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

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STATISTICAL ANALYSIS PLAN
FOR CLINICAL STUDY REPORT

PHASE 1/2A FIRST IN HUMAN STUDY OF BMS-986277 ADMINISTERED ALONE AND IN COMBINATION WITH NIVOLUMAB IN ADVANCED EPITHELIAL TUMORS

PROTOCOL(S) CA034001

VERSION # 1.0

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1 INTRODUCTION AND DOCUMENT HISTORY

This statistical analysis plan (SAP) supersedes the statistical considerations identified in the protocol; where considerations are substantially different, they will be identified as such in this document. In the event that the protocol has amendment(s) that do not have an impact on the statistical analysis methodology, this SAP will not require an amendment. If additional analyses are required to supplement the planned analyses described in this SAP, they may be performed and will be identified in the Clinical Study Report (CSR).

Revision History:

Version Number	Author(s)	Description
1.0	[redacted]	Original issue. Incorporates all Administrative Letters and Amendments up to Revised Protocol 03.

[redacted]

[redacted]

3 STUDY DESCRIPTION

3.1 Study Design

This is a Phase 1/2a, multicenter, open-label, non-randomized study of CD80/αCD3 Oncolytic Virus (BMS-986277) alone and in combination with nivolumab for the treatment of metastatic or advanced epithelial tumors in male and female participants. There will be up to 4 sequential IV dose panels of BMS-986277 in monotherapy and 2 sequential IV dose panels of BMS-986277 in combination with nivolumab (480 mg Q4W).

The study will be conducted in 3 Parts:

- Part 1: a single agent monotherapy dose escalation of BMS-986277
  - Four dose levels: 3×10^{10} vp, 3×10^{11} vp, 1×10^{12} vp, and 3×10^{12} vp.
  - 6 week dose limiting toxicity (DLT) period to assess safety with multiple injections.
  - 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 3 cycles (28 day cycles; up to 6 max) of BMS-986277.
  - This part will determine the recommended dose to administer in the combination dose escalation (Part 2), based on the Bayesian Logistic Regression Model Recommended Dose (BLRM-RD) and overall clinical assessment of all available safety, pharmacokinetics (PK), pharmacodynamics, and efficacy data.
- Part 2: a combination dose escalation of BMS-986277 in combination with nivolumab in participants with low or mid CD8 tumor infiltrating lymphocytes (TILs) only
  - 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
  - BMS-986277 will be administered for up to three 28-day cycles, and nivolumab will be administered at 480mg Q4W for up to 26 cycles.
  - Low CD8 TILs are defined as CD8 < 2%
  - Mid CD8 TILs are defined as 2% ≤ CD8 < 20%

  - This part will determine the recommended Phase 2 dose (RP2D) based on the recommendations from the BLRM-copula and overall clinical assessment of all available safety, PK/pharmacodynamic, and efficacy data.
- Part 3: a 2 cohort dose expansion phase of BMS-986277 in combination with nivolumab in participants with low or mid CD8 tumor infiltrating lymphocytes (TILs) only
  - Participants will receive BMS-986277 at the RP2D established in Part 2 for up to 3 cycles, and nivolumab will be administered at 480mg Q4W for up to 26 cycles.
  - Cohort 1 will treat participants with low CD8 TILs
  - Cohort 2 will treat participants with mid CD8 TILs

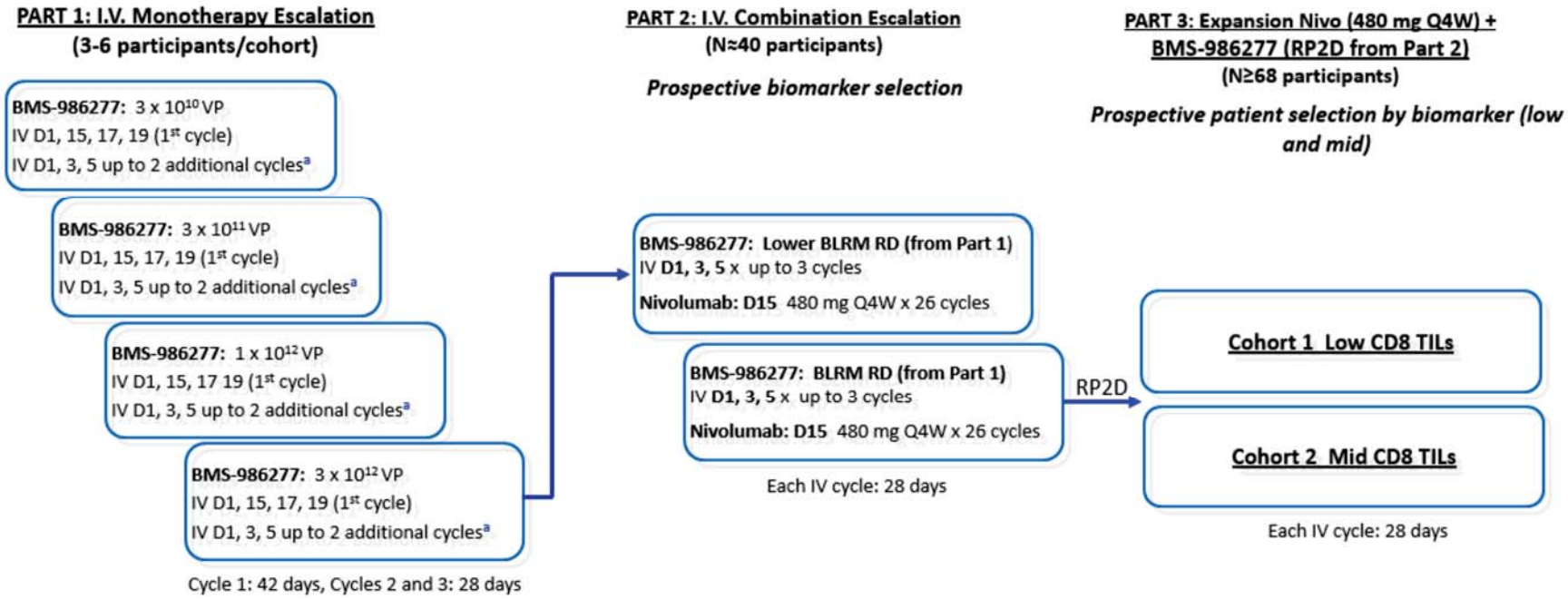
Participants with high CD8 TILs (defined as ≥ 20%) are not eligible for enrollment in Parts 2 and 3 of the study.

The study design schematic is presented in Figure 1.

The treatment regimens are described in more detail in Section 7.2

Details of the BLRM can be found in the Protocol Appendix 10[2].

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 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

Prospective biomarkers to be enrolled in Parts 2 and 3:

Low: CD8 < 2% **OR** Mid: 2% ≤ CD8 < 20%

[a]Optional Treatment up to 6 cycles if deemed safe and after risk/benefit evaluation with Medical Monitor (or designee) approval.

BLRM = Bayesian Logistic Regression Model Recommended Dose; D = day; IV = intravenous; N = number; PD-L1 = PD1 ligand; Q4W = every 4 weeks; RD = recommended dose; RP2D = recommended phase two dose; TIL = tumor-infiltrating lymphocytes; VP = viral particles.

3.2 Treatment Assignment

All enrolled participants, including those not dosed, will be assigned a participant number. Treatment group and dose level assignments will be performed using an Interactive Response Technology (IRT). The participant will be assigned to one of the following:

- Assigned to Part 1 and the assigned dose level in the monotherapy dose escalation portion of the study
- Assigned to Part 2 and the assigned 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 indication in each cohort.

Participants may be replaced in the same part and dose level under certain conditions, such as not being evaluable for the DLT period or having unevaluable tumor tissue to determine CD8 level.

3.3 Blinding and Unblinding

Not applicable. This is an open label study.

3.4 Protocol Amendments

Table 1 lists the protocol amendments and administrative letters and only highlights the changes which affect the analysis.

Table 1: List of Protocol Amendments and Administrative Letters

Document	Date	Summary of Major Changes
Amendment 01	27-Sep-2017	Does not affect analyses.
Amendment 02	24-Oct-2017	Does not affect analyses.
Administrative Letter 01	07-Nov-2017	Does not affect analyses.
Administrative Letter 02	11-Dec-2017	Modifies the dosing window, this change occurred before any participants were dosed on this study.
Amendment 03	15-Dec-2017	Updates to the following sections: schedule of activities (including safety labs, biomarker samples, pharmacokinetic samples, and shedding samples), exploratory objectives, inclusion/exclusion criteria
Amendment 04	02-Mar-2018	Does not affect analyses.

