Official Title of Study:

A Phase 1/2a Study of BMS-986178 Administered Alone or in Combination with Nivolumab and/or Ipilimumab in Subjects with Advanced Solid Tumors

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# STATISTICAL ANALYSIS PLAN
# FOR CLINICAL STUDY REPORT

## A PHASE 1/2A STUDY OF BMS-986178 ADMINISTERED ALONE OR IN COMBINATION WITH NIVOLUMAB AND/OR IPILIMUMAB IN SUBJECTS WITH ADVANCED SOLID TUMORS

**PROTOCOL(S) CA012004**

**VERSION # 2.0**

## REVISION HISTORY

| Revision | Date | Revised By | Changes Made -- Reasons for the Change |
|---|---|---|---|
| 1.0 | 08/08/2017 | [redacted] | Original issue |
| 2.0 | 15/06/2018 | [redacted] | Addition of Part 8 |

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[redacted]

## 2 STUDY DESCRIPTION

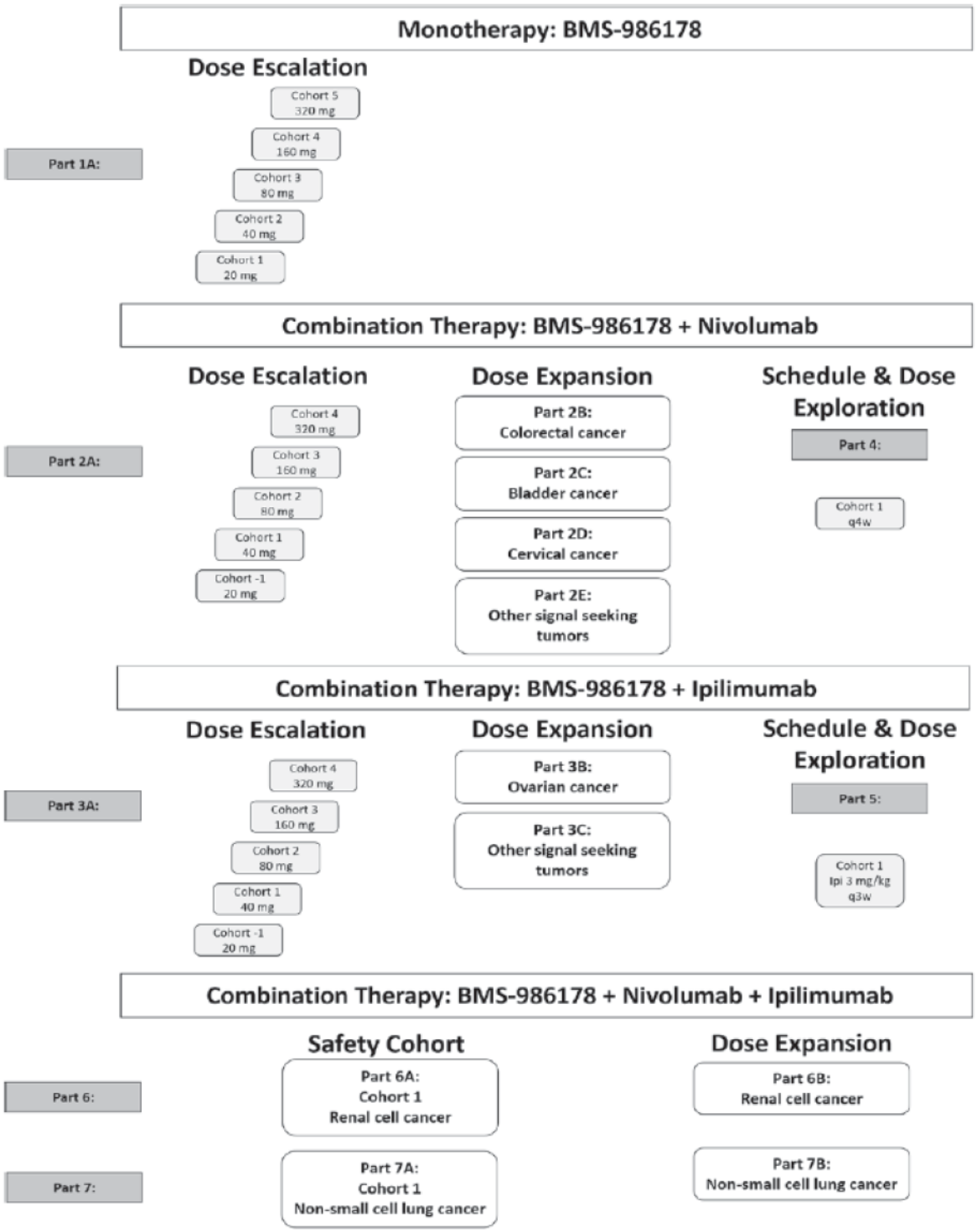
### 2.1 Study Design

This is a Phase 1/2a, open-label study of BMS-986178 in subjects with advanced solid tumors that integrates initial BMS-986178 monotherapy with subsequent nivolumab and/or ipilimumab combination therapy. Study sections (dose escalation and dose expansion) will proceed in a phased approach that is based upon study-emergent safety, PK, and PD data. The first section of the study will begin with BMS-986178 monotherapy dose escalation cohorts. The clinical data from the first 3 monotherapy dose cohorts will serve as a foundation for initiating dose escalation of BMS 986178 in combination with nivolumab. The clinical data from the first 3 monotherapy dose cohorts in addition to the clinical data from the first cohort of BMS-986178 in combination with nivolumab will then serve as a foundation for initiating dose escalation of BMS-986178 in combination with ipilimumab. The clinical data for BMS-986178 in combination with nivolumab and BMS-986178 in combination with ipilimumab will serve as the foundation for initiating combination therapy of BMS-986178 with nivolumab and ipilimumab in Parts 6 and 7. After

establishment of a tolerable and pharmacologically active MTD/RP2D of BMS-986178 in the dose escalation schedule and dose exploration sections, and dose expansion in specific tumor cohorts will be initiated.

The study design schematic is presented in Figure 2.1-1 and Figure 2.1-2.

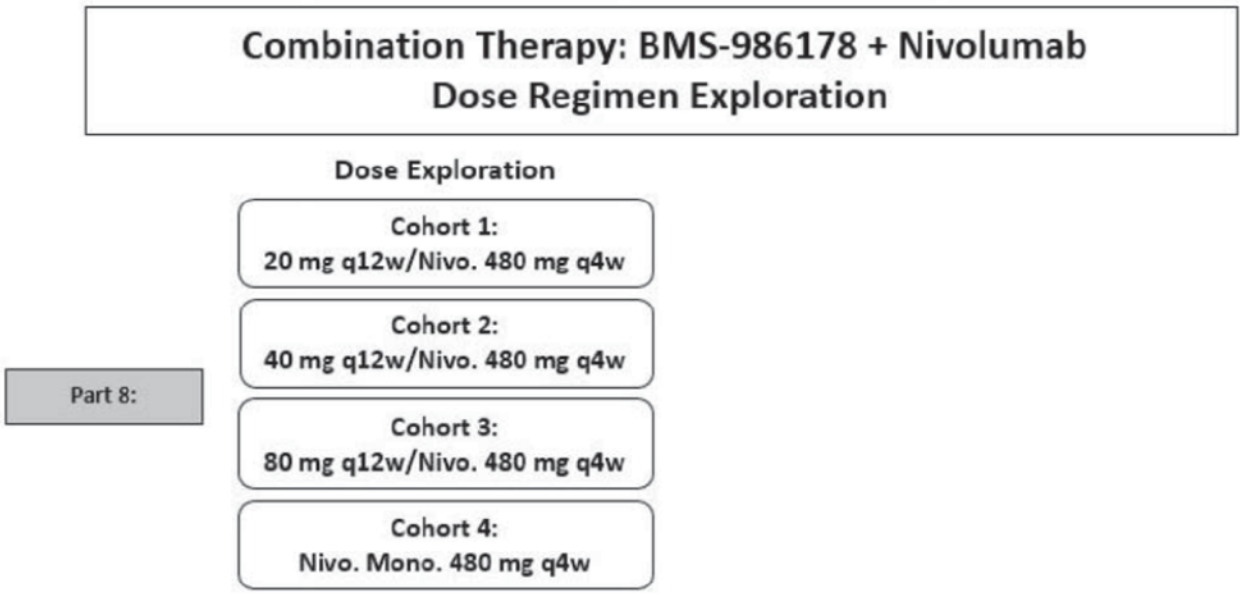
**Figure 2.1-1: Study Design Schematic (Parts 1 to 7)**




Dose levels are specific for each part. Dose expansion will begin only after MTD/RP2D determination in the corresponding dose escalation phases of the study.

Abbreviations: MTD = maximum tolerated dose; RP2D = recommended phase 2 dose.

**Figure 2.1-2: Study Design Schematic (Parts 8)**




### *2.1.1 Dose Escalation (Part 1A, 2A and 3A)*

The dose escalation part of the study will evaluate the safety and tolerability of BMS-986178 alone or in combination with nivolumab or ipilimumab, in subjects with advanced solid tumors.

The initial dose level of BMS-986178 planned for this study is 20 mg. Dose escalation decisions for subsequent doses will be based on DLTs (dose-limiting toxicities) using a Bayesian Logistic Regression Method (BLRM; for BMS-986178 monotherapy) or a BLRM (-Copula) model (for BMS-986178 in combination with nivolumab and/or ipilimumab). The DLT period is 28 days for both monotherapy and combination therapy dose escalation parts. The DLT rate will be determined based on the incidence, severity, and duration of AEs that occur within the DLT period and for which no alternative cause can be identified. Dose selection for the next monotherapy cohort/dose level will take into account the BLRM (-Copula) recommendation (Protocol Section 3.1.2.4) in conjunction with the clinical recommendation and all available PK, PD, immunogenecity, and clinical and laboratory safety data from all treated subjects. Starting dose selection of BMS-986178 for Part 2A will be determined using data available from Part 1A, including clinical and laboratory safety assessments, PK/PD data, immunogenecity data, and modeling recommendation within Bayesian modeling framework by incorporating single-agent toxicity profiles of both BMS-986178 (Part 1A) and nivolumab (CA209-003). Starting dose selection of BMS-986178 for Part 3A will be determined using data available from Parts 1A and 2A, including clinical and laboratory safety assessments, PK/PD data, immunogenecity data, and modeling recommendation within Bayesian modeling framework by incorporating single-agent toxicity profiles of both BMS-986178 (Part 1A) and ipilimumab (CA184-022). The final dose escalation decision will be made after discussion and agreement between the investigators and the BMS Medical Monitor. Actual doses can be modified per the BLRM (-Copula) but will not exceed doubling of the previously tested doses. Escalation by more than 1 dose level (dose skipping) is not permitted. In Parts 2A

and 3A doses intermediate to previously tested doses, or doses lower than the starting dose may be explored to further characterize the dose response for safety, immunogenecity, PK, or PD as appropriate based on clinical data collected.

Approximately 30 subjects will be enrolled in each dose escalation part. The number of subjects in each dose escalation cohort may vary depending on the BLRM (-Copula) recommendations. Initially, approximately 3 subjects will be treated at the starting dose levels of BMS-986178 or BMS-986178 in combination with nivolumab or ipilimumab. Additional cohorts of approximately 3 evaluable subjects will be treated at recommended dose levels per BLRM (-Copula) during the dose escalation phase. At least 6 DLT-evaluable subjects will be treated at the MTD.

#### 2.1.1.1 Part 1A: Monotherapy Dose Escalation

Part 1A is BMS-986178 monotherapy dose escalation. The initial dose of BMS-986178 for Part 1A will be 20 mg with expected subsequent doses of 40, 80, 160, and 320 mg. Dosing of BMS-986178 will begin on Day 1 of each cycle and will be administered q2w for up to 12 cycles.

#### 2.1.1.2 Part 2A: Combination With Nivolumab Dose Escalation

Part 2A is the combination arm of BMS-986178 with nivolumab that will be initiated only after at least 3 dose levels in the monotherapy dose escalation have been found to be tolerated or an MTD/RP2D has been determined in the monotherapy dose escalation (Part 1A). The starting dose of BMS-986178 in Part 2A will be at least 1 dose level below a dose that was demonstrated to be tolerated in Part 1A to ensure further safety of the combination. At no time will the dose for BMS-986178 in Part 2A exceed the highest tolerated dose in Part 1A. Nivolumab will be administered at a flat dose of 240 mg. Each treatment cycle will be 2 weeks in length and study drugs will be administered q2w starting on Day 1 of each cycle for up to 12 cycles.

#### 2.1.1.3 Part 3A: Combination With Ipilimumab Dose Escalation

Part 3A is the combination arm of BMS-986178 with ipilimumab that will be initiated only after at least 3 dose levels in the monotherapy dose escalation have been found to be tolerated or an MTD/RP2D has been determined in the monotherapy dose escalation (Part 1A) and at least 1 dose cohort has been found to be tolerated in the BMS-986178 with nivolumab dose escalation part (Part 2A). The starting dose of BMS-986178 in Part 3A will be at least 1 dose level below a dose that was demonstrated to be tolerated in Part 1A. At no time will the dose for BMS-986178 in Part 3A exceed the highest tolerated dose in Part 1A to further ensure safety of the combination doses in treated subjects. Ipilimumab will be administered at a dose of 1 mg/kg. Each treatment cycle will be 3 weeks in length. BMS-986178 will be administered q3w starting on Cycle 1 Day 1, up to and including 8 cycles, and ipilimumab will be administered q3w starting on Day 1 for 4 cycles. Only BMS-986178 will be administered in the last 4 cycles.

### 2.1.2 Schedule and Dose Exploration (Parts 4, 5 and 8)

#### 2.1.2.1 Part 4: Combination With Nivolumab on a 4-week Schedule

Part 4 is the combination arm of BMS-986178 with nivolumab (480 mg) to be administered q4w. The dose of BMS-986178 will be a dose previously evaluated in Part 2A that has been found to have a manageable safety profile. If the starting dose of BMS-986178 is not tolerated or to further characterize the dose response for safety, PK, or PD as appropriate based on clinical data collected, a dose(s) lower or higher than the previously administered dose in this part may be explored. To further ensure safety of the combination, at no time will the dose for BMS-986178 in Part 4 exceed the highest tolerated dose in Part 2A, in which q2w dosing is explored. Approximately 6 to 12 subjects will be treated in this schedule and dose exploration cohort.

