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Date: 08-Sep-2017
Revised Date: 15-Aug-2018

Clinical Protocol CA034001

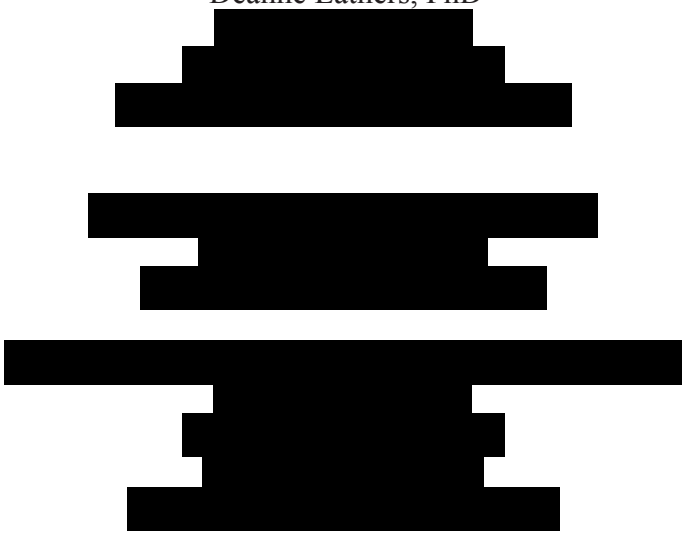
Phase 1/2a First in Human Study of BMS-986277 Administered Alone and in Combination with Nivolumab in Advanced Epithelial Tumors

Revised Protocol 06
Incorporates Administrative Letter 03

Short Title:

An Investigational Immuno-Therapy Study of BMS-986277 Alone and in Combination with Nivolumab in Epithelial Cancers

Medical Monitor/Study Director
Deanne Lathers, PhD



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

DOCUMENT HISTORY

Document	Date of Issue	Summary of Change
Revised Protocol 06	15-Aug-2018	Incorporates Administrative Letter 03 and clarifies that treatment algorithm in Appendix 10 applies to both infusion reactions and cytokine release syndrome. The revisions also includes title change to Appendix 5 to clarify that the algorithms are applicable to both nivolumab and BMS-986277-mediated IMAE.
Administrative Letter 03	04-Jun-2018	To add the IND number on the title page of the protocol.
Revised Protocol 05	18-May-2018	To add an additional expansion cohort and long-term follow-up requirements as well as limit BMS-986277 dosing to 2 cycles: • Schedule of Activities tables were updated • Clinical experience with enadenotucirev was updated • [redacted] • Overall design was updated • Blinded independent central review of efficacy scans was clarified • [redacted] • [redacted] • Inclusion and exclusion criteria were updated • Lifestyle restrictions were added • Treatments administered were updated • Dose-limiting toxicities were updated • Treatment delays were updated • Prohibited and/or restricted treatments were updated • Efficacy assessments were updated • Imaging assessments were updated • Adverse event and serious adverse event information was updated • Pregnancy was updated • Clinical safety laboratory assessments were updated • Pharmacokinetic section and tables were updated • Additional research collection was updated • [redacted] • Statistical considerations was updated • Appendices 1, 2, 3, 4, and 8 were updated • Appendix 11 was added Typographical errors were corrected, and edits were made for consistency and clarity.
Revised Protocol 04	02-Mar-2018	To implement revisions requested by a health authority [redacted]

Document	Date of Issue	Summary of Change
Revised Protocol 03	15-Dec-2017	Incorporates Administrative Letters 01 and 02 and the following: • Schedule of Activities tables were updated • Benefit/risk was updated • Exploratory objectives were updated • Overall design was updated • Inclusion and exclusion criteria were updated • Required concomitant medications were updated • Clinical safety laboratory assessments were updated • Pharmacokinetics tables were updated • [redacted] • Additional research collection was updated • Immunogenicity analyses was updated • Appendix 5 title was updated • Appendix 9 was updated • Appendix 10 was added • Typographical errors were corrected, and edits were made for consistency and clarity.
Administrative Letter 02	11-Dec-2017	To add a up to + 7 day dosing window to Day 15 in Cycle 1 and clarify the dosing window in order to alleviate administrative complications at clinical sites.
Administrative Letter 01	07-Nov-2017	To correct that only the participant number and the dose will be recorded on the syringe as well as to clarify how information will be collected.
Revised Protocol 02	24-Oct-2017	To prevent misinterpretation of the pre-medication recommendations for nivolumab treatment and to clarify infusion duration by dose.
Revised Protocol 01	27-Sep-2017	Updated the potency of BMS-986277 drug to be supplied.
Original Protocol	08-Sep-2017	Not applicable

TABLE OF CONTENTS

1 SYNOPSIS

Protocol Title: Phase 1/2a First in Human Study of BMS-986277 Administered Alone and in Combination with Nivolumab in Advanced Epithelial Tumors

Short Title:

An Investigational Immuno-Therapy Study of BMS-986277 Alone and in Combination with Nivolumab in Epithelial Cancers

Study Phase: Phase 1/2a

[redacted]

Research Hypothesis:

The CD80/αCD3 Oncolytic Virus (BMS-986277) is safe to be administered systemically to participants with advanced epithelial tumors alone and in combination with the anti-PD-1 checkpoint inhibitor, nivolumab. BMS-986277 will increase immune activation in the tumor microenvironment (TME) of advanced or metastatic epithelial tumors making tumors more susceptible to nivolumab-mediated anti-tumor activity.

Study Population:

Male and females, 18 years of age and older, diagnosed with metastatic or advanced colorectal cancer (CRC), prostate cancer, pancreatic cancer, triple-negative breast cancer (TNBC), ovarian cancer, or urothelial carcinoma, with tumor accessible for biopsy.

Objectives and Endpoints:

Objectives	Endpoints
Primary	
• To characterize the safety and tolerability of BMS-986277 administered alone and in combination with PD-1 inhibitor, nivolumab, in advanced epithelial tumors • To determine the RD and RP2D and dosing schedule of BMS-986277 administered alone (RD) and in combination with nivolumab in participants with advanced epithelial tumors	• Incidence of AEs, SAEs, AEs meeting protocol-defined DLT criteria, AEs leading to discontinuation, and AEs resulting in death • Incidence of clinical laboratory test abnormalities • Vital sign abnormalities or other safety biomarkers

Objectives	Endpoints
Secondary	
• To explore the preliminary anti-tumor activity of BMS-986277 alone and in combination with nivolumab in participants with advanced epithelial tumors (RECIST v1.1 and PCWG3)	• ORR, DCR, mDOR, mPFS, and PFSR at 8, 16, and 24 weeks depending on indication
• To assess the PK and IMG of BMS-986277 in blood following monotherapy or combination treatment	• Summary measures of PK and IMG parameters of BMS-986277
[redacted]	[redacted]

AE = adverse events; BICR = blinded independent central review; DCR = disease control rate; DLT = dose-limiting toxicity; IMG = immunogenicity; iRECIST = immune Response Evaluation Criteria in Solid Tumors; mDOR = median duration of response; mOS = median overall survival; mPFS = median progression-free survival; NPV = negative predictive value; ORR = objective response rate; OS = overall survival; OSR = overall survival rate; PCWG3 = Prostate Cancer Clinical Trials Working Group 3; PK = pharmacokinetics; PFSR = progression-free survival rate; PPV = positive predictive value; RD = recommended dose; RECIST = Response Evaluation Criteria in Solid Tumors; RP2D = recommended Phase 2 dose; SAE = serious adverse events; TPR = true positive rate

Overall Design:

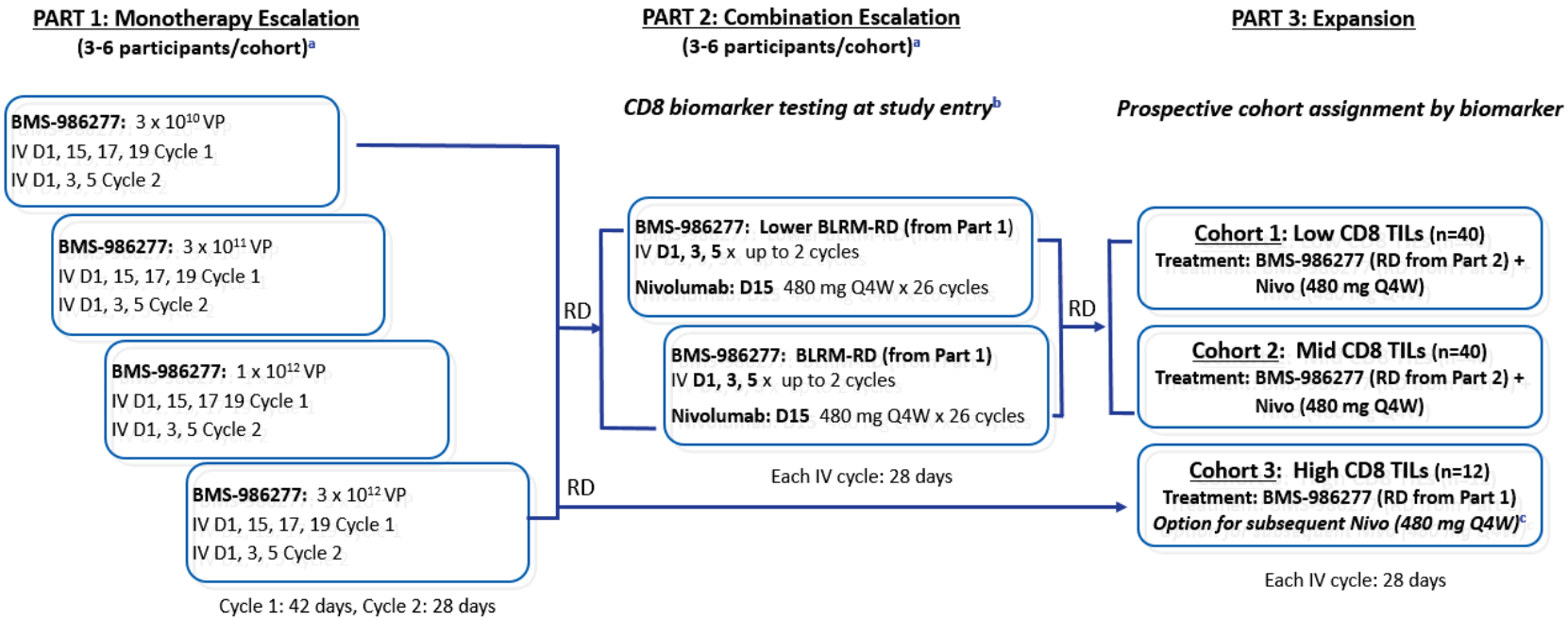
This is a Phase 1/2a, multicenter, open-label, non-randomized study of CD80/αCD3 Oncolytic Virus (BMS-986277) alone or in combination with nivolumab for the treatment of metastatic or advanced epithelial tumors in male and female participants.

The study will be conducted in 3 Parts:

- Part 1: a single agent monotherapy dose escalation to establish the Bayesian Logistic Regression Model-recommended dose (BLRM-RD) of BMS-986277 based on safety and tolerability
- Part 2: a combination dose escalation to establish the BLRM-RD of BMS-986277 (using the RD from Part 1) in combination with nivolumab (480 mg every 4 weeks [Q4W])
- Part 3: a 3-cohort expansion
  - Cohort 1 will treat participants with low CD8 tumor-infiltrating lymphocytes (TILs)(< 2%) with BMS-986277 (using the RD from Part 2) in combination with nivolumab (480 mg Q4W)
  - Cohort 2 will treat participants with mid CD8 TILs (2% ≤ CD8 < 20%) with BMS-986277 (using the RD from Part 2) in combination with nivolumab (480 mg Q4W)
  - Cohort 3 will treat participants with high CD8 TILs (≥ 20%) with BMS-986277 monotherapy (using the RD from Part 1) to further characterize the pharmacodynamics of BMS-986277 monotherapy. Following BMS-986277 monotherapy treatment (up to 2 cycles), participants will have the option to receive nivolumab treatment (480 mg Q4W) to explore sequential dosing.

The study design schematic is presented in Figure 1.

Figure 1: Study Design Schematic



For Parts 1 and 2, dosing of initial participants will be staggered by 7 days to mitigate against unexpected adverse drug reaction (ADR) as follows:

- Lowest Dose level: the first 3 participants may not begin dosing within 7 days of each other
- Other dose levels: the first 2 participants may not begin dosing within 7 days of one another

[a] Additional participants (up to a total of 12) may be treated at any dose level to further evaluate the safety, PK, and/or pharmacodynamic profile.

[b] As a minimum of 3 participants with low (< 2%) or mid (2% ≤ CD8 < 20%) CD8 TIL are required to be evaluated at each dose level, CD8 biomarker testing of fresh tumor samples (Section 9.8) will be required at study entry.

[c] Following 2 cycles of BMS-986277 monotherapy, participants may receive optional nivolumab treatment (480 mg Q4W) for up to 26 cycles if eligibility criteria continue to be met (see Sections 6.1 and 6.2). Participants whose disease progresses prior to receiving Cycle 2 of BMS-986277 may also receive nivolumab treatment if eligibility criteria continue to be met, skipping any remaining monotherapy visits and proceeding directly to Cycle 3, optional nivolumab treatment. For participants whose disease is responding (complete or partial) per RECIST v1.1 or PCWG3 at the 8 week scan, treatment must be discussed and agreed upon with the Medical Monitor (or designee) prior to the start of the optional subsequent nivolumab treatment.

BLRM-RD = Bayesian Logistic Regression Model-Recommended Dose; D = day; IV = intravenous; N = number; Q4W = every 4 weeks; RD = recommended dose; TIL = tumor-infiltrating lymphocytes; VP = viral particles.

Number of Participants:

- Part 1 (Monotherapy Dose Escalation - BMS-986277)
  - Initially, 3-6 participants per BMS-986277 monotherapy dose level, for a total of up to 24 participants. Additional participants (up to a total of 12) may be treated at any dose level to further evaluate the safety, PK, or pharmacodynamic profile. Therefore, the total sample size is up to 72.
- Part 2 (Combination Dose Escalation - BMS-986277 and nivolumab)
  - Initially, 3-6 participants per combination dose level. Additional participants (up to a total of 12) may be treated at any dose combination below or at the BLRM-RD for further evaluation of the safety, PK, or pharmacodynamic profile. Therefore, the total sample size is up to 36.
- Part 3 (Combination Expansion)
  - Cohorts 1-2 (BMS-986277 and nivolumab): Up to 40 evaluable participants per cohort. See Section 10.1 for further details on sample size calculation.
  - Cohort 3 (BMS-986277 monotherapy with option for subsequent nivolumab therapy): Up to approximately 12 participants evaluable for pharmacodynamic endpoints will be treated in this cohort. See Section 10.1 for further details on sample size.

Treatment Arms and Duration:

- Part 1: a monotherapy dose escalation of BMS-986277.
  - Four dose levels: 3×10^{10} viral particles (vp), 3×10^{11} vp, 1×10^{12} vp, and 3×10^{12} vp.
  - 6-week DLT evaluation period to assess safety with multiple injections which may be extended due to dose delays.
  - Dosing for the initial participants into each cohort in Part 1 will be staggered by 7 days to monitor for sentinel events.
  - Participants will receive 2 cycles (Cycle 1: 42 days, Cycle 2: 28 days) of BMS-986277.
- Part 2: a combination dose escalation of BMS-986277 (using the RD from Part 1; up to 2 cycles) in combination with nivolumab (480 mg Q4W; up to 26 cycles).
  - Participants will receive BMS-986277 at the BLRM-RD, or a lower dose than the BLRM-RD from Part 1.
    - Dosing for the initial participants into each cohort will be staggered by 7 days to monitor for sentinel events.
- Part 3: a 3-cohort expansion.
  - In Cohort 1, participants with low CD8 TILs (CD8 < 2%) will be treated with BMS-986277 (using the RD from Part 2; up to 2 cycles) in combination with nivolumab (480 mg Q4W; up to 26 cycles).
  - In Cohort 2, participants with mid CD8 TILs (2% ≤ CD8 < 20%) will be treated with BMS-986277 (using the RD from Part 2; up to 2 cycles) in combination with nivolumab (480 mg Q4W; up to 26 cycles).
  - In Cohort 3, participants with high CD8 TILs (≥ 20%) will be treated with BMS-986277 monotherapy (using the RD from Part 1; up to 2 cycles) with an option for subsequent nivolumab treatment (480 mg Q4W; up to 26 cycles).

Study treatment:

Study Drug for CA034001					
Medication	**Potency**	**IP[a]/Non-IP**	**Blinded or Open Label**	**Packaging / Appearance**	**Storage Conditions (per label)**
BMS-986277 Solution for Injection	2×10^{12} vp/mL 0.5 mL vial	IP[a]	Open Label	Vial	Refer to the label on container and/or pharmacy manual
Nivolumab BMS-936558-01 Solution for Injection	100 mg (10 mg/mL) 40 mg (10 mg/mL)	IP[a]	Open label	Vial	Refer to the label on container and/or pharmacy manual

Abbreviations: IP = investigational product

[a] IP is also known as IMP in some regions.

Data Monitoring Committee: No

Bristol-Myers Squibb (BMS) has developed a multi-layered process to ensure safety monitoring through close collaboration of study site investigators, the BMS study team, and the BMS Global Pharmacovigilance and Epidemiology (GPVE) led Medical Surveillance Team (MST). This collaborative process constitutes the safety monitoring plan for the study. To support safety oversight, BMS has established ongoing processes for collection, review, analysis, and submission of individual adverse event reports and their aggregate analyses. Because this is an open-label study, GPVE, the BMS medical monitor (or designee), and the investigators will have access to all data necessary for safety evaluation.

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

2 SCHEDULE OF ACTIVITIES

Table 2-1: Screening Procedural Outline (All Parts)(CA034001)

Procedure[a]	Screening Visit	Notes
Eligibility Assessments		
Informed Consent	X	A participant is considered enrolled only when a protocol specific informed consent is signed.
Inclusion/Exclusion Criteria	X	All inclusion/exclusion criteria should be assessed and confirmed prior to first dose. See Sections 6.1 and 6.2.
Medical History	X	Include any toxicities or allergy related to previous treatments.
Prior Anti-cancer Therapy	X	
Prior Radiotherapy	X	
ECOG	X	Within 14 days prior to first dose. See Appendix 6.
Tumor Tissue Sample	X	Participants must provide a fresh tumor biopsy within 35 days prior to first dose from the disease site (when possible) or from any metastatic site when the primary site is not available. For Parts 2 and 3 of the study, part of the samples will be used prospectively for CD8 evaluation by IHC. All tissue samples received must be suitable for testing to verify PD-L1 and CD8 status. See Section 9.8 and the Laboratory Manual for further details on procedures for collecting fresh tumor samples.
CD8 T-cell Assay	X	For Part 1, retrospective evaluation and not influencing enrollment. For Part 2, prospective evaluation to determine a minimum number of participants with low or mid CD8 TILs per dose level. For Part 3, prospective evaluation to determine cohort assignment. See Sections 5.1.2 and 5.1.3.
Safety Assessments		
Assessment of Signs and Symptoms	X	Within 14 days prior to first dose.
PE	X	If the screening PE is performed within 24 hours prior to dosing on Day 1, then a single exam may count as both the screening and predose evaluation.
Physical Measurements	X	Includes height and weight.

Table 2-1: Screening Procedural Outline (All Parts)(CA034001)

Procedure[a]	Screening Visit	Notes
Vital Signs	X	Includes body temperature, respiratory rate, seated BP and heart rate. BP and heart rate should be measured after the participant has been resting quietly for at least 5 minutes. Consider alternate position(s) for vital sign collection.
Pulse Oximetry	X	Oxygen saturation at rest.
Concomitant Medication Use	X	Includes medications taken within 14 days prior to first dose.
12-lead ECG	X	Within 14 days prior to first dose. ECGs should be recorded after the participant has been supine for at least 5 minutes.
Chemistry	X	To be performed locally within 14 days prior to first dose. See Section 9.4.5.
Hematology	X	To be performed locally within 14 days prior to first dose. See Section 9.4.5.
Thyroid Function Tests	X	To be performed locally within 14 days prior to first dose. See Section 9.4.5.
Urinalysis	X	To be performed locally within 14 days prior to first dose. See Section 9.4.5.
Serology Tests	X	To be performed locally within 28 days prior to first dose. See Section 9.4.5.
Pregnancy Test	X	For WOCBP only. Serum or urine pregnancy test (minimum sensitivity 25 IU/L or equivalent units of HCG) to be done at screening visit and within 24 hours prior to first dose. See Section 9.4.5.
FSH	X	Only required to confirm menopause in women with age < 55. See Section 9.4.5 and Appendix 4.
AE Reporting		
Monitor for SAE	X	All SAEs must be collected from the date of participant's written consent until 60 days (participants treated with BMS-986277 monotherapy) or 100 days (participants treated with BMS-986277 and nivolumab) post discontinuation of dosing. See Section 9.2.1 and Appendix 3.
Efficacy Assessments		
Body Imaging	X	Contrast enhanced CT of the chest, abdomen, pelvis, and all other known and/or suspected sites of disease should occur within 28 days prior to first dose. See Section 9.1.1 for further details. For participants with TNBC without measurable lesions outside the breast, contrast enhanced MRI of the breasts should also be performed.

Table 2-1: Screening Procedural Outline (All Parts)(CA034001)

Procedure[a]	Screening Visit	Notes
Brain Imaging	X	MRI of the brain without and with contrast is required for participants with known (if not had brain imaging within 30 days of study drug administration) or suspected brain metastases. CT of the brain without and with contrast can be performed if MRI is contraindicated. See Section 9.1.1 for further details.
Bone Scan	X	Required for participants with prostate cancer only (PCWG3 Assessment). Others only as clinically indicated (eg, participants with history or symptoms of bone metastases). See Section 9.1.1 for further details.
IRT		
Register Participant in IRT	X	IRT contact must occur for participant number assignment at the time informed consent is obtained.

Abbreviations: AE = adverse event; BP = blood pressure; CT = computed tomography; ECG = electrocardiogram; ECOG = Eastern Cooperative Oncology Group; FSH = follicle stimulating hormone; HCG = human chorionic gonadotropin; IHC = immunohistochemistry; IRT = interactive response technology; MRI = magnetic resonance imaging; PCWG3 = Prostate Cancer Clinical Trials Working Group 3; PD-L1 = programmed death-ligand 1; PE = physical examination; SAE = serious adverse events; TIL = tumor-infiltrating lymphocyte; TNBC = triple-negative breast cancer; WOCBP = women of childbearing potential

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

Table 2-2: On-Treatment Assessment Schedule (Monotherapy Dose Escalation - BMS-986277 [Part 1])(CA034001)

Procedure[a]	Cycle 1 (42 days: 14 day lead-in period + 28 days)[b]				Cycle 2 (28 days)[b]				EOT[c]	Notes
	D1	D8 (± 3 days)	D15[d,e], D17[e], D19[e]	D29 and D36 (± 3 days)	D1 (± 3 days)	D3[e] and D5[e]	D8 (± 3 days)	D15 and D22 (± 3 days)		
Safety										
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	
Targeted PE, Physical Measurements (weight only), Vital Signs, ECOG Performance Status	X	X	X	X	X	X	X	X	X	On each BMS-986277 dosing day, assessments (vital signs) will be performed at predose and every 15 minutes (± 5 minutes) until 60 minutes following completion of infusion and then at 4 hours (± 30 minutes) and 8 hours (± 1 hour) postdose.
Pulse Oximetry	X	X	X	X	X	X	X	X	X	On each BMS-986277 dosing day, oxygen saturation at rest will be performed at predose and every 15 minutes (± 5 minutes) until 60 minutes following completion of infusion and then at 4 hours (± 30 minutes) and 8 hours (± 1 hour) postdose.

Table 2-2: On-Treatment Assessment Schedule (Monotherapy Dose Escalation - BMS-986277 [Part 1])(CA034001)

Procedure[a]	Cycle 1 (42 days: 14 day lead-in period + 28 days)[b]				Cycle 2 (28 days)[b]				EOT[c]	Notes
	D1	D8 (± 3 days)	D15[d,e], D17[e], D19[e]	D29 and D36 (± 3 days)	D1 (± 3 days)	D3[e] and D5[e]	D8 (± 3 days)	D15 and D22 (± 3 days)		
SAE Assessment	Continuously									All SAEs must be collected from the date of participant's written consent until 60 days post discontinuation of dosing. See Section 9.2.1 and Appendix 3.
AE Assessment	Continuously									All AEs must be collected from the first dose of study treatment until 60 days post discontinuation of dosing or start of subsequent anti-cancer therapy, whichever is earlier. See Section 9.2.1 and Appendix 3.
Laboratory Tests										On-study laboratory tests to be done on-site/local within 72 hours prior to dosing. For the first dosing visit, labs need not be repeated if they were performed within 72 hours and the results are available and have been reviewed for eligibility. See Section 9.4.5.
Chemistry	X	X	X	X	X	X	X	X	X	See Section 9.4.5.
Hematology	X	X	X	X	X	X	X	X	X	See Section 9.4.5.

Table 2-2: On-Treatment Assessment Schedule (Monotherapy Dose Escalation - BMS-986277 [Part 1])(CA034001)

Procedure[a]	Cycle 1 (42 days: 14 day lead-in period + 28 days)[b]				Cycle 2 (28 days)[b]				EOT[c]	Notes
	D1	D8 (± 3 days)	D15[d,e], D17[e], D19[e]	D29 and D36 (± 3 days)	D1 (± 3 days)	D3[e] and D5[e]	D8 (± 3 days)	D15 and D22 (± 3 days)		
Thyroid Function Tests	X				X				X	TSH with reflex testing (free T3 and free T4), if applicable. Results should be examined by the investigator or appropriate designee within 48 hours of dose administration (or prior to the next dose if within < 48 hours). See Section 9.4.5.
Urinalysis	X	X	X	X	X	X	X	X	X	See Section 9.4.5.
[redacted]	[redacted]				[redacted]					[redacted]
Cytokine Release Monitoring	X	X	X	X	X	X	X	X	X	See Section 9.4.1. On each BMS-986277 dosing day: Predose, 4 hours (± 30 minutes), 8** hours (± 1 hour), and 12** hours (± 1 hour) post-virus infusion, and as clinically indicated. **Assessments at 8 and 12 hours are optional based on clinical symptoms and investigator judgment. Note: Indicated time points are samples to be collected. Analysis of samples will occur when clinically indicated.
12-lead ECG	X				X				X	D1 of each cycle prior to dosing (up to 3 days prior) and as clinically indicated.

Table 2-2: On-Treatment Assessment Schedule (Monotherapy Dose Escalation - BMS-986277 [Part 1])(CA034001)

Procedure[a]	Cycle 1 (42 days: 14 day lead-in period + 28 days)[b]				Cycle 2 (28 days)[b]				EOT[c]	Notes
	D1	D8 (± 3 days)	D15[d,e], D17[e], D19[e]	D29 and D36 (± 3 days)	D1 (± 3 days)	D3[e] and D5[e]	D8 (± 3 days)	D15 and D22 (± 3 days)		
										ECGs should be recorded after the participant has been supine for at least 5 minutes.
Pregnancy Test (WOCBP only)	X	See Notes.								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 first dose, and then Q4W (± 1 week) regardless of dosing schedule. See Section 9.4.5. See Section 9.2.5.
Efficacy Assessments										
Brain Imaging	For participants with history of brain metastases, surveillance scans to be done per SOC frequency, or sooner if clinically indicated. See Section 9.1.1 for further details.									
Body Imaging	Contrast enhanced CT of the chest, abdomen, pelvis, and all other known and/or suspected sites of disease should occur every 8 weeks (± 7 days) starting from date of first dose until withdrawal from study, or start of subsequent treatment, whichever occurs first. See Section 9.1.1 for further details. For participants with TNBC without measurable lesions outside the breast, contrast enhanced MRI of the breasts should also be performed. For participants with prostate cancer only (PCWG3 Assessment), contrast enhanced CT of the chest, abdomen, pelvis, and all other known and/or suspected sites of disease should occur every 8 weeks (± 7 days) for 24 weeks and then every 12 weeks (± 7 days).									

Table 2-2: On-Treatment Assessment Schedule (Monotherapy Dose Escalation - BMS-986277 [Part 1])(CA034001)

Procedure[a]	Cycle 1 (42 days: 14 day lead-in period + 28 days)[b]				Cycle 2 (28 days)[b]				EOT[c]	Notes
	D1	D8 (± 3 days)	D15[d,e], D17[e], D19[e]	D29 and D36 (± 3 days)	D1 (± 3 days)	D3[e] and D5[e]	D8 (± 3 days)	D15 and D22 (± 3 days)		
Bone Scan	For participants with prostate cancer only (PCWG3 Assessment), scans should occur every 8 weeks (± 7 days) for 24 weeks and then every 12 weeks (± 7 days). Others only as clinically indicated (eg, participants with history or symptoms of bone metastases). See Section 9.1.1 for further details.									
PK/IMG Collection										
PK and IMG Samples	See Table 9.5-1 for full details on PK and IMG sampling schedule.									
Viral Shedding Assessments	See Table 9.5-1 for full details on shedding sampling schedule.									
[redacted]										
[redacted]	[redacted]									
[redacted]								[redacted]	[redacted]	[redacted]
Clinical Drug Supply										
Treatment Assignment	X									See Section 7.2.
IRT Drug Vial Assignment	X		X		X	X				
Premedication	X		X		X	X				See Section 7.7.2.

Table 2-2: On-Treatment Assessment Schedule (Monotherapy Dose Escalation - BMS-986277 [Part 1])(CA034001)

Procedure[a]	Cycle 1 (42 days: 14 day lead-in period + 28 days)[b]				Cycle 2 (28 days)[b]				EOT[c]	Notes
	D1	D8 (± 3 days)	D15[d,e], D17[e], D19[e]	D29 and D36 (± 3 days)	D1 (± 3 days)	D3[e] and D5[e]	D8 (± 3 days)	D15 and D22 (± 3 days)		
BMS-986277 Administration[f]	X		X		X	X				Participants will receive BMS-986277 at 1 of 4 different concentrations. Participants must be observed for at least 4 hours following the completion of BMS-986277 infusion due to the potential risk of and to monitor for infusion reactions. See Section 7.1.3.1.

Abbreviations: AE = adverse event; C = cycle; CT = computed tomography; D = day; DLT = dose-limiting toxicity; ECG = electrocardiogram; ECOG = Eastern Cooperative Oncology Group; eCRF = electronic case report form; EOT = end of treatment; FU = follow-up; HCG = human chorionic gonadotropin; IMG = immunogenicity; IRT = interactive response technology; MRI = magnetic resonance imaging; PCWG3 = Prostate Cancer Clinical Working Group 3; PE = physical examination; PK = pharmacokinetic; Q4W = every 4 weeks; SAE = serious adverse event; SOC = standard of care; TNBC = triple-negative breast cancer; TSH = thyroid stimulating hormone; WOCBP = women of childbearing potential

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

[b] Participants who complete the first cycle and do not have a DLT, have not had clinical evidence of disease progression, and are considered suitable for further treatment may receive up to 1 additional cycle of BMS-986277 with Cycle 2 beginning no sooner than 42 days after C1D1.

[c] EOT visit is at C2D28 or at the time of study treatment discontinuation. If within 7 days prior to FU Visit 1, the EOT visit may be skipped and FU Visit 1 should be completed and include all EOT biomarker samples.

[d] Up to + 7 day dosing for C1D15.

[e] A minimum of 24 hours is required between doses during sequential dosing weeks (eg, C1D15-C1D19; C2D1-C2D5). Infusions of BMS 986277 on Day 17 and Day 19 must be administered within 7 days of Day 15. Infusions of BMS-986277 on Day 3 and Day 5 must be administered within 7 days of Day 1.

[f] Dosing for the initial participants into each dose level will be staggered by at least 7 days between participants (see Section 5.1.1).

Table 2-3: On-Treatment Assessment Schedule (Combination Dose Escalation - BMS-986277 and Nivolumab [Part 2])(CA034001)

Procedures[a]	Cycle 1 (28 days)[b]					Cycle 2 (28 days)[b]					Cycle 3 and each subsequent cycle (28 days; Nivolumab only)[c]			Notes
	D1	D3[d] and D5[d]	D8 (± 3 days)	D15 (± 3 days)	D22 (± 3 days)	D1 (± 3 days)	D3[d] and D5[d]	D8 (± 3 days)	D15 (± 3 days)	D22 (± 3 days)	D1 (± 3 days)	D15 (± 3 days)	EOT[e]	
Safety														
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	
Targeted PE, Physical Measurements, Vital Signs, ECOG Performance Status	X	X	X	X	X	X	X	X	X	X	X	X	X	On each BMS-986277 dosing day, assessments (vital signs) will be performed at predose and every 15 minutes (± 5 minutes) until 60 minutes following completion of infusion and then at 4 hours (± 30 minutes) and 8 hours (± 1 hour) postdose. See note in Table 2-1. On each nivolumab dosing day, vital signs will be performed at predose.

Table 2-3: On-Treatment Assessment Schedule (Combination Dose Escalation - BMS-986277 and Nivolumab [Part 2])(CA034001)

Procedures[a]	Cycle 1 (28 days)[b]					Cycle 2 (28 days)[b]					Cycle 3 and each subsequent cycle (28 days; Nivolumab only)[c]			Notes
	D1	D3[d] and D5[d]	D8 (± 3 days)	D15 (± 3 days)	D22 (± 3 days)	D1 (± 3 days)	D3[d] and D5[d]	D8 (± 3 days)	D15 (± 3 days)	D22 (± 3 days)	D1 (± 3 days)	D15 (± 3 days)	EOT[e]	
Pulse Oximetry	X	X	X	X	X	X	X	X	X	X	X	X	X	On each BMS-986277 dosing day, oxygen saturation at rest will be performed at predose and every 15 minutes (± 5 minutes) until 60 minutes following completion of infusion, and then at 4 hours (± 30 minutes) and 8 hours (± 1 hour) postdose. On each nivolumab dosing day, pulse oximetry will be performed at predose.
SAE Assessment	Continuously													All SAEs must be collected from the date of participant's written consent until 100 days post discontinuation of dosing. See Section 9.2.1 and Appendix 3.

Table 2-3: On-Treatment Assessment Schedule (Combination Dose Escalation - BMS-986277 and Nivolumab [Part 2])(CA034001)

Procedures[a]	Cycle 1 (28 days)[b]					Cycle 2 (28 days)[b]					Cycle 3 and each subsequent cycle (28 days; Nivolumab only)[c]			Notes
	D1	D3[d] and D5[d]	D8 (± 3 days)	D15 (± 3 days)	D22 (± 3 days)	D1 (± 3 days)	D3[d] and D5[d]	D8 (± 3 days)	D15 (± 3 days)	D22 (± 3 days)	D1 (± 3 days)	D15 (± 3 days)	EOT[e]	
AE Assessment	Continuously													All AEs must be collected from the first dose of study treatment until 100 days post discontinuation of dosing or start of subsequent anti-cancer therapy, whichever is earlier. See Section 9.2.1 and Appendix 3.
Laboratory Tests														On-study laboratory tests to be done on site/local within 72 hours prior to dosing. For the first dosing visit, labs need not be repeated if they were performed within 72 hours and the results are available and have been reviewed for eligibility. See Section 9.4.5.
Chemistry	X	X	X	X	X	X	X	X	X	X	X	X	X	See Section 9.4.5.

Table 2-3: On-Treatment Assessment Schedule (Combination Dose Escalation - BMS-986277 and Nivolumab [Part 2])(CA034001)

Procedures[a]	Cycle 1 (28 days)[b]					Cycle 2 (28 days)[b]					Cycle 3 and each subsequent cycle (28 days; Nivolumab only)[c]			Notes
	D1	D3[d] and D5[d]	D8 (± 3 days)	D15 (± 3 days)	D22 (± 3 days)	D1 (± 3 days)	D3[d] and D5[d]	D8 (± 3 days)	D15 (± 3 days)	D22 (± 3 days)	D1 (± 3 days)	D15 (± 3 days)	EOT[e]	
Hematology	X	X	X	X	X	X	X	X	X	X	X	X	X	See Section 9.4.5.
Thyroid Function Tests	X			X		X			X		X		X	TSH with reflex testing (free T3 and free T4), if applicable. Results should be examined by the investigator or appropriate designee within 48 hours of dose administration (or prior to the next dose if within < 48 hours). See Section 9.4.5.
Urinalysis	X	X	X	X	X	X	X	X	X	X	X	X	X	See Section 9.4.5.
[redacted]	[redacted]					[redacted]					[redacted]			[redacted].
Cytokine Release Monitoring	X	X	X	X	X	X	X	X	X	X	X	X	X	See Section 9.4.1. On each BMS-986277 dosing day: predose, 4 hours (± 30 minutes), 8** hours (± 1hour), and 12** hours (± 1 hour) post-virus infusion and as clinically indicated.