3.5 Blinded Independent Central Review

Images will be submitted to an imaging core lab for all participants. Images from participants in Part 2 and 3 may be reviewed by a Blinded Independent Central Review (BICR), in addition to the investigator. Images in Part 1 will be read locally, but may be read at a later date, or at any time during the study by the BICR.

The participants' best overall response (BOR), duration of response (DOR), and progression-free survival (PFS) will be assessed using the RECIST Version 1.1 criteria (Protocol Appendix 7[2]),

modified Response Evaluation Criteria in Solid Tumors for Immunotherapeutics (iRECIST) Version 1[3], and/or prostate cancer working group 3 (PCWG3, Protocol Appendix 8[2]).

Details of the BICR responsibilities and procedures will be specified in the BICR charter.

4 OBJECTIVES

The objectives and endpoints for this study are shown in the following table.

Table 2: Objectives and Endpoints

Objectives	Endpoints
Primary	
• To characterize the safety and tolerability of BMS-986277 administered alone and in combination with programmed death receptor 1 (PD-1) inhibitor, nivolumab, in 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
• To determine the recommended dose (RD) and recommended Phase 2 dose (RP2D) and dosing schedule of BMS-986277 administered alone (RD) and in combination with nivolumab (RP2D) in participants with advanced epithelial tumors	
Secondary	
• To explore the preliminary anti-tumor activity of BMS-986277 in combination with nivolumab in participants with advanced epithelial tumors (RECIST 1.1 and PCWG3)	• ORR, DCR, mDOR, mPFS, and PFSR at 8, 16, 24 weeks depending on indication
• To assess the pharmacokinetics and immunogenicity of BMS-986277 in blood following monotherapy or combination treatment	• Summary measures of PK and IMG parameters of BMS-986277
[redacted]	
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]

Table 2: Objectives and Endpoints

Objectives	Endpoints
• [redacted]	[redacted]

AEs = adverse events; DCR = disease control rate; IMG = immunogenicity; mDOR = median duration of response; mPFS = median progression-free survival; mOS = median overall survival; ORR = objective response rate; OSR = overall survival rate; PCWG = Prostate Cancer Working Group; PFSR = progression-free survival rate; PK = pharmacokinetics; RECIST = Response Evaluation Criteria in Solid Tumors; SAEs = serious adverse events.

5 ENDPOINTS

5.1 Primary Endpoints

The primary objectives relate to safety, tolerability, and determining the RP2D of BMS-986277 alone and/or in combination with nivolumab in advanced epithelial tumors. These will be measured by the following endpoints.

5.1.1 Adverse Events

- Incidence rate of adverse events (AEs), serious adverse events (SAEs), AEs meeting the protocol-defined DLT criteria (Protocol Section 7.4.1[2]), AEs leading to discontinuation, and AEs resulting in death
  - DLTs are identified as recorded on the case report form (CRF).
  - All non-serious AEs will be assessed from the start of dosing.
  - All SAEs and deaths will be assessed from the date of the participant's written informed consent.
  - All AEs (serious and non-serious), and deaths will be assessed up to 30 days after the last dose of BMS-986277 for participants enrolled in Part 1 or 100 days after the last dose of any study drug for participants enrolled in Parts 2 and 3.
  - Drug-related AEs are those events with relationship to study drug "Related", as recorded on the CRF. If the relationship to study drug is missing, the AE will be considered as drug-related.
  - Serious adverse events consist of AEs deemed serious by the Investigator and flagged accordingly in the CRF and clinical database.
  - Adverse events leading to study drug discontinuation are AEs with action taken = "Drug was discontinued".
  - AEs belonging to select AE categories will be assessed using the categorizations which are current at the time of database lock. An accompanying listing will be provided to define the categorizations at each analysis.

- ♦ The select AE categories from the CA209 dictionary will be used, as well as any additional categories and/or AEs within a category that may be particularly relevant or of interest for BMS-986277.

– Immune-mediated AEs may also be summarized if warranted based on sufficient data, relevance, interest, etc.

– AEs will be coded using the most current version of the Medical Dictionary for Regulatory Activities (MedDRA) at the time of each database lock

– AEs will be graded for severity according to the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) version 4.03.

5.1.2 Clinical Laboratory Test Abnormalities

- Incidence of clinical laboratory test abnormalities
  - 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
  - Laboratory values will be graded according to the NCI CTCAE version 4.03.
  - Potential drug induced liver injury (DILI) events are defined as:
    - ♦ AT (ALT or AST) elevation > 3 times upper limit of normal (ULN)

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

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

5.1.3 Vital Sign Abnormalities and Other Safety Biomarkers

- Vital signs collected as a continuous variable (eg, blood pressure) or categorical variable (eg, Eastern Cooperative Oncology Group [ECOG] performance status)
- Measures of renal function
  - MedDRA Preferred Terms: Nephritis and Renal Failure
  - Laboratory values for Blood Creatinine
- Measures of bladder hemorrhage
  - MedDRA Preferred Term: Urinary Bladder Hemorrhage
- Measures of cytokine release monitoring
  - MedDRA Preferred Term: Cytokine Release Syndrome

5.2 Secondary Endpoints

The secondary objectives relate to preliminary anti-tumor activity, pharmacokinetics, and immunogenicity of BMS-986277 alone and/or in combination with nivolumab in advanced epithelial tumors.

5.2.1 Preliminary Anti-Tumor Activity

Changes in tumor measurements and tumor response will be measured based on RECIST v1.1[4] (all indications except PRC) or PCWG3[5] (PRC participants only), hereafter referred to collectively as "RECIST 1.1/PCWG3". Tumor assessments will be performed at baseline, and then approximately every 8 weeks (all indications except PRC) or every 8 weeks for 24 weeks and then every 12 weeks afterward (for PRC participants). Tumor assessment should continue until disease progression (ideally confirmed with second assessments obtained at least 4 weeks apart) or discontinuation of study treatment, withdrawal from study, or start of subsequent anticancer treatment, whichever occurs later. For PRC participants, any clinical progression due to symptomatic skeletal events detected during bone scans may be counted as a progression event.

The following set of efficacy study-level endpoints will be used:

- **Objective Response Rate (ORR)**: The ORR is defined as the total number of participants whose best overall response (BOR) is either a complete response (CR) or partial response (PR) divided by the total number of participants in the population of interest (eg, all treated participants or response-evaluable participants).
  - The BOR for a participant will be assessed by investigator and/or by BICR, where available.
    - For interim analyses or internal monitoring of efficacy before the final BOR can be determined, the BOR (including a category for unconfirmed responses still in follow-up) may be derived using an internal algorithm.
  - The BOR for a participant is defined as the best response designation recorded between the date of first study drug administration and the date of first objectively documented progression per RECIST 1.1/PCWG3 or date of subsequent anticancer therapy, whichever occurs first.
    - For those participants who have surgical resection, only pre-surgical tumor assessments will be considered in the determination of BOR.
    - For participants without documented progression or subsequent anticancer therapy, all available response designations will contribute to the BOR assessment.
    - For participants who continue treatment beyond progression or begin subsequent anticancer therapy, the BOR should be determined based on response designations recorded up to the time of the initial RECIST 1.1/PCWG3-defined progression or subsequent anticancer therapy, whichever occurs first.
    - For a BOR of CR or PR, the response assessment must have been confirmed by a consecutive assessment meeting the criteria for response and performed no less than 4 weeks (28 days) after the criteria for response are first met.

- ♦ A BOR of stable disease (SD) can only be made after the participant is on-study for a minimum of 49 days from the date of treatment initiation (i.e., first dose).