#### 2.1.2.2 Part 5: Combination With Ipilimumab at 3 mg/kg

Part 5 is the combination arm of BMS-986178 with ipilimumab 3 mg/kg q3w for 4 doses, followed by monotherapy with BMS-986178 (maintenance therapy). The dose of BMS-986178 will be a dose previously evaluated in Part 3A that has been found to have a manageable safety profile. If the starting dose of BMS-986178 is not tolerated or to further characterize the dose response for safety, PK, or PD as appropriate based on clinical data collected, a dose(s) lower or higher than the previously administered dose in this part may be explored. To further ensure safety of the combination, at no time will the dose for BMS-986178 in Part 5 exceed the highest tolerated dose in Part 3A. Approximately 6 to 12 subjects will be treated in this schedule and dose exploration cohort.

#### 2.1.2.3 Part 8: Dose Regimen Exploration of Combination With Nivolumab in Bladder Cancer

Part 8 is a dose regimen exploration of BMS-986178 in combination with nivolumab or nivolumab monotherapy. Nivolumab will be administered at a flat dose of 480 mg to be administered every 4 weeks.

Approximately 20 evaluable subjects per cohort will be treated in Part 8.

**Part 8 Cohort 1-3:** BMS-986178 will be administered as a flat dose of either 20 mg, 40 mg, or 80 mg q12w in combination with nivolumab flat dose (480 mg; q4w). Each treatment cycle will be 12 weeks in length starting on Day 1 of each cycle. There will be up to 9 cycles, to allow for 24 months of treatment. A tetanus vaccine (Tdap preferred, Td or equivalent after discussion with the medical monitor) will be administered first on Cycle 1 Day 1 prior to administration of nivolumab and BMS-986178.

**Part 8 Cohort 4:** Nivolumab monotherapy will be administered as a flat dose of 480 mg (q4w). Each treatment cycle will be 12 weeks in length and will be dosed for up to 9 cycles, 24 months of dosing. Treatment will be given on Day 1, Day 29 and 57 of each cycle. A tetanus vaccine (Tdap preferred, Td or equivalent after discussion with the medical monitor) will be administered first on Cycle 1 Day 1 prior to administration of nivolumab monotherapy.

### 2.1.3 Safety Cohorts (Parts 6A and 7A)

#### 2.1.3.1 Part 6A:Combination With Nivolumab and Ipilimumab in RCC

Part 6A is the safety cohort for the combination of BMS-986178 with ipilimumab and nivolumab in subjects with RCC. BMS-986178 will be administered at a flat dose of 40 mg in combination with nivolumab (240 mg) and ipilimumab (1 mg/kg) q3w during Cycles 1 to 4, followed by maintenance therapy (Cycle 5 and beyond) in which BMS-986178 (40 mg) and nivolumab (480 mg) will be administered q4w. Study drugs will be administered accordingly starting on Day 1 of each cycle. If the starting dose of BMS-986178 is not tolerated or to further characterize the dose response for safety, PK, or PD as appropriate based on clinical data collected, a dose(s) lower than the previously administered dose in this part may be explored. Approximately 6 to 12 subjects will be treated in this safety cohort.

#### 2.1.3.2 Part 7A: Combination With Nivolumab and Ipilimumab in NSCLC

Part 7A is the safety cohort for the combination of BMS-986178 with ipilimumab and nivolumab in subjects with NSCLC. BMS-986178 will be administered at a flat dose of 40 mg (q2w) in combination with nivolumab (240 mg; q2w) and ipilimumab (1 mg/kg; q6w) for four 6-week cycles. Study drugs will be administered accordingly starting on Day 1 of each cycle. If the starting dose of BMS-986178 is not tolerated or to further characterize the dose response for safety, PK, or PD as appropriate based on clinical data collected, a dose(s) lower than the previously administered dose in this part may be explored. Approximately 6 to 12 subjects will be treated in this safety cohort.

### 2.1.4 Dose Expansion Parts (Parts 2B, 2C, 2D, 2E, 3B, 3C, 6B and 7B)

Treatment in the dose expansion cohorts will be initiated when the MTD/RP2D(s) has been determined based on the evaluation of totality of available clinical safety (DLTs, AEs occurring after the DLT period), immunogenecity, PK, PD, and modeling data from the dose escalation parts (1A, 2A, and 3A) or schedule and dose exploration parts (4 and 5). Mandatory pre- and on-treatment biopsies of tumor will be obtained for all study subjects.

#### 2.1.4.1 Part 2B: Combination With Nivolumab Dose Expansion in Colorectal Cancer

Part 2B is the combination therapy (BMS-986178 with nivolumab) dose expansion part in subjects with CRC at the MTD/RP2D(s) determined in Parts 2A or 4. Nivolumab will be administered at a flat dose of 240 or 480 mg. Each treatment cycle will be either 2 (240 mg) or 4 (480 mg) weeks in length and study drugs will be administered every 2 or 4 weeks starting on Day 1 of each cycle for up to 12 or 6 cycles, respectively. Approximately 35 subjects will be treated in this expansion cohort.

#### 2.1.4.2 Part 2C: Combination With Nivolumab Dose Expansion in Bladder Cancer

Part 2C is the combination therapy (BMS-986178 with nivolumab) dose expansion part in subjects with BC at the MTD/RP2D(s) determined in Parts 2A or 4. Nivolumab will be administered at a flat dose of 240 or 480 mg. Each treatment cycle will be either 2 (240 mg) or 4 (480 mg) weeks in length and study drugs will be administered every 2 or 4 weeks starting on Day 1 of each cycle for

up to 12 or 6 cycles, respectively. Approximately 27 subjects will be treated in this expansion cohort.

#### 2.1.4.3 Part 2D: Combination With Nivolumab Dose Expansion in Cancer of the Cervix

Part 2D is the combination therapy (BMS-986178 with nivolumab) dose expansion part in subjects with cervical cancer at the MTD/RP2D(s) determined in Parts 2A or 4. Nivolumab will be administered at a flat dose of 240 or 480 mg. Each treatment cycle will be ether 2 (240 mg) or 4 (480 mg) weeks in length and study drugs will be administered every 2 or 4 weeks starting on Day 1 of each cycle for up to 12 or 6 cycles, respectively. Approximately 37 subjects will be treated in this expansion cohort.

#### 2.1.4.4 Part 2E: Combination With Nivolumab Dose Expansion in Other Tumors for Signal Finding

Part 2E is the combination therapy (BMS-986178 with nivolumab) dose expansion part at the MTD/RP2D(s) determined in Part 2A or 4. Nivolumab will be administered at a flat dose of 240 or 480 mg. Each treatment cycle will be either 2 (240 mg) or 4 (480 mg) weeks in length and study drugs will be administered every 2 or 4 weeks starting on Day 1 of each cycle for up to 12 or 6 cycles, respectively. Approximately 40 subjects will be treated in this expansion cohort.

Tumor types for this cohort will be selected by Sponsor from those permitted in dose escalation which do not have a dedicated expansion cohort or plans for evaluation in other studies and those tumors selected will be communicated to the investigators. This cohort will allow for further exploration of early signs of clinical activity observed in tumors during the dose escalation phase of the trial as well as potential signals arising from ongoing trials of other anti OX40 agonists in combination with anti-PD(L)-1. Subjects enrolled in this cohort must be refractory to or intolerant of established therapy known to provide clinical benefit for their condition, i.e., subjects must not be candidates for regimens known to provide clinical benefit.

#### 2.1.4.5 Part 3B: Combination With Ipilimumab Dose Expansion in Ovarian Cancer

Part 3B is the combination therapy (BMS-986178 with ipilimumab) dose expansion part in subjects with OC at the MTD/RP2D(s) determined in Part 3A or 5. Ipilimumab will be administered at 1 or 3 mg/kg. Each treatment cycle will be 3 weeks in length. Ipilimumab will be administered in the initial 4 cycles in combination with BMS-986178. Then the subject will continue on BMS-986178 monotherapy for up to an additional 4 cycles for a total of up to 24 weeks (8 cycles) of treatment. Approximately 35 subjects with OC will be treated in this expansion cohort.

#### 2.1.4.6 Part 3C: Combination With Ipilimumab Dose Expansion in Other Tumors for Signal Finding

Part 3C is the combination therapy (BMS-986178 with ipilimumab) dose expansion part in subjects with other tumors from dose escalation for signal finding at the MTD/RP2D(s) determined in Part 3A or 5. Ipilimumab will be administered at 1 or 3 mg/kg. Each treatment cycle will be 3

weeks in length. Ipilimumab will be administered in the initial 4 cycles in combination with BMS-986178. Then the subject will continue on BMS-986178 monotherapy for up to an additional 4 cycles for a total of up to 24 weeks (8 cycles) of treatment. Approximately 40 subjects will be treated in this expansion cohort.

Tumor types for this cohort will be selected by Sponsor from those permitted in dose escalation which do not have a dedicated expansion cohort or plans for evaluation in other studies and those selected tumors will be communicated to the investigators. This cohort will allow for further exploration of early signs of clinical activity observed in tumors during the dose escalation phase of the trial as well as potential signals arising from ongoing trials of other anti OX40 agonists in combination with anti-CTLA-4. Subjects enrolled in this cohort must be refractory to or intolerant of established therapy known to provide clinical benefit for their condition, i.e., subjects must not be candidates for regimens known to provide clinical benefit.

#### *2.1.4.7 Part 6B: Combination With Nivolumab and Ipilimumab in Renal Cell Carcinoma*

Part 6B is the combination therapy (BMS-986178, nivolumab, and ipilimumab) dose expansion part in subjects with RCC at a dose determined to be tolerated in Part 6A. BMS-986178 will be administered at the RP2D(s) in combination with nivolumab (240 mg) and ipilimumab (1 mg/kg) q3w during Cycles 1 to 4 followed by maintenance therapy (Cycle 5 and beyond) in which BMS-986178 and nivolumab (480 mg) will be administered q4w. Study drugs will be administered accordingly starting on Day 1 of each cycle. Approximately 40 subjects will be treated in this expansion cohort.

#### *2.1.4.8 Part 7B: Combination With Nivolumab and Ipilimumab in Non-small Cell Lung Cancer*

Part 7B is the combination therapy (BMS-986178, nivolumab, and ipilimumab) dose expansion part in subjects with NSCLC at a dose determined to be tolerated in Part 7A. BMS-986178 will be administered at the RP2D(s) (q2w) in combination with nivolumab (240 mg; q2w) and ipilimumab (1 mg/kg; q6w) for four, 6-week cycles. Study drugs will be administered accordingly starting on Day 1 of each cycle. Approximately 40 subjects will be treated in this expansion cohort.

### 2.2 Treatment Assignment

CA012004 is an open label study. After the subject's initial eligibility is established and informed consent has been obtained, the subject must be enrolled into the study by calling an Interactive Response Technology (IRT) to obtain the subject number. The investigator or designee will register the subject for enrollment by following the enrollment procedures established by BMS.

The following information is required for registration:

- Gender
- Diagnosis (if applicable)
- Statement that subject is eligible
- Date of informed consent

- Date of Birth

Based on the rate of subject enrollment, the Sponsor will implement an IRT to assign subject numbers, study part and dose level as well as manage drug supply. IRT instructions will be provided to the sites in a separate instruction manual.

Treatment group/dose level will be provided to the site study team through the IRT after the subject has been deemed eligible and is assigned for the study. Site personnel/investigator will receive a receipt confirming the treatment assignment. A copy of this documentation should remain in the subject's chart. Because of the nature of the study design, limited early access to the assignment information will be granted to the study team.

Once it is determined that the subject meets the eligibility criteria, the investigative site will register the subject through IRT prior to the first study drug administration.

In the dose escalation phases, if a subject discontinues treatment with either BMS-986178, nivolumab, or ipilimumab during the DLT period for reasons other than a DLT, the subject may be replaced with a new subject, if necessary, for safety assessments. Replacement subjects will receive the same treatment but will be assigned a new subject number.

Subjects will be assigned to a part or a cohort within a part by IRT. Details about how the subjects will be assigned to a specific part/cohort will be provided in IRT training documentation.

Additional subjects may be added to expansion cohorts if adequate paired pre-treatment and on-treatment biopsy specimens are not obtained from previously assigned subjects. The additional subjects will receive the same treatment as the subjects being replaced, but new subject numbers will be assigned.

Subjects may be permitted to rescreen for the study following agreement between the investigator and the Sponsor/medical monitor

## 2.3 Blinding and Unblinding

This is an open label study.