Table 2-3: On-Treatment Assessment Schedule (Combination Dose Escalation - BMS-986277 and Nivolumab [Part 2])(CA034001)

Procedures[a]	Cycle 1 (28 days)[b]					Cycle 2 (28 days)[b]					Cycle 3 and each subsequent cycle (28 days; Nivolumab only)[c]			Notes
	D1	D3[d] and D5[d]	D8 (± 3 days)	D15 (± 3 days)	D22 (± 3 days)	D1 (± 3 days)	D3[d] and D5[d]	D8 (± 3 days)	D15 (± 3 days)	D22 (± 3 days)	D1 (± 3 days)	D15 (± 3 days)	EOT[e]	
														**Assessments at 8 and 12 hours are optional based on clinical symptoms and investigator judgment. Note: Indicated time points are samples to be collected. Analysis of samples will occur when clinically indicated.
12-lead ECG	X					X					X		X	D1 prior to dosing (up to 3 days before) of each of cycle and as clinically indicated. ECGs should be recorded after the participant has been supine for at least 5 minutes.
Pregnancy Test (WOCBP only)	X	See Notes.												Serum or urine pregnancy test to be done within 24 hours prior to first dose, and then Q4W (± 1 week) regardless of dosing schedule. See Sections 9.2.5 and 9.4.5.

Table 2-3: On-Treatment Assessment Schedule (Combination Dose Escalation - BMS-986277 and Nivolumab [Part 2])(CA034001)

Procedures[a]	Cycle 1 (28 days)[b]					Cycle 2 (28 days)[b]					Cycle 3 and each subsequent cycle (28 days; Nivolumab only)[c]			Notes
	D1	D3[d] and D5[d]	D8 (± 3 days)	D15 (± 3 days)	D22 (± 3 days)	D1 (± 3 days)	D3[d] and D5[d]	D8 (± 3 days)	D15 (± 3 days)	D22 (± 3 days)	D1 (± 3 days)	D15 (± 3 days)	EOT[e]	
Efficacy Assessments														
Brain Imaging	For participants with history of brain metastases, surveillance scans to be done per SOC frequency, or sooner if clinically indicated. See Section 9.1.1.													
Body Imaging	Contrast enhanced CT of the chest, abdomen, pelvis, and all other known and/or suspected sites of disease should occur every 8 weeks (± 7 days) starting from date of first dose until withdrawal from study, or start of subsequent treatment, whichever occurs first. See Section 9.1.1 for further details. For participants with TNBC without measurable lesions outside the breast, contrast enhanced MRI of the breasts should also be performed. For participants with prostate cancer only (PCWG3 Assessment), contrast enhanced CT of the chest, abdomen, pelvis, and all other known and/or suspected sites of disease should occur every 8 weeks (± 7 days) for 24 weeks and then every 12 weeks (± 7 days).													
Bone Scan	For participants with prostate cancer only (PCWG3 Assessment), scans should occur every 8 weeks (± 7 days) for 24 weeks and then every 12 weeks (± 7 days). Others only as clinically indicated (eg, participants with history or symptoms of bone metastases). See Section 9.1.1 for further details.													
PK/IMG Collection														
PK and IMG Samples	See Table 9.5-2 for full details on PK and IMG sampling schedule.													
Viral Shedding Assessments	See Table 9.5-2 for full details on shedding sampling schedule.													

Table 2-3: On-Treatment Assessment Schedule (Combination Dose Escalation - BMS-986277 and Nivolumab [Part 2])(CA034001)

Procedures[a]	Cycle 1 (28 days)[b]					Cycle 2 (28 days)[b]					Cycle 3 and each subsequent cycle (28 days; Nivolumab only)[c]			Notes
	D1	D3[d] and D5[d]	D8 (± 3 days)	D15 (± 3 days)	D22 (± 3 days)	D1 (± 3 days)	D3[d] and D5[d]	D8 (± 3 days)	D15 (± 3 days)	D22 (± 3 days)	D1 (± 3 days)	D15 (± 3 days)	EOT[e]	
[redacted]														
[redacted]														
[redacted]														
Clinical Drug Supply														
Treatment Assignment	X													See Section 7.2.
IRT Drug Vial Assignment	X	X		X		X	X		X			X		
Premedication	X	X				X	X							See Section 7.7.2.

Table 2-3: On-Treatment Assessment Schedule (Combination Dose Escalation - BMS-986277 and Nivolumab [Part 2])(CA034001)

Procedures[a]	Cycle 1 (28 days)[b]					Cycle 2 (28 days)[b]					Cycle 3 and each subsequent cycle (28 days; Nivolumab only)[c]			Notes
	D1	D3[d] and D5[d]	D8 (± 3 days)	D15 (± 3 days)	D22 (± 3 days)	D1 (± 3 days)	D3[d] and D5[d]	D8 (± 3 days)	D15 (± 3 days)	D22 (± 3 days)	D1 (± 3 days)	D15 (± 3 days)	EOT[e]	
BMS-986277 Administration[f]	X	X				X	X							BMS-986277 dose level will be dispensed as: Dose recommended from Part 1 OR Dose(s) lower than the recommended in Part 1 for up to 2 Cycles. Participants must be observed for at least 4 hours following the completion of BMS-986277 infusion due to the potential risk of and to monitor for infusion reactions. See Section 7.1.3.1.
Nivolumab Administration				X					X			X		Nivolumab to be administered as a flat dose (480 mg) Q4W for up to 26 cycles via an approximately 30 minute infusion. See Sections 7.1.2 and 7.1.4.

Abbreviations: AE = adverse event; C = cycle; CT = computed tomography; D = day; DLT = dose-limiting toxicity; ECG = electrocardiogram; ECOG = Eastern Cooperative Oncology Group; eCRF = electronic case report form; EOT = end of treatment; FU = follow-up; IMG = immunogenicity; IRT = interactive response technology; MRI = magnetic resonance imaging; PCWG3 = Prostate Cancer Clinical Working Group 3; PE = physical examination; PK = pharmacokinetic; Q4W = every 4 weeks; SAE = serious adverse event; SOC = standard of care; TNBC = triple-negative breast cancer; TSH = thyroid stimulating hormone; WOCBP = women of childbearing potential

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

[b] Participants who complete the first cycle and do not have a DLT, have not had clinical evidence of disease progression, and are considered suitable for further treatment may receive up to 1 additional cycle of BMS-986277 in combination with nivolumab with the subsequent cycle beginning no sooner than 28 days after C1D1.

[c] Up to 26 cycles of nivolumab.

[d] A minimum of 24 hours is required between doses during sequential dosing weeks (eg, C1D1-C1D5; C2D1-C2D5). Infusions of BMS-986277 on Day 3 and Day 5 must be administered within 7 days of Day 1.

[e] EOT visit is C26D29 (± 7 days) or at the time of study treatment discontinuation. If within 7 days prior to FU Visit 1, the EOT visit may be skipped and FU Visit 1 should be completed and include all EOT biomarker samples.

[f] Dosing for the initial 2 participants into each dose level in Part 2 will be staggered by at least 7 days between participants (see Section 5.1.2).

Table 2-4: On-Treatment Assessment Schedule (Combination Expansion - BMS-986277 and Nivolumab [Part 3 Cohorts 1-2])(CA034001)

Procedures[a]	Cycle 1 (28 days)[b]					Cycle 2 (28 days)[b]					Cycle 3 and each subsequent cycle (28 days; Nivolumab only)[c]			Notes
	D1 d	D3[d] and D5[d]	D8 (± 3 days)	D15 (± 3 days)	D22 (± 3 days)	D1[d] (± 3 days)	D3[d] and D5[d]	D8 (± 3 days)	D15 (± 3 days)	D22 (± 3 days)	D1 (± 3 days)	D15 (± 3 days)	EOT[e]	
Safety														
[redacted]	[redacted]													
Targeted PE, Physical Measurements, Vital Signs, ECOG Performance Status	X	X	X	X	X	X	X	X	X	X	X	X	X	On each BMS-986277 dosing day, assessments (vital signs) will be performed at predose, and every 15 minutes (± 5 minutes) until 60 minutes following completion of infusion and then at 4 hours (± 30 minutes) and 8 hours (± 1 hour) postdose. See note in Table 2-1. On each nivolumab dosing day, vital signs will be performed at predose only.

Table 2-4: On-Treatment Assessment Schedule (Combination Expansion - BMS-986277 and Nivolumab [Part 3 Cohorts 1-2])(CA034001)

Procedures[a]	Cycle 1 (28 days)[b]					Cycle 2 (28 days)[b]					Cycle 3 and each subsequent cycle (28 days; Nivolumab only)[c]			Notes
	D1 d	D3[d] and D5[d]	D8 (± 3 days)	D15 (± 3 days)	D22 (± 3 days)	D1[d] (± 3 days)	D3[d] and D5[d]	D8 (± 3 days)	D15 (± 3 days)	D22 (± 3 days)	D1 (± 3 days)	D15 (± 3 days)	EOT[e]	
Pulse Oximetry	X	X	X	X	X	X	X	X	X	X	X	X	X	On each BMS-986277 dosing day, oxygen saturation at rest will be performed at predose and every 15 minutes (± 5 minutes) until 60 minutes following completion of infusion and then at 4 hours (± 30 minutes) and 8 hours (± 1 hour) postdose. On each nivolumab dosing day, pulse oximetry will be performed predose only.
SAE Assessment	Continuously													All SAEs must be collected from the date of participant's written consent until 100 days post discontinuation of dosing. See Section 9.2.1 and Appendix 3.
AE Assessment	Continuously													All AEs must be collected from the first dose of study treatment until 100 days post discontinuation of dosing or start of subsequent anti-cancer therapy, whichever is earlier. See Section 9.2.1 and Appendix 3.

Table 2-4: On-Treatment Assessment Schedule (Combination Expansion - BMS-986277 and Nivolumab [Part 3 Cohorts 1-2])(CA034001)

Procedures[a]	Cycle 1 (28 days)[b]					Cycle 2 (28 days)[b]					Cycle 3 and each subsequent cycle (28 days; Nivolumab only)[c]			Notes
	D1 d	D3[d] and D5[d]	D8 (± 3 days)	D15 (± 3 days)	D22 (± 3 days)	D1[d] (± 3 days)	D3[d] and D5[d]	D8 (± 3 days)	D15 (± 3 days)	D22 (± 3 days)	D1 (± 3 days)	D15 (± 3 days)	EOT[e]	
Cytokine Release Monitoring	X	X	X	X	X	X	X	X	X	X	X	X	X	See Section 9.4.1 On each BMS-986277 dosing day: predose, 4 hours (± 30 minutes), 8** hours (± 1 hour), and 12** hours (± 1 hour) post-virus infusion, and as clinically indicated. **Assessments at 8 and 12 hours are optional based on clinical symptoms and investigator judgment. Note: Indicated time points are samples to be collected. Analysis of samples will occur when clinically indicated.
12-lead ECG	X					X					X		X	D1 prior to dosing (up to 3 days before) of each cycle and as clinically indicated. ECGs should be recorded after the participant has been supine for at least 5 minutes.

Table 2-4: On-Treatment Assessment Schedule (Combination Expansion - BMS-986277 and Nivolumab [Part 3 Cohorts 1-2])(CA034001)

Procedures[a]	Cycle 1 (28 days)[b]					Cycle 2 (28 days)[b]					Cycle 3 and each subsequent cycle (28 days; Nivolumab only)[c]			Notes
	D1 d	D3[d] and D5[d]	D8 (± 3 days)	D15 (± 3 days)	D22 (± 3 days)	D1[d] (± 3 days)	D3[d] and D5[d]	D8 (± 3 days)	D15 (± 3 days)	D22 (± 3 days)	D1 (± 3 days)	D15 (± 3 days)	EOT[e]	
Laboratory Tests														On-study laboratory tests to be done on site/local within 72 hours prior to dosing. For the first dosing visit, labs need not be repeated if they were performed within 72 hours and the results are available and have been reviewed for eligibility. See Section 9.4.5.
Chemistry	X	X	X	X	X	X	X	X	X	X	X	X	X	See Section 9.4.5.
Hematology	X	X	X	X	X	X	X	X	X	X	X	X	X	See Section 9.4.5.
Thyroid Function Tests	X			X		X			X		X		X	TSH with reflex testing (free T3 and free T4), if applicable. Results should be examined by the investigator or appropriate designee within 48 hours of dose administration (or prior to the next dose if within < 48 hours). See Section 9.4.5.
Urinalysis	X	X	X	X	X	X	X	X	X	X	X	X	X	See Section 9.4.5.

Table 2-4: On-Treatment Assessment Schedule (Combination Expansion - BMS-986277 and Nivolumab [Part 3 Cohorts 1-2])(CA034001)

Procedures[a]	Cycle 1 (28 days)[b]					Cycle 2 (28 days)[b]					Cycle 3 and each subsequent cycle (28 days; Nivolumab only)[c]			Notes
	D1 d	D3[d] and D5[d]	D8 (± 3 days)	D15 (± 3 days)	D22 (± 3 days)	D1[d] (± 3 days)	D3[d] and D5[d]	D8 (± 3 days)	D15 (± 3 days)	D22 (± 3 days)	D1 (± 3 days)	D15 (± 3 days)	EOT[e]	
[redacted]	[redacted]					[redacted]					[redacted]			[redacted]
Pregnancy Test (WOCBP only)	X	See Notes												Serum or urine pregnancy test to be done within 24 hours prior to first dose, and then Q4W (± 1 week) regardless of dosing schedule. See Sections 9.2.5 or 9.4.5.
Efficacy Assessments														
Body Imaging	Contrast enhanced CT of the chest, abdomen, pelvis, and all other known and/or suspected sites of disease should occur every 8 weeks (± 7 days) starting from date of first dose until withdrawal from study, or start of subsequent treatment, whichever occurs first. See Section 9.1.1 for further details. For participants with TNBC without measurable lesions outside the breast, contrast enhanced MRI of the breasts should also be performed. For participants with prostate cancer only (PCWG3 Assessment), contrast enhanced CT of the chest, abdomen, pelvis, and all other known and/or suspected sites of disease should occur every 8 weeks (± 7 days) for 24 weeks and then every 12 weeks (± 7 days).													
Brain Scan	For participants with history of brain metastases, surveillance scans to be done per SOC frequency, or sooner if clinically indicated. See Section 9.1.1 for further details.													
Bone Scan	For participants with prostate cancer only (PCWG3 Assessment), scans should occur every 8 weeks (± 7 days) for 24 weeks and then every 12 weeks (± 7 days). Others only as clinically indicated (eg, participants with history or symptoms of bone metastases). See Section 9.1.1 for further details.													

Table 2-4: On-Treatment Assessment Schedule (Combination Expansion - BMS-986277 and Nivolumab [Part 3 Cohorts 1-2])(CA034001)

Procedures[a]	Cycle 1 (28 days)[b]					Cycle 2 (28 days)[b]					Cycle 3 and each subsequent cycle (28 days; Nivolumab only)[c]			Notes
	D1 d	D3[d] and D5[d]	D8 (± 3 days)	D15 (± 3 days)	D22 (± 3 days)	D1[d] (± 3 days)	D3[d] and D5[d]	D8 (± 3 days)	D15 (± 3 days)	D22 (± 3 days)	D1 (± 3 days)	D15 (± 3 days)	EOT[e]	
PK/IMG Collection														
PK and IMG Samples	See Table 9.5-2 for full details on PK and IMG sampling schedule.													
Viral Shedding Assessments	See Table 9.5-2 for full details on shedding sampling schedule.													
[redacted]														
[redacted]	[redacted]													
[redacted]														[redacted]
Clinical Drug Supply														
Treatment Assignment	X													See Section 7.2.
IRT Drug Vial Assignment	X	X		X		X	X		X			X		

Table 2-4: On-Treatment Assessment Schedule (Combination Expansion - BMS-986277 and Nivolumab [Part 3 Cohorts 1-2])(CA034001)

Procedures[a]	Cycle 1 (28 days)[b]					Cycle 2 (28 days)[b]					Cycle 3 and each subsequent cycle (28 days; Nivolumab only)[c]			Notes
	D1 d	D3[d] and D5[d]	D8 (± 3 days)	D15 (± 3 days)	D22 (± 3 days)	D1[d] (± 3 days)	D3[d] and D5[d]	D8 (± 3 days)	D15 (± 3 days)	D22 (± 3 days)	D1 (± 3 days)	D15 (± 3 days)	EOT[e]	
Premedication	X	X				X	X							See Section 7.7.2.
BMS-986277 Administration	X	X				X	X							BMS-986277 will be administered at the RD from Part 2 and will be administered for up to 2 cycles. Participants must be observed for at least 4 hours following the completion of BMS-986277 infusion due to the potential risk of and to monitor for infusion reactions. See Section 7.1.5.
Nivolumab Administration				X					X			X		Nivolumab to be administered as a flat dose (480 mg) Q4W for up to 26 cycles via an approximately 30 minute infusion. See Sections 7.1.2 and 7.1.5.

Abbreviations: AE = adverse event; C = cycle; CT = computed tomography; D = day; DLT = dose-limiting toxicity; ECG = electrocardiogram; ECOG = Eastern Cooperative Oncology Group; eCRF = electronic case report form; EOT = end of treatment; FU = follow-up; IMG = immunogenicity; IRT = interactive response technology; MRI = magnetic resonance imaging; PCWG3 = Prostate Cancer Clinical Working Group 3; PE = physical examination; PK = pharmacokinetic; Q4W

= every 4 weeks; RD = recommended dose; SAE = serious adverse event; SOC = standard of care; TNBC = triple-negative breast cancer; TSH = thyroid stimulating hormone; WOCBP = women of childbearing potential

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

[b] Participants who complete the first cycle and do not have a DLT, have not had clinical evidence of disease progression, and are considered suitable for further treatment may receive up to 1 additional cycle of BMS-986277 in combination with nivolumab with the subsequent cycle beginning no sooner than 28 days after C1D1.

[c] Up to 26 cycles of nivolumab.

[d] A minimum of 24 hours is required between doses during sequential dosing weeks (eg, C1D1-C1D5; C2D1-C2D5). Infusions of BMS-986277 on Day 3 and Day 5 must be administered within 7 days of Day 1.

[e] EOT visit is C26D29 (± 7 days) or at the time of study treatment discontinuation. If within 7 days prior to FU Visit 1, the EOT visit may be skipped and FU Visit 1 should be completed and include all EOT biomarker samples.

Table 2-5: On-Treatment Assessment Schedule (Monotherapy Expansion - BMS-986277 [Part 3 Cohort 3] Monotherapy with Option for Subsequent Nivolumab Therapy)(CA034001)

Procedures[a]	Cycle 1 (28 days)[b]					Cycle 2 (28 days)[b]					Optional: Cycle 3 and each subsequent cycle (28 days; Nivolumab only)[c]			Notes
	D1[d]	D3[d] and D5[d]	D8 (± 3 days)	D15 (± 3 days)	D22 (± 3 days)	D1[d] (± 3 days)	D3 d and D5 d	D8 (± 3 days)	D15 (± 3 days)	D22 (± 3 days)	D1 (± 3 days)	D15 (± 3 days)	EOT[e]	
Safety														
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	
Targeted PE, Physical Measurements, Vital Signs, ECOG Performance Status	X	X	X	X	X	X	X	X	X	X	X	X	X	On each BMS-986277 dosing day, assessments (vital signs) will be performed at predose and every 15 minutes (± 5 minutes) until 60 minutes following completion of infusion and then at 4 hours (± 30 minutes) and 8 hours (± 1 hour) postdose. See note in Table 2-1. On each nivolumab dosing day, vital signs will be performed at predose only.

Table 2-5: On-Treatment Assessment Schedule (Monotherapy Expansion - BMS-986277 [Part 3 Cohort 3] Monotherapy with Option for Subsequent Nivolumab Therapy)(CA034001)

Procedures[a]	Cycle 1 (28 days)[b]					Cycle 2 (28 days)[b]					Optional: Cycle 3 and each subsequent cycle (28 days; Nivolumab only)[c]			Notes
	D1[d]	D3[d] and D5[d]	D8 (± 3 days)	D15 (± 3 days)	D22 (± 3 days)	D1[d] (± 3 days)	D3 d and D5 d	D8 (± 3 days)	D15 (± 3 days)	D22 (± 3 days)	D1 (± 3 days)	D15 (± 3 days)	EOT[e]	
Pulse Oximetry	X	X	X	X	X	X	X	X	X	X	X	X	X	On each BMS-986277 dosing day, oxygen saturation at rest will be performed at predose and every 15 minutes (± 5 minutes) until 60 minutes following completion of infusion and then at 4 hours (± 30 minutes) and 8 hours (± 1 hour) postdose. On each nivolumab dosing day, pulse oximetry will be performed at predose only.
SAE Assessment	Continuously													All SAEs must be collected from the date of participant's written consent until 60 days (participants treated with BMS-986277 monotherapy) or 100 days (participants treated with BMS-986277 and nivolumab) post discontinuation of dosing. See Section 9.2.1 and Appendix 3.

Table 2-5: On-Treatment Assessment Schedule (Monotherapy Expansion - BMS-986277 [Part 3 Cohort 3] Monotherapy with Option for Subsequent Nivolumab Therapy)(CA034001)

Procedures[a]	Cycle 1 (28 days)[b]					Cycle 2 (28 days)[b]					Optional: Cycle 3 and each subsequent cycle (28 days; Nivolumab only)[c]			Notes
	D1[d]	D3[d] and D5[d]	D8 (± 3 days)	D15 (± 3 days)	D22 (± 3 days)	D1[d] (± 3 days)	D3 d and D5 d	D8 (± 3 days)	D15 (± 3 days)	D22 (± 3 days)	D1 (± 3 days)	D15 (± 3 days)	EOT[e]	
AE Assessment	Continuously													All AEs must be collected from the first dose of study treatment until 60 days (participants treated with BMS-986277 monotherapy only) or 100 days (participants treated with BMS-986277 and nivolumab) post discontinuation of dosing or start of subsequent anti-cancer therapy, whichever occurs earlier. See Section 9.2.1 and Appendix 3.
Cytokine Release Monitoring	X	X	X	X	X	X	X	X	X	X	X	X	X	See Section 9.4.1. On each BMS-986277 dosing day, predose, 4 hours (± 30 minutes), 8** hours (± 1 hour), and 12** hours (± 1 hour) post-virus infusion, and as clinically indicated. **Assessments at 8 and 12 hours are optional based on clinical symptoms and investigator judgment.

Table 2-5: On-Treatment Assessment Schedule (Monotherapy Expansion - BMS-986277 [Part 3 Cohort 3] Monotherapy with Option for Subsequent Nivolumab Therapy)(CA034001)

Procedures[a]	Cycle 1 (28 days)[b]					Cycle 2 (28 days)[b]					Optional: Cycle 3 and each subsequent cycle (28 days; Nivolumab only)[c]			Notes
	D1[d]	D3[d] and D5[d]	D8 (± 3 days)	D15 (± 3 days)	D22 (± 3 days)	D1[d] (± 3 days)	D3 d and D5 d	D8 (± 3 days)	D15 (± 3 days)	D22 (± 3 days)	D1 (± 3 days)	D15 (± 3 days)	EOT[e]	
														Note: Indicated time points are samples to be collected. Analysis of samples will occur when clinically indicated.
12-lead ECG	X					X					X		X	D1 prior to dosing (up to 3 days before) of each cycle and as clinically indicated. ECGs should be recorded after the participant has been supine for at least 5 minutes.
Laboratory Tests														On-study laboratory tests to be done on site/local within 72 hours prior to dosing. For the first dosing visit, labs need not be repeated if they were performed within 72 hours and the results are available and have been reviewed for eligibility. See Section 9.4.5.
Chemistry	X	X	X	X	X	X	X	X	X	X	X	X	X	See Section 9.4.5.
Hematology	X	X	X	X	X	X	X	X	X	X	X	X	X	See Section 9.4.5.

Table 2-5: On-Treatment Assessment Schedule (Monotherapy Expansion - BMS-986277 [Part 3 Cohort 3] Monotherapy with Option for Subsequent Nivolumab Therapy)(CA034001)

Procedures[a]	Cycle 1 (28 days)[b]					Cycle 2 (28 days)[b]					Optional: Cycle 3 and each subsequent cycle (28 days; Nivolumab only)[c]			Notes
	D1[d]	D3[d] and D5[d]	D8 (± 3 days)	D15 (± 3 days)	D22 (± 3 days)	D1[d] (± 3 days)	D3 d and D5 d	D8 (± 3 days)	D15 (± 3 days)	D22 (± 3 days)	D1 (± 3 days)	D15 (± 3 days)	EOT[e]	
Thyroid Function Tests	X					X					X		X	TSH with reflex testing (free T3 and free T4), if applicable. Results should be examined by the investigator or appropriate designee within 48 hours of dose administration (or prior to the next dose if within < 48 hours). See Section 9.4.5.
Urinalysis	X	X	X	X	X	X	X	X	X	X	X	X	X	See Section 9.4.5.
[redacted]	[redacted]					[redacted]					[redacted]			[redacted]
Pregnancy Test (WOCBP only)	X	See Notes												Serum or urine pregnancy test to be done within 24 hours prior to first dose, and then Q4W (± 1 week) regardless of dosing schedule. See Sections 9.2.5 and 9.4.5.

Table 2-5: On-Treatment Assessment Schedule (Monotherapy Expansion - BMS-986277 [Part 3 Cohort 3] Monotherapy with Option for Subsequent Nivolumab Therapy)(CA034001)

Procedures[a]	Cycle 1 (28 days)[b]					Cycle 2 (28 days)[b]					Optional: Cycle 3 and each subsequent cycle (28 days; Nivolumab only)[c]			Notes
	D1[d]	D3[d] and D5[d]	D8 (± 3 days)	D15 (± 3 days)	D22 (± 3 days)	D1[d] (± 3 days)	D3 d and D5 d	D8 (± 3 days)	D15 (± 3 days)	D22 (± 3 days)	D1 (± 3 days)	D15 (± 3 days)	EOT[e]	
Efficacy Assessments														
Body Imaging	Contrast enhanced CT of the chest, abdomen, pelvis, and all other known and/or suspected sites of disease should occur every 8 weeks (± 7 days) starting from date of first dose until withdrawal from study, or start of subsequent treatment, whichever occurs first. See Section 9.1.1 for further details. For participants with TNBC without measurable lesions outside the breast, contrast enhanced MRI of the breasts should also be performed. For participants with prostate cancer only (PCWG3 Assessment), contrast enhanced CT of the chest, abdomen, pelvis, and all other known and/or suspected sites of disease should occur every 8 weeks (± 7 days) for 24 weeks and then every 12 weeks (± 7 days).													
Brain Scan	For participants with history of brain metastases, surveillance scans to be done per SOC frequency, or sooner if clinically indicated. See Section 9.1.1 for further details.													
Bone Scan	For participants with prostate cancer only (PCWG3 Assessment), scans should occur every 8 weeks (± 7 days) for 24 weeks and then every 12 weeks (± 7 days). Others only as clinically indicated (eg, participants with history or symptoms of bone metastases). See Section 9.1.1 for further details.													
PK/IMG Collection														
PK and IMG Samples	See Table 9.5-3 for full details on PK and IMG sampling schedule.													
Viral Shedding Assessments	See Table 9.5-3 for full details on shedding sampling schedule.													

Table 2-5: On-Treatment Assessment Schedule (Monotherapy Expansion - BMS-986277 [Part 3 Cohort 3] Monotherapy with Option for Subsequent Nivolumab Therapy)(CA034001)

Procedures[a]	Cycle 1 (28 days)[b]					Cycle 2 (28 days)[b]					Optional: Cycle 3 and each subsequent cycle (28 days; Nivolumab only)[c]			Notes
	D1[d]	D3[d] and D5[d]	D8 (± 3 days)	D15 (± 3 days)	D22 (± 3 days)	D1[d] (± 3 days)	D3 d and D5 d	D8 (± 3 days)	D15 (± 3 days)	D22 (± 3 days)	D1 (± 3 days)	D15 (± 3 days)	EOT[e]	
[redacted]														
[redacted]	[redacted]													
[redacted]														[redacted]
Clinical Drug Supply														
Treatment Assignment	X													See Section 7.2.
IRT Drug Vial Assignment	X	X				X	X				X			
Premedication	X	X				X	X							See Section 7.7.2.

Table 2-5: On-Treatment Assessment Schedule (Monotherapy Expansion - BMS-986277 [Part 3 Cohort 3] Monotherapy with Option for Subsequent Nivolumab Therapy)(CA034001)

Procedures[a]	Cycle 1 (28 days)[b]					Cycle 2 (28 days)[b]					Optional: Cycle 3 and each subsequent cycle (28 days; Nivolumab only)[c]			Notes
	D1[d]	D3[d] and D5[d]	D8 (± 3 days)	D15 (± 3 days)	D22 (± 3 days)	D1[d] (± 3 days)	D3 d and D5 d	D8 (± 3 days)	D15 (± 3 days)	D22 (± 3 days)	D1 (± 3 days)	D15 (± 3 days)	EOT[e]	
BMS-986277 Administration	X	X				X	X							BMS-986277 will be administered at the RD from Part 1 and will be administered for up to 2 cycles. Participants must be observed for at least 4 hours following the completion of BMS-986277 infusion due to the potential risk of and to monitor for infusion reactions. See Section 7.1.6.
Nivolumab Administration[c]											X			Nivolumab to be administered as a flat dose (480 mg) Q4W for up to 26 cycles via an approximately 30 minute infusion. See Sections 7.1.2 and 7.1.6.

Abbreviations: AE = adverse event; C = cycle; CT = computed tomography; D = day; DLT = dose-limiting toxicity; ECG = electrocardiogram; ECOG = Eastern Cooperative Oncology Group; eCRF = electronic case report form; EOT = end of treatment; FU = follow-up; IMG = immunogenicity; IRT = interactive response technology; MRI = magnetic resonance imaging; PCWG3 = Prostate Cancer Clinical Working Group 3; PE = physical examination; PK = pharmacokinetic; Q4W = every 4 weeks; RD = recommended dose; SAE = serious adverse event; SOC = standard of care; TNBC = triple-negative breast cancer; TSH = thyroid stimulating hormone; WOCBP = women of childbearing potential

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

[b] Participants who complete the first cycle and do not have a DLT, have not had clinical evidence of disease progression, and are considered suitable for further treatment may receive up to 1 additional cycle of BMS-986277 with the subsequent cycle beginning no sooner than 28 days after C1D1.

[c] Following 2 cycles of BMS-986277 monotherapy, participants may receive optional nivolumab treatment (480 mg Q4W) for up to 26 cycles if eligibility criteria continue to be met (see Sections 6.1 and 6.2). Participants whose disease progresses prior to receiving Cycle 2 of BMS-986277 may also receive nivolumab treatment if eligibility criteria continue to be met, skipping any remaining monotherapy visits and proceeding directly to Cycle 3, optional nivolumab treatment. For these participants, a minimum of 14 days will be required between Day 1 BMS-986277 administration and the first administration of nivolumab. For participants whose disease is responding (partial or complete) at the 8 week scan, further treatment must be discussed and agreed upon with the Medical Monitor (or designee) prior to the start of the optional subsequent nivolumab treatment.

[d] A minimum of 24 hours is required between doses during sequential dosing weeks (eg, C1D1-C1D5; C2D1-C2D5). Infusions of BMS-986277 on Day 3 and Day 5 must be administered within 7 days of Day 1.

[e] EOT visit is at C2D28 (for participants treated with BMS-986722 only) or at C26D29 (for participants treated with BMS-986722 and nivolumab) or at the time of study treatment discontinuation. If within 7 days prior to FU Visit 1, the EOT visit may be skipped and FU Visit 1 should be completed and include all EOT biomarker samples.

Table 2-6: Follow-Up Assessments (Monotherapy - BMS-986277 Only [Part 1 and Part 3 Cohort 3])(CA034001)

Procedure	30-Day Safety Follow Up Visit 1 (± 7 days)	60-Day Safety Follow Up Visit 2 (± 7 days)	Survival Follow-Up Visits (± 14 days)	Notes
Safety Assessments				
Targeted PE	X	X		To assess for potential late emergent study drug related issues.
Vital Signs	X	X		
AE Assessment	X	X		To be collected through 60 days after last dose of BMS-986277 or start of subsequent anti-cancer therapy, whichever occurs earlier.
SAE Assessment	X	X		To be collected through 60 days after last dose of BMS-986277 regardless of start of subsequent anti-cancer therapy.
[redacted]	[redacted]	[redacted]		
Document Subsequent Cancer Therapy	X	X	Every 3 months	
ECG	Only if not assessed at EOT visit			
Laboratory Tests	X	X		On site/local laboratory testing; CBC w/differential, LFTs, BUN, creatinine, amylase, and lipase. Repeat until normalization or return to baseline if clinically significant abnormalities.
Urinalysis	X	See Notes		Repeat until normalization or return to baseline if clinically significant abnormalities at 30 day follow-up visit.
Thyroid Function Tests	X	X		TSH with reflex testing (free T3 and T4), if applicable. See Section 9.4.5. Repeat until normalization or return to baseline if clinically significant abnormalities.
Pregnancy Test (WOCBP only)	X	X		Serum or urine pregnancy test to be performed. See Section 9.4.5.

Table 2-6: Follow-Up Assessments (Monotherapy - BMS-986277 Only [Part 1 and Part 3 Cohort 3])(CA034001)

Procedure	30-Day Safety Follow Up Visit 1 (± 7 days)	60-Day Safety Follow Up Visit 2 (± 7 days)	Survival Follow-Up Visits (± 14 days)	Notes
[redacted]				
[redacted]	[redacted]			[redacted]
[redacted]	[redacted]	[redacted]		[redacted]
PK/IMG Collection				
PK and IMG Samples	See Table 9.5-1 and Table 9.5-3 for full details on PK and IMG sampling schedule.			
Viral Shedding Assessments	See Table 9.5-1 and Table 9.5-3 for full details on shedding sampling schedule.			If virus is detected at the 60 Day Follow-up visit, samples should continue to be collected at least every 30 days until virus is no longer detected.
Efficacy Assessments[a]				
Brain Imaging	For participants with history of brain metastases, surveillance scans to be done per SOC frequency, or sooner if clinically indicated. See Sections 5.1.6 and 9.1.1 for further details.			
Body Imaging	Contrast enhanced CT of the chest, abdomen, pelvis, and all other known and/or suspected sites of disease should occur every 8 weeks (± 7 days) starting from date of first dose until withdrawal from study, or start of subsequent treatment, whichever occurs first. See Sections 5.1.6 and 9.1.1 for further details. For participants with TNBC without measurable lesions outside the breast, contrast enhanced MRI of the breasts should also be performed. For participants with prostate cancer only (PCWG3 Assessment), contrast enhanced CT of the chest, abdomen, pelvis, and all other known and/or suspected sites of disease should occur every 8 weeks (± 7 days) for 24 weeks and then every 12 weeks (± 7 days).			

Table 2-6: Follow-Up Assessments (Monotherapy - BMS-986277 Only [Part 1 and Part 3 Cohort 3])(CA034001)

Procedure	30-Day Safety Follow Up Visit 1 (± 7 days)	60-Day Safety Follow Up Visit 2 (± 7 days)	Survival Follow-Up Visits (± 14 days)	Notes
Bone Scan	For participants with prostate cancer only (PCWG3 Assessment), scans should occur every 8 weeks (± 7 days) for 24 weeks and then every 12 weeks (± 7 days). Others only as clinically indicated (eg, participants with history or symptoms of bone metastases). See Sections 5.1.6 and 9.1.1 for further details.			
Participant Status				
Long-term General Health Status	X	X	Every 3 months	Participants to be assessed for at least 1 year from last dose of BMS-986277. See Section 5.1.7.1 for required assessments.
Survival Status	X	X	Every 3 months[b]	To include assessment of survival and subsequent anti-cancer therapy. See Section 5.1.7.2 for details of required assessments.

Abbreviations: AE = adverse event; BMS = Bristol-Myers Squibb; BUN = blood urea nitrogen; CBC = complete blood count; CT = computed tomography; ECG = electrocardiogram; EOT = end of treatment; FU = follow-up; IMG = immunogenicity; LFT = liver function test; MRI = magnetic resonance imaging; PCWG3 = Prostate Cancer Clinical Working Group 3; PE = physical examination; PK = pharmacokinetic; SAE = serious adverse event; SOC = standard of care; TNBC = triple-negative breast cancer; TSH = thyroid stimulating hormone; WOCBP = women of childbearing potential

[a] Required during Response FU. See Section 5.1.6.

[b] Survival FU Visits may be conducted in clinic or via telephone contact every 3 months (± 7 days) from FU Visit 2. BMS may request that survival data be collected on all treated participants outside of the 3 month specified window. At the time of this request, each participant will be contacted to determine their survival status unless the participant has withdrawn consent for all contact.

Table 2-7: Follow-Up Assessments (Combination - BMS-986277 and Nivolumab [Part 2 and Part 3 Cohorts 1-3])(CA034001)

Procedure	30-Day Safety Follow Up Visit 1 (± 7 days)	60-Day and 100-Day Safety Follow Up Visits 2 and 3 (± 7 days)	Survival Follow-Up Visits (± 14 days)	Notes
Safety Assessments				
Targeted PE	X	X		To assess for potential late emergent study drug related issues.
Vital Signs	X	X		
AE Assessment	X	X		To be collected through 100 days after last dose of any study drug or start of subsequent anti-cancer therapy, whichever occurs earlier.
SAE Assessment	X	X		To be collected through 100 days after last dose of any study drug regardless of start of subsequent anti-cancer therapy.
[redacted]	[redacted]	[redacted]		
Document Subsequent Cancer Therapy	X	X	Every 3 months	
ECG	Only if not assessed at EOT visit			
Laboratory Tests	X	X		On site/local laboratory testing; CBC w/differential, LFTs, BUN, creatinine, amylase, and lipase. Repeat until normalization or return to baseline if clinically significant abnormalities.
Urinalysis	X	See Notes		Repeat until normalization or return to baseline if clinically significant abnormalities at 30 day follow-up visit.