- **Disease Control Rate (DCR)**: The DCR is defined as the total number of participants whose BOR is CR, PR, or SD, divided by the total number of participants in the population of interest (eg, all treated or response-evaluable).
- **Median Duration of Response (mDOR)**: The significance of ORR is assessed by its magnitude and duration of response.
  - The DOR for a participant will be calculated for participants with BOR of CR or PR only, and is defined as time between the date of first objectively documented response (which is subsequently confirmed) and the date of first subsequent objectively documented disease progression per RECIST v1.1/PCWG3 or death due to any cause, whichever occurs first.
    - ♦ For interim analyses or internal monitoring, DOR may also be calculated for unconfirmed responses.
  - Participants who remain alive and have not progressed will be censored on the date of their last evaluable tumor assessment (prior to subsequent anticancer therapy).
  - Participants who receive subsequent anticancer therapy without a prior documented disease progression will be censored on the date of their last evaluable tumor assessment prior to initiation of the subsequent anticancer therapy.
- **Median Progression-Free Survival (mPFS)**: The median of all participants' PFS is considered the study-level endpoint and is estimated using the Kaplan-Meier method.
  - The PFS for a participant is defined as the time from the first dosing date to the date of first objectively documented disease progression per RECIST v1.1/PCWG3 or death due to any cause, whichever occurs first.
  - Participants who died without a reported prior progression will be considered to have progressed on the date of their death.
  - Participants who remain alive and have not progressed will be censored on the date of their last evaluable tumor assessment (prior to subsequent anticancer therapy).
  - Participants who receive subsequent anticancer therapy without a prior documented disease progression will be censored on the date of their last evaluable tumor assessment prior to initiation of the subsequent anticancer therapy.
  - Participants who did not have any post-baseline tumor assessment and did not die will be censored on the date of first dose of study medication.
  - Clinical deterioration in the absence of radiographic evidence is not considered progression for the purpose of determining PFS per RECIST v1.1/PCWG3 when using objectively documented progression.
- **Progression Free Survival Rate (PFSR) at Week t**: The proportion of participants in the population of interest remaining progression free and surviving to time t, where t is a specific length of time, eg, 8, 16, or 24 weeks, which will depend on the indication and also be determined by the available data for each interim or final analysis. The specific length of time will be documented in the data presentation plan (DPP). The proportion will be calculated by the product-limit method (Kaplan-Meier estimate) which takes into account censored data.

5.2.2 Pharmacokinetics of BMS-986277

All PK analyses will be performed on the Pharmacokinetic population (described in Section 7.3). Refer to Protocol Section 9.5[2] for the definition of the PK parameters. The following set of pharmacokinetics endpoints will be used for BMS-986277:

- Cmax: maximum observed blood concentration
- AUC(0-T): area under the concentration-time curve from time zero to time of last quantifiable concentration
- AUC(0-8): area under the concentration-time curve from time zero to 8 hours postdose
- AUC(0-48): area under the concentration-time curve from time zero to 48 hours postdose
- 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
- C48: blood concentration 48 hours postdose
- Css-avg: average blood concentration over a dosing interval at steady state
- AI_AUC: AUC accumulation index
- AI_Cmax: Cmax accumulation index
- THALFeff: effective elimination half-life
- Tmax: time of maximum observed blood concentration
- Ctrough: trough observed blood concentrations

5.2.3 Immunogenicity of BMS-986277

All immunogenicity analyses will be performed on the Immunogenicity population (described in Section 7.3). Each endpoint will be summarized for BMS-986277 and nivolumab separately, pending availability of evaluable data. Immunogenicity of BMS-986277 are secondary endpoints while immunogenicity of nivolumab are exploratory endpoints and mentioned in Section 5.3.3. The definitions provided here apply to both.

The endpoint for the study is the incidence of anti-drug antibodies (ADA), defined as the proportion of the study population found to have seroconverted or boosted their pre-existing ADA during the study period.

Validated ADA test methods enable characterization of samples into ADA-positive vs ADA-negative. To classify the ADA status of a participant using data from an in vitro test method, each sample from a participant is categorized based on the following definitions:

Sample ADA Status:

- Baseline ADA-positive sample: ADA is detected in the last sample before initiation of treatment

- Baseline ADA-negative sample: ADA is not detected in the last sample before initiation of treatment
- ADA-positive sample: After initiation of treatment, (1) an ADA detected (positive seroconversion) sample in a participant for whom ADA is not detected at baseline, or (2) an ADA detected sample with ADA titer to be at least 4-fold or greater (≥) than baseline positive titer
- ADA-negative sample: After initiation of treatment, ADA not positive sample relative to baseline

Next, using the sample ADA status, participant ADA status is defined as follows:

Participant ADA Status:

- Baseline ADA-positive participant: A participant with baseline ADA-positive sample
- **ADA-positive participant**: A participant with at least one ADA positive-sample relative to baseline at any time after initiation of treatment
  - *Persistent Positive (PP)*: ADA-positive sample at 2 or more consecutive timepoints, where the first and last ADA-positive samples are at least 16 weeks apart
  - *Not PP-Last Sample Positive*: Not persistent positive with ADA-positive sample at the last sampling timepoint
  - *Other Positive*: Not persistent positive with ADA-negative sample at the last sampling timepoint
- **ADA-negative participant**: A participant with no ADA-positive sample after the initiation of treatment

[redacted]

[redacted]

6 SAMPLE SIZE AND POWER

6.1 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, because BMS-986277 is the genetically modified form of 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 25%.

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 (Protocol Appendix 9[2]).

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-recommended dose (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 recommended dose (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).

6.2 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 recommended dose 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 recommended dose for BMS-986277 in combination with nivolumab. Additional participants (up to a total of 15) may be treated at any dose combination below or at the BLRM-copula recommended dose 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 final recommended Phase 2 dose (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.

6.3 Cohort Expansion (Part 3)

Sample size calculations for cohort expansion assumes 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.
  - These cutoffs are based on CD8 IHC data from CA209275, a nivolumab-only clinical study in participants with UC for which response by BIRC data is available.
- 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 α=0.10 and β=0.20, but the actual power and type I error are shown in the tables below (Table 4 and Table 5), which accounts for the discrete nature of the binomial distribution.

[redacted]

6.3.1 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 4: Power Estimates and Type I 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)
	0.20	4, 28 (0.049, 0.840)	5, 35 (0.056, 0.857)
X is the min # of responders to show not futile			

6.3.2 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 5: Power Estimates and Type I Error for Cohort 2

		Historical Rate	
	X, N (alpha, power)	0.15	0.20
Target Rate	0.30	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)
	0.40	6, 19 (0.054, 0.837)	11, 33 (0.051, 0.831)
X is the min # of responders to show not futile			

7 STUDY PERIODS, TREATMENT REGIMENS AND POPULATIONS FOR ANALYSES

7.1 Study Periods

7.1.1 Baseline Period

Baseline evaluations or events will be defined as evaluations or events that occur before the date and time of the first dose of study treatment, for all treated population, unless otherwise specified.

In cases where the time (onset time of event or evaluation time and dosing time) is missing or not collected, the following definitions will apply:

- Pre-treatment AEs will be defined as AEs with an onset date prior to but not including the day of the first dose of study treatment
- Baseline evaluations (laboratory tests, pulse oximetry and vital signs) will be defined as evaluations with a date on or prior to the day of first dose of study treatment
- Baseline CD8 value is value recorded closest to (before or on) the first treatment date and no earlier than 35 days prior to first dose. If multiple records at same date then select the highest value.

If there are multiple valid assessments at baseline, then the assessment that is closest to the date (and time if collected) of the first dose of study treatment will be used as the baseline in the analyses. If multiple assessments are collected at the same date (and time if collected), the assessment with the latest database entry date (and time if collected) will be considered as baseline.

7.1.2 Post-Baseline Period

- On-treatment period for evaluation of AEs and measurements (including laboratory tests) post baseline is defined as on or after the first dose of study treatment up to and including 30 days or 100 days after the last dose of study treatment for participants who are off study treatment, for Part 1 and Parts 2-3, respectively. For participants who are still on study treatment, the entire post-baseline period will be counted as on-treatment.
- Primary analysis of safety endpoints will be based on the treatment period.
- DLTs will be evaluated during the 42-day DLT period.

7.2 Treatment Regimens

The treatment group "as assigned" will be retrieved from the IRT system. The treatment group "as treated" is expected to be the same as the arm as assigned by IRT. However, if a participant received an incorrect treatment for the entire period of treatment, this will be documented as a relevant protocol deviation (see Section 8.2.3) and the participant's treatment group will be defined as the incorrect treatment the participant actually received.

