation:	Revised Figure to include 12.5 mg dose	Reduced starting dose based on FDA feedback
Table 5.1.2.1-1	Added 12.5 mg dose	Reduced starting dose based on FDA feedback
Section 5.5.1	Dose and Schedule for BMS-986242	Reduced starting dose based on FDA feedback
Section 6.1 Inclusion Criteria	Modified inclusion criterion for participants harboring genetic aberrations (e.g. BRAF, EGFR, ALK, HER2)	Ensure participants with genetic aberrations have received appropriate standard of care targeted therapies prior to participation in this study
Section 6.2 Exclusion Criterion	Added exclusion criterion for participants with current or recent gastrointestinal disease	Per FDA feedback to assure gastrointestinal co-morbidities do not interfere with PK parameters of study drug
Section 7.1 Treatments Administered Table 7.1-1	12.5 mg dose level added	Reduced starting dose based on FDA feedback
Section 7.4.2 Guidelines for Dose Modifications	Clarified guideline on dose modification	Defined 25 mg as the lowest dose level permitted for dose reduction
Section 10.1 Sample Size Determination	Added statement regarding operating characteristics of BLRM for the addition of the 12.5 mg dose	To align with the addition of an escalation cohort.

SUMMARY OF KEY CHANGES FOR REVISED PROTOCOL 01		
Section Number & Title	**Description of Change**	**Brief Rationale**
All	Minor formatting and typographical corrections	Minor, therefore have not been summarized

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1 SYNOPSIS

Protocol Title: A Phase 1/2a Study of BMS-986242 Administered in Combination with Nivolumab (BMS-936558, Anti-PD-1) in Advanced Malignant Tumors

Study Phase:

Phase 1/2a

Rationale:

This study will consist of 2 parts, Part 1 Dose Escalation and Part 2 Dose-Expansion Cohorts. During Part 1 the study will evaluate the safety, tolerability, pharmacokinetics (PK), and pharmacodynamics of escalating oral doses of BMS-986242 in combination with a flat dose of nivolumab. In addition, the study is expected to identify dose limiting toxicities (DLTs), the maximum tolerated dose (MTD) (or maximum administered dose [MAD]/alternative dose, if applicable) of BMS-986242 in combination with nivolumab in participants with advanced malignant tumors. The purpose of Part 2 of the study is to gather additional safety, tolerability, preliminary efficacy, PK, and pharmacodynamics information regarding BMS-986242 in combination with nivolumab.

Study Population:

Participants of at least 18 years of age with advanced malignant tumors.

Objectives and Endpoints:

Objectives	Endpoints
Primary	
Part 1: Dose Escalation • To determine the safety, tolerability, DLTs, and MTD/MAD/alternative dose of BMS-986242 administered as monotherapy (lead-in cycle) and in combination with nivolumab in participants with advanced malignant tumors Part 2: Dose-Expansion Cohort(s) • To evaluate the safety and tolerability of BMS-986242 in combination with nivolumab in participants with advanced malignant tumors	• Incidence of DLTs, AEs, SAEs, AEs leading to discontinuation, deaths, and clinical laboratory test abnormalities • Additional safety endpoints include changes from baseline in laboratory parameters, vital signs, and ECGs.
Secondary	
• To characterize the PK of BMS-986242 administered alone and in combination with nivolumab	• Summary measures of selected BMS-986242 PK parameters, such as Cmax, Tmax, AUC(TAU), AUC(INF), Ctrough, T-HALF, CLT/F, Vss/F, AI, %UR24, %UR72, and exposure ratios of select BMS-986242 metabolites to BMS-986242 from concentration-time data during BMS-986242 monotherapy and BMS-986242 Ctrough during combination treatment.

Objectives	Endpoints
• To characterize the pharmacodynamic activity of BMS-986242 administered alone and in combination with nivolumab	• Summary measures of change from baseline (and/or percent change) for serum and tumor kynurenine and related metabolites
• To characterize the immunogenicity of nivolumab when administered in combination with BMS-986242	• Incidence of ADA to nivolumab in combination with BMS-986242
• To assess the preliminary anti-tumor activity of BMS-986242 administered in combination with nivolumab in advanced malignant tumors	• ORR in participants with a BOR of CR or PR per RECIST version 1.1 for solid tumors; mDOR, and PFSR at 6, 9, 12, and 24 months.
[redacted]	

Abbreviations: %UR24 = percent urinary recovery over 24 hours; %UR72 = percent urinary recovery over 72 hours ADA = anti-drug antibody; AE = adverse event; AI = accumulation index; AUC(0-T) = area under the concentration-time curve; AUC(INF) = area under the concentration-time curve from time zero to infinity; AUC(TAU) = area under the concentration-time curve in 1 dosing interval; BOR = best overall response; Ceoi = concentrations at end of infusion; Cmax = maximum observed plasma concentration; CR = complete response; Ctrough = trough observed plasma concentration at the end of the dosing interval; CLT/F = apparent total body clearance; DLT = dose-limiting toxicity; DOR = duration of response; mDOR = median duration of response; ECGs = 12-lead electrocardiograms; MAD = maximum administered dose; MR_AUC(0-T) = ratio of metabolite AUC(0-T) to parent AUC(0-T) corrected for molecular weight; MR_AUC(INF) = ratio of metabolite AUC(INF) to parent AUC(INF) corrected for molecular weight; MR_AUC(TAU) = ratio of metabolite AUC(TAU) to parent AUC(TAU) corrected for molecular weight; MR_Cmax = ratio of metabolite Cmax to parent Cmax corrected for molecular weight; ORR = overall response rate; OSR = overall survival rate; PFSR = progression-free survival rate; PR = partial response; RECIST = Response Evaluation Criteria in Solid Tumors; SAE = serious adverse event; T-HALF = apparent elimination half-life; Tmax = time of maximum observed plasma concentration; Vss/F = apparent volume of distribution at steady state.

Overall Design:

Part 1 open-label dose escalation and Part 2 dose-expansion cohort phase

- To assess the short-term safety and clinical pharmacology profile of BMS-986242 monotherapy prior to allowing participants to receive treatment in combination with nivolumab (see Section 3.1.2 for further details), dose escalation will start with a lead-in Cycle 0, whereby BMS-986242 is administered as monotherapy of 2-week duration in each dose escalation cohort. Decision to proceed to combination treatment with nivolumab (Cycle 1) for each participant in dose escalation will be determined after tolerability of the monotherapy lead-in is established in the 2-week Cycle 0 at each dose (see Section 5.1.2.1). The starting dose of BMS-986242 is 12.5 mg administered orally daily. Nivolumab will be administered at a dose of 480 mg intravenously (IV) Q4W. In the event the 12.5-mg dose level of BMS-986242 is determined to exceed the MTD in monotherapy or in combination with nivolumab, no lower BMS-986242 dose level will be further explored. At no point will the dose of BMS-986242 administered in combination with nivolumab exceed doses of BMS-986242 that have been demonstrated previously to be safe in the monotherapy lead-in Cycle 0. In addition, a clinical pharmacology substudy will be conducted in which a single-dose PK, BMS-986242 exposure-QTc relationship, and exploratory food effect of BMS-986242 will be assessed.
- The study will be restricted to 6 disease types (melanoma, non-small cell lung cancer [NSCLC], squamous cell carcinoma of the head and neck [SCCHN], bladder urothelial carcinoma [BUC], renal cell carcinoma [RCC], and gastric cancer).
- Upon completion of study treatment, participants will enter the Clinical/Safety Follow-up for at least 100 days (3 visits) after the last dose of study treatment.
- After completion of the Clinical/Safety Follow-up period, participants will enter the Survival/Long-term Follow-up period, during which clinic visits or telephone contact every 3 months will be performed to assess survival status up to 2 years from the last dose of study treatment.

Number of Participants:

Up to 298 participants will be enrolled for this study; approximately 78 participants for Part 1 (dose-escalation cohorts) and the clinical pharmacology substudy, and approximately 220 participants for Part 2 (dose-expansion cohorts).

Treatment Arms and Duration:

Study Treatment:

Study Treatments for CA024-001

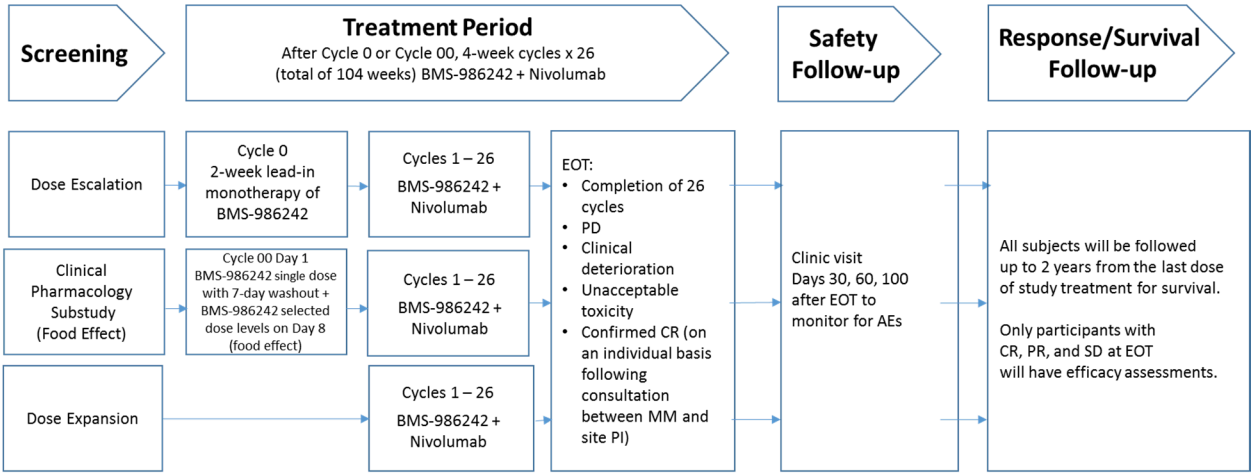
Medication	Potency	IP/Non-IP
BMS-986242-01 Film-Coated Tablet	25 mg	IP
BMS-986242-01 Film-Coated Tablet	100 mg	IP

Study Treatments for CA024-001

Medication	Potency	IP/Non-IP
Nivolumab Injection	10 mg/mL (100 mg/vial)	IP

Abbreviations: IP = investigational product.

Figure 1-1: Study Design Schematic



Abbreviations: AE = adverse event; CR = complete response; EOT = end of treatment; MM = Medical Monitor; PD = progressive disease; PI = principal investigator; PK = pharmacokinetics; PR = partial response; SD = stable disease.

Study Periods

Screening (up to 28 days):

Participants will sign informed consent and be evaluated for study eligibility.

Treatment Phase (consists of 104 weeks for all Parts):

In Part 1, the dose-escalation phase will start with Cycle 0, a lead-in period of 2 weeks in duration, during which monotherapy with BMS-986242 is administered (see Section 3.1.2 and Section 5.1.2 for further details). In both Part 1 and Part 2, each treatment cycle is 4 weeks (except Cycle 0) and is comprised of daily doses of BMS-986242 and 1 dose of nivolumab administered every 4 weeks on Day 1 of the treatment cycle. The total treatment period is 104 weeks or 26 cycles (excluding Cycle 0). Following every 2 treatment cycles (8 weeks), the decision to treat a participant with additional cycles of study treatment will be based on radiological tumor assessments (initial evaluation performed at baseline, end of Cycle 2, and every 8 weeks). Assessment of PR and CR must be confirmed at least 4 weeks following initial assessment. Tumor progression or response endpoints will be assessed using RECIST version 1.1 criteria for solid tumors.

Treatment beyond progression may be allowed in select participants with initial RECIST v1-defined progressive disease (PD) after discussion and agreement with the BMS Medical Monitor that the benefit/risk assessment favors continued administration of study treatment (eg, participants are continuing to experience clinical benefit as assessed by the investigator, tolerating treatment, and do not meet treatment discontinuation criteria). See Section 5.1.2.3 for further details.

Clinical/Safety Follow-up Period:

Upon completion of study treatment, participants will enter the Clinical/Safety Follow-up period.

For participants who complete all scheduled cycles of study treatment, the End-of-Treatment (EOT) visit will be the same as the last scheduled and completed on-treatment visit, and the start of the Week 1 Clinical/Safety Follow-up visit. For participants who do not complete all scheduled cycles of study treatment, the EOT visit will be the most recent on-treatment visit (with all available safety and response data) and does not need to be repeated, and will be considered the start of the Week 1 Clinical/Safety Follow-up visit.

Participants who discontinue the treatment phase will enter the Clinical/Safety Follow-up period. Participants must be followed for at least 100 days (representing approximately 5 half-lives for nivolumab) after the last dose of study treatment. Follow-up visits should occur at Days 30, 60, and 100 (±10 days) after the last dose of study treatment or coinciding with the date of discontinuation (±10 days) if the date of discontinuation is greater than 30 days after the last dose of study treatment to monitor for adverse events.

Participants will be required to complete 3 Clinical/Safety Follow-up visits regardless of whether they start new anti-cancer therapy, except those participants who withdraw consent for study participation.

Survival/Long-term Follow-up:

After completion of the Clinical/Safety Follow-up period, participants will then enter the Survival/Long-term Follow-up period. During this period, clinic visits or telephone contact every 3 months will be performed to assess survival status. The duration of Survival/Long-term Follow-up period will be 2 years from the last dose of study treatment.

Duration of Study:

The total duration of the study is expected to be approximately 5 years from the onset of the first visit of the first subject to the required Survival/Long-term Follow-up of the last subject enrolled.

2 SCHEDULE OF ACTIVITIES

Study assessments and procedures are presented in Table 2-1, Table 2-2, Table 2-3, Table 2-4, Table 2-5.

Abbreviations used in the protocol are shown in Appendix 1.

In limited instances, scheduled events can occur outside of the indicated timeframes, but BMS should be notified. In the event that multiple procedures are required at a single time point, electrocardiograms may be obtained up to 15 minutes earlier, vital signs may be obtained up to 10 minutes earlier or later, and clinical laboratory samples may be obtained up to 5 minutes earlier than the nominal time point, ensuring the pharmacokinetics samples can be collected on time.

Table 2-1: Screening Procedural Outline

Procedure	Screening[a] Visit 28 Days	Day-14 to -1 Visit	Day-1 Visit	Notes
Eligibility Assessments				
Informed Consent	X			A participant is considered enrolled only when a protocol-specific informed consent is signed. Obtain participant number from IRT.
Inclusion/Exclusion Criteria	X			
Medical History	X			Also include any toxicities or allergy related to previous treatments.
Prior Systemic Therapies	X			Including prior cancer treatment regimens and medications administered within 4 weeks of dosing
Tobacco History/Status	X			
Archival Tumor Tissue Samples	X			An archival, FFPE tumor tissue block or slide samples is to be provided by all participants, if available. One paraffin block or 15 to 20 FFPE unstained slides are to be identified and located prior to dosing.
Fresh Pretreatment Tumor Biopsy	X			Note that **mandatory pre- and on-treatment biopsies** will be collected at all dose levels. If biopsy is collected during screening, an additional pretreatment biopsy will not be needed. Biopsy is performed during screening in participants for whom an archived tumor tissue sample is unavailable. Tumor tissue is to be sent to the central laboratory after performing specified tests locally (see "Laboratory Tests" in this table below).
Safety Assessments				
Physical Examination	X			If the screening PE is performed within 24 hours prior to dosing on Day 1, then a single examination may count as both the screening and predose evaluation. Includes neurological examination.
Physical Measurements	X			Includes height and weight
ECOG Performance Status	X			See Appendix 5.
Vital Signs	X			Includes body temperature, seated blood pressure, and heart rate. Blood pressure and heart rate should be measured after the participant has been seated quietly for at least 5 minutes.

Table 2-1: Screening Procedural Outline

Procedure	Screening[a] Visit 28 Days	Day-14 to -1 Visit	Day-1 Visit	Notes
Oxygen Saturation	X			Pulse oximetry collected while the participant is at rest
12-lead ECG	X			ECGs should be recorded after the participant has been supine for at least 5 minutes.
Laboratory Tests				*Laboratory tests listed below must be completed within 2 weeks of Day 1 unless otherwise noted.*
Chemistry (Excluding LFTs)		X		Includes assessments for sodium, potassium, chloride, total serum calcium, magnesium, bicarbonate/carbon dioxide, phosphorus, BUN, creatinine, creatinine clearance, fasting glucose, total protein, albumin, amylase, lipase, uric acid, ferritin, LDH, HDL, and LDL.
CBC with Differential and Platelets		X		
LFT Assessments		X		Includes AST, ALT, total bilirubin, direct bilirubin (only if total bilirubin is elevated), alkaline phosphatase, and GGT (only when alkaline phosphatase increases to ≥ Grade 2)
PT/PTT		X		
Urinalysis		X		Urine to be checked for protein, glucose, blood, leukocyte esterase, specific gravity, and pH. Microscopic examination of sediment will be done if blood, protein, or leukocyte esterase is positive on dipstick.
Thyroid Function Tests		X		TSH with reflex testing to free T3 and free T4 if TSH is abnormal. Results should be examined by the investigator or appropriate designee within 48 hours of dose administration.
Mutational and Viral Status	X			Document EGFR, ALK and, if available, KRAS for participants with NSCLC. Document BRAF for participants with melanoma. **SCCHN participants only**: Sites must submit and document prior HPV status within 28 days of dosing. See Section 9.8.1.3 and Inclusion Criteria (Section 6.1).
Serology	X			Within 28 days of dosing: hepatitis B surface antigen, hepatitis C antibody (if hepatitis C antibody is positive reflex to hepatitis C RNA), or hepatitis C RNA

Table 2-1: Screening Procedural Outline

Procedure	Screening[a] Visit 28 Days	Day-14 to -1 Visit	Day-1 Visit	Notes
				Note: Testing for HIV-1 and HIV-2 must be performed at sites where mandated by local requirements.
Pregnancy Test	X		X	WOCBP only **at screening and within 24 hours prior to dosing.** The serum pregnancy test may be completed on the first day of treatment provided the results are available before the start of study treatment. If performed within 24 hours of dosing on Cycle 0 Day 1, then Cycle 0 Day 1 pregnancy test is not required.
Follicle-stimulating Hormone	X			If needed to document postmenopausal status
Concomitant Medications		X		Collected during the 2 weeks prior to Cycle 1 Day 1
Clinical Complaints		X		Collected during the 2 weeks prior to Cycle 1 Day 1
Adverse Event Reporting				
Monitor for Serious Adverse Events	X	X	X	All SAEs must be collected from the date of participant's written consent until 100 days after discontinuation of nivolumab or participation in the study (if the last scheduled visit occurs at a later time). eSAEs should be approved in the BMS EDC tool within 5 business days of entry.
Efficacy Assessments				
Diagnostic Imaging (Body Imaging)	X			CT with contrast is the preferred modality (MRI if CT is not feasible). Assessment should include the chest/abdomen/pelvis at a minimum, and should include other anatomic regions as indicated by individual participant disease histories.
Brain Imaging	X			Brain imaging (CT/MRI) is only required for participants with known history or symptoms of brain metastases who have not had brain imagining within 30 days of anticipated first study treatment administration.
Bone Scan	X			As clinically indicated (eg, participants with history of symptoms of bone metastases), but bone scans will not be considered a modality for assessment for measurable disease.

[a] The screening period will be 28 days.

Abbreviations: ALK = anaplastic lymphoma receptor tyrosine kinase; ALT = alanine aminotransferase; AST = aspartate aminotransferase; BMS EDC = Bristol-Myers Squibb Electronic Data Capture; BUN = blood urea nitrogen; CBC = complete blood count; CRF = case report form; CT = computed tomography; ECG = electrocardiogram; ECOG = Eastern Cooperative Oncology Group; EGFR = epidermal growth factor receptor; eSAE = electronic serious adverse event; FFPE = formalin-fixed, paraffin-embedded; GGT = gamma-glutamyl transferase; HIV = human immunodeficiency virus; HPV = human papillomavirus; IRT = Interactive Response Technology; LDH = lactate dehydrogenase; LFT = liver function test; MRI = magnetic resonance imaging; NSCLC = non-small cell lung cancer; PE = physical examination; PT = prothrombin time; PTT = partial thromboplastin time; RNA = ribonucleic acid; SAE = serious adverse event; SCCHN = squamous cell carcinoma of the head and neck; TSH = thyroid-stimulating hormone; WOCBP = women of childbearing potential.

Table 2-2: On-treatment Procedural Outline (BMS-986242 Monotherapy in Part 1 Dose Escalation)

Procedure	Cycle 0				Notes
	Day 1	Day 2	Day 8	Day 14	
IRT Assignment	X				Cycle 0 Day 1 only. BMS-986242 IP assignment. Once participant eligibility has been confirmed, IRT assignment can be performed within 3 days prior to first study treatment administration. (Discuss with Sponsor if institutional policies and procedures require additional lead-time.)
Complete PE	X[a]				Predose. Includes neurological examination.
Symptom-directed PE		X	X	X	Predose.
Vital Signs and Oxygen Saturations	X				Includes temperature, seated blood pressure, and heart rate. Blood pressure and heart rate should be measured after the participant has been seated quietly for at least 5 minutes. Pulse oximetry should be collected while the participant is at rest.
12-lead ECG	X			X	Collect triplicate ECG on Cycle 0 Day 1 and Cycle 0 Day 14 at -1 hour and 2 and 4 hours postdose. All ECG tests during Cycle 0 will be performed in triplicates (eg, 1 ECG test equals 3 consecutive individual 12-lead ECGs performed 5 minutes apart). ECGs should be performed after the participant has been supine for at least 5 minutes and should be completed prior to any PK/pharmacodynamic sample blood collections when assessments occur at the same time points.
Laboratory Test[a,b]					
Chemistry (Excluding LFTs)	X[b]		X	X	Collect predose; includes assessments for sodium, potassium, chloride, total serum calcium, magnesium, bicarbonate/carbon dioxide, phosphorus, BUN, creatinine, glucose, total protein, albumin, amylase, lipase, uric acid, ferritin, LDH, HDL, and LDL.
CBC with Differential and Platelets	X[b]	X	X	X	Collect predose. In addition, please collect predose on Day 4 (±1) day.

Table 2-2: On-treatment Procedural Outline (BMS-986242 Monotherapy in Part 1 Dose Escalation)

Procedure	Cycle 0				Notes
	Day 1	Day 2	Day 8	Day 14	
LFT Assessments	X[b]		X	X	Includes AST, ALT, total bilirubin, direct bilirubin (only if total bilirubin is elevated), alkaline phosphatase, and GGT (only when alkaline phosphatase is increased to ≥ Grade 2). Collect predose; LFTs should be repeated 4 hours postdose on Cycle 0 Day 14.
Pregnancy Test (WOCBP)	X				Serum or urine pregnancy test must be performed (urine pregnancy test: minimum sensitivity 25 IU/L or equivalent units of hCG) within 24 hours prior to administration of study treatment. If pregnancy test is positive, hold all study treatment and perform confirmatory testing. If pregnancy is confirmed, permanently discontinue all study treatment and immediately notify the Sponsor per Section 9.2.5.
Concomitant Medication Assessments	X	X	X	X	Review prior to dosing.
Monitor for Nonserious Adverse Events	X	X	X	X	Nonserious AEs will be collected starting with the first dose of study treatment until 100 days after discontinuation of nivolumab.
Monitor for Serious Adverse Events	X	X	X	X	All SAEs must be collected from the date of participant's written consent until 100 days after discontinuation of nivolumab or participation in the study (if the last scheduled visit occurs at a later time). eSAEs should be approved in the BMS EDC tool within 5 business days of entry.
Pharmacokinetic Assessments	See Section 9.5.3 and Table 9.5.3-1.				Performed in all participants
Immunogenicity Assessments	See Section 9.5.3, Section 9.8.3, and Table 9.5.3-1.				Performed in all participants

Table 2-2: On-treatment Procedural Outline (BMS-986242 Monotherapy in Part 1 Dose Escalation)

Procedure	Cycle 0				Notes
	Day 1	Day 2	Day 8	Day 14	
[redacted]	[redacted]				
Additional Research	See Section 9.8.2.				
Study Treatment Administration	Details regarding preparation and administration are provided in the site training materials.				
BMS-986242 Administration	X	**Continuous daily dosing during all cycles**			BMS-986242 to be administered daily at approximately the same time.
Tablet Diary	X	**Tablet diary must be completed with each administered daily dose of BMS-986242**			Review tablet diary during each visit for compliance of daily administration of BMS-986242. Collect tablet diary at the completion of each cycle.

[a] For Cycle 0 Day 1, PE and laboratory tests do not need to be repeated if completed within the last 72 hours (for all laboratory tests).

[b] Participants who meet discontinuation criteria during or after Cycle 0 will have CBC with differential, platelets, and chemistry with LFTs done at the EOT and during the follow-up visit at 7 days.

Abbreviations: AE = adverse event; ALT = alanine aminotransferase; AST = aspartate aminotransferase; BMS EDC = Bristol-Myers Squibb Electronic Data Capture; BUN = blood urea nitrogen; CBC = complete blood count; ECG = electrocardiogram; EOT = end of treatment; eSAE = electronic serious adverse event; GGT = gamma-glutamyl transferase; hCG = human chorionic gonadotropin; IP = investigational product; IRT = Interactive Response Technology; LDH = lactate dehydrogenase; LFT = liver function test; PE = physical examination; SAE = serious adverse event; WOCBP = women of childbearing potential.

Table 2-3: On-treatment Procedural Outline (BMS-986242 + Nivolumab Part 1 Dose Escalation and Part 2 Dose-Expansion Cohorts)

Procedure	Cycle 1 (4 weeks)				Cycles 2 to 4 (4 weeks)			Cycles 4+ (4 weeks)		End of Treatment[a,b,c]	Notes
	Day 1	Day 8	Day 15	Day 22	Day 1	Day15 (±2 days)	Days 22-28	Day 1	Days 22-28		
IRT Assignment											
IRT Assignment	X				X			X			Once participant eligibility has been confirmed, IRT assignment can be performed within 3 days prior to first study treatment administration. (Discuss with Sponsor if institutional policies and procedures require additional lead-time.)
Safety Assessments											
Complete PE	X				X			X			Predose. Includes neurological examination.
Symptom-directed PE			X			X				X	

Table 2-3: On-treatment Procedural Outline (BMS-986242 + Nivolumab Part 1 Dose Escalation and Part 2 Dose-Expansion Cohorts)

Procedure	Cycle 1 (4 weeks)				Cycles 2 to 4 (4 weeks)			Cycles 4+ (4 weeks)		End of Treatment[a,b,c]	Notes
	Day 1	Day 8	Day 15	Day 22	Day 1	Day15 (±2 days)	Days 22-28	Day 1	Days 22-28		
Vital Signs and Oxygen Saturations	X	X	X	X	X	X		X		X	Includes temperature, seated blood pressure, and heart rate. Blood pressure and heart rate should be measured after the participant has been seated quietly for at least 5 minutes. Pulse oximetry should be collected while the participant is at rest. For nivolumab, vital signs should be obtained prior to the infusion and then every 30 min (± 10 min) until 1 hour following completion of the infusion, except on Cycle 1 Day 1, when vital signs will be obtained until 4 hours following completion of the infusion. If any vital sign is abnormal (based upon clinician assessment) at the final check, the participant must be observed further for a period of time, as clinically indicated.
12-lead ECG	X				X			X			12-lead ECG should be recorded after the participant has been supine for at least 5 minutes. A single ECG must be collected at predose on Day 1 of each cycle.

Table 2-3: On-treatment Procedural Outline (BMS-986242 + Nivolumab Part 1 Dose Escalation and Part 2 Dose-Expansion Cohorts)

Procedure	Cycle 1 (4 weeks)				Cycles 2 to 4 (4 weeks)			Cycles 4+ (4 weeks)		End of Treatment[a,b,c]	Notes
	Day 1	Day 8	Day 15	Day 22	Day 1	Day15 (±2 days)	Days 22-28	Day 1	Days 22-28		
Laboratory Tests	**On-study laboratory assessments (including pregnancy testing) to be done on site/locally. Laboratory assessments do not need to be repeated on Day 1 for Cycles 1 and onward if completed within the last 24 hours. All laboratory assessments will be done weekly for Cycle 1 only, unless otherwise specified.**										
Chemistry (Excluding LFTs)	X	X	X	X	X	X		X		X	Predose; includes assessments for sodium, potassium, chloride, total serum calcium, magnesium, bicarbonate/carbon dioxide, phosphorus, BUN, creatinine, glucose, total protein, albumin, amylase, lipase, uric acid, ferritin, LDH, HDL, and LDL.
CBC with Differential and Platelets	X	X	X	X	X	X		X		X	Predose.
LFT Assessments	X	X	X	X	X	X		X		X	Predose; includes AST, ALT, total bilirubin, direct bilirubin (only if total bilirubin is elevated), alkaline phosphatase, and GGT (only when alkaline phosphatase is increased to ≥ Grade 2)

Table 2-3: On-treatment Procedural Outline (BMS-986242 + Nivolumab Part 1 Dose Escalation and Part 2 Dose-Expansion Cohorts)

Procedure	Cycle 1 (4 weeks)				Cycles 2 to 4 (4 weeks)			Cycles 4+ (4 weeks)		End of Treatment[a,b,c]	Notes
	Day 1	Day 8	Day 15	Day 22	Day 1	Day15 (±2 days)	Days 22-28	Day 1	Days 22-28		
Thyroid Function Tests	X				X			X		X	If collected at screening, do not repeat on Cycle 1 Day 1. Collect every 2 cycles, predose, beginning with Cycle 3 Day 1 and at EOT. To include TSH with reflex testing (free T3 and free T4) if TSH is abnormal. Results should be examined by the investigator or appropriate designee within 48 hours of dose administration.
Pregnancy Test (WOCBP)	X		X		X	X		X		X	Serum or urine pregnancy test must be performed (urine pregnancy test: minimum sensitivity 25 IU/L or equivalent units of hCG) within 24 hours prior to administration of study treatment. If pregnancy test is positive, hold all study treatment and perform confirmatory testing. If pregnancy is confirmed, permanently discontinue all study treatment and immediately notify the Sponsor per Section 9.2.5.