## 2.4 Protocol Amendments

**Table 2.4-1: List of Protocol Amendment**

| Amendment number | Date | Summaries |
|---|---|---|
| 1 | 26-Apr-2016 | • The timing of the initiation of combination therapy dose escalation cohorts was revised, a sentinel subject was added to all dose cohorts, Parts 1B and 2B were removed and the subsequent study parts were renamed (Part 1C to Part 1B, Part 2C to Part 2B, and Part 2D to Part 2C), DLT period across the study (28 days) was made uniform, the post-infusion observation period was extended to 4 hours, contraceptive requirements were updated, lipase and amylase ≤ 1.5×ULN were removed as criteria for adequate organ |

**Table 2.4-1: List of Protocol Amendment**

| Amendment number | Date | Summaries |
|---|---|---|
| | | function, DLT criteria were revised, a timepoint was added for safety monitoring, the rationale for use of blood and tumor tissue in biomarker studies was clarified, prior therapy requirements for dose expansion cohorts were updated, and BLRM language was clarified<br>• Typographical errors were corrected, and clarifications were made for consistency. |
| 2 | 08-Jun-2016 | • Change the definition for "Related AE's" and "Not Related AE's".<br>• Update prior therapy inclusion criteria for dose escalation subjects<br>• Remove timeframe from hematologic DLT grade 3 febrile neutropenia.<br>• Change to have CBC with differential processed through LLDS.<br>• Add new model document language for Additional Research Collection and Imaging scans.<br>• Typographical errors were corrected, and clarifications were made for consistency. |
| 3 | 23-Nov-2016 | • Removal of Part 1B<br>• Addition of Part 2D, 2E, 3C and Part 2A cohort dose -1<br>• Change to have imaging as central read<br>• Add text to allow for intermediate and lower doses in escalation<br>• Included text to add potentially more than 1 dose at RP2D<br>• Updated versions numbers for current IB's.<br>• Updating to the new PMD for WOCBP Section<br>• Require fresh tumor biopsy from all subjects<br>• Additional sample to be collected in combination cohorts for RO<br>• Update to not require archived tumor biopsies<br>• Updated Statistical Analysis section<br>• Typographical errors were corrected, and clarifications were made for consistency. |
| 4 | 04-Apr-2017 | • Addition of Parts 4,5,6 and 7<br>• biomarker sampling schedule<br>• [redacted]<br>• [redacted]<br>• Update of study design and study visit schematic |

**Table 2.4-1: List of Protocol Amendment**

| Amendment number | Date | Summaries |
|---|---|---|
| | | • Update of inclusion and exclusion criteria to include the new parts and clarify the maximum number of prior treatments allowed<br>• Update of study drug dosing and method of assigning subjects<br>• Update of dose delay language and addition of criteria for resuming treatment in subjects with an infusion reaction<br>• Update/addition of tables for treatment procedures, pharmacokinetic and anti-drug antibody sampling schedule, and pharmacodynamic/ biomarker sampling schedule<br>• Update of sample size information to include the new parts<br>• Update of Appendix 1 to include statistical methods for the new parts<br>• Typographical errors were corrected, and edits were made for consistency and clarity. |
| 5 | 11-Dec-2017 | • Addition of Part 8<br>• Update of Appendix 1<br>• Update schedule of assessments<br>• Update of address<br>• Typographical errors were corrected, and edits were made for consistency and clarity |

# 3 OBJECTIVES

## 3.1 Primary

- To determine the safety, tolerability, DLTs, and MTD/RP2D of BMS-986178 administered alone or in combination with nivolumab and/or ipilimumab in subjects with advanced solid tumors

## 3.2 Secondary

- To investigate the preliminary anti-tumor activity of BMS-986178 administered alone or in combination with nivolumab and/or ipilimumab in subjects with advanced solid tumors
- To characterize the PK of BMS-986178 administered alone or in combination with nivolumab and/or ipilimumab
- To characterize the immunogenicity of BMS-986178 administered alone or in combination with nivolumab and/or ipilimumab, and the immunogenicity of nivolumab or ipilimumab administered with BMS-986178
- To assess the proportion of subjects showing a change in peripheral pharmacodynamic biomarkers such as soluble OX40 and peripheral OX40 receptor occupancy along with tumor

pharmacodynamic of BMS-986178 in combination with nivolumab or nivolumab monotherapy (Part 8)

[redacted]

# 4 ENDPOINTS

## 4.1 Primary Endpoints

The assessment of safety will be based on the incidence of DLTs, AEs, SAEs, AEs leading to discontinuation, and deaths. In addition, clinical laboratory test abnormalities will be examined. AEs and laboratory values will be graded according to NCI CTCAE v4.03.

## 4.2 Secondary Endpoints

### *4.2.1 Efficacy*

The anti-tumor activity of BMS-986178 alone or in combination with nivolumab and/or ipilimumab will be measured by Objective Response Rate (ORR), duration of response, and Progression Free Survival Rate (PFSR) at 24 weeks based on RECIST v1.1. The above will be determined based on tumor measurements occurring at baseline, every 8 weeks (± 1 week) for Parts 1-7 and every 12 weeks (± 1 week) for Part 8 during the treatment period, and every 12 weeks during the Response Follow-up Period.

- Best overall response (BOR) is assessed by Investigator per RECIST 1.1 criteria.

- ORR: the total number of subjects whose BOR is either a complete response (CR) or partial response (PR) divided by the total number of subjects in the population of interest.
- Duration of response, computed for subjects with a BOR of CR or PR, is defined as the time between the date of first response and the subsequent date of disease progression or death (death after re-treatment will not be considered), whichever occurs first. The detailed censoring scheme is defined in Table 4.2.1-1
- PFSR at 24 weeks is defined as the proportion of treated subjects remaining progression free and surviving at 24 weeks since the first dosing date. The proportion will be calculated by the Kaplan-Meier estimate, which takes into account censored data.
- Progression Free Survival (PFS) is specified as the time between the date of first dose and the first date of documented progression, (as per RECIST 1.1 criteria), or death due to any cause, whichever occurs first. The detailed censoring scheme is defined in Table 4.2.1-1.

**Table 4.2.1-1: Censoring Scheme Used for Analysis of PFS on Initial Treatment**

| Situation | Date of Progression or Censoring | Outcome |
|---|---|---|
| No baseline tumor assessments[a] | First Dosing date | Censored |
| No on study tumor assessments and no death[a] | First Dosing date | Censored |
| Documented progression[a] | Date of the first documented progression per RECIST 1.1 | Progressed |
| No progression and no death[a] | Date of last evaluable tumor assessment prior to re-treatment or subsequent therapy if exist | Censored |
| New anticancer therapy, tumor-directed radiotherapy, tumor-directed surgery on target lesions or re-treatment therapy received without progression reported prior or on the same day | Date of last evaluable tumor assessment prior to initiation of the subsequent therapy or re-treatment | Censored |
| Death without progression[a] | Date of death | Progressed |

[a]Death and study tumor assessments after subsequent therapy or re-treatment are not considered

### *4.2.2 Pharmacokinetics*

The PK of BMS-986178 may be characterized using the following endpoints:

- Cmax: Maximum observed serum concentration
- Tmax: Time of maximum observed serum concentration
- Ctau: Observed serum concentration at the end of a dosing interval when intensive samples are collected
- AUC(0-t): Area under the serum concentration-time curve from time 0 to time t

- AUC(TAU): Area under the serum concentration-time curve in 1 dosing interval
- CLT: Total body clearance
- Ctrough: Trough observed plasma concentration (this includes predose concentrations and Ctau concentrations).
- Css-avg: Average concentration over a dosing interval (AUC(TAU)/tau)
- AI: Accumulation Index. Ratio of an exposure measure at steady state (eg, following Cycle 3 Day 1 dose) to that after the first dose (exposure measure includes AUC(TAU), Cmax and Ctau)
- T-HALFeff: Effective elimination half-life that explains the degree of accumulation observed for a specific exposure measure (exposure measure includes AUC(TAU), Cmax)

### *4.2.3 Immunogenicity*

The secondary objective of immunogenicity will be assessed by the frequency of positive ADA to BMS-986178 or nivolumab or ipilimumab.

At the sample level, individual samples will be characterized into following category as shown below.

**Table 4.2.3-1: Sample ADA Status**

| Sample ADA Status | Definition |
|---|---|
| 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:

**Table 4.2.3-2: Participant ADA Status**

| ADA Status | Definition |
|---|---|
| Baseline ADA-positive subject | A participant with baseline ADA-positive sample |
| **ADA-positive subject** | 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*[b] weeks apart |
| • *Not PP-Last Sample Positive* | Not persistent positive with ADA-positive sample at the last sampling timepoint |

**Table 4.2.3-2: Participant ADA Status**

| ADA Status | Definition |
|---|---|
| • *Other Positive* | Not persistent positive with ADA-negative sample at the last sampling timepoint |
| • | |
| **ADA-negative subject** | A participant with no ADA-positive sample after the initiation of treatment |

[b] 16 week threshold was chosen based on the long half-life of immunoglobulin.

### 4.2.4 Pharmacodynamics

The secondary objective of pharmacodynamics will be assessed by the proportion of subjects showing a change in pharmacodynamic biomarkers such as soluble OX40 and peripheral OX40 receptor occupancy along with tumor pharmacodynamic of BMS-986178 in combination with nivolumab or nivolumab monotherapy (Part 8).

[redacted]

[redacted]

| [redacted] | [redacted] | [redacted] |
|---|---|---|
| [redacted] | [redacted] | [redacted] |
| [redacted] | [redacted] | [redacted]sy |

[redacted]

# 5 SAMPLE SIZE AND POWER

## 5.1 Dose Escalation

As a Phase 1 dose escalation trial, the sample size for each dose escalation cohort depends on observed toxicity and posterior inference. Approximately 30 subjects are expected to be treated during each dose escalation part (BMS-986178 monotherapy [Part 1A], BMS-986178 in combination with nivolumab [Part 2A], and BMS-986178 in combination with ipilimumab [Part 3A]) for a combined total of approximately 90 subjects in Parts 1A, 2A and 3A. Initially, approximately 3 subjects will be treated at the starting dose levels of BMS-986178 or BMS-986178 in combination with nivolumab or ipilimumab. Additional cohorts of approximately 3 evaluable subjects will be treated at recommended dose levels per BLRM (-Copula) recommendations during the dose escalation phase. At least 6 DLT-evaluable subjects will be treated at the MTD. At most, 12 DLT-evaluable subjects will be treated at each dose level. 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. Escalation by more than 1 dose level (dose skipping) is not permitted.

As in any dose escalation study, the exact number of subjects in the dose escalation cannot be predicted. However, different estimates with the pre-specified parameters of the dose escalation design under various scenarios are provided. A maximum of 30 subjects is prespecified as one of the simulation parameters (assuming approximately 6 subjects per dose level). The simulation provided in Appendix 1 of protocol uses combination therapy as an illustration(containing 5 dose levels for BMS-986178 and a fixed dose level for nivolumab [240 mg]). The simulation estimated a total of 15 to 21 subjects on average under different scenarios. Note the following difference

between simulation setting and the conduct of the actual trial: 1) dose skipping is allowed in the simulation setting whereas in the actual clinical trial, dose skipping is not permitted, 2) the clinical team can override BLRM (-Copula) dose recommendation based on the totality of data (clinical safety data along with available PK, immunogenecity and PD data). Based on these factors, there may be more subjects in the dose escalation phase than the number estimated in the simulation. For planning purposes, it is assumed that approximately 30 subjects may be treated in each dose escalation part.

## 5.2 Dose Expansion

The purpose of dose expansion is to gather additional safety, tolerability, preliminary efficacy, immunogenecity, PK, and PD information regarding BMS-986178 alone or in combination with nivolumab and/or ipilimumab.

In general, the estimated sample size for Parts 2B, 2C, 2D, 3B, 6B, and 7B in expansion phase is guided by Simon 2-stage design, which is based on target response rates (target ORR), and the ability to identify a signal for such clinical response that is above the SOC (historical ORR). Enrollment of subjects at the end of Stage 1 will continue while the initial efficacy evaluation is ongoing. Decisions regarding continuing or not continuing enrollment of a specific arm will be based on a combination of model guidance, clinical judgment on the totality of data (clinical safety, PK, PD, and efficacy), and communication between the Sponsor and investigators. Parts 2E and 3C include tumors from dose escalation for signal seeking. Due to the heterogeneity of response rates of the mixed tumors, approximately 40 subjects is assigned for each part(Part 2E and Part 3C). It is not the intent of the study to use Simon 2-stage design for formal hypothesis testing.

The Simon 2-stage design will be used as a guide for the disease-restricted expansion cohorts in Parts 2B, 2C, 2D, 3B, 6B and 7B. The total sample size for each expansion cohort will be calculated to provide a reasonable false-positive rate (FPR) and false-negative rate (FNR) based on assumptions of true (target) and historic ORR for each indication. The sample size and operating characteristics of the Simon 2-stage design are provided in Table 5.2-1, although this is not used for hypothesis testing. Approximately 12 subjects for CRC and OCs. 10 subjects for BC. 17 subjects for Cervical Cancer, and 28 subjects for RCC and NSCLC will be treated in Stage 1 for an initial evaluation of efficacy. This will inform potential early decisions and guide planning/operations or early termination after taking into consideration additional data, (eg, duration of response and/or SD and safety). If the true response rate is 10% for CRC and OC, the study has a 66% probability of early termination of the cohort. If the true response rate is 25% for BC, the study has a 53% probability of early termination of the cohort. If the true response rate is 20% for cervical cancer, the study has a 55% probability of early termination of the cohort. If the true response rate is 40% for RCC and NSCLC, the study has a 55% probability of early termination of the cohorts.

For an expansion cohort of 35 subjects in CRC and OC and the assumed true response rate of 30%, there is a 94% chance of observing at least 7 responses (in other words, the FNR is 6%). If the true response rate is only 10% rather than 30%, then there is a 6% chance that there will be at least 7 responses in 35 subjects (in other words, FPR is 6%). Also, if 7 responses are observed (eg, 20%

observed response rate), the lower bound of the 80% confidence interval (CI) for the ORR is 11% (higher than historical ORR of 10%). The CI is calculated using Clopper-Pearson method.

**Table 5.2-1: Dose Expansion - Characteristics of the Simon 2-Stage Design**

| Expansion Cohort | Historic ORR (%) | Target ORR (%) | Stage 1/ Total N | Stage 1 Responses Futility Boundary | FPR/1-FNR (%) | Probability Of Early Stopping (%) |
|---|---|---|---|---|---|---|
| CRC, Ovarian Cancer | 10 | 30 | 12/35 | 1 | 10/90 | 66 |
| Bladder Cancer | 25 | 50 | 10/27 | 2 | 10/90 | 53 |
| Cervical Cancer | 20 | 40 | 17/37 | 3 | 10/90 | 55 |
| NSCLC, RCC | 40 | 60 | 28/41 | 11 | 10/90 | 55 |

Abbreviations: CRC = colorectal cancer; FNR = false-negative rate; FPR = false-positive rate; ORR = objective response rate.

For an expansion cohort of 27 subjects with BC and the assumed true response rate of 50%, there is an 88% chance of observing at least 11 responses (in other words, the FNR is 12%). If the true response rate is only 25% rather than 50%, then there is a 5% chance that there will be at least 11 responses in 27 subjects (in other words, FPR is 5%). If 11 responses are observed (eg, 41% observed response rate), the lower limit of the 80% CI for the ORR is 28% (higher than historical ORR of 25%). The CI is calculated using Clopper-Pearson method.

For an expansion cohort of 37 subjects with cervical cancer and the assumed true response rate of 40%, there is an 87% chance of observing at least 12 responses (in other words, the FNR is 13%). If the true response rate is only 20% rather than 40%, then there is a 5% chance that there will be at least 12 responses in 37 subjects (in other words, FPR is 5%). If 12 responses are observed (eg, 32% observed response rate), the lower limit of the 80% CI for the ORR is 22% (higher than historical ORR of 20%). The CI is calculated using Clopper-Pearson method.

The number of subjects receiving treatment for efficacy evaluation is approximate and additional subjects may be treated in order to have sufficient response-evaluable subjects per expansion cohort.

## 5.3 Schedule and Dose Exploration and Safety Exploration

The purpose of Parts 4, 5, 6A, 7A, and 8 is to assess safety, tolerability, preliminary efficacy, PK, and PD information of BMS-986178 in combination with nivolumab administered with a less frequent dosing schedule (q4w Part 4 and q12w Part 8 for BMS-986178) or BMS-986178 in combination with higher dose of ipilimumab (Part 5) or BMS-986178 in combination with nivolumab and ipilimumab (Parts 6A and 7A).