7.2.1 Monotherapy Dose Escalation (Part 1)

In the monotherapy dose escalation part of the study, participants will receive BMS-986277 at one of the four planned dose levels (3×10^{10}, 3×10^{11}, 1×10^{12}, or 3×10^{12} vp). At each dose level BMS-986277 will be administered as a single IV infusion (D1) before proceeding to a single dosing cycle (3 doses, Days 15, 17, and 19). 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 two more cycles of BMS-986277. Optional treatment up to 6 cycles if deemed safe and after risk/benefit evaluation and approval by Medical Monitor (or designee) are permitted.

7.2.2 Combination Dose Escalation (Part 2)

In the combination dose escalation part of the study, participants will receive combination treatment with nivolumab (480 mg Q4W up to 26 cycles) plus BMS-986277 at one of two dose levels (for up to 3 cycles). These two dose levels will be determined based on the results from the monotherapy dose escalation part. 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 two more cycles of BMS-986277 with each subsequent cycle beginning no sooner than 28 days after Day 1 of the previous cycle.

7.2.3 Cohort Expansion (Part 3)

In the cohort expansion part of the study, participants will receive combination treatment with nivolumab (480 Q4W up to 26 cycles) in combination with BMS-986277 (at the RP2D based on Part 2 for up to 3 cycles). 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 2 more cycles of BMS-986277, with each subsequent cycle beginning no sooner than 28 days after day 1 of the previous cycle.

7.3 Populations for Analyses

- All Enrolled: All participants who signed an informed consent form and are registered into the IRT
- All Treated: All participants who received at least one dose of any study medication
- Response-evaluable: All treated participants with measurable disease at baseline and one of the following: (a) at least one post-baseline tumor assessment, (b) clinical progression, or (c) death
- Pharmacokinetic: All treated participants who have evaluable concentration-time data
- Immunogenicity: All treated participants who have a baseline and at least one post baseline immunogenicity assessment
- Biomarker: All treated participants with evaluable biomarker data for the specific analysis
  - It is expected that all treated participants in Parts 2 and 3 are the same as the CD8 biomarker evaluable population.

8 STATISTICAL ANALYSES

All analysis will be performed in SAS (Statistical Analysis System software, SAS Institute, North Carolina, USA) using version 9.2 or higher. Some figures may be generated using S-Plus.

8.1 General Methods

Continuous variables will be summarized by using descriptive statistics, using the mean, standard deviation/standard error of the mean, median, minimum, and maximum values. Some continuous

variables may also be summarized using the geometric mean and coefficient of variation. Categorical variables will be summarized by frequencies and percentages of participants in the population falling into each category. Percentages given in these tables will be rounded and, therefore, may not always sum to 100%. Percentages less than 0.1 will be indicated as "< 0.1". If a missing category is not being presented in the data display, only those participants with non missing values for the parameter being assessed are included in the percentage calculation.

Statistical analyses will be presented by part, dose level, cohort, indication, and biomarker level; and any of the groups may be combined, where reasonable, to increase the number of participants for analyses. The grouping schemes for analyses are further described in the DPP.

Unless otherwise specified, listings will be sorted by part, dose level, cohort, and unique participant ID.

8.2 Study Conduct

8.2.1 Accrual

The following will be presented on the All Enrolled population.

Summary:

- Number (%) of participants accrued by part, country and investigational site: Include country, site number, number of participants enrolled, and number of participants treated

Listing:

- Participants accrued by part, country and investigational site

8.2.2 Protocol Deviations

A listing of deviations from the protocol inclusion and exclusion criteria for the All Enrolled population will be provided, along with the description of the criteria and whether they were treated. Participants who do not meet the inclusion and exclusion criteria and are subsequently treated are considered as protocol deviations. In the event that the inclusion and exclusion criteria are changed during the course of the trial, each participants' inclusion/exclusion criteria entered on the CRF will be linked to the criteria used at the time of their enrollment.

8.2.3 Relevant Protocol Deviations

A relevant protocol deviation is a deviation from the protocol which is programmed in the database and which could potentially affect the interpretability of the study results. Non-programmable relevant eligibility and on-treatment protocol deviations, as well as significant (both programmable and non-programmable) will be reported through ClinSIGHT listings. The following programmable deviations will be considered as relevant protocol deviations and a listing based on the All Treated population will be provided. During the conduct of the trial, if any relevant protocol deviation is discovered that is not on this list, this SAP may be amended prior to the final database lock. Relevant protocol deviations, their implications, and subsequent data handling will be reported in the CSR.

At Entrance:

In the event that either of the following occur, the study team will consider whether the time relative to first dose is acceptable to be considered as the baseline assessment.

- Participants with a tumor tissue sample earlier than 35 days prior to first dose
- Participants whose baseline efficacy assessments are more than 28 days prior to first dose

In the event that any of the following occur, the participants may be excluded from specific (or all) analyses upon study team agreement. Any exclusions due to relevant protocol deviations will be documented in the CSR.

- Participants in Parts 2 and 3 without an evaluable CD8 value prior to first dose.
- Participants without measurable disease at baseline (Inclusion Criteria 2.b).
- Participants in Parts 2 and 3 with a CD8 value ≥ 20% (Inclusion Criteria 2.f).
- Participants with screening ECOG performance status > 2 (Inclusion Criteria 2.g).
- Participants with prior exposure to checkpoint inhibitors or cytotoxic agents within 28 days prior to first dose (Inclusion Criteria 2.i and Exclusion Criteria 2.a).
- Participants with prior antiviral agents within 7 days prior to first dose or PEG-IFN within 14 days prior to first dose (Exclusion Criteria 2.e).

On-Treatment:

- Participants receiving treatment that is different than what they were assigned
  - In the event that this occurs, the participant may be grouped with others receiving the actual treatment for analyses, if such a group exists.
- Participants receiving anti-cancer therapy (chemotherapy, hormonal therapy, immunotherapy, or non-palliative radiation therapy; standard or investigational) before the last dose of study drug
  - In the event that this occurs, this will be treated as the participants' subsequent therapy for certain efficacy assessments described in Section 5.2.1.

8.3 Study Population

8.3.1 Disposition of Participants

Status of participants at the end of pre-treatment period will be summarized and listed for the All Enrolled population. Status of participants at the end of treatment period will be summarized by part, dose level/cohort, indication, and overall, based on the All Treated population. In addition, the status of participants at the end of each study period will be summarized as appropriate. A listing will be provided for those participants who were treated and reason for discontinuation of treatment or not being followed will be described.

8.3.2 Demographics and Other Baseline Characteristics

Summary:

Descriptive statistics will be summarized for the following baseline characteristics for the All Treated population by part, dose level, cohort, indication, biomarker level, and overall.

- Age at Consent (in years); age category (<65, ≥65), female age category (≤50, >50, NA for male - for the TNBC indication only)
- Sex at Birth
- Race
- Ethnicity (for US only)
- Region (North America, EU, Asia, Rest of World)
- Height at Baseline
- Weight at Baseline
- ECOG Performance Status at Baseline
- Disease characteristics at Baseline
  - CRC: Stage at study entry, microsatellite instability status, mismatch repair status, KRAS status, and BRAF status
  - Ovarian: Stage at study entry, BRCA1 status and BRCA2 status
  - PC: Stage at study entry and disease classification subtype
  - PRC: Stage at study entry
  - TNBC: Stage at study entry, disease classification subtype, BRCA1 status, BRCA2 status, ER status, PR status, and HER-2 status
  - UC: Stage at study entry

Listing:

- All relevant data, generally variables listed above
- General medical history
- Tobacco use
- Disease recurrence
- Specific disease history
- Clinical complaints

8.4 Extent of Exposure

Unless otherwise specified, the analysis of extent of exposure will be characterized according to the number of participants exposed, the duration of exposure, and the dose to which they were exposed. Analyses in this section will be performed on the All Treated population "as treated" as described in Section 7.2.

8.4.1 Study Therapy

Summary:

Unless otherwise specified, administration of study therapy will be summarized separately for BMS-986277 and nivolumab and presented by dose level and biomarker level; tabulations by part, cohort, and indications may also be performed, as appropriate.

- Number (%) of treated participants exposed for specified periods of time such as:

- **Part 1**: less than 2 weeks (lead-in period only), 2 weeks to 6 weeks (1 cycle), 6weeks to 14 weeks (up to 3 cycles), and more than 14 weeks (up to 6 cycles).
- **Parts 2 and 3**: less than 2 weeks (sequential dosing of BMS-986277 prior to nivolumab), 2 weeks to 4 weeks (1 combination cycle), 4 weeks to 12 weeks (up to 3 cycles), and more than 12 weeks (nivolumab maintenance).
- For this analysis, the exposure period is defined as first dose of either study drug to last dose of either study drug and will be summarized as a treatment regimen (rather than separately).