Table 2-3: On-treatment Procedural Outline (BMS-986242 + Nivolumab Part 1 Dose Escalation and Part 2 Dose-Expansion Cohorts)

Procedure	Cycle 1 (4 weeks)				Cycles 2 to 4 (4 weeks)			Cycles 4+ (4 weeks)		End of Treatment[a,b,c]	Notes
	Day 1	Day 8	Day 15	Day 22	Day 1	Day15 (±2 days)	Days 22-28	Day 1	Days 22-28		
Adverse Event Reporting and Concomitant Medication Assessments											
Concomitant Medication Assessments	X	X	X	X	X	X	X	X	X	X	Review prior to dosing.
Monitor for Nonserious Adverse Events	X	X	X	X	X	X	X	X	X	X	Nonserious AEs will be collected starting with the first dose of study treatment until 100 days after discontinuation of nivolumab.
Monitor for Serious Adverse Events	X	X	X	X	X	X	X	X	X	X	All SAEs must be collected from the date of participant's written consent until 100 days after discontinuation of nivolumab or participation in the study (if the last scheduled visit occurs at a later time). eSAEs should be approved in the BMS EDC tool within 5 business days of entry.
Sample Collection											
Pharmacokinetic Assessments	See Section 9.5.3 and Table 9.5.3-1.										
Immunogenicity Assessments	See Section 9.5.3, Section 9.8.3, and Table 9.5.3-1.										
[redacted]	[redacted]										[redacted]

Table 2-3: On-treatment Procedural Outline (BMS-986242 + Nivolumab Part 1 Dose Escalation and Part 2 Dose-Expansion Cohorts)

Procedure	Cycle 1 (4 weeks)				Cycles 2 to 4 (4 weeks)			Cycles 4+ (4 weeks)		End of Treatment[a,b,c]	Notes
	Day 1	Day 8	Day 15	Day 22	Day 1	Day15 (±2 days)	Days 22-28	Day 1	Days 22-28		
Additional Research Sampling	See Section 9.8.2										
Efficacy Assessments											
Diagnostic Imaging[d] (Body Imaging)							X		X	X	To be collected at the end of Cycle 2 and then every 8 weeks by methods used at baseline. Same modality/scanner should be used for all assessments. Assessed by RECIST v1.1; see Appendix 6. Assessment must be performed prior to initiating the next cycle of study treatment.
Brain Imaging[d]							X		X	X	As clinically indicated
Bone Scan Imaging[d]							X		X	X	As clinically indicated

Table 2-3: On-treatment Procedural Outline (BMS-986242 + Nivolumab Part 1 Dose Escalation and Part 2 Dose-Expansion Cohorts)

Procedure	Cycle 1 (4 weeks)				Cycles 2 to 4 (4 weeks)			Cycles 4+ (4 weeks)		End of Treatment[a,b,c]	Notes
	Day 1	Day 8	Day 15	Day 22	Day 1	Day15 (±2 days)	Days 22-28	Day 1	Days 22-28		
Study Treatment Administration											Details regarding preparation and administration are provided in the site training materials.
BMS-986242 Administration	X	**Continuous daily dosing during all cycles**									BMS-986242 to be administered daily at approximately the same time
Nivolumab Administration	X				X			X			For participants receiving nivolumab 480 mg Q4W, nivolumab should be dispensed at Day 1 of each cycle
Tablet Diary	X	**Tablet diary must be completed with each administered daily dose of BMS-986242.**								X	Review tablet diary during each visit for compliance of daily administration of BMS-986242. Collect pill diary at the completion of each cycle and EOT.

[a] EOT is defined as the visit where decision is made to discontinue the participant from treatment.

[b] For participants who complete all scheduled cycles of study treatment, the EOT visit will be the same as the last scheduled and completed on-treatment visit (eg, Cycle 2 Day 22), and the start of the Week 1 Clinical/Safety Follow-up visit.

[c] For participants who do not complete all scheduled cycles of study treatment, the EOT visit will be the most recent on-treatment visit (with all available safety and response data) and does not need to be repeated, and will be considered the start of the Week 1 Clinical/Safety Follow-up visit.

[d] To be collected at the end of Cycle 2, at the end of every 8 weeks, by methods used at baseline. Same modality/scanner should be used for all assessments. Assessed by RECIST v1.1; see Appendix 6. Assessment must be performed prior to initiating the next cycle of study treatment.

Abbreviations: AE = adverse event; ALT = alanine aminotransferase; AST = aspartate aminotransferase; BMS EDC = Bristol-Myers Squibb Electronic Data Capture; BUN = blood urea nitrogen; CBC = complete blood count; CR = complete response; ECG = electrocardiogram; EOT = end of treatment; eSAE = electronic serious adverse event; GGT = gamma-glutamyl transferase; hCG = human chorionic gonadotropin; IRT = Interactive Response Technology;;

LDH = lactate dehydrogenase; LFT = liver function test; PE = physical examination; Q4W = every 4 weeks; RECIST = Response Evaluation Criteria in Solid Tumors; SAE = serious adverse event; TSH = thyroid-stimulating hormone; WOCBP = women of childbearing potential.

Table 2-4: Follow-up Procedural Outline

Procedure	Clinical/Safety Follow-up			Survival/Long-Term Follow-up	Response Follow-up (participants with CR, PR, SD)	Notes
	FU 1 30 days[a] (± 10 days)	FU 2 60 days (± 10 days)	FU 3 100 days (± 10 days)	All Participants; Begins After Completion of Clinical/Safety (± 2 weeks), Every 12 weeks (± 2 weeks) Until 2 Years After LAST Dose of Study Treatment	Begins After Completion of Safety Follow-up (±2 weeks) Until End of Survival Follow-up	
Safety Assessments						
Symptom-Directed Physical Examination	X	X	X			
Vital Signs	X	X	X			Includes body temperature, seated blood pressure, and heart rate. Blood pressure and heart rate should be measured after the participant has been seated quietly for at least 5 minutes.
Laboratory Tests						
Chemistry (Excluding LFTs)	X	X	X			Includes assessments for sodium, potassium, chloride, total serum calcium, magnesium, bicarbonate/ carbon dioxide, phosphorus, BUN, creatinine, glucose, total protein, albumin, amylase,

Table 2-4: Follow-up Procedural Outline

Procedure	Clinical/Safety Follow-up			Survival/Long-Term Follow-up	Response Follow-up (participants with CR, PR, SD)	Notes
	FU 1 30 days[a] (± 10 days)	FU 2 60 days (± 10 days)	FU 3 100 days (± 10 days)	All Participants; Begins After Completion of Clinical/Safety (± 2 weeks), Every 12 weeks (± 2 weeks) Until 2 Years After LAST Dose of Study Treatment	Begins After Completion of Safety Follow-up (±2 weeks) Until End of Survival Follow-up	
						lipase, uric acid, ferritin, LDH, HDL, and LDL
CBC with Differential and Platelets	X	X	X			Predose.
LFT Assessment	Collect at 30, 60, and 100 days following the last dose of BMS-986242 and/or nivolumab. For participants with LFT abnormalities following the last dose of study treatment, consider collecting weekly until normalized.					Includes AST, ALT, total bilirubin, direct bilirubin (only if total bilirubin is elevated), alkaline phosphatase, and GGT (only when alkaline phosphatase is increased to ≥ Grade 2)
Thyroid Function Tests	X	X	X			TSH with reflex testing to free T3 and free T4 if TSH is abnormal. Results should be examined by the investigator or appropriate designee within 48 hours of dose administration.

Table 2-4: Follow-up Procedural Outline

Procedure	Clinical/Safety Follow-up			Survival/Long-Term Follow-up	Response Follow-up (participants with CR, PR, SD)	Notes
	FU 1 30 days[a] (± 10 days)	FU 2 60 days (± 10 days)	FU 3 100 days (± 10 days)	All Participants; Begins After Completion of Clinical/Safety (± 2 weeks), Every 12 weeks (± 2 weeks) Until 2 Years After LAST Dose of Study Treatment	Begins After Completion of Safety Follow-up (±2 weeks) Until End of Survival Follow-up	
Pregnancy Test	X	X	X			For WOCBP; serum or urine pregnancy test may be performed (clinic urine pregnancy test: minimum sensitivity 25 IU/L or equivalent units of hCG). If positive, perform confirmatory testing. If pregnancy is confirmed, immediately notify the Sponsor per Section 9.2.5.
Adverse Event Reporting and Concomitant Medication Assessments						
Monitor for Nonserious Adverse Events	X	X	X			Nonserious AEs will be collected starting with the first dose of study treatment until 100 days after discontinuation of nivolumab.

Table 2-4: Follow-up Procedural Outline

Procedure	Clinical/Safety Follow-up			Survival/Long-Term Follow-up	Response Follow-up (participants with CR, PR, SD)	Notes
	FU 1 30 days[a] (± 10 days)	**FU 2 60 days (± 10 days)**	**FU 3 100 days (± 10 days)**	**All Participants; Begins After Completion of Clinical/Safety (± 2 weeks), Every 12 weeks (± 2 weeks) Until 2 Years After LAST Dose of Study Treatment**	**Begins After Completion of Safety Follow-up (±2 weeks) Until End of Survival Follow-up**	
Monitor for Serious Adverse Events	X	X	X			All SAEs must be collected from the date of participant's written consent until 100 days after discontinuation of nivolumab or participation in the study (if the last scheduled visit occurs at a later time). eSAEs should be approved in the BMS EDC tool within 5 business days of entry.
Concomitant Medication Assessments	X	X	X			
Sample Collection						
Pharmacokinetic Assessments	See Section 9.5.3 and Table 9.5.3-1.					
Immunogenicity Assessments	See Section 9.5.3, Section 9.8.3, and Table 9.5.3-1.					

Table 2-4: Follow-up Procedural Outline

Procedure	Clinical/Safety Follow-up			Survival/Long-Term Follow-up	Response Follow-up (participants with CR, PR, SD)	Notes
	FU 1 30 days[a] (± 10 days)	**FU 2 60 days (± 10 days)**	**FU 3 100 days (± 10 days)**	**All Participants; Begins After Completion of Clinical/Safety (± 2 weeks), Every 12 weeks (± 2 weeks) Until 2 Years After LAST Dose of Study Treatment**	**Begins After Completion of Safety Follow-up (±2 weeks) Until End of Survival Follow-up**	
Efficacy Assessments						
Tumor/Response Assessments			X		X	Diagnostic imaging by method used at baseline. An unconfirmed PR or CR must be confirmed at least 4 weeks after initial assessments. Assessed by RECIST v1.1; see Appendix 6. Participants with SD/PR/CR at EOT visit will have imaging every 3 months (12 weeks) for the first year after the EOT visit and then every 6 months thereafter, up to 2 years after last study treatment (or until disease progression or withdrawal from the study).

Table 2-4: Follow-up Procedural Outline

Procedure	Clinical/Safety Follow-up			Survival/Long-Term Follow-up	Response Follow-up (participants with CR, PR, SD)	Notes
	FU 1 30 days[a] (± 10 days)	FU 2 60 days (± 10 days)	FU 3 100 days (± 10 days)	All Participants; Begins After Completion of Clinical/Safety (± 2 weeks), Every 12 weeks (± 2 weeks) Until 2 Years After LAST Dose of Study Treatment	Begins After Completion of Safety Follow-up (±2 weeks) Until End of Survival Follow-up	
Assessment of Participant Survival Status				X		Participant status will be assessed every 3 months (12 weeks) by either a clinic visit or telephone contact.
New Subsequent Anti-cancer Therapies	X	X	X	X		Any new anti-cancer therapies (including surgery and radiotherapy) will be recorded.

[a] Follow-up visits at Days 30, 60, and 100 (± 10 days) should occur after the last dose of study treatment or should coincide with the date of discontinuation ± 10 days if date of discontinuation is greater than 30 days after the last dose to monitor for adverse events.

Abbreviations: ADA = anti-drug antibody; AE = adverse event; ALT = alanine aminotransferase; AST = aspartate aminotransferase; BMS EDC = Bristol-Myers Squibb Electronic Data Capture; BUN = blood urea nitrogen; CBC = complete blood count; CR = complete response; EOT = end of treatment; eSAE = electronic serious adverse event; FU = follow-up; GGT = gamma-glutamyl transferase; hCG = human chorionic gonadotropin; LDH = lactate dehydrogenase; LFT = liver function test; PR = partial response; RECIST = Response Evaluation Criteria in Solid Tumors; SAE = serious adverse event; SD = stable disease; TSH = thyroid-stimulating hormone; WOCBP = women of childbearing potential.

Table 2-5: On-treatment Procedural Outline Clinical Pharmacology Substudy

Procedure	Cycle 00				Notes
	Day 1	Day 2	Day 8[a]	Day 9[a]	Day 8 and 9 for food effect participants only
IRT Assignment	X		X[a]		Cycle 00 Day 1 single-dose BMS-986242 administration under fasting conditions. For food effect participants only, Cycle 00 Day 8 at selected dose level of BMS-986242, administered with a high-fat meal. Once participant eligibility has been confirmed, IRT assignment can be performed within 3 days prior to first study treatment administration. (Discuss with Sponsor if institutional policies and procedures require additional lead-time.)
Complete PE	X[b]				Predose. Includes neurological examination.
Symptom-directed PE		X	X[a,b]	X[a]	Predose.
Vital Signs and Oxygen Saturations	X		X[a, b]		Includes temperature, seated blood pressure, and heart rate. Blood pressure and heart rate should be measured after the participant has been seated quietly for at least 5 minutes. Pulse oximetry should be collected while the participant is at rest.
12-lead ECG (Holter)	X				Serial ECGs (reviewed by a core laboratory) will be collected with matching PK samples (See Table 9.5.3-2). 12-lead continuous ECG (Holter) monitoring will be started no later than 1.5 hour predose and continue until at least 6.5 hours postdose. From these recordings, after transmission to the central ECG laboratory, triplicate ECGs will be extracted during a 5-minute sampling period starting at the nominal times specified. Each 5-minute sampling period should be preceded by at least 10 minutes of rest in a supine position, which will be continued until the end of the 5-minute sampling period.
12-lead ECG	X				For monitoring subject safety, at least 5 minutes after the end of triplicate ECG period at 4 hours post dose on Cycle 00 Day 1,

Table 2-5: On-treatment Procedural Outline Clinical Pharmacology Substudy

Procedure	Cycle 00				Notes
	Day 1	**Day 2**	**Day 8[a]**	**Day 9[a]**	Day 8 and 9 for food effect participants only
					the site's standard ECG machine will be connected using dual-snap electrodes without interrupting the Holter monitoring.
Laboratory Tests					
Chemistry (Excluding LFTs)	X[b]		X[a,b,c]	X	Collect predose; includes assessments for sodium, potassium, chloride, total serum calcium, magnesium, bicarbonate/carbon dioxide, phosphorus, BUN, creatinine, glucose, total protein, albumin, amylase, lipase, uric acid, ferritin, LDH, HDL, and LDL.
CBC with Differential and Platelets	X[b]	X	X[a,b,c]	X	Collect predose.
LFT Assessments	X[b]		X[a,b,c]	X	Includes AST, ALT, total bilirubin, direct bilirubin (only if total bilirubin is elevated), alkaline phosphatase, and GGT (only when alkaline phosphatase is increased to ≥ Grade 2).
Pregnancy Test (WOCBP)	X		X[a]		Serum or urine pregnancy test must be performed (urine pregnancy test: minimum sensitivity 25 IU/L or equivalent units of hCG) within 24 hours prior to administration of study treatment. If pregnancy test is positive, hold all study treatment and perform confirmatory testing. If pregnancy is confirmed, permanently discontinue all study treatment and immediately notify the Sponsor per Section 9.2.5.
Concomitant Medication Assessments	X	X	X[a]	X	Review prior to dosing.
Monitor for Nonserious Adverse Events	X	X	X[a]	X	Nonserious AEs will be collected starting with the first dose of study treatment until 100 days after discontinuation of nivolumab.

Table 2-5: On-treatment Procedural Outline Clinical Pharmacology Substudy

Procedure	Cycle 00				Notes
	Day 1	**Day 2**	**Day 8[a]**	**Day 9[a]**	Day 8 and 9 for food effect participants only
Monitor for Serious Adverse Events	X	X	X[a]	X	All SAEs must be collected from the date of participant's written consent until 100 days after discontinuation of nivolumab or participation in the study (if the last scheduled visit occurs at a later time). eSAEs should be approved in the BMS EDC tool within 5 business days of entry.
Pharmacokinetic Assessments	See Section 9.5.3 and Table 9.5.3-1.				On Day 1, a single dose of BMS-986242 will be administered under fasting condition; a 7-day washout period will follow during which serial PK samples with time-matched serial ECGs will be collected. For food effect participants only, on Day 8, selected dose level of BMS-986242 will be administered with a high-fat meal; a 2-day washout period will follow during which serial PK samples will be collected.
Study Treatment Administration	Details regarding preparation and administration are provided in the site training materials.				
BMS-986242 Administration	X		X[a]		

Abbreviations: AE = adverse event; ALT = alanine aminotransferase; AST = aspartate aminotransferase; BMS EDC = Bristol-Myers Squibb Electronic Data Capture; BUN = blood urea nitrogen; CBC = complete blood count; ECG = electrocardiogram; EOT = end of treatment; eSAE = electronic serious adverse event; GGT = gamma-glutamyl transferase; hCG = human chorionic gonadotropin; IP = investigational product; IRT = Interactive Response Technology; LDH = lactate dehydrogenase; LFT = liver function test; PE = physical examination; SAE = serious adverse event; WOCBP = women of childbearing potential.

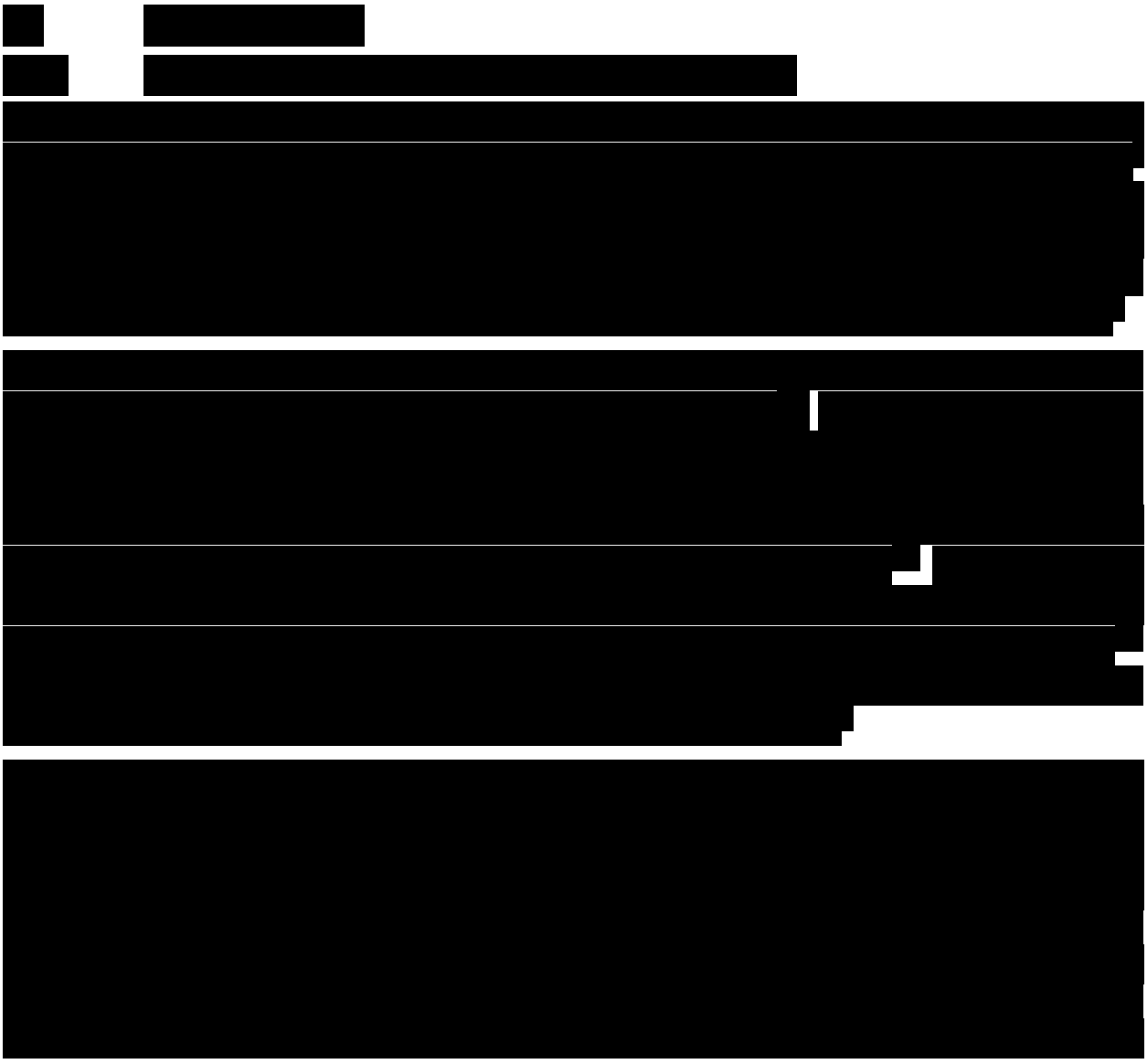
[a] Day 8 and 9 for food effect participants only

[b] For Cycle 00 Day 1 and Day 8, PE and laboratory tests do not need to be repeated if completed within the last 72 hours (for all laboratory tests).

[c] Participants who meet discontinuation criteria during or after Cycle 00 will have CBC with differential, platelets, and chemistry with LFTs done at the EOT and during the follow-up visit at 7 days.

3 INTRODUCTION

This is a dose-escalation and dose-expansion cohort study of BMS-986242, a small molecule inhibitor of the indoleamine 2,3-dioxygenase 1 (IDO1) enzyme, in combination with nivolumab (anti-programmed cell death-1 [PD-1]), in humans with advanced malignant tumors. This study will evaluate the safety, tolerability, pharmacokinetics (PK), pharmacodynamics, and preliminary efficacy of escalating oral doses of BMS-986242 in combination with a flat dose of nivolumab. In addition, the study is expected to identify the maximum tolerated dose (MTD)/recommended Phase 2 dose of BMS-986242 in combination with nivolumab to be used in the dose-expansion cohort phase. Part 2 (dose-expansion cohorts) will assess the preliminary efficacy of BMS-986242 in combination with nivolumab in specific malignant disease populations and will also serve to generate further data to support dose optimization of the combination. The study also includes a clinical pharmacology substudy designed to evaluate the PK of a single dose of BMS-986242, exposure-QTc relationship, and the effect of food on the bioavailability of BMS-986242.



3.3 Overall Benefit/Risk Assessment

3.3.1 Risk/Benefit for BMS-986242

There is no prior human experience with BMS-986242; therefore, clinical benefit has not been assessed in participants with advanced cancer. Other IDO1 inhibitors have entered human trials, both as monotherapy and in combination with other anti-cancer treatments (epacadostat from Incyte Corporation, GDC-0919 from Roche, indoximod from NewLink Genetics, and BMS-986205, from Bristol-Myers Squibb). Published safety information for epacadostat shows a favorable safety profile as monotherapy (ie, well tolerated across all dose levels, with the most common AEs being Grade 1 or 2 fatigue and gastrointestinal disturbances)[19], suggesting no intrinsic risk of suggesting no intrinsic risk of severe toxicity with IDO1 blockade. The assessment of potential clinical benefit of BMS-986242 is based upon preclinical human xenograft model SKOV3, in which significant IDO1 inhibition was achieved.

In the absence of clinical studies, the assessment of the risk of side effects of BMS-986242 in clinical trials is based upon data from nonclinical toxicology studies in rats and dogs. In rats, multiple doses up to 10 mg/kg/day were well-tolerated, while single doses ≥ 20 mg/kg resulted in overt CNS toxicity. In dogs, the top dose studied exceeded the MTD. Clinical signs included vomiting, diarrhea, dehydration, and weight loss. Chronic inflammation was noted in the gallbladder at 100 mg/kg/day and corresponded with increases in serum GGT and ALT activity. The gallbladder inflammation and serum chemistry changes were reversible. CNS and respiratory safety pharmacology assessments were conducted as part of the pivotal 1-month oral toxicity studies in rats and dogs. There were no BMS-986242-related CNS signs or effects on cranial or spinal nerve function or respiratory function at doses up to 10 mg/kg/day in rats and up to 100 mg/kg/day in dogs.

The nonclinical toxicity profile was used to determine the human starting dose and to develop appropriate exclusion criteria and safety monitoring for this study. Complete blood counts and chemistry test results (including liver and kidney functions) will be assessed weekly during monotherapy and Cycle 1 of combination and every 4 weeks (Q4W) thereafter. In addition, complete physical examinations (PEs) will be conducted on Day 1 of each cycle, with additional symptom-directed PEs at least weekly during monotherapy and Q2W for the first 12 weeks during combination. Participants with viral hepatitis or other liver disease, such as nonalcoholic fatty liver disease, will be excluded to minimize the potential for hepatotoxicity. Assays for cardiac ion channels did not indicate a potential for cardiovascular liability. Nevertheless, participants with QTc prolongation at baseline will be excluded, medications known to cause prolonged QT will be prohibited, and electrocardiograms (ECGs) will be monitored during the study.

Continuous safety assessments will be utilized by the investigators and Sponsor to determine whether dose modification, additional safety measures, or termination of the study is required at any time. In addition, AEs and serious adverse events (SAEs) will be reviewed on an ongoing basis by the Sponsor's Medical Monitor and Global Pharmacovigilance and Epidemiology representatives to monitor for any safety signals or trends.

As BMS-986242 is an experimental agent, it is possible that unforeseen, unknown, or unanticipated reactions may occur. Based on the nonclinical safety profile of BMS-986242, and with a 60-fold safety margin built into the planned starting dose of 25 mg daily, the potential safety risks are expected to be minimized. Taking a conservative approach, an initial 12.5 mg starting dose will be used (see Section 5.5.1). A Bayesian Logistic Regression Method (BLRM) with overdose control principle will be employed to ensure that safety is not compromised during dose escalation. This method limits the risk of exposing participants in the next cohort to an unsafe or toxic dose.

3.3.2 Risk/Benefit for Combination with Nivolumab

Nivolumab has demonstrated clinical activity in patients with advanced NSCLC, RCC, melanoma, and lymphomas, as well as other tumors. While preclinical testing of IDO1 inhibitors does not suggest that IDO inhibition alone will bring benefit to patients, it is hypothesized that inhibition of IDO1 will relieve the immunosuppressive milieu within the tumor, thus allowing greater depth of response and ultimately improved survival benefit of other therapies. Early clinical data from a trial of epacadostat in combination with pembrolizumab (a PD-1 inhibitor) is suggestive of the potential synergy between these mechanisms. The largest cohort of participants in this study was melanoma, in which there were 54 evaluable participants. Thirty (30) of these participants were responders, including 8 CRs and 22 PRs, for an ORR of 56%.[43] Per the United States Prescribing Information for pembrolizumab, the ORR for monotherapy in advanced melanoma is 34%. Similarly, epacadostat plus nivolumab in 40 patients with melanoma yielded an ORR of 63%.[44] In several other tumor types epacadostat combined with pembrolizumab also showed high ORRs: NSCLC 35% (n=40), bladder cancer 35% (n=37), SCCHN 31% (n=36), and RCC 30% (n=30).[45] As a reference from the pembrolizumab prescribing information, pembrolizumab ORRs are 18% (PD-L1 Tumor Proportion Score [TPS] ≥1% subset, n=344) for NSCLC, 21% (n=270) for bladder cancer, and 16% (n=174) for SCCHN. While these are different studies with slightly different patient populations, the data suggest that IDO1 inhibition has the potential to improve ORRs in tumor types that respond to PD-1 inhibition.

Nivolumab has demonstrated a manageable safety profile. Nivolumab is indicated as monotherapy in patients with BRAF V600 wild-type and BRAF V600 mutation-positive unresectable or metastatic melanoma. Nivolumab in combination with ipilimumab is indicated in patients with unresectable or metastatic melanoma. Nivolumab is also indicated in patients with metastatic NSCLC and progression on or after platinum-based chemotherapy, in patients with advanced RCC who have received prior antiangiogenic therapy, in adult patients with classical Hodgkin lymphoma that has relapsed or progressed, in patients with recurrent or metastatic SCCHN with disease progression on or after a platinum-based therapy; in patients with locally advanced or metastatic urothelial carcinoma, in adult and pediatric (12 years and older) patients with microsatellite instability-high or mismatch repair deficient metastatic colorectal cancer that has progressed following treatment with a fluoropyrimidine, oxaliplatin, and irinotecan.

The overall safety experience, when used either as a monotherapy or in combination with another therapeutic, is based on experience in approximately 12,300 participants treated to date. There is

no pattern in the incidence, severity, or causality of AEs to nivolumab dose level. The most common AEs include fatigue, rash, pruritus, diarrhea, and nausea. Side effects of nivolumab therapy may include those associated with immune-mediated activation, such as pneumonitis, thyroiditis, and hepatitis. Most of these events resolved with immune-modulating medication. To mitigate risk from serious immune-mediated AEs, participant management algorithms for nivolumab-related AEs from prior collective nivolumab experience have been included. In addition, participants will have to meet a set of safety criteria in order to continue from monotherapy to combination treatment so that the risk of cumulative toxicity is minimized (see Section 5.1.2.1).