In Parts 4, 5, 6A, and 7A, a minimum of 6 subjects will be treated at the MTD/RP2D chosen from Part 2A or Part 3A. Up to 12 subjects may be treated for further evaluation of safety, PK, or PD parameters. Administration of BMS-986178 in combination with nivolumab and/or ipilimumab in

6 to 12 subjects per dose and schedule level provides 90% probability of observing at least 1 occurrence of a specific AE that would occur with a 32% or 17% incidence in the population, respectively. Furthermore, 6 to 12 subjects provide some precision of PD biomarker effect estimation. To assess the PD effects, pre-treatment and on-treatment whole blood and serum samples and tumor biopsies will be required. It is of interest to ensure the precision of the estimate of the ratio of on-treatment biomarker assessments to pre-treatment (baseline) levels. Assuming that a biomarker is measured as a continuous variable, a given number of subjects will provide the confidence that the estimate of the ratio of on-treatment to baseline values will be within 20% of the true value, as shown in Table 5.3-1.

**Table 5.3-1: 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 |
|---|---|---|---|---|---|---|---|---|
| Probability | N=6 | 92% | 76% | 62% | 52% | 44% | 38% | 34% |
| | N=12 | 99% | 90% | 78% | 68% | 59% | 52% | 46% |

For example, for a biomarker (eg, activated and memory CD4 and CD8 T-cells) with an intra-subject standard deviation of 0.5, if the true ratio of post-baseline to baseline geometric means is 1.2 (increase from baseline is 20%), there is 68% probability that the estimated ratio would be within 0.96 and 1.44 (or a percent change between -4% and 44%) with 12 subjects per treatment arm. If the true increase from baseline is 60%, for a biomarker with the same variability, then there is 68% probability that the estimated percent change would be between 28% and 92% with 12 subjects per treatment arm.Up to approximately 20 evaluable subjects per dose cohort will be treated in Part 8. This sample size provides a 90% CI for the true proportion of subjects showing a change in receptor occupancy with width of 37% and 26% respectively when the observed proportion of subjects showing a change in receptor occupancy is 70% and 90%, as shown in Table 5.3-2. The maximum width of all 90% CIs is 40% and the maximum margin of error is 21% with a sample size of 20 per cohort.

**Table 5.3-2: 90% Confidence Interval for the True Proportion of Subjects Showing a Biomarker Change**

| n | # subjects showing the trend | 90% CI |
|---|---|---|
| 20 | 14 | (49%, 86%) |
| | 18 | (72%, 98%) |

# 6 STUDY PERIODS, TREATMENT REGIMENS AND POPULATIONS FOR ANALYSES STUDY PERIODS

## 6.1 Study Periods

For the purpose of analysis, baseline period (Section 6.1.1) and post baseline period (Section 6.1.2) will be considered.

### *6.1.1 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 medication.

The following definitions will apply:

- Pre-treatment AEs will be defined as AEs with an onset date and time prior to but not including the day and time of the first dose of study treatment (or with an onset date prior to the day of the first dose of study treatment if time is not collected or is missing).
- Baseline evaluations (laboratory tests, pulse oximetry, vital signs, and ECG) will be defined as evaluations with a date and time on or prior to the day and time of the first dose of study treatment (or with an onset date on or prior to the day of the first dose of study treatment if time is not collected or is missing).

If there are multiple valid assessments, the assessment that is closest to day (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 considered as baseline.

Tumor assessments will be slotted in the baseline period if assessments are before or on start of the treatment date. Baseline tumor assessment is the last assessment in the baseline period.

### *6.1.2 Post Baseline Period*

Post baseline period is further characterized into Treatment, and Re-treatment Periods.

Treatment Period

Treatment Period starts with the first dose date-time of initial study treatment.

- On-treatment AEs will be defined as AEs with an onset date-time on or after the datetime of the first dose of study treatment (or with an onset date on or after the day of the first dose of study treatment if time is not collected or is missing). For subjects who are off initial treatment, AEs will be counted as on-treatment if the event occurred within 100 days of the last dose of initial study medication and prior to the first dose of re-treatment (if exist). No "subtracting rule" will be applied when an AE occurs both pre-treatment and post-treatment with the same preferred term and grade. For subjects who are still on initial study treatment, all available AEs will be counted as on-treatment after the datetime (or date if time is not collected or missing) of the first dose.
- On-treatment evaluations (laboratory tests, pulse oximetry and vital signs) will be defined as evaluations taken after the day (and time, if collected and not missing) of the first dose of study treatment. For subjects who are off initial treatment, evaluations will be counted

as on-treatment if evaluation is taken within 100 days of the last dose of initial study medication and on or prior to the first dose of the re-treatment (if exist). For subjects who are still on initial study treatment, all available evaluations will be considered as on-treatment after the datetime of the first dose.

- Principal analysis of safety endpoints will be based on the treatment period. AEs and other evaluations reported during the re-treatment period will be listed and summarized separately.
- Tumor assessments will be slotted in the post-baseline period if assessments are after start of the treatment date and prior to the first dose of re-treatment (if exist).

Optional Re-treatment Period

Optional Re-treatment Period starts with the first dose date-time of re-treatment

- On-re-treatment AEs, will be defined as AEs with an onset date-time on or after the date-time of the the first dose of re-treatment (or with an onset date on or after the day of the first dose re-treatment if time is not collected or is missing). For subjects who are off treatment in the re-treatment period, AEs will be counted as on re-treatment if event occurred within 100 days of the last dose of re-treatment. For subjects who are still on re-treatment of study medication, all available AEs with onset date-time on or after the datetime (or date if time is not collected or missing) of the first dose of re-treatment will be counted as on-re-treatment.
- On-re-treatment evaluations (laboratory tests, pulse oximetry and vital signs) will be defined as evaluations taken after the day (and time, if collected and not missing) of the first dose of re-treatment. For subjects who are off treatment in the re-treatment period, evaluations will be counted as on-re-treatment if evaluation is taken within 100 days of the last dose of re-treatment. For subjects who are still on re-treatment, all available evaluations taken after the day of the first dose of re-treatment will be considered as on-re-treatment.
- Tumor assessments will be slotted in the post-baseline period if assessments are after the day (and time, if collected and not missing) of the first dose of re-treatment.

Baseline tumor assessment for re-treatment period is the last assessment prior to or on the date of the first dose of re-treatment.

## 6.2 Treatment Regimens

The BMS-986178 monotherapy and combination arm of BMS-986178 with nivolumab 240 mg will be given on Day 1 of each cycle and will be administered every 2 weeks for up to 12 cycles in Part 2 and Part 4.

The combination arm of BMS-986178 with nivolumab 480 mg will be given on Day 1 of each cycle. Nivolumab will be administered every 4 weeks. BMS-986178 will be administered every 4 weeks in Part 4 and every 12 weeks for Part 8.

For combination arm of BMS-986178 with ipilimumab, BMS-986178 will be administered every 3 weeks starting on Cycle 1 Day 1, up to and including 8 cycles, and ipilimumab will be

administered every 3 weeks starting on Day 1 for 4 cycles. Only BMS-986178 will be administered in the last 4 cycles in Part 3 and Part 5.

In Part 6, For combination arm of BMS-986178 with nivolumab and ipilimumab for RCC, BMS-986178 will be administred at a flat dose of 40 mg every 3 weeks during Cycles 1 to 4 starting on Cycle 1 Day 1, followed by maintenance therapy (Cycle 5 and beyond) in which BMS-986178 (40 mg) will be admistered every 4 weeks. Nivolumab 240 mg will be administered every 3 weeks during Cycles 1 to 4 starting on Cycle 1 Day 1, followed by maintenance therapy (Cycle 5 and beyond) in which Nivolumab 480 mg will be admistered every 4 weeks. Ipilimumab 1 mg/kg will be administered every 3 weeks starting on Cycle 1 Day 1 for 4 cycles.

In Part 7, For combination arm of BMS-986178 with nivolumab and ipilimumab for NSCLC, BMS-986178 will be administred at a flat dose of 40 mg every 2 weeks starting on Cycle 1 Day 1. Nivolumab 240 mg will be administered every 2 weeks starting on Cycle 1 Day 1. Ipilimumab 1 mg/kg will be administered every 6 weeks starting on Cycle 1 Day 1 for 4, 6-week cycles.

Planned treatment are listed below. Some of the treatment arm may not have any subjects. Dose level for BMS-986178 in expasion cohort will be decided later based on esclation results.

| Treatment Arm | Treatment Description |
|---|---|
| Esc BMS20 | Escalation Part 1 BMS 20 mg Q2W |
| Esc BMS40 | Escalation Part 1 BMS 40 mg Q2W |
| Esc BMS80 | Escalation Part 1 BMS 80 mg Q2W |
| Esc BMS160 | Escalation Part 1 BMS 160 mg Q2W |
| Esc BMS320 | Escalation Part 1 BMS 320 mg Q2W |
| Esc BMS20+NIVO240 Q2W | Escalation Part 2 BMS 20 mg + Nivo 240 mg Q2W |
| Esc BMS40+NIVO240 Q2W | Escalation Part 2 BMS 40 mg + Nivo 240 mg Q2W |
| Esc BMS80+NIVO240 Q2W | Escalation Part 2 BMS 80 mg + Nivo 240 mg Q2W |
| Esc BMS160+NIVO240 Q2W | Escalation Part 2 BMS 160 mg + Nivo 240 mg Q2W |
| Esc BMS320+NIVO240 Q2W | Escalation Part 2 BMS 320 mg + Nivo 240 mg Q2W |
| Esc BMS20+IPI1 | Escalation Part 3 BMS 20 mg + Ipi 1 mg/kg Q3W |
| Esc BMS40+IPI1 | Escalation Part 3 BMS 40 mg + Ipi 1 mg/kg Q3W |
| Esc BMS80+IPI1 | Escalation Part 3 BMS 80 mg + Ipi 1 mg/kg Q3W |
| Esc BMS160+IPI1 | Escalation Part 3 BMS 160 mg + Ipi 1 mg/kg Q3W |
| Esc BMS320+IPI1 | Escalation Part 3 BMS 320 mg + Ipi 1 mg/kg Q3W |
| Exp 2B | Expansion Part 2B (CRC) |
| Exp 2C | Expansion Part 2C BMS 80 mg + Nivo 240 mg Q2W (BDC) |
| Exp 2D | Expansion Part 2D (CVC) |
| Exp 2E | Expansion Part 2E (OT) |
| Exp 3B | Expansion Part 3B (OC) |
| Exp 3C | Expansion Part 3C (OT) |

| Treatment Arm | Treatment Description |
|---|---|
| SDE Part 4 | Schedule and Dose Exploration Part 4 BMS 80 mg + Nivo 480 mg Q4W |
| SDE Part 5 | Schedule and Dose Exploration Part 5 BMS 80 mg + Ipi 3 mg/kg Q3W |
| SC Part 6A | Safety Cohort Part 6A BMS 40 mg + Nivo 240 mg + Ipi 1 mg/kg Q3W / BMS 40 mg + Nivo 480 mg Q4W (for RCC) |
| Exp Part 6B | Expansion Part 6B BMS 40 mg + Nivo 240 mg + Ipi 1 mg/kg Q3W / BMS 40 mg + Nivo 480 mg Q4W(for RCC) |
| SC Part 7A | Safety Cohort Part 7A BMS 40mg Q2W + Nivo 240 mg Q2W + Ipi 1 mg/kg Q6W (NSCLC) |
| Exp Part 7B | Expansion Part 7B BMS 40mg Q2W + Nivo 240 mg Q2W + Ipi 1 mg/kg Q6W (NSCLC) |
| SDE Part 8 Cohort 1 | Schedule and Dose Exploration Part 8 Cohort 1 BMS 20 mg Q12W + Nivo 480 mg Q4W |
| SDE Part 8 Cohort 2 | Schedule and Dose Exploration Part 8 Cohort 2 BMS 40 mg Q12W + Nivo 480 mg Q4W |
| SDE Part 8 Cohort 3 | Schedule and Dose Exploration Part 8 Cohort 3 BMS 80 mg Q12W + Nivo 480 mg Q4W |
| SDE Part 8 Cohort 4 | Schedule and Dose Exploration Part 8 Cohort 4 Nivo 480 mg Q4W |

The treatment group "**as treated**" will be the same as the arm as assigned by IRT. However, if a subject received the incorrect drug for **the entire period** of treatment, the subject's treatment group will be defined as the incorrect drug the subject actually received.

## 6.3 Populations for Analyses

- **All enrolled subjects**: All subjects who signed an informed consent form and were registered into the IRT.
- **All treated subjects**: All subjects who received any dose of study therapy. This is the primary population for drug exposure, efficacy and safety analysis.
- **PK subjects**: All subjects with available serum time-concentration data from subjects who received any BMS-986178 or Nivolumab or Ipilimumab.
- **Immunogenicity subjects**: All subjects with available data from subjects who received any BMS-986178 or Nivolumab or Ipilimumab and have baseline and at least one post baseline immunogenicity measurement.
- **Biomarker Evaluable Subjects**: All Treated Subjects with at least one evaluable measurement for a specific marker will be included in the dataset for that marker. Evaluable may differ depending on the analysis.
- **Response Evaluable Subjects**: All treated subjects with measurable disease at baseline and one of the following: 1) at least one postbaseline tumor measurement, 2) clinical progression or 3) death. This population may be used for interim efficacy analysis due to insufficient follow up

# 7 STATISTICAL ANALYSES

All analyses will be performed in SAS using version 9.2 or higher.

## 7.1 General Methods

Continuous variables will be summarized by treatment group using the mean, standard deviation, 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. Percentages will be rounded and may not always add up to 100. Percentages less than 0.1 will be indicated as "< 0.1".

## 7.2 Study Conduct

### *7.2.1 Study Information*

**Listing**:

- Batch number. Sort by batch number and subject. It is noted that a subject may appear multiple times under different batch numbers.

### *7.2.2 Accrual*

The following will be presented on the All Enrolled Subjects.

**Summary**:

- Number (%) of subjects accrued by country and investigational site: Include country, site number, Principal Investigator's name, number of subjects enrolled, and number of subjects treated

**Listing**:

- Subjects accrued by country and investigational site

### *7.2.3 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 from inclusion and exclusion criteria will be considered as relevant protocol deviations and a listing will be provided.