Descriptive statistics will be provided for the following:

- Number of doses
- Duration of therapy
- Cumulative dose
- Relative dose intensity (RDI)
  - Categories: < 50%; 50 - < 70%; 70 - < 90%; 90 - < 110%; ≥ 110%

Details for the calculations of these parameters are presented in Table 6 and Table 7.

Table 6: Study Therapy Parameter Definition for Part 1

Parameter	BMS-986277
Dosing Schedule per Protocol	**Cycle 1**: 2 week lead-in period followed by 4 week sequential dosing period **Cycles 2-6**: sequential dosing every 4 weeks
Duration of Therapy	**If only 1 dose is administered**: Duration of therapy (weeks) = 2 weeks **If more than 1 dose is administered**: Duration of therapy (weeks) = (last dose date - first dose date + 24) / 7 (Note: 24 days is the time between Day 19 and Day 43)
Dose	Dose (vp) is defined as total dose administered in vp/dose at each dosing date as collected on the CRF.
Cumulative Dose	Cum dose (vp) is sum of the doses (vp) administered to a participant.
Relative Dose Intensity	**If only 1 dose is administered**: RDI (%) = [cumulative dose (vp) / (planned* dose (vp)] x 100 **If more than 1 dose is administered**: RDI (%) = {cumulative dose (vp) / [(duration of therapy (weeks) x {planned* dose (vp) + 3 x number of cycles x planned* dose (vp)}) / (2 weeks + number of cycles x 4 weeks)]} x 100

*Planned dose is the assigned dose recorded on the CRF.

Table 7: Study Therapy Parameter Definition for Parts 2 and 3

Parameter	BMS-986277	Nivolumab
Dosing Schedule per Protocol	Sequential dosing on Days 1, 3, and 5 in a 28 day cycle for up to 3 cycles	480 mg on Day 15 in a 28 day cycle for up to 26 cycles
Duration of Therapy	Duration of therapy (weeks) = (last dose date of BMS-986277 - first dose date of BMS-986277 + 24) / 7 (Note: 24 days is the time between Day 5 and Day 29)	Duration of therapy (weeks) = (last dose date of nivolumab - first dose date of nivolumab + 28) / 7
Dose	Dose (vp) is defined as total dose administered in vp/dose at each dosing date as collected on the CRF.	Dose (mg) is defined as total dose administered in mg at each dosing date as collected on the CRF.
Cumulative Dose	Cum dose (vp) is sum of the doses (vp) administered to a participant.	Cum dose (mg) is sum of the doses (mg) administered to a participant.
Relative Dose Intensity	RDI (%) = {cumulative dose (vp) / [(duration of therapy (weeks) x 3 x number of cycles x planned* dose (vp)) / (number of cycles x 4 weeks)]} x 100	RDI (%) = {cumulative dose (mg) / [(duration of therapy (weeks) x number of cycles x 480 mg) / (number of cycles x 4 weeks)]} x 100

*Planned dose is the assigned dose recorded on the CRF.

Listing:

- Batch numbers
- Administration of study medication (including CRF records of study medication, infusion details, and dose changes)
- Derived parameters (number of doses, duration of therapy, cumulative dose, RDI)

8.4.2 Discontinuation of Study Therapy

Discontinuation of study therapy will be summarized separately for BMS-986277 and nivolumab and presented by dose level and biomarker level; tabulations by part, cohort, and indications may also be performed, as appropriate.

Summary:

- Number (%) of participants with discontinuation along with the reason(s)

Listing:

- Dose discontinuation and reason(s)

8.4.3 Interruption or Delay of Study Therapy

Modification of study therapy will be summarized separately for BMS-986277 and nivolumab and presented by dose level and biomarker level; tabulations by part, cohort, and indications may also be performed, as appropriate.

These modifications are as reported by investigators on the CRF. In the event that there is a modification with a missing reason, a category for "Unknown" will be included in the tabulations.

Summary:

- Number (%) of participants with dose delay, interruption and IV rate reduction along with the reason(s)
  - Number (%) of participants with at least one dose delay along with the reason(s)*
  - Number of dose delays per participant
  - Number (%) of participants with at least one interruption along with the reason(s)*
  - Number of interruptions per participant
  - Duration of interruption*
  - Number (%) of participants with at least one IV rate reduction along with the reason(s)*
  - Number of IV rate reductions per participant

*More than one reason or one interruption per participant may be counted in these statistics

Listing:

- All relevant information on dose modification listed above

8.4.4 Prior and Concomitant Therapy

Prior and concomitant medications will be coded using the World Health Organization (WHO) Drug Dictionary.

Concomitant medications are defined as medications other than study medications which are taken at any time on-treatment, either with a start date on or after the initiation of study therapy, or with a start date prior to initiation of study therapy and continuing during the study therapy.

Prior and concomitant therapies are presented by dose level, biomarker level, and overall; tabulations by part, cohort, and indication may also be performed, as appropriate.

Summary:

- Any prior therapy (radiotherapy, surgery, or systemic cancer therapy)
- Prior radiotherapy (Y/N) and site of radiotherapy
- Prior surgery (Y/N)
  - Ovarian: Debulking surgery outcome
- Prior standard of care medication therapy (Y/N)
- Prior platinum based medication therapy (Y/N)
- Prior systemic cancer therapy (Y/N)
  - Regimen number*
  - Setting of regimen*
  - Line of therapy*
  - Best response to regimen*

*More than one prior systemic cancer therapy may be counted in these frequencies

- Premedications and postmedications (Y/N)

- Prior and concomitant medications (including related AEs and for prophylactic vaccination) (Y/N)

Listing:

- All relevant information on prior and concomitant therapies listed above, along with dates/times, total daily dose, site of radiotherapy, type of surgery, and any other information collected on the CRFs
- Subsequent therapy (surgery, radiotherapy, systemic cancer therapy) that occurs after first dose of study drug

8.5 Efficacy

Efficacy analyses will be based on the endpoints defined in Sections 5.2.1, 5.3.1, and 5.3.2.

The primary efficacy analyses will be performed on the All Treated population for the final analysis. Efficacy analyses based on Response-evaluable and/or CD8 Biomarker Evaluable populations may be performed as supportive analyses, particularly if these populations differ substantially from the All Treated population. If the majority of the All Treated population is included in Response-evaluable and/or CD8 Biomarker Evaluable populations, limited efficacy analyses may be performed on those populations (eg, ORR). For interim analyses when the minimum follow-up period is less than sufficient to warrant adequate interpretation of the result, efficacy analyses may be performed on Response-evaluable Participants.

Time to event distributions (eg, PFS, OS, and DOR) will be estimated using Kaplan-Meier (K-M) techniques. When appropriate, the median along with 95% confidence interval (CI) will be estimated using the Brookmeyer and Crowley methodology[7] (using log-log transformation for constructing the CIs). Rates at fixed timepoints (eg, PFSR at 24 weeks or OSR at 12 months) will be derived from the K-M estimate and corresponding 95% CI will be derived based on the Greenwood formula using log-log transform[8]. Confidence intervals for binomial proportions will be derived using the Clopper-Pearson method[9].

If BICR data is available, certain analyses (eg, ORR) may be repeated using the BICR data and presented by the accepted record after adjudication, Radiologist 1, and Radiologist 2. To assess concordance between BICR and investigator assessments, BOR may be cross-tabulated for the All Treated population for the assessment type (Investigator vs. BICR). Concordance will be assessed using the Gamma statistic and/or the Kappa coefficient. The concordance rate of responders will be computed as the frequency with which Investigator and BICR agree on the classification of a participant as a responder/non-responder. The concordance rate of progressors may be assessed similarly.

Indications for which the primary efficacy analysis is being performed using RECIST 1.1 may also be analyzed using iRECIST, if data is available. Analyses for iRECIST endpoints will use the same statistical methods as the analyses for RECIST 1.1 endpoints.

Summary:

The following will be summarized by part, dose level, cohort, indication, biomarker level, and overall.