In addition, significant clinical data indicates that IDO1 inhibitors can be combined safely with nivolumab. Epacadostat was combined with nivolumab in 36 patients during a dose-escalation study with no occurrence of DLTs and in 230 additional patients in dose-expansion cohorts with an acceptable safety profile.[44] Similarly, BMS-986205 was combined with nivolumab and administered to 44 patients during a dose-escalation study with DLTs occurring in 1 out of 9 participants at a dose of 100 mg QD (autoimmune hepatitis, which could be caused by PD-1 inhibition alone) and in 1 out of 10 participants at a dose of 200 mg QD (anemia), as reported at the annual meeting of the American Association for Cancer Research (AACR) 2017. [46] Subsequent to this report, 200 mg QD BMS-986205 was determined to be the MTD, and 100 mg QD is being studied in Phase 2 cohorts (preliminary unpublished data).

3.3.3 Summary

Despite innovations in cancer treatment, alternative therapies are needed for participants with advanced cancer that has progressed or not responded to other treatments. The emerging role of combination immune-modulating therapies in producing deep and durable responses in a variety of tumor types suggests that once a pharmacologically-active dose range is reached, there may be a potential benefit of IDO inhibition with BMS-986242 for participants when used in combination with nivolumab. Preclinical safety signals were monitorable and reversible and are to be closely monitored in this study. This supports the evaluation of BMS-986242 as monotherapy and in combination with nivolumab in participants with advanced cancer who have few treatment options.

4 OBJECTIVES AND ENDPOINTS

The objective and endpoints for this study are shown in Table 4-1.

Table 4-1: Objectives and Endpoints

Objectives	Endpoints
Primary	
• Part 1: Dose Escalation • To determine the safety, tolerability, DLTs, and MTD/MAD/alternative dose of BMS-986242 administered as monotherapy (lead-in cycle) and in combination with nivolumab in participants with advanced malignant tumors • Part 2: Dose-Expansion Cohort(s) • To evaluate the safety and tolerability of BMS-986242 in combination with nivolumab in participants with advanced malignant tumors	• Incidence of DLTs, AEs, SAEs, AEs leading to discontinuation, deaths, and clinical laboratory test abnormalities • Additional safety endpoints include changes from baseline in laboratory parameters, vital signs, and ECGs.
Secondary	
• To characterize the PK of BMS-986242 administered alone and in combination with nivolumab	• Summary measures of selected BMS-986242 PK parameters, such as Cmax, Tmax, AUC(TAU), AUC(INF), Ctrough, T-HALF, CLT/F, Vss/F, AI, %UR24, %UR72, and exposure ratios of select BMS-986242 metabolites to BMS-986242 from concentration-time data during BMS-986242 monotherapy and BMS-986242 Ctrough during combination treatment
• To characterize the pharmacodynamic activity of BMS-986242 administered alone and in combination with nivolumab	• Summary measures of change from baseline (and/or percent change) for serum and tumor kynurenine and related metabolites
• To characterize the immunogenicity of nivolumab when administered in combination with BMS-986242	• Incidence of ADA to nivolumab in combination with BMS-986242
• To assess the preliminary anti-tumor activity of BMS-986242 administered in combination with nivolumab in advanced malignant tumors	• ORR in participants with a BOR of CR or PR per RECIST version 1.1 for solid tumors; mDOR, and PFSR at 6, 9, 12, and 24 months
[redacted]	[redacted]

Table 4-1: Objectives and Endpoints

Objectives	Endpoints
[redacted]	[redacted]

Abbreviations: %UR24 = percent urinary recovery over 24 hours; %UR72 = percent urinary recovery over 72 hours ADA = anti-drug antibody; AE = adverse event; AI = accumulation index; AUC(0-T) = area under the concentration-time curve; AUC(INF) = area under the concentration-time curve from time zero to infinity; AUC(TAU) = area under the concentration-time curve in 1 dosing interval; BOR = best overall response; Ceoi = concentrations at end of infusion; Cmax = maximum observed plasma concentration; CR = complete response; Ctrough = trough observed plasma concentration at the end of the dosing interval; CLT/F = apparent total body clearance; DLT = dose-limiting toxicity; DOR = duration of response; mDOR = median duration of response; ECGs = 12-lead electrocardiograms; MAD = maximum administered dose; MR_AUC(0-T) = ratio of metabolite AUC(0-T) to parent AUC(0-T) corrected for molecular weight; MR_AUC(INF) = ratio of metabolite AUC(INF) to parent AUC(INF) corrected for molecular weight; MR_AUC(TAU) = ratio of metabolite AUC(TAU) to parent AUC(TAU) corrected for molecular weight; MR_Cmax = ratio of metabolite Cmax to parent Cmax corrected for molecular weight; ORR = overall response rate; OSR = overall survival rate; PFSR = progression-free survival rate; PR = partial response; RECIST = Response Evaluation Criteria in Solid Tumors; SAE = serious adverse event; T-HALF = apparent elimination half-life; Tmax = time of maximum observed plasma concentration; Vss/F = apparent volume of distribution at steady state.

5 STUDY DESIGN

5.1 Overall Design

This is a Phase 1/2a, open-label study of BMS-986242 administered as a single agent and in combination with nivolumab in participants with advanced malignant tumors. The study will be conducted in 2 parts, dose escalation (Part 1) and dose-expansion cohorts (Part 2). In addition, a clinical pharmacology substudy will be conducted in which BMS-986242 single-dose PK, exposure-QTc relationship and exploratory food effect on BMS-986242 bioavailability will be assessed.

Dose escalation (Part 1) will start with a lead-in **Cycle 0** (see Section 3.1.2 for details on lead-in rationale), whereby BMS-986242 is administered as monotherapy of 2-week duration in each dose-escalation cohort. The decision to proceed to combination treatment with nivolumab (Cycle 1) for each participant in dose escalation will be determined after tolerability of the monotherapy lead-in is established in the 2-week Cycle 0 at each dose (see Section 5.1.2.1). The starting dose of BMS-986242 is 12.5 mg administered orally daily. Nivolumab will be administered IV at a dose of 480 mg Q4W. In the event the 12.5-mg dose level of BMS-986242 is determined to exceed the MTD in monotherapy or in combination with nivolumab, no lower BMS-986242 dose level will be further explored.. Please refer to Appendix 7.

Dose escalation may be stopped prior to reaching the MTD if pharmacodynamic data indicate that maximum inhibition of IDO1 has been achieved. In such a case, the MAD or an alternate dose

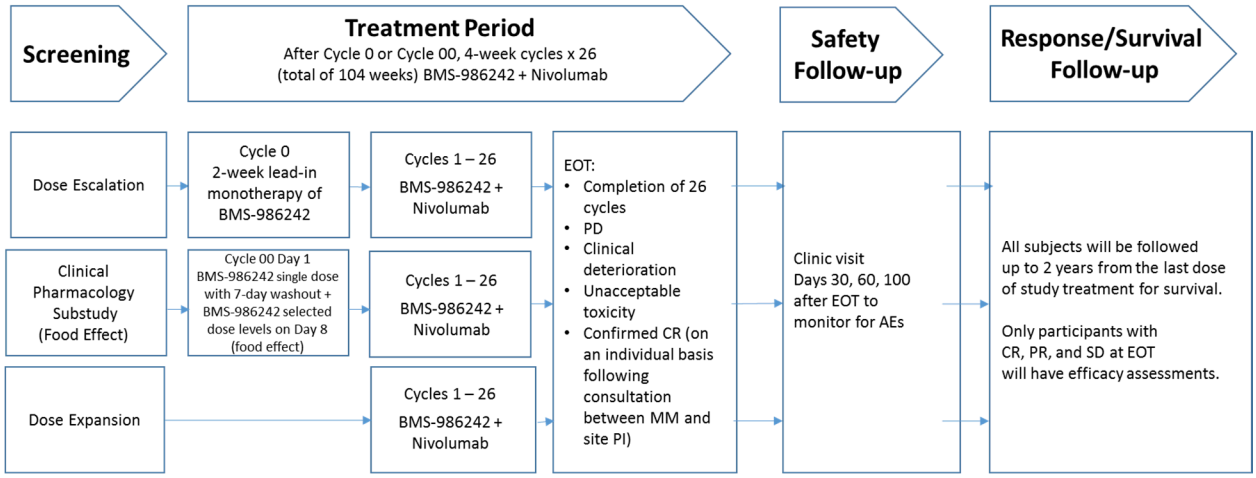
below the MAD will be used for the expansion cohorts. At no point will the dose of BMS-986242 administered in combination with nivolumab exceed doses of BMS-986242 that have been demonstrated previously to be safe in the monotherapy lead-in Cycle 0 (Section 5.1.2.1). Participants will be enrolled per inclusion criteria in Section 6.1.

Cycle 0: Each dose-escalation cohort will start with **Cycle 0**, which is a 2-week BMS-986242 monotherapy lead-in**.** If there are no dose-limiting toxicities (DLTs) (see Section 7.4.1), participants will proceed to receive the combination of nivolumab and BMS-986242 (Cycle 1).

Dose-expansion cohorts will be carried out at the dose of BMS-986242 selected from dose escalation in combination with nivolumab 480 mg and may represent the MTD, maximum administered dose (MAD), or an alternate dose for the combination. Study therapy consisting of BMS-986242 daily and nivolumab Q4W will be administered in 4-week cycles for up to 26 cycles. Participants in 6 disease-restricted populations will be enrolled as follows: melanoma, NSCLC, SCCHN, BUC, RCC, and gastric cancer. The dose(s) selected for cohort expansion will not exceed the MTD or MAD determined in dose escalation.

Participants will complete up to 4 phases of the study: Screening, Treatment, Clinical/Safety Follow-up, and Survival/Long-term Follow-up, as described below. The study design schematic is presented in Figure 5.1-1.

Figure 5.1-1: Study Design Schematic



Abbreviations: AE = adverse event; CR = complete response; EOT = end of treatment; MM = Medical Monitor; PD = progressive disease; PI = principal investigator; PK = pharmacokinetics; PR = partial response; SD = stable disease.

5.1.1 Screening Phase

The screening phase will last for up to 28 days. The screening phase begins by establishing the participant's initial eligibility and signing of the informed consent form (ICF). Participants will be enrolled using the Interactive Response Technology (IRT).

If a participant surpasses the 28-day window during the screening phase because of a study-related procedure (eg, scheduling of a tumor biopsy or waiting time for a study-related laboratory value),

the participant must be re-consented but does not need to be assigned a new participant identification number. In this situation, the least amount of repeat procedures from the initial screening to qualify the participant while maintaining safety and eligibility under the discretion of the BMS Medical Monitor and investigator may be done to reduce any undue burden of procedure in this population.

5.1.2 Treatment Phase

The treatment phase consists of up to twenty-six 4-week treatment cycles. Each treatment cycle is comprised of a daily oral dose of BMS-986242 and 1 dose of nivolumab administered IV Q4W on Day 1 of the treatment cycle. In addition, dose escalation will start with Cycle 0, a lead-in period of 2-week duration, during which monotherapy with BMS-986242 is administered. The total treatment period is 104 weeks or 26 cycles. This is in addition to the 2-week Cycle 0.

Following every 2 treatment cycles (8 weeks), the decision to treat a participant with additional cycles of study treatment will be based on radiological tumor assessments (initial evaluation performed at baseline, end of Cycle 2, and every 8 weeks). Assessments of partial response (PR) and complete response (CR) must be confirmed at least 4 weeks following initial assessment. Tumor progression or response endpoints will be assessed using Response Evaluation Criteria in Solid Tumors (RECIST) v1.1 criteria for solid tumors (Appendix 6).

Treatment beyond progression may be allowed in select participants with initial RECIST v1.1-defined progressive disease (PD) after discussion and agreement with the BMS Medical Monitor that the benefit/risk assessment favors continued administration of study treatment (eg, participants are continuing to experience clinical benefit as assessed by the investigator, tolerating treatment, and meeting other criteria specified in Section 5.1.2.3).

Participants with a response of stable disease (SD), PR, or CR at the end of a given cycle will continue to the next treatment cycle. Participants will generally be allowed to continue study treatment until the first occurrence of either: 1) completion of the maximum number of cycles, 2) PD, 3) clinical deterioration suggesting that no further benefit from treatment is likely, 4) intolerability to study treatment, or 5) the participant meets criteria for discontinuation of study treatment as outlined in protocol Section 8. Individual participants with confirmed CR will be given the option to discontinue study treatment 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 treatment.

5.1.2.1 Part 1: Dose Escalation

Six disease-restricted populations will be included in the dose-escalation part. These are melanoma, NSCLC, SCCHN, RCC, BUC, and gastric cancer. The dose-escalation part of the study will evaluate doses of BMS-986242 in combination with nivolumab based on DLTs using a BLRM model (for BMS-986242 monotherapy lead-in) and BLRM-copula model (for BMS-986242 in combination with nivolumab). The Bayesian models will be used for recommendation of the next dose to be investigated. BLRM (combined with copula) framework with an escalation with overdose control principle will be employed to ensure that safety is not compromised during dose escalation.

The initial dose level of BMS-986242 will be 12.5 mg administered orally daily. After a 2-week period, once initial lead-in monotherapy (Cycle 0) is deemed tolerable, combination with 480 mg flat dose nivolumab (Cycle 1) will be initiated.

Dose levels to be considered for the next combination cohort (with monotherapy lead-in) will be based on recommended monotherapy dose from BLRM and recommended combination dose from BLRM-copula. The lower dose from these 2 recommendations will be considered. Potential dose levels for dose escalation are provided in Table 5.1.2.1-1. The maximum allowable increase in dose will be 100%. Final dose selection for the next cohort/dose level will be made in conjunction with all data available from PK and pharmacodynamic assessments, and will be made after discussion and agreement between investigators and BMS Medical Monitor. Accordingly, intermediate or lower doses, or less frequent dosing of BMS-986242 may be tested if none of the planned doses/schedules are found to be tolerated as the lead-in phase or in combination with nivolumab.

Initially, approximately 4 participants will be treated at the starting dose level of BMS-986242. During the dose-escalation phase, once a dose level has been decided, a set of approximately 4 participants will be initially treated at that specified dose level. Increments of approximately 3 participants will be added to each dose level depending on model recommendation and clinical judgment. Due to the potential for early discontinuation, additional participant(s) may be enrolled to ensure at least 3 evaluable participants at each dose level.

Cohort tolerability assessment and subsequent dose recommendation may occur when 2 DLT-evaluable participants within a cohort have completed the 6-week DLT observation period (see Section 7.4.1 for criteria for DLTs). DLTs occurring within the 2-week lead-in period (DLT observation period for monotherapy) will be used to fit the BLRM model for monotherapy. DLTs occurring within the 4 weeks of combination period (DLT observation period for combination) will be used to fit the BLRM-copula model. If a potential DLT occurring in any third evaluable participant does not influence the dose recommendation by BLRM (-copula), then the BLRM (-copula)-recommended next dose level may proceed without waiting for the third participant to complete the corresponding DLT observation period after discussion and agreement by the sponsor and investigators. The lower recommended dose from both models will be considered for the next dose escalation. Participants receiving ≥ 75% (11 out of 14 doses) of BMS-986242 in the 2-week lead-in cycle will be considered as DLT-evaluable participants for BMS-986242 monotherapy. Participants who receive at least 1 dose of nivolumab and have been followed at least 5 days and receive ≥ 75% BMS-986242 (21 out of 28 doses) in the 4-week DLT observation period for combination therapy will be considered as DLT-evaluable participants. Continuous re-assessment of dose recommendation by BLRM will be carried out at each dose level after each cohort of participants with consideration of all available DLT information. In order to allow additional safety, PK, and pharmacodynamic assessment, in Part 1 up to 12 additional participants may be enrolled at any dose level at or below the MTD, up to a total of 24 additional participants.

No intra-participant dose escalation is allowed, although dose modifications of BMS-986242 may be permitted (see Table 7.4.2-1).

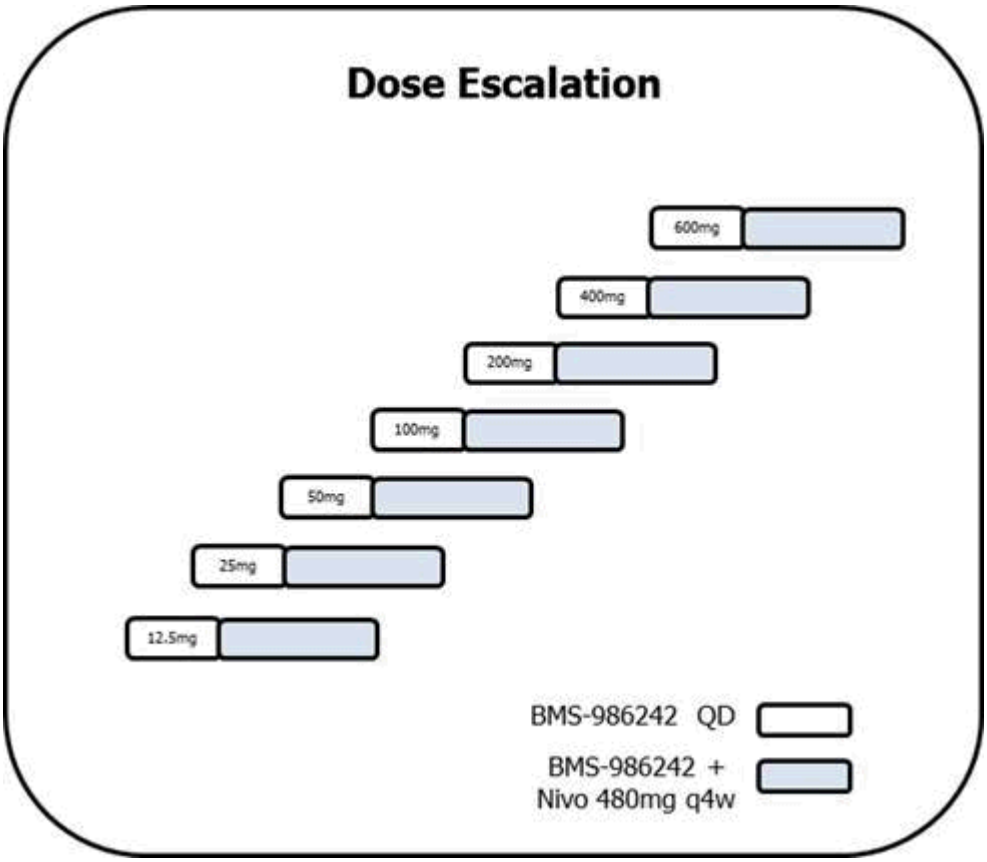
Sentinel Participant: During dose escalation, a staggered dosing (sentinel participant) approach will be used. In the first dose level, the first participant in both lead-in and combination will receive the Cycle 0 Day 1 or Cycle 1 Day 1 dose(s) of study treatment(s) and be observed for 5 days before additional participants in that cohort receive monotherapy or combination study treatment. In subsequent dose levels, a sentinel participant with a 5 day observation period will be used for Cycle 0 Day 1.

The dose-escalation planned dose levels for selection of the MTD/MAD/alternative dose is depicted in Table 5.1.2.1-1 and Figure 5.1.2.1-1.

Table 5.1.2.1-1: Dose Escalation Schedule

Dose Level	BMS-986242	Nivolumab
1	12.5 mg	480 mg IV Q4W
2	25 mg	480 mg IV Q4W
3	50 mg	480 mg IV Q4W
4	100 mg	480 mg IV Q4W
5	200 mg	480 mg IV Q4W
6	400 mg	480 mg IV Q4W
7	600 mg	480 mg IV Q4W

Figure 5.1.2.1-1: Study Design Schematic - Dose Escalation



Clinical Pharmacology Substudy:

A clinical pharmacology substudy will be conducted to characterize the PK profile of BMS-986242 after a single-dose administration, BMS-986242 exposure-QTc relationship and to evaluate of the effect of food on the bioavailability of BMS-986242. The substudy will evaluate selected dose levels that have already been determined to be tolerable during dose escalation.

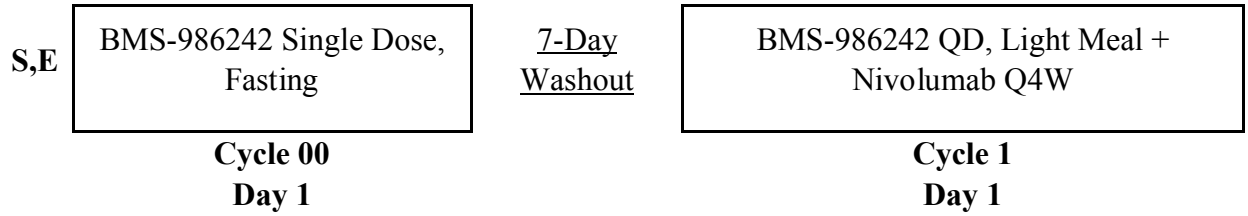
Participants in the substudy will receive a single dose of BMS-986242 under fasting condition on Cycle 00 (Day 1) followed by a 7-day washout period during which serial PK samples will be collected (Table 9.5.3-2). Triplicate ECGs will be collected at predose and select time points postdose on Day 1 (with matching PK samples) to allow the assessment of the effect of BMS-986242 exposure on QTc intervals. All participants will then receive BMS-986242 under the usual dosing condition with a light meal once daily in combination with nivolumab on Cycle 1 Day 1 and will follow all assessments as per Table 2-3. The inclusion criteria used in the dose-escalation phase apply to participants enrolled in the clinical pharmacology substudy (Section 6.1). The doses to be evaluated in the substudy will be determined based on available safety, PK and biomarker data. At least 3 doses (below, at, and above the expected dose for expansion) are expected to be evaluated in at least 6 evaluable participants per dose level in the substudy. Additional dose levels at may be evaluated if warranted.

At a designated dose level, an exploratory food effect evaluation will be conducted. After receiving a single dose of BMS-986242 under fasting condition on Cycle 00 (Day 1) followed by a 7-day washout period, participants will receive 1 dose of BMS-986242 with a high-fat meal on Day 8. Serial PK samples will be collected during a 2-Day washout period (Table 9.5.3-2). Participants will then receive BMS-986242 under the usual dosing condition with a light meal once daily in combination with nivolumab on Cycle 1 Day 1 and will follow all assessments as per Table 2-3. For the dose to be evaluated in the food effect substudy, either a higher dose would need to be demonstrated to be safe in the dose-escalation phase or sufficient exposure multiples should have been obtained following multiple doses at the same dose level. Additional doses may be evaluated if warranted.

Study design schematics for the clinical pharmacology substudy are shown in Figure 5.1.2.1-2 (single-dose PK and exposure-QTc assessment) and Figure 5.1.2.1-3(food effect).

Figure 5.1.2.1-2: Study Design Schematic for the Clinical Pharmacology Substudy

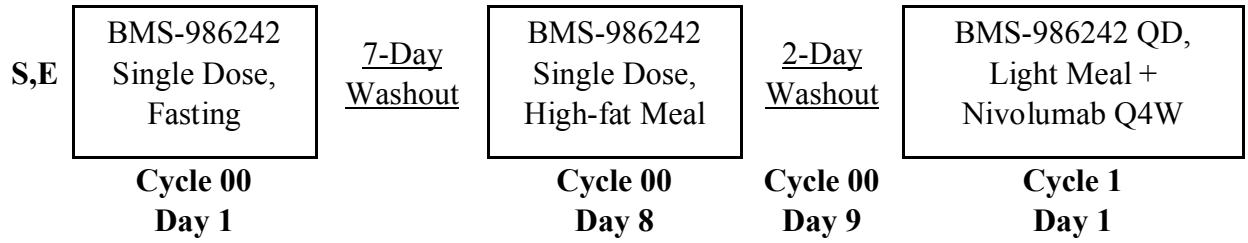
Single-dose PK and Exposure-QTc Assessment (Selected Dose Levels)



S,E = screening, enrollment

Figure 5.1.2.1-3: Food Effect Assessment (Designated Dose Group*)

Food Effect Assessment (Designated Dose Group*)



S,E = screening, enrollment

* A designated dose group from the selected dose levels will evaluated for both single-dose

PK/exposure-QTc and food effect. One cohort of at least 6 evaluable participants will be included.

Up to approximately 78 participants are planned to be enrolled for Part 1 (dose escalation) and clinical pharmacology substudy: approximately 30 participants for the dose-escalation phase, with up to 24 additional participants in Part 1 for additional characterization of the safety, PK, and pharmacodynamic profile of BMS-986242, and approximately 24 participants for the clinical pharmacology substudy (including food effect).

5.1.2.2 Part 2: Dose-Expansion Cohorts

The purpose of cohort expansion is to gather additional safety, tolerability, preliminary efficacy, PK, and pharmacodynamic information regarding BMS-986242 in combination with nivolumab.

Six disease-restricted populations will be included in the dose-expansion cohort phase. These are melanoma, NSCLC, SCCHN, RCC, BUC, and gastric cancer. PD-(L)1 inhibitors are an approved treatment option for melanoma, NSCLC, SCCHN, RCC, and BUC, and prior treatment may impact preliminary efficacy; thus separate cohorts (PD-(L)1 inhibitor naive or experienced) will be enrolled for these 5 tumor types. Approximately 20 participants will be included in each dose-expansion cohort, for a total of approximately 220 participants in Part 2.

Continuous evaluation of toxicity events in the cohort expansions will be performed throughout enrollment in the expansion cohorts. If, at any time, the aggregate rate of treatment-related toxicities meeting DLT criteria exceeds 33% across all participants treated in cohort expansions, the findings will be discussed and further enrollment may be interrupted. Depending on the nature and grade of the toxicity and after assessing the risk/benefit ratio, a new dose(s) for all cohorts may be initiated at a previously tested lower dose level or at a dose level intermediate to previously tested lower dose levels.

5.1.2.3 Treatment Beyond Progression

A subset of participants with solid tumors treated with immunotherapy may derive clinical benefit despite initial evidence of PD. Participants will be permitted to continue on treatment beyond initial RECIST v1.1-defined PD (see Appendix 6) as long as they meet the following criteria:

- Investigator-assessed clinical benefit and not having rapid disease progression
- Absence of signs or symptoms indicating disease progression
- Continue to meet all other study protocol eligibility criteria
- Tolerance of study treatment
- Stable performance status
- Treatment beyond progression will not delay an imminent intervention to prevent serious complications of disease progression (eg, CNS metastases)
- Participant provides written informed consent prior to receiving additional nivolumab and BMS-986242 treatment, using an ICF describing any reasonably foreseeable risks or discomforts or other alternative treatment options

The assessment of clinical benefit should take into account whether the participant is clinically deteriorating and unlikely to receive further benefit from continued treatment. All decisions to continue treatment beyond initial progression must be discussed with the BMS Medical Monitor, and an assessment of the benefit/risk of continuing with study treatment must be documented in the study records. Participants will be re-consented to explain the rationale for this ongoing treatment.

Participants should continue to receive monitoring according to the on-treatment assessments in Section 9.4. Radiographic assessment by computed tomography (CT; preferred) or magnetic resonance imaging (MRI) described in Section 2 and in Section 9.1.1 is required when participants

continue post-progression treatment. For participants who discontinue post-progression treatment with study treatment, no additional radiographic assessments will be required.

5.1.2.4 Discontinuation Due to Further Progression

Participants should discontinue study treatment upon further evidence of further progression, defined as an additional 10% or greater increase in tumor burden volume from time of initial progression (including all target lesions and new measurable lesions).

The tumor burden volume from time of initial progression should be used as the reference baseline for comparison with the post-progression assessment.

Any new lesion considered non-measurable at the time of initial progression may become measurable and, therefore, must be included in the tumor burden measurement as follows:

For solid tumors: New lesions are considered measurable at the time of initial progression if the longest diameter is at least 10 mm (except for pathological lymph nodes, which must have a short axis of at least 15 mm).

For statistical analyses that include the investigator-assessed progression date, participants who continue treatment beyond initial investigator-assessed, RECIST v1.1 -defined progression will be considered to have investigator-assessed PD at the time of the initial progression event.

5.1.3 Clinical/Safety Follow-up

Upon completion of study treatment, participants will enter the Clinical/Safety Follow-up period (refer to Section 5.3 and Section 5.1.4 for definitions for end of treatment [EOT]).

Participants must be followed for at least 100 days after the last dose of study treatment. Follow-up visits should occur at Days 30, 60, and 100 (± 10 days) after the last dose of study treatment or should coincide with the date of discontinuation (± 10 days) if date of discontinuation is greater than 30 days after the last dose of study treatment to monitor for AEs. Participants will be required to complete 3 Clinical/Safety Follow-up visits regardless of whether they start a new anti-cancer therapy, except those participants who withdraw consent for study participation.

5.1.4 Survival/Long-Term/Response Follow-up

After completion of the Clinical/Safety Follow-up period, all participants will then enter the Survival/Long-term Follow-up period. During this period, clinic visits or telephone contact every 3 months will be performed to assess survival status. The duration of Survival/Long-term Follow-up period will be 2 years from the last dose of study treatment.

After completion of the Safety Follow-up period, participants who discontinue study with ongoing SD, PR, or CR at the EOT visit will enter the Response Follow-up period. These periods will occur simultaneously with the Survival Follow-up period for mentioned participants. During the Response Follow-up period (or until disease progression or withdrawal of study), these participants will continue to have radiological and clinical tumor assessments every 12 weeks for the first year after the EOT visit and then every 6 months thereafter up to 2 years from the last dose of study treatment. Radiological tumor assessments for participants who have ongoing clinical benefit may continue to be collected after participants complete the survival phase of the study.

Participants in the Survival/Long-term Follow-up period who have progression of disease will be allowed to receive tumor-directed therapy as required.