**At Entrance:**

- Subject without measurable disease at baseline
- Subjects with baseline ECOG performance status > 1
  - Subjects with inadequate organ function defined as one of the following:Neutrophils < 1500/µL
  - Platelets < $80 \times 10^3$/µL
  - Hemoglobin < 8 g/dL
  - ALT or AST > 3 × upper limit of normal (ULN)

- Total bilirubin > 1.5 × ULN (subjects with Gilbert's Syndrome will be excluded only if the information is available in the database)
- Albumin < 2 g/dL
- Serum creatinine > 1.5 × ULN with creatinine clearance (CrCl) < 40 mL/min

**On-Treatment:**

- Subjects receiving doses or frequencies that is different than what they was assigned.

## 7.3 Study Population

### *7.3.1 Subject Disposition*

**Summary**:

- Pre-treatment period: The number (%) of subjects of the following will be summarized on the All Enrolled Subjects.
  - Subjects enrolled
  - Subjects treated
  - Subjects enrolled but not treated with the reasons
- End of treatment period: The number (%) of subjects of the following will be summarized by treatment and part, based on the All Treated Subjects.
  - Subject completing the treatment (including additonal cycles when applicable)
  - Subject still on treatment (subjects who continued to additional cycles and still being treated are considered as on-treatment)
  - Subject discontinued treatment
  - Reasons for discontinuation (including the reason for discontinuation from additional cycles when subjects continued to them after completing 24 weeks for parts 1-7 and 24 months for Part 8)
  - Subjects continuing in the study
  - Subjects not continuing in the study
  - Reason for not continuing in the study
  - Subject received re-treatment

**Listing**:

- Pre-treatment period: Screen failure Subjects with reason
- End of treatment period: Treated subjects with off discontinuation reason for initial treatment ( by treatment), Treated subjects with off discontinuation reason for re-treatment.

### 7.3.2 Demographics and Other Baseline Characteristics

The following subject demographics and baseline characteristics will be summarized by treatment arm and overall for each part where applicable using descriptive statistics or frequency statistics. The definition of baseline defined in Section 6.1.1 will be applied here.

- Age (in years); age category (<65, >=65)
- Gender
- Race
- Ethnicity
- Height
- Weight
- ECOG status
- Prior therapy (surgery, radiotherapy, systemic therapy setting, number of regimen)
- Mutation status (B-RAF, ALK/EGFR/K-RAS/ROS1 etc.)
- Disease characteristics
  - Colorectal Cancer
    - Stage at initial diagnosis and at study entry
    - Cell type
  - Bladder Cancer
    - Tumor type
    - Stage at initial diagnosis and at study entry
    - Cell type
    - Minor Histological Variants
    - Subtype of disease
  - Cancer of the Cervix
    - Stage at initial diagnosis and at study entry
    - Cell type
  - Ovarian Cancer
    - Stage at initial diagnosis and at study entry
    - Cell type
    - Histologic
  - Other Tumors
    - Stage at initial diagnosis and at study entry
    - Cell type

**Listing**:

- All relevant data, generally variables listed above

- General medical history

## 7.4 Extent of Exposure

The extent of exposure will be characterized according to the number of subjects exposed, the duration of exposure, and the dose to which they were exposed. Analyses in this section will be performed on the population of All Treated Subjects "as treated" as described in Section 6.2.

Extent of Exposure will be assessed separately for original treatment and re-treatment.

### *7.4.1 Study Therapy*

**Summary:**

- Number (%) of treated subjects exposed for specified periods of time such as less than 1 week, 1 week to 1 month, 1 month to 6 months by treatment group (initial treatment and re-treatment).
- Descriptive statistics will be provided by study drug and treatment period (initial treatment and re-treatment) for the following. For part 6, the following information will be summarized by treatment period, treatment cycle (first 4 cycle vs. cycle 5 and above) and study drug.
  - Number of doses
  - Duration of therapy (weeks)
  - Cumulative dose, dose intensity, relative dose intensity may also be presented if deemed appropriate.

Table 7.4.1-1, Table 7.4.1-2 and Table 7.4.1-3 summarizes the key parameters used to calculate dosing data for each treatment group.

**Table 7.4.1-1: Study Duration of Therapy Parameter Definitions for BMS-986178**

| Treatment | Duration of Therapy (day) |
|---|---|
| BMS-986178 Q2W in Parts 1,2 and 7 | Last dose date - Start dose date +14 |
| BMS-986178 Q3W in Parts 3 and 5 | Last dose date - Start dose date +21 |
| BMS-986178 Q4W in Parts 2 and 4 | Last dose date - Start dose date +28 |
| BMS-986178 in Part 6 | Last dose date prior to cycle 5 dosing - Start dose date +21 for Cycle 1 to Cycle 4<br>Last dose date - first cycle 5 dose date +28 for Cycle 5 or above |
| BMS-986178 Q12W in Part 8 | Last dose date - Start dose date +84 |

**Table 7.4.1-2: Study Duration of Therapy Parameter Definitions for Nivolumab**

| Treatment | Duration of Therapy (day) |
|---|---|
| Nivolumab Q2W in Parts 2 and 7 | Last dose date - Start dose date +14 |
| Nivolumab Q4W in Parts 2, 4 and 8 | Last dose date - Start dose date +28 |

**Table 7.4.1-2: Study Duration of Therapy Parameter Definitions for Nivolumab**

| Treatment | Duration of Therapy (day) |
|---|---|
| Nivolumab in Part 6 | Last dose date prior to cycle 5 dosing - Start dose date +21 for Cycle 1 to Cycle 4<br>Last dose date - first cycle 5 Start dose date +28 for Cycle 5 or above |

**Table 7.4.1-3: Study Duration of Therapy Parameter Definitions for Ipilimumab**

| Treatment | Duration of Therapy (day) |
|---|---|
| Ipilimumab Q3W in Parts 3, 5 and 6 | Last dose date - Start dose date +21 |
| Ipilimumab Q6W in Part 7 | Last dose date - Start dose date +42 |

**Listing:**

- Drug administration of study medication
- Number of doses, duration of therapy, cumulative dose, dose intensity, and relative dose intensity

### *7.4.2 Modification of Study Therapy*

**Summary:**

The following will be provided by study drug and treatment period (initial treatment and re-treatment).

- Number (%) of subjects with dose delay along with the reason
- Number (%) of subjects with treatment discontinuation along with the reason
- Infusion interruptions
  - Number (%) of subjects with at least one infusion interruption along with the reason*
  - Number of infusion interruptions per subject
  - Number (%) of subjects with at least one IV infusion rate reduction along with the reason*

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

**Listing:**

All relevant information on dose modification listed above

[redacted]

[redacted]

[redacted]

## 7.5 Efficacy

The primary efficacy analyses will be performed on All Treated Subjects for the final analysis. 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 Subjects.

All analysis listed below will be performed for initial treatment. Some of the analysis may be performed for re-treatment if deemed appropriate.

Summary analysis will be performed for expansion cohorts only (include subjects treated at the same dose level in dose escalation with same tumor type if appropriate). In the case of superior response observed in escalation phase, summary analysis may also be performed for escalation dose levels as appropriate. All analyses will be presented by part , treatment group and/or tumor type (if appropriate), unless otherwise specified. Listings will be provided for all dose levels.

Time to event distribution (e.g. progression free survival, overall survival, and duration of response) will be estimated using Kaplan-Meier (K-M) method. When appropriate, the median along with 95% confidence interval (CI) will be provided using Brookmeyer and Crowley methodology. Rates at fixed timepoints (eg, PFSR at 6 months) will be derived from the K-M estimate and corresponding CI will be derived based from Greenwood's formula. Confidence intervals for binomial proportions will be derived using the Clopper-Pearson method. Time to event rates will not be reported if the number of subjects at risk at that time is too small (eg, <5).

**Summary**:

The following will be summarized

- The ORR with corresponding 2-sided 95% CI based on the Clopper-Pearson method, along with each category of BOR. .
- The DOR with median (95% CI) by K-M method along with the range (min, max). The number of subjects still in response at the time of database lock will be indicated.
- The PFS and [redacted] with median (95% CI) by K-M method along with the range (min, max).
- The PFSR at specified timepoints by K-M method.
- [redacted]

**Figure**:

- Percent change from baseline in target lesion tumor burden over time (spider plot)

- Maximum reduction in target lesions tumor burden (waterfall plot)
- Kaplan-Meier plot of DOR for responders only
- Swimmer plot of DOR, and time on therapy for responders only
- Kaplan-Meier plot of PFS
- Kaplan-Meier plot of OS

**Listing**:

The following will be listed by tumor type and treatment group.

- Tumor lesion measurements
- Tumor evaluation at each visit, including non-target lesions and new lesions, tumor change from smallest sum of diameters in target lesions, and corresponding change (or percent change) from baseline
- Subject level efficacy for All Treated Subjects: BOR, OS, PFS, best response in target lesions, death indicator, duration of response for responders
- Survival - survival status, first dose date, last dose date, last known alive date, death date, time to death

## 7.6 Safety

Analysis of safety will be based on All Treated Subjects and presented by treatment arm and overall. Deaths and SAEs will be listed using All Enrolled Subjects.

Adverse events will be coded according to the most recent version of Medical Dictionary for Regulatory Activities (MedDRA) at the time of database lock and the severity will be graded using the NCI CTCAE version 4.03. Drug-related AEs are those events with relationship to study drug "Related" as recorded on the Case Report Form (CRF). If the relationship to study drug is missing, the AE will be considered as drug-related.

Listing of adverse events will include all enrolled subjects as SAEs and deaths are collected pretreatment. Summaries of adverse events will include all on-treatment adverse events as defined in section 6.1.2. Adverse events occurred after original treatment or re-treatment will be summarized and listed separately.

When reporting adverse events by CTC grade, summary tables will be provided based on the event with worst CTC grade (independent of relationship to study medication). Subjects will only be counted (1) once at the preferred term (PT) level, (2) once at the system organ class (SOC) level, and (3) once in the 'Total subject' row at their worst CTC grade, regardless of SOC or PT.

The analysis of laboratory results will be based on All Treated Subjects. Laboratory results will be categorized according to NCI CTCAE (version 4.03) grade. Baseline is defined as the last non-missing measurement prior to the first dosing date and time. Summaries of laboratory results include baseline and on-treatment results as defined in section 6.1.2.

After trial completion, the final posteriors for parameters of BLRM (-Copula) model that describe the DLT profile of BMS-986178 alone or in combination with nivolumab will be summarized.

### 7.6.1 All Adverse Events

**Summary:**

AEs and drug-related AEs will be tabulated by descending frequency of SOC and descending frequency of PT within each SOC, unless specified otherwise.

- Overall summary of any AEs by worst CTC grade (grade 1, 2, 3, 4, 3-4, 5, unknown, total) presented by SOC/PT
- Overall summary of drug-related AEs by worst CTC grade (grade 1, 2, 3, 4, 3-4, 5, unknown, total) presented by SOC/PT

DLT rate will be summarized by treatment group.

**Listing:**

- All recorded Adverse Events will be listed.
- All recorded DLTs will be listed.

### 7.6.2 Deaths

**Summary:**

- All deaths will be summarized for cause of deaths by treatment group.

**Listing:**

- All recorded deaths for All Enrolled Subjects will be listed

### 7.6.3 Serious Adverse Events

**Summary:**

The following will be summarized by treatment arm and study part.

- Overall summary of SAEs by worst CTC grade (grade 1, 2, 3, 4, 3-4, 5) presented by SOC/PT
- Overall summary of drug-related SAEs by worst CTC grade (grade 1, 2, 3, 4, 3-4, 5) presented by SOC/PT.

**Listing:**

- By-subject SAE listing will be provided for the All Enrolled Subjects.

### 7.6.4 Adverse Events Leading to Discontinuation of Study Therapy

Adverse events leading to study drug discontinuation are AEs with action taken as "Drug was discontinued".

**Summary:**

- Overall summary of AEs leading to discontinuation by worst CTC grade (grade 1, 2, 3, 4, 3-4, 5, total) presented by SOC/PT
- Overall summary of drug-related AEs leading to discontinuation by worst CTC grade (grade 1, 2, 3, 4, 3-4, 5, total) presented by SOC/PT

**Listing:**

- By-subject AEs leading to discontinuation listing will be provided

### 7.6.5 Adverse Events Leading to Dose Delay

Adverse events leading to study drug dose delay are AEs with action taken as "Dose was delayed".

**Summary:**

- Overall summary of AEs leading to dose delay by worst CTC grade (grade 1, 2, 3, 4, 3-4, 5, total) presented by SOC/PT
- Overall summary of drug-related AEs leading to dose delay by worst CTC grade (grade 1, 2, 3, 4, 3-4, 5, total) presented by SOC/PT

**Listing:**

- By-subject AEs leading to dose delay listing will be provided

### 7.6.6 Events of Special Interest

The events of special interest (EOSI) consist of a list of preferred terms grouped by specific categories (endocrinopathies, infusion reactions, gastrointestinal, hepatobiliary, pulmonary, renal, skin). These categories are defined by the Sponsor and the list that is most current at the time of analysis will be used. Changes may be made to this list with each new version of MedDRA and the final list used for the CSR will be included in an Appendix of the CSR. At the time this SAP is finalized, Select AEs and IMAEs identified in the Nivolumab program will be used for this study.

**Summary**:

The following will be summarized by treatment arm and overall.

- Overall summary of any EOSI by worst CTC grade presented by Category/PT (grade 1, 2, 3, 4, 3-4, 5, total).

- Overall summary of drug-related EOSI by worst CTC grade presented by Category/ PT (grade 1, 2, 3, 4, 3-4, 5, total).
- Overall summary of any serious EOSI by worst CTC grade presented by Category/PT (grade 1, 2, 3, 4, 3-4, 5, total).
- Overall summary of any drug related serious EOSI by worst CTC grade presented by Category/PT (grade 1, 2, 3, 4, 3-4, 5, total).
- Overall summary of any EOSI leading to discontinuation by worst CTC grade presented by Category/PT (grade 1, 2, 3, 4, 3-4, 5, total).
- Overall summary of drug-related EOSI leading to discontinuation by worst CTC grade presented by Category/PT (any grade, grade 3-4, grade 5).

**Listing**:

- EOSI definition
- Listings for the EOSI will be provided.