Table 2-7: Follow-Up Assessments (Combination - BMS-986277 and Nivolumab [Part 2 and Part 3 Cohorts 1-3])(CA034001)

Procedure	30-Day Safety Follow Up Visit 1 (± 7 days)	60-Day and 100-Day Safety Follow Up Visits 2 and 3 (± 7 days)	Survival Follow-Up Visits (± 14 days)	Notes
Thyroid Function Tests	X	X		TSH with reflex testing (free T3 and T4), if applicable. See Section 9.4.5. Repeat until normalization or return to baseline if clinically significant abnormalities.
Pregnancy Test (WOCBP only)	X	X		Serum or urine pregnancy test to be performed. See Section 9.4.5.
[redacted]				
[redacted]	[redacted]			[redacted]
[redacted]	[redacted]	[redacted]		[redacted]
PK/IMG Collection				
PK and IMG Samples	See Table 9.5-2 and Table 9.5-3 for full details on PK and IMG sampling schedule.			
Viral Shedding Assessments	See Table 9.5-2 and Table 9.5-3 for full details on shedding sampling schedule.			If virus is detected at the 60 Day Follow-up visit, samples should continue to be collected at least every 30 days until virus is no longer detected.
Efficacy Assessments[a]				
Brain Imaging	For participants with history of brain metastases, surveillance scans to be done per SOC frequency, or sooner if clinically indicated. See Sections 5.1.6 and 9.1.1 for further details.			

Table 2-7: Follow-Up Assessments (Combination - BMS-986277 and Nivolumab [Part 2 and Part 3 Cohorts 1-3])(CA034001)

Procedure	30-Day Safety Follow Up Visit 1 (± 7 days)	60-Day and 100-Day Safety Follow Up Visits 2 and 3 (± 7 days)	Survival Follow-Up Visits (± 14 days)	Notes
Body Imaging	Contrast enhanced CT of the chest, abdomen, pelvis, and all other known and/or suspected sites of disease should occur every 8 weeks (± 7 days) starting from date of first dose until withdrawal from study, or start of subsequent treatment, whichever occurs first. See Sections 5.1.6 and 9.1.1 for further details. For participants with TNBC without measurable lesions outside the breast, contrast enhanced MRI of the breasts should also be performed. For participants with prostate cancer only (PCWG3 Assessment), contrast enhanced CT of the chest, abdomen, pelvis, and all other known and/or suspected sites of disease should occur every 8 weeks (± 7 days) for 24 weeks and then every 12 weeks (± 7 days).			
Bone Scan	For participants with prostate cancer only (PCWG3 Assessment), scans should occur every 8 weeks (± 7 days) for 24 weeks and then every 12 weeks (± 7 days). Others only as clinically indicated (eg, participants with history or symptoms of bone metastases). See Sections 5.1.6 and 9.1.1 for further details.			
Participant Status				
Long-term General Health Status	X	X	Every 3 months	Participants to be assessed for at least 1 year from last dose of BMS-986277. See Section 5.1.7.1 for required assessments.
Survival Status	X	X	Every 3 months[b]	To include assessment of survival and subsequent anti-cancer therapy. See Section 5.1.7.2 for details of required assessments.

Abbreviations: AE = adverse event; BMS = Bristol-Myers Squibb; BUN = blood urea nitrogen; CBC = complete blood count; CT = computed tomography; ECG = electrocardiogram; EOT = end of treatment; FU = follow-up; IMG = immunogenicity; LFT = liver function test; MRI = magnetic resonance imaging; PCWG3 = Prostate Cancer Clinical Working Group 3; PE = physical examination; PK = pharmacokinetic; SAE = serious adverse event; SOC = standard of care; TNBC = triple-negative breast cancer; TSH = thyroid stimulating hormone; WOCBP = women of childbearing potential

[a] Required during Response FU. See Section 5.1.6.

[b] Survival FU Visits may be conducted in clinic or via telephone contact every 3 months (± 7 days) from FU Visit 3. BMS may request that survival data be collected on all treated participants outside of the 3 month specified window. At the time of this request, each participant will be contacted to determine their survival status unless the participant has withdrawn consent for all contact.

3 INTRODUCTION

This Phase 1/2a first-in-human (FIH) study will evaluate the safety profile, tolerability, pharmacokinetics (PK), and pharmacodynamics of intravenous (IV) CD80/αCD3 Oncolytic Virus (BMS-986277), administered alone (Part 1) and in combination with nivolumab (Part 2) in advanced or metastatic epithelial carcinomas to establish the recommended dose for further study. The expansion cohorts in Part 3 are designed to inform future studies.

4 OBJECTIVES AND ENDPOINTS

Table 4-1: Objectives and Endpoints

Objectives	Endpoints
Primary	
• To characterize the safety and tolerability of BMS-986277 administered alone and in combination with PD-1 inhibitor, nivolumab, in advanced epithelial tumors • To determine the RD and RP2D and dosing schedule of BMS-986277 administered alone and in combination with nivolumab in participants with advanced epithelial tumors	• Incidence of AEs, SAEs, AEs meeting protocol-defined DLT criteria, AEs leading to discontinuation, and AEs resulting in death • Incidence of clinical laboratory test abnormalities • Vital sign abnormalities or other safety biomarkers
Secondary	
• To explore the preliminary anti-tumor activity of BMS-986277 alone and in combination with nivolumab in participants with advanced epithelial tumors (RECIST v1.1 and PCWG3)	• ORR, DCR, mDOR, mPFS, and PFSR at 8, 16, and 24 weeks depending on indication
• To assess the PK and IMG of BMS-986277 in blood following monotherapy or combination treatment	• Summary measures of PK and IMG parameters of BMS-986277
[redacted]	

Abbreviations: AE = adverse events; BICR = blinded independent central review; DCR = disease control rate; DLT = dose-limiting toxicity; IMG = immunogenicity; iRECIST = immune Response Evaluation Criteria in Solid Tumors; mDOR = median duration of response; mOS = median overall survival; mPFS = median progression-free survival; NPV = negative predictive value; ORR = objective response rate; OS = overall survival; OSR = overall survival rate; PCWG3 = Prostate Cancer Clinical Trials Working Group 3; PK = pharmacokinetics; PFSR = progression-free survival rate; PPV = positive predictive value; RD = recommended dose; RECIST = Response Evaluation Criteria in Solid Tumors; RP2D = recommended Phase 2 dose; SAE = serious adverse events; TPR = true positive rate

5 STUDY DESIGN

5.1 Overall Design

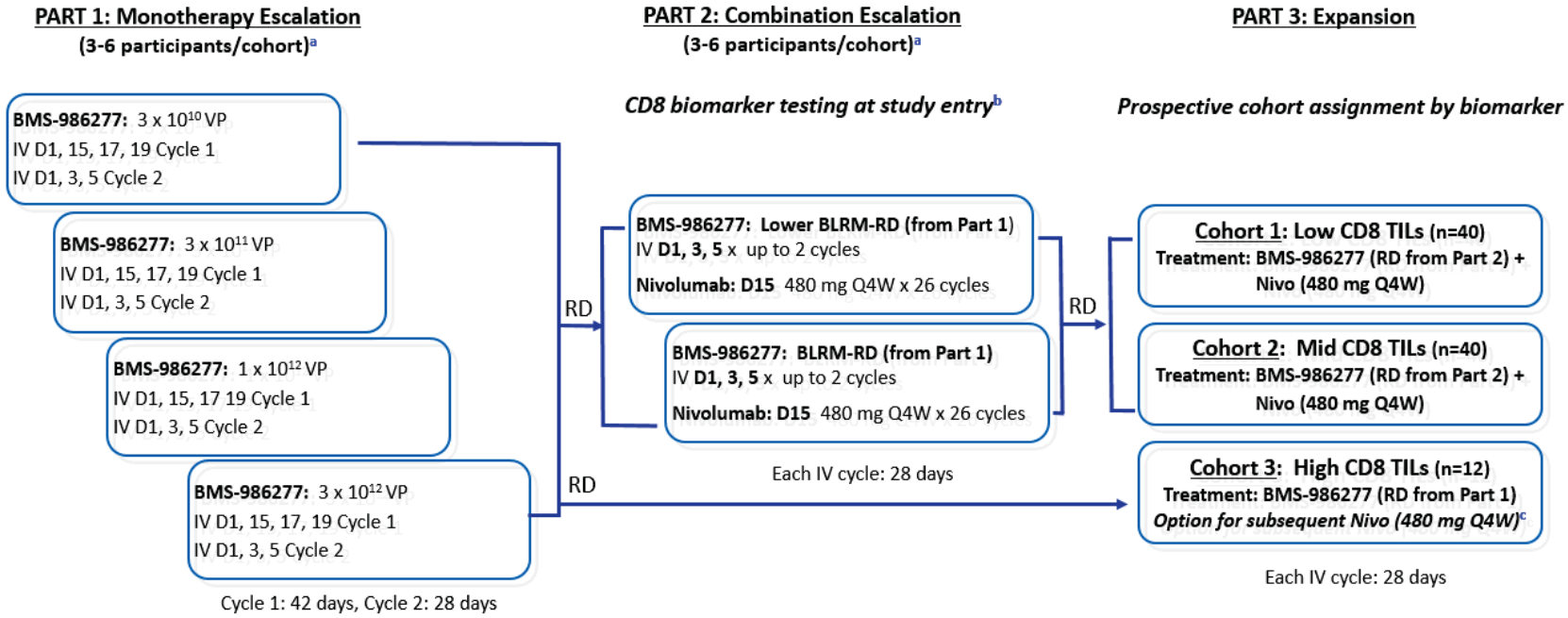
This is a Phase 1/2a, multicenter, open-label, non-randomized study of CD80/αCD3 Oncolytic Virus (BMS-986277) alone or in combination with nivolumab for the treatment of metastatic or advanced epithelial tumors in male and female participants.

The study will be conducted in 3 Parts:

- Part 1: a single agent monotherapy dose escalation to establish the Bayesian Logistic Regression Model-recommended dose (BLRM-RD) of BMS-986277 based on safety and tolerability
- Part 2: a combination dose escalation to establish the BLRM-RD of BMS-986277 (using the RD from Part 1) in combination with nivolumab (480 mg Q4W)
- Part 3: a 3-cohort expansion
  - Cohort 1 will treat participants with low CD8 TILs (< 2%) with BMS-986277 (using the RD from Part 2) in combination with nivolumab (480 mg Q4W)
  - Cohort 2 will treat participants with mid CD8 TILs (2% ≤ CD8 < 20%) with BMS-986277 (using the RD from Part 2) in combination with nivolumab (480 mg Q4W)
  - Cohort 3 will treat participants with high CD8 TILs (≥ 20%) with BMS-986277 monotherapy (using the RD from Part 1) to further characterize the pharmacodynamics of BMS-986277 monotherapy. Following BMS-986277 monotherapy treatment (up to 2 cycles), participants will have the option to receive nivolumab treatment (480 mg Q4W) to explore sequential dosing.

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

Figure 5.1-1: Study Design Schematic



For Parts 1 and 2, dosing of initial participants will be staggered by 7 days to mitigate against unexpected adverse drug reaction as follows:

- Lowest Dose level: the first 3 participants may not begin dosing within 7 days of each other
- Other dose levels: the first 2 participants may not begin dosing within 7 days of one another

Abbreviations: BLRM-RD = Bayesian Logistic Regression Model-Recommended Dose; D = day; IV = intravenous; N = number; Q4W = every 4 weeks; RD = recommended dose; TIL = tumor-infiltrating lymphocytes; VP = viral particles.

[a] Additional participants (up to a total of 12) may be treated at any dose level to further evaluate the safety, PK, and/or pharmacodynamic profile.

[b] As a minimum of 3 participants with low (< 2%) or mid (2% ≤ CD8 < 20%) CD8 TIL are required to be evaluated at each dose level, CD8 biomarker testing of fresh tumor samples (Section 9.8) will be required at study entry.

[c] Following 2 cycles of BMS-986277 monotherapy, participants may receive optional nivolumab treatment (480 mg Q4W) for up to 26 cycles if eligibility criteria continue to be met (see Sections 6.1 and 6.2). Participants whose disease progresses prior to receiving Cycle 2 of BMS-986277 may also receive nivolumab treatment if eligibility criteria continue to be met, skipping any remaining monotherapy visits and proceeding directly to Cycle 3, optional nivolumab treatment. For participants whose disease is responding (complete or partial) per RECIST v1.1 or PCWG3 at the 8 week scan, treatment must be discussed and agreed upon with the Medical Monitor (or designee) prior to the start of the optional subsequent nivolumab treatment.

Screening

The screening period will begin at the signature of the informed consent. Informed consent will be obtained prior to any study specific procedures. IRT contact must occur for participant number assignment at the time informed consent is obtained.

Participants will be evaluated based on the assessments as outlined in the Table 2-1 and Inclusion and Exclusion criteria (Sections 6.1 and 6.2).

A fresh tumor biopsy from the disease site (when possible) or from any metastatic site when the primary site is not available will be submitted to the central laboratory (see Section 9.8).

Eligible participants will then enter the On Treatment period.

On Treatment

- In Part 1 (Monotherapy Dose Escalation), participants will receive BMS-986277 monotherapy (at one of 4 dose levels) for 2 cycles. See Section 5.1.1 and Table 2-2.
- In Part 2 (Combination Dose Escalation), participants will receive treatment with BMS-986277 (up to 2 cycles of 28 days each) in combination with nivolumab (480 mg Q4W) for up to 26 cycles of 28 days each. See Section 5.1.2 and Table 2-3.
  - Cohort 1: BMS-986277 starting at a lower dose level than the BLRM-RD.
  - Cohort 2: BMS-986277 at the BLRM-RD.
    - In Part 2, a minimum of 3 participants with low (< 2%) or mid (2% ≤ CD8 < 20%) CD8 TILs will be evaluated at each dose level.
- Dosing for the initial participants into each dose level in Parts 1 and 2 will be staggered by 7 days between participants (see Sections 7.1.3 and 7.1.4). Specifically, at the lowest dose level the first 3 participants may not begin dosing within 7 days of each other, while at any other dose level the first 2 participants may not begin dosing within 7 days of one another.
- In Part 3 (3-Cohort Expansion), participants will be enrolled into 1 of 3 cohorts based on the % of CD8 TILs.
  - Cohort 1 will include participants with low CD8 TILs < 2% who will receive treatment with BMS-986277 (up to 2 cycles of 28 days each) at the dose level recommended for BMS-986277 from the doses studied in Part 2 in combination with nivolumab (480 mg Q4W) for up to 26 cycles of 28 days each. See Section 5.1.3 and Table 2-4.
  - Cohort 2 will include participants with mid CD8 TILs 2% ≤ CD8 < 20% who will receive treatment with BMS-986277 (up to 2 cycles of 28 days each) at the dose level recommended for BMS-986277 from the doses studied in Part 2 in combination with nivolumab (480 mg Q4W) for up to 26 cycles of 28 days each. See Section 5.1.3 and Table 2-4.
  - Cohort 3 will include participants with high CD8 TILs CD8 ≥ 20% who will receive treatment with BMS-986277 (up to 2 cycles of 28 days each) at the dose level recommended for BMS-986277 monotherapy in Part 1. Following 2 cycles of BMS-986277 monotherapy, participants may receive nivolumab treatment (480 mg Q4W) for up to 26 cycles of 28 days each if eligibility criteria continue to be met (see Sections 6.1 and 6.2). Participants whose disease progresses prior to receiving Cycle 2 of BMS-986277 may also receive nivolumab treatment if eligibility criteria continue to be met (see Sections 6.1 and 6.2), skipping any remaining monotherapy visits and proceeding directly to Cycle 3, optional nivolumab treatment. See Section 5.1.3 and Table 2-5. For

participants whose disease is responding (complete or partial) per RECIST v1.1 or PCWG3 at the 8 week scan, treatment must be discussed and agreed upon with the Medical Monitor (or designee) prior to the start of the optional subsequent nivolumab treatment.

- Participants treated with BMS-986277 monotherapy only (Part 1 and Part 3 Cohort 3) will be treated until disease progression, unacceptable toxicity, withdrawal of consent, or the completion of the 2 cycles of BMS-986277, whichever occurs first. However, participants treated with nivolumab sequentially in Cohort 3 Part 3 will follow the criteria for BMS-986277 and nivolumab treatment.
- Participants treated with BMS-986277 and nivolumab (Part 2 and Part 3 Cohorts 1-3) will be treated until disease progression, unacceptable toxicity, withdrawal of consent, or the completion of the 26 cycles of nivolumab, whichever occurs first.
- All participants treated with BMS-986277 monotherapy only (Part 1 and Part 3 Cohort 3) will attend at least two safety follow-up visits (see Table 2-6 and Sections 5.1.5 and 5.1.6), and be monitored during long-term follow-up (ie, survival, overall health, and response) for up to 3 years post first dose of study medication (specific durations are specified in Sections 5.1.7.1 and 5.1.7.2).
- All participants treated with BMS-986277 and nivolumab (Part 2 and Part 3 Cohorts 1-3) will attend at least three safety follow-up visits (see Table 2-7 and Sections 5.1.5 and 5.1.6), and be monitored during long-term follow-up (ie, survival, overall health, and response) for up to 3 years post first dose of study medication (specific durations are specified in Sections 5.1.7.1 and 5.1.7.2).

For all participants, tumor assessments should occur as outlined in Section 2 (Schedule of Activities). Images will be submitted to an imaging core lab for all participants and may be reviewed by Blinded Independent Central Review (BICR) at any time during the study. Treatment decisions will be assessed by the investigator per study design using RECIST v1.1 or PCWG3 criteria.

Clinical progression/deterioration of disease will be monitored throughout the study for all participants.

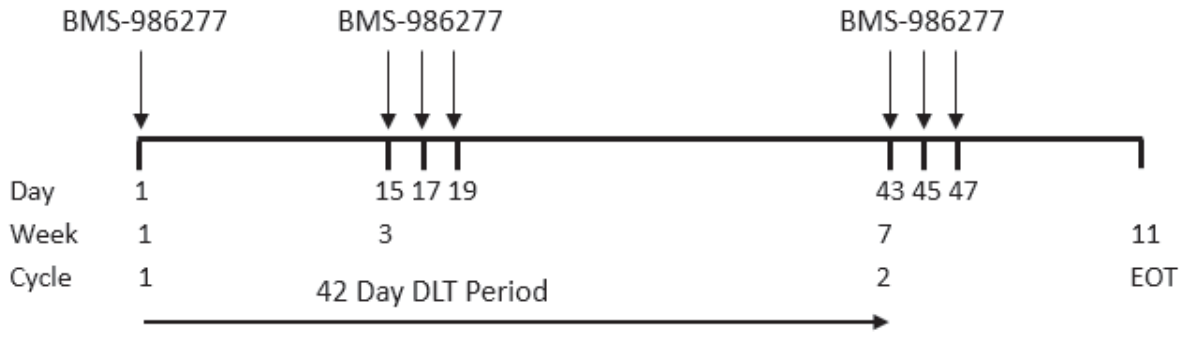
Safety assessments (AEs, PE, vital signs, laboratory safety tests, 12-lead ECGs, cytokine release monitoring, and ECOG performance status) will be evaluated throughout the study treatment and required follow-up visits. Viral shedding and ADA will be monitored at the 30 and 60 day follow-up visits. Additional monitoring may occur at subsequent follow-up visits as clinically indicated in Table 2-6 (participants treated with BMS-986277 monotherapy only [Part 1 and Part 3 Cohort 3]) and Table 2-7 (participants treated with BMS-986277 and nivolumab [Part 2 and Part 3 Cohorts 1-3]). AE monitoring will be continued throughout the study treatment and required follow-up visits as indicated in Table 2-6 and Table 2-7. Concomitant medications will be collected throughout the study treatment (14 days prior to C1D1) and required follow-up visits as indicated in Table 2-6 and Table 2-7.

5.1.1 Part 1: Monotherapy Escalation

During Part 1, the dose escalation with BMS-986277 monotherapy, participants with advanced or metastatic CRC, pancreatic cancer, prostate cancer, TNBC, ovarian cancer, or urothelial carcinoma meeting eligibility criteria will be permitted to receive BMS-986277.

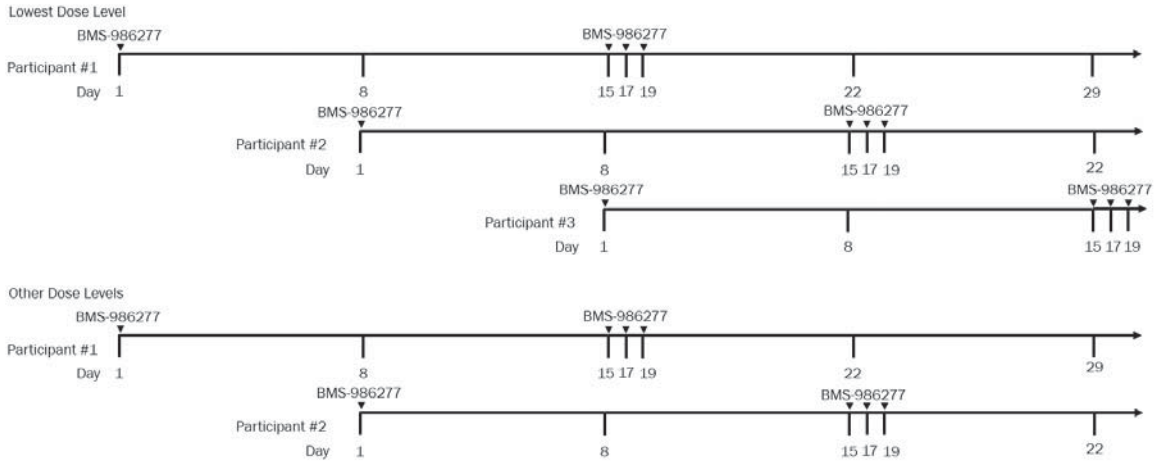
- Initial dose of IV BMS-986277 is 100-fold below current RD for enadenotucirev.
- IV doses at 3 x 10^{10}, 3 x 10^{11}, 1 x10^{12}, and 3 x 10^{12} vp are planned.
- At each dose level, Cycle 1 of BMS-986277 will be administered as a single IV infusion (D1) before proceeding to sequential dosing (consisting of 3 doses administered on Days 15, 17, and 19). A minimum of 24 hours is required between doses of BMS-986277.
- Prophylactic medication will be administered prior to each dose of BMS-986277. Pre-hydration can be administered, unless clinically contraindicated (see details of prophylaxis in Section 7.7.2).
- The 42-day Cycle 1 in Part 1 is due to a 2-week monitoring of a single virus injection, then at Day 15 (+ 7 days) BMS-986277 will be administered as in other cycles with 3 infusions within 7 days. The DLT evaluation period will include multiple virus injections. The DLT evaluation period may be extended due to non-DLT dose delays (see Sections 7.4.1, 7.4.2, and 7.4.3).
- Participants who complete the first cycle without a DLT, who have no clinical evidence of disease progression, and are considered suitable for further treatment may receive up to 1 additional cycle of BMS-986277 with the subsequent cycle beginning no sooner than 42 days after C1D1.
- Once the safety (during the DLT evaluation) of a dose level has been established, additional participants (up to a total of 12) may be added at that dose level to further evaluate the safety, PK, and pharmacodynamic profile.

Figure 5.1.1-1: Part 1: Monotherapy Escalation



Dosing for the initial participants into each cohort in Part 1 will be staggered by 7 days to monitor for sentinel events (See Figure 5.1.1-2).

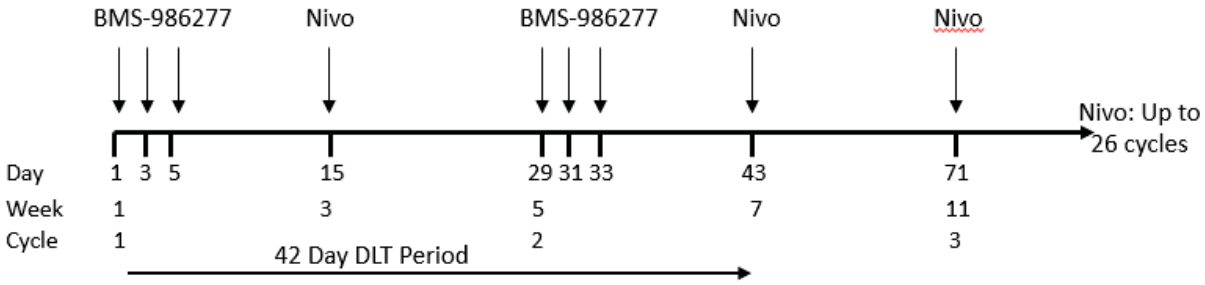
Figure 5.1.1-2: Sentinel Participants in Part 1



5.1.2 Part 2: Combination Escalation

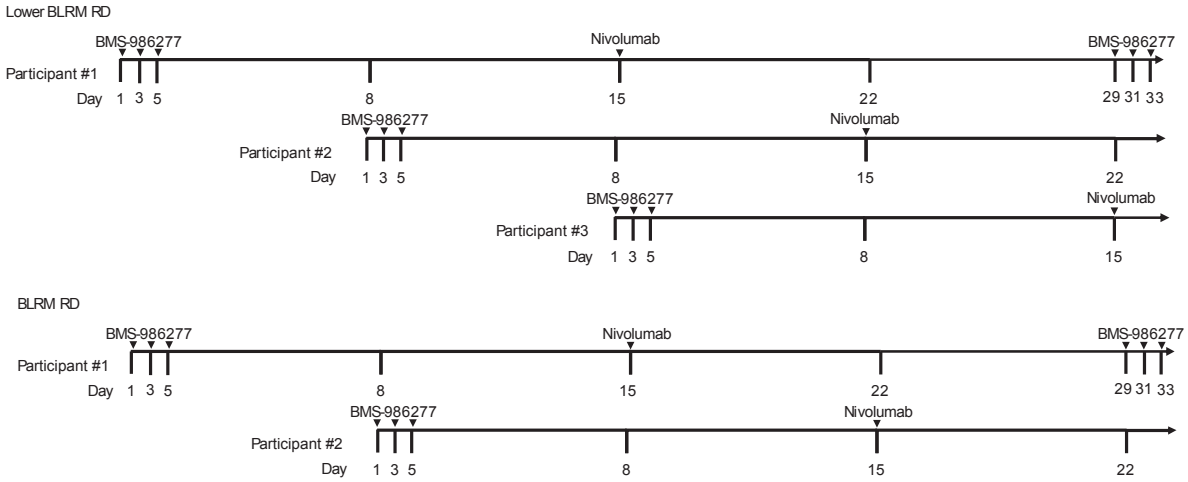
- Participants will receive treatment with BMS-986277 at one of 2 dose levels (for a maximum of up to 2 cycles) in combination with nivolumab (480 mg Q4W up to 26 cycles). A minimum of 24 hours is required between doses of BMS-986277.
  - Cohort 1: BMS-986277 starting at a lower dose level than the BLRM-RD
  - Cohort 2: BMS-986277 at the BLRM-RD
  - Note: A combination with a lower, intermediate, or higher dose level of BMS-986277 may be considered if the BLRM recommends it, after consideration of all available safety, PK, and pharmacodynamic data.
- A minimum of 3 participants with low (< 2%) or mid (2% ≤ CD8 < 20%) CD8 TILs are required to be evaluated at each dose level. Therefore, prior to treatment in Part 2 of the study (combination escalation of BMS-986277 in combination with nivolumab), participants will undergo tumor biopsies to determine the percentage of intratumoral CD8 cells utilizing an IHC-based assay. This assay quantitates the percentage of intratumoral CD8 cells using participant tumor samples obtained during the screening period. Specific cut-offs will be used to determine the percentage of CD8 cells within a participant's tumor (low, mid, or high). See Section 9.8 of the protocol for details.
- Participants who complete the first cycle and do not have a DLT, have not had disease progression, and are considered suitable for further treatment may receive up to 1 additional cycle of BMS-986277 with the subsequent cycle beginning no sooner than 28 days after C1D1. Nivolumab may be administered for up to 26 cycles.
- Once the safety (during the DLT evaluation) of a dose level has been established, additional participants (up to a total of 12) may be added at that dose level to further evaluate the safety, PK, and pharmacodynamic profile.

Figure 5.1.2-1: Part 2: Combination Escalation



Dosing for the initial participants into each cohort in Part 2 will be staggered by 7 days to monitor for sentinel events (see Figure 5.1.2-2).

Figure 5.1.2-2: Sentinel Participants in Part 2



5.1.3 Part 3: Expansion

Participants enrolled in Part 3 will undergo biomarker selection to determine cohort assignment and treatment. The biomarker assay used is IHC-based and quantitates percentage of intratumoral CD8+ cells using participant tumor samples obtained during the screening period. Specific cut-offs for percent CD8+ cells will be used to identify participants with either "low," "mid," or "high" CD8+ tumors. Participants with "low" (Cohort 1) or "mid" (Cohort 2) CD8+ tumors will be eligible for BMS-986277 in combination with nivolumab and participants with "high" (Cohort 3) CD8+ tumors will be eligible for BMS-986277 monotherapy with an option for subsequent nivolumab treatment. Please see Section 9.8 of protocol for details on the biopsy requirements.

- In Part 3 Cohorts 1-2, participants will receive BMS-986277 (at the RD based on Part 2 for up to 2 cycles) in combination with nivolumab (480 mg Q4W up to 26 cycles). A minimum of 24 hours is required between doses of BMS-986277 during sequential dosing for an individual participant.

- In Part 3 Cohort 3, participants will receive BMS-986277 (at the RD based on Part 1 for up to 2 cycles). A minimum of 24 hours is required between doses of BMS-986277 during sequential dosing for an individual participant. Following 2 cycles of BMS-986277 monotherapy, participants may receive optional nivolumab treatment (480 mg Q4W) for up to 26 cycles if eligibility criteria continue to be met (see Sections 6.1 and 6.2). Participants whose disease progresses prior to receiving Cycle 2 of BMS-986277 may also receive nivolumab treatment if eligibility criteria continue to be met (see Sections 6.1 and 6.2), skipping any remaining monotherapy visits and proceeding directly to Cycle 3, optional nivolumab treatment as indicated in Table 2-5. For these participants, a minimum of 14 days will be required between the Day 1 BMS-986277 administration (Cycle 1 or Cycle 2) and the start of nivolumab administration. For participants whose disease is responding (complete or partial) per RECIST v1.1 or PCWG3 at the 8 week scan, treatment must be discussed and agreed upon with the Medical Monitor (or designee) prior to the start of the optional subsequent nivolumab treatment.
- Participants will be enrolled into 1 of 3 cohorts based on percentage of CD8 TILs:
  - Cohort 1 will treat participants with low CD8 TILs
    - Low: CD8 < 2%
  - Cohort 2 will treat participants with mid CD8 TILs
    - Mid: 2% ≤ CD8 < 20%
  - Cohort 3 will treat participants with high CD8 TILs
    - High: CD8 ≥ 20%
- Enrollment may focus on, but not be limited to, two indications per each cohort based on higher prevalence of the specific biomarker expression

Participants who complete the first cycle and do not have a DLT, have not had disease progression, and are considered suitable for further treatment may receive up to a maximum of 1 additional cycle of BMS-986277, with the subsequent cycle beginning no sooner than 28 days after C1D1. Nivolumab may be administered for up to 26 cycles as indicated per cohort.

Figure 5.1.3-1: Part 3 Cohorts 1 and 2

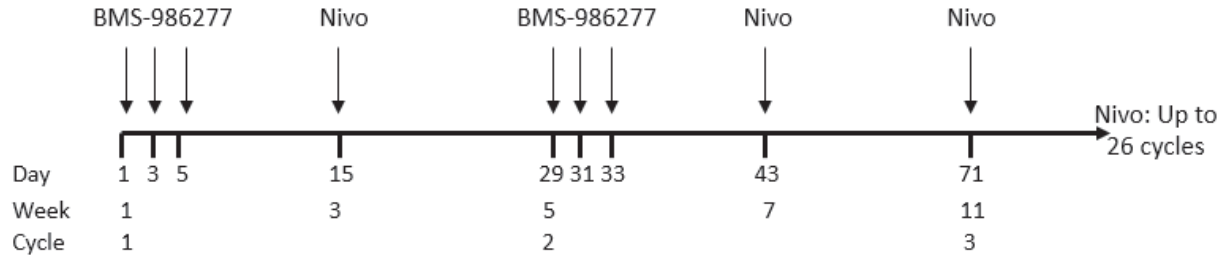
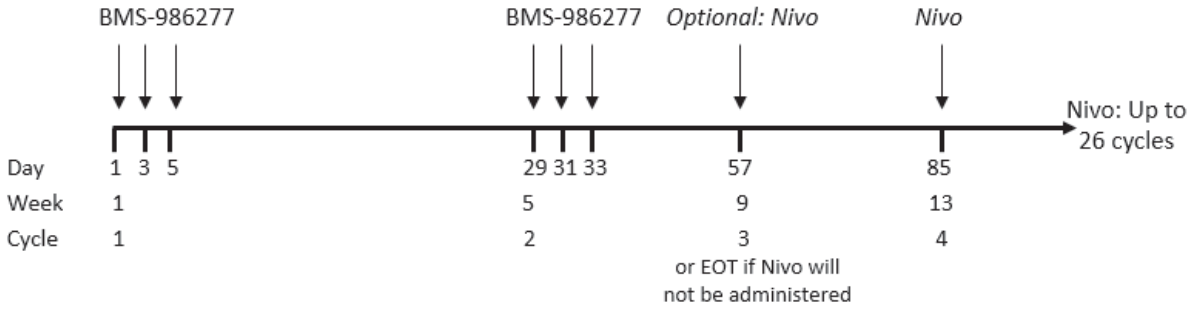


Figure 5.1.3-2: Part 3 Cohort 3



5.1.4 End of Treatment

EOT visits are defined by study part in Section 2.

5.1.5 Safety Follow-up

Participants will enter safety follow-up when the maximum treatment permitted per protocol has been administered (2 cycles of BMS-986277 for participants treated with BMS-986277 monotherapy [Part 1 and Part 3 Cohort 3] or 26 cycles of nivolumab for participants treated with BMS-986277 and nivolumab [Part 2 and Part 3 Cohorts 1-3]) or once the participant discontinues from study treatment (eg, at EOT).

During safety follow-up, all participants will be evaluated for any new and/or ongoing AEs for at least 60 days for participants treated with BMS-986277 monotherapy and 100 days for participants treated with BMS-986277 and nivolumab after the last dose of study treatment. All AEs considered related to study treatment must be followed to resolution, return to baseline or when deemed irreversible as indicated in Sections 9.2 and 9.2.3. Although AE reporting is not required following the start of subsequent anti-cancer therapies, assessments at safety follow-up visits should continue and events considered related to study treatment reported. Note that participants treated with BMS-986277 monotherapy (Part 1 and Part 3 Cohort 3) will be required to attend safety follow-up visits 1 and 2. Participants treated with BMS-986277 and nivolumab (Part 2 and Part 3 Cohorts 1-3) will be required to attend all 3 safety follow-up visits.

Safety follow-up visit 1 (FU1) should occur 30 days from the last dose (± 7 days) or may be performed on the date of discontinuation. Safety follow-up visit #2 (FU2) occurs approximately 60 days (± 7 days) from last dose of study drug. Safety follow-up visit #3 (FU3) occurs approximately 100 days (± 7 days) from last dose of study drug. Safety follow-up visits must be conducted in person.

During FU1 and FU2, participants will also be evaluated for viral shedding. If virus is detected during FU2, samples should continue to be collected at least every 30 days until virus is no longer detected.

All participants will be required to complete the safety follow-up visits as indicated in Table 2-6 or Table 2-7 regardless of whether or not they start new anti-cancer treatment, except those participants who withdraw consent for study participation.

5.1.6 Response Follow-up

Participants with ongoing stable disease (SD), partial response (PR), or complete response (CR) at the EOT visit will enter the Response Follow-up period. This period will occur simultaneously with the safety, long-term general health status, and survival follow-up for the mentioned participants.

Participants will continue to have tumor assessments performed as outlined in Table 2-6 or Table 2-7 and Section 9.1.1. Images should continue to be submitted to the imaging core lab during this period. Radiological tumor assessments for participants who have ongoing clinical benefit may continue to be collected after participants complete the survival phase of the study at the Sponsor's discretion.

5.1.7 Long-term Follow-up

Long-term follow-up will include long-term general health status and survival follow-up. These assessments will be conducted in parallel to safety and response follow-up for the duration specified in the subsections below (see Sections 5.1.7.1 and 5.1.7.2).