5.1.5 Data Monitoring Committee and Other External Committees

BMS has elected not to use a Data Monitoring Committee for this study. In addition to the comprehensive safety monitoring plan outlined below, the following key points were considered for this decision:

- This is an open-label study.
- The eligibility criteria exclude participants with disease characteristics that could predispose to higher risk of morbidity, eg, uncontrolled or significant cardiovascular disease, etc.
- Exclusion of participants with active, known, or suspected autoimmune disease also applies, as they could be at risk for exacerbation of their condition by the administration of therapies that relieve immune suppression such as BMS-986242 and nivolumab.
- Participants will be observed frequently for clinical evaluation and blood counts during dose escalation.
- Well-defined discontinuation criteria are established in the protocol for individual participants for both safety and treatment futility with clear criteria for treatment discontinuation, dose delay, and toxicity management.

BMS has in place a multi-layered process for ensuring patient safety through close collaboration of study site investigators, the BMS study team, and the BMS GPVE-led Medical Surveillance Team (MST). This collaborative process constitutes the Data Safety Monitoring Plan for the study as detailed below:

Study safety is evaluated continuously by representatives of BMS GPVE, who operate independently from the clinical team and monitor safety across all BMS protocols. AEs are monitored continuously by GPVE. Signal detection is performed at least monthly and ad hoc throughout the study by the MST composed, at a minimum, of the GPVE medical safety assessment physician (Chairman of the MST) and GPVE single case review physician, the study Medical Monitor(s), the study biostatistician, and epidemiologist. The MST monitors actual or potential issues related to patient safety that could result in a significant change in the medical risk-benefit balance associated with the use of study treatments. Furthermore, investigators will be kept updated of important safety information, such as DLTs, during teleconferences between investigators and the BMS clinical team that will be held at least Q4W during dose escalation and at least monthly during cohort expansion. If appropriate, select safety issues may be escalated to a senior-level, multidisciplinary, BMS-wide Medical Review Group for further evaluation and action.

To support safety oversight, BMS has established ongoing processes for collection, review, analysis, and submission of individual AE reports and their aggregate analyses. Because this is an open-label study, the BMS Medical Monitor and the investigators will have access to all data necessary for safety evaluation.

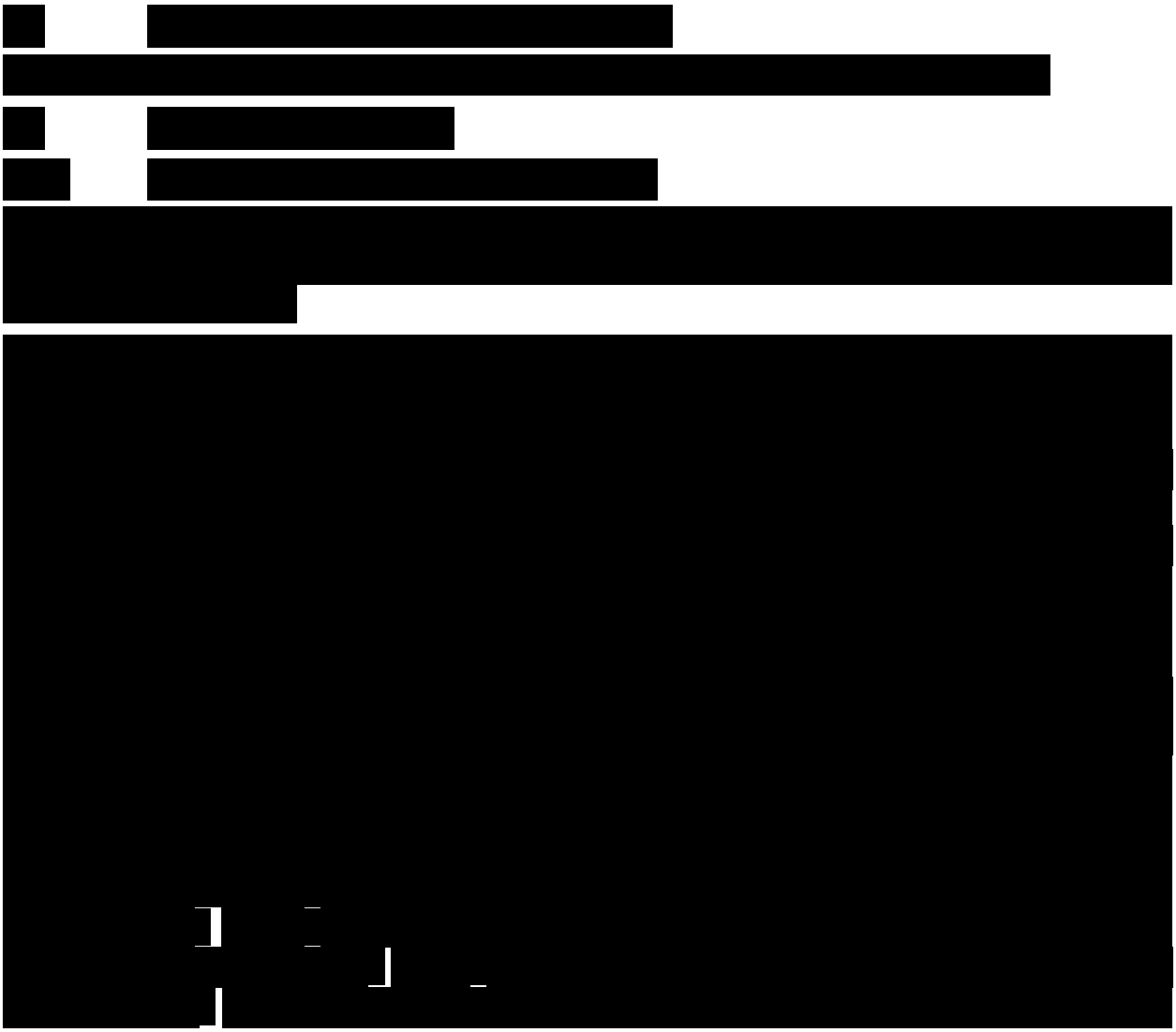
5.2 Number of Participants

A maximum of 298 participants may be enrolled in the study. Approximately 78 participants are planned to be enrolled for Part 1 (dose escalation, additional safety, PK, and PD, and clinical pharmacology substudy) and approximately 220 participants for Part 2 (dose-expansion cohorts).

These are discussed further in Section 5.1.2.1, Section 5.1.2.2, and Section 10.1.

5.3 End of Study Definition

The start of the trial is defined as the first visit for the first participant screened. End of trial is defined as the last visit scheduled or scheduled procedure shown in the Schedule of Activities for the last participant. Study completion is defined as the final date on which data for the primary endpoint was or is expected to be collected, if this is not the same. The total duration of the study is expected to be approximately 5 years from the onset of the first visit of the first subject to the required Survival/Long-term Follow-up of the last subject enrolled.



6 STUDY POPULATION

For entry into the study, the following criteria MUST be met prior to dosing on Day 1. No exceptions will be granted.

6.1 Inclusion Criteria

1) Signed Written Informed Consent

a) The participant must sign the ICF prior to the performance of any study-related procedures that are not considered part of standard of care.

2) Type of Participant and Target Disease Characteristics

a) Participants must be at least 18 years old and have histologic or cytological confirmation of a malignancy that is advanced (metastatic and/or unresectable) with measureable disease per RECIST v1.1 (see Appendix 6).

Part 1 and Part 2:

i) Participants must have received and then progressed or been intolerant to at least 1 standard treatment regimen in the advanced or metastatic setting if such a therapy exists

(1) Participants with tumor subtypes, harboring genetic aberrations that are amenable to targeted therapy (e.g. BRAF, EGFR, ALK, HER2) should have received the appropriate, standard of care therapy for their specific genetic aberration.

(2) BRAF-mutation negativemelanoma participants can be treatment-naïve, as they will be given concomitant nivolumab, which constitutes standard of care.

ii) The following tumor histologies will be permitted except for participants with primary CNS tumors or CNS metastases as the only site of active disease.

The following tumor types will be permitted:

(1) SCCHN- oral cavity, pharynx, larynx

(a) Histologically confirmed recurrent or metastatic SCCHN not amenable to local therapy with curative intent (surgery or radiation with or without chemotherapy)

(b) Documentation of p16-positive or p16-negative disease to determine HPV status of tumor for SCC of the oropharynx.47 Must have evidence of progression or recurrence within 6 months of last dose of platinum therapy in the adjuvant (ie, with radiation after surgery), primary (ie, with radiation), recurrent, or metastatic setting.

(c) Radiation therapy must have been completed at least 4 weeks prior to study treatment administration.

(2) Bladder Urothelial Carcinoma

(a) Evidence of metastatic or surgically unresectable transitional cell carcinoma of the urothelium involving the bladder, urethra, ureter or renal pelvis

(b) Progression or recurrence after treatment

- With at least 1 platinum-containing chemotherapy regimen for metastatic or surgically unrespectable locally advanced urothelial cancer, or

- Within 12 months of peri-operative (neo-adjuvant or adjuvant) treatment with a platinum agent in the setting of cystectomy for localized muscle-invasive urothelial cancer

(3) Renal Cell Carcinoma

(a) Advanced or metastatic RCC with a clear cell component

(b) 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 (eg, IL-2 IFN-α), vaccine therapy, or treatment with cytotoxics is allowed.

(c) 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.

(4) NSCLC

(a) Histologically confirmed recurrent or metastatic NSCLC not amenable to local therapy with curative intent (surgery or radiation with or without chemotherapy)

(5) Melanoma

(a) Histologically confirmed recurrent or metastatic melanoma not amenable to local therapy with curative intent (surgery or radiation with or without chemotherapy)

(6) Gastric cancer

(a) Histologically confirmed recurrent or metastatic gastric cancer not amenable to local therapy with curative intent (surgery or radiation with or without chemotherapy)

General Inclusion Criteria:

iii) Eastern Cooperative Oncology Group (ECOG) performance status of ≤ 1

iv) Ability to swallow tablets

v) Presence of at least 1 lesion with measurable disease as defined by RECIST v1.1 for solid tumors for response assessment. Participants with lesions in a previously irradiated field as the sole site of measurable disease will be permitted to enroll provided the lesion(s) have demonstrated clear progression and can be measured accurately.

vi) Participants with prior exposure to therapy with any agent specifically targeting checkpoint pathway inhibition (such as anti-PD-1, anti-PD-L1, anti-PD-L2, anti-LAG-3, and anti-CTLA-4 antibody) are permitted after a washout period of any time greater than 4 weeks from the last treatment.

Note: *(i) Participants who experienced prior Grade 1 to 2 checkpoint therapy-related immune-mediated AEs must have confirmed recovery from these events at the time of study entry* ***other than endocrinopathies treated with supplementation*** *as documented*

by resolution of all related clinical symptoms, abnormal findings on PE, and/or associated laboratory abnormalities. Where applicable, these participants must also have completed steroid tapers for treatment of these AEs by a minimum of 14 days prior to commencing treatment with study treatment.

(ii) Eligibility of participants with prior ≥ Grade 3 checkpoint therapy-related immune AEs will be considered on a case-by-case basis after discussion with the Medical Monitor (eg, asymptomatic, isolated, Grade 3 lipase elevations without clinical or radiological features of pancreatitis will be permitted to enroll).

vii) Participants with prior therapy with any agent specifically targeting T-cell co-stimulation pathways, such as anti-glucocorticoid-induced tumor necrosis factor receptor family-related gene antibody, anti-CD137, or anti-OX40 antibody, are permitted after a washout period of any time greater than 4 weeks from the last treatment.

viii) Prior palliative radiotherapy must have been completed at least 2 weeks prior to first dose of study treatment. Participants with symptomatic tumor lesions at baseline that may require palliative radiotherapy within 4 weeks of first dose of study treatment are strongly encouraged to receive palliative radiotherapy prior to enrollment.

ix) Participant must consent to allow the acquisition of existing formalin-fixed, paraffin-embedded tumor tissue, either a block or 15 to 20 unstained slides, for performance of correlative studies.

x) All participants will be required to undergo mandatory pretreatment and on-treatment biopsies at acceptable clinical risk as judged by the investigator.

(1) Tissue may have been collected at any time prior to first dose of study treatment.

(2) The tumor tissue specimen must be a core needle biopsy, excisional or incisional biopsy. Fine needle biopsies, drainage of pleural effusions with cytospins, or punch biopsies are not considered adequate for biomarker review and randomization. Biopsies of bone lesions that do not have a soft tissue component or decalcified bone tumor samples are also not acceptable.

(3) Biopsies cannot be collected in participants with a single measureable lesion, even if accessible.

xi) Adequate marrow function for participants with solid tumor histologies as defined by the following:

(1) White blood cells ≥ 2,000/μL (stable off any growth factor within 4 weeks of first study treatment administration)

(2) Neutrophils ≥ 1,500/μL (stable off any growth factor within 4 weeks of first study treatment administration)

(3) Platelets ≥ 100× 103/μL (transfusion to achieve this level is not permitted within 2 weeks of first study treatment administration)

(4) Hemoglobin ≥ 8.5 g/dL (transfusion to achieve this level is not permitted within 2 weeks of first study treatment administration)

xii) Adequate other organ functions as defined by the following:

(1) ALT and AST ≤ 3× institutional upper limit of normal (ULN)

(2) Total bilirubin ≤ 1.5× institutional ULN (except participants with Gilbert's syndrome who must have normal direct bilirubin)

(3) Normal thyroid function, subclinical hypothyroidism (thyroid-stimulating hormone < 10 mIU/mL) or have controlled hypothyroidism on appropriate thyroid supplementation

(4) Serum creatinine ≤ 1.5× ULN or creatinine clearance (CrCl) ≥ 40 mL/min (measured using the Cockcroft-Gault formula below):

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

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

(5) Ability to comply with treatment, PK, and pharmacodynamic sample collection and required study follow-up

3) Age and Reproductive Status

a) Males and females at least 18 years old at the time of informed consent

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

c) Women must not be breastfeeding.

d) WOCBP must agree to follow instructions for method(s) of contraception for the duration of treatment with study treatment(s) plus 5 half-lives of study treatment plus 30 days (duration of ovulatory cycle) for a total of 23 weeks post-treatment completion.

e) Males who are sexually active with WOCBP must agree to follow instructions for method(s) of contraception for the duration of treatment with study treatment plus 5 half-lives of study treatment plus 90 days (duration of sperm turnover) for a total of 31 weeks post treatment completion. In addition, male participants must be willing to refrain from sperm donation during this time.

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

Investigators shall counsel WOCBP and male participants who are sexually active with WOCBP on the importance of pregnancy prevention and the implications of an unexpected pregnancy. Investigators shall advise WOCBP and male participants who are sexually active with WOCBP on the use of highly effective methods of contraception (see Appendix 4). Highly effective methods of contraception have a failure rate of < 1% when used consistently and correctly.

6.2 Exclusion Criteria

1) Target Disease Exceptions

a) Participants with known or suspected CNS metastases, untreated CNS metastases, or with the CNS as the only site of disease are excluded. Participants with controlled brain

metastases, however, will be allowed to enroll. 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 off of steroids for at least 2 weeks, and no new or progressive neurological signs and symptoms. Please note that participants with direct extension of tumor through the base of skull will not be excluded, as they are considered distinct from hematogenously spread parenchymal brain metastasis.

b) Participants with ocular melanoma will not be allowed to enroll.

2) Medical Conditions

a) Women who are pregnant or breastfeeding

b) Any significant acute or chronic medical illness

c) A known or underlying medical condition that, in the opinion of the investigator or Sponsor, could make the administration of study treatment hazardous to the participants or could adversely affect the ability of the participant to comply with or tolerate the study

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

e) Participants with a prior malignancy are excluded. Participants with other second malignancies diagnosed more than 2 years ago who have received therapy with curative intent with no evidence of disease during the interval who are considered by the investigator to present a low risk for recurrence will be eligible.

f) Other active malignancy requiring concurrent intervention

g) Prior organ allograft or allogeneic bone marrow transplantation

h) Any anti-cancer therapy (eg, chemotherapy, biologics, vaccines, or hormonal treatment), including investigational drugs, within 4 weeks prior to the first dose of study drug administration, except for non-cytotoxic therapies, for which at least 4 weeks or 5 half-lives (whichever is shorter) must have elapsed between last dose and first treatment with any study drugs; if 5 half-lives is shorter than 4 weeks, agreement with the Medical Monitor must be obtained.

i) Prior exposure to BMS-986242 or other IDO inhibitor

j) Participants with active, known, or suspected autoimmune disease. Participants with vitiligo, type I diabetes mellitus, residual hypothyroidism due to autoimmune condition only requiring hormone replacement, euthyroid participants with a history of Grave's disease (participants with suspected autoimmune thyroid disorders must be negative for thyroglobulin and thyroid peroxidase antibodies and thyroid-stimulating immunoglobulin prior to first dose of study treatment), psoriasis not requiring systemic treatment, or conditions not expected to recur in the absence of an external trigger are permitted to enroll.

k) Participants with a condition requiring systemic treatment with either corticosteroids (> 10 mg daily prednisone equivalents) or other immunosuppressive medications within 14 days of study treatment administration except for adrenal replacement steroid doses > 10 mg daily prednisone equivalent in the absence of active autoimmune disease

   i) **Note:** Treatment with a short course of steroids (< 5 days) up to 7 days prior to initiating study treatment is permitted.

l) Requirement for daily supplemental oxygen

m) 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) QT interval corrected for heart rate using Fridericia's formula (QTcF) prolongation > 480 msec

   v) History of other clinically significant heart disease (eg, cardiomyopathy, congestive heart failure with New York Heart Association functional classification III to IV, pericarditis, significant pericardial effusion, or myocarditis)

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

n) History of any chronic hepatitis evidenced by:

   i) Positive test for hepatitis B surface antigen

   ii) Positive test for qualitative hepatitis C viral load (by polymerase chain reaction [PCR])

   ***Note**: 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.*

o) History of other preexisting liver disease (eg, nonalcoholic fatty liver disease)

p) Evidence of active infection ≤ 7 days prior to initiation of study treatment (does not apply to viral infections that are presumed to be associated with the underlying tumor type required for study entry)

q) Known history of testing positive for human immunodeficiency virus or known acquired immunodeficiency syndrome

r) Evidence or history of active or latent tuberculosis infection, including PPD, recently converted to positive; chest X-ray with evidence of infectious infiltrate; and recent unexplained changes in fever/chill patterns

s) All toxicities attributed to prior anti-cancer therapy other than alopecia and fatigue must have resolved to Grade 1 (National Cancer Institute Common Terminology Criteria for Adverse Events [NCI CTCAE] v4.03) or baseline before administration of study treatment. Participants with toxicities attributed to prior anti-cancer therapy that are not expected to resolve and result in long-lasting sequelae, such as neuropathy after platinum-based therapy, are permitted to enroll.

t) Participants with a 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 recur with standard countermeasures (eg, hormone replacement after adrenal crisis)

u) Concomitant use of strong inhibitors of CYP3A4 or strong inducers of CYP3A4 (see Appendix 8)

v) Use of non-oncology vaccines containing live virus for prevention of infectious diseases within 12 weeks prior to study treatment. The use of inactivated seasonal influenza vaccines, eg, Fluzone®, will be permitted on study without restriction.

w) Use of packed red blood cells or platelet transfusion within 2 weeks prior to the first dose of study treatment

x) Current or recent (within 3 months of study drug administration) gastrointestinal disease such as chronic or intermittent diarrhea, or uncontrolled disorders that increase the risk of diarrhea, such as inflammatory bowel disease, or other conditions known to interfere significantly with the absorption, distribution, metabolism, or excretion of drugs. Non-chronic conditions (eg, infectious diarrhea) that are completely resolved for at least 2 weeks prior to starting study treatment are not exclusionary.

3) Physical and Laboratory Test Findings

a) Positive tests for hepatitis B virus surface antigen or hepatitis C ribonucleic acid (RNA). (Participants with positive hepatitis C antibody and negative quantitative hepatitis C by PCR are eligible.) Additional testing or substitute testing per institutional guidelines to rule out infection is permitted.

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

i) QRS ≥ 120 msec, except right bundle branch block

ii) QTcF ≥ 480 msec, except right bundle branch block

iii) Second or third degree heart block at Screening (Clinical Pharmacology Substudy only)

c) History of resolved hepatitis A virus infection is not an exclusion criterion.

d) Testing for human immunodeficiency virus must be performed at sites where mandated by local requirements.

4) Allergies and Adverse Drug Reaction

a) History of allergy to nivolumab or related compounds

b) History of any significant drug allergy (such as anaphylaxis or hepatotoxicity) to prior anti-cancer immune-modulating therapies (eg, checkpoint inhibitors and T-cell co-stimulatory antibodies)

5) Other Exclusion Criteria

a) Prisoners or participants who are involuntarily incarcerated (Note: Under certain specific circumstances, a person who has been imprisoned may be included or permitted to continue as a participant. Strict conditions apply, and BMS approval is required.)

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

c) Inability to comply with restrictions and prohibited activities/treatments as listed in Section 6.3

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

6.3.1 Meals and Dietary Restrictions

Grapefruit and Seville oranges and their juices can inhibit CYP3A4 and should not be consumed while on study.

BMS-986242 should be administered following a light meal. However, the participant should avoid heavy meals with high fat content 4 hours prior to until 4 hours after BMS-986242 dose, except for participants in the substudy exploring food effect.

6.3.2 Caffeine, Alcohol, and Tobacco

Not applicable.

6.3.3 Activity

Not applicable.

6.4 Screen Failures

Screen failures are defined as participants who consent to participate in the clinical study but 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 publishing requirements, and to respond to queries from regulatory authorities. Minimal information includes date of consent, demography, screen failure details, eligibility criteria, and any serious AEs.

6.4.1 Retesting During Screening or Lead-in Period

This study permits the re-enrollment of a participant who has discontinued the study as a screen failure. If re-enrolled, the participant must be re-consented.

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

The most current result prior to enrollment 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 may be repeated in an effort to find all possible well-qualified participants. Consultation with the Medical Monitor may be needed to identify whether repeat testing of any particular parameter is clinically relevant.

7 TREATMENT

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

An IP, also known as IMP in some regions, is defined a pharmaceutical form of an active substance or placebo being tested or used as a reference in a clinical study, including products already with

a marketing authorization but used or assembled (formulated or packaged) differently than the authorized form, or used for an unauthorized indication, or when used to gain further information about the authorized form.

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

Both treatments used in this open-label study qualify as IPs, as per previous text, and their description and storage information are described in Table 7-1.

Table 7-1: Study Treatments

Product Description / Class and Dosage Form	Potency	IP/Non-IMP	Blinded or Open Label	Storage Conditions
BMS-986242-01 Film-coated Tablet	25 mg	IP	Open	Per label
BMS-986242-01 Film-coated Tablet	100 mg	IP	Open	Per label
Nivolumab Injection	10 mg/mL (100 mg/vial)	IP	Open	Per label

7.1 Treatments Administered

Participants will be assigned to a specific dose level as listed in Section 5.1.2.1 in sequential order during dose escalation.

The selection and timing of dose for each participant are as follows (Table 7.1-1):

Table 7.1-1: Selection and Timing of Dose

Study Treatment	Unit Dose Strength(s)/ Dosage Level(s)	Dosage Formulation Frequency of Administration	Route of Administration
BMS-986242	12.5-600 mg (dose levels 1-7)	QD	PO
Nivolumab	480 mg (flat dose)	Q4W	IV

Abbreviations: PO = per os, orally.

BMS-986242 (Part 1 and Part 2)

BMS-986242 should be administered in the morning following a light meal, approximately 24 hours apart. On the morning of Days 1 and 14, after an overnight fast of at least 10 hours, each participant will receive a single oral dose of BMS-986242 within, approximately, 5 minutes of completing a light meal. At the time of dosing, approximately 240 mL of water will be

administered to the participant along with BMS-986242. Serial PK samples will be collected on Days 1 and 14. The time of BMS-986242 administration will be called "0" hour. A description of a sample light breakfast meal is provided in Table 7.1-2.

Table 7.1-2: Representative Light Breakfast Meal

Food Item	Calories (kcal)	Fat (g)	Carbohydrates (g)	Protein (g)
2 slices of white bread	128	1.8	24.0	4.0
1 teaspoonful low-fat margarine	26	2.9	trace	trace
1 tablespoon jam	56	trace	13.8	trace
5 oz apple juice	71	0.2	17.5	0.2
5 oz skim (nonfat) milk	54	0.3	7.5	5.3
Total grams (g)	-	5.2	62.8	9.5
Total calories (kcal)	335	47	251	38
% of total calories	100	14	75	11

Source: US Department of Agriculture Nutrient Database for Standard Reference, Release 28 (September 2015)[48]

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Fasting Treatment: Following an overnight fast of at least 10 hours, participants should be administered BMS-986242 with approximately 240 mL of water. No food should be allowed for at least 4 hours postdose. Water is allowed ad libitum except for 1 hour before and 1 hour after drug administration.

High-fat Meal Treatments: Following an overnight fast of at least 10 hours, participants will start the recommended meal 30 minutes prior to administration of BMS-986242. Study participants should eat this meal within 30 minutes or less; however, BMS-986242 should be administered 30 minutes after the start of the meal. BMS-986242 should be administered with approximately 240 mL of water. No food should be allowed for at least 4 hours postdose. Water is allowed ad libitum except for 1 hour before and 1 hour after drug administration.

A high-fat (approximately 50% of total caloric content of the meal) and high-calorie (approximately 800 to 1,000 calories) meal is recommended for the high-fat test meal treatment. This test meal should derive approximately 150, 250, and 500 to 600 calories from protein, carbohydrate, and fat, respectively. A description of a sample high-fat breakfast meal is provided in Table 7.1-3.

Table 7.1-3: Representative High-fat Breakfast

Food Item[a]	Calories (kcal)	Fat (g)	Carbohydrates (g)	Protein (g)
2 eggs fried	180	13.7	0.8	12.5

Table 7.1-3: Representative High-fat Breakfast

Food Item[a]	Calories (kcal)	Fat (g)	Carbohydrates (g)	Protein (g)
2 slices of white bread toasted	128	1.8	24.0	4.0
1 tablespoon butter	102	11.5	trace	0.1
2 strips of bacon fried	108	8.1	0.4	7.8
4 ounces of hash brown potatoes	207	9.8	27.4	2.3
8 fluid ounces (237 mL) of whole milk	149	8.0	11.7	7.7
Total grams (g)	-	52.9	64.3	34.4
Total calories (kcal)	874	477	257	138
% of total calories	100	55	29	16

[a] Substitutions in this test meal can be made as long as the meal provides a similar amount of calories from protein, carbohydrate, and fat and has a comparable meal volume and viscosity.

Source: US Department of Agriculture Nutrient Database for Standard Reference, Release 28 (September 2015)[48]

Restrictions related to food and fluid intake are described in Section 6.3.1.

Nivolumab (Part 1 and Part 2)

During combination treatment, infusion of nivolumab should start approximately 30 minutes following BMS-986242. Nivolumab should be infused over 30 minutes. Further details regarding preparation and administration will be provided separately in site/pharmacy training materials.

Nivolumab will be administered IV as a flat dose. There will be no dose escalations or reductions of nivolumab allowed once assigned. There are no premedications recommended for nivolumab on the first cycle. If an acute infusion reaction is noted, participants should be managed according to Section 7.7.1.5.

7.2 Method of Treatment Assignment

During the screening visit, the investigative site will call into the enrollment option of the IRT designated by BMS for assignment of a 5-digit participant number that will be unique across all sites. Enrolled participants, including those not dosed, will be assigned sequential participant numbers starting with 00001 (eg, 00001, 00002, 00003… 00010). The participant identification number will ultimately be composed of the site number and participant number. For example, the first participant screened (ie, enrolled) at site number 1 will have a participant identification number of 0001 00001. Once it is determined that the participant meets the eligibility criteria following the screening visit, the investigator site will call the IRT within 3 days prior to the first study treatment administration for the participant to be assigned to a treatment group.

During dose escalation, participants who are not evaluable for DLT determination may be replaced. Replacement participants will be assigned to the same treatment but will be assigned a new participant number.

7.3 Blinding

Not applicable.

7.4 Dosage Modification

7.4.1 Dose-limiting Toxicity

For the purpose of guiding dose escalation, DLTs will be defined based on the incidence and grade of AEs for which no alternate cause can be identified.

Part 1: Cycle 0 BMS-986242 (monotherapy lead-in) will have a 2-week DLT evaluation period (DLT1). The combination regimen will have 4-week DLT evaluation period (DLT2). Therefore, the total DLT assessment period is 6 weeks. Participants may proceed from Cycle 0 to Cycle 1 at each cohort unless any of the following events is observed: any DLT, Grade 2 or higher immune-related AEs considered related to BMS-986242 (eg, immune-mediated pneumonitis, colitis, hepatitis, nephritis, renal dysfunction) with the exception of immune-mediated hypothyroidism and hyperthyroidism, or Grade 2 AST and ALT elevation that does not resolve to Grade 1 within 1 week. For Grade 2 AST and ALT elevations that resolve to Grade 1 or baseline within 1 week, participants can be rechallenged with BMS-986242 monotherapy for a minimum of 5 days before proceeding to combination with nivolumab provided there is not a recurrence of Grade 2 event.

The total DLT period is 6 weeks, and participants must have received at least 75% of the BMS-986242 doses and 1 dose of nivolumab with observation for a minimum of 21 days following the first combination treatment dose to be considered evaluable for dose escalation decisions. Based on the predicted human half-life of BMS-986242 of 13 hours, this interval is expected to cover the anticipated timeframe for the occurrence of clinically significant immediate and early-onset AEs related to BMS-986242 monotherapy during Cycle 0 and repeat dosing of BMS-986242 in combination with nivolumab in Cycle 1.