### *7.6.7 Multiple 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 in order to collapse AE records into unique records based on the PT. This data will be presented as the rate per 100 person-years of exposure. These analyses will take into account all on-treatment events (allowing more than 1 event per subject) and the total duration of exposure. The person-year exposure will be computed as the sum over the subjects' exposure expressed in years where the duration of exposure is defined as:

- Date of last dose of study treatment - date of first dose of study treatment + 101 days, for subject who are off study treatment and were followed for at least 100 days after last dose of study medication.
- Last known date alive - date of first dose of study medication + 1, for subjects who are still on-treatment or who are off study treatment and were followed less than 100 days after last dose of study medication.

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

**Summary**:

The following summary tables will be provided:

- Total number and rate (exposure adjusted) of occurrences for all AEs.
- For EOSI:

– Frequency of unique AEs, meaning the number of subjects experiencing an AE once or multiple times by treatment arm and dose

**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.

### *7.6.8 Clinical Laboratory Evaluations*

Clinical laboratory data will be analyzed using International System of Units (SI). Analyses may be repeated using US conventional units. In addition, further analyses on specific laboratory parameters will be performed by treatment group and is described in Sections 7.6.8.1 and 7.6.8.2.

**Summary**:

The number (%) of subjects with the following will be summarized by treatment group and study part, if appropriate, using the worst CTC grade on-treatment per subject.

- Post-baseline grade
- Shift-table of worst on-study CTC grade compared to baseline CTC grade

**Listing**:

- A by-subject listing of these laboratory parameters will be provided.
- Laboratory abnormality criteria
- Laboratory results outside of normal range

#### *7.6.8.1 Abnormal Hepatic Function Test*

**Summary:**

The number of subjects with the following laboratory abnormalities from on-treatment evaluations will be summarized by treatment group.

- 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:**

The following scatter plots will be produced for the following hepatic laboratory parameters. On-treatment peak total bilirubin and on-treatment peak AST/ALT may or may not happen on the same day of liver testing.

- Total bilirubin peak vs. AST peak

- Total bilirubin peak vs. ALT peak

**Listing:**

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

#### 7.6.8.2 Abnormal Thyroid Function Test

**Summary:**

The number of subjects with the following laboratory abnormalities from on-treatment evaluations will be summarized by treatment group.

- TSH value > ULN and
  - with baseline TSH value ≤ ULN
  - at least one T3/T4 test value < LLN

- TSH < LLN and
  - with baseline TSH value ≥ LLN
  - at least one T3/T4 test value > ULN

**Listing:**

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

### 7.6.9 Electrocardiograms

**Summary**:

Summary statistics of baseline and change from baseline will be presented for heart rate, PR interval, QRS width, QT interval, QTcF and change in QTcF (ΔQTcF) by treatment group.

In addition, the frequency distribution of subjects' maximum recorded post-dose PR interval, QRS width, QTcF and change in QTcF (ΔQTcF) will be tabulated by treatment and summarized for the following ranges:

- For PR:
  - PR ≤ 200 msec
  - PR > 200 msec

- For QRS:
  - QRS ≤ 120 msec
  - QRS > 120 msec

- For QTcF:
  - QTcF ≤ 450 msec
  - 450 msec < QTcF ≤ 480 msec
  - 480 msec < QTcF ≤ 500 msec
  - QTcF > 500 msec

- For ΔQTcF:
  - ΔQTcF ≤ 30 msec
  - 30 msec < ΔQTcF ≤ 60 msec
  - ΔQTcF > 60 msec

**Listing:**

- A by-subject listing of all ECG measures
- A listing of only abnormal ECG interpretations

### *7.6.10 Vital Signs and Physical Findings*

**Summary:**

The following parameters and their corresponding change from baseline will be summarized by timepoint and treatment group.

- Vital Signs

**Listing**:

- Vital Signs
- Abnormal physical examination findings
- Diagnostic procedures
- Medical treatment procedures

### *7.6.11 Exploratory Safety Analysis: DLT*

All available DLT information (DLTs within DLT observation period and outside DLT observation period) may be considered to assess posterior dose-toxicity profile.

**Summary:**

- After completion of dose escalation, the final posteriors for parameters of BLRM and BLRM-Copula models that describe the DLT profile of BMS-986178 alone and in combination with nivolumab and/or ipilimumab may be summarized.

- Plots of fitted dose-DLT curve may be presented for BMS-986178 alone and in combination with nivolumab and/or ipilimumab.

## 7.7 *Immunogenicity*

Analysis dataset and data listing will include all available ADA samples.

**Summary:**

Number (%) of subjects will be reported for the following parameters based on Immunogenicity (ADA) Population by treatment for BMS-986178, nivolumab and ipilimumab: Impact of re-treatment might be explored.

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

**Listings:**

- A listing all ADA assessments will be provided.

Associations between immunogenicity measures and PK and/or selected AEs may be explored.

## 7.8 *Pharmacokinetics*

**Summary:**

- Summary statistics will be provided for PK parameters for BMS-986178 by treatment across all Parts:

  Geometric means and coefficients of variation (CV[%]) will be presented for Cmax, AUC, Ctau, AI, CLT, Ctrough, and Css-avg. Medians and ranges will be presented for time of maximum observed serum concentration (Tmax). Means and standard deviations will be presented for all other PK parameters (e.g. T-HALFeff).
- Geometric means and coefficients of variation (CV[%]) for Ctrough for BMS-986178, Nivo and Ipi will be summarized by treatment and time point.
- Nivolumab and ipilimumab end of infusion and trough (Ctrough) concentrations and BMS-986178 trough concentration will be tabulated by treatment and study day using summary statistics. These data may also be pooled with other datasets for population PK analysis, which will be presented in a separate report.

**Listing:**

- All individual PK parameters will be listed for PK Subjects by treatment
- Ctrough will be listed by treatment, treatment cycle, and study day.

**Figure:**

- The following scatter plots will be produced for the following PK parameters for BMS-986178 by treatment across all Parts:
    - Cmax
    - Ctrough
    - AUC(0-t)
    - AUC(TAU)

### *7.8.1 Dose Proportionality*

Summary statistics as well as plots will be provided for dose proportionality analyses focusing on initial treatment and additional treatments. Re-treatment phase might be explored if data permits. Plot of individual BMS-986178 serum PK parameter (Cmax, AUC(TAU)) values with fitted regression line versus dose will also be presented on a log-log scale by treatment and cycle/day.

To assess the dose proportionality, the power model described by Gough et al[4]

$$\text{PK Parameter} = A*\text{Dose}^{\beta}$$

will be estimated by the simple linear regression of the natural log of the PK Parameter (Cmax, AUC(TAU)) on the natural log of Dose:

$$E[\log(\text{PK Parameter})|\ \text{Dose}] = \alpha + \beta*\log(\text{Dose}).$$

A slope ($\beta$) equal to 1 would indicate perfect dose proportionality. For each PK parameters (Cmax, AUC (TAU)), the point estimates and 90% CI of the slopes will be provided.

AUC(0-T) will not be used for dose proportionality as it is largely redundant with AUC(TAU).

## 7.9 Biomarker Analysis

Due to the exploratory nature of this study, analyses listed below may or may not be performed depending on data availability (some exploratory measurements in the study may be subject to change as technologies and assay methods evolve). Additional types of analyses may be conducted on a post-hoc basis pending review of data. Not all exploratory analyses will be included in the Clinical Study Report (CSR) unless they represent meaningful findings or are relevant to subject management. The biomarker subject population will be used to present results.

### *7.9.1 Primary Biomarker Analysis*

Not applicable.

### *7.9.2 Secondary Biomarker Analysis*

Not applicable.

[redacted]

[redacted]

[redacted]

## 8 CONVENTIONS

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[1]. 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[2].

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 present 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 cases where 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.

The following conversion factors will be used to convert days to months or years: 1 month = 30.4375 days and 1 year = 365.25 days.

Duration (e.g. time from first diagnosis to first dosing date, duration of response, and time to response) will be calculated as follows:

Duration = (Last date - first date + 1)

All statistical analyses will be carried out using SAS (Statistical Analysis System software, SAS Institute, North Carolina, USA) unless otherwise noted.

## 8.1 Pharmacokinetic Summaries

In-text Tables

For in-text PK tables, %CV will be reported as integers. For other statistics except for SDs, values of 100 or higher will be presented as integers, values of 10 to < 100 will be displayed to 1 decimal place, and values of 1 to < 10 will be displayed to 2 decimal places. Values less than 1 will be displayed to 3 decimal places. Ratios will also be displayed to 3 decimal places. Standard deviations will be reported to the same precision as the mean.

Handling of Non-quantifiable Concentrations

For the summaries of plasma 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, predose 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.

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

Treatment of Outliers

Individual plasma concentrations, if deemed to be anomalous, may be excluded from the analysis following a review of available documentation (e.g., bioanalytical report, clinical data). Any such exclusion will be clearly listed in the clinical study report (CSR) along with justification for exclusion.

Entire plasma concentration-time profiles for a participant may be excluded following review of available documentation (e.g., bioanalytical report, clinical data). However, results of analysis with and without the excluded profiles may be presented in the CSR. Any such exclusion will be clearly listed in the clinical study report (CSR) along with justification for exclusion.

Pharmacokinetic Exclusions[3]

Pharmacokinetic analysis, reporting, and exclusion criteria should following the BMS PK Harmonization document Version 2.0. Specific guidelines for exclusionary criteria for half-life and how other PK parameters are affected for exclusion are included in Section 9.2 of the BMS PK Harmonization document.

Exclusion of 1 or more parameters or the entire dataset may be considered due to incomplete profiles such as AUC(INF) or when T-HALF cannot be reliably calculated, or there is no sample around the suspected Cmax. In addition, participants may be excluded from the analysis if they missed doses, had diarrhea, or vomited at or before a time equal to twice the median Tmax for

immediate-release products, or vomited at any time during sampling after the administration of modified-release formulations.

# 9 CONTENT OF REPORTS

[redacted]

# STATISTICAL ANALYSIS PLAN
# FOR CLINICAL STUDY REPORT

A Phase 1/2a Study of BMS-986178 Administered Alone or in Combination with Nivolumab and/or Ipilimumab in Subjects with Advanced Solid Tumors

**PROTOCOL(S) CA012004**

**VERSION # 3.0**

## REVISION HISTORY

| Revision | Date | Revised By | Changes Made -- Reasons for the Change |
|---|---|---|---|
| 1.0 | 08/08/2017 | [redacted] | Original issue |
| 2.0 | 15/06/2018 | [redacted] | Addition of Part 8 |
| 3.0 | Aug 11 2021 | [redacted] | For Part 9 only |

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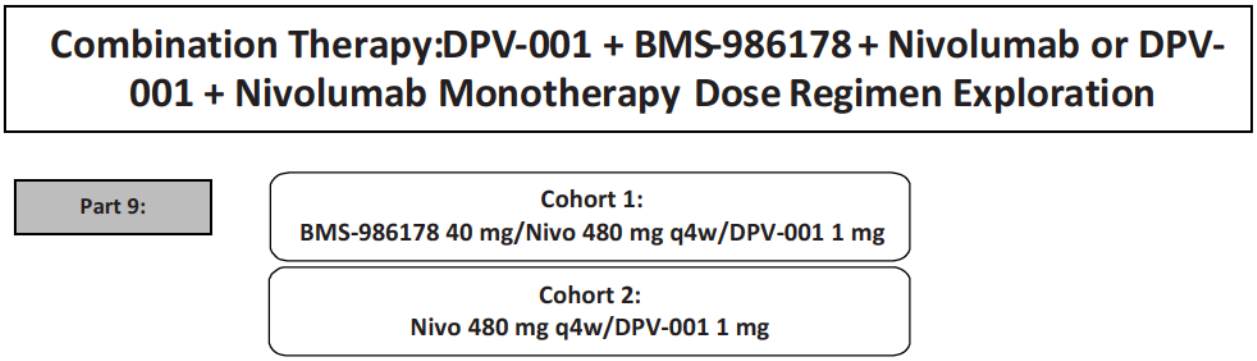
# 2 STUDY DESCRIPTION

## 2.1 Study Design

This is a Phase 1/2a, open-label study of BMS-986178 in subjects with advanced solid tumors that integrates initial BMS-986178 monotherapy with subsequent nivolumab and/or ipilimumab combination therapy.

Parts 1-8 have been completed, and the scope of this SAP is limited to Part 9 expansion. In Part 9, subjects will be randomized to cohort 1 or cohort 2. The study design schematic for Part 9 is presented in Figure 2.1-1.

**Figure 2.1-1: Study Design Schematic (Part 9)**




**Part 9 Cohort 1**

Cohort 1 is a combination of BMS-986178, nivolumab, DPV-001 (UbiLT3 and UbiLT6) vaccine, and single dose cyclophosphamide. Single-dose cyclophosphamide 300 mg/m$^2$ is to be administered IV over a 30 to 60 minute infusion, 3 days prior to C1D1. On C1D1 the subjects will receive both UbiLT3 and UbiLT6 intranodal (IN) injection by ultrasound guidance. DPV-001 on C1D1 will consist of both UbiLT3 and UbiLT6 vaccine (total of 1.0 mL suspension, 0.5 mL suspension UbiLT3 into 1 lymph node and 0.5 mL of UbiLT6 into another lymph node). After the DPV-001 is administered on C1D1, the subject will be administered BMS-986178, as a flat dose of 40 mg (q4w) over a 30-minute infusion. The order of dose administration is DPV-001 then BMS-986178 for C1D1.

On day C1D8, the subject will be administered both UbiLT3 and UbiLT6, at the same dose listed on C1D1, but it will be administered intradermally (ID).

On C1D15, the subject with be administered UbiLT3 ID which will then commence alternating between UbiLT3 and UbiLT6 on subsequent doses, then the subject will be administered nivolumab at 240 mg infusion over 30 minutes. BMS-986178 will only be given on day 1 of cycles 1-6, 9, and 12.

DPV-001 vaccine will be given as a total of 1 mg (in 1.0 mL) flat dose at each adminstration starting on C1D15. Vaccine may be given as multiple injections due to volume, according to institutional policy.

Subsequent doses of DPV-001 are delivered ID q2w (1.0 mL suspension ID rotating between UbiLT3 and UbiLT6 on alternate vaccinations, starting with UbiLT3) which starts at C1D15 for a total of 4 doses. From C3D1 to C6D1, subjects will receive this vaccine q4w, (still alternating between the UbiLT3 and UbiLT6). After cycle 6, the vaccine will be given 2 more times, at C9D1 and C12D1 (still alternating between the UbiLT3 and UbiLT6).