5.1.7.1 Long-Term General Health Status Follow-up

After completion of the safety follow-up visits and in parallel to survival and response follow-up, all treated participants will enter long-term general health status follow-up. During either a visit or phone contact, general health status will be collected and must include specific assessment of new infections, malignancy, and serious adverse events that are hematologic, immunologic, or neurologic. Participation on other clinical trials and subsequent anti-cancer therapy (eg, chemotherapy exposure) will be collected as part of survival follow-up. Participants will be followed approximately every 3 months (± 14 days) from the last required safety follow-up visit, for a minimum of 1 year from the last dose of BMS-986277 treatment.

5.1.7.2 Survival Follow-up

After completion of the safety follow-up visits and in parallel to long-term general health and response follow-up, all treated participants will enter survival follow-up. Participants will be followed approximately every 3 months (± 14 days) from the last required safety follow-up visit, until death, loss to follow-up, withdrawal of consent, or conclusion of the study, whichever occurs first. The duration of survival follow-up is at least 3 years from the first dose of study treatment, although a longer follow-up period could be considered in selected cases if an efficacy signal is apparent. When contacted for survival by visit or phone contact, survival status and subsequent anti-cancer therapy including treatment on other clinical trials will be collected. BMS may request that survival data be collected on all treated participants outside of the 3 month specified window. At the time of this request, each participant will be contacted to determine their survival status unless the participant has withdrawn consent for all contact.

5.1.8 Data Monitoring Committee and Other External Committees

BMS has developed a multi-layered process to ensure safety monitoring through close collaboration of study site investigators, the BMS study team, and the BMS Global Pharmacovigilance and Epidemiology (GPVE) led Medical Surveillance Team (MST). This

collaborative process constitutes the safety monitoring plan for the study. To support safety oversight, BMS has established ongoing processes for collection, review, analysis, and submission of individual adverse event reports and their aggregate analyses. Because this is an open-label study, GPVE, the BMS medical monitor (or designee), and the investigators will have access to all data necessary for safety evaluation.

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

5.1.9 Blinded Independent Central Review

Images will be submitted to an imaging core lab and may be reviewed by Blinded Independent Central Review (BICR) at any time during the study. See Section 9.1.1 for further details.

5.2 Number of Participants

- Part 1 (Monotherapy Dose Escalation - BMS-986277)
  - Initially, 3-6 participants per BMS-986277 monotherapy dose level, for a total of up to 24 participants. Additional participants (up to a total of 12) may be treated at any dose level to further evaluate the safety, PK, or pharmacodynamic profile. Therefore, the total sample size is up to 72.
- Part 2 (Combination Dose Escalation - BMS-986277 and nivolumab)
  - Initially, 3-6 participants per combination dose level. Additional participants (up to a total of 12) may be treated at any dose combination below or at the BLRM-RD for further evaluation of the safety, PK, or pharmacodynamic profile. Therefore, the total sample size is up to 36.
- Part 3 (Combination Expansion)
  - Cohorts 1-2 (BMS-986277 and nivolumab): Up to 40 evaluable participants per cohort. See Section 10.1 for further details on sample size calculation.
  - Cohort 3 (BMS-986277 monotherapy with option for subsequent nivolumab therapy): Up to approximately 12 participants evaluable for pharmacodynamic endpoints will be treated in this cohort. See Section 10.1 for further details on sample size.

5.3 End of Study Definition

The start of the trial is defined as first visit for first participant screened. End of trial is defined as last visit or scheduled procedure shown in the Schedule of Activities for the last participant. Study completion is defined as the final date on which data for the primary endpoint was or is expected to be collected, if this is not the same.

The estimated duration of the study is approximately 5 years.

[redacted]

6 STUDY POPULATION

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

6.1 Inclusion Criteria

1) Signed Written Informed Consent

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

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

2) Type of Participant and Target Disease Characteristics

a) Participants must be at least 18 years old and have histological or cytological confirmation of metastatic and/or unresectable metastatic colorectal, pancreatic, breast, ovarian, or urothelial carcinoma with measureable disease per RECIST v1.1 or per PCWG3 criteria for prostate carcinoma (see Appendix 7 or Appendix 8, respectively).

b) Presence of at least 2 lesions: at least one with measurable disease as defined by RECIST v1.1 (per PCWG3 criteria for prostate carcinoma) for solid tumors for response assessment; at least 1 lesion must be accessible for biopsy in addition to the target lesion.

c) 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.

d) 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, and have been considered for all other potentially efficacious therapies prior to enrollment. Participants who are ineligible for standard therapy (due to medical factors such as co-morbid illness, age, etc.) will be allowed to enroll provided the reason for their ineligibility is documented in their medical records. Specific details are provided in Section 3) below for each indication.

e) The Dose Escalation (Parts 1 and 2)

   i) Participants with colorectal, prostate, urothelial, ovarian, triple-negative breast, or pancreatic carcinoma will be permitted.

   ii) All comers CD8 TIL are permitted in Parts 1 and 2. However, at least 3 participants with low or mid CD8 TIL must be evaluated at each dose level in Part 2.

f) The Expansion (Part 3)

   i) Participants must have tumors classified by CD8+ TILs prior to treatment to determine cohort assignment:

      (1) Low: CD8 < 2%

      (2) Mid: 2% ≤ CD8 < 20%

      (3) High: ≥ 20%

g) ECOG performance status ≤ 2.

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

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

3) **The Following Tumor Types Will Be Explored:**
   a) **Colorectal Cancer (CRC)**: Participants with histologically confirmed CRC that is metastatic or recurrent with documented disease progression and that meets all of the following:
      i) Document microsatellite instability, mismatch repair, KRAS, and BRAF status, if known.
      ii) Prior therapy requirement: Participants must have received at least 1, but no more than 3, prior systemic therapies for metastatic and/or unresectable disease (or have progressed within 6 months of adjuvant therapy).
      iii) Participant must have incurable metastatic disease (ie, participants with disease that is potentially curable by surgical resection are not eligible for treatment).
      iv) **Prior therapy requirement as of Revised Protocol 05:** Participants must have been offered an oxaliplatin-containing regimen and an irinotecan- containing regimen (including as part of a combined oxaliplatin- and irinotecan-containing regimen). If the participant refuses these regimens, the reason must be documented in the medical record.
   b) **Prostate Cancer**: Participants with histologically or cytologically confirmed adenocarcinoma of the prostate and that meet all of the following:
      i) Metastatic disease by any 1 of the following modalities: computerized tomography (CT), magnetic resonance imaging (MRI), and/or bone scan.
      ii) Participants with bone-only disease should have progression confirmed as per PCWG3 criteria[139] and require confirmatory scans.
      iii) Prior therapy, participants:
         (1) Must have been treated by orchiectomy or are receiving a luteinizing hormone-releasing hormone analog, and have a testosterone level ≤ 50 ng/dL.
         (2) Must have received abiraterone or enzalutamide.
         (3) May have received anti-androgens (bicalutamide, flutamide, nilutamide) or adrenal androgen production inhibitors (aminoglutethamide or ketoconazole) therapy. This therapy should be discontinued prior to starting study treatment:
            (a) Participants with a history of response to an anti-androgen or adrenal androgen production inhibitor and subsequent progression should be assessed for anti-androgen withdrawal response for 4 weeks, and must demonstrate progression as described in inclusion criteria below (iv)
            (b) For participants who have never responded to anti-androgens, observation for anti-androgen withdrawal response is not necessary; however, a 2-week washout period is required prior to start of study treatment
         (4) No more than 1 chemotherapeutic regiment for mCRPC.
      iv) Participants treated with hormonal therapy must have progressed during treatment. For eligibility purposes, PD is defined as:
         (1) Rising prostate-specific antigen values at a minimum of 1-week intervals and a 2.0-ng/mL minimum starting value

         OR

(2) Progression per bone scan: the appearance of 2 or more new lesions

OR

(3) Progression per target lesions/measurable disease: nodal progression, per modified RECIST v1.1. Only lymph nodes > 2 cm will be considered to assess a change in size qualifying for disease progression.

c) **Urothelial Cancer**: Participants with histologically confirmed urothelial carcinoma (originating in bladder, ureter, or renal pelvis) who meet all of the following criteria:

i) Histological or cytological evidence of metastatic or surgically unresectable transitional cell carcinoma of the urothelium involving the bladder, urethra, ureter, or renal pelvis. Minor histologic variants (< 50% overall) are acceptable.

ii) Participants must have metastatic or surgically unresectable (cT4b, or any N+ [N1-3], or any M-1) disease.

iii) Participants must have progression or recurrence after treatment:

(1) With at least 1 platinum-containing chemotherapy regimen (if platinum eligible) but no more than 2 regimens for metastatic or surgically unresectable locally advanced urothelial cancer

OR

(2) 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.

iv) Participants may have received prior Bacillus Calmette–Guérin (BCG) vaccine and/or anti-PD-1/PD-L1 therapies.

v) Sequential chemotherapy given as a planned sequence to optimize response will count as 1 regimen.

d) **Ovarian Cancer**: Participants with histologically confirmed ovarian carcinoma (including epithelial ovarian cancer, primary peritoneal, fallopian tube carcinoma, or clear cell carcinoma) who must meet all of the following:

i) Documented somatic or germline BRCA status, if known. If unknown, participants must consent to allow the fresh tumor tissue to be tested. Participants can also submit an additional archived tumor tissue sample (block or unstained slides) to be tested. The archived tumor tissue sample is not a substitute for the fresh tumor tissue sample.

ii) Participants must have received no more than 5 prior systemic lines of therapy.

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

(2) One regimen must have been a prior platinum-based chemotherapeutic regimen for management of primary disease, possibly including intraperitoneal therapy,

consolidation, biologic/targeted (non-cytotoxic) agents (eg, bevacizumab) or extended therapy administered after surgical or non-surgical assessment.

(3) For the purposes of this study, PARP inhibitors given for recurrent or progressive disease will be considered a line of therapy. PARP inhibitors given as maintenance therapy will not be considered another line of therapy.

(4) **As of Revised Protocol 05**, participants with refractory ascites, indwelling gastric drainage catheters for bowel obstruction, or bowel obstruction within 1 month of consent are excluded.

(5) **As of Revised Protocol 05**, participants who have undergone diverting colostomy/ileostomy for bowel obstruction will be eligible, provided that they have been free of obstructive symptoms for > 1 month.

iii) Participants must have progressed less than 12 months after completion of their last platinum-based therapy. The number of months (platinum-free interval) should be calculated form the date of the last administered dose of platinum therapy to the date of the documented progression.

iv) **As of Revised Protocol 05**, participants with histologic subtypes of carcinosarcoma, mucinous, and low grade serous cancers are excluded.

e) **Triple-Negative Breast Cancer (TNBC)**: Women with histologically or cytologically confirmed breast carcinoma who must meet all of the following:

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

AND

ii) Participants must have progression or refractory disease. Participants must have had at least 1 and not more than 2 chemotherapeutic regimens for the treatment of metastatic or locally advanced and unresectable disease

OR

iii) Participants may refuse chemotherapy for their disease. Participants actively refusing chemotherapy must have had best response of stable disease, or progression or refractory disease to other treatment options such as radiotherapy, targeted agents, or investigational therapy prior to starting study treatment. The participant's refusal must be thoroughly documented. The investigator will discuss each individual participant refusing chemotherapy with the sponsor's Medical Monitor (or designee) to confirm eligibility.

f) **Pancreatic Cancer**: Participants with histologically confirmed pancreatic adenocarcinoma who meet all of the following:

i) Participants must not have clinically relevant ascites at baseline, such as ascites in need of paracentesis

AND

ii) Participants must have had best response of stable disease, or progression or refractory disease during or after at least 1 but not more than 2 chemotherapeutic regimens for the treatment of metastatic (Stage IV) or locally advanced disease

OR

iii) Participants may refuse chemotherapy for their disease. Participants actively refusing chemotherapy must have had best response of stable disease, or progression or refractory disease to other treatment options such as radiotherapy, targeted agents, or investigational therapy prior to starting study treatment. The participant's refusal must be thoroughly documented. The investigator will discuss each individual participant refusing chemotherapy with the sponsor's Medical Monitor (or designee) to confirm eligibility.

4) **Physical and Laboratory Test Findings**

a) Adequate hematologic function

i) White blood cells ≥ 2,000/μL

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

iii) Platelets ≥ 100× 10^3/μL (transfusion to achieve this level is not permitted within 2 weeks of first study treatment administration)

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

b) Adequate hepatic function

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

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

c) Normal thyroid function or stable on hormone supplementation per investigator assessment

d) Serum creatinine ≤ 1.5× ULN or creatinine clearance (CrCl) ≥ 50 mL/min (measured using the Cockcroft-Gault formula below):

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

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

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

f) Participant re-enrollment: This study permits the re-enrollment of a participant who has discontinued the study as a pretreatment failure (eg, participant has not been treated). If re-enrolled, the participant must be re-consented

g) Willing to consent to tumor biopsies during the study

h) All participants must provide a fresh tumor biopsy from the disease site (when possible) or from any metastatic site when the primary site is not available. Collection of the fresh tumor biopsy must be performed at minimal acceptable clinical risk as judged by the investigator. Participants who are unable to provide a fresh tumor biopsy are not eligible for this study. For Parts 2 and 3 of the study, part of the samples will be used prospectively for CD8 evaluation by IHC. All tissue samples must be suitable for testing to verify both CD8 and PD-L1 status by IHC. Refer to the Laboratory Manual and Section 9.8 for further

details on procedures for collecting fresh tumor samples and for determining suitability for both CD8 and PD-L1 IHC

i) If possible, the immediate confirmation (eg, touch imprint cytopathology) for presence of ≥ 100 viable tumor cells from collected tissue samples is strongly recommended by participating sites prior to submitting samples

j) Prior palliative radiotherapy completed at least 2 weeks before study treatment administration

5) Age and Reproductive Status

a) Males and Females, ages 18 or age of majority or older at the time of the informed consent

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

c) Women must not be breastfeeding for the duration of study treatment and for 3 months following the last study treatment if treated with BMS-986277 monotherapy only or for 5 months following the last study treatment if treated with BMS-986277 and nivolumab.

d) Participants treated with BMS-986277 monotherapy only: Women of childbearing potential (WOCBP) must agree to follow instructions for method(s) of contraception for the duration of study treatment with BMS-986277 and 3 months following the last study treatment.

e) Participants treated with BMS-986277 and nivolumab: Women of childbearing potential (WOCBP) must agree to follow instructions for method(s) of contraception for the duration of study treatment with nivolumab and 5 months after the last dose of study treatment.

f) Participants treated with BMS-986277 monotherapy only: Males who are sexually active with WOCBP must agree to follow instructions for method(s) of contraception (Appendix 4) for the duration of study treatment with BMS-986277 and 6 months following the last dose of study treatment. In addition, male participants must be willing to refrain from sperm donation during this time.

g) Participants treated with BMS-986277 and nivolumab: Males who are sexually active with WOCBP must agree to follow instructions for method(s) of contraception (Appendix 4) for the duration of study treatment with nivolumab and 7 months after the last dose of study treatment. In addition, male participants must be willing to refrain from sperm donation during this time.

h) WOCBP who are continuously not heterosexually active are also exempt from contraceptive requirements, and still must undergo pregnancy testing as described in this section.

i) Due to the unknown risk of viral shedding in semen, all male participants (irrespective of the participant's vasectomy status or partner's pregnancy status) must agree to remain abstinent from penile intercourse or use a male condom during each episode of penile penetration during the treatment and until 6 months after the end of BMS-986277 treatment. Please see contraception requirements above in 5 f) and g).

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 on the use of highly effective methods of contraception, (Appendix 4) which have a failure rate of < 1% when used consistently and correctly.

6.2 Exclusion Criteria

1) Target Disease Exceptions

a) Participants with active central nervous system (CNS) metastases, untreated CNS metastases, or with the CNS as the only site of disease are excluded. However, participants with controlled brain metastases 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), off steroids for at least 2 weeks, and no new or progressive neurological signs and symptoms.

b) Participants with carcinomatous meningitis.

c) Participants with disease in areas which would not tolerate swelling (ie, airways)

d) Participants who are unable to provide a fresh tumor biopsy with minimal clinical risk as judged by the investigator.

2) Prohibited Treatments

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

b) Non-cytotoxic agents, unless at least 4 weeks or 5 half-lives (whichever is shorter) have elapsed from the last dose of prior anti-cancer therapy and the initiation of study treatment. If less than 5 half-lives or 4 weeks have elapsed from the last dose of prior non-cytotoxic therapy and the initiation of study treatment, the participant can be treated at the investigator's discretion and in agreement with the Medical Monitor (or designee).

c) Treatment with botanical preparations (eg, herbal supplements or traditional Chinese medicines) intended for general health support or to treat the disease under study within 4 weeks prior to treatment. If less than 4 weeks have elapsed from the last botanical supplement and the initiation of study treatment, the participant can be treated at the investigator's discretion and in agreement with the Medical Monitor (or designee). Use of marijuana and its derivatives for treatment of symptoms related to cancer or cancer treatment are permitted if obtained by medical prescription or if its use (even without a medical prescription) has been legalized locally.

d) Receipt of non-oncology vaccines containing live virus for prevention of infectious diseases within 4 weeks prior to first dose of study treatment.

   i) The use of inactivated seasonal influenza vaccines (eg, Fluzone®) will be permitted on study without restriction.

e) Antiviral agents eg, ribavirin, adefovir, lamivudine or cidofovir in the 7 days before the first dose of study treatment; or PEG-IFN in the 14 days before the first dose of study treatment.

3) Medical History and Concurrent Conditions

a) Participants with prior malignancy active within the previous 2 years except for locally curable cancers that have been apparently cured, such as basal or squamous cell skin cancer, superficial bladder cancer, or carcinoma in situ of the prostate, cervix, or breast.

b) Prior organ allograft.

c) Toxicity (except for alopecia) related to prior anti-cancer therapy and/or surgery, unless the toxicity is either resolved, returned to baseline or Grade 1, or deemed irreversible.
   i) Any active neuropathy Grade > 2 (NCI CTCAE v4.03).
d) Participants with the following:
   i) Active, known, or suspected autoimmune disease are excluded.
      (1) Participants with well-controlled asthma and/or mild allergic rhinitis (seasonal allergies) are eligible.
      (2) Participants with the following disease conditions are also eligible:
         (a) Vitiligo.
         (b) Type 1 diabetes mellitus.
         (c) Residual hypothyroidism due to autoimmune condition only requiring hormone replacement.
         (d) 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 Ig prior to the first dose of study treatment).
         (e) Psoriasis, alopecia, or other autoimmune skin disorders not requiring systemic treatment, or conditions not expected to recur in the absence of an external trigger.
e) Participants with history of life-threatening toxicity related to prior immune therapy (eg, anti-CTLA-4 or anti-PD-1/PD-L1 treatment or any other antibody or drug specifically targeting T-cell co-stimulation or immune checkpoint pathways) except those that are unlikely to re-occur with standard countermeasures (eg, Hormone replacement after adrenal crisis)
f) Interstitial lung disease that is symptomatic or that may interfere with the detection or management of suspected drug-related pulmonary toxicity.
g) Conditions 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) Treatment with a short course of steroids (< 5 days) up to 7 days prior to initiating study treatment is permitted.
h) Uncontrolled or significant cardiovascular disease including, but not limited to, any of the following:
   i) Myocardial infarction or stroke/transient ischemic attack within the past 6 months.
   ii) Uncontrolled angina within the past 3 months.
   iii) Any history of clinically significant arrhythmias (such as ventricular tachycardia, ventricular fibrillation, or torsades de pointes).
   iv) History of other clinically significant heart disease (eg, myocarditis, cardiomyopathy, congestive heart failure with New York Heart Association functional classification III to IV [Appendix 9], pericarditis, or significant pericardial effusion).

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

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

i) History of chronic hepatitis as evidenced by the following:

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

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

Known history of testing positive for human immunodeficiency virus (HIV) or known acquired immunodeficiency syndrome (AIDS). **Note:** Testing for HIV-1 and HIV-2 must be performed at sites where mandated by local requirements.

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

l) Receipt of packed red blood cells or platelet transfusion within 2 weeks of the first dose of study treatment.

m) Any known or underlying medical or psychiatric condition and/or social reason 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.

n) WOCBP who are pregnant or breastfeeding.

o) History of severe nephritis or nephrotic syndrome or prior requirement for dialysis.

4) Allergies and Adverse Drug Reaction

a) History of allergy or hypersensitivity to study drug components

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 Bristol-Myers Squibb approval is required).

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

c) Participants with serious or uncontrolled medical disorders.

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

Please see participant contact precautions in Section 7.7.3 and required condom use in Section 6.1, criteria 5.

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 (CONSORT) publishing requirements as applicable, and to respond to queries from regulatory authorities. Minimal information includes date of consent, demography, screen failure details, eligibility criteria, and any serious AEs.

6.4.1 Retesting During Screening

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

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

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

Laboratory parameters and/or assessments that are included in Table 2-1, Screening Procedural Outline may be repeated in an effort to find all possible well-qualified participants. Consultation with the Medical Monitor (or designee) 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 treatment allocation.

Study treatment includes both Investigational Product (IP) and Non-investigational Product (Non-IP) and can consist of the following:

- BMS-986277
- Nivolumab

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

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

Table 7-1: Study treatments for CA034001

Product Description / Class and Dosage Form	Potency	IP[a]/ Non-IP	Blinded or Open Label	Packaging / Appearance	Storage Conditions (per label)
BMS-986277 Solution for Injection	2×10^{12} vp/mL 0.5 mL vial	IP[a]	Open Label	Vial	Refer to the label on container and/or pharmacy manual
Nivolumab BMS-936558-01 Solution for injection	100 mg (10 mg/mL) 40 mg (10 mg/mL)	IP[a]	Open label	Vial	Refer to the label on container and/or pharmacy manual

[a] IP is also known as IMP in some regions.

7.1 Treatments Administered

7.1.1 BMS-986277

Participants will receive BMS-986277 at the doses and schedules outlined below (see Sections 7.1.3, 7.1.4, 7.1.5, and 7.1.6). There will be no dose escalations or reductions of BMS-986277 for individual participants permitted.

Participants should be carefully monitored for infusion reactions during and following BMS-986277 administration as indicated in Section 2. If an infusion reaction is noted, participants should be managed according to Section 7.4.5 and Appendix 10.

The BMS-986277 solution is dispensed when thawed from storage and made up in to suitable dilutions and quantities for infusion. The dilution preparation is carried out using varying quantities of sterile saline for injection (0.9% sterile saline solution). This allows the administration of the required dose of BMS-986277.

The BMS-986277 dose preparation will be performed by an appropriately trained and accredited person who has been specifically trained for the study. Each dose will be prepared in a syringe as a 30 mL volume, according to the detailed instructions in the pharmacy manual.

The syringe will be labelled with the participant number and the dose.

BMS-986277 will be prepared in accordance with a specified standard operating procedure (SOP) under the direction of an accredited pharmacist.

A spill kit must be available whenever BMS-986277 is handled or transported (including at the time of administration to the participant). In the event of a spill, people in the immediate area will be alerted and other personnel will be notified as required by study site policies. The spill area will be contained by limiting non-essential traffic in the area and using barriers to prevent the flow of material beyond the local area. Clean-up must be conducted strictly according to the guidance in the pharmacy manual.

Gloves, gown, surgical/procedure mask and safety glasses with side shields will be worn at all times during handling of BMS-986277 (including clean-up of spills).

7.1.2 Nivolumab

Participants will receive nivolumab at the doses and schedules outlined below (see Sections 7.1.4, 7.1.5, and 7.1.6).

There will be no dose escalations or reductions of nivolumab allowed. Participants may be dosed within a ± 3 day window.

Participants should be carefully monitored for infusion reactions during nivolumab administration. If an acute infusion reaction is noted, participants should be managed according to Section 7.4.5.

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

Nivolumab Injection, 100 mg/10 mL (10 mg/mL) and 40 mg/4 mL (10 mg/mL) Nivolumab injection is to be administered as an IV infusion through a 0.2-micron to 1.2-micron pore size,

low-protein binding in-line filter at the protocol-specified doses. It is not to be administered as an IV push or bolus injection. Nivolumab injection can be infused undiluted (10 mg/mL) or diluted with 0.9% Sodium Chloride Injection, United States Pharmacopeia (USP) or 5% Dextrose Injection, USP to protein concentrations as low as 1 mg/mL. Instructions for dilution and infusion of nivolumab injection may be provided in the clinical protocol, pharmacy binder, or pharmacy reference sheet. Care must be taken to assure sterility of the prepared solution as the product does not contain any antimicrobial preservative or bacteriostatic agent.

Nivolumab infusions are compatible with polyvinyl chloride (PVC) or polyolefin containers and infusion sets, and glass bottles.

7.1.3 Monotherapy Dose Escalation

Table 7.1.3-1: Selection and Timing of Dose for Part 1

Study Treatment	Unit dose strength(s)/Dosage level(s)	Dosage formulation Frequency of Administration	Route of Administration
BMS-986277	3×10^{10} vp	C1: D1, D15, D17, and D19 C2: D1, D3, and D5	IV
BMS-986277	3×10^{11} vp	C1: D1, D15, D17, and D19 C2: D1, D3, and D5	IV
BMS-986277	1×10^{12} vp	C1: D1, D15, D17, and D19 C2: D1, D3, and D5	IV
BMS-986277	3×10^{12} vp	C1: D1, D15, D17, and D19 C2: D1, D3, and D5	IV

In Part 1, to mitigate against unexpected ADR, a staggered enrollment (sentinel participant) approach will be employed during monotherapy dose escalation (see Section 5.1.1, Figure 5.1.1-1, and Figure 5.1.1-2).

7.1.3.1 BMS-986277 Infusion (Part 1)

In Part 1 (monotherapy dose escalation), four dose levels of BMS-986277 (3×10^{10} vp, 3×10^{11} vp, 1×10^{12} vp, and 3×10^{12} vp) are planned. Eligible participants will receive an IV infusion of BMS-986277 at the assigned dose, starting at time zero administered directly into the venous access point using a syringe pump on Days 1, 15, 17, and 19 on Cycle 1 and on Days 1, 3, and 5 on Cycle 2. BMS-986277 will be administered over 5 minutes except for the 3×10^{12} vp dose, which will be administered over 15 minutes. Participants will receive a maximum of 2 cycles of treatment (see Section 7.1.1).

On BMS-986277 dosing days, participants will receive antipyretic prophylaxis predose and postdose (see Section 7.7.2). This will generally be acetaminophen/paracetamol and/or ibuprofen at a dose and schedule to manage the participant's clinical condition, providing that it follows the prescribing information for the product(s). Other medications, including diphenhydramine and

indomethacin may be used in line with the study site's standard practice providing they are not excluded concomitant medications (see Section 7.7.1). Corticosteroid use may be considered under certain circumstances but should be discussed with the Medical Monitor (or designee) prior to initiation.

At the end of the infusion the administration line should be flushed with normal saline to ensure that the full viral dose has been administered. This flush should only use a sufficient amount of saline to flush the line and should not exceed 30 mL.

Participants can receive prophylactic IV hydration after the end of each infusion, unless clinically contraindicated (see Section 7.7.2). Up to 1 L of normal saline may be administered over 4 hours, adjusted to meet the physiological and clinical requirements of the individual participant (eg, participant body mass index [BMI], concurrent conditions).

Every effort will be made to administer the planned doses of BMS-986277. If a participant is unable to receive a dose on a scheduled day for reasons other than for toxicity, then every effort must be made to reschedule the dosing as early as possible up to a maximum of 7 days after the scheduled date. In Part 1, for the first cycle of monotherapy escalation, infusions of BMS-986277 on Day 17 and Day 19 must be administered within 7 days of Day 15, with a minimum of 24 hours required between each of the three infusions. For Part 1, Cycle 2, infusions of BMS-986277 on Day 3 and Day 5 must be administered within 7 days of Day 1, with a minimum of 24 hours required between each of the three infusions. Participants should begin study treatment within 3 calendar days of treatment assignment.

7.1.4 Combination Dose Escalation (Part 2)

Table 7.1.4-1: Selection and Timing of Dose for Part 2

Study Treatment	Unit dose strength(s)/Dosage level(s)	Dosage formulation Frequency of Administration	Route of Administration
BMS-986277	Dose < BLRM-RD[a]	C1 to C2: D1, D3, and D5 (up to 2 cycles of 28 days each)	IV
Nivolumab	480 mg	Day 15 Q4W up to 26 cycles	IV
BMS-986277	BLRM-RD[b]	C1 to C2: D1, D3, and D5 (up to 2 cycles of 28 days each)	IV
Nivolumab	480 mg	Day 15 Q4W up to 26 cycles	IV

[a] Dose lower than the BLRM-RD from Part 1

[b] BLRM-RD from Part 1

In Part 2, to mitigate against unexpected ADR, a staggered enrollment (sentinel participant) approach will be employed during combination dose escalation (see Figure 5.1.2-1 and Figure 5.1.2-2).

7.1.4.1 BMS-986277 Infusion in Combination with Nivolumab

In Part 2, two dose levels of BMS-986277 are planned in the combination escalation phase. The RD from Part 1 will be based on the BLRM-RD and overall clinical assessment of all available safety, PK, pharmacodynamic, and efficacy data. Lower doses of BMS-986277 may be considered if none of the pre-planned doses in Part 1 are found to be tolerable. Such decisions will be made after discussion and agreement between the investigators and the BMS Medical Monitor (or designee).

On BMS-986277 dosing days, participants will receive antipyretic prophylaxis predose and postdose (see Section 7.7.2). This will generally be acetaminophen/paracetamol and/or ibuprofen at a dose and schedule to manage the participant's clinical condition, providing that it follows the prescribing information for the product(s). Other medications, including diphenhydramine and indomethacin may be used in line with the study site's standard practice providing they are not excluded concomitant medications (see Section 7.7.1). Corticosteroid use may be considered under certain circumstances but should be discussed with the Medical Monitor (or designee) prior to initiation.

Furthermore, at Day 1 of Cycle 2, participants will receive an antipyretic plus an H1-antagonist and, following approval from the Medical Monitor (or designee), hydrocortisone 100 mg IV (or equivalent) one hour prior to BMS 986277 dosing and approximately 3 hours postdose.

BMS-986277 and nivolumab will be administered by IV infusion using a syringe pump (nivolumab may also be administered using an infusion bag). Infusion duration of BMS-986277 will be based on dose level chosen for Part 1, and will match infusion duration for that dose level in Part 1. Nivolumab is infused over 30 minutes. Study treatment preparation and administration are described in Section 7.1.

Participants should receive nivolumab at a dose of 480 mg as an approximate 30 minute infusion on Day 15 (± 3 days) of each treatment cycle until progression, unacceptable toxicity, withdrawal of consent, completion of up to 26 cycles, or the study ends, whichever occurs first. Participants should begin study treatment within 3 calendar days of treatment assignment.

At the end of the BMS-986277 infusion the administration line should be flushed with normal saline to ensure that the full viral dose has been administered. This flush should only use a sufficient amount of saline to flush the line and should not exceed 30 mL.

Participants can receive prophylactic IV hydration after the end of each infusion, unless clinically contraindicated. Up to 1 L of normal saline may be administered over 4 hours, adjusted to meet the physiological and clinical requirements of the individual participant (eg, participant BMI, concurrent conditions).

Every effort will be made to administer the planned doses of BMS-986277. If a participant is unable to receive a dose on a scheduled day for reasons other than for toxicity, then every effort must be made to reschedule the dosing as early as possible up to a maximum of 3 days after the previous dose. The infusions of BMS-986277 on Day 3 and Day 5 must be administered within 7 days of Day 1, with a minimum of 24 hours required between each of the three infusions.

7.1.5 Combination Expansion (Part 3 Cohorts 1-2)

Table 7.1.5-1: Selection and Timing of Dose for Part 3 Cohorts 1-2

Study Treatment	Unit dose strength(s)/Dosage level(s)	Dosage formulation Frequency of Administration	Route of Administration
BMS-986277	RD[a]	C1 to C2: D1, D3, and D5 (up to 2 cycles of 28 days each)	IV
Nivolumab	480 mg	D15 Q4W up to 26 cycles	IV

[a] RD from Part 2.

Participants will receive BMS-986277 at the dose recommended from the combination escalation phase of the study.

On BMS-986277 dosing days, participants will receive antipyretic prophylaxis predose and postdose (see Section 7.7.2). This will generally be acetaminophen/paracetamol and/or ibuprofen at a dose and schedule to manage the participant's clinical condition, providing that it follows the prescribing information for the product(s). Other medications, including diphenhydramine and indomethacin may be used in line with the study site's standard practice providing they are not excluded concomitant medications (see Section 7.7.1). Corticosteroid use may be considered under certain circumstances but should be discussed with the Medical Monitor (or designee) prior to initiation.

Furthermore, at Day 1 of Cycle 2, participants will receive an antipyretic plus an H1-antagonist and, following approval from the Medical Monitor (or designee), hydrocortisone 100 mg IV (or equivalent) one hour prior to BMS 986277 dosing and approximately 3 hours postdose.

BMS-986277 and nivolumab will be administered by IV infusion using a syringe pump (nivolumab may also be administered using an infusion bag).

Infusion duration of BMS-986277 will be based on the dose level chosen for Part 2, and will match the infusion duration for that dose level in Part 1. BMS-986277 will be administered over 5 minutes except for the 3 x 10^{12} vp dose, which will be administered over 15 minutes.

Nivolumab is infused over 30 minutes. Study treatment preparation and administration are described in Section 7.1.

Participants should receive nivolumab at a dose of 480 mg as an approximate 30 minute infusion on Day 15 of each treatment cycle until progression, unacceptable toxicity, withdrawal of consent, completion of up to 26 cycles of treatment, or the study ends, whichever occurs first. Participants should begin study treatment within 3 calendar days of treatment assignment.

At the end of the infusion the administration line should be flushed with normal saline to ensure that the full viral dose has been administered. This flush should only use a sufficient amount of saline to flush the line and should not exceed 30 mL.

Participants can receive prophylactic IV hydration after the end of each infusion, unless clinically contraindicated. Up to 1 L of normal saline may be administered over 4 hours, adjusted to meet the physiological and clinical requirements of the individual participant (eg, participant BMI, concurrent conditions).

Every effort will be made to administer the planned doses of BMS-986277. If a participant is unable to receive a dose on a scheduled day for reasons other than for toxicity, then every effort must be made to reschedule the dosing as early as possible up to a maximum of 3 days after the previous dose. The infusions of BMS-986277 on Day 3 and Day 5 must be administered within 7 days of Day 1, with a minimum of 24 hours required between each of the three infusions.

7.1.6 Monotherapy Expansion with Option for Subsequent Nivolumab Treatment (Part 3 Cohort 3)

Table 7.1.6-1: Selection and Timing of Dose for Part 3 Cohort 3

Study Treatment	Unit dose strength(s)/ Dosage level(s)	Dosage formulation Frequency of Administration	Route of Administration
BMS-986277	RD[a]	C1 to C2: D1, D3, and D5 (up to 2 cycles of 28 days each)	IV
Optional: Nivolumab	480 mg	D1 Q4W up to 26 cycles starting at C3	IV

[a] RD from Part 1.

In Part 3 Cohort 3, participants will receive an IV infusion of BMS-986277 at the RD determined in Part 1, starting at time zero administered directly into the venous access point using a syringe pump on Days 1, 3, 5 of each cycle. BMS-986277 will be administered over 5 minutes except for the 3 x 10^{12} vp dose, which will be administered over 15 minutes. The RD from Part 1 will be determined as indicated in Section 7.1.3. Participants should begin study treatment within 3 calendar days of treatment assignment.

On BMS-986277 dosing days, participants will receive antipyretic prophylaxis predose and postdose (see Section 7.7.2). This will generally be acetaminophen/paracetamol and/or ibuprofen at a dose and schedule to manage the participant's clinical condition, providing that it follows the prescribing information for the product(s). Other medications, including diphenhydramine and indomethacin may be used in line with the study site's standard practice providing they are not excluded concomitant medications (see Section 7.7.1). Corticosteroid use may be considered under certain circumstances but should be discussed with the Medical Monitor (or designee) prior to initiation.

Participants will receive a maximum of 2 cycles of BMS-986277 monotherapy. Following 2 cycles of BMS-986277 monotherapy, participants may receive optional nivolumab treatment (480 mg Q4W) for up to 26 cycles if eligibility criteria continue to be met (see Sections 6.1 and 6.2) as indicated in Table 2-5. Participants whose disease progresses prior to receiving Cycle 2 of BMS-986277 may also receive nivolumab treatment if eligibility criteria continue to be met, skipping any remaining monotherapy visits and proceeding directly to Cycle 3, optional nivolumab treatment. For participants whose disease has progressed, a minimum of 14 days will be required between the Day 1 BMS-986277 administration (Cycle 1 or Cycle 2) and the start of nivolumab administration. For participants whose disease is responding (complete or partial) per RECIST v1.1 or PCWG3 at the 8 week scan, treatment must be discussed and agreed upon with the Medical Monitor (or designee) prior to the start of the optional subsequent nivolumab treatment.

BMS-986277 and nivolumab (if participant meets subsequent treatment criteria above) will be administered by IV infusion using a syringe pump (nivolumab may also be administered using an infusion bag).

Infusion duration of BMS-986277 will be based on the dose level chosen for Part 1, and will match the infusion duration for that dose level in Part 1. BMS-986277 will be administered over 5 minutes except for the 3 x 10^{12} vp dose, which will be administered over 15 minutes.