- The ORR and DCR with corresponding 2-sided 95% CI based on the Clopper-Pearson method, along with each category of BOR.
  - For interim analyses or internal monitoring of efficacy before the final BOR can be determined, this table may be repeated with unconfirmed responses.
- The DOR with median (95% CI) and range (min, max) by K-M method. The number of participants still in response at the time of database lock will be indicated. This summary includes responders (BOR of CR or PR) only.
  - For interim analyses or internal monitoring of efficacy before the final BOR can be determined, this table may be repeated with unconfirmed responses.
- The PFS and OS with median (95% CI) and range (min, max) by K-M method.
- The PFSR at specified timepoints (eg, Week 8, 16, or 24) by K-M method.
- The OSR (eg, Month 3, 6, 9, or 12) by K-M method. If the number of participants at risk is too small (eg, <5 due to high censoring), OSR will not be presented.
  - The minimum follow-up will be reported. The minimum follow-up is defined as the time interval between the last participant's first treatment date and the clinical cut-off date.
  - The currentness of follow-up, defined as the time between last OS contact (ie, last known alive date or death date) and data cut-off date, will be summarized by part, dose level, cohort, indication, biomarker level, and overall. Participants who died before the data cut-off date will automatically have zero value for currentness of follow-up. For participants with last known alive date after the data cut-off date, they will have zero value for currentness of follow-up as well. The currentness of follow-up will be categorized based on the actual available data and will be described in each deliverable's DPP. An example of the categories are: 0 days, 0-3 months, 3-6 months, 6-9 months, 9-12 months and ≥ 12 months.
  - The extent of follow-up defined as the time between first dose and last known alive date (for participants who are alive) or death date (for participants who died) will be summarized descriptively (median, min, max) for all treated participants.
- The iORR with corresponding 2-sided 95% CI based on Clopper-Pearson method along with frequencies of participants in each category of iBOR (CR/iCR, PR/iPR, SD/iSD, iUPD, iCPD, NE)
  - The categories may also be split into their respective subcategories
- The iDCR with corresponding 2-sided 95% CI based on Clopper-Pearson method
- The iDOR with median (95% CI) and range (min, max) by K-M method. The number of participants still in response at the time of database lock will be indicated. This summary includes responders (iBOR of CR, iCR, PR, or iPR) only
- The iPFS with median (95% CI) and range (min, max) by K-M method
- The iPFSR at specified timepoints (eg, Week 8, 16, or 24) by K-M method

Figure:

- Percent change from baseline in target lesions over time (ie, spider plot)

- Best Change in baseline target lesions (ie, waterfall plot)
- These will also include tumor assessments after the RECIST 1.1-defined progression.Swimmer plot of time to response, DOR, and time on therapy for responders only
- K-M plot of DOR for participants with BOR of CR or PR only
- K-M plot of iDOR for participants with iBOR of CR, iCR, PR, or iPR only
- K-M plot of PFS
- K-M plot of iPFS
- K-M plot of OS

Listing:

The following will be listed by using the listing convention described in Section 8.1, unless otherwise specified in the DPP. Some iRECIST data may be combined with the RECIST 1.1 listings.

- Tumor lesion measurements, including categorizations (new lesion - target or new lesion - non-target) and measurements for new lesions)
- Tumor evaluation at each visit, including non-target lesions and new lesions, tumor change from smallest sum of diameters in target lesions, corresponding change (or percent change) from baseline, a symbol denoting the index iUPD visit, and change from iUPD visit
- Participant level efficacy per RECIST 1.1/PCWG3 for all treated participants, including tumor best overall response (BOR), maximum response in tumor burden, PFS, death indicator
- For responders per RECIST 1.1/PCWG3: BOR, time on therapy, DOR, response duration after treatment discontinuation, reason for treatment discontinuation
- Participant level data for endpoint determination per iRECIST, including death date, iDOP, date of clinical progression, date of subsequent therapy, date of last evaluable scan prior to subsequent therapy, date of last evaluable scan, and the end date of the evaluable period
- Participant level efficacy per iRECIST for all treated participants, including tumor immune best overall response (iBOR), maximum response in tumor burden (including tumor assessments after the RECIST 1.1-defined progression), iPFS, death/censoring indicator
- For responders per iRECIST (iBOR of CR, iCR, PR, or iPR) - iBOR, time on therapy, iDOR, response duration after treatment discontinuation, response duration after index iUPD, reason for treatment discontinuation
- Survival - survival status, first dose date, last dose date, last known alive date, death date, time to death

8.5.1 Other Observations Related to Efficacy

Additional exploratory efficacy analysis may be performed if deemed appropriate by the study team, provided there is sufficient data. These will be detailed in the DPP. Examples include, but are not limited to:

- Summary measures and corresponding plots of indication-specific efficacy biomarkers such as:
  - PRC: absolute PSA and PSA doubling time

  - CRC: CEA
  - Ovarian: CA125
  - PC: CA19-9
- Efficacy by clinically meaningful disease characteristics such as prior therapy or mutation status

8.6 Safety

Analysis of safety will be based on the All Treated population and presented by part, dose level, and overall; tabulations by cohort, indication, and biomarker level may also be performed, as appropriate. Deaths and SAEs will be listed using the All Enrolled population. The treatment groups will be "as treated" as defined in Section 7.2.

Adverse events will be coded according to the most current version of MedDRA at the time of each database lock and the severity will be graded using the NCI CTCAE version 4.03. Treatment-related AEs are those events with relationship to study treatment "Related" as recorded on the CRF. If the relationship to study treatment is missing, the AE will be considered as treatment related.

Listing of AEs will include all enrolled participants, as SAEs and deaths are collected pretreatment. Summaries of AEs will include (1) events occurring from the first dose date to 30 or 100 days (inclusive) after the last dose of either study treatment for Part 1 or Parts 2-3, respectively, for participants who are off study treatment and (2) all events occurring from first dose date for participants who are still on study medication.

Unless otherwise specified, the AE summary tables will be restricted to on-treatment events regardless of the causality. AEs and treatment-related AEs will be tabulated by descending frequency of system organ class (SOC) and descending frequency of preferred term (PT) within each SOC, unless otherwise specified. When reporting AEs by CTC grade, summary tables will be provided based on the event with the worst CTC grade (independent of relationship to study medication). 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.

The analysis of laboratory results will be based on the All Treated population with available data. Laboratory results will be categorized according to NCI CTCAE version 4.03 grade. Baseline is defined in Section 7.1.1. Summaries of laboratory results include baseline and (1) post-baseline results up to 100 days (inclusive) after the last dose of either study treatment for participants who are off study treatment and (2) all available post-baseline results for participants who are still on study medication.

8.6.1 Dose Limiting Toxicities

Participants with DLTs as captured on the CRF, including AEs meeting the protocol-defined DLT criteria outside the DLT window will be tabulated using frequency statistics by part and dose level using the All Treated population "as assigned" and "as treated". A listing of DLTs will be provided.

8.6.2 Deaths

All deaths during the study within 100 days after the last dose of either study treatment will be summarized for cause of death. All recorded deaths for the All Enrolled population will be listed.

8.6.3 Other Serious Adverse Events

Overall summary of SAEs and treatment-related SAEs by worst CTC grade will be presented by SOC/PT. An SAE listing will be provided for the All Enrolled population.

8.6.4 Adverse Events Leading to Discontinuation of Study Therapy

AEs leading to study treatment discontinuation are AEs with action taken = "Drug Withdrawn". Overall summary of AEs leading to discontinuation and treatment-related AEs leading to discontinuation by worst CTC grade will be presented by SOC/PT. An AEs leading to discontinuation listing will be provided.

8.6.5 Adverse Events Leading to Dose Modification

AEs leading to dose delay and drug interruption will be summarized. Listings for AEs leading to dose delay and drug interruption will be provided.

8.6.6 Overall Adverse Events

Overall summary of any AEs and treatment-related AEs by worst CTC grade will be presented by SOC/PT. All recorded AEs occurring in the pre-treatment, on-treatment, and post-treatment period will be listed.

8.6.7 Select Adverse Events

The select AEs consist of a list of PTs grouped by specific categories (eg, pulmonary events, gastrointestinal events, etc.). Categories of select AEs may include subcategories (eg, adrenal disorders, diabetes, pituitary disorders, and thyroid disorders are subcategories of the endocrine event category).