From C2D1 through C6D1, nivolumab will be administered as a 480 mg flat dose q4w. It will be administered as an infusion over a 30-minute period, after DPV-001 is given. BMS-986178 will be administered following a 30-minute observation period after the nivolumab dosing. Nivolumab will continue to be administered as a 480 mg flat dose q4w. At C7D1, C8D1, C10D1, C11D1 and C13D1 to C26D1, nivolumab will be given as a monotherapy dose.

Approximately 12 subjects will be treated in this cohort. All cycles will be 4 weeks in length.

**Part 9 Cohort 2**

Cohort 2 is a combination of nivolumab, DPV-001 (UbiLT3 and UbiLT6) vaccine, and single dose cyclophosphamide. Single-dose cyclophosphamide 300 mg/m$^2$ is to be administered IV over a 30 to 60 minute infusion, 3 days prior to C1D1. On C1D1 the subjects will receive DPV-001 IN by ultrasound guidance. DPV-001 on C1D1 will consist of both UbiLT3 and UbiLT6 vaccine (total of 1.0 mL suspension, 0.5 mL suspension UbiLT3 into one lymph node and 0.5 mL of UbiLT6 into another lymph node).

On day C1D8, the subject will be administered both UbiLT3 and UbiLT6, at the same dose level above, but it will be administered ID.

On C1D15, the subject will be administered UbiLT3 ID which will then commence alternating between UbiLT3 and UbiLT6 on subsequent doses. Then the subject will be administered nivolumab at 240 mg infusion over 30 minutes on C1D15.

DPV-001 vaccine will be given as a total of 1 mg (in 1.0 mL) flat dose at each adminstration starting on C1D16. Vaccine may be given as multiple injections due to volume, according to institutional policy.

Subsequent doses of DPV-001 are delivered ID q2w (1.0 mL suspension ID rotating between UbiLT3 and UbiLT6 on alternate vaccinations, starting with UbiLT3), which starts at C1D15 for a total of 4 doses. From C3D1 to C6D1, subjects will receive this vaccine q4w, still alternating between the UbiLT3 and UbiLT6). After cycle 6, the vaccine will be given 2 more times, at C9D1 and C12D1.

Beginning at C2D1 through C26D1, nivolumab will be administered as a 480 mg flat dose q4w on Day 1 of each cycle, as an infusion over a 30-minute period. When nivolumab and DPV-001 are given together, DPV-001 will be given first.

Approximately 6 subjects will be treated in this cohort. All cycles will be 4 weeks in length.

One sentinel subject will be dosed initially in each cohort in Part 9, prior to dosing of subsequent subjects. The sentinel subject will be observed for 5 days before the next subject is dosed. If cytokine release syndrome or unexpected toxicity occurs in the first treated subject during the

sentinel observation period, subsequently 2 subjects will be treated sequentially, with an interval period of at least 5 days between the beginning of treatment for patient 2 and 3. If cytokine release syndrome is observed in 2 of the first 3 treated subjects, then the regimen and/or schedule will be re-evaluated, with consideration for lower doses of study drug(s) before additional subjects are enrolled.

## 2.2 Treatment Assignment

CA012004 is an open label study. After the subject's initial eligibility is established and informed consent has been obtained, the subject must be enrolled into the study by calling an Interactive Response Technology (IRT) to obtain the subject number. The investigator or designee will register the subject for enrollment by following the enrollment procedures established by BMS.

The following information is required for registration:

- Gender
- Diagnosis (if applicable)
- Statement that subject is eligible
- Date of informed consent
- Date of Birth

Based on the rate of subject enrollment, the Sponsor will implement an IRT to assign subject numbers, study part and dose level as well as manage drug supply. IRT instructions will be provided to the sites in a separate instruction manual.

Treatment group/dose level will be provided to the site study team through the IRT after the subject has been deemed eligible and is assigned for the study. Site personnel/investigator will receive a receipt confirming the treatment assignment. A copy of this documentation should remain in the subject's chart. Because of the nature of the study design, limited early access to the assignment information will be granted to the study team.

Once it is determined that the subject meets the eligibility criteria, the investigative site will register the subject through IRT prior to the first study drug administration.

Subjects will be assigned to a part or a cohort within a part by IRT. Details about how the subjects will be assigned to a specific part/cohort will be provided in IRT training documentation.

Subjects may be permitted to rescreen for the study following agreement between the investigator and the Sponsor/medical monitor

## 2.3 Blinding and Unblinding

This is an open label study.

## 2.4 Protocol Amendments

**Table 2.4-1: List of Protocol Amendment**

| Amendment number | Date | Summaries |
|---|---|---|
| 1 | 26-Apr-2016 | • The timing of the initiation of combination therapy dose escalation cohorts was revised, a sentinel subject was added to all dose cohorts, Parts 1B and 2B were removed and the subsequent study parts were renamed (Part 1C to Part 1B, Part 2C to Part 2B, and Part 2D to Part 2C), DLT period across the study (28 days) was made uniform, the post-infusion observation period was extended to 4 hours, contraceptive requirements were updated, lipase and amylase ≤ 1.5×ULN were removed as criteria for adequate organ function, DLT criteria were revised, a timepoint was added for safety monitoring, the rationale for use of blood and tumor tissue in biomarker studies was clarified, prior therapy requirements for dose expansion cohorts were updated, and BLRM language was clarified<br>• Typographical errors were corrected, and clarifications were made for consistency. |
| 2 | 08-Jun-2016 | • Change the definition for "Related AE's" and "Not Related AE's".<br>• Update prior therapy inclusion criteria for dose escalation subjects<br>• Remove timeframe from hematologic DLT grade 3 febrile neutropenia.<br>• Change to have CBC with differential processed through LLDS.<br>• Add new model document language for Additional Research Collection and Imaging scans.<br>• Typographical errors were corrected, and clarifications were made for consistency. |
| 3 | 23-Nov-2016 | • Removal of Part 1B<br>• Addition of Part 2D, 2E, 3C and Part 2A cohort dose -1<br>• Change to have imaging as central read<br>• Add text to allow for intermediate and lower doses in escalation<br>• Included text to add potentially more than 1 dose at RP2D<br>• Updated versions numbers for current IB's.<br>• Updating to the new PMD for WOCBP Section<br>• Require fresh tumor biopsy from all subjects<br>• Additional sample to be collected in combination cohorts for RO<br>• Update to not require archived tumor biopsies |

**Table 2.4-1: List of Protocol Amendment**

| Amendment number | Date | Summaries |
|---|---|---|
| | | • Updated Statistical Analysis section<br>• Typographical errors were corrected, and clarifications were made for consistency. |
| 4 | 04-Apr-2017 | • Addition of Parts 4,5,6 and 7<br>• [redacted]<br>• Update of study design and study visit schematic<br>• Update of inclusion and exclusion criteria to include the new parts and clarify the maximum number of prior treatments allowed<br>• Update of study drug dosing and method of assigning subjects<br>• Update of dose delay language and addition of criteria for resuming treatment in subjects with an infusion reaction<br>• Update/addition of tables for treatment procedures, pharmacokinetic and anti-drug antibody sampling schedule, and pharmacodynamic/ biomarker sampling schedule<br>• Update of sample size information to include the new parts<br>• Update of Appendix 1 to include statistical methods for the new parts<br>• Typographical errors were corrected, and edits were made for consistency and clarity. |
| 5 | 11-Dec-2017 | • Addition of Part 8<br>• Update of Appendix 1<br>• Update schedule of assessments<br>• Update of address<br>• Typographical errors were corrected, and edits were made for consistency and clarity |
| 5a | 22-Jun-2018 | • Incorporates DRibble vaccine (DPV-001) as a new combination with BMS 986178 in Part 9<br>• Update Schedule of assessments to incorporate Part 9<br>• Typographical errors were corrected, and edits were made for consistency and clarity |
| 5b | 26-Nov-2019 | • Included all changes from Revised Protocol 05a<br>• Updated introduction, study and dosing rationales, objectives, and schedule and dose exploration and safety exploration to reflect the addition of Part 9 |

**Table 2.4-1: List of Protocol Amendment**

| Amendment number | Date | Summaries |
|---|---|---|
| | | • Clarified that Parts 1-8 have been completed<br>• Updated subject treated numbers for BMS986178 and nivolumab based on most current IBs.<br>• Added references to myocarditis based on most current nivolumab IB.<br>• Removed Retreatment and Survival/Response FU visits for subjects in Part 1-9.<br>• Defined maximum treatment duration.<br>• Removed select PK/PD samples<br>• Updated inclusion criteria for ER and PR for TNBC (Part 9) consistent with ASCO/CAP guidelines.<br>• Updated criteria for complete abstinence.<br>• Typographical errors were corrected, and edits were made for consistency and clarity |

# 3 OBJECTIVES

## 3.1 Primary

- To determine the safety, tolerability, DLTs, and MTD/RP2D of BMS-986178 administered alone or in combination with nivolumab and/or ipilimumab or DPV-001 in subjects with advanced solid tumors

## 3.2 Secondary Objectives for Part 9

- To investigate the preliminary anti-tumor activity of BMS 986178 in combination with nivolumab and DPV-001 and nivolumab in combination with DPV-001 in subjects with triple negative breast cancer (TNBC)
- To characterize the pharmacokinetics (PK) of BMS 986178 in combination with nivolumab and DPV-001
- To characterize the immunogenicity of BMS 986178 in combination with nivolumab and DPV-001
- To assess the proportion of subjects showing a change in peripheral or tumor pharmacodynamic biomarkers such as sustained T cell expansion with DPV-001 in combination with BMS-986178 and nivolumab or nivolumab monotherapy

[redacted]

[redacted]

# 4 ENDPOINTS

## 4.1 Primary Endpoints

The assessment of safety will be based on the incidence of dose-limiting toxicities (DLTs), adverse events (AEs), serious adverse events (SAEs), AEs leading to discontinuation, and deaths. In addition, clinical laboratory test abnormalities will be examined. AEs and laboratory values will be graded according to NCI CTCAE v4.03 (National Cancer Institute Common Terminology Criteria for Adverse Events).

## 4.2 Secondary Endpoints

### *4.2.1 Efficacy*

The anti-tumor activity of BMS-986178 in combination with nivolumab and DPV-001, and nivolumab in combination with DPV-001 will be measured by Objective Response Rate (ORR) based on RECIST v1.1. BMS-986178 alone or in combination with nivolumab and/or ipilimumab is not applicable for Part 9.

- Best overall response (BOR) is assessed by Investigator per RECIST 1.1 criteria.
- ORR: the total number of subjects whose BOR is either a complete response (CR) or partial response (PR) divided by the total number of subjects in the population of interest.

### *4.2.2 Pharmacokinetics*

The PK of BMS-986178 may be characterized using the following endpoints:

- Cmax: Maximum observed serum concentration
- Tmax: Time of maximum observed serum concentration
- Ctau: Observed serum concentration at the end of a dosing interval when intensive samples are collected
- AUC(0-t): Area under the serum concentration-time curve from time 0 to time t
- AUC(TAU): Area under the serum concentration-time curve in 1 dosing interval
- CLT: Total body clearance
- Ctrough: Trough observed plasma concentration (this includes predose concentrations and Ctau concentrations).
- Css-avg: Average concentration over a dosing interval (AUC(TAU)/tau)
- AI: Accumulation Index. Ratio of an exposure measure at steady state (eg, following Cycle 3 Day 1 dose) to that after the first dose (exposure measure includes AUC(TAU), Cmax and Ctau)
- T-HALFeff: Effective elimination half-life that explains the degree of accumulation observed for a specific exposure measure (exposure measure includes AUC(TAU), Cmax)

### 4.2.3 Immunogenicity

The secondary objective of immunogenicity will be assessed by the frequency of positive ADA to BMS-986178 or nivolumab. Ipilimumab is not applicable for Part 9.

At the sample level, individual samples will be characterized into following category as shown below.

**Table 4.2.3-1: Sample ADA Status**

| Sample ADA Status | Definition |
|---|---|
| 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:

**Table 4.2.3-2: Participant ADA Status**

| ADA Status | Definition |
|---|---|
| Baseline ADA-positive subject | A participant with baseline ADA-positive sample |
| **ADA-positive subject** | 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*[a] 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 subject** | A participant with no ADA-positive sample after the initiation of treatment |

[a]16 week threshold was chosen based on the long half-life of immunoglobulin.

### 4.2.4 Pharmacodynamics

The secondary objective of pharmacodynamics will be assessed by the proportion of subjects showing a change in pharmacodynamic biomarkers such as soluble OX40 and peripheral OX40 receptor occupancy along with tumor pharmacodynamic of BMS-986178 in combination with

nivolumab or nivolumab monotherapy (Part 8), and sustained T cell expansion with DPV-001 in combination with nivolumab or nivolumab monotherapy (Part 9).

[redacted]

[redacted]

# 5 SAMPLE SIZE AND POWER

## 5.1 Schedule and Dose Exploration and Safety Exploration

The purpose of Part 9 is primarily to evaluate safety and tolerability and secondarily to assess PD and investigate preliminary anti-tumor activity of DPV-001 in combination with nivolumab with and without BMS-986178. Part 9 includes a cohort for the combination of BMS-986178, nivolumab, DPV-001 vaccine, single dose cyclophosphamide (cohort 1) and a cohort for the combination of nivolumab, DPV-001 vaccine, and single dose cyclophosphamide (cohort 2). Subjects are to be randomized in a 2:1 ratio. A total of 12 subjects will be treated in cohort 1 and 6 evaluable subjects will be treated in cohort 2. Approximately 20% additional subjects may be enrolled in each cohort to ensure the number of evaluable subjects is achieved.

Administration of DPV-001 in combination with nivolumab +/- BMS-986178 in 6 to 12 subjects per dose and schedule level provides some precision of PD biomarker effect estimation. If more

precise estimation is needed based on data observed, Part 9 may be further expanded to 24 subjects for Cohort 1 and 12 subjects for Cohort 2. To assess the PD effects, pre-treatment and on-treatment whole blood and serum samples and tumor biopsies will be required. It is of interest to ensure the precision of the estimate of the ratio of on-treatment biomarker assessments to pre-treatment (baseline) levels. Assuming that a biomarker is measured as a continuous variable, a given number of subjects will provide the confidence that the estimate of the ratio of on-treatment to baseline values will be within 20% of the true value, as shown in Table 5.1-1.