The incidence of DLTs that occur within 6 weeks following the start of study treatment will guide dose escalation decisions. AEs will be graded according to the NCI CTCAE v4.03. For the purposes of participant management, study treatment-related AEs occurring at any time that meet the DLT definition will lead to dose interruption, dose modifications, and/or permanent discontinuation of study treatment as defined in Section 8. Participants who withdraw from the study during the DLT evaluation interval for reasons other than a DLT may be replaced at the same dose level. The incidence of DLT(s) during the first cycle of treatment (the DLT evaluation period) will be used in dose escalation decisions and to define the MTD. AEs occurring after the DLT period will be considered for the purposes of defining the MTD, upon agreement between the Sponsor/Medical Monitor and investigators, if they are determined to have no clear alternative cause and are not related to disease progression.

For the purpose of guiding dose escalation, DLTs are defined below based on the incidence and grade of AEs for which no alternate cause can be identified.

Guidelines for management algorithms for immuno-oncology (I-O) agents and treatment of study treatment-related infusion reactions are provided in Sections 7.7.1.4 and 7.7.1.5, respectively.

7.4.1.1 Dose-limiting Toxicities

Dose-limiting Toxicities for DLT1 and DLT2 Periods

Nonhematologic DLT:

A. Hepatic, Nonhematologic DLT

Any of the following events will be considered a hepatic DLT:

- Any ≥ Grade 3 elevation of AST, ALT, or total bilirubin
- Grade 2 AST or ALT with symptomatic liver inflammation (eg, right upper quadrant tenderness, jaundice, pruritus)
- AST or ALT > 3× ULN and concurrent total bilirubin > 2× ULN without initial findings of cholestasis (elevated serum alkaline phosphatase; eg, findings consistent with Hy's law or Food and Drug Administration definition of potential drug-induced liver injury [DILI])*

*Note that this special category of DLT uses ULN rather than Common Toxicity Criteria Grade for definition.

B. Nonhepatic, Nonhematologic DLT

Any of the following events will be considered a nonhepatic, nonhematologic DLT:

- Grade 2 or greater epscleritis, uveitis, or iritis
- Any other Grade 2 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
- Any Grade 3 or greater nondermatologic, nonhepatic, nonhematologic toxicity will be considered a DLT with the following specific EXCEPTIONS:
  - Grade 3 or Grade 4 electrolyte abnormalities that are not complicated by associated clinical adverse experiences, last less than 48 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
  - Isolated Grade 3 elevation of amylase or lipase not associated with clinical or radiographic evidence of pancreatitis
  - Isolated Grade 3 fever not associated with hemodynamic compromise (eg, 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 site of known or suspected tumor)
  - Grade 3 fatigue
  - Grade 3 infusion reaction that returns to Grade 1 in less than 6 hours

C. Dermatologic DLT

- Grade 3 rash if no improvement (ie, resolution to ≤ Grade 1) after a 1- to 2-week infusion delay. Participants who have not experienced a Grade 3 study treatment-related skin AE may resume treatment in the presence of Grade 2 skin toxicity.

- Grade 4 rash of any duration.

D. Hematologic DLT

- Grade 4 neutropenia ≥ 5 days in duration
- Grade 4 thrombocytopenia or Grade 3 thrombocytopenia with bleeding or any requirement for platelet transfusion
- Grade ≥ 3 febrile neutropenia for 48 hours
- Grade ≥ 3 hemolysis (ie, requiring transfusion or medical intervention such as steroids)
- Grade 4 anemia not explained by underlying disease
-
- In addition to the above criteria, any toxicity that results in a participant not receiving at least 75% of the doses of BMS-986242 and the dose of nivolumab during the DLT evaluation period or causing greater than 2 weeks of dose delay will be classified as a DLT.

7.4.2 Guidelines for Dose Modification

Participants will be monitored continuously for AEs while on study treatment. Participants will be instructed to notify their physician immediately for any and all AEs. The criteria presented in this section and Table 7.4.2-1 for dose modifications for BMS-986242 and delays are meant as general guidelines.

Participants will continue to receive study treatment as long as they have not had disease progression or study treatment-related AEs requiring dose modification as described below.

- Dose modification, interruption, or delay may occur in the setting of a lower-grade AE and/or be more conservative than indicated in Table 7.4.2-1 based on the clinical judgment of the investigator and in consultation with the Sponsor/Medical Monitor.
- Dose reductions of BMS-986242 should be to the previous lower dose level.
- If several AEs of varying grades or severities occur simultaneously, the dose modification applied should be the greatest reduction applicable.
- Assessment of causality (chronology, confounding factors such as disease, concomitant medications, diagnostic tests, and previous experience with the agent) must be determined and documented by the investigator prior to dose modification.
- If the same AE recurs despite a dose reduction, a second dose reduction versus discontinuation of BMS-986242 will be discussed and agreed upon by the Sponsor/Medical Monitor and investigators.
- No more than 2 dose reductions of BMS-986242 will be allowed per participant. If a third dose reduction is required, the participant must discontinue BMS-986242. Dose re-escalation after a dose reduction may occur in limited circumstances (such as a change in attribution of an AE) after discussion and agreement of the Sponsor/Medical Monitor and investigators.
- Skipped doses will not be administered within the same cycle.
- For an AE requiring dose modification, BMS-986242 and nivolumab should be interrupted to allow recovery from the AE. Re-initiation of study treatment cannot occur until AE decreases to ≤ Grade 1 or baseline assessment. In case of delayed recovery to ≤ Grade 1 or baseline (except for alopecia) from treatment-related AEs that results in a delay of treatment for > 6 weeks, the participant will not receive additional protocol-related treatment and will be removed from study unless discussed and agreed upon by the Sponsor/Medical Monitor and

investigators that it is in the best interest of the participant to receive additional treatment with BMS-986242 and nivolumab (eg, if the participant has demonstrated a response to treatment).

- During the DLT evaluation period, if a participant receives dose reduction and experiences a DLT at the lower dose, this DLT will be attributed to the highest dose level administered.
- For data collection and analysis purposes, all participants will continue to be classified by the original treatment arm.

Table 7.4.2-1: Dose Modifications

Dose Modification Criteria for Study Treatment-Related Adverse Events	BMS-986242 Monotherapy Modification at the Next Dose	BMS-986242 Combination Modification at the Next Dose
QTcF > 500 msec confirmed by at least 1 repeat ECG and at least 60 msec above baseline	Interrupt if needed to optimize electrolyte management. If event persists after electrolyte optimization (including dose modification of BMS-986242, if necessary), discontinue. Participants may proceed to get nivolumab monotherapy.	Interrupt if needed to optimize electrolyte management. If event persists after electrolyte optimization (including dose modification of BMS-986242, if necessary), discontinue. However, treatment with nivolumab may continue after discussion between PI and Medical Monitor.
Any other study treatment-related ≥ Grade 3 adverse event that does not meet permanent discontinuation criteria (Section 8)	Decrease 1 level of BMS-986242 (no lower than 25 mg).	Decrease 1 level of BMS-986242 (no lower than 25 mg) in combination with same dose of nivolumab.
Grade 2 LFT abnormalities that do not resolve within 1 week	Interruption of BMS-986242 Continuation of BMS-986242 at a lower dose level may be considered after discussion with the Study Director/Medical Monitor. Participants may proceed to get nivolumab monotherapy.	NA
Grade 2 LFT abnormalities that resolve in 1 week	Interrupt dosing until improvement to Grade 1 or baseline and resume at same dose. If recurrence of Grade 2 LFT elevations, decrease 1 level.	NA

Abbreviations: LFT = liver function test; QTcF = QT interval corrected for heart rate using Fridericia's formula; NA = not applicable; PI = principal investigator.

7.4.3 Dose Delays Due to Toxicity

- Participants who experience a DLT must have study treatment held. Participants who are required to permanently discontinue both study treatments are listed in Section 8.2. In addition, all Grade 2 hepatic, pulmonary, renal, gastrointestinal, and neurological AEs should be evaluated and managed per the toxicity management algorithms for immuno-oncology agents (see Appendix 9). Participants not meeting guidelines for permanent discontinuation will be

permitted to resume study treatment based on the criteria specified below in Section 7.4.4. Participants eligible to resume study treatment will resume study treatment at the treatment visit following their last received study treatment dose.

- The end of cycle tumor assessments (ie, CT/MRI, positron emission tomography [PET], etc) will continue on an every-8-week schedule relative to the participant's first dose regardless of any treatment delay incurred.

7.4.4 Criteria to Resume Treatment

Participants experiencing AEs not meeting criteria for permanent discontinuation as outlined in Section 8.1 and Section 8.2 may resume treatment with study treatment under the following criteria:

- Participants may resume treatment with study treatment when the study treatment-related AE(s) resolves 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 study treatment-related skin AE may resume treatment in the presence of Grade 2 skin toxicity.
- Participants with Grade 2 uveitis or eye pain or blurred vision not meeting DLT criteria (Section 7.4.1) must resolve to baseline prior to resuming study treatment.
- Study treatment-related pulmonary toxicity, diarrhea, or colitis must have resolved to baseline before treatment is resumed.
- Participants with study treatment-related endocrinopathies adequately controlled with only physiologic hormone replacement may resume treatment.
- If the criteria to resume treatment are met, the participant should restart treatment at the next scheduled time point per protocol.
- The consideration to re-initiate study treatment under these exceptions will be made on a case-by-case basis after considering the overall benefit/risk profile and in consultation between the investigator and the study Sponsor. Any AE with clinical risk will be assessed on a case-by-case basis with the investigator and the BMS Medical Monitor to determine the risks and benefits of continuing on study treatment following resolution versus discontinuing study treatment permanently.
- If treatment with study treatment is delayed > 6 weeks, the participant must be permanently discontinued from study treatment, except as specified in Section 7.4.2.

7.4.5 Guidelines for Permanent Discontinuation Secondary to Adverse Events

Participants will be required to permanently discontinue both study treatments for the following AEs:

- Clinical deterioration, as assessed by the investigator
- Grade 3 infusion reaction that does not return to Grade 1 in less than 6 hours
- Grade 3 pneumonitis, bronchospasm, neurologic toxicity, uveitis, or myocarditis
- Life-threatening skin toxicity (toxic epidermal necrolysis)

- Any Grade 4 AE; however, an exception may be made for the following upon consultation between the investigator and BMS Medical Monitor:
  - Grade 4 electrolyte abnormalities < 72 hours in duration
  - Grade 4 neutropenia < 7 days in duration
  - Grade 4 lymphopenia
  - Grade 4 increase in amylase or lipase that is not associated with clinical or radiographic evidence of pancreatitis
- Abnormal liver function tests meeting criteria for a potential DILI.
- Any dosing delay lasting > 6 weeks will be cause for permanent discontinuation. Extensions to the period of dose delays may be granted for individual participants on a case-by-case basis after specific consultation and agreement between the investigator and BMS Medical Monitor in settings where benefit/risk may justify continued study treatment (eg, participant deriving clinical benefit who requires prolonged steroid taper for management of non-DLT immune-related AEs or experiences delays for management of a non-treatment-related AE).
- Accordingly, dosing delays to allow for prolonged steroid tapers to manage study treatment-related AEs are allowed. Additionally, dosing delays > 6 weeks that occur for non-treatment-related reasons may be allowed if approved by the BMS Medical Monitor.
- The consideration to re-initiate study treatment under these exceptions will be made on a case-by-case basis after considering the overall benefit/risk profile and in consultation between the investigator and the Sponsor.
- Prior to re-initiating treatment in a participant with a dosing delay lasting > 6 weeks, the BMS Medical Monitor must be consulted.
- Tumor assessments should continue per protocol even if dosing is delayed.

All participants who discontinue the IP should comply with protocol-specified follow-up procedures as outlined in Section 8.2. The only exception to this requirement is when a participant withdraws consent for all study procedures, including post-treatment study follow-up, or loses the ability to consent freely (eg, is imprisoned or involuntarily incarcerated for the treatment of either a psychiatric or physical illness).

If study 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.

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 study treatment is accurately administered. This includes documentation of study treatment storage, administration and, as applicable, storage temperatures, reconstitution, and use of required processes (eg, required diluents, administration sets).

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

7.5.1 Retained Samples for Bioavailability/Bioequivalence

Not applicable.

7.6 Treatment Compliance

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

BMS-986242 will be administered on an outpatient basis, except when participants are seen in the clinic for administration of nivolumab, assessment of AEs, PK sample collection, and laboratory evaluation. At those visits, the participant will take BMS-986242 at the clinic.

7.7 Concomitant Therapy

7.7.1 Prohibited and/or Restricted Treatments

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

7.7.1.1 Prohibited Therapies

A. Prior exposure to BMS-986242 or other IDO inhibitor

B. Concurrent administration of any anti-cancer therapies (investigational or approved) with the exception of participants in the follow-up and survival period of the study

C. Concomitant use of strong inhibitors of CYP3A4 or strong inducers of CYP3A4 (see Appendix 8)

D. Drugs that may prolong QT intervals are prohibited during Cycle 00 of the clinical pharmacological substudy. See Appendix 10 for a list of common medications associated with QT prolongation.

E. Immunosuppressive agents (except as stated in Section 7.7.1.3) unless they are utilized to treat an AE

F. Participants receiving RANK-L inhibitors or bisphosphonates are permitted as clinically indicated but should be avoided, if possible, prior to completion of Cycle 1.

G. Palliative radiotherapy is permitted only under certain conditions as described in Section 6.1.

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.

The investigator should contact and confirm agreement with the BMS Medical Monitor (and acknowledgement from the contract research organization Medical Monitor) prior to the administration of any concomitant medications.

[redacted]

[redacted]

7.8 Treatment After the End of the Study

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

8 DISCONTINUATION CRITERIA

8.1 Discontinuation from Study Treatment

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

- Participant's request to stop study treatment. Participants who request to discontinue study treatment will remain in the study and must continue to be followed for protocol-specified follow-up procedures. The only exception to this is when a participant specifically withdraws consent for any further contact with him/her or persons previously authorized by participant to provide this information.
- Any clinical AE, laboratory abnormality, or intercurrent illness, which, in the opinion of the investigator, indicates that continued participation in the study is not in the best interest of the participant
- Termination of the study by 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
- Inability to comply with protocol
- Discretion of the investigator
- Pregnancy
- Completion of study-required procedures
- Documented and confirmed PD as defined by RECIST v1.1 (see Appendix 6) unless participant meets criteria for treatment beyond progression (Section 5.1.2.3)
- Clinical deterioration while receiving active study treatment that, in the opinion of the investigator, indicates that continued participation in the study is not in the best interest of the participant
- Protocol-defined reasons for discontinuation (see Section 7.4.5)

Refer to the Schedule of Activities (Section 2) for data to be collected at the time of treatment discontinuation and follow-up and for any further evaluations that can be completed.

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

Discontinuation of the study treatment for abnormal liver tests should be considered by the investigator when a participant meets the conditions outlined in Section 9.2.7.

8.1.1 Post Study Treatment Study Follow-up

Poststudy 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 for collection of outcome and/or survival follow-up data as required and in line with Section 5.1.3 until death or the conclusion of the study.

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 the 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 as the inability to reach the participant after a minimum of 3 documented phone calls, faxes, or emails as well as lack of response by the 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 the date and cause of death.
- If the investigator's use of a third-party representative to assist in the follow-up portion of the study has been included in the participant's informed consent, then the investigator may use a Sponsor-retained third-party representative to assist site staff with obtaining the participant's contact information or other public vital status data necessary to complete the follow-up portion of the study.
- The site staff and representative will consult publicly available sources, such as public health registries and databases, in order to obtain updated contact information.
- If after all attempts, the participant remains lost to follow-up, then the last known alive date as determined by the investigator should be reported and documented in the participant's medical records.

9 STUDY ASSESSMENTS AND PROCEDURES

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

9.1 Efficacy Assessments

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. Data for these assessments, however, 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.

Disease assessment with CT and/or MRI, as appropriate, will be performed at baseline, the end of Cycle 2, and every 8 weeks until disease progression, at the completion of follow-up, or until participants withdraw from the study (every 12 weeks for the first year after the EOT visit and then every 6 months thereafter up to 2 years from the last dose of study treatment). Disease assessments at other time points may be performed if the investigator is concerned about tumor progression. Assessment of tumor response will be reported based on investigator assessed tumor measurements as defined by RECIST v1.1 (see Appendix 6) for participants with solid tumors.

Investigators will also report the number and size of new lesions that appear while on study. The time point tumor assessments will be reported on the CRF based on investigators' assessment using RECIST.

9.1.1 Imaging Assessment for the Study

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.

Body Imaging

CT with contrast is the preferred modality (MRI if CT is not feasible). Assessment should include the chest/abdomen/pelvis at a minimum; and other known/suspected sites of disease should be performed.

Disease assessment with CT and/or MRI as appropriate will be performed at baseline and as follows:

- **Parts 1 and 2:** end of Cycle 2 and then every 8 weeks throughout the treatment period and every 12 weeks for the first year after the EOT visit, and then every 6 months thereafter, up to 2 years from the last dose of study treatment during the follow-up period.

Disease assessments at other time points may be performed as clinically indicated.

Brain Imaging

Brain imaging is only required at screening for participants with known history or symptoms of brain metastases and who have not had brain imaging within 30 days of anticipated first study treatment administration. After screening, brain imaging is required only as clinically indicated.

Bone Scan

Bone scans may be performed as clinically indicated at baseline (eg, participants with history of symptoms of bone metastases), but bone scans will not be considered a modality for assessment for measurable disease. After baseline, bone scans are required only as clinically indicated.

Imaging Modalities

For all the solid tumor types, the following imaging assessments should be performed at a study-specified schedule: CT of the chest, CT or MRI of the abdomen, pelvis, and other known sites of disease, which is also summarized Table 9.1.1-1:

Table 9.1.1-1: Acceptable Imaging Assessment Methods for Different Anatomic Regions

Anatomic Region	Preferred Method	Alternative Methods
Chest, abdomen, and pelvis Note: Scan must cover lung apices to diaphragm, diaphragm through entire liver, and to below the pubic symphysis	CT with IV contrast	**For chest:** • CT without contrast can be used only if the participant has a clinical contraindication for iodine-based IV contrast (eg, hypersensitivity, renal insufficiency) **For abdomen and pelvis:** • MRI with gadolinium-based IV contrast is the first alternative method if the participant has a clinical contraindication for iodine-based IV contrast

Table 9.1.1-1: Acceptable Imaging Assessment Methods for Different Anatomic Regions

Anatomic Region	Preferred Method	Alternative Methods
		• CT without contrast can be used as the second alternative method only if the participant has a clinical contraindication for both contrast-enhanced CT and MRI.
Brain	MRI with IV contrast	• CT with IV contrast is the first alternative method if IV gadolinium is clinically contraindicated. • MRI without contrast can be used as a second alternative method if a participant has clinical contraindications for both contrast-enhanced CT and MRI

In all study parts, scans will be collected centrally and may be reviewed by a blinded independent central review at a later date or at any time during the study per Sponsor request.

9.1.2 Secondary Efficacy Assessment

The efficacy assessments will include the overall response rate (ORR) (eg, PR + CR rate), duration of response (DOR), and PFSR at time points (eg, 6, 9, 12, and 24 months) based on the assessment of tumor response using RECIST v1.1 criteria.

[redacted]

9.2 Adverse Events

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

AEs will be reported by the participant (or, when appropriate, by a caregiver, 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 are specified in Appendix 3**.**

9.2.1 Time Period and Frequency for Collecting AE and SAE Information

The collection of nonserious AE information should begin at initiation of study treatment until 100 days after discontinuation of study treatment, at the time points specified in the Schedule of Activities (Section 2). Nonserious AE information should also be collected from the start of a placebo lead-in period or other observational period intended to establish a baseline status for the participants.

Sections 5.6.1 and 5.6.2 in the IB represent the Reference Safety Information to determine expectedness of SAEs for expedited reporting. Following the participant's written consent to participate in the study, all SAEs, whether related or not related to study treatment, must be collected, including those thought to be associated with protocol-specified procedures.

All SAEs must be collected from the date of participant's written consent until 100 days after discontinuation of nivolumab or participation in the study (if the last scheduled visit occurs at a later time).

Medical occurrences that begin before the start of study treatment but after obtaining informed consent will be recorded on the appropriate section of the electronic CRF.

- All SAEs will be recorded and reported to the Sponsor or designee within 24 hours, as indicated in Appendix 3.
- The investigator will submit any updated SAE data to the Sponsor within 24 hours of this being available.

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

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

9.2.2 Method of Detecting AEs and SAEs

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

9.2.3 Follow-up of AEs and SAEs

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

After the initial AE/SAE report, the investigator is required to proactively follow each participant at subsequent visits/contacts. All SAEs will be followed until resolution, until the condition stabilizes, until the event is otherwise explained, or until the participant is lost to follow-up (as defined in Section 8.3).

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

9.2.4 Regulatory Reporting Requirements for SAEs

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

The 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 Food and Drug Administration Code of Federal Regulations 21 CFR Parts 312 and 320. A Suspected, Unexpected Serious Adverse Reaction is a subset of SAEs and will be reported to the appropriate regulatory authorities and investigators following local and global guidelines and requirements.

9.2.5 Pregnancy

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

In most cases, the study treatment will be permanently discontinued in an appropriate manner (eg, dose tapering if necessary for participant safety). Please call the BMS Medical Monitor within 24 hours of awareness of the pregnancy.

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

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

Any pregnancy that occurs in a female partner of a male study participant should be reported to Sponsor or designee. In order for Sponsor or designee to collect any pregnancy surveillance

information from the female partner, the female partner must sign an ICF for disclosure of this information. Information on this pregnancy will be collected on the Pregnancy Surveillance Form.

9.2.6 Laboratory Test Result Abnormalities

The following laboratory test result abnormalities should be captured on the nonserious AE CRF page or electronic SAE Report Form, 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 Potential Drug-induced Liver Injury

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

Potential DILI is defined as:

- AT (ALT or AST) elevation > 3×ULN

AND

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

AND

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

9.2.8 Other Safety Considerations

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

9.3 Overdose

For this study, any dose of BMS-986242 greater than the assigned dose and considered both excessive and medically important by the investigator in consultation with the Medical Monitor will be considered an overdose. All occurrences of overdose must be reported as SAEs (see Section 9.2)

In the event of an overdose, the investigator/treating physician should:

- Contact the Medical Monitor immediately
- Closely monitor the participant for AEs/SAEs and laboratory abnormalities until BMS-986242 can no longer be detected systemically (at least 7 days)
- Obtain a plasma sample for PK analysis within 3 days from the date of the last dose of study treatment 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

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

9.4.1 Physical Examinations

Refer to the Schedule of Activities for timing of assessments in Section 2.

9.4.2 Vital Signs

Refer to the Schedule of Activities for timing of assessments in Section 2.

9.4.3 Electrocardiograms

Refer to the Schedule of Activities for timing of assessments in Section 2.

For the purposes of monitoring participant safety, investigators will review 12-lead ECGs per the protocol-specified schedule as outlined in time and events tables (see Section 2) using their site's standard ECG machines.

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 up to 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 BMS, either recorded 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: Laboratory Assessments

Hematology	
Hemoglobin Hematocrit Total leukocyte count, including differential Platelet count	
Serum Chemistry	
Aspartate aminotransferase Alanine aminotransferase Total bilirubin Direct bilirubin Alkaline phosphatase Lactate dehydrogenase Creatinine Blood urea nitrogen Uric acid Glucose (Fasting at screening only) Amylase Lipase HDL, LDL	Total Protein Albumin Sodium Potassium Chloride Total serum calcium Phosphorus Magnesium Creatinine clearance- screening only Bicarbonate/Carbon dioxide Ferritin PTT/PT
Gamma-glutamyl transferase only when alkaline phosphatase increases to Grade ≥2.	
Urinalysis	
Protein Glucose Blood Leukocyte esterase Specific gravity pH Microscopic examination (performed if blood, protein, or leukocyte esterase is present on dipstick)	
Serology	
Serum for hepatitis C antibody (if hepatitis C antibody is positive reflex to hepatitis C RNA) or hepatitis C RNA, hepatitis B surface antigen; HPV status; and HIV-1 and HIV-2 antibody. (Testing for HIV-1, HIV-2 must be performed at sites where mandated by local requirements)	
Other Analyses	
Serum or urine pregnancy test (WOCBP only) TSH with reflex testing to free T3 and free T4 if TSH is abnormal. FSH (if needed to document postmenopausal status)	

9.4.5 Suicidal Risk Monitoring

Not applicable.

9.4.6 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 Pharmacokinetic

9.5.1 Pharmacokinetic Assessment Following BMS-986242 Monotherapy

The PK of BMS-986242 and its metabolites (if applicable) will be derived from plasma concentration versus time and urinary excretion data. Individual participant PK parameter values will be derived by noncompartmental methods by a validated PK analysis program. Actual times will be used for the analyses.

The PK parameters to be assessed for BMS-986242 and selected metabolites following single-dose administration in Cycle 00 and multiple-dose administration in Cycle 0 include but are not limited to:

Cmax	Maximum observed plasma concentration
Tmax	Time of maximum observed plasma concentration
AUC(0-T)	Area under the concentration-time curve from 0 to last observed collection time (clinical pharmacology substudy)
AUC(INF)	Area under the concentration-time curve from 0 extrapolated to infinity time (clinical pharmacology substudy only)
AUC(TAU)	Area under the concentration-time curve in 1 dosing interval
Ctrough	Trough observed plasma concentration at the end of the dosing interval
CLT/F	Apparent total body clearance
Vss/F	Apparent volume of distribution at steady-state
T-HALF	Apparent terminal phase half-life
AI	Accumulation index, calculated based on ratio of AUC and Cmax at steady state to after the first dose
%UR24	Percent urinary recovery over 24 hours
%UR72	Percent urinary recovery over 72 hours (clinical pharmacology substudy only)

In addition, the following PK parameters for select BMS-986242 metabolites may also be assessed if data permit:

MR_Cmax	Ratio of metabolite Cmax to parent Cmax, corrected for molecular weight
MR_AUC(TAU)	Ratio of metabolite AUC(TAU) to parent AUC(TAU), corrected for molecular weight
MR_AUC(0-T)	Ratio of metabolite AUC(0-T) to parent AUC(0-T), corrected for molecular weight (clinical pharmacology substudy only)
MR_AUC(INF)	Ratio of metabolite AUC(INF) to parent AUC(INF), corrected for molecular weight (clinical pharmacology substudy only)

9.5.2 Pharmacokinetic Assessment Following Combination Treatment with BMS-986242 and Nivolumab

Plasma samples for BMS-986242 will be collected for all participants receiving combination treatment with BMS-986242 and nivolumab. Plasma concentration data will be tabulated using summary statistics. These data, together with data from the monotherapy, may also be pooled with other datasets for PPK analysis, which will be presented in a separate report.

Serum samples for nivolumab PK and immunogenicity assessments will be collected for all participants receiving combination treatment of BMS-986242 and nivolumab. End-of-infusion and trough concentrations will be tabulated using summary statistics. These data may also be pooled with other datasets for PPK analysis, which will be presented in a separate report.

9.5.3 Pharmacokinetics: Collection and Processing

Detailed sampling schedules to be followed for the assessment of PK and immunogenicity for all analytes in the study are provided in Table 9.5.3-1. All time points are relative to the start of BMS-986242 dosing. Predose samples should be taken within 30 minutes before the start of BMS-986242 administration. Nivolumab end-of-infusion samples should be taken just prior to the end of infusion (preferably within 2 minutes). Further details of sample collection, processing, and shipment will be provided in the laboratory procedures manual. On-treatment PK samples are intended to be drawn relative to actual dosing days; if a dose occurs on a different day within the cycle due to delays or minor schedule adjustments, PK samples should be adjusted accordingly.

Table 9.5.3-2 lists the PK sampling and ECG collection schedules to be followed for the clinical pharmacology substudy (Cycle 00). Serial ECGs (reviewed by a core laboratory) will be collected with matching PK samples. Twelve-lead continuous ECG (Holter) will be used in the QTc substudy. Each ECG time point will be collected in triplicates. ECGs should be performed after the participant has been resting supine for at least 10 minutes and should be completed prior to any PK/pharmacodynamic sample blood collections when assessments occur at the same time points. All serial ECGs will be transmitted to a central laboratory for measurement of intervals and classification of ECG abnormalities. At the end of the clinical pharmacology substudy, participants will follow PK collection schedule after BMS-986242 + nivolumab combination treatment provided in Table 9.5.3-1.

Table 9.5.3-1: Pharmacokinetic, Anti-drug Antibody (ADA/Immunogenicity) Sampling Schedule for BMS-986242 and Nivolumab (Dose Escalation Part 1 and Dose-Expansion Cohorts Part 2)

Study Day of Sample Collection	Event	Time (Relative To BMS-986242 Dosing) Hour:Min	BMS-986242 and Metabolites Plasma Sample	BMS-986242 Plasma Sample (Biotransformation)	BMS-986242 and Metabolites Urine Sample	Nivolumab Serum Sample	Nivolumab ADA Sample
C0D1	Predose	00:00					
		01:00	X		X (0-8 h)		
		02:00	X				
		03:00	X				
		04:00	X				
		06:00	X				
		08:00	X				
C0D2	Predose	00:00	X		X (8-24 h)		
C0D8	Predose	00:00	X				
C0D14	Predose	00:00	X	X			
		01:00	X	X			
		02:00	X	X			
		03:00	X	X			
		04:00	X	X			
		06:00	X	X			
		08:00	X	X			
C0D15	Predose[a]		X	X			
C1D1	Predose	00:00	X	X		X	X

Table 9.5.3-1: Pharmacokinetic, Anti-drug Antibody (ADA/Immunogenicity) Sampling Schedule for BMS-986242 and Nivolumab (Dose Escalation Part 1 and Dose-Expansion Cohorts Part 2)

Study Day of Sample Collection	Event	Time (Relative To BMS-986242 Dosing) Hour:Min	BMS-986242 and Metabolites Plasma Sample	BMS-986242 Plasma Sample (Biotransformation)	BMS-986242 and Metabolites Urine Sample	Nivolumab Serum Sample	Nivolumab ADA Sample
	EOI[b]	01:00	X			X	
		02:00	X				
		04:00	X				
C3D1	Predose	00:00	X			X	X
	EOI	01:00	X			X	
Every 4 Cycles from C5D1	Predose	00:00	X			X	X
EOT			X			X	X
FUc[c]			X			X	X

Note: Each treatment cycle is 4 weeks (except Cycle 0).