Nivolumab is infused over 30 minutes. Study treatment preparation and administration are described in Sections 7.1.1 and 7.1.2.

Participants should receive nivolumab at a dose of 480 mg as an approximate 30 minute infusion on Day 1 of each treatment cycle starting with Cycle 3 until progression, unacceptable toxicity, withdrawal of consent, completion of up to 26 cycles of treatment, or the study ends, whichever occurs first.

At the end of the infusion the administration line should be flushed with normal saline to ensure that the full viral dose has been administered. This flush should only use a sufficient amount of saline to flush the line and should not exceed 30 mL.

Participants can receive prophylactic IV hydration after the end of each infusion, unless clinically contraindicated. Up to 1 L of normal saline may be administered over 4 hours, adjusted to meet the physiological and clinical requirements of the individual participant (eg, participant BMI, concurrent conditions).

Every effort will be made to administer the planned doses of BMS-986277. If a participant is unable to receive a dose on a scheduled day for reasons other than for toxicity, then every effort must be made to reschedule the dosing as early as possible up to a maximum of 3 days after the previous dose. The infusions of BMS-986277 on Day 3 and Day 5 must be administered within 7 days of Day 1, with a minimum of 24 hours required between each of the three infusions.

7.2 Method of Treatment Assignment

All participants will be centrally assigned to treatment using an IRT. Before the study is initiated, each user will receive log in information and directions on how to access the IRT.

Enrolled participants, including those not dosed, will be assigned sequential participant numbers starting with 00001, (eg, 00001, 00002, 00003,.... 00010). Those enrolled participants meeting inclusion and exclusion criteria will be eligible to be dosed. Sequential numbering may restart at 00001 for each participating site as the distinct patient identification number (PID) will ultimately be comprised of the site number and participant number, (eg, 0002 00001).

Once it is determined that the participant meets the eligibility criteria following the screening visit, the assigned treatment group and dose level will be provided by the site study team through the IRT prior to the first study treatment administration. The participant will be informed of one of the following:

- Assigned to Part 1 and which dose level in the monotherapy dose escalation portion of the study
- Assigned to Part 2 and which dose level in the combination dose escalation portion of the study
- Assigned to Part 3 and which biomarker category in the cohort expansion portion of the study
  - There should be a minimum of 5 participants per each selected indication in each cohort.

During dose escalation, all participants will be assigned to Part 1 until the decision is made to start combination dose escalation. If there are no openings available in the part to which the participant would be assigned by this algorithm, then the participant will be assigned to the next open part/cohort.

During monotherapy and combination dose escalation, participants who are not evaluable for DLT evaluation may be replaced. Replacement participants will be assigned to the same part (Part 1 or 2) and dose level, but will be assigned a new participant number. Please refer to the IRT manual for complete details on replacement of participants.

Participants in cohort expansion (Part 3) will be replaced if there is insufficient or unevaluable tumor tissue to determine CD8 level. The replacement participant will receive treatment as determined by CD8 TILs (see Section 5.1.3) and a new participant number will be assigned.

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

7.3 Blinding

Not applicable.

7.4 Dosage Modification

7.4.1 Dose-Limiting Toxicities

For the purpose of guiding dose escalation, DLTs will be defined based on the incidence, intensity, and duration of AEs for which no clear alternative cause is identified. The DLT evaluation period will be 42 days (6 weeks). In the event of dose delays for reasons other than a potential DLT, the DLT evaluation period may be extended to include at least 28 days after the start of the sequential doses in Part 1 or at least 14 days after the start of Cycle 2 Day 1 sequential doses in Part 2. Participants requiring dose delays >7 days may be replaced for the purposes of DLT evaluation

but permitted to remain on study treatment unless permanent discontinuation criteria (Section 8.1) are met.

In all study parts, participants who complete the first cycle and do not have a DLT, have not had clinical evidence of disease progression, and are considered suitable for further treatment may receive up to 1 additional cycle of BMS-986277.

Additionally DLT's as defined below will require permanent discontinuation for all study participants regardless of treatment cycle.

In Parts 1 and 2, participants who discontinue due to a DLT during the DLT evaluation period, will be considered as DLT-evaluable participants. Participants who withdraw from the study during the DLT evaluation period for reasons other than a DLT may be replaced with a new participant at the same dose level. The incidence of DLT(s) during the DLT evaluation period will be used in dose escalation decisions and to define the BLRM-RD. AEs occurring after the DLT period will be considered for the purposes of defining the BLRM-RD upon agreement between the Sponsor, Medical Monitor (or designee), and investigators.

Participants experiencing a DLT will enter the safety follow-up period of the study. DLTs occurring after the 6-week DLT evaluation period for Part 1 will be accounted for in determining the BLRM-RD for the combination part.

A DLT is defined as one of the following and considered by the Investigator to be possibly, probably or definitely related to BMS-986277 and/or nivolumab.

AEs will be graded according to the NCI CTCAE v4.03, as listed below:

1) Hepatic Non-hematological DLT

Any one of the following study treatment-related events will be considered a hepatic DLT:

- Any Grade ≥ 3 elevation of aspartate aminotransferase (AST), alanine aminotransferase (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 [ALP] [eg, findings consistent with Hy's law or FDA definition of potential drug-induced liver injury or potential drug-induced liver injury [p-DILI]). Note that this special category of DLT uses ULN rather than Common Toxicity Criteria (CTC) grade for definition.

2) Non-hepatic Non-hematological DLT

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

- Any Grade 2 drug-related uveitis or eye pain or blurred vision that does not respond to topical therapy and does not improve to Grade 1 severity ≤ 2 weeks *or* requires systemic treatment.
- Grade 3 drug-related uveitis, pneumonitis, bronchospasm, neurologic toxicity, hypersensitivity reaction, or myocarditis, of any duration or infusion reaction not returning to baseline in < 1 hour, will require discontinuation.

- Any Grade 3 or greater nondermatologic, nonhepatic nonhematological study treatment-related 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 72 hours, and either resolve spontaneously or respond to conventional medical intervention
  - ♦ Grade 3 nausea, vomiting, or diarrhea that lasts less than 72 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 or with other symptoms of infusion-related reactions that returns to ≤ Grade 1 with standard treatment in ≤ 1 hour)
  - ♦ Grade 3 endocrinopathy that is well controlled by hormone replacement
  - ♦ Grade 3 tumor flare (defined as pain, irritation, or rash that localizes to sites of known or suspected tumor)
  - ♦ Grade 3 fatigue for ≤ 7 days
  - ♦ Grade 3 infusion reaction that returns to Grade 1 in ≤ 1 hour

3) Dermatologic DLT

- Grade 3/4 rash if no improvement (ie, resolution to Grade ≤ 1) after a 1-week to 2-week infusion delay. Participants who have not experienced a Grade 3 drug-related skin AE may resume treatment in the presence of Grade 2 skin toxicity.
- Grade 4 rash of any duration

4) Hematologic DLT

- Grade 4 neutropenia ≥ 5 days in duration
- Grade 4 thrombocytopenia or Grade 3 thrombocytopenia with clinically significant bleeding or any requirement for platelet transfusion
- Grade 4 anemia not explained by underlying disease
- Grade 4 febrile neutropenia
- Grade 3 febrile neutropenia that lasts > 48 hours
- Grade ≥ 3 hemolysis (ie, requiring transfusion or medical intervention such as steroids)

7.4.2 Dose Delay Criteria for Study Treatment

Study treatment administration should be delayed for the following:

- Potential DLT, until DLT-relatedness is defined.
- Select AEs and laboratory abnormalities:
  - Grade ≥ 1 pneumonitis
  - Grade ≥ 2 abnormality in AST, ALT, or total bilirubin
  - Grade ≥ 2 abnormality in creatinine
  - Grade ≥ 2 diarrhea or colitis
  - Grade ≥ 2 neurological AE
  - AE, laboratory abnormality, or concurrent illness that, in the judgment of the investigator, warrants delaying study treatment administration.

- Criteria for participants who are required to permanently discontinue both study treatments are listed in Section 8.1. Participants not meeting guidelines for permanent discontinuation will be permitted to resume therapy based on the criteria specified below in Section 8.1.1. Participants eligible to resume study treatment will resume study treatment at the nominal treatment visit following their last received study treatment dose.

7.4.3 Treatment Delays

Participants who experience a potential DLT must have the study treatment held. Participants who are required to permanently discontinue both study treatments are listed in Section 8.1. In addition, all Grade 2 hepatic, pulmonary, renal, gastrointestinal (GI), and neurological AEs should be evaluated and managed per the toxicity management algorithms (Appendix 5). Participants not meeting guidelines for permanent discontinuation will be permitted to resume study treatment based on the criteria specified below in Section 8.1.1. Participants eligible to resume study treatment will resume study treatment at the visit following their last received dose.

If the reason for a dosing delay is not due to a potential DLT, then the DLT evaluation period may be extended to include at least 28 days after the start of the sequential doses in Part 1 or at least 14 days after the start of Cycle 2 Day 1 sequential doses in Part 2 to allow for adequate time to observe any potential DLTs following these sequential administrations.

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 (or designee) in settings where benefit/risk may justify continued study treatment (eg, participant deriving clinical benefit who requires prolonged steroid taper for the management of non-DLT drug-related AEs or experiences delays for the management of a nondrug-related AE).

The tumor assessments (ie, CT/MRI, positron emission tomography [PET], etc) will continue relative to the participant's first dose as outlined in Section 2 (Schedule of Activities) regardless of any treatment delay incurred.

7.4.4 Exceptions to Permanent Discontinuation Criteria

Detailed exceptions to permanent discontinuation are listed in Section 8.1.

Any drug-related AE occurring at any time that meets DLT criteria as outlined in Section 7.4.1 will require permanent discontinuation except in cases of non-life-threatening AEs that meet DLT criteria and that have been resolved to Grade 1 or baseline. In these specific cases consideration to resume treatment will be made on a case-by-case basis in a discussion between the investigator and BMS Medical Monitor (or designee), taking into account the overall benefit/risk ratio for the individual participant and considering the following factors:

- A 2-week washout period is required after completing the immune suppressive treatment used to manage the AE (eg, steroids). The AE should not recur/worsen during the washout period.
- Evidence for clinical or radiographic benefit must be present, which can include improvement of physical symptoms (eg, ECOG status, shortness of breath), symptomatic improvement in combination with assessment of SD, or radiographic response.

In the event of recurrence of the AE that met the DLT criteria, study therapy will be permanently discontinued for the participant.

Additionally, consideration to permanently discontinue study therapy for participants with any severe Grade 3 drug-related AE that recurs will be made on a case-by-case basis in a discussion between the investigator and BMS Medical Monitor (or designee).

All participants who discontinue treatment should comply with protocol-specified follow-up procedures as outlined in Sections 2 (Schedule of Activities) and 5.1.5. 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, imprisonment or involuntarily incarceration 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.

7.4.5 Management of Drug-related Infusion Reactions

BMS-986277 has the potential to induce hypersensitivity reactions following administration. There is potential risk of cytokine release exhibited with enadenotucirev coupled with potential immune activation from transgenes. These events will be mitigated by an up to 12 hour post infusion observation, laboratory measurements for cytokine release monitoring, staggered dosing of initial participants in each cohort of monotherapy treatment (Part 1) and combination treatment (Part 2) to have no more than 1 patient at a time dosed, and a starting dose selected that is 100× below the enadenotucirev RP2D. Refer to Appendix 10 for the treatment algorithm for BMS-986277-associated infusion reactions.

Since nivolumab contains only human immunoglobulin protein sequences, it is unlikely to be immunogenic and induce infusion or hypersensitivity reactions. However, if such a reaction were to occur, it might manifest with fever, chills, rigors, headache, rash, pruritus, arthralgia, hypotension, hypertension, bronchospasm, or other allergic-like reactions. All Grade 3 or 4 infusion reactions should be reported within 24 hours to the study Medical Monitor (or designee) and reported as an SAE if it meets the criteria. Infusion reactions should be graded according to NCI CTCAE (Version 4.03) guidelines.

Treatment recommendations for nivolumab-associated infusion reactions are provided below and may be modified based on local treatment standards and guidelines, as appropriate:

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

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

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

- Stop the study drug infusion, begin an IV infusion of normal saline, and treat the participant with diphenhydramine 50 mg IV (or equivalent) and/or acetaminophen/paracetamol 325 to 1000 mg; remain at bedside and monitor participant until resolution of symptoms. Corticosteroid and/or bronchodilator therapy may also be administered as appropriate. If the infusion is interrupted, then restart the infusion at 50% of the original infusion rate when symptoms resolve; if no further complications ensue after 30 minutes, the rate may be increased to 100% of the original infusion rate. Monitor participant closely. If symptoms recur, then no further study medication will be administered at that visit.
- For future infusions, the following prophylactic premedications are recommended: diphenhydramine 50 mg IV (or equivalent) and/or acetaminophen/paracetamol 325 to 1000 mg should be administered at least 30 minutes before treatment infusions. If necessary, corticosteroids (up to 25 mg of hydrocortisone or equivalent) may be used.

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

- Immediately discontinue infusion of study drug. Begin an IV infusion of normal saline and treat the participant as follows: Recommend bronchodilators, epinephrine 0.2 to 1 mg of a 1:1000 solution for subcutaneous administration or 0.1 to 0.25 mg of a 1:10,000 solution injected slowly for IV administration, and/or diphenhydramine 50 mg IV (or equivalent) with methylprednisolone 100 mg IV (or equivalent), as needed. Participant should be monitored until the Investigator is comfortable that the symptoms will not recur. Study drug will be permanently discontinued. Investigators should follow their institutional guidelines for the treatment of anaphylaxis. Remain at bedside and monitor participant until recovery of the symptoms.

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

[redacted]

[redacted]

7.5 Preparation/Handling/Storage/Accountability

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

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

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

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

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

7.5.1 Retained Samples for Bioavailability/Bioequivalence

Not applicable.

7.6 Treatment Compliance

Not applicable.

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

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

- Documented and confirmed disease progression as defined by RECIST v1.1 or PCWG3 (Appendix 7 and 8, respectively) unless participants meet criteria for treatment beyond progression (Section 8.1.2)
- 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
- Discretion of the investigator
- Inability to comply with the protocol requirements
- 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 (or designee) in settings where benefit/risk justifies discontinuation of study treatment
- Any drug-related AE occurring at any time that meets DLT criteria as outlined in Section 7.4.1 will require permanent discontinuation except in cases of non-life-threatening AEs that meet DLT criteria and that have been resolved to Grade 1 or baseline. See Section 8.1.1 for considerations regarding resuming treatment.
- Any Grade ≥ 2 study treatment-related pneumonitis or interstitial lung disease that does not resolve following dose delay and systemic steroids
- Any Grade 3 non-skin, study treatment-related AE lasting > 7 days, or recurs, with the following exceptions for uveitis, pneumonitis, bronchospasm, diarrhea, colitis, neurologic toxicity, myocarditis, hypersensitivity reactions, infusion reactions not returning to baseline in ≤ 1 hour, endocrinopathies and laboratory abnormalities:
  - Grade 3 drug-related uveitis, pneumonitis, bronchospasm, neurologic toxicity, myocarditis, hypersensitivity reaction of any duration, or infusion reaction not returning to baseline in ≤ 1 hour requires discontinuation
  - Grade 3 study treatment-related endocrinopathies adequately controlled with only physiologic hormone replacement do not require discontinuation. Adrenal insufficiency requires discontinuation regardless of control with hormone replacement.
  - Grade 3 drug-related laboratory abnormalities do not require treatment discontinuation except:
    - Grade 3 drug-related thrombocytopenia > 7 days or associated with bleeding requires discontinuation
    - Grade ≥ 3 drug-related AST, ALT or Total Bilirubin requires discontinuation*
    - Concurrent AST or ALT > 3 x ULN and total bilirubin > 2x ULN

* In most cases of Grade 3 AST or ALT elevation, study treatment will be permanently discontinued. If the investigator determines a possible favorable benefit/risk ratio that warrants continuation of study treatment, a discussion between the investigator and the BMS Medical Monitor/designee must occur.

- Any Grade 4 drug-related AE or laboratory abnormality (including but not limited to creatinine, AST, ALT, or Total Bilirubin), except for the following events which do not require discontinuation:
  - Grade 4 neutropenia ≤ 5 days

  - Grade 4 lymphopenia or leukopenia or asymptomatic amylase or lipase
  - Isolated Grade 4 electrolyte imbalances/abnormalities that are not associated with clinical sequelae and are corrected with supplementation/appropriate management within 72 hours of their onset
  - Grade 4 drug-related endocrinopathy AEs, such as, hyper- or hypothyroidism, or glucose intolerance, which resolve or are adequately controlled with physiologic hormone replacement (corticosteroids, thyroid hormones) or glucose-controlling agents, respectively, may not require discontinuation after discussion with and approval from the BMS Medical Monitor (or designee). Grade 4 adrenal insufficiency must discontinue.
- Any event that leads to delay in dosing lasting > 6 weeks from the previous dose requires discontinuation, with the following exceptions:
  - Dosing delays to allow for prolonged steroid tapers to manage drug-related AEs are allowed.
  - Dosing delays lasting > 6 weeks from the previous dose that occur for non-drug-related reasons may be allowed if approved by the BMS Medical Monitor (or designee).

Prior to re-initiating treatment in a participant with a dosing delay lasting > 6 weeks, the BMS Medical Monitor (or designee) must be consulted.

Tumor assessments should continue as per protocol even if dosing is delayed. Periodic study visits to assess safety and laboratory studies should also continue every 6 weeks or more frequently if clinically indicated during such dosing delays.

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

In the case of pregnancy, the investigator must immediately, within 24 hours of awareness of the pregnancy, notify the BMS Medical Monitor/designee of this event. In most cases, the study treatment will be permanently discontinued in an appropriate manner (eg, dose tapering if necessary for participant safety). Refer to Section 9.2.5 Pregnancy.

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

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

The assessment for discontinuation of nivolumab should be made separately from the assessment made for discontinuation of BMS-986277. Although there is overlap among the discontinuation criteria, if discontinuation criteria are met for BMS-986277 but not for nivolumab, treatment with nivolumab may continue if BMS-986277 is discontinued.

If a participant in any of the nivolumab/BMS-986277 combination arms meets criteria for discontinuation and investigator is unable to determine whether the event is related to both or one study drug, the participant should discontinue both nivolumab and BMS-986277 and be taken off the treatment phase of the study.

8.1.1 Criteria to Resume Treatment

Participants will be permitted to resume study treatment at the same dose level(s) following resolution of the AE to ≤ Grade 1 or to baseline with the exception of participants who meet criteria for permanent discontinuation of study treatment (see Section 8.1):

- For participants receiving two cycles of combination treatment, the first dose of BMS-986277 in Cycle 2 may be delayed by up to 7 days (up to study Day 36) in the case of persistence of AEs from the preceding cycle as listed above. After this time, nivolumab monotherapy may be continued.
- Nivolumab dosing may be delayed by up to 6 weeks; the participant should restart treatment on the next regularly scheduled nivolumab dosing visit. Doses are not to be replaced only delayed. If nivolumab treatment is delayed > 6 weeks the participant must permanently discontinue study treatment except as specified in Section 8.1.

Tumor assessments for all participants should continue according to the schedule of assessments (Section 2) **even if dosing is delayed**.

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

- Participants may resume treatment in the presence of Grade 2 fatigue.
- Participants who have not experienced a Grade 3 drug-related skin AE may resume treatment in the presence of Grade 2 skin toxicity.
- For participants with Grade 2 AST, ALT and/or Total Bilirubin Abnormalities, dosing may resume when laboratory values return to baseline and management with corticosteroids, if needed, is complete.
- Drug-related pulmonary toxicity, diarrhea or colitis must have resolved to baseline before treatment is resumed. Participants with persistent Grade 1 pneumonitis after completion of a steroid taper over at least 1 month may be eligible for retreatment if discussed with and approved by BMS Medical Monitor (or designee).

Participants with drug-related endocrinopathies adequately controlled with only physiologic hormone replacement may resume treatment after consultation with the BMS Medical Monitor (or designee). Adrenal insufficiency (Grade 4) requires discontinuation regardless of control with hormone replacement.

8.1.2 Treatment Beyond Disease Progression with Nivolumab in Parts 2 and 3

Accumulating evidence indicates a minority of participants treated with immunotherapy may derive clinical benefit despite initial evidence of progressive disease (PD).[104]

Participants will be permitted to continue nivolumab treatment beyond initial PD defined by RECIST 1.1 or PCWG3 for prostate cancer, as assessed by the investigator, up to a maximum of 2 years from date of first dose of study treatment as long as they meet the following criteria:

- Investigator-assessed clinical benefit
- Tolerance of study treatment
- Stable performance status
- Treatment beyond progression will not delay an imminent intervention to prevent serious complications of disease progression (eg, CNS metastases)
- Participant provides written informed consent prior to receiving additional nivolumab treatment. All other elements of the main consent including description of reasonably foreseeable risks or discomforts, or other alternative treatment options will still apply.
- For participants in Part 3 Cohort 3, progression must be subsequent to start of nivolumab treatment

The assessment of clinical benefit should be balanced by clinical judgment as to whether the participant is clinically deteriorating and unlikely to receive any benefit from continued treatment with nivolumab. If the investigator feels that the participant continues to achieve clinical benefit by continuing nivolumab treatment, the participant should remain on the trial and continue to receive monitoring according to the Schedule of Activities (see Section 2). All decisions to continue treatment beyond initial progression must be approved by the BMS Medical Monitor (or designee), and an assessment of the risk/benefit of continuing with study therapy must be documented in the study records (see Appendix 2).

Participants must be re-consented with an ICF addendum or similar document to continue treatment beyond progression. Treatment beyond progression will require continued tumor assessments and scans should continue to be submitted to the imaging core laboratory.

For the participants who continue nivolumab therapy beyond progression, participants will continue to receive monitoring according to the on-treatment assessments in Section 2 and radiographic assessment, per Section 9.1.1 to determine whether there has been continued disease progression or not.

Further progression is defined as an additional 10% increase in tumor burden with a minimum 5 mm absolute increase from time of initial PD. This includes an increase in the sum of diameters of all target lesions and/or the diameters of new measurable lesions compared to the time of initial PD. Nivolumab treatment should be discontinued permanently upon documentation of further progression.

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

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

8.1.3 Post Study Treatment Follow-up

In this study, OS is an exploratory endpoint of the study. Post study follow-up is of critical importance and is essential to preserving participant safety and the integrity of the study. Participants who discontinue study treatment must continue to be followed for collection of outcome and/or survival follow-up data as required and in line with Section 5 until death, completion of the long-term general health status (Section 5.1.7.1), or the conclusion of the study.

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

Participants who discontinue study treatment will continue to be followed for at least 1 year in the long-term general health status follow-up (Section 5.1.7.1).

8.2 Discontinuation from the Study

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

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

8.3 Lost to Follow-Up

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

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

9 STUDY ASSESSMENTS AND PROCEDURES

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

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

If a participant shows pulmonary-related signs (hypoxia, fever) or symptoms (eg, dyspnea, cough, fever) consistent with possible pulmonary AEs, the participant should be immediately evaluated to rule out pulmonary toxicity, according to the suspected pulmonary toxicity management algorithm in the nivolumab IB.[120]

Some of the assessments referred to in this section may not be captured as data in the eCRF. They are intended to be used as safety monitoring by the treating physician. Additional testing or

assessments may be performed as clinically necessary or where required by institutional or local regulations.

9.1 Efficacy Assessments

Efficacy assessments for the anti-tumor activity of study treatments will use investigator assessed tumor assessments per RECIST v1.1 or PCWG3 for prostate cancer. Efficacy evaluation of study treatment per iRECIST (excluding participants with prostate cancer) using BICR is an exploratory objective.[140]

Treatment decisions will be assessed by the investigator per study design using RECIST v1.1 and PCWG3 criteria.

Assessments of PR and CR must be confirmed at least 4 weeks after initial response. A Best Response of SD can only be made after the participant is on-study for a minimum of 49 days from the date of treatment initiation (ie, first dose). Investigators will also report the number and size of new lesions that appear while on study. The time point of tumor assessments will be reported on the eCRF based on the investigator's assessment.

9.1.1 Imaging Assessment for the Study

Images will be submitted to an imaging core lab and may be reviewed by Blinded Independent Central Review (BICR) at any time during the study. Sites should be trained prior to scanning the first study participant. Image acquisition guidelines and submission process will be outlined in the CA034001 Imaging Manual to be provided by the core lab.

Screening and on-study images should be acquired as outlined in Section 2 (Schedule of Activities). Tumor assessments at other time points may be performed if clinically indicated and should be submitted to the central imaging vendor. Every attempt should be made to image each participant using an identical acquisition protocol on the same scanner for all imaging time points. Tumor measurements should be made by the same investigator or radiologist for each assessment whenever possible.

For participants with prostate cancer, bone lesions should be assessed using technetium-99m radionuclide bone scans at each imaging assessment. Anterior and posterior whole body planar images should be acquired. Additional (including spot views and single-photon emission computerized tomography [SPECT]) images should also be submitted if acquired. Participants with other malignancies may have bone scans as clinically indicated.

For participants with TNBC without measurable lesions outside the breast, contrast enhanced MRI of the breasts should also be performed.

Contrast-enhanced CT of the chest, abdomen, pelvis, and other known/suspected sites of disease should be performed for all tumor assessments. Images should be acquired with slice thickness of 5 mm or less with no intervening gap (contiguous).

Should a participant have contraindication for CT intravenous contrast, a non-contrast CT of the chest and a contrast-enhanced MRI of abdomen, pelvis, and other known/suspected sites of disease should be obtained.

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

Should a participant have contraindication for MRI (eg, incompatible pacemaker) in addition to contraindication to CT intravenous contrast, a non-contrast CT of the chest, abdomen, pelvis, and other known/suspected sites of disease is acceptable.

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

Bone scan or PET scan is not adequate for assessment of RECIST 1.1 response in target lesions. In selected circumstances where such modalities are the sole modality used to assess certain non-target organs, those non-target organs may be evaluated less frequently. For example, bone scans may need to be repeated only when CR is identified in target disease or when progression in bone is suspected.

MRI of brain should be acquired as outlined in Section 2 (Schedule of Activities). CT of the Brain (without and with contrast) can be performed if MRI is contraindicated.

9.1.2 Primary Efficacy Assessments

Not applicable.

9.1.3 Secondary Efficacy Assessments

The secondary efficacy assessments will include the ORR (eg, PR + CR), DCR, mDOR, mPFS and PFSR at 8, 16, and 24 weeks (dependent on indication) based on assessment of tumor response using RECIST v1.1 or PCWG3.

ORR is defined as the proportion of all treated participants whose best overall response (BOR) is either a CR or PR. BOR is defined as the best response designation over the study as a whole, recorded between the dates of first dose until the last tumor assessment prior to subsequent therapy. For participants whose treatment continued beyond RECIST v1.1 or PCWG3 defined disease progression, BOR is defined as the best response recorded between the dates of first dose until the time of the initial disease progression defined by RECIST v1.1 or PCWG3. CR or PR determinations included in the BOR assessment must be confirmed by a second scan performed no less than 4 weeks after the criteria for response are first met. For those participants who have

surgical resection, only pre-surgical tumor assessments will be considered in the determination of BOR.

DCR is defined as the proportion of all treated participants who have achieved CR, PR, and SD. BOR for a participant will be assessed per RECIST v1.1 or PCWG3 by BICR and/or by investigator, where available.

mDOR, computed for all treated participants with a BOR of CR or PR, is defined as the time between the date of first response and the date of disease progression or death, whichever occurs first.

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. mPFS and PFSR will be assessed at 8, 16, and 24 weeks (indication dependent).

The proportion will be calculated by the Kaplan-Meier estimate, which takes into account censored data.

9.2 Adverse Events

The definitions of an AE or serious adverse event (SAE) can be found in Appendix 3.

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

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

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

Contacts for SAE reporting specified in Appendix 3

9.2.1 Time Period and Frequency for Collecting AE and SAE Information

Sections 5.6.1 and 5.6.2 in the Investigator Brochure (IB) represent the Reference Safety Information to determine expectedness of SAEs for expedited reporting.

All SAEs must be collected from the time of signing the consent, including those thought to be associated with protocol-specified procedures and within 60 days of discontinuation of dosing for participants treated with BMS-986277 monotherapy only or within 100 days of discontinuation of dosing for participants treated with BMS-986277 and nivolumab.

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

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

AEs will be reported as indicated in Sections 2 and 5.1.5.

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

AEs can be spontaneously reported or elicited during open-ended questioning, examination, or evaluation of a participant. Care should be taken not to introduce bias when collecting AE and/or SAEs. Inquiry about specific AEs should be guided by clinical judgement in the context of known adverse events, when appropriate for the program or protocol. (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 or stabilization, or reported as SAEs if they become serious (see Appendix 3).
- Follow-up is also required for nonserious AEs that cause interruption or discontinuation of study treatment and for those present at the end of study treatment as appropriate.
- All identified nonserious AEs must be recorded and described on the nonserious AE page of the CRF (paper or electronic). Completion of supplemental CRFs may be requested for AEs and/or laboratory abnormalities that are reported/identified during the course of the study.

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 Investigator Brochure and will notify the IRB/IEC, if appropriate according to local requirements.

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

9.2.5 Pregnancy

If, following initiation of the study treatment, it is subsequently discovered that a participant is pregnant or may have been pregnant at the time of study exposure, including during at least 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 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 (or designee) within 24 hours of awareness of the pregnancy.

If, for whatever reason, the pregnancy has ended, confirmed by negative serum pregnancy test, treatment may be resumed (at least 3 weeks and not greater than 6 weeks after the pregnancy has ended), following approvals of participant /sponsor /IRB/EC, as applicable.

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

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

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

9.2.6 Laboratory Test Result Abnormalities

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

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

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

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

9.2.7 Potential Drug-Induced Liver Injury (DILI)

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

Potential drug-induced liver injury is defined as:

1) Aminotransaminase (AT)(ALT or AST) elevation > 3 times upper limit of normal (ULN)

AND

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

AND

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

9.2.8 Other Safety Considerations

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

9.3 Overdose

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

9.4 Safety

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

9.4.1 Serum Inflammatory Cytokine -Release Monitoring

Serum inflammatory cytokines (including: Il-2, IL-4, IL-6, IL-12, IFN-γ, TNF-α, and MCP-1) will be collected in the schedule outlined in the Schedule of Activities (Section 2), and as clinically indicated. Samples will be analyzed as clinically indicated during treatment.

On each BMS-986277 dosing day assessments will be performed predose, and 4 hours (± 30 minutes) post-viral infusion. Additional assessments at 8 (± 1 hour) and 12 hours (± 1 hour) post-virus infusion, may be performed based on clinical symptoms and investigator judgement.

9.4.2 Physical Examinations

Refer to Schedule of Activities.

9.4.3 Vital signs

Refer to Schedule of Activities.

9.4.4 Electrocardiograms

Refer to Schedule of Activities.

9.4.5 Clinical Safety Laboratory Assessments

- Investigators must document their review of each laboratory safety report.
- Lab assessments are to be performed as described in the Schedule of Activities (Section 2).

Table 9.4.5-1: Clinical Laboratory Tests

Hematology	
Hemoglobin	
Hematocrit	
Total leukocyte count, including differential	
Platelet count	
Prothrombin time, activated partial thromboplastin time, and *international normalized ratio* (at screening only)	
Chemistry	
Aspartate aminotransferase (AST) Alanine aminotransferase (ALT) Total bilirubin Alkaline phosphatase (ALP) Lactate dehydrogenase (LDH) Creatinine (if abnormal creatinine clearance should be reported) Blood Urea Nitrogen (BUN) or serum UREA Glucose Lipase Amylase	Albumin (screening only, if clinically indicated) Sodium Potassium Chloride Calcium Phosphorus TSH, free T3 and free T4 - screening TSH, with reflexive fT3 and fT4 if TSH is abnormal - on treatment. Results should be examined by the investigator or appropriate designee within 48 hours of dose administration (or prior to the next dose if within < 48 hours). Magnesium
Serology (at screening only)	
Serum for hepatitis C antibody (if hepatitis C antibody is positive reflex to hepatitis C RNA) or hepatitis C RNA, hepatitis B surface antigen	
HIV-1 and HIV-2 antibody only required to be performed at sites where mandated by local requirements	

Table 9.4.5-1: Clinical Laboratory Tests

Other Analyses
Serum or urine pregnancy test (WOCBP only, minimum sensitivity 25 IU/L or equivalent units of HCG).
Follicle stimulating hormone (FSH) screening -only required to confirm menopause in women < age 55).
Urinalysis including protein, glucose, blood, leukocyte esterase, specific gravity, PH.
Urinalysis or urine dipstick. If blood, protein or leukocytes esterase are positive on the dipstick, microscopic examination of the sediment is required.

A local laboratory will perform the analyses and will provide reference ranges for these tests.

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 Pharmacokinetics

Samples for PK and IMG assessments will be collected for all participants receiving BMS-986277 as monotherapy and in combination with nivolumab. PK of BMS-986277 will be characterized by noncompartmental analysis method using a validated PK analysis program. Data may be pooled with other future studies for PPK analysis of BMS-986277, the results of which will be reported in a separate pharmacometric report.

The PK parameters of BMS-986277 to be assessed following C1D1 dose administration, if data permit, include:

Cmax	Maximum observed blood concentration
Tmax	Time of maximum observed blood concentration
AUC(0-T)	Area under the blood concentration-time curve from time zero to time of last quantifiable concentration
AUC(INF)	Area under the blood concentration-time curve from time zero extrapolated to infinite time
T-HALF	Apparent terminal half-life
CLT	Total body clearance
Vss	Volume of distribution at steady-state
Vz	Volume of distribution of the elimination phase

The PK parameters of BMS-986277 to be assessed following C1D15 and C1D19 doses (Part 1 monotherapy), C1D1 and C1D5 doses (Part 3 Cohort 3), and C1D1 and C1D5 doses (Part 2 and Part 3 Cohorts 1-3 BMS-986277 and nivolumab therapy), if data permit, include:

Cmax	Maximum observed blood concentration
Tmax	Time of maximum observed blood concentration

AUC(0-T)	Area under the concentration-time curve from time zero to time of last quantifiable concentration
AUC(0-48)	Area under the concentration-time curve from time zero to 48 hours postdose
AUC(0-8)	Area under the concentration-time curve from time zero to 8 hours postdose
C48	Blood concentration 48 hours postdose

In addition, the PK parameters of BMS-986277 listed below may be assessed, if data permit, following the C1D19 dose (monotherapy) and C1D5 dose (combination therapy):

CLT	Total body clearance
Css-avg	Average blood concentration over a dosing interval at steady state (AUC[0-48]/48)
AI_AUC	AUC accumulation index; ratio of AUC(0-48) on Cycle 1 Day 19 to AUC(0-48) on Cycle 1 Day 15 for monotherapy, and ratio of AUC(0-48) on Cycle 1 Day 5 to AUC(0-48) on Cycle 1 Day 1 for combination therapy
AI_Cmax	Cmax accumulation index; ratio of Cmax on Cycle 1 Day 19 to Cmax on Cycle 1 Day 15, and ratio of Cmax on Cycle 1 Day 5 to Cmax on Cycle 1 Day 1 for combination therapy
T-HALF	Apparent terminal half-life
T-HALFeff	Effective elimination half-life that explains the degree of accumulation observed for a specific exposure measure (exposure measure includes AUC, Cmax)

The following PK parameter of BMS-986277 will be reported as a separate listing, summary, and plot:

Ctrough	Trough observed blood concentration

The Ctrough and Cmax of nivolumab in serum will be reported as a separate listing, summary, and plot.

Table 9.5-1, Table 9.5-2, and Table 9.5-3 list a detailed sampling schedule to be followed for the assessment of PK and IMG for BMS-986277 as a monotherapy in Part 1, in combination with nivolumab in Part 2 and Part 3 Cohorts 1-2, and with optional subsequent nivolumab therapy in Part 3 Cohort 3, respectively. Time points are relative to the start of BMS-986277 administration, except for nivolumab PK samples, where the time points are relative to the start of nivolumab administration. Predose samples should be taken within 30 minutes before the start of dose administration. End-of-infusion samples should be taken just prior to the end of infusion (EOI; less than 2 minutes apart from the end of infusion is preferred). 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. However, if a predose sample is collected but the dose is subsequently delayed, an additional predose sample should not be collected.

Additional samples for IMG assessments and blood concentration, referred to as "ADA Event Driven" samples, may be collected and justified in cases of Grade 3/4 infusion or hypersensitivity reactions. The IMG (and corresponding concentration) data from these samples will be reported as part of a participant's overall IMG assessment. Uniquely identified specimen collection kits and instructions for collection of "ADA Event Driven" samples will be provided by the central laboratory vendor.