**Table 5.1-1: 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 |
|---|---|---|---|---|---|---|---|---|
| Probability | N = 6 | 92% | 76% | 62% | 52% | 44% | 38% | 34% |
| | N = 12 | 99% | 90% | 78% | 68% | 59% | 52% | 46% |
| | N = 24 | 100% | 98% | 92% | 84% | 76% | 68% | 62% |

For example, for a biomarker (eg, activated and memory CD4 and CD8 T-cells) with an intrasubject standard deviation of 0.5, if the true ratio of post-baseline to baseline geometric means is 1.2 (increase from baseline is 20%), there is 68% probability that the estimated ratio would be within 0.96 and 1.44 (or a percent change between -4% and 44%) with 12 subjects per treatment arm and the probability is 84% with 24 subjects per arm. If the true increase from baseline is 60%, for a biomarker with the same variability, then there is 68% probability that the estimated percent change would be between 28% and 92% with 12 subjects per treatment arm and between 37% and 83% with 24 subjects per treatment arm.

# 6 STUDY PERIODS, TREATMENT REGIMENS AND POPULATIONS FOR ANALYSES STUDY PERIODS

## 6.1 Study Periods

For the purpose of analysis, baseline period (Section 6.1.1) and post baseline period (Section 6.1.2) will be considered.

### *6.1.1 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 medication.

The following definitions will apply:

- Pre-treatment AEs will be defined as AEs with an onset date and time prior to but not including the day and time of the first dose of study treatment (or with an onset date prior to the day of the first dose of study treatment if time is not collected or is missing).
- Baseline evaluations (laboratory tests, pulse oximetry, vital signs, and ECG) will be defined as evaluations with a date and time on or prior to the day and time of the first dose of study

treatment (or with an onset date on or prior to the day of the first dose of study treatment if time is not collected or is missing).

If there are multiple valid assessments, the assessment that is closest to day (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 considered as baseline.

Tumor assessments will be slotted in the baseline period if assessments are before or on start of the treatment date. Baseline tumor assessment is the last assessment in the baseline period.

### *6.1.2 Post Baseline Period*

Treatment Period starts with the first dose date-time of study treatment.

- On-treatment AEs will be defined as AEs with an onset date-time on or after the date and time of the first dose of study treatment (or with an onset date on or after the day of the first dose of study treatment if time is not collected or is missing). For subjects who are off treatment, AEs will be counted as on-treatment if the event occurred within 100 days of the last dose of study medication. No "subtracting rule" will be applied when an AE occurs both pre-treatment and post-treatment with the same preferred term and grade. For subjects who are still on study treatment, all available AEs will be counted as on-treatment after the datetime (or date if time is not collected or missing) of the first dose.
- On-treatment evaluations (laboratory tests, pulse oximetry and vital signs) will be defined as evaluations taken after the day (and time, if collected and not missing) of the first dose of study treatment. For subjects who are off treatment, evaluations will be counted as on-treatment if evaluation is taken within 100 days of the last dose of study medication. For subjects who are still on study treatment, all available evaluations will be considered as on-treatment after the datetime of the first dose.
- Principal analysis of safety endpoints will be based on the treatment period.
- Tumor assessments will be slotted in the post-baseline period if assessments are after start of the treatment date.

## 6.2 Treatment Regimens

The treatment group "as treated" will be the same as the arm as assigned by IRT. However, if a subject received the incorrect drug for the entire period of treatment, the subject's treatment group will be defined as the incorrect drug the subject actually received.

## 6.3 Populations for Analyses

- **All enrolled subjects**: All subjects who signed an informed consent form and were registered into the IRT.
- **All treated subjects**: All subjects who received any dose of study therapy. This is the primary population for drug exposure, efficacy and safety analysis.
- **PK subjects**: All subjects with available serum time-concentration data from subjects who received any BMS-986178 or Nivolumab.

- **Immunogenicity subjects**: All subjects with available data from subjects who received any BMS-986178 or Nivolumab and have baseline and at least one post baseline immunogenicity measurement.
- **Biomarker Evaluable Subjects**: All Treated Subjects with at least one evaluable measurement for a specific marker will be included in the dataset for that marker. Evaluable may differ depending on the analysis.
- **Response Evaluable Subjects**: All treated subjects with measurable disease at baseline and one of the following: 1) at least one post-baseline tumor measurement, 2) clinical progression or 3) death. This population may be used for interim efficacy analysis due to insufficient follow up

# 7 STATISTICAL ANALYSES

All analyses will be performed in SAS using version 9.2 or higher.

## 7.1 General Methods

Continuous variables will be summarized by treatment group using the mean, standard deviation, 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. Percentages will be rounded and may not always add up to 100. Percentages less than 0.1 will be indicated as "< 0.1".

Data will be summarized only if there are more than 5 subjects in Part 9.

## 7.2 Study Population

### *7.2.1 Subject Disposition*

The following subject disposition will be listed

**Listing**:

- Pre-treatment period: All enrolled Subjects with reason
- End of treatment period: Treated subjects with reason for discontinuation of treatment.

### *7.2.2 Demographics and Other Baseline Characteristics*

The following subject demographics will be listed by treatment arm.

- Age (in years);
- Gender
- Race
- Ethnicity

**Listing**:

- All relevant data, variables listed above

## 7.3 Extent of Exposure

Listings will include all available exposure data, and will be performed on the population of All Treated Subjects "as treated" as described in Section 6.2.

**Listing:**

- Drug administration of study medication

## 7.4 Efficacy

The primary efficacy analyses will be performed on All Treated Subjects for the final analysis. Summary analysis including ORR and BOR summary will be performed only if there are more than 5 subjects in Part 9. All analyses will be presented by part, treatment group and/or tumor type (if appropriate), unless otherwise specified. Listings of BOR will be provided.

**Summary**:

The following will be summarized only if there are more than 5 subjects in Part 9

- The ORR with corresponding 2-sided 95% CI based on the Clopper-Pearson method, along with each category of BOR. .

**Listing**:

The following will be listed by tumor type and treatment group.

- Subject level efficacy for All Treated Subjects: BOR, best response in target lesions, duration of response for responders

## 7.5 Safety

Analysis of safety will be based on All Treated Subjects and presented by treatment arm and overall. Deaths and SAEs will be listed using All Enrolled Subjects. Data will be summarized only if there are more than 5 subjects in Part 9. Moreover, a single Adverse Event listing is sufficient if there are 5 subjects or less in Part 9.

Adverse events will be coded according to the most recent version of Medical Dictionary for Regulatory Activities (MedDRA) at the time of database lock and the severity will be graded using the NCI CTCAE version 4.03. Drug-related AEs are those events with relationship to study drug "Related" as recorded on the Case Report Form (CRF). If the relationship to study drug is missing, the AE will be considered as drug-related.

Listing of adverse events will include all enrolled subjects as SAEs and deaths are collected pretreatment. Summaries of adverse events will include all on-treatment adverse events as defined in section 6.1.2.

When reporting adverse events by CTC grade, summary tables will be provided based on the event with worst CTC grade (independent of relationship to study medication). Subjects will only be counted (1) once at the preferred term (PT) level, (2) once at the system organ class (SOC) level, and (3) once in the 'Total subject' row at their worst CTC grade, regardless of SOC or PT.

The analysis of laboratory results will be based on All Treated Subjects. Laboratory results will be categorized according to NCI CTCAE (version 4.03) grade. Baseline is defined as the last non-missing measurement prior to the first dosing date and time. Summaries of laboratory results include baseline and on-treatment results as defined in section 6.1.2.

### 7.5.1 All Adverse Events

**Summary:** (Applicable only if there are more than 5 subjects in Part 9)

AEs and drug-related AEs will be tabulated by descending frequency of SOC and descending frequency of PT within each SOC, unless specified otherwise.

- Overall summary of any AEs by worst CTC grade (grade 1, 2, 3, 4, 3-4, 5, unknown, total) presented by SOC/PT
- Overall summary of drug-related AEs by worst CTC grade (grade 1, 2, 3, 4, 3-4, 5, unknown, total) presented by SOC/PT
- DLT rate will be summarized by treatment group.

**Listing:**

- All recorded Adverse Events will be listed.
- All recorded DLTs will be listed.

### 7.5.2 Deaths

**Summary:** (Applicable only if there are more than 5 subjects in Part 9)

- All deaths will be summarized for cause of deaths by treatment group.

**Listing:**

- All recorded deaths for All Enrolled Subjects will be listed

### 7.5.3 Serious Adverse Events

**Summary:** (Applicable only if there are more than 5 subjects in Part 9)

The following will be summarized by treatment arm and study part.

- Overall summary of SAEs by worst CTC grade (grade 1, 2, 3, 4, 3-4, 5) presented by SOC/PT
- Overall summary of drug-related SAEs by worst CTC grade (grade 1, 2, 3, 4, 3-4, 5) presented by SOC/PT.

**Listing:**

- By-subject SAE listing may be provided for the All Enrolled Subjects.

### 7.5.4 Adverse Events Leading to Discontinuation of Study Therapy

Adverse events leading to study drug discontinuation are AEs with action taken as "Drug was discontinued".

**Summary:** (Applicable only if there are more than 5 subjects in Part 9)

- Overall summary of AEs leading to discontinuation by worst CTC grade (grade 1, 2, 3, 4, 3-4, 5, total) presented by SOC/PT

- Overall summary of drug-related AEs leading to discontinuation by worst CTC grade (grade 1, 2, 3, 4, 3-4, 5, total) presented by SOC/PT

**Listing:**

- By-subject AEs leading to discontinuation listing may be provided

### 7.5.5 *Clinical Laboratory Evaluations*

Clinical laboratory data will be analyzed using International System of Units (SI).

**Summary**: (Applicable only if there are more than 5 subjects in Part 9)

The number (%) of subjects with the following will be summarized by treatment group and study part, if appropriate, using the worst CTC grade on-treatment per subject.

- Post-baseline grade
- Shift-table of worst on-study CTC grade compared to baseline CTC grade

**Listing**:

- A by-subject listing of these Laboratory results outside of normal range will be provided

## 7.6 *Immunogenicity*

Analysis dataset and data listing may be performed if data from ADA samples are available.

**Summary:**

Number (%) of subjects may be reported for the following parameters based on Immunogenicity (ADA) Population by treatment for BMS-986178, nivolumab and ipilimumab:

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

**Listings:**

- A listing all ADA assessments may be provided.

Associations between immunogenicity measures and PK and/or selected AEs may be explored.

## 7.7 *Pharmacokinetics*

PK analysis may be performed if data is available.

**Summary:**

- Summary statistics may be provided for PK parameters for BMS-986178 by treatment across all Parts:

Geometric means and coefficients of variation (CV[%]) may be presented for Cmax, AUC, Ctau, AI, CLT, Ctrough, and Css-avg. Medians and ranges may be presented for time of maximum observed serum concentration (Tmax). Means and standard deviations may be presented for all other PK parameters (e.g. T-HALFeff).

- Geometric means and coefficients of variation (CV[%]) for Ctrough for BMS-986178, Nivo and Ipi may be summarized by treatment and time point.
- Nivolumab and ipilimumab end of infusion and trough (Ctrough) concentrations and BMS-986178 trough concentration may be tabulated by treatment and study day using summary statistics. These data may also be pooled with other datasets for population PK analysis, which may be presented in a separate report.

**Listing:**

- All individual PK parameters may be listed for PK Subjects by treatment
- Ctrough may be listed by treatment, treatment cycle, and study day.

## 7.8 Biomarker Analysis

Due to the exploratory nature of this study, analyses listed below may or may not be performed depending on data availability (some exploratory measurements in the study may be subject to change as technologies and assay methods evolve). Additional types of analyses may be conducted on a post-hoc basis pending review of data. Not all exploratory analyses will be included in the Clinical Study Report (CSR) unless they represent meaningful findings or are relevant to subject management.

[redacted]

Summary statistics for biomarkers and their corresponding changes (or percent changes) from baseline may be tabulated by planned study day and dose in each arm. The time course of biomarker measures may be investigated graphically. If there is indication of meaningful pattern over time, further analysis (eg, by linear mixed model) may be performed to characterize the relationship. Methods such as, but not limited to, logistic regression may be used to explore possible associations between biomarker measures from peripheral blood or tumor biopsy and clinical outcomes.

**Summary**:

The following parameters and their corresponding change (or percent change) from baseline may be summarized by part, cohort/arm, and overall

- Receptor Occupancy data (%RO), and OX40 expression (MFI)
- Soluble OX40

**Listing:**

- All clinically relevant biomarkers may be listed, by treatment, and subject

## 8 CONVENTIONS

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[1]. 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[2].

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 present 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 cases where 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.

The following conversion factors will be used to convert days to months or years: 1 month = 30.4375 days and 1 year = 365.25 days.

Duration (e.g. time from first diagnosis to first dosing date, duration of response, and time to response) will be calculated as follows:

Duration = (Last date - first date + 1)

All statistical analyses will be carried out using SAS (Statistical Analysis System software, SAS Institute, North Carolina, USA) unless otherwise noted.

## 8.1 Pharmacokinetic Summaries

In-text Tables

For in-text PK tables, %CV will be reported as integers. For other statistics except for SDs, values of 100 or higher will be presented as integers, values of 10 to < 100 will be displayed to 1 decimal place, and values of 1 to < 10 will be displayed to 2 decimal places. Values less than 1 will be displayed to 3 decimal places. Ratios will also be displayed to 3 decimal places. Standard deviations will be reported to the same precision as the mean.

Handling of Non-quantifiable Concentrations

For the summaries of plasma 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, predose 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.

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

Treatment of Outliers

Individual plasma concentrations, if deemed to be anomalous, may be excluded from the analysis following a review of available documentation (e.g., bioanalytical report, clinical data). Any such exclusion will be clearly listed in the clinical study report (CSR) along with justification for exclusion.

Entire plasma concentration-time profiles for a participant may be excluded following review of available documentation (e.g., bioanalytical report, clinical data). However, results of analysis with and without the excluded profiles may be presented in the CSR. Any such exclusion will be clearly listed in the clinical study report (CSR) along with justification for exclusion.

Pharmacokinetic Exclusions[3]

Pharmacokinetic analysis, reporting, and exclusion criteria should following the BMS PK Harmonization document Version 2.0. Specific guidelines for exclusionary criteria for half-life and how other PK parameters are affected for exclusion are included in Section 9.2 of the BMS PK Harmonization document.

Exclusion of 1 or more parameters or the entire dataset may be considered due to incomplete profiles such as AUC(INF) or when T-HALF cannot be reliably calculated, or there is no sample around the suspected Cmax. In addition, participants may be excluded from the analysis if they missed doses, had diarrhea, or vomited at or before a time equal to twice the median Tmax for

immediate-release products, or vomited at any time during sampling after the administration of modified-release formulations.

# 9 CONTENT OF REPORTS

[redacted]