Abbreviations: ADA = anti-drug antibody; EOI = end of infusion; FU = follow-up.

[a] This sample should be taken 24 hours after the previous BMS-986242 dose on Cycle 0 Day 14 if Cycle 1 Day 1 does not occur on the next day after Cycle 0 Day 14.

[b] This sample should be taken preferably within 2 minutes prior to the end of infusion. If the end of infusion is delayed to beyond the nominal infusion duration, the collection of this sample should also be delayed accordingly.

[c] Performed at the first 2 follow-up visits (up to 100 days from the EOT visit) EXCEPT for participants who have WITHDRAWN CONSENT.

Table 9.5.3-2: Pharmacokinetic Sampling and ECG Collection Schedule for BMS-986242 in the Clinical Pharmacology Substudy

Study Day of Sample Collection	Event	Time (Relative to BMS-986242 Dose) Hour: Min	BMS-986242 and Metabolites Plasma Sample	BMS-986242 and Metabolites Urine Sample	ECG
C00D1	Predose	-01:00			X
C00D1	Predose	-00:45			X
C00D1	Predose	-00:30			X
C00D1	Predose	00:00			
		01:00	X	X (0-8 h)	
		01:45			X
		02:00	X		
		02:45			X
		03:00	X		
		03:45			X
		04:00	X		
		06:00	X		
		08:00	X		
C00D2		24:00	X	X (8-24 h)	
C00D3		48:00	X	X (24-48 h)	
C00D4		72:00	X	X (48-72 h)	

Table 9.5.3-2: Pharmacokinetic Sampling and ECG Collection Schedule for BMS-986242 in the Clinical Pharmacology Substudy

Study Day of Sample Collection	Event	Time (Relative to BMS-986242 Dose) Hour: Min	BMS-986242 and Metabolites Plasma Sample	BMS-986242 and Metabolites Urine Sample	ECG
C00D8[a,b]	Predose	00:00[b]	X	X	
		01:00	X	X (0-8 h)	
		02:00	X		
		03:00	X		
		04:00	X		
		06:00	X		
		08:00	X		
C00D9[a]		24:00	X	X (8-24 h)	
C00D10[a]		48:00[c]	X		

Abbreviations: ADA = anti-drug antibody; EOT = end of treatment; FU = follow-up.

[a] Exploratory food effect cohort only.

[b] For participants not in the Food Effect cohort, C00D8 predose samples should be taken approximately 168 hours after dosing on Cycle 00 Day 1 if Cycle 1 Day 1 does not occur on the next day after Cycle 00 Day 7.

[c] For participants in the Food Effect cohort, this sample should be taken 48 hours after dosing on Cycle 00 Day 8 if Cycle 1 Day 1 does not occur on the next day of Cycle 00 Day 9.

9.5.4 Pharmacokinetic Sample Analyses

The plasma and urine samples of BMS-986242 and select metabolites will be analyzed by validated liquid chromatography-mass spectrometry (LC-MS) assays, and serum samples of nivolumab and anti-nivolumab antibody will be analyzed by validated immunoassays. In addition, plasma samples will be archived for potential additional metabolite and biotransformation analysis if the need arises and to the extent possible.

9.6 Pharmacodynamics

Details on biomarker sampling and analysis are provided in Section 9.8.

9.7 Pharmacogenomics

Details on biomarker sampling and analysis are provided in Section 9.8.

9.7.1 Absorption, Distribution, Metabolism, and Excretion Sampling

A 6-mL whole blood sample will be drawn at baseline (Cycle 0 Day 1) for potential analysis of deoxyribonucleic acid (DNA) variants in absorption, distribution, metabolism, and excretion (ADME)-related genes (see list of ADME-related genes from http://pharmaadme.org). Further details of blood collection and processing will be provided to the site in the procedure manual.

Details on biomarker sampling and analysis are provided in Section 9.8, Table 9.8-1, and Table 9.8-2.

[redacted]

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

10.1.1 Dose Escalation

During the dose-escalation trial, the sample size at each dose in these arms depends on observed toxicity and posterior inference.

Up to approximately 78 participants are planned to be enrolled for Part 1 (dose escalation) and clinical pharmacology substudy: approximately 30 participants for the dose-escalation phase, with up to 24 additional participants in Part 1 for additional characterization of the safety, PK, and pharmacodynamic profile of BMS-986242, and approximately 24 participants for the clinical pharmacology substudy (including food effect). Appendix 7 provides additional details for the operating characteristics of the BLRM for monotherapy and BLRM-copula for combination therapy based on doses from 25 mg; an addition of 12.5 mg is expected to provide similar operating characteristics..

For the food effect assessment, the sample size is not based on statistical power for comparison but on consideration of the precision of the estimates of geometric means of Cmax and AUC(0-T) of BMS-986242.

For a sample size of 6 participants, there is an 80% probability for the 90% confidence interval to be within 79.6% to 125.7% of the point estimate of the geometric mean for Cmax and within 80.4% to 124.4% of the point estimate of the geometric mean for AUC(0-T). This calculation assumes that log(Cmax) and log(AUC[0-T]) of BMS-986242 are normally distributed with a standard deviation (SD) of 0.23 and 0.22, respectively, as estimated from a study of a related compound.

10.1.2 Dose-expansion Cohort

Dose-expansion cohorts of BMS-986242 administered in combination with nivolumab in 6 disease-restricted populations will be included. These are melanoma, NSCLC, SCCHN, RCC, bladder, and gastric cancer, with separate cohorts based on prior PD-(L)1 exposure in 5 of the tumor types (except gastric cancer). Approximately 20 participants will be included for each dose-expansion cohort, for a total of 220 participants for Part 2. The sample size of 20 participants per dose-expansion cohort is not based on statistical power for comparison but on consideration of the precision of the estimates for ORR proportion. A total of 20 participants are expected to provide a standard error of the estimate of 7% to 11% for ORR proportions between 10% and 50%.

10.2 Populations for Analyses

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

Population	Description
Enrolled	All participants who sign informed consent and are registered into the IRT
Treated	All participants who received at least 1 dose of study treatment
Pharmacokinetic	All treated participants who have available concentration-time data from the participants who received any BMS-986242 or nivolumab
Immunogenicity	All treated participants who have received nivolumab and have a baseline and at least 1 post-treatment immunogenicity measurement
Biomarker	All treated participants who have available biomarker data

Note: Analyses of safety, extent of exposure, biomarkers, PK, efficacy, and pharmacodynamics will be based on the treated population.

10.3 Statistical Analyses

The statistical analysis plan will be developed and finalized before database lock. Below is a summary of planned statistical analyses of the primary and secondary endpoints.

10.3.1 Efficacy Analyses

Listings of participant efficacy will be provided. The following efficacy analyses may be performed on the treated population for the final analysis, if appropriate (Table 10.3.1-1). Details on censoring scheme on time-to-event endpoints such as DOR for each tumor type, progression-free survival, and overall survival will be described in the statistical analysis plan.

Table 10.3.1-1: Efficacy - Statistical Analyses

Endpoint	Statistical Analysis Methods
ORR BOR for a participant will be assessed per RECIST v1.1 for solid tumors by investigator	Estimate of ORR and corresponding 2-sided exact 95% exact CI by the Clopper-Pearson method by treatment.
Median DOR DOR for a participant with a BOR of CR or PR, defined as the time between the date of first response and the date of the first objectively documented disease progression (per RECIST v1.1) or death, whichever occurs first	Median DOR using the Kaplan-Meier method and corresponding 2-sided 95% CI using Brookmeyer and Crowley methodology (using log-log transformation) by treatment
PFSR at 6, 9, 12, and 24 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
OSR at 6, 12, and 24 months (after the last dose of study treatment) OS for a participant is defined as the time from date of first dose of study treatment to the date of death from any cause	Estimate by the Kaplan-Meier method and corresponding 2-sided 95% CI will be derived based on Greenwood formula by treatment

Note: ORR/DOR analysis may not be performed in case there are too few responses.
Abbreviations: BOR = best overall response; OS = overall survival.

10.3.2 Safety Analyses

The safety analyses will be performed on the treated population for the final analysis (Table 10.3.2-1).

Table 10.3.2-1: Safety - Statistical Analyses

Endpoint	Statistical Analysis Methods
Incidence of DLTs, AEs, SAEs, AEs leading to discontinuation and deaths	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. AEs will be graded according to CTCAE v4.03 and coded using the latest version of MedDRA
Laboratory abnormalities	Laboratory shift table using the worst CTC grade on treatment per participant Laboratory values will be graded according to CTCAE v4.03
Changes from baseline in laboratory parameters, vital signs, and ECG	Summary statistics for timepoint and change from baseline by time and dose.
Summary measures of parameters from posterior distribution of the dose-DLT profile	Summary statistics for posterior distribution parameters and plot of final dose-DLT curve

Abbreviations: MedDRA = Medical Dictionary for Regulatory Activities; PT = preferred term.

Additional exposure response analyses will be performed for QTc during the clinical pharmacological substudy.

10.3.3 Other Analyses

Table 10.3.3-1: Pharmacokinetic Analyses for BMS-986242 and Nivolumab

Endpoint	Statistical Analysis Methods
BMS-986242	
Cmax, AUC(TAU), AUC(0-T), AUC(INF), Ctrough, CLT/F, Vss/F, AI, %UR24, %UR72, MR_Cmax, MR_AUC(TAU)	Summary statistics: geometric means and coefficients of variation
Cmax, AUC(TAU), AUC(INF) (Only)	Scatter plots vs dose for each day measured; dose proportionality based on a power model and a CI around the power coefficient
T-HALF	Summary statistics: means and standard deviations
Tmax.	Summary statistics: medians and ranges

Table 10.3.3-1: Pharmacokinetic Analyses for BMS-986242 and Nivolumab

Endpoint	Statistical Analysis Methods
Ctrough and Ceoi	Summary statistics to assess attainment of steady state: geometric means and coefficients of variation, by treatment and by day; plots vs time by dose
Nivolumab	
Ctrough and Ceoi	Summary statistics: geometric means and coefficients of variation, by treatment and by day, plots vs time by dose

Abbreviations: AI = accumulation index, calculated based on ratio of AUC and Cmax at steady state to 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; Ceoi = concentration at the end of infusion; CLT/F = apparent total body clearance; Cmax = maximum observed concentration; Ctrough = trough observed plasma concentration; Tmax = time of maximum observed concentration; Vss/F = apparent volume of distribution at steady-state.

Geometric means and geometric mean ratios for Cmax and AUC(0-T) will be estimated for participants in the substudy exploring food effect. PK time-concentration data may be pooled with data from other studies for PPK analysis, which will be presented in a separate report.

A concentration-response analysis may be used to characterize the effects of BMS-986242 on QTcF, based on data from the clinical pharmacology substudy QTc assessment. Additional ECG data and time matched concentrations may be pooled from other studies to perform an integrated analysis. The results of the analysis will be reported separately.

[redacted]

Table 10.3.3-3: Immunogenicity Analyses

Endpoint	Statistical Analysis Methods
Incidence of ADA to nivolumab in combination with BMS-986242 Baseline ADA-positive participant is defined as a participant who has a ADA detected sample at baseline.[a] ADA-positive participant is a participant with at least 1 ADA-positive sample relative to baseline after initiation of the treatment	Frequency distribution of baseline ADA-positive participants and ADA-positive participants after initiation of the treatment

[a] Baseline sample is the last sample before initiation of the treatment
Abbreviations: ADA = anti-drug antibody.

10.3.4 Interim Analyses

Administrative interim analysis for internal decision making or external publication purposes may be performed. No formal inferences requiring any adjustment to statistical significance level will be performed.

12 APPENDICES

APPENDIX 1 ABBREVIATIONS AND TRADEMARKS

Term	Definition
ADA	anti-drug antibody
ADME	absorption, distribution, metabolism, and excretion
AE	adverse event
AI	accumulation index
ALT	alanine aminotransferase
APC	antigen-presenting cell
AST	aspartate aminotransferase
AUC	area under the concentration-time curve
AUC(0-24)	area under the concentration-time curve from time zero to 24 hours postdose
AUC(INF)	area under the concentration-time curve from time zero to infinity
AUC(TAU)	area under the concentration-time curve in 1 dosing interval
BCRP	breast cancer resistance protein
BLRM	Bayesian Logistic Regression Method
BMS	Bristol-Myers Squibb
BOR	best overall response
BUN	blood urea nitrogen
C24	observed plasma concentration at 24 hours
CBC	complete blood count
Ceoi	concentration at the end of infusion
CI	confidence interval
CLT/F (or CLT)	apparent total body clearance
Cmax	maximum observed plasma concentration
Cmaxss	steady-state peak concentration
CNS	central nervous system
CR	complete response
CrCl	creatinine clearance
CRF	case report form
CT	computed tomography

Term	Definition
CTLA-4	cytotoxic T lymphocyte-associated antigen 4
Ctrough	trough observed plasma concentration at the end of the dosing interval
CYP	cytochrome P450
DDI	drug-drug interaction
DILI	drug-induced liver injury
DLT	dose-limiting toxicity
DNA	deoxyribonucleic acid
DOR	duration of response
ECG	electrocardiogram
ECOG	Eastern Cooperative Oncology Group
ELISA	enzyme-linked immunosorbent assay
EOI	end of infusion
EOT	end of treatment
FDG	fludeoxyglucose
FNR	false negative rate
FPR	false positive rate
FU	follow-up
GGT	gamma-glutamyl transferase
HDPE	high-density polyethylene
HNSTD	highest non-severely toxic dose
HPV	human papillomavirus
IB	Investigator Brochure
IC50	half-maximal inhibitory concentration
ICF	informed consent form
IDO1	indoleamine 2,3-dioxygenase 1
IFNγ	interferon-gamma
IHC	immunohistochemistry
IMP	investigational medicinal products
I-O	immuno-oncology
IP	investigational product

Term	Definition
IV	intravenous
IRT	interactive response technology
LC-MS	liquid chromatography-mass spectrometry
LFT	liver function test
mDOR	median duration of response
MedDRA	Medical Dictionary for Regulatory Activities
miRNA	micro ribonucleic acid
MR_AUC(TAU)	ratio of metabolite AUC(TAU) to parent AUC(TAU), corrected for molecular weight
MR_Cmax	ratio of metabolite Cmax to parent Cmax, corrected for molecular weight
MRI	magnetic resonance imaging
MRSD	maximum recommended starting dose
MTD	maximum tolerated dose
NA	not applicable
NCI CTCAE	National Cancer Institute Common Terminology Criteria for Adverse Events
NHL	non-Hodgkin's lymphoma
NOAEL	no-observed adverse effect level
NSCLC	non-small cell lung cancer
ORR	objective response rate
OS	overall survival
OSR	overall survival rate
PBMC	peripheral blood mononuclear cells
PCR	polymerase chain reaction
PD	progressive disease
PD-1	programmed cell death-1
PD-L1	programmed death receptor-ligand 1
PE	physical examination
PET	positron emission tomography
PFSR	progression-free survival rate
P-gp	P-glycoprotein

Term	Definition
PI	principal investigator
PK	pharmacokinetic(s)
PPK	population pharmacokinetics
PO	per os, orally
PR	partial response
PT	preferred term
Q2W	every 2 weeks
Q4W	every 4 weeks
QD	quaque die, once daily
QTcF	QT interval corrected for heart rate using Fridericia's formula
RCC	renal cell carcinoma
RECIST	Response Evaluation Criteria in Solid Tumors
SAE	serious adverse event
SD	stable disease
SCCHN	squamous cell carcinoma of the head and neck
SD	stable disease
SNP	single nucleotide polymorphism
STD10	severely toxic dose to 10%
TCGA	The Cancer Genome Atlas
TDO	tryptophan 2,3-dioxygenase
Teff	effector T cells
T-HALF	apparent elimination half-life
Tmax	time of maximum observed plasma concentration
tMLR	tolerogenic mixed lymphocyte reaction
Treg	regulatory T cells
TSH	thyroid-stimulating hormone
UGT1A1	uridine diphosphate glucuronosyltransferase 1A1
ULN	upper limit of normal
%UR24	percent urinary recovery over 24 hours
%UR72	percent urinary recovery over 72 hours

Term	Definition
US	United States
VS	vital signs
Vss/F (or Vss)	apparent volume of distribution at steady state
WBC	white blood cell
WOCBP	women of childbearing potential

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 eCRF is intended to refer to a person (participant) who has consented to participate in the clinical research study.

REGULATORY AND ETHICAL CONSIDERATIONS

GOOD CLINICAL PRACTICE

This study will be conducted in accordance with:

- Good Clinical Practice (GCP), as defined by the International Council on Harmonisation (ICH)
- 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 serious breach is a breach of the conditions and principles of GCP in connection with the study or the protocol, which is likely to affect, to a significant degree, the safety or physical or mental integrity of the subjects of the study or the scientific value of the study.

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

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

INSTITUTIONAL REVIEW BOARD/INDEPENDENT ETHICS COMMITTEE

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

COMPLIANCE WITH THE PROTOCOL AND PROTOCOL REVISIONS

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

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

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

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

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

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

FINANCIAL DISCLOSURE

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

INFORMED CONSENT PROCESS

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

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

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

Investigators must:

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

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

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

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

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

Subjects unable to give their written consent (eg, because of stroke or severe dementia) may only be enrolled in the study with the consent of a legally acceptable representative. The participant must also be informed about the nature of the study to the extent compatible with his or her understanding, and should this participant become capable, he or she should personally sign and date the consent form as soon as possible. The explicit wish of a participant who is unable to give his or her written consent, but who is capable of forming an opinion and assessing information to refuse participation in, or to be withdrawn from, the clinical study at any time should be considered by the investigator.

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

SOURCE DOCUMENTS

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

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

STUDY TREATMENT RECORDS

Records for study treatments (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, 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 site's stock or commercial supply or a specialty pharmacy)	The investigator or designee accepts responsibility for documenting traceability and study drug integrity in accordance with requirements applicable under law and the SOPs/standards of the sourcing pharmacy. These records should include: • label identification number or batch number • amount dispensed to and returned by each participant, including unique participant identifiers • dates and initials of person responsible for Investigational Product dispensing/accountability, as per the Delegation of Authority Form

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

CASE REPORT FORMS

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

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

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

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

The completed CRF, including 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 the Sponsor or designee. User accounts are not to be shared or reassigned to other individuals

MONITORING

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

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

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

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

RECORDS RETENTION

The investigator (or head of the study site in Japan) must retain all study records and source documents for the maximum period required by applicable regulations and guidelines, or institutional 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 site's stock or commercial supply or a specialty pharmacy)	It is the investigator's or designee's responsibility to dispose of all containers according to the institutional guidelines and procedures.

It is the investigator's or designee's responsibility to arrange for disposal, 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, eg, incinerator, licensed sanitary landfill, or licensed waste disposal vendor, must be documented.
- Accountability and disposal records are complete, up-to-date, and available for the Medical 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 Medical Monitor will make arrangements for return of study treatments provided by BMS (or its vendors). Destruction of nonstudy treatments sourced by the site, not supplied by BMS, is solely the responsibility of the investigator or designee.

CLINICAL STUDY REPORT AND PUBLICATIONS

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

For this protocol, the Signatory Investigator will be the Study Steering Committee chair or their designee.

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

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 drug 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 drug, whether or not considered related to the study drug.

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. The following hospitalizations are not considered SAEs in BMS clinical studies: o 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) o elective surgery, planned prior to signing consent o admissions as per protocol for a planned medical/surgical procedure o routine health assessment requiring admission for baseline/trending of health status (e.g., routine colonoscopy) o medical/surgical admission other than to remedy ill health and planned prior to entry into the study. Appropriate documentation is required in these cases o admission encountered for another life circumstance that carries no bearing on health status and requires no medical/surgical intervention (eg, lack of housing, economic inadequacy, caregiver respite, family circumstances, administrative reason) o admission for administration of anticancer therapy in the absence of any other SAEs (applies to oncology protocols)
Results in persistent or significant disability/incapacity or substantial disruption of the ability to conduct normal life functions
Results in a congenital anomaly/birth defect
Is an important medical event (defined as a medical event[s] that may not be immediately life-threatening or result in death or hospitalization but, based upon appropriate medical and scientific judgment, may jeopardize the participant or may require intervention [eg, medical, surgical] to prevent one of the other serious outcomes listed in the definition above). Examples of such events include, but are not limited to, intensive treatment in an emergency room or at home for allergic bronchospasm and blood dyscrasias or convulsions that do not result in hospitalization. Potential drug-induced liver injury (DILI) is also considered an important medical event. (See Section 9.2.7 for the definition of potential DILI.)

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

Although pregnancy, overdose, cancer, and potential DILI are not always serious by regulatory definition, these events must be handled as SAEs. (See Section 9.2.5 for reporting pregnancies.)

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

EVALUATING AES AND SAES

Assessment of Causality

The causal relationship to study drug is determined by a physician and should be used to assess all AEs. The causal relationship can be one of the following:

Related: There is a reasonable causal relationship between study drug administration and the AE.

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

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

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 drug 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 until resolution, until the condition stabilizes, until the event is otherwise explained, or until the participant is lost to follow-up.

REPORTING OF SAES TO SPONSOR OR DESIGNEE

- SAEs, whether related or not related to study drug, and pregnancies must be reported to BMS (or designee) within 24 hours of awareness of the event.
- SAEs must be recorded on the SAE Report Form; pregnancies on a Pregnancy Surveillance Form (electronic or paper forms).
- The preferred method for SAE data reporting collection is through the eCRF.
- The paper SAE/pregnancy surveillance forms are only intended as a back-up option when the eCRF system is not functioning.
    - In this case, the paper forms are to be transmitted via email or confirmed facsimile (fax) transmission to:

SAE Email Address: Refer to Contact Information list.

SAE Facsimile Number: Refer to Contact Information list.

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

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 postmenopausal unless permanently sterile. Permanent sterilization methods include hysterectomy, bilateral salpingectomy, and bilateral oophorectomy.

Women in the following categories are not considered WOCBP:

- Premenarchal
- Premenopausal 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
  - 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.

*Females treated with hormone replacement therapy 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 hormone replacement therapy used. The durations of the washout period below are suggested guidelines and the investigators should use their judgement in checking serum FSH levels.

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

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

CONTRACEPTION GUIDANCE FOR FEMALE PARTICIPANTS OF CHILD BEARING POTENTIAL

One of the highly effective methods of contraception listed below is required during study duration and until the end of relevant systemic exposure, as approximately 5 half-lives after the end of study treatment, plus 30 days.

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[b] – oral – intravaginal – transdermal
• Progestogen-only hormonal contraception associated with inhibition of ovulation[b] – oral – injectable
Highly Effective Contraceptive Methods That Are User Independent
• Implantable progestogen-only hormonal contraception associated with inhibition of ovulation [b] • Intrauterine device (IUD)[c] • Intrauterine hormone-releasing system (IUS)[c] • Bilateral tubal occlusion
• Vasectomized partner *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 drug. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the study and the preferred and usual lifestyle of the participant.* – 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.
NOTES:

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

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

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

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

CONTRACEPTION GUIDANCE FOR MALE PARTICIPANTS WITH PARTNER(S) OF CHILD BEARING POTENTIAL

Male participants with female partners of childbearing potential are eligible to participate if they agree to the following during the treatment and until the end of relevant systemic exposure.

- Inform any and all partner(s) of their participation in a clinical drug study and the need to comply with contraception instructions as directed by the investigator.
- Male participants are required to use a condom for study duration and until the end of relevant systemic exposure defined as approximately 5 half-lives after the end of treatment plus an additional 90 days.

- Female partners of males participating in the study to consider use of effective methods of contraception until the end of relevant systemic exposure, defined as approximately 5 half-lives after the end of treatment in the male participant plus an additional 90 days.
- Male participants with a pregnant or breastfeeding partner must agree to remain abstinent from penile vaginal intercourse or use a male condom during each episode of penile penetration during the treatment and until approximately 5 half-lives after the end of treatment plus an additional 90 days.
- Refrain from donating sperm for the duration of the study treatment and for approximately 5 half-lives after the end of treatment plus an additional 90 days.

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 3 for Adverse Events and Serious Adverse Events: Definitions and Procedures for Recording, Evaluating, Follow Up and Reporting.

APPENDIX 5 ECOG PERFORMANCE STATUS

ECOG PERFORMANCE STATUS	
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

[redacted]

APPENDIX 6 RECIST V1.1

1 ASSESSMENT OF OVERALL TUMOR BURDEN AND MEASURABLE DISEASE

Only subjects with measurable disease at baseline should be included in protocols where objective tumor response is the primary endpoint. In studies where the primary endpoint is tumor progression (either time to progression or proportion with progression at a fixed date), the protocol must specify if entry is restricted to those with measurable disease or whether subjects having non-measurable disease only are also eligible.

To assess objective response or future progression, it is necessary to estimate the overall tumor burden at baseline and use this as a comparator for subsequent measurements. Measurable disease is defined by the presence of at least 1 measurable tumor lesion. When computed tomography (CT) scans have slice thickness greater than 5 mm, the minimum size for a measurable lesion should be twice the slice thickness.

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

1.1 Measurable Lesions

Measurable lesions must be accurately measured in at least 1 dimension (longest diameter in the plane of the measurement to be recorded) with the following minimum size:

- 10 mm by CT/magnetic resonance imaging (MRI) scan (CT/MRI scan slice thickness no greater than 5 mm)
- 10 mm caliper measurement by clinical exam (lesions that cannot be accurately measured with calipers should be recorded as non-measurable)
- 20 mm by chest x-ray
- Malignant lymph nodes: To be considered pathologically enlarged and measurable, a lymph node must be ≥ 15 mm in **short** axis when assessed by CT scan (CT scan slice thickness recommended to be no greater than 5 mm). At baseline and in follow-up, only the **short** axis will be measured and followed.

1.2 Non-measurable Lesions

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

1.3 Special Considerations Regarding Lesion Measurability

1.3.1 Bone Lesions

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

1.3.2 Cystic Lesions

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

1.3.3 Lesions with Prior Local Treatment

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

1.4 Specifications by Methods of Measurements

1.4.1 Measurement of Lesions

All measurements should be recorded in metric notation (mm). All baseline evaluations should be performed as close as possible to the treatment start and never more than 30 days before the beginning of the treatment.

1.4.2 Method of Assessment

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

1.4.2.1 CT/MRI Scan

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

1.4.2.2 Chest X-ray

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

1.4.2.3 Clinical Lesions

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

1.4.2.4 Ultrasound

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

1.4.2.5 Endoscopy and Laparoscopy

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

1.4.2.6 Tumor Markers

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

2 BASELINE DOCUMENTATION OF "TARGET" AND "NON-TARGET" LESIONS

2.1 Target Lesions

When more than 1 measurable lesion is present at baseline, all lesions up to a maximum of 5 lesions total (and a maximum of 2 lesions per organ) representative of all involved organs should be identified as *target lesions* and will be recorded and measured at baseline.

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

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

2.1.1 Lymph Nodes

Lymph nodes merit special mention because they are normal anatomical structures that may be visible by imaging even if not involved by tumor. Pathological nodes that are defined as measurable and may be identified as target lesions must meet the criterion of a **short axis of ≥ 15 mm by CT scan**. Only the *short* axis of these nodes will contribute to the baseline sum. Nodes that have a short axis < 10 mm are considered non-pathological and should not be recorded or followed.

2.2 Non-target Lesions

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

3 TUMOR RESPONSE EVALUATION

3.1 Evaluation of Target Lesions

Complete Response (CR): **Disappearance of all target lesions.** Any pathological lymph nodes (whether target or non-target) must have reduction in short axis to < 10 mm.

Partial Response (PR): At least a **30% decrease in the sum of diameters of target lesions,** taking as reference the baseline sum diameters.

Progressive Disease (PD): At least a **20% increase in the sum of diameters of target lesions, taking as reference the *smallest sum on study*** (this includes the baseline sum if that is the smallest on study). In addition to the relative increase of 20%, the sum must also demonstrate an **absolute increase of at least 5 mm**. (Note: the appearance of 1 or more new lesions is also considered progression.)

Stable Disease (SD): Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as reference the smallest sum diameters while on study.

3.1.1 Special Notes on the Assessment of Target Lesions

3.1.1.1 Lymph Nodes

Lymph nodes merit special mention because they are normal anatomical structures that may be visible by imaging even if not involved by tumor. Pathological nodes that are defined as measurable and may be identified as target lesions must meet the criterion of a **short axis of ≥ 15 mm by CT scan**. Only the *short* axis of these nodes will contribute to the baseline sum. Nodes that have a short axis < 10 mm are considered non-pathological and should not be recorded or followed.

3.1.1.2 Target Lesions That Become "Too Small to Measure"

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

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

- If it is the opinion of the radiologist that the lesion has likely disappeared, the measurement should be recorded as 0 mm.
- If the lesion is believed to be present and is faintly seen but too small to measure, a default value of 5 mm should be assigned. (Note: In case of a lymph node believed to be present and faintly seen but too small to measure, a default value of 5 mm should be assigned in this circumstance as well.) This default value is derived from the 5-mm CT slice thickness (but should not be changed with varying CT slice thickness).

3.1.1.3 Target Lesions That Split or Coalesce on Treatment

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

3.2 Evaluation of Non-target Lesions

While some non-target lesions may actually be measurable, they need not be measured and instead should be assessed only qualitatively at the time points specified in the protocol.