- For BMS-986277, custom Standard MedDRA Queries (cSMQs) for AE categories and PTs within categories may be defined based on a priori knowledge, new or evolving knowledge from this study, from similar studies (eg, SPICE), and evolving knowledge about oncolytic viruses in general. For Part 1, the BMS-986277, this list, if exists, will be used.
- For nivolumab, AEs that may differ from or are more severe than AEs caused by non-immunotherapies and AEs whose early recognition and management may mitigate severe toxicity are included as select AEs. For Parts 2 and 3, the cSMQs for BMS-986277 will be merged with the nivolumab dictionary.

These select AE lists and the categories are defined by the Sponsor and the lists that is the most current at the time of analysis will be used. Changes may be made to these lists with each new version of MedDRA prior to database lock. The lists that are most current at the time of analysis will be used and included as a listing in each deliverable with select AE analysis.

Overall summary of any select AEs, treatment-related select AEs, serious select AEs, treatment-related serious select AEs, select AEs leading to discontinuation, treatment-related select AEs

leading to discontinuation, by worst CTC grade will be presented by category or subcategory/PT. Select AE definition and an event-level select AE listing will also be provided.

8.6.8 Exposure-Adjusted Adverse Events

Analyses that take into account the multiple occurrences of a given AE will be conducted. In order to prepare these analyses, the CRF data will be processed according to standard BMS algorithms[10] in order to collapse AE records into unique records based on the PT. This data will be presented as the rate per 100 patient-years. These analyses will take into account all on-treatment events (allowing more than 1 event per participant) and the total duration of AE follow-up that is based on exposure to the study medication(s), defined as the first dose of either study treatment to last dose of either study treatment. The patient-years will be computed as the sum over the participants' follow-up expressed in years and is defined as:

- Date of last dose of either study treatment - date of first dose of study treatment + 100 + 1 days, for participants who are off study treatment and were followed for at least 100 days after the last dose of either study treatment.
- Last known alive date - date of first dose of study medication +1, for participants who are still on treatment or who are off study treatment and were followed less than 100 days after the last dose of either study treatment.

When specified the 95% CI of the rate per 100 person-year of exposure will be derived using normal approximation and variance estimation proposed in Cook and Lawless[11].

Summary:

The following summary tables will be provided:

- Total number and rate (exposure adjusted, ie, patient-year event rate) of occurrences for all AEs
- For select AEs
  - The number of participants experiencing an AE once or multiple times by part and dose level

Listing:

- Unique instances of all AEs, ie, after duplicates have been eliminated and overlapping and contiguous occurrences of the same event (ie, same PT) have been collapsed.

8.6.9 Immune-Mediated Adverse Events

In order to further characterize AEs of special clinical interest, analysis of immune-mediated AEs (IMAEs) will be conducted. Immune-mediated AEs are specific events (or groups of PTs describing specific events) that include pneumonitis, diarrhea/colitis, hepatitis, nephritis/renal dysfunction, rash, endocrine (adrenal insufficiency, hypothyroidism/thyroiditis, hyperthyroidism, diabetes mellitus, and hypophysitis), and other specific events, considered as potential immune-mediated events by investigator, that meet the definition summarized below:

- those occurring within 30 or 100 days of the last dose for Part 1 or Parts 2-3, respectively,
- regardless of causality,

- treated with immune-modulating medication (of note, endocrine adverse events such as adrenal insufficiency, hypothyroidism/thyroiditis, hyperthyroidism, diabetes mellitus, and hypophysitis are considered IMAEs regardless of immune-modulating medication use, since endocrine drug reactions are often managed without immune-modulating medication).
- with no clear alternate etiology based on investigator assessment, or with an immune-mediated component

The list of MedDRA preferred terms used to identify Immune-Mediated adverse events is revisited quarterly and updated accordingly. The preferred terms used for the selection at the time of the database lock by categories will be provided. IMAEs will be summarized for Parts 2 and 3 only for each immune mediated category/PT. A by-participant listing of IMAEs will be provided. A listing of AEs considered as Immune-Mediated Events per Investigator as recorded on the CRF but not Qualified for Immune-Mediated AE Definition will also be provided.

8.6.10 Clinical Laboratory Evaluations

Clinical laboratory data will be first analyzed using International System of Units (SI). Analyses will be repeated using US conventional units. In addition, further analyses on specific laboratory parameters will be performed as described in Sections 8.6.10.1 and 8.6.10.2. The analysis population for each laboratory test is restricted to treated participants who underwent that laboratory test.

Summary:

The number (%) of participants with the following will be summarized using the worst CTC grade on-treatment per participant.

- Post-baseline grade
- Shift table of worst on-study CTC grade compared to baseline CTC grade (grade change from baseline)

Listing:

A by-participant listing of these laboratory parameters will be provided. Laboratory abnormality criteria and laboratory results outside of normal range will be listed. Differences between the SI and US grades will also be provided.

8.6.10.1 Abnormal Hepatic Test

Summary:

The number of participants with the following laboratory abnormalities from on-treatment evaluations will be summarized:

- ALT or AST > 3 x ULN, > 5 x ULN, > 10 x ULN and > 20 x ULN
- Total bilirubin > 2 x ULN
- Concurrent (within 1 day) ALT or AST > 3 x ULN and total bilirubin > 2 x ULN
- Concurrent (within 30 days) ALT or AST > 3 x ULN and total bilirubin > 2 x ULN

Figure:

- Scatter plot of Total bilirubin peak vs AST peak
- Scatter plot of Total bilirubin peak vs ALT peak

On-treatment peak total bilirubin and on-treatment peak AST/ALT may or may not happen on the same day of liver testing.

Listing:

A by-participant listing of these specific abnormalities will be provided.

8.6.10.2 Abnormal Thyroid Test

Summary:

The number of participants with the following laboratory abnormalities from on-treatment evaluations will be summarized by part, dose level, and overall:

- Elevated TSH value > ULN and
  - with baseline TSH value ≤ ULN
  - with at least one FT3/FT4 test value < LLN within 2-week window after the abnormal TSH test
  - with all FT3/FT4 test values ≥ LLN within 2-week window after the abnormal TSH test
  - with F3/F4 missing within 2-week window after the abnormal TSH test
- Low TSH < LLN and
  - with baseline TSH value ≥ LLN
  - with at least one FT3/FT4 test value > ULN within 2-week window after the abnormal TSH test
  - with all FT3/FT4 test values ≤ ULN within 2-week window after the abnormal TSH test
  - with F3/F4 missing within 2-week window after the abnormal TSH test

Listing:

A by participant listing of these specific abnormalities will be provided.

8.6.11 Vital Signs and Physical Findings

Listing:

- Abnormal findings from the physical exam (long form)
- Vital signs
- Height, body weight, BMI, and ECOG performance status
- Pulse oximetry
- All 12-Lead ECG results
- ECG abnormalities
- Pregnancy testing

8.6.12 Other Observations Related to Safety

Summary:

- Summary statistics of blood creatinine
- Frequency statistics of renal function
- Frequency statistics of bladder hemorrhage
- Frequency statistics of cytokine release syndrome

Listing:

- Other adverse events of special interest (AEOSI) consist of a list of PTs grouped by specific category (eg, Guillain-Barre Syndrome, etc.). These are rare events so this analysis will only be performed for the CSR or final analysis, whichever occurs first, unless emerging data suggests otherwise. The dictionary for nivolumab which is most current at the time of analysis will be used and additional categories may be added if deemed relevant for BMS-986277. The dictionary list will along with an event-level listing will be provided.
- Cytokine release monitoring data will be listed by part, dose level, participant ID, and date/time, subject to data availability.
- Diagnostic/Medical procedures

8.7 Pharmacokinetic Analyses

All available blood/serum concentration-time data from participants who receive BMS-986277 and/or nivolumab will be reported by part, dose level, and treatment for BMS-986277 and nivolumab, separately. All available derived PK parameter values described in Sections 5.2.2 and 5.3.3 will be included in the PK dataset and reported for the Pharmacokinetic population for BMS-986277 and Pharmacokinetic population for nivolumab, respectively. Only participants with adequate PK profiles will be included in summary statistics and statistical analysis.

8.7.1 Pharmacokinetic Concentrations

Summary:

Summary statistics will be provided for blood/serum concentrations for each treatment by part, dose level, and nominal collection time.

- Blood concentrations of BMS-986277
- Serum concentrations of nivolumab

Summary statistics will also be tabulated for trough concentrations by study day, for each analyte.

Figure:

Plots of individual concentration profiles over time as separate plots for each participant and altogether in one figure will be provided. Plots of mean (and standard deviation) concentration profiles versus time will be presented by part and dose level, with different graphical annotations for each study treatment on the same plot.