Table 9.5-1: Pharmacokinetic (PK), Anti-Drug Antibody (ADA), and Shedding Sampling Schedule for Monotherapy Dose Escalation - BMS-986277 (Part 1)(CA034001)

Study Day of Sample Collection	Event	Time (Relative To Start of Infusion of BMS-986277 Dose) Hour: Min	BMS-986277 Whole Blood PK Sample	BMS-986277 Serum ADA Sample	BMS-986277 Shedding Sample (urine)	BMS-986277 Shedding Sample (saliva)	BMS-986277 Shedding Sample (stool) (± 7 days)
C1D1, C1D15	predose	00:00	X	X	X	X	X
C1D1, C1D15	EOI [a]	00:15	X				
C1D1, C1D15		01:00	X				
C1D1, C1D15		02:00	X				
C1D1, C1D15		03:00	X				
C1D1, C1D15		04:00	X				
C1D1, C1D15		08:00	X				
C1D2		24:00	X				
C1D8		168:00	X	X	X	X	X
C1D17	predose	00:00	X		X	X	X
C1D17	EOI[a]	00:15	X				
C1D19	predose	00:00	X		X	X	X
C1D19	EOI[a]	00:15	X				
C1D19		01:00	X				
C1D19		02:00	X				
C1D19		03:00	X				
C1D19		04:00	X				
C1D19		08:00	X				
C1D21		48:00	X	X			

Table 9.5-1: Pharmacokinetic (PK), Anti-Drug Antibody (ADA), and Shedding Sampling Schedule for Monotherapy Dose Escalation - BMS-986277 (Part 1)(CA034001)

Study Day of Sample Collection	Event	Time (Relative To Start of Infusion of BMS-986277 Dose) Hour: Min	BMS-986277 Whole Blood PK Sample	BMS-986277 Serum ADA Sample	BMS-986277 Shedding Sample (urine)	BMS-986277 Shedding Sample (saliva)	BMS-986277 Shedding Sample (stool) (± 7 days)
C1D29		240:00	X	X	X	X	X
C2D1	predose	00:00	X	X	X	X	X
C2D1	EOI[a]	00:15	X				
C2D3	predose	00:00	X		X	X	X
C2D3	EOI[a]	00:15	X				
C2D5	predose	00:00	X		X	X	X
C2D5	EOI[a]	00:15	X				
C2D8		72:00	X		X	X	X
C2D15		240:00	X	X	X	X	X
C2D22		408:00	X	X	X	X	X
Grade 3/4 hypersensitivity reaction			X	X			
EOT[b]			X	X	X	X	X
Follow up visit 1			X	X	X	X	X
Follow up visit 2[c]			X	X	X	X	X

[a] EOI = End of Infusion, This sample should be taken immediately prior to stopping the infusion (preferably less than 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.

[b] If within 3 days of other visits, the EOT samples may be skipped.

[c] If virus is detected at the 60 Day Follow-up visit, samples should continue to be collected at least every 30 days until virus is no longer detected.

Infusion duration: BMS-986277 will be administered over 5 minutes except for the 3×10^{12} vp dose, which will be administered over 15 minutes.

Table 9.5-2: Pharmacokinetic (PK), Anti-Drug Antibody (ADA), and Shedding Sampling Schedule for Combination Dose Escalation (Part 2) and Combination Expansion - BMS-986277 and Nivolumab (Part 3 Cohorts 1-2)(CA034001)

Study Day of Sample Collection	Event	Time (Relative To Start of Infusion of BMS-986277 Dose) Hour: Min	BMS-986277 Whole Blood PK Sample	BMS-986277 Serum ADA Sample	Nivolumab Serum PK Sample	Nivolumab Serum ADA Sample	BMS-986277 Shedding Sample (urine)	BMS-986277 Shedding Sample (saliva)	BMS-986277 Shedding Sample (stool) (± 7 days)
C1D1, C2D1	predose	00:00	X	X			X	X	X
C1D1, C2D1	EOI[a]	00:15	X						
C1D1, C1D5		01:00	X						
C1D1, C1D5		02:00	X						
C1D1, C1D5		03:00	X						
C1D1, C1D5		04:00	X						
C1D1, C1D5		08:00	X						
C1D3, C2D3	predose	00:00	X				X	X	X
C1D3, C2D3	EOI[a]	00:15	X						
C1D5, C2D5	predose	00:00	X				X	X	X
C1D5, C2D5	EOI[a]	00:15	X						
C1D7, C2D7		48:00	X				X	X	X
C1D15, C2D15[b]	predose	00:00	X	X	X	X[c]	X	X	X
C1D15, C2D15[b]	EOI[a]	00:30			X				
C1D22, C2D22		408:00	X	X			X	X	X
C3D15[b]	predose	00:00			X	X	X	X	X

Table 9.5-2: Pharmacokinetic (PK), Anti-Drug Antibody (ADA), and Shedding Sampling Schedule for Combination Dose Escalation (Part 2) and Combination Expansion - BMS-986277 and Nivolumab (Part 3 Cohorts 1-2)(CA034001)

Study Day of Sample Collection	Event	Time (Relative To Start of Infusion of BMS-986277 Dose) Hour: Min	BMS-986277 Whole Blood PK Sample	BMS-986277 Serum ADA Sample	Nivolumab Serum PK Sample	Nivolumab Serum ADA Sample	BMS-986277 Shedding Sample (urine)	BMS-986277 Shedding Sample (saliva)	BMS-986277 Shedding Sample (stool) (± 7 days)
C3D15	EOI[a]	00:30			X				
C4D15, C8D15, C12D15[f]	predose	00:00			X	X			
Grade 3/4 hypersensitivity reaction			X	X	X	X			
EOT[d]			X	X	X	X	X	X	X
Follow up visit 1			X	X	X	X	X	X	X
Follow up visit 2[e]			X	X	X	X	X	X	X

[a] EOI = End of Infusion, This sample should be taken immediately prior to stopping the infusion (preferably less than 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.

[b] Samples are relative to the start of nivolumab infusion on these days.

[c] Nivolumab ADA samples are only needed at C1D15 predose.

[d] EOT visit is at the time of study treatment discontinuation. If within 3 days of other visits, the EOT samples may be skipped.

[e] If virus is detected at the 60 Day Follow-up visit, samples should continue to be collected at least every 30 days until virus is no longer detected.

[f] Nivolumab PK and ADA samples will continue to be collected every 16 weeks (4 cycles) until end of treatment.

Table 9.5-3: Pharmacokinetic (PK), Anti-Drug Antibody (ADA), and Shedding Sampling Schedule for Monotherapy Expansion - BMS-986277 (Part 3 Cohort 3) Monotherapy with Option for Subsequent Nivolumab Therapy (CA034001)

Study Day of Sample Collection	Event	Time (Relative To Start of Infusion of BMS-986277 Dose) Hour: Min	BMS-986277 Whole Blood PK Sample	BMS-986277 Serum ADA Sample	Nivolumab Serum PK Sample	Nivolumab Serum ADA Sample	BMS-986277 Shedding Sample (urine)	BMS-986277 Shedding Sample (saliva)	BMS-986277 Shedding Sample (stool) (± 7 days)
C1D1, C2D1	predose	00:00	X	X			X	X	X
C1D1, C2D1	EOI[a]	00:15	X						
C1D1, C1D5		01:00	X						
C1D1, C1D5		02:00	X						
C1D1, C1D5		03:00	X						
C1D1, C1D5		04:00	X						
C1D1, C1D5		08:00	X						
C1D3, C2D3	predose	00:00	X				X	X	X
C1D3, C2D3	EOI[a]	00:15	X						
C1D5	predose	00:00	X				X	X	X
C1D5	EOI[a]	00:15	X						
C1D8, C2D8		72:00	X				X	X	X
C1D15, C2D15		240:00	X	X			X	X	X
C1D22, C2D22		408:00	X	X			X	X	X
C2D5	predose	00:00	X				X	X	X
C2D5	EOI[a]	00:15	X						
C3D1[b]	predose	00:00[f]	X	X	X	X	X	X	X

Table 9.5-3: Pharmacokinetic (PK), Anti-Drug Antibody (ADA), and Shedding Sampling Schedule for Monotherapy Expansion - BMS-986277 (Part 3 Cohort 3) Monotherapy with Option for Subsequent Nivolumab Therapy (CA034001)

Study Day of Sample Collection	Event	Time (Relative To Start of Infusion of BMS-986277 Dose) Hour: Min	BMS-986277 Whole Blood PK Sample	BMS-986277 Serum ADA Sample	Nivolumab Serum PK Sample	Nivolumab Serum ADA Sample	BMS-986277 Shedding Sample (urine)	BMS-986277 Shedding Sample (saliva)	BMS-986277 Shedding Sample (stool) (± 7 days)
C3D1[b]	EOI[a]	00:30[f]			X				
C4D1[b]	predose	00:00[f]	X	X	X	X	X	X	X
C4D1[b]	EOI[a]	00:30[f]			X				
C8D1, C12D1, C16D1[e]		00:00[f]			X	X			
Grade 3/4 hypersensitivity reaction			X	X					
EOT[c]			X	X			X	X	X
Follow up visit 1			X	X	X	X	X	X	X
Follow up visit 2[d]			X	X			X	X	X

[a] EOI = End of Infusion, This sample should be taken immediately prior to stopping the infusion (preferably less than 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.

[b] Samples are relative to the start of nivolumab infusion on these days. These samples are only collected if patients receive subsequent nivolumab therapy after 2 cycles of BMS-896277.

[c] EOT visit is at the time of study treatment discontinuation. If within 3 days of other visits, the EOT samples may be skipped.

[d] If virus is detected at the 60 Day Follow-up visit, samples should continue to be collected at least every 30 days until virus is no longer detected.

[e] Nivolumab PK and ADA samples will continue to be collected every 16 weeks (4 cycles) until end of treatment.

[f] Relative to nivolumab dose.

Infusion duration: BMS-986277 will be administered over 5 minutes except for the 3×10^{12} vp dose, which will be administered over 15 minutes.

The whole blood PK samples will be analyzed for BMS-986277 by a validated qPCR assay. Serum samples will be analyzed for nivolumab and ADA (anti-BMS-986277 antibodies and/or anti-nivolumab antibodies) by validated immunoassays. Samples designated for PK or biomarker assessments may also be used for IMG analysis if required (eg, insufficient volume for complete IMG assessment or to follow up on suspected IMG related AE). Detailed instructions for the PK blood collection, labeling, processing, storage, and shipping will be provided to the site in the procedure manual.

Selected whole blood and serum samples may be analyzed by an exploratory orthogonal method that measures BMS-986277, infectivity, and/or anti-BMS-986277 antibodies. Potential results generated from any orthogonal method are intended as informational for technology exploration purposes and may be reported separately.

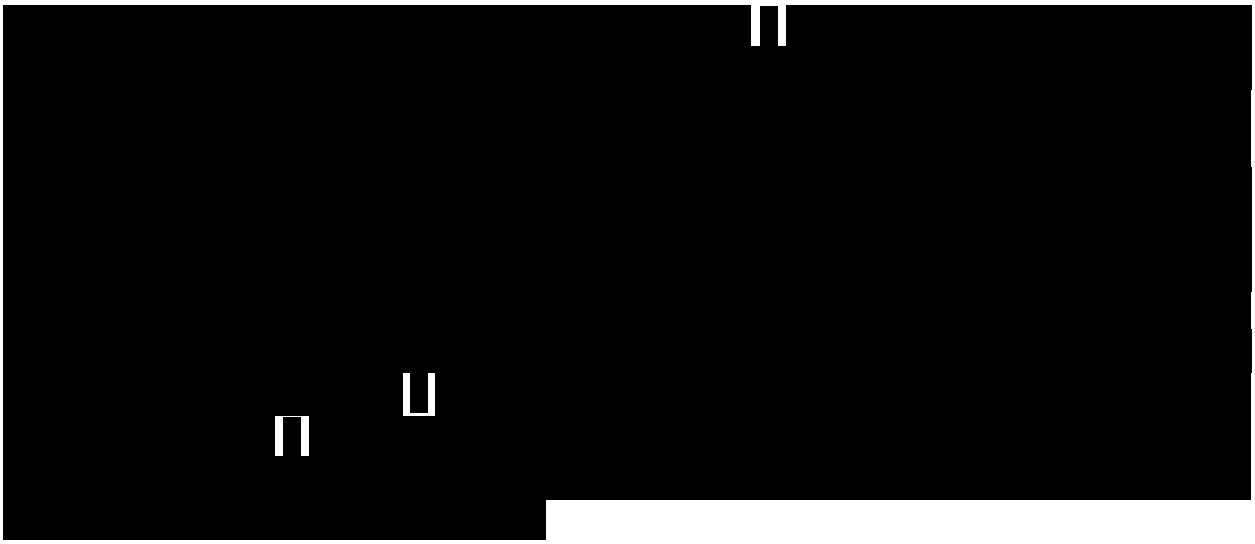
In addition, ad hoc serum samples designated for PK or biomarker assessments may also be used for IMG analysis if required (eg, insufficient volume for complete IMG assessment or to follow up on suspected IMG related AE).

Viral Shedding Assessments

Viral shedding will be assessed during the study treatment period before the drug administration and also during the follow-up period.

Urine samples, saliva samples, and stool samples will be taken on the days as specified in Table 9.5-1, Table 9.5-2, and Table 9.5-3. Samples will be measured for virus genome copies by qPCR. In addition, viral shedding samples may be analyzed in an exploratory method that assess infectivity and the results may be reported separately.

[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

10.1.1.1 Monotherapy Dose Escalation (Part 1)

Dose escalation during the BMS-986277 monotherapy dose escalation (Part 1) will be guided by BLRM employing the Escalation With Overdose Control (EWOC) principle. The BLRM method is fully adaptive, makes use of all the information available at the time of each dose assignment, not just data from the current dose level, and directly addresses the ethical need to control the probability of overdosing. Furthermore, the BLRM uses the knowledge gained from participants treated with enadenotucirev. The targeted toxicity rate in this study is in the range of [16%, 33%]. The boundary is similar to the toxicity boundary used by a rule-based design (ie, 3 + 3 design) in that a minimum is set to 16% (approximately 1 in 6) DLT rate and a maximum at 33% (approximately 2 in 6) DLT rate. The use of the EWOC principle limits the risk of exposing participants in the next cohort to an intolerable dose by ensuring the posterior probability of the DLT rate exceeding 33% at any dose is capped at 35%.

Due to the nature of the dose escalation process, the exact number of participants to be treated at each dose level cannot be precisely determined. The maximum number of participants to be treated is approximately 24. However, simulation studies with various scenarios show that the expected number of DLT-evaluable participants is no more than approximately 18 (Appendix 9). Additional participants (up to a total of 12) may be treated at any dose level to further evaluate the safety, PK, and/or pharmacodynamics profile. The total sample size is up to 72.

Approximately 3 participants will be treated at the starting dose levels of BMS-986277. While the BLRM will use DLT information from the DLT period only, clinical assessment will take into consideration the totality of available data, including PK/pharmacodynamics from all treated participants in assigning a dose level for the next cohort of 3 participants. At least 6 DLT-evaluable participants will be treated at a dose level before it can be recommended as the BLRM-RD for BMS-986277 monotherapy.

The BLRM-RD for BMS-986277 monotherapy is the dose that satisfies the following 3 conditions:

1) The empirical posterior probability that the "DLT rate of 16% to < 33%" is greater than a pre-specified value (ie, 50%);
2) This probability needs to be the largest among the dose levels that satisfy the EWOC condition (ie, the probability that the "DLT rate ≥ 33%" must be no greater than 35%);
3) A minimum number of participants (ie, 6) was treated at this dose level.

The final RD for BMS-986277 monotherapy will be based on the recommendations from the BLRM and overall clinical assessment of all available safety, PK, pharmacodynamic, and efficacy data. Lower doses of BMS-986277 may be tested if none of the planned doses are found to be tolerable as monotherapy. Such decisions will be made after discussion and agreement between the investigators and the BMS Medical Monitor (or designee).

10.1.1.2 Combination Dose Escalation (Part 2)

The dose level for BMS-986277 in combination with nivolumab will be determined based on the RD for BMS-986277 monotherapy established in Part 1, the BLRM-copula RD with nivolumab monotherapy, and incorporating knowledge gained from participants treated with enadenotucirev in combination with PD-1 inhibitor (nivolumab or pembrolizumab). The starting dose for BMS-986277 in combination with nivolumab will be 1 dose level below the RD.

Initially, approximately 3 participants will be treated at this dose level and escalation will be guided by BLRM-copula. While the BLRM-copula will use DLT information from the DLT period only, clinical assessment will take into consideration the totality of available data, including PK/pharmacodynamics from all treated participants in assigning a dose level for the next cohort of 3 participants. At least 6 DLT-evaluable participants will be treated at a dose level before it can be recommended as the BLRM-copula RD for BMS-986277 in combination with nivolumab. Additional participants (up to a total of 12) may be treated at any dose combination below or at the BLRM-copula RD for further evaluation of safety, PK, or pharmacodynamic parameters as required. A combination with a lower, intermediate, or higher dose level of BMS-986277 may be considered if the BLRM-copula recommends it, after consideration of all available safety, PK, and pharmacodynamic data. The total sample size in this part is up to 36.

The final RP2D for BMS-986277 in combination with nivolumab will be based on the recommendations from the BLRM-copula and overall clinical assessment of all available safety, PK, pharmacodynamic, and efficacy data. This final RP2D will be used in the cohort expansion.

10.1.2 Cohort Expansion (Part 3)

The sample size for Cohort 1 and 2 is up to 40 participants per cohort. Cohort 3 will treat up to approximately 12 evaluable participants.

Sample size calculations for Cohorts 1 and 2 assume the following:

- Assumes response rates below 6% and 20% for the low CD8 and mid CD8 cohorts, respectively, would not warrant further study. These are the approximate response rates in CA209275 participants with CD8 < 2% and 2% ≤ CD8 < 20%, respectively.
- Assumes 2 or more indications per cohort.
- Assumes the treatment effect is the same across indications within a cohort.
- The nominal error rates are controlled at one-sided $\alpha = 0.10$ and $\beta = 0.20$, but the actual power and type I error are shown in the tables below (Table 10.1.2.1-1 and Table 10.1.2.2-1), which accounts for the discrete nature of the binomial distribution.

10.1.2.1 Cohort 1 (CD8 < 2%)

Assuming a 6% response rate for nivolumab monotherapy, the interesting rate for the combination therapy is 20%, then 35 participants are needed to detect at least 14.3% response rate.

Table 10.1.2.1-1: Power Estimates and Type 1 Error for Cohort 1

		Historical Rate	
	X, N (alpha, power)	0.05	0.06
Target Rate	0.15	6, 55 (0.056, 0.852)	8, 72 (0.066, 0.864)
	0.2	4, 28 (0.049, 0.840)	5, 35 (0.056, 0.857)
X is the minimum # of responders to show not futile			

10.1.2.2 Cohort 2 (2% ≤ CD8 < 20%)

Assuming a 20% response rate for nivolumab monotherapy, the interesting rate for the combination therapy is 40%, then 33 participants are needed to detect at least a 33% response rate.

Table 10.1.2.2-1: Power Estimates and Type 1 Error for Cohort 2

		Historical Rate	
	X, N (alpha, power)	0.15	0.2
Target Rate	0.3	12, 49 (0.055, 0.841)	31, 121 (0.079, 0.876)
	0.35	8, 29 (0.059, 0.849)	16, 57 (0.091, 0.893)
	0.4	6, 19 (0.054, 0.837)	11, 33 (0.051, 0.831)
X is the minimum # of responders to show not futile			

10.1.2.3 Cohort 3 (≥ 20%)

Cohort 3 is a monotherapy expansion of BMS-986277 which will treat participants with high CD8 TILs (≥20%) to further characterize the pharmacodynamics of BMS- 986277 alone at RD from Part 1. Up to 12 participants evaluable for pharmacodynamic endpoints will be treated in this cohort. Approximately 20% additional participants may be enrolled in this cohort to ensure the number of evaluable participants is achieved. To assess the PD effects, assuming that a biomarker

is measured as a continuous variable, 12 evaluable participants will provide the confidence that the estimate of the ratio of on-treatment biomarker values to baseline values will be within 20% of the true value as shown in Table 10.1.2.3-1.

Table 10.1.2.3-1: Probability that Estimated Ratio of On-treatment to Pre-treatment (Baseline) Value is Within 20% of True Value

Intra-subject Standard Deviation (Log-scale)	0.2	0.3	0.4	0.5	0.6	0.7	0.8
N = 12	99%	90%	78%	68%	59%	52%	46%

For example, for a biomarker with an intra-subject standard deviation of 0.5 on the log-scale, if the true ratio of on-treatment to baseline value geometric means is 1.2 (20% increase from baseline), there is a 68% probability that the estimated ratio is within 0.96 to 1.44 (a percent change from -4% to 44% from baseline) with 12 evaluable participants. If the true ratio is 1.3 (30% increase from baseline), with the same variability, there is a 68% probability that the estimated ratio is within 1.04 to 1.56 (a percent change from 4% to 56% from baseline).

10.2 Populations for Analyses

For purposes of analysis, the following populations are defined:

Population	Description
Enrolled	All participants who sign informed consent and are registered into the IRT
Treated	All participants who take at least 1 dose of study treatment
Response-evaluable	All treated participants with measurable disease at baseline and 1 of the following: (a) at least 1 post baseline tumor assessment, (b) clinical progression, or (3) death
Pharmacokinetic	All treated participants who have evaluable concentration-time data
Immunogenicity	All treated participants who have a baseline and at least 1 post baseline immunogenicity assessment
Biomarker	All treated participants with evaluable biomarker data for the specific analysis

10.3 Statistical Analyses

Final analysis will be performed after all participants are enrolled and have been followed for the minimum time to evaluate the primary endpoint. The statistical analysis plan will be developed and finalized before the database lock for the final analysis. Below is a summary of planned statistical analyses of the primary and secondary endpoints, and select exploratory endpoints. In general, summaries will be performed by dose level, cohort, and indication. If sufficient data are not available such that adequate interpretation of the result is not warranted, some summaries may not be performed and only listings will be presented.

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

10.3.1 Efficacy Analyses

The primary efficacy analyses (see Table below) will be performed on the treated population for the final analysis. Efficacy analyses based on the response-evaluable population may be performed for interim analyses when the minimum follow-up period is less than sufficient to warrant adequate interpretation of the result. Efficacy analyses will be performed using the RECIST v1.1 (all indications except prostate) or PCWG3 criteria (prostate), and may be repeated by BICR using iRECIST (all except prostate), if data permits. Details of the censoring scheme on time-to-event endpoints such as DOR (all except prostate), PFS, OS, immune DOR (iDOR), and immune PFS (iPFS) will be described in the Statistical Analysis Plan.

Endpoint	Statistical Analysis Methods
ORR is defined as the proportion of all treated participants whose BOR is either CR or PR. DCR includes CR, PR, and SD. BOR for a participant will be assessed per RECIST v1.1 or PCWG3 by BICR and/or by investigator, where available.	Estimate of ORR and DCR and corresponding 2-sided exact 95% CI using the Clopper-Pearson method
mDOR DOR for a participant with a BOR of CR or PR is defined as the time between the date of first response and the date of the first objectively documented tumor progression per RECIST v1.1/PCWG3 or death, whichever occurs first.	Estimate by the Kaplan-Meier method and corresponding 2-sided 95% CI using Brookmeyer and Crowley methodology (using log-log transformation)
mPFS and PFSR at 8, 16, and 24 weeks 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 2-sided 95% CI using Brookmeyer and Crowley methodology (using log-log transformation) for the median and Greenwood formula for the rate
mOS and OSR at 3, 6, 9, and 12 months OS for a participant is defined as the time from the first dosing date to the date of death for any cause	Estimate by the Kaplan-Meier method and corresponding 2-sided 95% CI using Brookmeyer and Crowley methodology (using log-log transformation) for the median and Greenwood formula for the rate
Summary measures of indication-specific efficacy biomarkers, such as absolute PSA and PSA doubling time (prostate), CEA (colorectal), Ca125 (ovarian), and Ca19-9 (pancreatic)	Summary statistics/plots by visit Spider plots

Abbreviations: BICR = blinded independent central review; BOR = best overall response; CI = confidence interval; CR = complete response; DCR = disease control rate; DOR = duration of response; iRECIST = immune Response Evaluation Criteria In Solid Tumors; mDOR = median duration of response; mOS = median overall survival; mPFS = median progression-free survival; ORR = objective response rate; OS = overall survival; OSR = overall survival rate; PCWG = Prostate Cancer Working Group; PFS = progression-free survival; PFSR = progression-free survival rate; PR = partial response; RECIST = Response Evaluation Criteria in Solid Tumors, SD = stable disease

10.3.2 Safety Analyses

All safety analyses will be performed on the treated population.

Endpoint	Statistical Analysis Methods
Incidence of AEs, SAEs, AEs meeting protocol-defined DLT criteria, AEs leading to discontinuation, AEs resulting in death, and deaths AEs will be graded according to CTCAE v4.03	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 SOC level, and (3) once in the "total participant" row at their worst CTC grade, regardless of SOC or PT.
Incidence of clinical laboratory test abnormalities Laboratory values will be graded according to CTCAE v4.03	Laboratory shift table using the worst CTC grade on treatment per participant
Vital sign abnormalities or other safety biomarkers	Summary tables of vital signs Frequency statistics of renal function and bladder hemorrhage

Abbreviations: AE = adverse event; CTC = common terminology criteria; CTCAE = common terminology criteria for adverse events; DLT = dose-limiting toxicity; PT = preferred term; SAE = serious adverse event; SOC = system organ class

10.3.3 Pharmacokinetic Analyses

All PK analyses will be performed on the PK population. Each endpoint will be summarized for BMS-986277 and nivolumab separately, where available. Refer to Section 9.5 for the definition of the PK parameters.

Endpoint	Statistical Analysis Methods
Cmax, AUC(0-T), AUC(0-8), AUC(0-48), AUC(INF), T-HALF, CLT, Vss, Vz, C48, Css-avg, AI_AUC, AI_Cmax, and T-HALFeff	Summary statistics: geometric means and coefficients of variation
Cmax, AUC(0-T), AUC(0-8), AUC(0-48)	Scatter plots versus dose for each cycle measured; dose proportionality based on a power model and a CI around the power coefficient
Tmax	Summary statistics: medians and ranges
Ctrough	Summary statistics to assess attainment of steady state: geometric means and coefficients of variation, by treatment and by day, plots versus time by dose

Abbreviations: AI = accumulation index; AUC = area under the concentration-time curve; C48 = plasma concentration 48 hours postdose; CLT = total body clearance; Cmax = maximum observed plasma concentration; Css-avg = average plasma concentration over a dosing interval at steady state; Ctrough = trough observed plasma concentrations; T-HALF = apparent terminal half-life; T-HALFeff = effective elimination half-life; Tmax = time of maximum observed plasma concentration; Vss = volume of distribution at steady-state; Vz = volume of distribution of the elimination phase.

10.3.3.1 Exploratory Population PK and Exposure Response Analyses

BMS-986277 alone or in combination with nivolumab concentration data and baseline characteristic data from this study may be combined with data from other studies for an integrated PPK analysis. The PPK analysis can be used to understand BMS-986277 PK in monotherapy and combination therapy with nivolumab, to explore effects of baseline characteristics on BMS-986277 PK, and to understand if BMS-986277 affects the PK of nivolumab. These analyses may be described in a separate analysis plan, and the results of these analyses may be presented in a separate report.

BMS-986277 alone or in combination with nivolumab concentration and clinical and biomarker data (eg, baseline characteristic, biomarker response, clinical response, and/or safety data) from this study may be analyzed separately or combined with data from other studies to understand exposure-response relationships following monotherapy and combination therapy. Exposure-response analyses may be conducted to explore relationships between BMS-986277 alone or in combination with nivolumab PK parameters (eg, AUC, Cmax, etc) and clinical responses and/or safety effects following treatment administration. Details of these analyses may be described in a separate analysis plan, and the results of these analyses may be presented in a separate report.

10.3.4 Immunogenicity Analyses

All IMG analyses will be performed on the IMG population. Each endpoint will be summarized for BMS-986277 and nivolumab separately, pending availability of evaluable data. Details of the IMG data analysis, including ADA titers, will be provided in the Statistical Analysis Plan.

Endpoint	Statistical Analysis Methods
Incidence of ADA Baseline ADA-positive participant is defined as a participant who has an 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. ADA, anti-drug antibody

[redacted]

[redacted]

[redacted]

[redacted]

10.3.7 Assay Performance Analyses

Assay performance analysis will be performed on the biomarker and response evaluable population. This analysis is only applicable to the Combination Dose Escalation (Part 2) and Cohort Expansion (Part 3 Cohorts 1-2).

A logistic regression model will be used to explore the association between a diagnostic assay and response to BMS-986277 in combination with nivolumab. This model may be adjusted for BMS-986277 dose and/or biomarker level and/or indication. The model will inform a biomarker cutpoint(s), along with the efficacy achieved for participants at each cutpoint and the prevalence rate of participants at each cutpoint. The cutpoint performance characteristics will be evaluated with the following endpoints.

Endpoint	Statistical Analysis Methods
Sensitivity and specificity PPV and NPV TPR and FPR	Logistic regression model Receiver Operating Characteristics (ROC) plot and corresponding AUC Plot of estimated TPR, FPR, PPV, NPV, and prevalence rate of participants versus biomarker level or the predicted probability of response from the full model (x-axis)

Abbreviations: FPR = false positive rate; NPV = negative predictive value; PPV = positive predictive value; TPR = true positive rate.

10.3.8 Other Analyses

Further exploratory analyses not specified here will be described in the Statistical Analysis Plan, which will be finalized before database lock and may be presented separately from the main clinical study report.

10.3.9 Interim Analyses

Administrative interim analyses on safety, efficacy, PK, IMG, and selected biomarkers may be performed at various times prior to the final analysis in order to inform subsequent parts of the study, facilitate program decisions, and to support scientific publications or presentations. The timing of these database locks (and their associated last patient last visits [LPLVs]) and analyses will depend on the rate in which the data matures. No formal inferences requiring any adjustment to statistical significance level will be performed

12 APPENDICES

APPENDIX 1 ABBREVIATIONS AND TRADEMARKS

Term	Definition
5-FU	5-fluorouracil
ADA	anti-drug antibodies
ADR	adverse drug reaction
AE	adverse event
AI_AUC	AUC accumulation index
AI_Cmax	Cmax accumulation index
AIDS	acquired immunodeficiency syndrome
ALP	Alkaline phosphatase
ALT	alanine aminotransferase
AR	additional research
AST	aspartate aminotransferase
AT	aminotransaminase
AUC	area under the concentration-time curve
AUC(0-T)	area under the concentration-time curve from time zero to the time of the last quantifiable concentration
AUC(INF)	area under the concentration-time curve from time zero extrapolated to infinite time
BCG	bacillus Calmette-Guérin
BICR	blinded independent central review
BLRM	Bayesian Logistic Regression Model
BLRM-RD	Bayesian Logistic Regression Model-Recommended Dose
BMI	body mass index
BMS	Bristol-Myers Squibb
BOR	best overall response
BP	blood pressure
BRCA	breast cancer susceptibility gene
BSC	best supportive care
BUN	blood urea nitrogen
C	Cycle
Cavgss	time-averaged steady state concentration

Term	Definition
CBC	complete blood count
CFR	Code of Federal Regulations
CI	confidence interval
CISCA	cisplatin, adriamycin, and cyclophophamide chemotherapy
CLT	total body clearance
cm	centimeter
Cmax, CMAX	maximum observed concentration
Cmaxss	maximum steady state concentration
Cminss	steady-state trough concentration
CMV	cytomegalovirus
CNS	central nervous system
CONSORT	Consolidated Standards of Reporting Trials
CR	complete response
CRC	colorectal cancer
CrCl	creatinine clearance
CRF	case report form
Css-avg	average concentration over a dosing interval at steady state
CT	computed tomography
CTC	Common Toxicity Criteria
CTLA	cytotoxic T-lymphocyte-associated protein
Ctrough	trough observed concentration
D	day
DCR	disease control rate
DILI	drug induced liver injury
dL	deciliter
DLT	dose-limiting toxicity
DNA	deoxyribonucleic acid
DOR	duration of response
ECG	electrocardiogram
ECOG	Eastern Cooperative Oncology Group

Term	Definition
eCRF	electronic case report form
EDC	Electronic Data Capture
eg	exempli gratia (for example)
EGFR	epidermal growth factor receptor
EMA	European Medicines Agency
EOI	end of infusion
EOT	end of treatment
ER	estrogen receptor
EUDRACT	European Union Drug Regulating Authorities Clinical Trials
EWOC	Escalation With Overdose Control
FDA	Food and Drug Administration
FFPE	formalin-fixed paraffin embedded
FIGO	International Federation of Gynecology and Obstetrics
FIH	first-in-human
FPR	false positive rate
FSH	follicle stimulating hormone
FU	follow-up
g	gram
GCP	Good Clinical Practice
GEP	gene expression profiling
GI	gastrointestinal
GM-CSF	granulocyte-macrophage colony-stimulating factor
GPVE	global pharmacovigilance and epidemiology
HCG	human chorionic gonadotropin
HER2	human epidermal growth factor receptor 2
HIV	Human Immunodeficiency Virus
HLA	human leukocyte antigen
HR	hazard ratio
IB	investigator brochure
ICH	International Conference on Harmonisation

Term	Definition
iDOR	immune duration of response
ie	id est (that is)
IEC	Independent Ethics Committee
IFN	interferon
IHC	immunohistochemistry
IMAE	immune-mediated adverse event
IMG	immunogenicity
IMP	investigational medicinal product
IND	Investigational New Drug Exemption
I-O	immuno-oncology
IP	investigational product
iPFS	immune progression-free survival
IRB	Institutional Review Board
iRECIST	immune Response Evaluation Criteria in Solid Tumors
IRT	Interactive Response Technology
IU	International Unit
IV	intravenous
kg	kilogram
L	liter
LDH	lactate dehydrogenase
LFT	liver function tests
LPLV	last patient last visit
mCRC	metastatic colorectal cancer
mCRPC	metastatic castration-resistant prostate cancer
mDOR	median duration of response
MFD	maximum feasible dose
mg	milligram
µg	microgram
min	minute
mL	milliliter

Term	Definition
MM	medical monitor
MOA	mechanism of action
mOS	median overall survival
mPFS	median progression-free survival
MRI	magnetic resonance imaging
mRNA	messenger ribonucleic acid
MSI-high	microsatellite instable
MSS	microsatellite stable
MST	medical surveillance team
MTD	maximum tolerated dose
MVAC	methotrexate, vinblastine, adriamycin, and cisplatin
N	number of subjects or observations
NCCN	National Comprehensive Cancer Network
NCI CTCAE	National Cancer Institute Common Terminology Criteria for Adverse Events
ng	nanogram
NPV	negative predictive value
NSCLC	non-small cell lung cancer
ORR	objective response rate
OS	overall survival
OSR	overall survival rate
PARP	poly (ADP-ribose) polymerase
PBMC	peripheral blood mononuclear cell
pCR	complete pathological response
PCWG3	Prostate Cancer Clinical Trials Working Group 3
PD	progressive disease
PD-1	programmed death receptor 1
p-DILI	potential drug-induced liver injury
PD-LI	programmed death-ligand 1
PE	physical examination
PEG-IFN	pegylated interferon
PET	positron emission tomography

Term	Definition
PFS	progression-free survival
PFSR	progression-free survival rate
PID	patient identification number
PK	pharmacokinetics
pMMR	proficient mismatch repair
PO	per os (by mouth/oral route of administration)
PPK	population pharmacokinetics
PPV	positive predictive value
PR	partial response
PS	performance status
PT	preferred term
PVC	polyvinyl chloride
Q2W	every 2 weeks
Q4W	every 4 weeks
Q8W	every 8 weeks
qPCR	qualitative polymerase chain reaction
RCC	renal cell carcinoma
RD	recommended dose
RECIST	Response Evaluation Criteria in Solid Tumors
RNA	ribonucleic acid
ROC	receiver operating characteristics
RP2D	recommended Phase 2 dose
SAE	serious adverse event
SCCHN	squamous cell carcinoma of the head and neck
SD	stable disease
SOC	standard of care
SOP	Standard Operating Procedures
SPECT	single-photon emission computerized tomography
SUSAR	suspected, unexpected serious adverse reaction
T-HALF	half life
T-HALFeff	effective elimination half-life
TIL	tumor-infiltrating lymphocyte

Term	Definition
Tmax, TMAX	time of maximum observed concentration
TME	tumor microenvironment
TNBC	triple-negative breast cancer
TPR	true positive rate
TSH	thyroid stimulating hormone
ULN	upper limit of normal
US	United States
USP	United States Pharmacopeia
VEGF	vascular endothelial growth factor
VP	viral particles
Vss	volume of distribution at steady-state
Vz	volume of distribution of the elimination phase
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:

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

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

All potential serious breaches must be reported to Sponsor or designee immediately. A breach of the conditions and principles of Good Clinical Practice (GCP)(occurring in any country) in connection with that trial or the protocol related to the trial which is likely to affect to a significant degree the safety or physical or mental integrity of 1 or more subjects of the trial 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 to be provided to subjects and any updates.

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

COMPLIANCE WITH THE PROTOCOL AND PROTOCOL REVISIONS

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

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

INFORMED CONSENT PROCESS

Investigators must ensure that subjects 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.

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

Investigators must:

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

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 (e.g., 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 sites stock or commercial supply, or a specialty pharmacy)	The investigator or designee accepts responsibility for documenting traceability and study treatment integrity in accordance with requirements applicable under law and the SOPs/standards of the sourcing pharmacy.

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

CASE REPORT FORMS

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

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

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

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

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

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

MONITORING

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 Sponsor or designee.