CR: Disappearance of all non-target lesions and normalization of tumor marker level. All lymph nodes must be non-pathological in size (< 10 mm short axis).

Non-CR/Non-PD: Persistence of 1 or more non-target lesion(s) and/or maintenance of tumor marker level above the normal limits.

PD: Unequivocal progression of existing non-target lesions. (Note: The appearance of 1 or more new lesions is also considered progression.)

3.2.1 Special Notes on the Assessment of Non-target Lesions

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

3.2.1.1 When the Subject Also Has Measurable Disease

- To achieve "unequivocal progression" on the basis of the non-target disease, there must be an overall level of substantial worsening in non-target disease such that, even in the presence of SD or PR in the target disease, the overall tumor burden has increased sufficiently to merit discontinuation of therapy.
- A modest "increase" in the size of 1 or more non-target lesions is usually not sufficient to quality for unequivocal progression status.

3.2.1.2 When the Subject Has Only Non-measurable Disease

- To achieve "unequivocal progression" on the basis of the non-target disease, there must be an overall level of substantial worsening such that the overall tumor burden has increased sufficiently to merit discontinuation of therapy.
- A modest "increase" in the size of 1 or more non-target lesions is usually not sufficient to qualify for unequivocal progression status.
- Because worsening in non-target disease cannot be easily quantified (by definition: if all lesions are non-measurable), a useful test that can be applied when assessing subjects for unequivocal progression is to consider if the increase in overall disease burden based on the change in non-measurable disease is comparable in magnitude to the increase that would be required to declare PD for measurable disease, ie, an increase in tumor burden representing an additional 73% increase in "volume" (which is equivalent to a 20% increase diameter in a measurable lesion). Examples include an increase in a pleural effusion from "trace" to "large," an increase in lymphangitic disease from localized to widespread, or may be described in protocols as "sufficient to require a change in therapy."
- If "unequivocal progression" is seen, the subject should be considered to have had overall PD at that point.

3.2.1.3 Tumor Markers

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

3.3 New Lesions

The appearance of new malignant lesions denotes disease progression. The finding of a new lesion should be unequivocal, ie, not attributable to differences in scanning technique, change in imaging modality, or findings thought to represent something other than tumor (for example, some "new" bone lesions may be simply healing or flare of pre-existing lesions). This is particularly important when the subject's baseline lesions show PR or CR. For example, necrosis of a liver lesion may be reported on a CT scan report as a new cystic lesion, which it is not.

A lesion identified on a follow-up study in an anatomical location that was *not* scanned at baseline is considered a new lesion and will indicate disease progression. An example of this is the subject who has visceral disease at baseline and, while on study, has a CT or MRI brain scan ordered that reveals metastases. The subject's brain metastases are considered to be evidence of PD even if he/she did not have brain imaging at baseline.

For example, if a new lesion is equivocal because of its small size, continued therapy and follow-up evaluation will clarify if it represents truly new disease. *If repeat scans confirm there is definitely a new lesion, then progression should be declared using the date of the initial scan.*

4 RESPONSE CRITERIA

4.1 Time Point Response

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

For subjects who have **measurable disease** at baseline, Table 4.1-1 provides a summary of the overall response status calculation at each time point.

Table 4.1-1: Time Point Response: Subjects with Target (+/– Non-target) Disease

Target Lesions	Non-target Lesions	New Lesions	Overall Response
CR	CR	No	CR
CR	Non-CR/non-PD	No	PR
CR	Not evaluated	No	PR
PR	Non-PD or not all evaluated	No	PR
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; NE = not evaluable; PD = progressive disease; PR = partial response; SD = stable disease.

4.1.1 Missing Assessments and Not Evaluable Designation

When no imaging/measurement is done at all at a particular time point, the subject is **not evaluable (NE)** at that time point. If only a subset of lesion measurements is made at an assessment, the case is also considered NE at that time point, unless a convincing argument can be made that the contribution of the individual missing lesion(s) would not have changed the assigned time point response.

4.1.2 Confirmation Scans

Verification of Response: Confirmation of PR and CR is required at least 4 weeks later to ensure that the responses identified are not the result of measurement error.

4.2 Best Overall Response: All Time Points

The best overall response is determined once all the data for the subject are known. It is the best response recorded from the start of the study treatment until objectively documented progression per RECIST Criteria or subsequent cancer therapy, whichever happens first, taking into account any requirement for confirmation. The subject's best overall response assignment will depend on

the findings of both target and non-target disease and will also take into consideration the appearance of new lesions.

Best response is defined as the best response across all time points with subsequent confirmation. CR or PR may be claimed only if the criteria for each are met at a subsequent time point as specified in the protocol (generally 4 weeks later).

In this circumstance, the best overall response can be interpreted as specified in Table 4.2-1. When SD is believed to be the best response, it must meet the protocol-specified minimum time from baseline. Measurements must have met the SD criteria at least once after study entry at a minimum interval (in general, not less than 6 weeks).

Table 4.2-1: Best Overall Response When Confirmation of CR and PR Is Required

Overall Response		Best Overall Response
First Time Point	**Subsequent Time Point**	
CR	CR	CR
CR	PR	SD, PD, or PR[a]
CR	SD	SD provided minimum criteria for SD duration met, otherwise, PD
CR	PD	SD provided minimum criteria for SD duration met, otherwise, PD
CR	NE	SD provided minimum criteria for SD duration met, otherwise NE
PR	CR	PR
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; NE = not evaluable; PD = progressive disease; PR = partial response; SD = stable disease.

[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 (because disease must have reappeared after CR). Best response would depend on whether the minimum duration for SD was met. However, sometimes CR may be claimed when subsequent scans suggest that small lesions were likely still present and in fact the subject had PR, not CR, at the first time point. Under these circumstances, the original CR should be changed to PR, and the best response is PR.

4.3 Duration of Response

4.3.1 Duration of Overall Response

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

The duration of overall CR is measured from the time measurement criteria are first met for CR until the first date that recurrent disease is objectively documented.

4.3.2 Duration of Stable Disease

SD is measured from the start of the treatment (in randomized trials, from date of randomization) until the criteria for progression are met, taking as reference the smallest sum on study (if the baseline sum is the smallest, this is the reference for calculation of PD).

APPENDIX 7 STATISTICAL METHODOLOGY

STATISTICAL DETAILS FOR BAYESIAN LOGISTIC REGRESSION METHOD (BLRM AND BLRM-COPULA) MODEL AND PRIORS FOR DOSE ESCALATION

1 MODEL SETUP FOR BMS-986242 MONOTHERAPY (LEAD IN)

1.1 Monotherapy Methodology Description

An adaptive 2-parameter Bayesian Logistic Regression Method (BLRM) model guided by the escalation with overdose control (EWOC) principle[1,2,3] will be used to guide the dose escalation of BMS-986242 in the monotherapy lead-in phase and to provide dose recommendation during dose escalation.

The BLRM will be fitted on the dose-limiting toxicity (DLT) data during the first 2 weeks of treatment accumulated throughout the dose escalation to model the dose-toxicity relationship of BMS-986242 in the monotherapy lead-in phase.

The dose-toxicity relationship for BMS-986242 monotherapy is assumed to follow a logistic model:

$$logit(p_i) = log(\alpha_1) + \beta_1 log(^{d_{1i}}/_{d_1^*}),$$

where p_i is the probability of toxicity at dose level d_{1i}. Note that the α_1 and β_1 parameters are assumed positive and d_1^* is the reference dose for BMS-986242 (please refer to the meaning of α_1 and β_1 in Section 1.2.1 for detailed implementation).

1.2 Prior Specification for BMS-986242 Monotherapy

The Bayesian approach requires the specification of prior distributions for model parameters, which include parameters (α_1, β_1) for BMS-986242. The prior distributions for BMS-986242 single-agent activity were derived using a weakly informative prior, as well as discussion with the Bristol-Myers Squibb (BMS) clinical team.

Derivation of prior distribution of these parameters is provided in the following subsections.

1.2.1 Prior Derivation for BMS-986242 Parameters ($log\ (\alpha_1), log\ (\beta_1)$)

A weakly informative prior will be used for parameters (α_1, β_1) for BMS-986242 to reflect the potential of the different toxicities of BMS-986242 and allow for considerable prior uncertainty.

Further details are provided below.

Weakly Informative Prior

- The median DLT rate at the reference dose (BMS-986242 at 600 mg QD) was assumed to be 30%, that is, mean ($\log(\alpha_1)$) = logit (0.3) = log(0.3/(1-0.3)) = -0.847.
- A doubling in dose was assumed to double the odds of DLT, that is, mean($\log(\beta_1)$) = 0.

The standard deviation of $\log(\alpha_1)$ was set to 1.53 using the following steps:

- If the toxicity probability range was set to be [1%, 99%], then the toxicity interval would be logit (0.99)-logit (0.01) = 9.19.

- To cover 99.7% of the variance, the toxicity interval will cover 6*standard deviation (SD) ($\log(\alpha_1)$), which gives us SD ($\log(\alpha_1)$) = 9.19/6 = 1.53.

Correspondingly, the standard deviation of $\log(\beta_1)$ was set to 1, which allows for considerably larger prior uncertainty for the dose toxicity.

1) The correlation between $\log(\alpha_1)$ and $\log(\beta_1)$ was set to 0.
2) $\log(\alpha_1)$ and $\log(\beta_1)$ follow a bivariate normal distribution.

Table 1: Prior Distribution for Model Parameters for BMS-986242

Parameter	Means	Standard Deviations	Correlation
$\log(\alpha_1)$, $\log(\beta_1)$	(-0.847, 0)	(1.53, 1)	0

2 MODEL SETUP FOR BMS-986242 AND NIVOLUMAB COMBINATION

2.1 Methodology Description for Combination Therapy

Toxicity profiles of both BMS-986242 monotherapy and nivolumab monotherapy will be incorporated to develop the combination model framework. A copula-type model will be used to cover all general combination cases, including additive and synergistic effects. The combination of the 2 treatments will be explored using a Bayesian hierarchical model by utilizing the toxicity profiles of the single agents as prior marginal profiles for the combination. The following copula-type model[4] will be used to describe the probability p_{ij} of toxicity when dose level i of agent A and dose level j of agent B are administered in combination:

$$p_{ij} = 1 - exp(-\left[\{-log(1-p_i{}^m)\}^{1/\gamma_1} + \{-log(1-q_j{}^n)\}^{1/\gamma_1}\right]^{\gamma_1}),$$

where p_i is the prespecified best guess toxicity probability for agent A, q_j is the prespecified best guess toxicity probability for agent B, m and n characterize the individual drug effect, and γ_1 characterizes the drug-drug interactive effect.

The joint toxicity framework models the toxicity rates of both agents as well as their interaction effects in a 7-parameter hierarchical model, where each monotherapy dose-toxicity relationship will be characterized by a 2-parameter BLRM model (see Section 1.1). There are 3 additional parameters for the copula-type model, 1 for each agent (m and n) as well as 1 for the interaction term (γ_1). A dose-toxicity surface will be characterized for different dose combinations of these 2 agents.

As there are currently no historical data or prior knowledge to indicate how much information is to be borrowed for each of the single agents, parameters m and n are both set to be 1, meaning borrowing 100% of the information from the 2 agents. The above formula is then simplified into a 5-parameter model as follows:

$$p_{ij} = 1 - exp(-\left[\{-log(1-p_i)\}^{1/\gamma_1} + \{-log\left(1-q_j\right)\}^{1/\gamma_1}\right]^{\gamma_1}.$$

Since only a fixed nivolumab dose (480 mg) will be used in the BMS-986242 and nivolumab combination, this surface will be simplified into a 2-dimensional dose-toxicity curve. Posteriors for the corresponding 5 parameters (2 logistic regression parameters $[\alpha_1, \beta_1]$ for BMS-986242 and 2 logistic regression parameters $[\alpha_2, \beta_2]$ for nivolumab, as well as 1 interaction parameter for the copula-type model [γ_1, which will be discussed in detail in the following section]) will be fitted into the in-house developed model. It implements the above-described theoretical setup.

2.2 Prior Specification for Combination Therapy

2.2.1 Marginal Prior for BMS-986242

Posterior information on $\log(\alpha_1)$ and $\log(\beta_1)$ from the monotherapy Lead in will be used as marginal BMS-986242 prior for combination with nivolumab. This prior information is not prespecified and will be continuously updated when additional DLT information from the monotherapy is available. In the simulation (see Section 3, the prior of BMS-986242 as described in Section 1.2.1 (Table 1) is used for illustration purposes because no real-time DLT data are available at this time.

2.2.2 Marginal Prior Derivation for Nivolumab Parameters ($\log(\alpha_2)$, $\log(\beta_2)$)

Similar to BMS-986242 monotherapy in the monotherapy phase, the logistic model for nivolumab is as follows:

$$logit(q_j) = log(\alpha_2) + \beta_2 log(^{d_{2j}}/_{d_2^*}),$$

where q_j is the probability of toxicity at dose level d_{2j}. Note that the α_2 *and* β_2 parameters are assumed positive, and d_2^* is the reference dose for nivolumab.

The toxicity profile of nivolumab has been studied in several studies. A bivariate normal prior for the nivolumab model parameters ($\log(\alpha_2)$, $\log(\beta_2)$) was obtained by extracting a posterior of nivolumab using DLT and safety data from the Study CA209003, which is used later as the meta-analytical-predictive (MAP) prior for nivolumab.

The MAP prior for the model parameters ($\log(\alpha_2)$, $\log(\beta_2)$) was obtained in the following steps.

First, a prior distribution for nivolumab was developed:

- The median DLT rate at the reference dose (3 mg/kg every 2 weeks) was assumed to be 10%, that is, mean ($\log(\alpha_2)$) = logit(1/10) = log(1/9) = -2.197.
- A doubling in dose was assumed to double odds of DLT, that is, mean($\log(\beta_2)$) = 0.
- The standard deviation of $\log(\alpha_2)$ was set to 2, and the standard deviation of $\log(\beta_2)$ to 1, which allows for considerable prior uncertainty for the dose-toxicity profile.
- The correlation between $\log(\alpha_2)$ and $\log(\beta_2)$ is assumed to be 0 (assuming independence of $\log(\alpha_2)$ and $\log(\beta_2)$).
- In addition, heterogeneity between the historical study and current study was incorporated using a meta-analytic predictive approach by defining between-trial standard deviations τ_1 and τ_2 for $\log(\alpha_2)$ and $\log(\beta_2)$, respectively. The between-trial variability is assumed to be

moderate. Therefore, τ_1 and τ_2 were set to follow a log-normal distribution, with mean log(0.25) and log(0.125), respectively, with a common standard deviation log(2)/1.96.

With this prior, the clinical trial data below (Table 2) were used to generate the posterior for nivolumab, which is then used as the MAP prior for this study (Table 3).

Table 2: Data From Single-agent Nivolumab (Study CA209003)

Dose of Nivolumab (mg/kg)	Every 2 Weeks
	No. of DLTs/No. of Evaluable Participants in the Escalation Phase
0.1	0/3
0.3	0/3
1	0/3
3	0/3
10	1/6

Abbreviation: DLT = dose limiting toxicity.

Table 3: Marginal Prior Distribution for Model Parameters for Nivolumab (ie, Posterior from MAP Method)

Parameter	Means	Standard Deviations	Correlation
log(α_2), log(β_2)	(-3.269, -0.152)	(1.186, 0.771)	-0.369

Note: Nivolumab prior information was based on a milligram-per-kilogram dosing instead of flat dosing. If real PK data from this study show difference from the milligram-per-kilogram assumption, the nivolumab prior will be revisited and modified accordingly.

2.2.3 Prior for Interaction Parameters for Joint Toxicity of BMS-986242 and Nivolumab Combination

A gamma prior distribution for the interaction parameter γ_1 is derived to reflect the current uncertainty about the toxicity profile of the combination of BMS-986242 and nivolumab. Although no PK drug-drug interaction is expected, the possibility of a significant positive interaction between BMS-986242 and nivolumab cannot be totally excluded. The interaction parameter γ_1 was chosen accordingly but with a degree of uncertainty to allow for the possibility that the interaction may be positive or negative. Therefore, the following assumptions are made for the interaction parameter:

- γ_1 follows a gamma distribution and with a mean centered at 1.1, which means the combination of 2 agents is likely to have only a small synergistic effect.
- The 97.5 percentile of γ_1 is log(3), that is, a 3-fold increase in odds of DLT due to the interaction over independence at the starting dose of the combination.

This model assigns the highest probability to there being small synergistic interaction and also allows for the potential of larger synergism of the toxic profiles. It also does not completely ignore the possibility of antagonism because there is a 40% prior probability that γ_1 is less than 1.

3 DECISION RULE FOR DOSE ESCALATION AND SIMULATION

Dose escalation recommendations for BMS-986242 monotherapy and in combination with nivolumab will be based on the inference from the Bayesian posterior and the probability that the true DLT rate for each dose lies in 1 of the following categories:

- [0%, 16%) under-dosing
- [16%, 33%) targeted toxicity
- [33%, 100%] excessive toxicity

These boundaries are similar to the toxicity boundaries used by a rule-based design (ie, 3 + 3 design) in that a minimum is set at 16% (about 1 in 6) DLT rate and a maximum at 33% (about 2 in 6) DLT rate. Following the principle of EWOC, dose recommendations for the next cohort will be based on the Bayesian model after DLT information becomes available during the DLT period, accounting for all of the available data from the administered doses, and the candidate doses are the ones fulfilling the overdose criterion that there is less than 25% (for monotherapy) and 35% (for combination therapy) chances of excessive toxicity. Only the candidate doses will be considered for the next cohort. While the Bayesian model will use DLT information from the DLT period only, clinical assessment will take into consideration of the totality of available data including PK/Pharmacodynamics from all treated participants.

The MTD is the highest administered dose not expected to cause DLT in more than 33% of the treated participants during the DLT period. The final recommended MTD/RP2D will be based on the recommendation from the BLRM/BLRM-copula, and on an overall assessment of all available safety, PK/Pharmacodynamic, and efficacy data.

3.1 Simulation Parameters

One thousand trial simulations were used for each scenario. All simulations were run using EAST 6.3.1® software for BLRM model for BMS-986242 monotherapy and in-house developed code via R and Openbugs for BLRM-copula method for BMS-986242 in combination with nivolumab. The number of participants to be treated in each cohort in a specific dose level and the stopping rules used to declare MTD are defined as:

- Fixed cohort size: 3
- Probability of overdosing: < 25% for BLRM and 35% for BLRM-Copula
- Probability of achieving the target toxicity: > 50%
- Maximum number of participants treated: 30
- Minimum number of participants treated at a given dose level in order to declare MTD: 6
- Maximum number of participants at a dose:12

The provisional dose levels for BMS-986242 monotherapy are 25 mg through 600 mg. For the combination therapy, nivolumab is fixed at 480 mg flat dose for Q4W.

3.2 Operating Characteristics

Section 3.2.1 demonstrates operating characteristics of BLRM for monotherapy and Section 3.2.2 demonstrates operating characteristics of BLRM-copula for combination therapy accounting for joint toxicity of the combination therapy.

3.2.1 Operating Characteristics of BLRM for Monotherapy

Three scenarios were investigated by selecting (1) dose-DLT relationship derived by prior, (2) narrow safety window in order to explore how EWOC limits the risk of exposing participants from a toxic dose level, and (3) all doses above the target toxicity (Table 4).

Table 4: Simulation Results of BLRM for Monotherapy

Scenario	BMS-986242 Dose (mg)	25	50	100	200	400	600	MTD not selected (%)	Fitted MTD	Toxicity Observed (%)	Avg # Pts
By Prior	% DLT	2	4	7	13	22	30	0.2	598.8	17.6	18.4
	% MTD	0	0	2.6	25.9	46.5	24.7				
	# Pts	3.1	0.2	0.8	4.2	6.6	3.5				
	# DLTs	0.0	0.0	0.0	0.1	1.3	1.2				
Narrow Safety Window	% DLT	2	4	7	13	22	60	0.4	546.6	19.6	18.3
	% MTD	0.2	0.3	1.7	29.7	62.9	4.8				
	# Pts	3.1	0.2	0.9	4.7	7.3	2.1				
	# DLTs	0.1	0.0	0.0	0.6	1.6	1.3				
All High	% DLT	40	50	60	70	75	80	86.1	28.7	54.8	7.7
	% MTD	8.8	3.9	1	0.2	0	0				
	# Pts	4.6	1.5	0.7	0.3	0.6	0				
	# DLTs	1.8	0.7	0.4	0.2	0.4	0				

Note: % DLT = true DLT rate; % MTD = proportion of the dose selected as the MTD; # Pts = average number of participants by adjusting for skipped dose level where the true toxicity rate is below the target rate; # DLTs = average number of DLTs by adjusting for skipped dose level where the true toxicity rate is below the target rate; Fitted MTD = fitted MTD at 33% as the target toxicity rate; % toxicity observed = average proportion of DLTs given the doses were tried

Doses with true target toxicity within the target toxicity interval [16%, 33%)

Abbreviations: Pts = participants.

The average sample size was no more than 20 participants. The results for the scenarios of narrow safety window and all high show how the EWOC principle limits the risk of exposing participants from a toxic dose level. Overall, the scenarios illustrated above demonstrate that the model performs well in the hypothetical scenarios investigated by correctly identifying the MTD at least 62% of the time while limiting participants from receiving excessive/unacceptable toxic dose levels.

3.2.2 Operating Characteristics of BLRM-copula for Combination Therapy

Three hypothetical scenarios were investigated: (1) additive joint toxicity; (2) toxicity rates 25% higher than the additive scenario; (3) toxicity rates 50% higher than the additive scenario (Table 5).

Table 5: Simulation Results of BLRM-Copula for Combination

Scenario	BMS-986242 Dose	25	50	100	200	400	600	MTD not selected (%)	Fitted MTD	Toxicity Observed (%)	Avg # Pts
Additive	% DLT	12	14	17[a]	23[a]	32[a]	40	10	464.7	24.3	19.5
	% MTD	2.7	5.7	23.6	24.6	23.6	9.8				
	# Pts	3.6	3.2	4.7	3.6	2.4	2.2				
	#DLT	0.5	0.4	0.7	0.8	0.7	0.9				
25% Higher	% DLT	15	18[a]	21[a]	29[a]	40	50	14.1	357.2	27.7	17.7
	% MTD	5.5	8.7	26.4	29.8	12.9	2.6				
	# Pts	3.8	3.2	4.5	3.5	1.7	1.1				
	#DLT	0.6	0.6	0.9	0.9	0.7	0.6				
50% Higher	% DLT	18[a]	21[a]	26[a]	34	48	60	21.8	291.7	31.7	15.5
	% MTD	7.9	10.7	29.5	24.5	5.4	0.2				
	# Pts	3.9	3.2	4.1	2.8	0.9	0.6				
	#DLT	0.7	0.7	1.0	0.9	0.5	0.3				

[a] Doses with true target toxicity within the target toxicity interval [16%, 33%)

Note: % DLT = true DLT rate; % MTD = proportion of the dose selected as the MTD; #DLT = average number of DLTs; MTD not selected = dose was below lowest dose or above highest dose; Fitted MTD = fitted MTD at 33% as the target toxicity rate; Toxicity observed = Average proportion of DLTs out of all simulated trials; # Pts = average number of participants

The average sample size was around 20 participants. The results show how the EWOC principle limits the risk of exposing participants from unacceptable toxic dose levels. Overall, the scenarios illustrated above demonstrate that the model performs well by correctly identifying the MTD ranging from 49% to 72% in the hypothetical scenarios investigated while limiting participants from receiving unacceptable toxic dose levels.

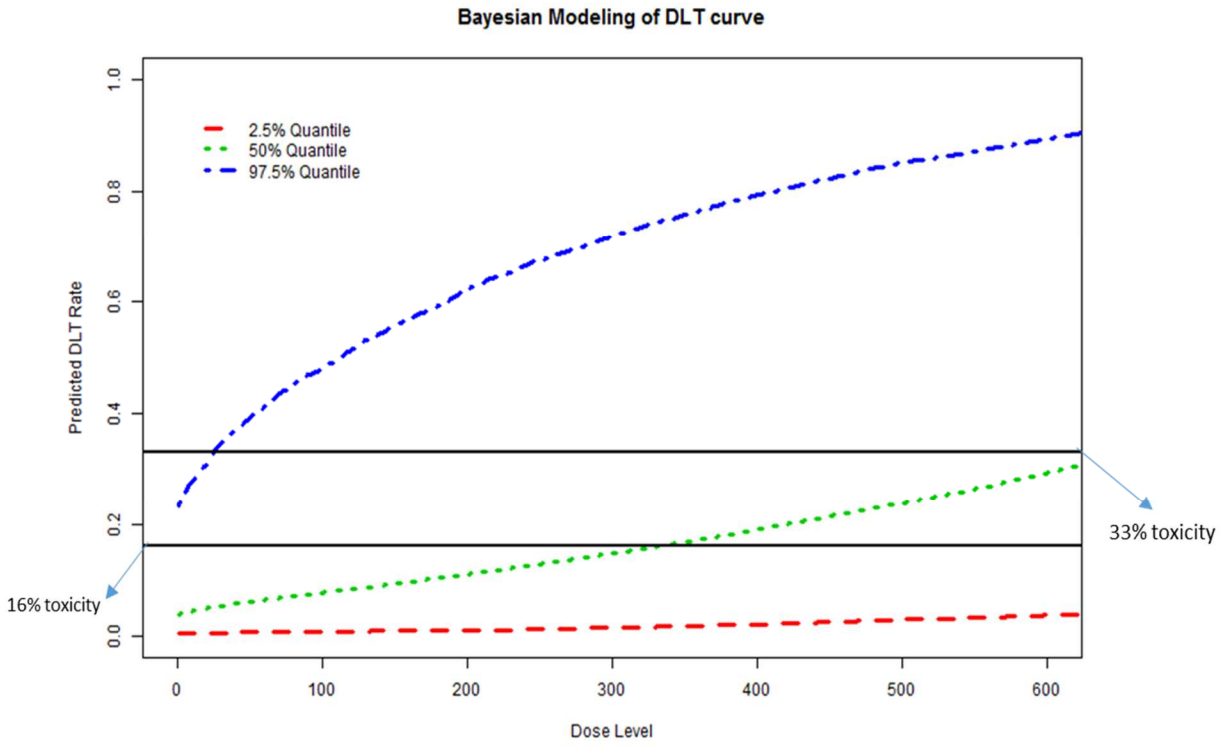
4 INTERIM MONITORING CASE STUDY TO ILLUSTRATE PROVISION OF DOSE RECOMMENDATIONS DURING DOSE ESCALATION

In order to provide a comprehensive view of the dynamics of the models, different hypothetical scenarios exploring different possibilities are examined. For the simplicity of illustration purposes, a static cohort size of 3 subjects is applied for dose level 25 mg. This cohort size could vary during the actual clinical trial, and the BLRM (-Copula) models are designed to fit various different cohort sizes, adaptively. In general, there are many possible scenarios for a specific dose level, especially with a monotherapy lead-in followed by combination treatment. For example, there could be 0, 1, 2, or 3 DLTs observed in the monotherapy lead-in period, and similarly 0, 1, 2, or 3 DLTs observed in the combination period.

During interim monitoring, posterior probabilities will be updated when there is new DLT information available. The following two visualization plots will be produced to reflect the real time dose-DLT relationship, to quantify benefit (in the form of target dosing) and risk (in the form of overdosing and underdosing) during the model's recommendation process, and to facilitate clinical team's interpretation of the model recommendations for the final decision making:

- Dose-DLT profile for the doses ranging between 0 mg and 600 mg (Figure 1).
- Stacking histograms displaying predictive probabilities on DLT rates classified into 3 different categories (Underdosing, Target Dosing and Overdosing) (Figure 2).

Figure 1: An Example of Updated Dose-DLT Profile After Incorporating Prior Information and DLT Information at 25 mg (0/3 DLTs in Monotherapy Lead-in and 0/3 DLTs in Combination at 25 mg for BMS-986242)



Interpretation and usage of Figure 1:

Figure 1 is a snapshot of an updated dose-DLT profile with DLT information available at dose level 25 mg after the combination period (assuming there was no DLT in either monotherapy lead-in or combination period). The dose-DLT profile is captured with a continuous dose spectrum ranging from 0 mg through 600 mg, which is a slice of the dose-DLT surface of the combination of two drugs with nivolumab fixed at 480 mg. For each dose within the range, there is a corresponding distribution of the predicted DLT rates calculated from the posterior samples of the

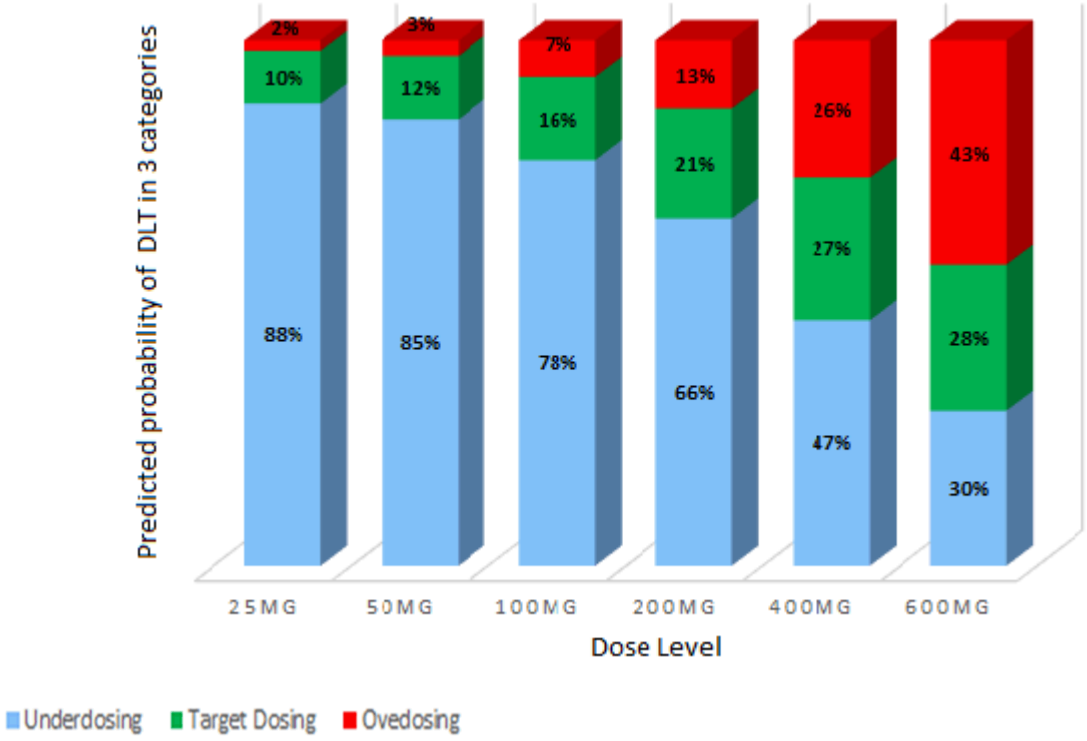
model parameters. This figure will be updated each time new DLT information becomes available from different dose levels.