Listing:

- BMS-986277 blood concentrations
- Nivolumab serum concentrations

8.7.2 Pharmacokinetic Parameters

Summary:

Summary statistics for all parameters described in Sections 5.2.2 and 5.3.3 will be tabulated for BMS-986277 and nivolumab, separately by part and dose level, where data is available.

Geometric means and coefficients of variation will be presented for Cmax, AUC(0-T), AUC(0-8), AUC(0-48), AUC(INF), CLT, Vss, Vz, C48, Css-avg, AI_AUC, AI_Cmax, and Ctrough. Medians and ranges will be presented for Tmax. Means and standard deviations will be presented for T-HALF and T-HALFeff.

Figure:

- For Cmax, AUC(0-T), AUC(INF), AUC(0-8), AUC(0-48), scatter plots vs dose for each cycle measured; dose proportionality based on a power model and a CI around the power coefficient
- To evaluate the steady state of BMS-986277 concentration in the body, the geometric mean of Ctrough vs. cycle will be plotted by part and dose level with individual participant measurements superimposed on the plots.
- If there are at least 5 participants in an indication and if dose proportionality has been established, then the dose normalized Ctrough values may be presented graphically by indication in order to explore a potential effect of tumor on BMS-986277 pharmacokinetics.

Listing:

- All individual PK parameters will be listed including any data points excluded from analysis.

Statistical Analysis of Dose Proportionality in Monotherapy Dose Escalation

To assess the dose proportionality, the power model described by Gough et al[12].

PK Parameter = A*Doseβ

will be estimated by the simple linear regression of the natural log of the PK Parameters Cmax, AUC(0-T), and AUC(INF) of BMS-986277 in blood on the natural log of Dose:

E[log(PK Parameter)| Dose] = α + β*log(Dose).

A slope (β) equal to 1 would indicate perfect dose proportionality. For each PK parameter (Cmax, AUC(0-T), and AUC(INF)), the point estimates and 90% CI of the slopes will be provided.

As this study is neither optimally designed nor powered to confirm the presence or absence of meaningful departures from dose proportionality, these results should be interpreted with caution. Plots of individual BMS-986277 PK parameter (Cmax, AUC(0-T), and AUC(INF)) values versus dose with fitted regression line on a log-log scale will be presented.

[redacted]

[redacted]

8.8 Immunogenicity

To evaluate the incidence of ADA, the following analyses will be performed.

Summary:

The number (%) of participants with the following ADA responses will be reported by part, dose level, and overall based on the Immunogenicity population for each treatment.

- Baseline ADA-positive
- ADA-positive
  - Persistent Positive (PP)
  - Not PP - Last Sample Positive
  - Other Positive
- ADA-negative

Listing:

- All collected immunogenicity data will be listed with flags indicating baseline-positive sample, ADA-positive sample or ADA-negative sample.

[redacted]

[redacted]

9 CONVENTIONS

9.1 General Conventions

- All statistical analyses will be carried out using SAS (Statistical Analysis System software, SAS Institute, North Carolina, USA) unless otherwise noted.
- In general, the BMS Global Standard time windowing, imputation rules, and counting rules will be applied.
- The following conversion factors will be used to convert days to months or years.
  - 1 month = 30.4375 days
  - 1 year = 365.25 days
- Duration (eg, duration of response) will be calculated as follows:
  - Duration = (Last date - first date + 1)
- Last known date alive will be defined based on all appropriate dates collected on the CRF.
- Safety data will be handled according to the BMS safety data conventions[13]. This document includes descriptions on how to analyze AE data as well as how to handle partial dates, missing dates, and unknown end dates when analyzing safety data.

9.2 Multiple Measurements

Adverse Events

The algorithm for collapsing adverse event records is using the following conventions:

For each participant and specified category, the corresponding adverse event records will be collapsed when:

- Multiple adverse event records have the same onset date.
- The onset date of an event record is either the same day or 1 day later than the resolution date of a preceding event record (contiguous events).
- The onset date of an event record is after the onset date and prior to or on the resolution date of a preceding event record (overlapping events).

Laboratory Measures

For tabulations of changes from baseline the following will be used, in a hierarchical sequence, to select the post-treatment measurement included in the analysis (if a criterion does not apply it would be skipped in the sequence):

- If multiple laboratory measurements are obtained within the same scheduled time frame, then the measurement obtained on the time closest to the target time/day will be used;
- If more than one value meets the above criterion, then the measurement obtained on the earlier time will be used;
- For tabulations by CTC grade and summarized by worst toxicity grade, if multiple laboratory measurements are obtained within a analysis period (post-baseline), then the worst measurement within the analysis period, respectively, will be used.

Vital Signs

The following criteria will be used, in a hierarchical sequence, to select the post-treatment measurement included in the analysis:

- If multiple vital sign measurements are obtained within the same scheduled time frame, then the measurement obtained on the time closest to the target time/day will be used;
- If more than one value meets the above criterion, then the measurement obtained on the earlier time will be used;
- If more than one value meets the above criterion, then the average value will be used.

9.3 Partial Dates

The following conventions may be used for imputing partial dates for analyses requiring dates:

- For missing and partial **adverse event onset dates**, imputation will be performed using the Adverse Event Domain Requirements Specification[14]
- For missing and partial **adverse event resolution dates**, imputation will be performed as follows (these conventions may change):
  - If only the day of the month is missing, the last day of the month will be used to replace the missing day
  - If the day and month are missing or a date is completely missing, it will be considered as missing.
  - In case of the date of death is present and complete, the imputed AE resolution date will be compared to the date of death. The minimum of the imputed AE resolution date and date of death will be considered as the date of AE resolution.

- Missing and partial **non-study medication domain dates** will be imputed using the derivation algorithm described in 4.3.3 of BMS Non-Study Medication Domain Requirements Specification[15]
- For **death dates**, the following conventions will be used for imputing partial dates:
  - If only the day of the month is missing, the 1st of the month will be used to replace the missing day. The imputed date will be compared to the last known date alive and the maximum will be considered as the death date.
  - If the month or the year is missing, the death date will be imputed as the last known date alive.
  - If the date is completely missing but the reason for death is non-missing, the death date will be imputed as the last known date alive
- For **date of progression**, the following conventions will be used for imputing partial dates:
  - If only the day of the month is missing, the 1st of the month will be used to replace the missing day.
  - If the day and month are missing or a date is completely missing, it will be considered as missing.
  - In case of the date of death is present and complete, the imputed progression date will be compared to the date of death. The minimum of the imputed progression date and date of death will be considered as the date of progression.
- For **other partial/missing dates**, the following conventions may be used:
  - If only the day of the month is missing, the 15th of the month will be used to replace the missing day.
  - If both the day and the month are missing, "July 1" will be used to replace the missing information.
  - If a date is completely missing, it will be considered as missing.

9.4 Pharmacokinetic Summaries

In-text Tables

For in-text pharmacokinetic tables, coefficient of variation (%CV) will be reported as integers. For other statistics except for standard deviations, values of 100 or higher will be presented as integers, values of 10 - <100 will be displayed to one decimal place, and values of 1 - < 10 will be displayed to two decimal places. Values less than 1 will be displayed to three decimal places. Ratios will also be displayed to three decimal places. Standard deviations will be reported to a precision of 1 decimal place more than the mean.

Handling of Non-Quantifiable Concentrations

For the summaries of concentration-time data, concentrations that are less than the lower limit of quantification (LLOQ) should be displayed as "< LLOQ" in the listings and be treated as missing in summary tables and plots. For the purpose of calculating PK parameters, other than Ctrough, pre-dose concentrations that are less than LLOQ and concentrations prior to the first quantifiable

concentration that are less than LLOQ will be set to zero, and all other concentrations less than LLOQ will be set to missing.

Summary statistics for Ctrough concentrations will be calculated by imputing values less than LLOQ as ½ * LLOQ. This imputation is done for Ctrough concentrations because it is treated like a PK parameter; the imputation is not done for Day 1 pre-dose concentrations. Individual Ctrough listings will display these concentrations as "< LLOQ."

All available concentration-time data and derived pharmacokinetic parameter values will be included in the PK data set and listed accordingly.

10 CONTENT OF REPORTS

The complete list of analyses contributing to the clinical study report and other interim analyses will be given in the Data Presentation Plan.