RECORDS RETENTION

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

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

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

RETURN OF STUDY TREATMENT

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

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

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

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

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

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

CLINICAL STUDY REPORT AND PUBLICATIONS

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

For this protocol, the Signatory Investigator will be selected as appropriate based on the following criteria:

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

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

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

ADVERSE EVENTS

Adverse Event Definition:

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

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

Events Meeting the AE Definition

- Any abnormal laboratory test results (hematology, clinical chemistry, or urinalysis) or results from other safety assessments (eg, ECG, radiological scans, vital signs measurements), including those that worsen from baseline, considered clinically significant in the medical and scientific judgment of the investigator (eg, not related to progression of underlying disease). This includes worsening of an abnormal baseline result.
- Exacerbation of a chronic or intermittent pre-existing condition including either an increase in frequency and/or intensity of the condition.
- New conditions detected or diagnosed after study intervention administration even though it may have been present before the start of the study.
- Signs, symptoms, or the clinical sequelae of a suspected drug-drug interaction.
- Signs, symptoms, or the clinical sequelae of a suspected overdose of either study intervention or a concomitant medication. Overdose per se will not be reported as an AE/SAE unless it is an intentional overdose taken with possible suicidal/self-harming intent. Such overdoses should be reported regardless of sequelae.
- "Lack of efficacy" or "failure of expected pharmacological action" per se will not be reported as an AE or SAE. Such instances will be captured in the efficacy assessments. However, the signs, symptoms, and/or clinical sequelae resulting from lack of efficacy will be reported as AE or SAE if they fulfil the definition of an AE or SAE.

Events NOT Meeting the AE Definition

- Any clinically significant abnormal laboratory findings or other abnormal safety assessments which are associated with the underlying disease, unless judged by the investigator to be more severe than expected for the participant's condition.
- The disease/disorder being studied or expected progression, signs, or symptoms of the disease/disorder being studied, unless more severe than expected for the participant's condition.
- Medical or surgical procedure (eg, endoscopy, appendectomy): the condition that leads to the procedure is the AE.

• Situations in which an untoward medical occurrence did not occur (social and/or convenience admission to a hospital). Anticipated day-to-day fluctuations of pre-existing disease(s) or condition(s) present or detected at the start of the study that do not worsen.

DEFINITION OF SAE

If an event is not an AE per definition above, then it cannot be an SAE even if serious conditions are met (eg, hospitalization for signs/symptoms of the disease under study, death due to progression of disease).

SERIOUS ADVERSE EVENTS

Serious Adverse Event (SAE) is defined as any untoward medical occurrence that, at any dose:
Results in death
Is life-threatening (defined as an event in which the participant was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe)
Requires inpatient hospitalization or causes prolongation of existing hospitalization (see NOTE below) NOTE: The following hospitalizations are not considered SAEs in BMS clinical studies: • a visit to the emergency room or other hospital department < 24 hours, that does not result in admission (unless considered an important medical or life-threatening event) • elective surgery, planned prior to signing consent • admissions as per protocol for a planned medical/surgical procedure • routine health assessment requiring admission for baseline/trending of health status (e.g., routine colonoscopy) • medical/surgical admission other than to remedy ill health and planned prior to entry into the study. Appropriate documentation is required in these cases • admission encountered for another life circumstance that carries no bearing on health status and requires no medical/surgical intervention (e.g., lack of housing, economic inadequacy, caregiver respite, family circumstances, administrative reason) • admission for administration of anticancer therapy in the absence of any other SAEs (applies to oncology protocols)
Results in persistent or significant disability/incapacity

Is a congenital anomaly/birth defect
is an important medical event (defined as a medical event(s) that may not be immediately life-threatening or result in death or hospitalization but, based upon appropriate medical and scientific judgment, may jeopardize the participant or may require intervention [e.g., medical, surgical] to prevent one of the other serious outcomes listed in the definition above.) Examples of such events include, but are not limited to, intensive treatment in an emergency room or at home for allergic bronchospasm; blood dyscrasias or convulsions that do not result in hospitalization.) Potential drug induced liver injury (DILI) is also considered an important medical event. (See Section 9.2.7 for the definition of potential DILI.)

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

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

EVALUATING AES AND SAES

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

Follow-up of AEs and SAEs
If only limited information is initially available, follow-up reports are required. (Note: Follow-up SAE reports must include the same investigator term(s) initially reported.) If an ongoing SAE changes in its intensity or relationship to study treatment or if new information becomes available, the SAE report must be updated and submitted within 24 hours to BMS (or designee) using the same procedure used for transmitting the initial SAE report. All SAEs must be followed to resolution or stabilization. Every adverse event must be assessed by the investigator with regard to whether it is considered immune-mediated. For events which are potentially immune-mediated, additional information will be collected on the participant's case report form.

REPORTING OF SAES TO SPONSOR OR DESIGNEE

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

SAE Email Address: Refer to Contact Information list.

SAE Facsimile Number: Refer to Contact Information list.

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

APPENDIX 4 WOMEN OF CHILDBEARING POTENTIAL DEFINITIONS AND METHODS OF CONTRACEPTION

DEFINITIONS

Woman of Childbearing Potential (WOCBP)

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

Women in the following categories are not considered WOCBP

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

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

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

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

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

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

CONTRACEPTION GUIDANCE FOR FEMALE PARTICIPANTS OF CHILD BEARING POTENTIAL

One of the highly effective methods of contraception listed below is required during study duration and until the end of relevant systemic exposure, defined as 5 months after the end of study treatment.

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 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 treatment. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the study and the preferred and usual lifestyle of the participant.* • 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 treatment, which may reduce the efficacy of the contraceptive method. Hormonal contraception is permissible only when there is sufficient evidence that the IMP and other study medications will not alter hormonal exposures such that contraception would be ineffective or result in increased exposures that could be potentially hazardous. In this case, alternative methods of contraception should be utilized.

[c] Intrauterine 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 end of relevant systemic exposure defined as 6 months after the end of treatment if treated with BMS-986277 and 7 months after the end of treatment if treated with BMS-986277 and nivolumab in the male participant.
- Female partners of males participating in the study to consider use of effective methods of contraception until the end of relevant systemic exposure, defined as 6 months after the end of study treatment if treated with BMS-986277 and 7 months after the end of treatment if treated with BMS-986277 and nivolumab in the male participant.

- Male participants with a pregnant or breastfeeding partner must agree to remain abstinent from penile vaginal intercourse or use a male condom during each episode of penile penetration during the treatment and until 7 months after the end of treatment.
- Refrain from donating sperm for the duration of the study treatment and for 7 months after the end of treatment.

COLLECTION OF PREGNANCY INFORMATION

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

APPENDIX 6 ECOG PERFORMANCE STATUS

These scales and criteria are used by doctors and researchers to assess how a patient's disease is progressing, assess how the disease affects the daily living abilities of the patient, and determine appropriate treatment and prognosis. They are included here for health care professionals to access.

ECOG PERFORMANCE STATUS*	
Grade	**ECOG**
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, e.g., 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]

[redacted]

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

1 EVALUATION OF LESIONS

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

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

1.1 Measurable

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

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

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

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

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

1.2 Non-Measurable

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

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

1.3 Special considerations regarding lesion measurability

1.3.1 Bone lesions

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

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

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

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

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

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

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

2. RESPONSE CRITERIA

2.1 Evaluation of Target Lesions

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

2.1.1 Special Notes on the Assessment of Target Lesions

2.1.1.1 Lymph nodes

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

2.1.1.2 Target lesions that become 'too small to measure'

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

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

2.1.1.3 Lesions that split or coalesce on treatment

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

2.2 Evaluation of Non-Target Lesions

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

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

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

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

2.2.1.1 When the patient also has measurable disease

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

2.2.1.2 When the patient has only non-measurable disease

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

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

2.2.2 New Lesions

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

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

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

1. Negative FDG-PET at baseline, with a positive FDG-PET at follow-up is a sign of PD based on a new lesion.
2. No FDG-PET at baseline and a positive FDG-PET at follow-up: If the positive FDG-PET at follow-up corresponds to a new site of disease confirmed by CT, this is PD. If the positive FDG-PET at follow-up is not confirmed as a new site of disease on CT, additional follow-up

CT scans are needed to determine if there is truly progression occurring at that site (if so, the date of PD will be the date of the initial abnormal FDG-PET scan). If the positive FDG-PET at follow-up corresponds to a pre-existing site of disease on CT that is not progressing on the basis of the anatomic images, this is not PD.

2.3 Response Assessment

2.3.1 Evaluation of Best Overall Response

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

2.3.2 Time Point Response

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

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

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

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

Table 2.3.2-2: Time Point Response: Patients with Non-target Disease Only

Non-Target Lesions	New Lesions	Overall Response
CR	No	CR

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

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

2.3.3 Best Overall Response

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

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

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

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

Table 2.3.3-1: Best Overall Response (Confirmation of CR and PR Required)		
Overall Response First Time Point	**Overall Response Subsequent Time Point**	**Best Overall Response**
CR	NE	SD provided minimum criteria for SD duration met, otherwise, NE
PR	CR	PR
PR	PR	PR
PR	SD	SD
PR	PD	SD provided minimum criteria for SD duration met, otherwise, PD
PR	NE	SD provided minimum criteria for SD duration met, otherwise, NE
NE	NE	NE
CR = complete response, PR = partial response, SD = stable disease, PD = progressive disease, and NE = inevaluable		

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

2.3.4 Confirmation Scans

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

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

[redacted]

APPENDIX 8 PCWG3 GUIDELINES (WITH MODIFIED RECIST CRITERIA FOR SOFT TISSUE LESION ASSESSMENT)

1 EVALUATION OF LESIONS

Bone lesions should be evaluated with Technecium-99m based radionuclide bone scan as per PCWG3.

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

1.1 Measurable

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

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

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

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

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

1.2 Non-Measurable

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

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

1.3 Special considerations regarding bone lesions

Bone lesions will be assessed with Technecium-99m based radionuclide bone scans as per PCWG3.

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

When more than one measurable lesion is present at baseline all lesions up to a maximum of 20 lesions total (and a maximum of 5 lesions per organ system) representative of all involved organs should be identified as target lesions and will be recorded and measured at baseline.

Note: A maximum of 5 lesions can be selected per organ system. For example, a maximum of 5 lung lesions can be selected. A maximum of 5 lymph nodes can be selected at baseline, as the lymphatic system is considered one organ.

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

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

All other lesions (or sites of disease) including pathological lymph nodes should be identified as non-target lesions and should also be recorded at baseline. Pelvic lymph nodes and extrapelvic lymph nodes (retroperitoneal, mediastinal, thoracic and other) may be reported separately, per PCWG3. Measurements are not required and these lesions should be followed as 'present', 'absent', or in rare cases 'unequivocal progression' (more details to follow). In addition, it is possible to record multiple non-target lesions involving the same organ as a single item on the case record form (e.g., 'multiple enlarged pelvic lymph nodes' or 'multiple liver metastases').

2 RESPONSE CRITERIA

2.1 Evaluation of Target Lesions

- **Complete Response (CR):** Disappearance of all target lesions. Any pathological lymph nodes (whether target or non-target) must have reduction in short axis to < 10 mm.
- **Partial Response (PR):** At least a 30% decrease in the sum of diameters of target lesions, taking as reference the baseline sum diameters.
- **Progressive Disease (PD):** At least a 20% increase in the sum of diameters of target lesions, taking as reference the smallest sum on study (this includes the baseline sum if that is the smallest on study). In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 5 mm. (Note: the appearance of one or more new lesions is also considered progression).

- **Stable Disease (SD):** Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as reference the smallest sum diameters while on study.
- **Not Evaluable (NE):** If one or more target lesions cannot be measured or adequately assessed as either fully resolved or too small to measure (due to missing or poor quality images), and the sum of diameters of the remaining measured target lesions (if any) has not increased sufficiently to meet Progressive Disease as defined above.

2.1.1 Special Notes on the Assessment of Target Lesions

2.1.1.1 Lymph nodes

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

2.1.1.2 Target lesions that become 'too small to measure'

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

2.1.1.3 Lesions that split or coalesce on treatment

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

vector of the longest diameter in this instance should be the maximal longest diameter for the 'coalesced lesion'.

2.2 Evaluation of Non-Target Lesions

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

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

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

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

2.2.1.1 When the patient also has measurable disease

In this setting, to achieve 'unequivocal progression' on the basis of the non-target disease, there must be an overall level of substantial worsening in non-target disease such that, even in presence of SD or PR in target disease, the overall tumor burden has increased sufficiently to merit discontinuation of therapy (see examples in Appendix 2 and further details below). A modest 'increase' in the size of one or more non-target lesions is usually not sufficient to qualify for unequivocal progression status. Pleural effusions, pericardial effusions and ascites will not be followed as target or non-target lesions and will not contribute to response or progression. The designation of overall progression solely on the basis of change in non-target disease in the face of SD or PR of target disease will therefore be extremely rare.

2.2.1.2 When the patient has only non-measurable disease

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

objective criteria to apply to non-measurable disease, the very nature of that disease makes it impossible to do so; therefore the increase must be substantial.

2.2.2 New Lesions

New bone lesions

New bone lesions should be evaluated as per PCWG3 criteria. Bone lesions will be assessed by radionuclide bone scan only. Radiographic progression on bone scan is defined by the following criteria:

- At least 2 new lesions on the first posttreatment bone scan, confirmed on the next scan (performed at least 6 weeks later) AND with at least two additional lesions as compared to the first post-treatment bone scan. Date of progression is then the date of first post-treatment scan,
- For scans after the first post-treatment scan, at least 2 new lesions relative to the first post-treatment scan AND confirmed on a subsequent scan (performed at least 6 weeks later). Date of progression is the date of the scan that first documents at least 2 new lesions relative to the first post-treatment scan.

New soft tissue lesions

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

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

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

2.3 Response Assessment

2.3.1 Evaluation of Best Overall Response

The best overall response is the best response recorded from the start of the study treatment until disease progression per PCWG3 criteria, or the last response recorded, taking into account any requirement for confirmation and censoring rules regarding subsequent therapy. The patient's best overall response assignment will depend on the findings of both target and non-target disease and will also take into consideration the appearance of new lesions. Furthermore, depending on the nature of the study and the protocol requirements, it may also require confirmatory measurement.

2.3.2 Time Point Response

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

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

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

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

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

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

2.3.3 Best Overall Response

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

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

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

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

Table 2.3.3-1: Best Overall Response (Confirmation of CR&PR Required)		
Overall Response First Time Point	**Overall Response Subsequent Time Point**	**BEST Overall Response**
CR	NE	SD provided minimum criteria for SD duration met, otherwise, NE
PR	CR	PR
PR	PR	PR
PR	SD	SD
PR	PD	SD provided minimum criteria for SD duration met, otherwise, PD
PR	NE	SD provided minimum criteria for SD duration met, otherwise, NE
NE	NE	NE
CR = complete response, PR = partial response, SD = stable disease, PD = progressive disease, and NE = inevaluable		

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

2.3.4 Confirmation Scans

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

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

[redacted]

[redacted]

APPENDIX 9 STATISTICAL METHODOLOGY

STATISTICAL DETAILS FOR BAYESIAN LOGISTIC REGRESSION MODEL (BLRM AND BLRM-COPULA) TO GUIDE DOSE ESCALATION AND BASKET DESIGNS TO ASSESS HOMOGENEITY AND FUTILITY IN COHORT EXPANSION

1 MODEL SETUP FOR BMS-986277 MONOTHERAPY

1.1 Methodology Description for Monotherapy

An adaptive 2-parameter Bayesian Logistic Regression Model (BLRM) guided by the escalation with overdose control (EWOC) principle[1,2,3] will be used to guide the dose escalation of BMS-986277 monotherapy in the monotherapy phase, providing dose recommendations during dose escalation.

The BLRM will be fitted on the dose-limiting toxicity (DLT) data during the first 6 weeks of treatment accumulated throughout the dose escalation to model the dose-toxicity relationship of BMS-986277 in the monotherapy dose escalation phase.

[redacted]

1.2 Prior Specification for BMS-986277 Monotherapy

The Bayesian approach requires the specification of prior distributions for model parameters, which include parameters (α_1, β_1) for BMS-986277. A mixture prior will be used for parameters (α_1, β_1) for BMS-986277. There are two bivariate normal components in generating this mixture prior:

- Meta-analytic predictive (MAP) component: Obtained based on the clinical safety and exposure profiles of enadenotucirev using the MAP approach, because BMS-986277 is the genetically modified form of enadenotucirev.
- Weakly informative prior for BMS-986277 component: Reflecting the potential higher toxicity of BMS-986277 than enadenotucirev from activating T-cells and allowing for considerable prior uncertainty.

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

1.2.1 Meta-analytic Predictive Component

The MAP component provides a prediction of the dose-toxicity curve for BMS-986277 based on prior data from enadenotucirev. This dose-toxicity curve combines a weakly informative prior for enadenotucirev with toxicities from a range of doses observed in set of enadenotucirev studies,

and then adding an extra layer of variability to account for heterogeneity among subjects receiving a single dose vs subjects receiving >1 doses in the enadenotucirev studies. Note that this weakly informative prior is for enadenotucirev and is different from the weakly informative prior for BMS-986277 described in Section 1.2.

- Weakly informative prior for enadenotucirev:
  - The median toxicity rate at the enadenotucirev reference dose ($1x10^{13}$) was assumed to be 30%, ie, mean ($\log(\alpha_1)$) = logit(0.30)= -0.847.
  - A doubling in dose was assumed to double the odds of DLT, ie, mean($\log(\beta_1)$) = 0.
  - The standard deviation of $\log(\alpha_1)$ was set to 2, and the standard deviation of $\log(\beta_1)$ was set to 1, which allows for considerable prior uncertainty for the dose-toxicity profile.
  - The correlation between $\log(\alpha_1)$ and $\log(\beta_1)$ was assumed to follow a uniform(-1, 1) distribution with mean 0 (assuming independence of $\log(\alpha_1)$ and $\log(\beta_1)$).
- Dose-toxicity data:
  - Two studies of enadenotucirev monotherapy have been completed in patients with a range of epithelial solid cancers. The first evaluated escalating doses of intravenous enadenotucirev and repeat cycle schedules (ColoAd1-1001); the second was a mechanism of action study with administration of a single cycle of intratumoral or intravenous enadenotucirev (ColoAd1-1002).
  - In these studies, a total of 73 subjects received intravenous enadenotucirev for a range of doses, cycles, and schedules
  - In ColoAd1-1001:
    - During the initial dose escalation evaluation, enadenotucirev was given on Days 1, 3, and 5 at doses ranging from $1x10^{10}$ to $1x10^{13}$ viral particles (vp) per administration.
    - Subsequently, repeat cycles with a three-weekly schedule (21-day cycle) were evaluated with doses of $1x10^{12}$ to $6x10^{12}$ vp per administration given on Days 1, 3, and 5 of each cycle.
    - Additionally, a weekly dosing schedule was investigated at doses of $3x10^{12}$ and $6x10^{12}$ where treatment was administered on Days 1, 3, 5, 8, and 15 in the first cycle and on Days 1, 8, and 15 in subsequent cycles.
  - In ColoAd1-1002: a single cycle of enadenotucirev at a dose of $1x10^{12}$ vp was given on Days 1, 3, and 5.
  - Across ColoAd1-1001 and ColoAd1-1002, 40 subjects received 1 cycle of enadenotucirev and 33 subjects received >1 cycle
  - Two subjects experienced similar DLTs after the first dose of enadenotucirev at $1x10^{13}$ vp. One subject experienced hypoxia and dyspnoea and the second subject experienced acute

lung injury. These events were all considered Grade 3 per the NCI CTCAE, definitely related to treatment, and resulted in discontinuation of treatment.

– The data are summarized in Table 1.

Table 1: Data from ColoAd1-1001 and ColoAd1-1002

Dose of BMS-986277 (vp)	Dose of Enadenotucirev (vp)	DLT (percentage [number of participants/total participants])		
		Single Dose	Multiple Dose	Total
	$1x10^{10}$	0% (0/3)		0% (0/3)
$3x10^{10}$				
	$1x10^{11}$	0% (0/3)		0% (0/3)
$3x10^{11}$				
$1x10^{12}$	$1x10^{12}$	0% (0/15)	0% (0/3)	0% (0/18)
$3x10^{12}$	$3x10^{12}$	0% (0/6)	0% (0/14)	0% (0/20)
	$6x10^{12}$	0% (0/10)	0% (0/15)	0% (0/25)
	$1x10^{13*}$	67% (2/3)	0% (0/1)	50% (2/4)

*Enadenotucirev reference dose

In addition, heterogeneity between the historical study and the current study was incorporated using a MAP, by defining between-trial standard deviations τ_1 and τ_2 for $\log(\alpha_1)$ and $\log(\beta_1)$, 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.

1.2.2 Weakly Informative Prior for BMS-986277 Component

- The median toxicity rate at the BMS-986277 reference dose ($3x10^{12}$) was assumed to be 30%, ie, mean ($\log(\alpha_1)$) = logit(0.30)= -0.847.
- A doubling in dose was assumed to double the odds of DLT, ie, 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*sd ($\log(\alpha_1)$), which results in sd ($\log(\alpha_1)$) = 9.19/6 = 1.53.
- The standard deviation of $\log(\beta_1)$ was set to 2, which allows for considerably large prior uncertainty for the dose toxicity relationship.

- The correlation between log(α_1) and log(β_1) was assumed to follow a uniform(-1, 1) distribution with mean 0 (assuming independence of log(α_1) and log(β_1)).
- log(α_1) and log(β_1) follow a bivariate normal distribution.

1.2.3 Mixture Prior

To obtain the mixture prior, 50% weight is assigned to the MAP component (described in Section 1.2.1), and 50% weight is assigned to the weakly informative component (described in Section 1.2.2) to balance the previous experience with enadenotucirev and potential unknown toxicity profile of BMS-986277.

The mixture prior will be fitted into EAST® v6.3.1 Dose Escalation Module by Cytel for the Monotherapy Escalation (Part 1A) as stated in model setup section.

The mixture prior with both MAP and weakly informative components for the BLRM parameters of BMS-986277 is generated using R v3.4.1 and R2OpenBUGS package v3.2 and summarized in Table 2.

Table 2 Prior Distribution for Model Parameters (log(α_1), log(β_1)) for BMS-986277

Parameter	Means	Standard Deviations	Correlation
MAP component	(-1.065, 1.786)	(1.005, 0.697)	0.470
Weakly informative prior for BMS-986277 component	(-0.847, 0)	(1.53, 2)	0
Mixture Priors for BMS-986277	(-0.959, 0.884)	(1.005, 1.240)	0.055

2 DOSE ESCALATION PROCESS AND SIMULATIONS IN MONOTHERAPY

2.1 Dose Escalation Process

Dose escalation recommendations for BMS-986277 monotherapy 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

Note: "[" or "]" is inclusive of the respective endpoint, and "(" or ")"exclusive of the respective endpoint.

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% (~ 1 in 6) DLT rate and a maximum at 33% (~ 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 for the next cohort are the ones fulfilling the overdose criterion that there is no greater than 35% chance 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 the totality of available data including PK/pharmacodynamics from all treated participants.

Stopping Rules:

The following are the general stopping rules of BLRM during monotherapy dose escalation:

- If all of 24 DLT-evaluable participants are treated.
- If all of the current prespecified doses are considered intolerable according to the prespecified cutoff (ie, EWOC criteria), then the model will recommend stopping the current dose level and a new dose level lower than the current lowest dose level can be identified.
- The maximum number of DLT-evaluable participants in a dose level will be 12. This limit is set to avoid instances in which the model could recommend adding subjects indefinitely to a specific dose level due to uncertainty in the tolerability profile.
- If, for a specific dose level, 6 subjects have been treated and the chance of determining that the dose level to be the "target" dose is > 50%, then the model will suggest to stop and declare the current dose level to be the BLRM-recommended dose (BLRM-RD).

BLRM-RD:

The BLRM-RD is the dose that satisfies the following 3 conditions:

1) The empirical posterior probability that the 'DLT rate of 16% to < 33%' is greater than 50%,
2) This probability needs to be the largest among the dose levels that satisfy the EWOC condition (ie, the probability that 'DLT rate ≥ 33%' must be no greater than 35%);
3) Minimum number of participants (ie, 6), were treated at this dose level.

Final Recommended Dose:

The final recommended dose will be based on the BLRM-RD and overall clinical assessment of all available safety, PK/pharmacodynamic, and efficacy data. Lower doses of BMS-986277 may be tested if none of the planned doses are found to be tolerable. Such decisions will be made after discussion and agreement between the investigators and the BMS Medical Monitor.

2.2 Simulation Parameters

Simulation study was done for monotherapy dose escalation using various hypothetical scenarios.

One thousand trial simulations were used for each scenario. All simulations were run using EAST 6.3.1® software BLRM module for BMS-986277 monotherapy. The number of participants to be

treated in each cohort in a specific dose level, the stopping rules used to identify the BLRM-RD, and other simulation parameters are defined as:

- Fixed cohort size: 3
- Probability of overdosing: ≤ 35%
- Target probability of toxicity: 0.33, the upper boundary of the targeted toxicity interval
- Probability of achieving the target toxicity: > 50%
- Maximum number of participants treated: 24
- Prior specification on model parameters:
  - Mean: $\log(\alpha_1) = -0.959$, $\log(\beta_1) = 0.884$
  - Variance: $\log(\alpha_1) = 1.010$, $\log(\beta_1) = 1.537$
  - Correlation: 0.055
- Posterior sampling method: Metropolis Hastings
- Minimum number of participants treated at a given dose level in order to identify the BLRM-RD: 6
- Maximum number of participants at a dose:12

The provisional dose levels for BMS-986277 monotherapy are $3x10^{10}$, $3x10^{11}$, $1x10^{12}$, and $3x10^{12}$ vp, with $3x10^{12}$ as the reference dose (dose expected to have 30% DLT).

2.3 Operating Characteristics of BLRM for Monotherapy

Several scenarios were investigated by selecting (1) dose-DLT relationship derived by the prior, (2) dose-DLT curve flatter than the one by the prior; (3) narrow safety window (this scenario reflects a left-ward shift of the enadenotucirev dose-DLT relationship), (4) all doses below the target toxicity (this scenario reflects the enadenotucirev dose-DLT relationship at the BMS-986277 doses), and (5) all doses within the target toxicity range. Ten thousand simulations per scenario were performed using EAST v6.3.1 BLRM which allows dose skipping. However, there will be no dose skipping in dose escalation during the study conduct.

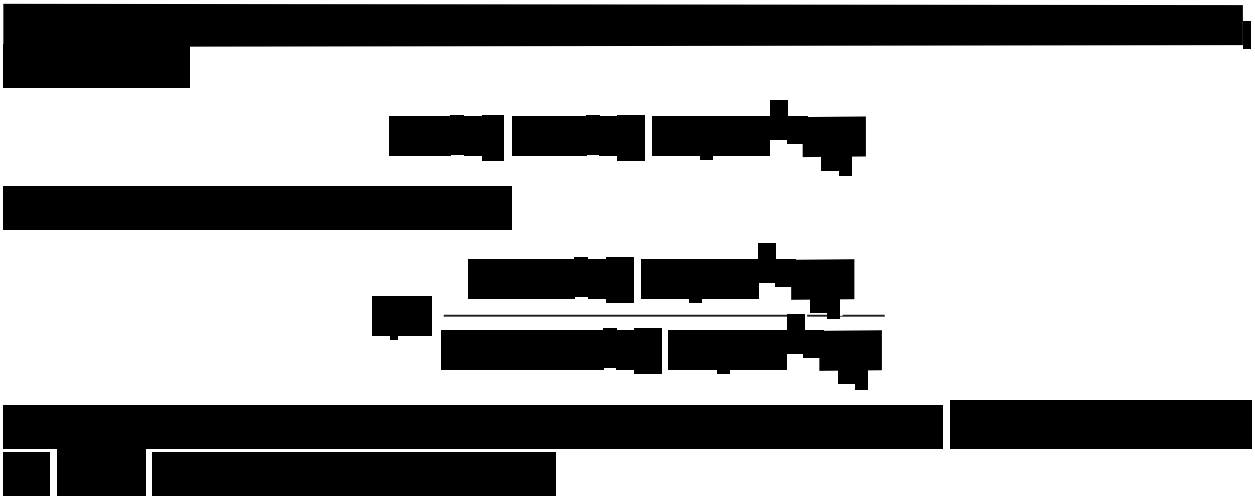


Table 3: Simulation Results of BLRM for Monotherapy

Scenario	BMS-986277 Dose	$3x10^{10}$	$3x10^{11}$	$1x10^{12}$	$3x10^{12}$	MTD not Selected (%)	Fitted Median MTD	Avg Toxicity Observed (%)	Avg # Pts
By prior	% DLT	0	0	3	**28**	0.0	$3.2x10^{12}$	11.0	18.3
	% MTD	0.0	0.0	50.7	49.3				
	# Pts	3.0	3.0	9.5	6.7				
	# DLTs	0.0	0.0	0.3	1.9				
Flatter than the one by the prior	% DLT	5	10	**15**	**25**	0.4	$3.1x10^{12}$	16.0	16.4
	% MTD	0.3	4.2	62.8	32.3				
	# Pts	3.1	4.7	9.0	6.7				
	# DLTs	0.2	0.5	1.4	1.7				
Narrow safety window	% DLT	0	2	5	50	0.0	$2.9x10^{12}$	13.9	18.2
	% MTD	0.0	0.0	85.8	14.2				
	# Pts	3	3.4	11.3	4.6				
	# DLTs	0.0	0.1	0.6	2.3				
All low	% DLT	0	0	0	10	0.0	$3.6x10^{12}$	5.5	18.6
	% MTD	0.0	0.0	11.0	89.0				
	# Pts	3.0	3.0	6.5	10.0				
	# DLTs	0.0	0.0	0.0	1.0				
All within	% DLT	**16**	**21**	**27**	**32**	5.1	$1.9x10^{12}$	25.5	14.5
	% MTD	6.5	22.9	54.8	10.7				
	# Pts	3.8	5.5	8.0	5.4				
	# DLTs	0.6	1.1	2.2	1.8				

Note: Bolded numbers are 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; # Pts, average number of pts given the dose was tried; # DLTs, average number of DLTs given the dose was tried; Fitted MTD: fitted MTD at 33% as the target toxicity rate; % toxicity observed, average proportion of DLTs given the doses were tried

Abbreviation: Avg = average; NA = not applicable; Pts = participants.

The average sample size was no more than approximately 18 participants. Most scenarios have a fitted median MTD that is close to the reference dose and the $1x10^{12}$ vp dose was chosen as the MTD most frequently in all scenarios except the all low scenario. These results demonstrate how the EWOC principle limits the risk of exposing participants from a toxic dose level, where only the all low would select $3x10^{12}$ vp as the MTD most frequently. The prior parameters derived from the enadenotuceriv DLT data suggests the selected doses are all relatively safe, with the DLT rate at $3x10^{12}$ vp artificially increased to allow for the potential increase in DLT due to the mechanism of activating T cells. This results in the $1x10^{12}$ vp dose selected as the MTD approximately 50% of the time. If, however, emerging data suggests the $1x10^{12}$ vp dose is relatively safe, the model will still allow $3x10^{12}$ vp to be selected as the MTD and this occurs approximately 50% of the time as well. This nicely illustrates the EWOC principle. The model performs well in the flatter than prior and all within scenarios by correctly identifying the MTD within the target toxicity interval, [16%, 33%) about 95% of the time and performs adequately by the prior scenario. Overall, the scenarios illustrated above demonstrate that the model performs satisfactorily in the hypothetical scenarios investigated by correctly identifying the MTD while limiting participants from receiving excessive/unacceptable toxic dose levels.

3 INTERIM MONITORING EXAMPLE TO ILLUSTRATE PROVISION OF DOSE RECOMMENDATIONS DURING DOSE ESCALATION IN MONOTHERAPY

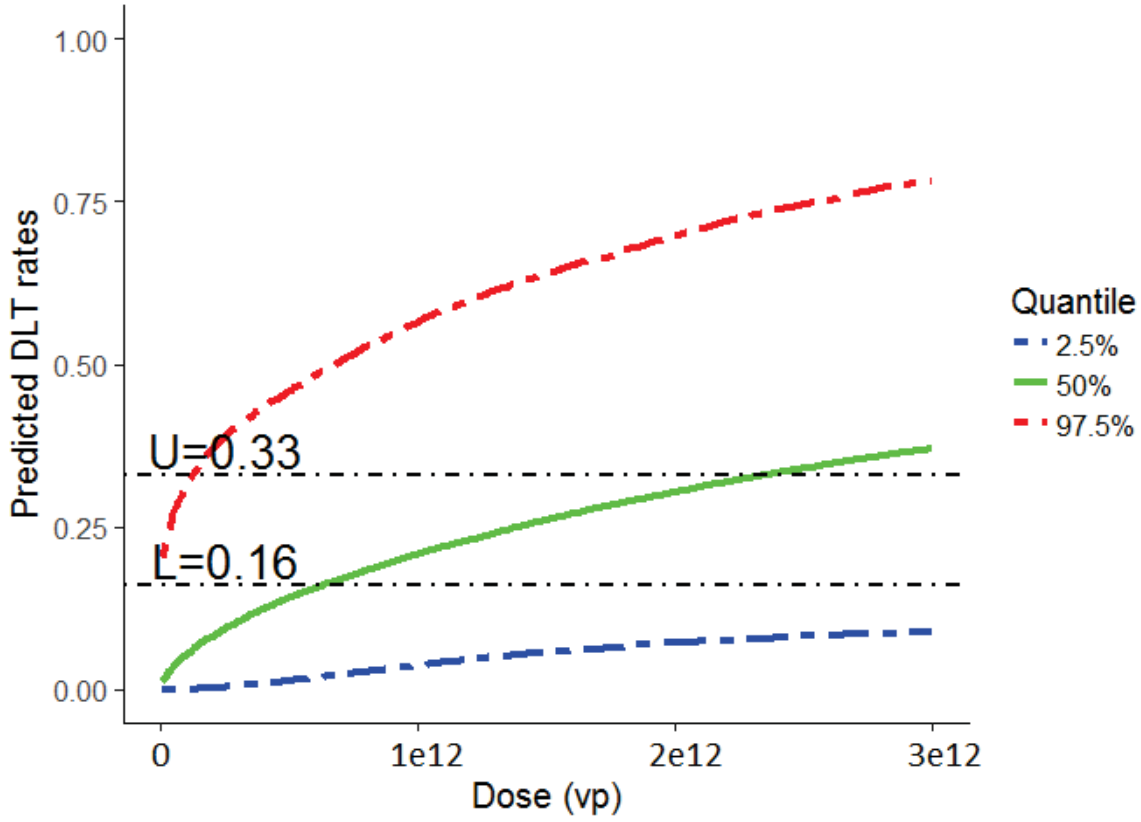
In order to provide a comprehensive view of the dynamics of the models, different hypothetical scenarios exploring all possibilities are examined. For the simplicity of illustration purposes, a static cohort size of 3 subjects is applied for dose levels $3x10^{10}$, $3x10^{11}$, $1x10^{12}$, and $3x10^{12}$ vp in the BMS-986277 monotherapy. This cohort size could vary during the actual clinical trial, and the BLRM models are designed to fit various different cohort sizes, adaptively. In general, there are 4 possible scenarios for a specific dose level; these are 0 DLT observed in 3 total subjects in that cohort (denoted as 0/3), 1 DLT observed in 3 subjects (1/3), 2 DLTs observed in 3 subjects (2/3), and 3 DLTs observed in 3 subjects (3/3).

During interim monitoring, posterior probabilities will be updated when there is new DLT information available. The following 3 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 model's recommendation process, and to facilitate clinical team's interpretation of the model recommendations for decision making:

- Dose-DLT profile for the doses ranging between 0 and $3x10^{12}$ vp (Figure 1).
- Stacking histograms displaying predictive probabilities on DLT rates classified into 3 different categories (Underdosing, Target dosing and Overdosing) (Figure 2).
- Box plots summarizing the Markov Chain Monte Carlo samples of predicted DLT rates for the 4 prespecified dose levels (Figure 3).

In the following illustrations, Figure 1 to Figure 3 are produced using a hypothetical example assuming 0/3 DLTs observed in the $3x10^{10}$ vp cohort and 1/3 DLTs observed in the $3x10^{11}$ vp cohort.

Figure 1: Updated Dose-DLT Profile After Incorporating Prior Information and All Previous and Current DLT Information



Abbreviations: L = lower DLT boundary; U = upper DLT boundary.

Interpretation and Use of Figure 1:

Figure 1 is a snapshot of an updated dose-DLT profile with DLT information available at dose level $3x10^{10}$ vp for monotherapy. The dose-DLT profile is captured with a continuous dose spectrum ranging from 0 to $3x10^{12}$ vp. 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 the study.