In Figure 1, there are 3 different quantiles (2.5%, 50%, and 97.5%) plotted to characterize the current trend of the toxicity profile (as shown by the 50% quantile), as well as the variation of the dose-DLT profile (as shown by the 2.5% quantile and the 97.5% quantile), according to the accumulation of DLT data from all previous and current dose levels. The toxicity boundaries (0.16 and 0.33) are illustrated in two horizontal lines to benchmark the way in which the dose-DLT profile is trending.

Intermediate dose levels can be identified using different boundary cutoffs. For example, using the 50% quantile curve (green highlight), which represents the nearly average DLT distribution for each dose level, 350 mg could be a potential intermediate dose level corresponding to the lower pre-specified DLT rate boundary of 0.16, and 600 mg could be a fitted MTD dose level associated with the upper boundary of 0.33.

Moreover, if all of the current pre-specified doses are considered intolerable (overdosing probabilities > 0.35 for combination therapy, for example, a case not shown on the current Figure 1), the model will recommend to stop the current dose level, and the clinical team can leverage the current updated dose-DLT curve to pinpoint a new dose, which is lower than pre-specified lowest dose (25 mg) by using the DLT rate boundaries.

Figure 2: **An Example of Updated Stacking Histogram After Incorporating Prior Information and DLT Information at 25mg (0/3 DLTs at Monotherapy Lead-in and 0/3 DLTs at Combination) to Classify Predicted DLT Rates into 3 Categories (Underdosing, Target Dosing, and Overdosing)**



Interpretation and usage of Figure 2:

Figure 2 is a snapshot of stacking histogram with DLT information available at dose level 25 mg after combination period (assuming there was no DLT in either monotherapy lead-in or combination period). This figure will be updated each time new DLT information becomes available in different dose levels.

When recommending the next dose level, the model will first exclude doses that are intolerable (with overdosing probabilities ≥ 35% or ≥ 25% for combination and monotherapy respectively). Among those qualified candidate doses that are considered "tolerable", the model will select the dose that maximizes the probability of being within the target toxicity range (DLT rate of 16% up to 33%).

As illustrated in Figure 2, when there is 0 DLT observed out of 3 subjects for the dose level 25 mg in both monotherapy lead-in and combination, the distribution of predicted DLT rates will be characterized into possibilities falling into 3 different categories. Some dose levels for BMS-986242 might be excluded according to the higher-than-cutoff overdosing probabilities (eg, 600mg, > 35%). Among the remainder of tolerable dose levels, the BLRM (-Copula) model recommends the dose that maximizes the probability of being within the target dosing interval.

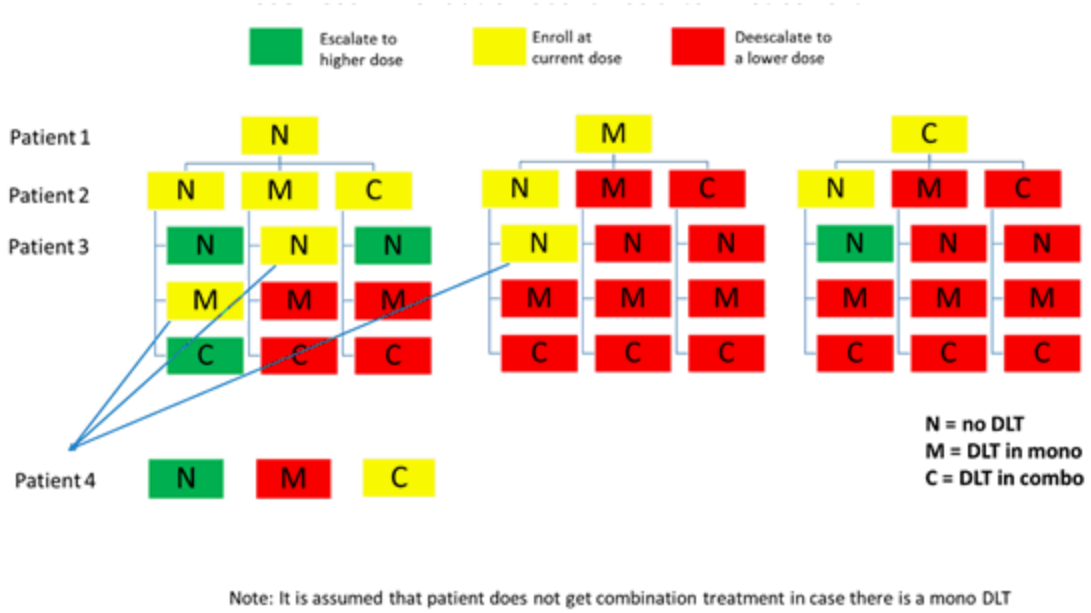
Therefore, the model's recommendation would be to escalate to 400 mg, which is associated with the highest target dosing probability of 27% compared with that of other dose levels.

Similarly (although not shown on Figure 2), according to the rules specified above, the model could possibly recommend to de-escalate to a lower dose level than current treated dose level, extend the current dose level, or even to stop and identify a new dose level lower than 25 mg, the lowest pre-specified dose level. Please refer to description of Figure 1 for details on how to specify the new dose levels.

4.1 Example of the BLRM Using BMS-986242 Monotherapy Dose Escalation

According to safety consideration and clinical judgement, dose level 25 mg is recommended as the starting dose for BMS-986242 monotherapy. With the current BMS-986242 prior specified in the Section 1.2.1 the following flow chart illustrates possible scenarios (the model's recommendations) after dose level 25mg using available DLT information in Figure 3.

Figure 3: Hypothetical Scenarios for BMS-986242 Dose Escalation After Dose Level 25mg Based on BLRM (-Copula) Model



[redacted]

[redacted]

APPENDIX 8 CYP3A AND CYP2B6 GUIDANCE

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

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

Table 1: Classification of In Vivo Inhibitors of CYP Enzymes

CYP Enzymes	Strong Inhibitors[a] ≥ 5-fold Increase in AUC or > 80% Decrease in CL	Moderate Inhibitors[b] ≥ 2 but < 5-fold Increase in AUC or 50-80% Decrease in CL	Weak Inhibitors[c] ≥ 1.25 but < 2-fold Increase in AUC or 20-50% Decrease in CL
CYP3A	Boceprevir, clarithromycin, conivaptan, grapefruit juice,[d] indinavir, itraconazole, ketoconazole, lopinavir/ritonavir, mibefradil,[e] nefazodone, nelfinavir, posaconazole, ritonavir, saquinavir, telaprevir, telithromycin, voriconazole	Amprenavir, aprepitant, atazanavir, ciprofloxacin, darunavir/ritonavir, diltiazem, erythromycin, fluconazole, fosamprenavir, grapefruit juice,[d] imatinib, verapamil	Alprazolam, amiodarone, amlodipine, atorvastatin, bicalutamide, cilostazol, cimetidine, cyclosporine, fluoxetine, fluvoxamine, ginkgo,[f] goldenseal,[f] isoniazid, nilotinib, oral contraceptives, ranitidine, ranolazine, tipranavir/ritonavir, zileuton

Please note that this is not an exhaustive list.

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

[b] A moderate inhibitor for a specific CYP is defined as an inhibitor that increases the AUC of a sensitive substrate for that CYP by less than 5-fold but equal to or more than 2-fold.

[c] A weak inhibitor for a specific CYP is defined as an inhibitor that increases the AUC of a sensitive substrate for that CYP by less than 2-fold but equal to or more than 1.25-fold.

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

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

[f] Herbal product.

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

Table 2: Classification of In Vivo Inducers of CYP Enzymes

CYP Enzymes	Strong Inducers ≥ 80% Decrease in AUC	Moderate Inducers 50-80% Decrease in AUC	Weak Inducers 20-50% Decrease in AUC
CYP3A	Avasimibe,[a] carbamazepine, phenytoin, rifampin, St. John's wort[b]	Bosentan, efavirenz, etravirine, modafinil, nafcillin	Amprenavir, aprepitant, armodafinil, echinacea,[c] pioglitazone, prednisone, rufinamide

Please note that this is not an exhaustive list.

[a] Not a marketed drug.

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

[c] Herbal product.

Abbreviations: AUC = area under the concentration-time curve; CYP = cytochrome P450.

Table 3: Examples of Sensitive In Vivo CYP Substrates and CYP Substrates with Narrow Therapeutic Range

CYP Enzymes	Sensitive Substrates[a]	Substrates with Narrow Therapeutic Range[b]
CYP3A	Alfentanil, aprepitant, budesonide, buspirone, conivaptan, darifenacin, darunavir, dasatinib, dronedarone, eletriptan, eplerenone, everolimus, felodipine, indinavir, fluticasone, lopinavir, lovastatin, lurasidone, maraviroc, midazolam, nisoldipine, quetiapine, saquinavir, sildenafil, simvastatin, sirolimus, tolvaptan, tipranavir, triazolam, vardenafil	Alfentanil, astemizole,[c] cisapride,[c] cyclosporine, dihydroergotamine, ergotamine, fentanyl, pimozide, quinidine, sirolimus, tacrolimus, terfenadine[c]
CYP2B6	Bupropion, efavirenz	

Please note that this is not an exhaustive list.

[a] Sensitive CYP substrates refers to drugs whose plasma AUC values have been shown to increase 5-fold or higher when co-administered with a known CYP inhibitor.

[b] CYP substrates with narrow therapeutic range refers to drugs whose exposure-response relationship indicates that small increases in their exposure levels by the concomitant use of CYP inhibitors may lead to serious safety concerns (eg, Torsades de Pointes).

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

Abbreviations: AUC = area under the concentration-time curve; CYP = cytochrome P450.

APPENDIX 9 MANAGEMENT ALGORITHMS FOR IMMUNO-ONCOLOGY AGENTS

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 (I-O) 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 I-O drug-related adverse events. The oral equivalent of the recommended intravenous doses may be considered for ambulatory patients with low-grade toxicity. The lower bioavailability of oral corticosteroids should be taken into account when switching to the equivalent dose of oral corticosteroids.

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

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

Updated: 05-Jul-2016

GI Adverse Event Management Algorithm

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

Grade of Diarrhea/ Colitis (NCI CTCAE v4)	Management	Follow-up
Grade 1 Diarrhea:< 4 stools/day over baseline; Colitis: asymptomatic	• Continue I-O therapy per protocol • Symptomatic treatment	• Close monitoring for worsening symptoms. • Educate patient to report worsening immediately If worsens: • Treat as Grade 2 or 3/4
Grade 2 Diarrhea: 4-6 stools per day over baseline; IV fluids indicated <24 hrs; not interfering with ADL Colitis: abdominal pain; blood in stool	• Delay I-O therapy per protocol • Symptomatic treatment	If improves to grade 1: • Resume I-O therapy per protocol If persists > 5-7 days or recur: • 0.5-1.0 mg/kg/day methylprednisolone or oral equivalent • When symptoms improve to grade 1, taper steroids over at least 1 month, consider prophylactic antibiotics for opportunistic infections, and resume I-O therapy per protocol. If worsens or persists > 3-5 days with oral steroids: • Treat as grade 3/4
Grade 3-4 Diarrhea (G3): ≥7 stools per day over baseline; incontinence; IV fluids ≥24 hrs; interfering with ADL Colitis (G3): severe abdominal pain, medical intervention indicated, peritoneal signs G4: life-threatening, perforation	• Discontinue I-O therapy per protocol • 1.0 to 2.0 mg/kg/day methylprednisolone IV or IV equivalent • Add prophylactic antibiotics for opportunistic infections • Consider lower endoscopy	If improves: • Continue steroids until grade 1, then taper over at least 1 month If persists > 3-5 days, or recurs after improvement: • Add infliximab 5 mg/kg (if no contraindication). Note: Infliximab should not be used in cases of perforation or sepsis

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

Updated 05-Jul-2016

Renal Adverse Event Management Algorithm

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

Grade of Creatinine Elevation (NCI CTCAE v4)	Management	Follow-up
Grade 1 Creatinine > ULN and > than baseline but ≤ 1.5x baseline	• Continue I-O therapy per protocol • Monitor creatinine weekly	<u>If returns to baseline</u>: •Resume routine creatinine monitoring per protocol <u>If worsens:</u> •Treat as Grade 2 or 3/4
Grade 2-3 Creatinine > 1.5x baseline to ≤ 6x ULN	• Delay I-O therapy per protocol • Monitor creatinine every 2-3 days • 0.5 to 1.0 mg/kg/day methylprednisolone IV or oral equivalent • Consider renal biopsy with nephrology consult	<u>If returns to Grade 1:</u> •Taper steroids over at least 1 month, consider prophylactic antibiotics for opportunistic infections, and resume I-O therapy and routine creatinine monitoring per protocol <u>If elevations persist > 7 days or worsen:</u> •Treat as Grade 4
Grade 4 Creatinine > 6x ULN	• Discontinue I-O therapy per protocol • Monitor creatinine daily • 1.0-2.0 mg/kg/day methylprednisolone IV or IV equivalent • Consult nephrologist • Consider renal biopsy	<u>If returns to Grade 1</u> : Taper steroids over at least 1 month and add prophylactic antibiotics for opportunistic infections

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

Updated 05-Jul-2016

Pulmonary Adverse Event Management Algorithm

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

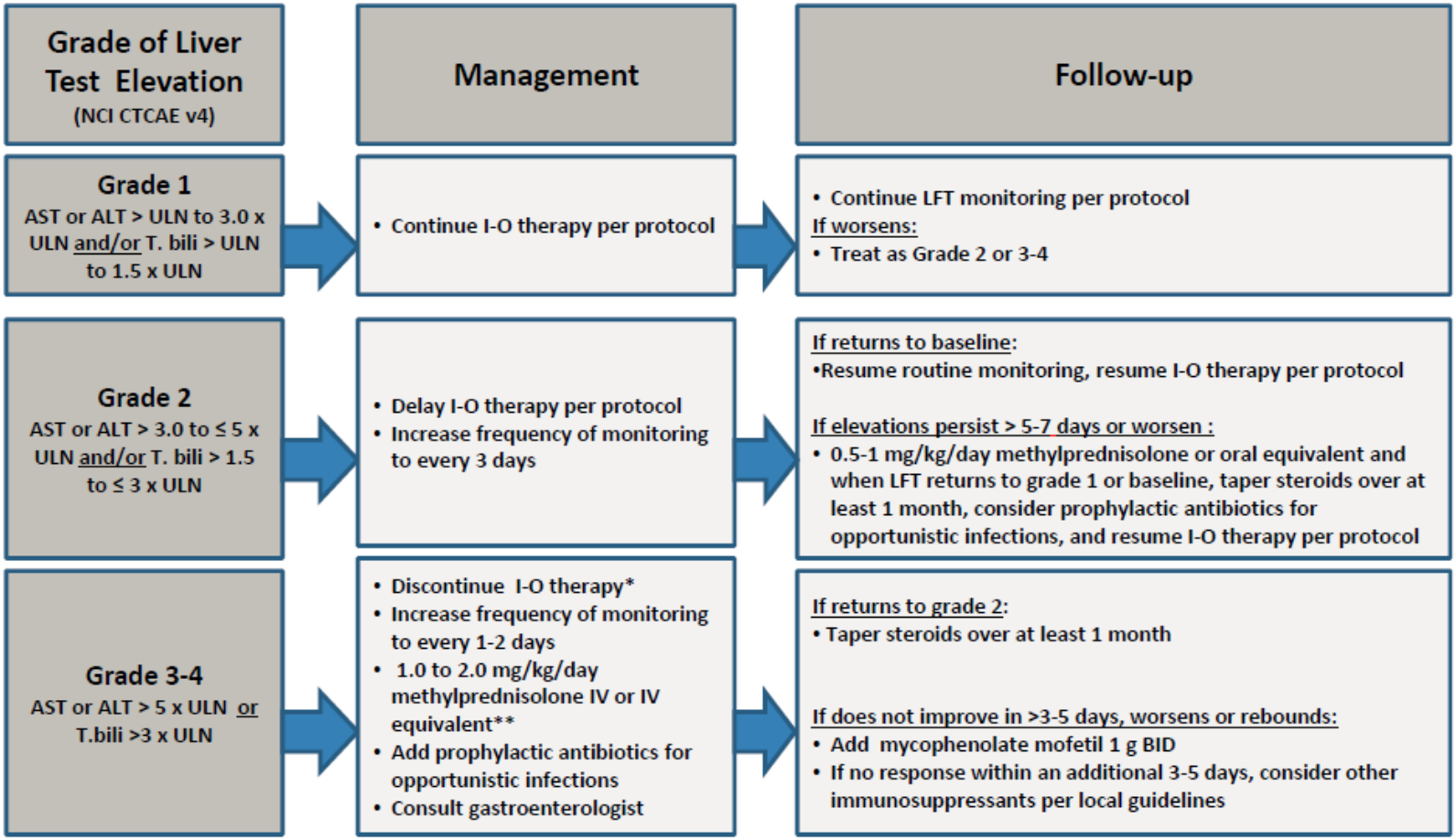
Grade of Pneumonitis (NCI CTCAE v4)	Management	Follow-up
Grade 1 Radiographic changes only	• Consider delay of I-O therapy • Monitor for symptoms every 2-3 days • Consider Pulmonary and ID consults	• Re-image at least every 3 weeks If worsens: • Treat as Grade 2 or 3-4
Grade 2 Mild to moderate new symptoms	• Delay I-O therapy per protocol • Pulmonary and ID consults • Monitor symptoms daily, consider hospitalization • 1.0 mg/kg/day methyl-prednisolone IV or oral equivalent • Consider bronchoscopy , lung biopsy	• Re-image every 1-3 days If improves: • When symptoms return to near baseline, taper steroids over at least 1 month and then resume I-O therapy per protocol and consider prophylactic antibiotics If not improving after 2 weeks or worsening: • Treat as Grade 3-4
Grade 3-4 Severe new symptoms; New/worsening hypoxia; Life-threatening	• Discontinue I-O therapy per protocol • Hospitalize • Pulmonary and ID consults • 2-4 mg/kg/day methylprednisolone IV or IV equivalent • Add prophylactic antibiotics for opportunistic infections • Consider bronchoscopy, lung biopsy	If improves to baseline: • Taper steroids over at least 6 weeks If not improving after 48 hours or worsening: • Add additional immunosuppression

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

Updated 05-Jul-2016

Hepatic Adverse Event Management Algorithm

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



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

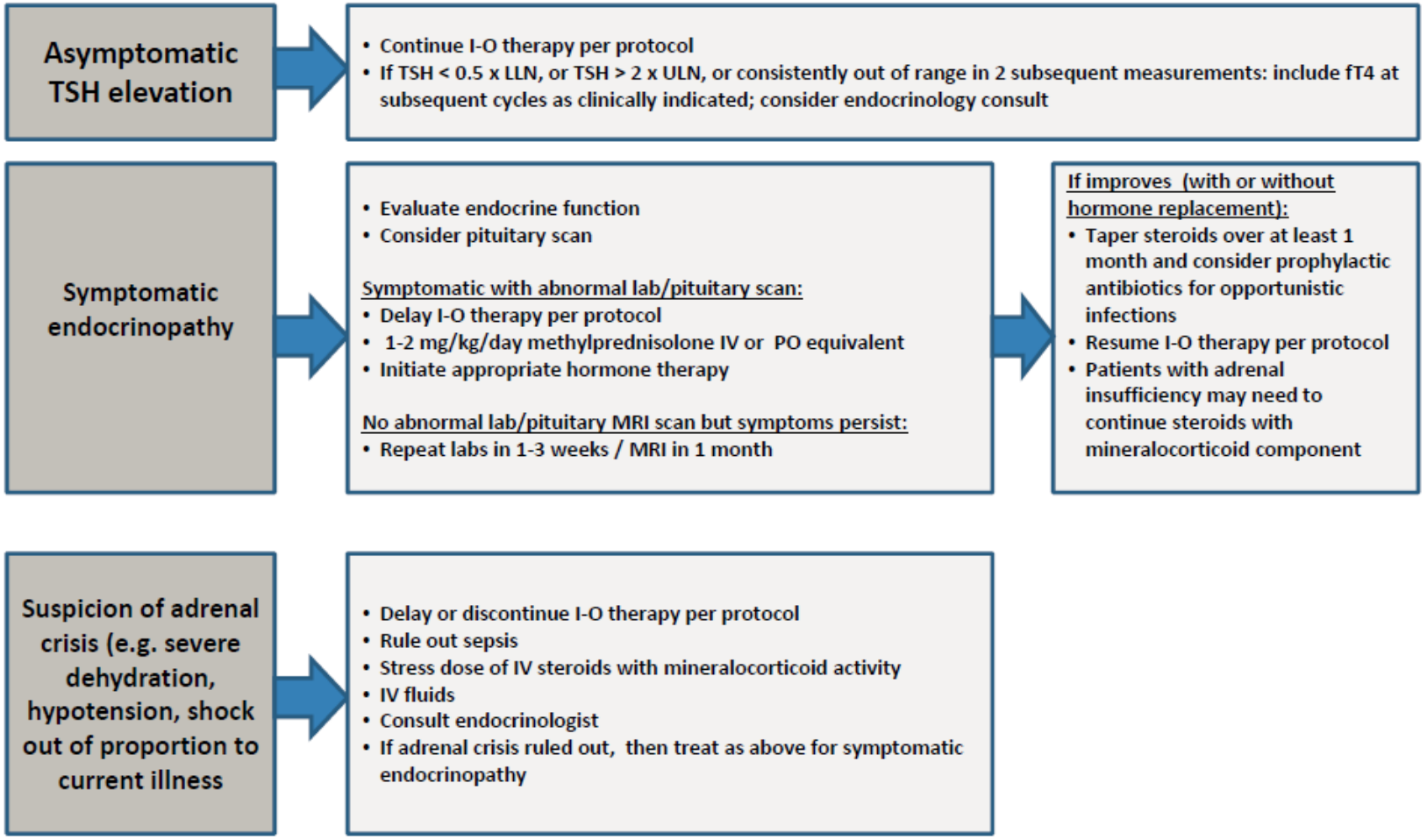
***I-O therapy may be delayed rather than discontinued if AST/ALT ≤ 8 x ULN or T.bili ≤ 5 x ULN.**

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

Updated 05-Jul-2016

Endocrinopathy Management Algorithm

Rule out non-inflammatory causes. If non-inflammatory cause, treat accordingly and continue I-O therapy. Consider visual field testing, endocrinology consultation, and imaging.

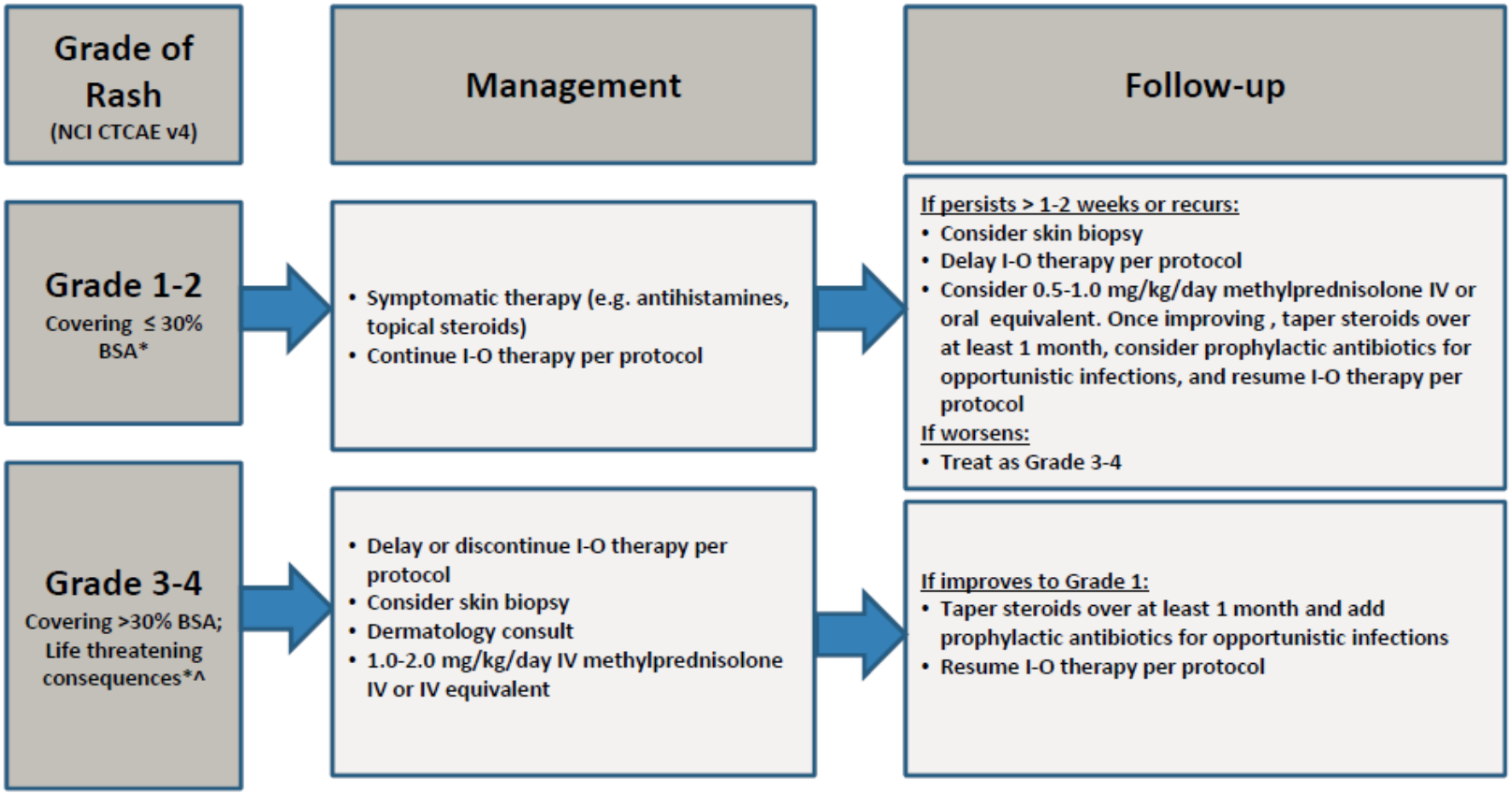


Patients on IV steroids may be switched to an equivalent dose of oral corticosteroids (e.g. prednisone) at start of tapering or earlier, once sustained clinical improvement is observed. Lower bioavailability of oral corticosteroids should be taken into account when switching to the equivalent dose of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

Updated 05-Jul-2016

Skin Adverse Event Management Algorithm

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



Patients on IV steroids may be switched to an equivalent dose of oral corticosteroids (e.g. prednisone) at start of tapering or earlier, once sustained clinical improvement is observed. Lower bioavailability of oral corticosteroids should be taken into account when switching to the equivalent dose of oral corticosteroids.
*Refer to NCI CTCAE v4 for term-specific grading criteria.
^If SJS/TEN is suspected, withhold I-O therapy and refer patient for specialized care for assessment and treatment. If SJS or TEN is diagnosed, permanently discontinue I-O therapy.

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Neurological Adverse Event Management Algorithm

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

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

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

Updated 05-Jul-2016

APPENDIX 10 MEDICATIONS ASSOCIATED WITH QT PROLOGATION

The list below is not meant to be all inclusive. Please consult individual drug labels for further information.

quinidine, procainamide, disopyramide,
amiodarone, sotalol, ibutilide, dofetilide,
erythromycins, clarithromycin,
chlorpromazine, haloperidol, mesoridazine, thioridazine, pimozide,
cisapride, bepridil, droperidol, methadone, arsenic, chloroquine, domperidone,
halofantrine, levomethadyl, pentamidine, sparfloxacin, lidoflazine

APPENDIX 11 P-GP AND BCRP GUIDANCE

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

[redacted]

Table 1: Examples of In Vivo Substrates for Selected Transporters

Transporter	Gene	Substrate
P-gp	ABCB1	Aliskiren, ambrisentan, colchicine, dabigatran etexilate, digoxin, everolimus, fexofenadine, imatinib, lapatinib, maraviroc, nilotinib, posaconazole, ranolazine, saxagliptin, sirolimus, sitagliptin, talinolol, tolvaptan, topotecan
BCRP	ABCG2	Methotrexate, mitoxantrone, imatinib, irinotecan, lapatinib, rosuvastatin, sulfasalazine, topotecan

Please note that this is not an exhaustive list.
Abbreviations: BCRP = breast cancer resistance protein; P-gp = P-glycoprotein.