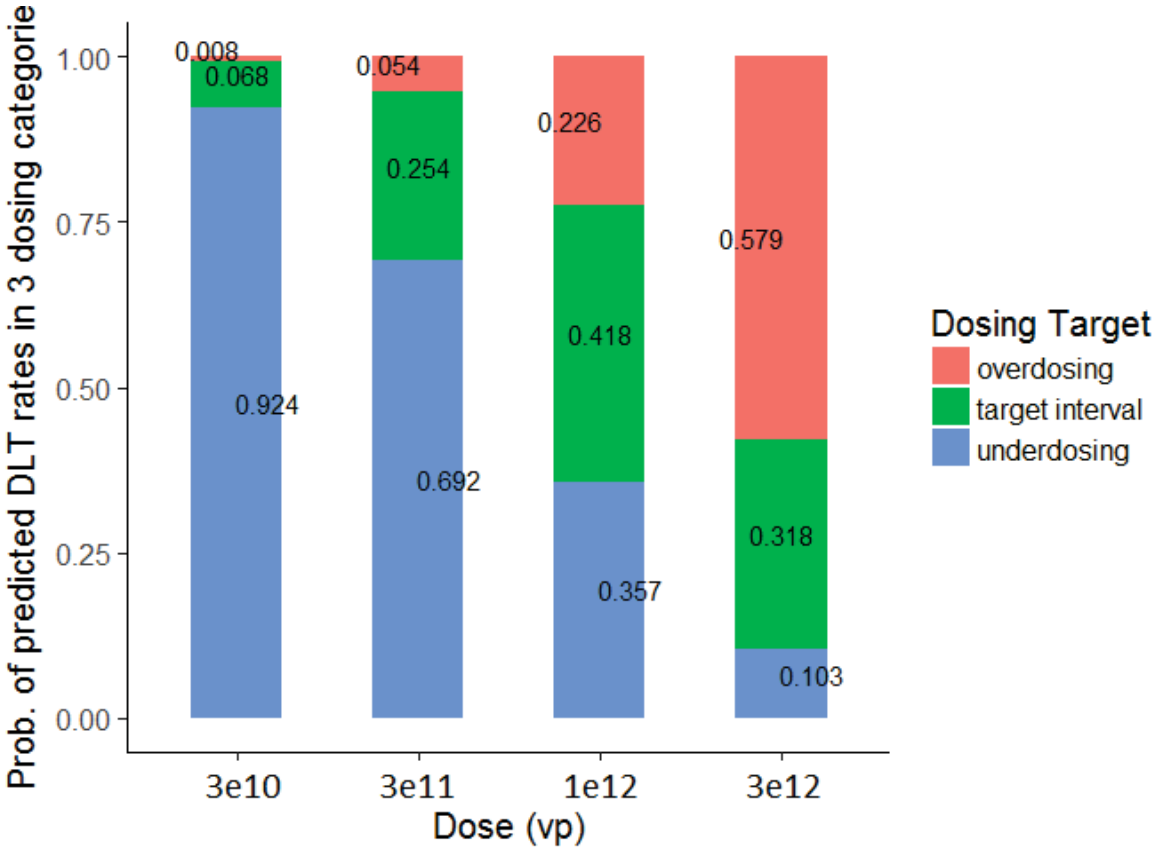
In Figure 1, there are 3 different quantiles (2.5%, 50%, and 97.5%) plotted to characterize the current trend of the toxicity profile (as shown by the 50% quantile), as well as the variation of the dose-DLT profile (as shown by the 2.5% percentile and the 97.5% percentile), according to the accumulation of DLT data from all previous and current dose levels. The toxicity boundaries (low

boundary 0.16 and high boundary 0.33) are illustrated in two dotted 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% percentile curve (green highlight), which represents the nearly average DLT distribution for each dose level, the $7x10^{11}$ vp could be a potential intermediate dose level corresponding to the lower prespecified DLT rate boundary of 0.16, and the $2.4x10^{12}$ vp dose 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 monotherappy, 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 ($3x10^{10}$ vp) by using the DLT-rate boundaries.

Figure 2: **Updated Stacking Histogram After Incorporating Prior Information and All Previous and Current DLT Information to Classify Predicted DLT Rates into 3 Categories (Underdosing, Target Dosing, and Overdosing)**



Interpretation and Use of Figure 2:

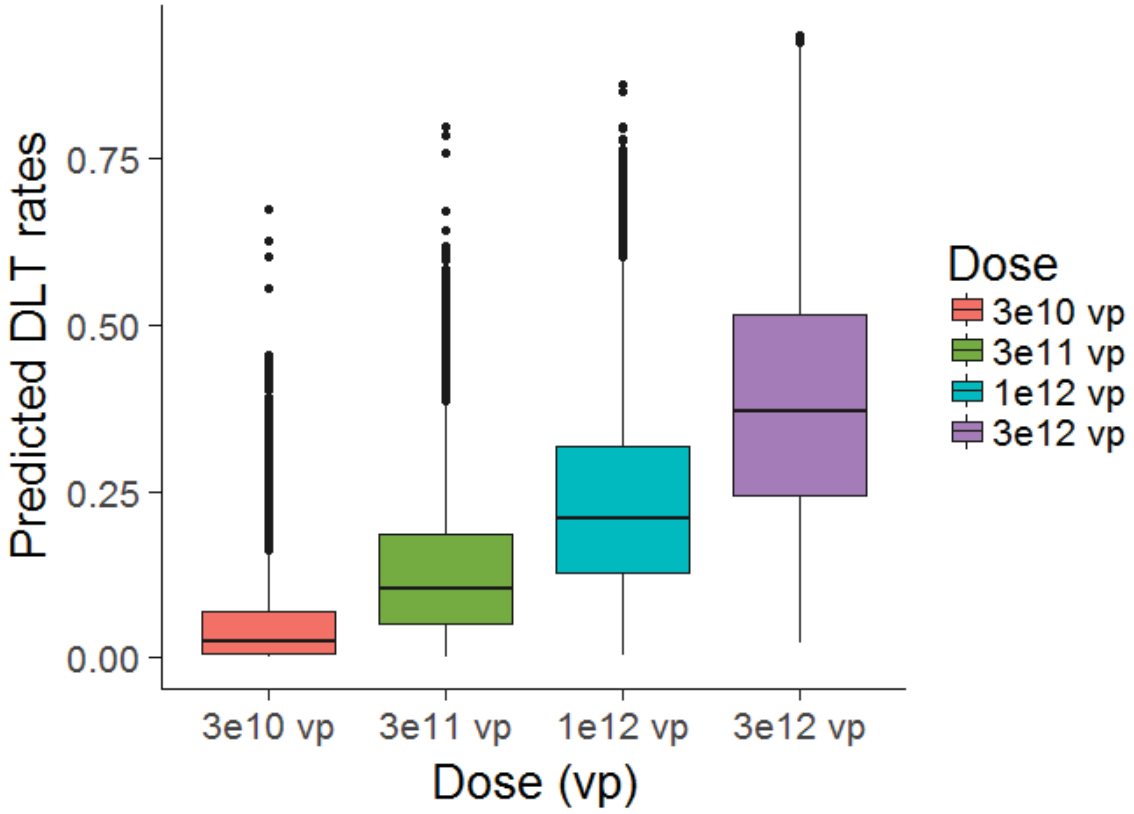
Figure 2 is a snapshot of stacking histogram with DLT information available at dose level $3x10^{10}$ vp and $3x10^{11}$ vp. This figure will be updated each time new DLT information becomes available.

When recommending the next dose level, the model will first exclude doses that are intolerable (with overdosing probabilities > 35%, the rate that has been specified for BMS-986277). 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 between 16% and 33%). However, there will be no dose skipping during the dose escalation monotherapy phase of the study.

As illustrated in Figure 2, the distribution of predicted DLT rates will be characterized into possibilities falling into 3 different categories. First, dose levels $3x10^{12}$ vp for BMS-986277 are excluded according to the higher-than-cutoff overdosing probabilities (0.579 for $3x10^{12}$ vp). Among the remainder of tolerable dose levels, the BLRM recommends the dose that maximizes the probability of being within the target dosing interval. Therefore, the model's recommendation would be to stay at $1x10^{12}$ vp, which is associated with the highest target dosing probability of 0.418 compared with that of $3x10^{10}$ vp (0.068) and $3x10^{11}$ vp (0.254).

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 the current treated dose level, escalate to the next dose level, or even recommend to stop and identify a new dose level lower than $3x10^{10}$ vp, the lowest pre-specified dose level. Please refer to the description of Figure 1 for details on how to specify the new dose levels.

Figure 3: Updated Box Plot After Incorporating Prior Information and All Previous and Current DLT Information



Interpretation and Use of Figure 3:

Figure 3 is a snapshot with DLT information available at dose level $3x10^{10}$ vp and $3x10^{11}$ vp. The dose-DLT distributions calculated from the posterior samples of the model parameters are characterized in the format of boxplots for the pre-specified dose levels. This figure will be updated each time there is new DLT information available.

This plot supplements the information provided in Figure 1. It allows for a more in-depth and focused visualization of general trend of dose-DLT relationship, as well as the magnitude and variability in the DLT rates for each pre-specified dose level.

The illustration in this section is for the monotherapy dose escalation, but the same concepts can be applied to BMS-986277 in combination with nivolumab.

3.1 Example of using the BLRM for BMS-986277 Monotherapy Dose Escalation

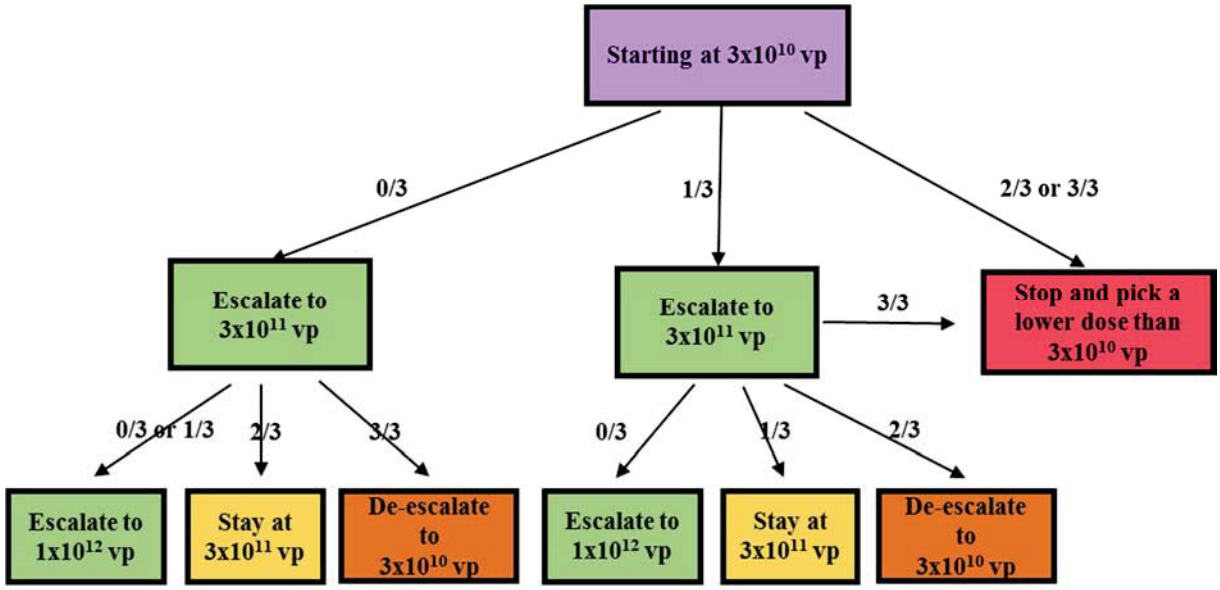
According to safety consideration and clinical judgement, the dose level $3x10^{10}$ vp is recommended as the starting dose for BMS-986277 monotherapy. With the current BMS-986277 prior specified in the Section 1.2 and all available DLT information up to $3x10^{12}$ vp, a

corresponding decision tree illustrating various models' recommendations under all possible scenarios for the first two cohorts is provided in Figure 4.

Tracing a branch of the decision tree in Figure 4 illustrates the decision making process. Taking the left-most branch of the tree as an example, starting at $3x10^{10}$ vp, if there were 0 DLTs observed in the real clinical trial, the model would recommend to escalate to $3x10^{11}$ vp (the BLRM actually recommends escalating to the highest dose $3x10^{12}$ vp, but since this is a 100-fold increase of dose and dose skipping is not allowed, the dose level $3x10^{11}$ vp is selected), one level above the current treated dose level according to the escalation rules per protocol. Next, if there is 0 DLTs observed at $3x10^{11}$ vp, the model would recommend to escalate further to $1x10^{12}$ vp. At $1x10^{12}$ vp, there would be 3 potential decisions (0/3 escalate, 1/3 and 2/3 would stay, and 3/3 would de-escalate); this is not shown due to crowding the diagram.

During the actual clinical study, the tree would be narrowed or deepened based on actual DLTs observed. The clinical team will be able to leverage this decision tree to preview decisions at each interim monitoring step and to plan proactively.

Figure 4: The BLRM Model Hypothetical Decision Tree for BMS-986277 Monotherapy during Dose Escalation (for the first 2 cohorts)



Abbreviations: DE = de-escalation; E = escalation; S = stay.

4 MODEL SETUP FOR BMS-986277 AND NIVOLUMAB COMBINATION

4.1 Methodology Description for Combination Therapy

For Part 2 of this study, the BLRM-Copula model will be used to guide the selection of the dose of BMS-986277 in combination with nivolumab. The toxicity profiles of both BMS-986277 monotherapy and nivolumab monotherapy will be incorporated to develop the combination model

framework. We briefly introduce the technical background of the BLRM-Copula model in the following paragraph.

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 effects, and γ 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). A dose-toxicity surface will be characterized for different dose combinations of these 2 agents.

One dose for nivolumab (480 mg) and 2 doses for BMS-986277 (recommended dose and 1 dose level below the recommended dose to be determined in Part 1) will be used in the BMS-986277 and nivolumab combination arms. The joint toxicity probability surface will be simplified into a 2-dimensional dose-toxicity curve for each of the two dose combinations that can be evaluated for the purpose of determining the BLRM-RD. Posteriors for the corresponding 5 (or 7) parameters (2 logistic regression parameters $[\alpha_1, \beta_1]$ for BMS-986277, 2 logistic regression parameters

$[\alpha_2, \beta_2]$ for nivolumab, 1 interaction parameter for the copula-type model [γ, which will be discussed in detail in the following section], and possibly 2 contribution parameters [m, n]) will be fitted into the in-house developed model. It implements the above-described theoretical setup.

4.2 Prior Specification for Combination Therapy

In this section, we illustrate the prior specification of parameters in the BLRM-Copula model for BMS-986277 in combination with nivolumab. While we give prior examples for illustration purposes, all of those specifications may be subject to change when new data of either monotherapy agent becomes available.

To obtain the prior estimates for the remaining 5 parameters, log(α_1), log(β_1), log(α_2), log(β_2), and γ, an initial marginal prior for BMS-986277 monotherapy (Section 4.2.1) will be combined with an initial marginal prior for nivolumab monotherapy (Section 4.2.2) with a weakly informative interaction parameter (Section 4.2.3) to create an initial BLRM-Copula model. Using this initial model, data from enadenotucirev in combination with nivolumab will be incorporated to identify posterior estimates, which are then used as the prior for BMS-986277 in combination with nivolumab.

4.2.1 Marginal Prior for BMS-986277

Posterior information on log(α_1) and log(β_1) from the monotherapy part of the study will be used as the marginal BMS-986277 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 2), the prior of BMS-986277 as described in Section 1.2.1 is used for illustration purposes because no real-time DLT data are available at this time.

4.2.2 Marginal Prior Derivation for Nivolumab Parameters (log(α_2), log(β_2))

[redacted]

The toxicity profile of nivolumab has been studied in several studies. A bivariate normal prior for the nivolumab model parameters (log(α_2), log(β_2)) was obtained by extracting a posterior of nivolumab using incidence of treatment-related Grade 3 to 4 AEs from a Phase 1 dose-escalation study and several Phase 3 nivolumab studies, which are used later as the MAP prior for nivolumab. These include a Phase 1 dose-escalation study of nivolumab (Study CA209003, N=306 in doses of 0.1, 0.3, 1, 3, and 10 mg/kg across multiple tumor types), a randomized Phase 3 study in advanced melanoma participants progressing post anti-CTLA-4 therapy (Study CA209037, N=268 in a dose of 3 mg/kg), a Phase 3 study in previously treated participants with squamous cell NSCLC (Study CA209017, N=131 in a dose of 3 mg/kg), a Phase 3 study in previously treated participants with non-squamous cell NSCLC (Study CA209057, N=287 in a dose of 3 mg/kg), and a Phase 3 study in previously treated participants with clear-cell RCC (Study CA209025, N=406 in a dose

of 3 mg/kg). The results from the simulation of nivolumab flat dose exposures, the corresponding exposure-response analyses, and review of nivolumab safety support nivolumab flat dose and the overall distributions of nivolumab exposures are comparable after treatment with either 3 mg/kg Q2W or 240 mg Q2W nivolumab. In addition, dose proportionality of nivolumab exposures supports nivolumab 240 mg Q2W being comparable to 480 mg Q4W.

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 toxicity rate at the nivolumab reference dose (3 mg/kg every 2 weeks) was assumed to be 10%, that is, mean ($\log(\alpha_2)$) = logit(0.10) = log(0.1/0.9) = -2.197.
  - A doubling in dose was assumed to double odds of toxicity, ie, mean($\log(\beta_2)$) = 0.
  - The standard deviation of $\log(\alpha_2)$ was set to 2, and the standard deviation of $\log(\beta_2)$ was set to 1, which allows for considerable prior uncertainty for the dose-toxicity profile.
  - The correlation between $\log(\alpha_2)$ and $\log(\beta_2)$ was assumed to follow a uniform(-1, 1) distribution with mean 0 (assuming independence of $\log(\alpha_2)$ and $\log(\beta_2)$).
  - In addition, heterogeneity between the historical studies and the current study was incorporated using a MAP 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 4) were used to generate the posterior for nivolumab, which is then used as the MAP prior for this study (Table 5).

Table 4: Data from Nivolumab Studies

Nivolumab Flat Dose (mg), Q4W	Dose of Nivolumab (mg/kg), Q2W	Toxicity[a]
	0.1	29% (5/17)
	0.3	17% (3/18)
160	1	14% (12/86)
480	3	13% (150/1146)
	10	16% (21/131)

[a] % of participants with treatment-related Grade 3-4 AEs

Abbreviation: Q2W = every 2 weeks.

Table 5: Marginal Prior Distribution for Model Parameters for Nivolumab (ie, Posterior from MAP Method)

Parameter	Means	Standard Deviations	Correlation
$\log(\alpha_2)$, $\log(\beta_2)$	(-1.856, -2.131)	(0.404, 0.546)	-0.009

4.2.3 Prior for Interaction Parameters for Joint Toxicity of BMS-986277 and Nivolumab Combination

A gamma prior distribution for the interaction parameter γ is derived to reflect the current uncertainty about the toxicity profile of the combination of BMS-986277 and nivolumab. Although no pharmacokinetic (PK) drug-drug interaction is expected, the possibility of a significant positive interaction between BMS-986277 and nivolumab cannot be totally excluded. The interaction parameter γ 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 follows a gamma distribution with a mean centered at 1.2, which means the combination of 2 agents is likely to have only a small synergistic effect.
- The standard deviation of γ is 0.5 such that there is a 61% prior probability that γ is larger than 1.

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 39% prior probability that γ is less than 1.

4.2.4 Incorporating Prior Data

The means of the initial marginal priors of the 5 parameters are as follows:

- $\log(\alpha_1) = -0.959$
- $\log(\beta_1) = 0.884$
- $\log(\alpha_2) = -1.856$
- $\log(\beta_2) = -2.131$
- $\gamma=1.2$

The data from the ColoAd1-1003 study (also known as "SPICE") for enadenotucirev in combination with a PD-1 inhibitor is described below and summarized in Table 6. The trial is ongoing at the time of writing, but DLT information are available for the first 5 cohorts.

- Cohort 1: 1 cycle of $1x10^{12}$ enadenotucirev + pembrolizumab: 2 DLTs out of 3 treated
- Cohort 2: 1 cycle of $1x10^{12}$ enadenotucirev + nivolumab: 0 DLTs out of 3 treated
- Cohort 3: 1 cycle of $3x10^{12}$ enadenotucirev + nivolumab: 0 DLTs out of 3 treated

- Cohort 4: 2 cycles of $1x10^{12}$ enadenotucirev + nivolumab: 1 DLTs out of 9 treated
- Cohort 5: 2 cycles of $3x10^{12}$ enadenotucirev + nivolumab: still in the DLT observation period

Table 6: Data from ColoAd1-1003

Dose of Enadenotucirev (vp)	DLT (percentage [number of participants/total participants])		
	1 Cycle	2 Cycles	Total
$1x10^{12}$	33% (2/3 pembro + 0/3 nivo)	11% (1/9)	20% (3/15)
$3x10^{12}$	0% (0/3)	Ongoing	0% (0/3)

After incorporating the combination data, the BLRM-Copula provides the following parameter estimates shown in Table 7, which will be used as the prior for BMS-986277 in combination with nivolumab.

Table 7: Prior Distribution for Model Parameters for BMS-986277 in Combination with Nivolumab (ie, Posterior from EnAd in Combination with PD-1 Inhibitor)

Parameter	Means	Standard Deviations	Correlation
$\log(\alpha_1)$, $\log(\beta_1)$ - BMS-986277	(-1.653, 0.8457)	(0.8304, 1.484)	0.145
$\log(\alpha_2)$, $\log(\beta_2)$ - Nivolumab	(-1.852, -2.135)	(0.1621, 0.3025)	-0.04503
γ	1.021	0.399	

5 DOSE ESCALATION PROCESS AND SIMULATIONS IN COMBINATION THERAPY

5.1 Dose Escalation Process

Similar to the dose escalation process for BMS-986277 monotherapy (Section 2.1), the dose escalation recommendations, the selection of the BLRM-RD, and any potential dose recommendations for the combination cohorts will be based on the inference from the Bayesian posterior and the probability (obtained from the BLRM-Copula model) 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

Note: "[" or "]" is inclusive of the respective endpoint, and "(" or ")"exclusive of the respective endpoint.

While the Bayesian model will use DLT information of all available data from the DLT period only, clinical assessment will take into consideration the totality of available data including PK/PD from all treated participants.

Following the principle of EWOC, after gaining information of each cohort of subjects, the candidate doses are the ones fulfilling the overdose criterion that there is less than 35% chance of excessive toxicity. Only the candidate doses will be considered for the next dose decision by Investigators and BMS study personnel based on a synthesis of all relevant data available from all dose levels evaluated in the ongoing study.

Any information on the dose-DLT relationship generated by the ongoing SPICE trial as well as BMS-986277 monotherapy data from the current study (CA034001), as well as any new toxicity information arising from the nivolumab program will be incorporated into the prior distribution before the first dose-escalation decision is made within the combination escalation portion of this study in order to reflect all relevant information at that time.

A combination with a lower, intermediate, or higher dose level of BMS-986277 may be considered and tested if the model recommends it. Such decisions will be made after discussion and agreement between the investigators and the BMS Medical Monitor.

BLRM-RD:

The BLRM-RD for BMS-986277 is the dose that satisfies the following conditions:

(1) The empirical posterior probability that the 'DLT rate of 16% to < 33%' is greater than 50%,

(2) This probability needs to be the largest among the dose levels that satisfy the EWOC condition (ie, the probability that 'DLT rate ≥ 33%' must be no greater than 35%);

Final RP2D:

The Final Recommended Phase 2 Dose (RP2D) will be based on the recommendations from the BLRM-RD and overall clinical assessment of all available safety, PK/pharmacodynamic, and efficacy data.

5.2 Simulation Parameters

A simulation study was done for combination dose escalation using various hypothetical scenarios.

For each scenario, 1000 trial simulations were used. All simulations were run using in house-developed code via Rv3.1.0, R2OpenBugs v3.2, and OpenBUGS v3.2.3 rev 1012 software. The number of participants to be treated in each cohort in a specific dose level, the stopping rules used to identify the BLRM-RD, and other simulation parameters are defined as:

- Fixed cohort size: 3
- Probability of overdosing: ≤ 35%
- Target probability of toxicity: 0.33, the upper boundary of the targeted toxicity interval
- Probability of achieving the target toxicity: > 50%
- Maximum number of participants treated: 30

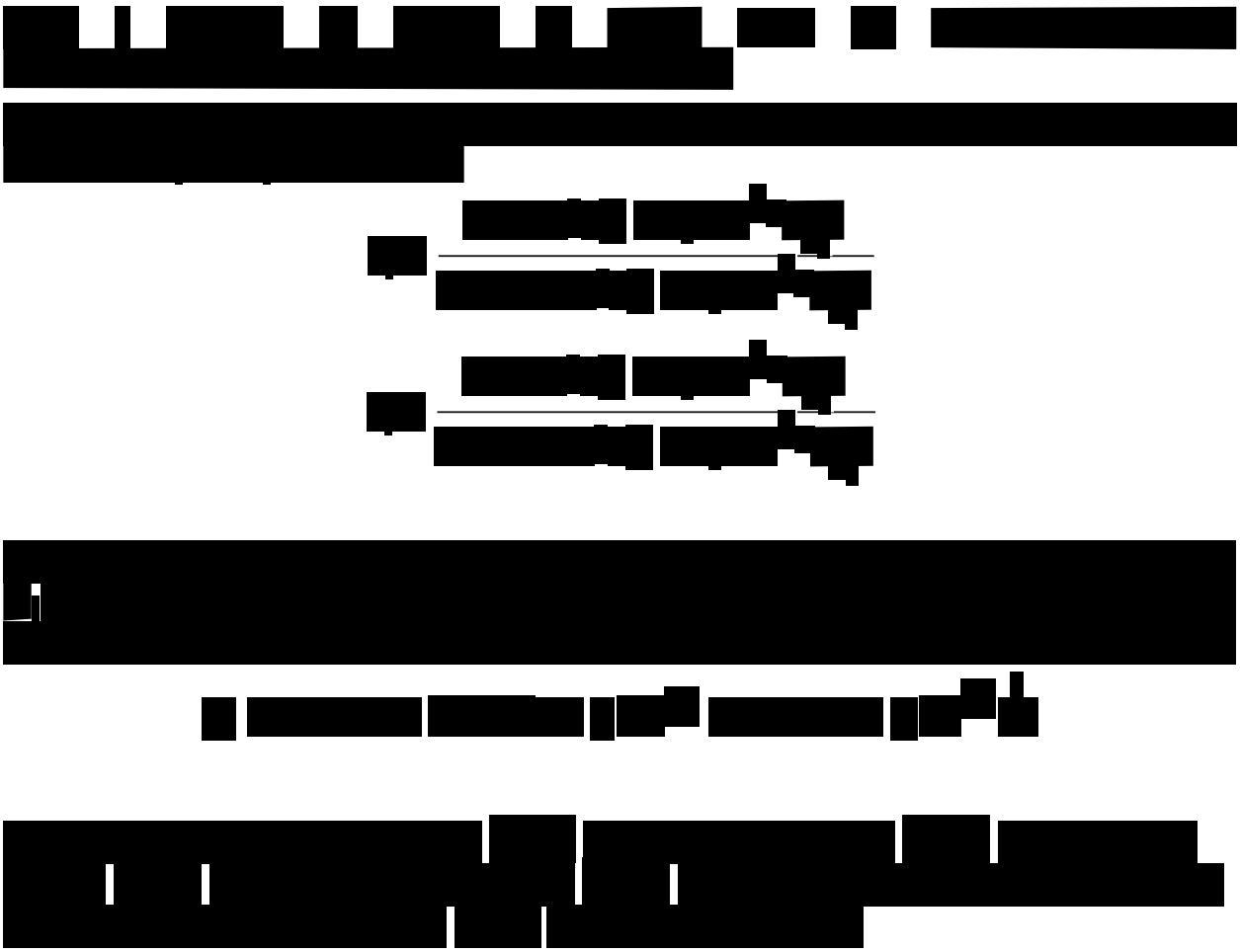
- Dose skipping ratio: 10 (ie, do not allow > 10-fold increase)
- Prior specification on model parameters: See Table 7
- Minimum number of participants treated at a given dose level in order to identify the BLRM-RD: 6
- Maximum number of participants at a dose:12

The provisional dose levels for BMS-986277 in combination with nivoluamb are $3x10^{10}$, $3x10^{11}$, $1x10^{12}$, and $3x10^{12}$ vp, with $3x10^{12}$ as the reference dose (dose expected to have 30% DLT).

5.3 Operating Characteristics of BLRM-Copula for Combination Therapy

In order to show how the design performs, 6 hypothetical scenarios were investigated:

- Scenario 1 (Additive): Dose-DLT relationship derived by the prior (shown below)
- Scenario 2 (Synergistic): All higher toxicity rates 50% higher than the additive scenario, with the highest toxicity level within the "excessive toxicity" window.
- Scenario 3 (Sub-Additive): All dose levels with toxicities 25% lower than the additive scenario.



For Scenario 2, 50% higher than additive yields a prior probability of 0.13, 0.16, 0.20, and 0.42, for the combination with the true MTD as the $1x10^{12}$ vp dose + nivolumab 480 mg (20% DLT rate).

For Scenario 3, 25% lower than additive yields a prior probability of 0.06, 0.08, 0.10, and 0.21, for the combination with the true MTD as the $3x10^{12}$ vp dose + nivolumab 480 mg (21% DLT rate).

Simulation Results

Operating characteristics from the simulations were reviewed to assess the relative performance under each true scenario. Table 8 below summarizes the simulated operating characteristics of the model for the 12 different scenarios studied. One thing to note is that the following simulation results are only for illustrative purposes. This might not fully represent real trial conduction scenarios due to software/current programming code limitations as well as not considering the clinical team's decision overwriting BLRM-Copula recommendation based on the totality of data.

Table 8: Simulation Results of BLRM for BMS-986277 in Combination with Nivolumab

Scenario	BMS-986277 Dose	$3x10^{10}$	$3x10^{11}$	$1x10^{12}$	$3x10^{12}$	MTD not Selected (%)	Fitted Median MTD (vp)	Avg Toxicity Observed (%)	Avg # Pts
Additive (m=1, n=1)	% DLT	8	11	13	**28**[a]	0	$3.8x10^{12}$	15.45	16.4
	% MTD	0	0	29	71				
	# Pts	3.01	3.02	5.21	5.18				
	# DLTs	0.25	0.33	0.66	1.41				
Synergistic (m=1, n=1)	% DLT	13	16	**20**[a]	42	0	$3.3x10^{12}$	23.4	18.1
	% MTD	41	3	58	38				
	# Pts	3.05	3.14	7.70	4.17				
	# DLTs	0.38	0.51	1.55	1.75				
Sub-Additive (m=1, n=1)	% DLT	6	8	10	**21**[a]	0	$4.0x10^{12}$	12.4	15.3
	% MTD	0	0	19	81				
	# Pts	3.00	3.00	3.80	5.46				
	# DLTs	0.18	0.26	0.41	1.16				
Additive ((E(m)=1; E(n)=1.5)	% DLT	8	11	13	**28**[a]	0	$4.3x10^{12}$	17.5	16.9
	% MTD	0	1	19	80				
	# Pts	3.00	3.06	4.01	6.86				
	# DLTs	0.24	0.33	40.54	1.89				

Table 8: Simulation Results of BLRM for BMS-986277 in Combination with Nivolumab

Scenario	BMS-986277 Dose	$3x10^{10}$	$3x10^{11}$	$1x10^{12}$	$3x10^{12}$	MTD not Selected (%)	Fitted Median MTD (vp)	Avg Toxicity Observed (%)	Avg # Pts
Synergistic ((E(m)=1; E(n)=1.5)	% DLT	13	16	**20**[a]	42	0	$1.6x10^{12}$	24.3	19.2
	% MTD	1	5	45	50				
	# Pts	3.06	3.34	7.58	5.20				
	# DLTs	0.40	0.57	1.50	2.19				
Sub-Additive ((E(m)=1; E(n)=1.5)	% DLT	6	8	10	**21**[a]	0	$2.7x10^{12}$	14.2	17.2
	% MTD	0	0	12	88				
	# Pts	3.00	3.02	2.72	8.44				
	# DLTs	0.17	0.24	0.28	1.72				

% 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 30% as the target toxicity rate and the dose range falls into the target toxicity range of [16%, 33%); Toxicity observed: Average proportion of DLTs out of all simulated trials; # Pts, average number of participants; NC: not calculated

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

The average sample size was between 15-20 participants. The simulation results for the various scenarios (additive, synergistic, and sub-additive) shows the model performs as expected. The scenarios illustrated above demonstrate that the model performs well by correctly identifying the MTD ranging from 58% to 81% in the hypothetical scenarios investigated when assuming equal contribution of BMS-986277 and nivolumab to the combination dose-DLT relationship.

When treating the nivolumab contribution with a higher weight, the % of simulations choosing the MTD at the higher doses were higher when compared to their equal weight counterparts, which suggests that the BMS-986277 dose can be safely escalated. This may be driven by the fact that there were no DLTs in the enadenotucirev monotherapy at the dose levels under investigation for BMS-986277, yet a positive DLT rate in the enadenotucirev + nivolumab combination data. Weighing nivolumab with an equal contribution may be more conservative and safer for the participants, due to a higher chance of selecting lower MTDs.

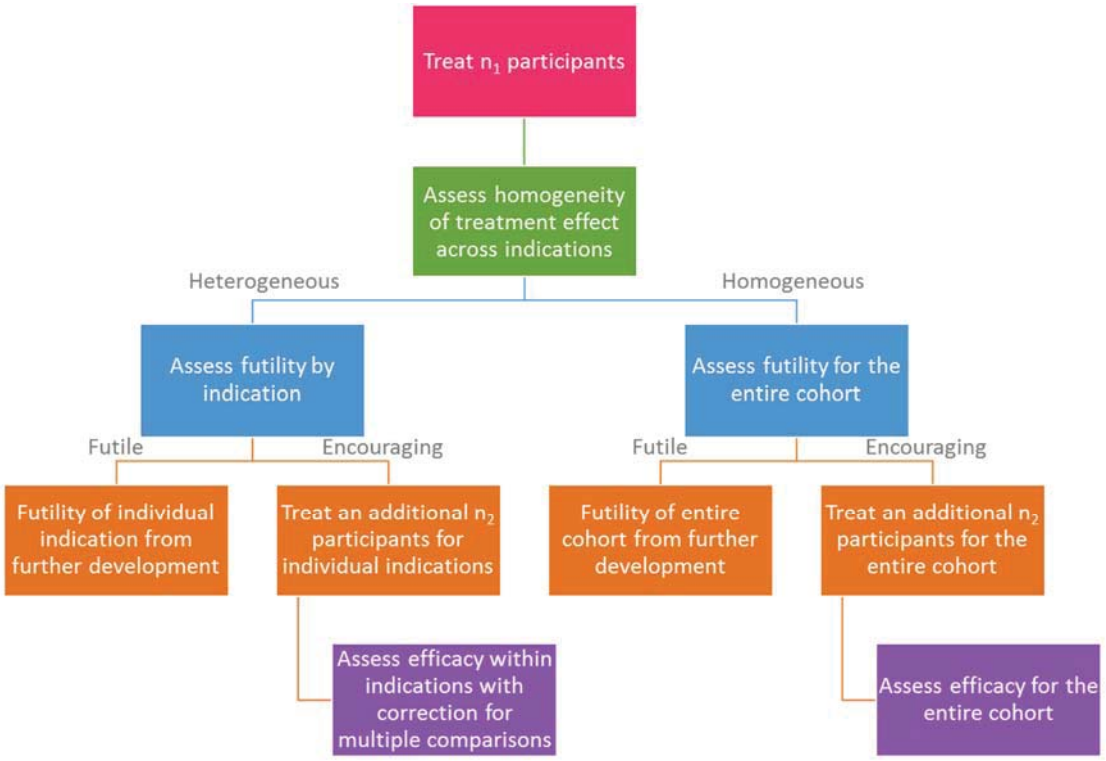
The scenario which most reflects the current understanding of BMS-986277 in combination with nivolumab is the first scenario, additive with equal contribution. This will be represented by a 5-parameter BLRM-copula (where m=n=1) and will be primarily used to guide dose escalation in Part 2 of the study.

6 BASKET DESIGN

The cohort expansion portion of this study is not specifically designed using a basket design, but concepts from basket designs[5] may still be used to inform decision-making. In particular,

homogeneity among different indications within each of the CD8 cohorts will be assessed and indications may be expanded if there is sufficient evidence treatment effect differ among indications within a cohort. This allows sufficient sample size to adequately address preliminary efficacy by indication. Currently, the trial is designed to assume homogeneity within cohort based on the biological rationale and proposed mechanism of action. An example of possible outcomes are shown in Figure 5. Enrollment will not be affected or paused to conduct the homogeneity evaluation. In the event that additional sample size is needed, the protocol may be amended to expand certain indications.

Figure 5: Example of Flow Chart of Assessment



Adapted from Cunanan et. al. 2017

As an example, in the CD8 low cohort, suppose all k=6 indications are enrolled, assuming an uninteresting response rate of 6%, and an interesting response rate of 20%. To control the family wise Type I error rate at 10% to achieve 80% power to detect active indications if the drug truly works in only 2 out of 6 of the indications, and at least 70% marginal power if the drug truly works in only 1 out of 6 indications, a homogeneity assessment would be conducted at approximately 16 response evaluable subjects for a total of 42 subjects, if homogeneous, and 31 per indication if heterogeneous.

[redacted]