*Official Title of Study:*

# A Phase I/IIa Trial With BMS-986158, a Small Molecule Inhibitor of the Bromodomain and Extra-Terminal (BET) Proteins, as Monotherapy or in Combination with Nivolumab in Subjects with Selected Advanced Solid Tumors or Hematologic Malignancies

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# CLINICAL PROTOCOL CA011001

A Phase I/IIa Trial With BMS-986158, a Small Molecule Inhibitor of the Bromodomain and Extra-Terminal (BET) Proteins, as Monotherapy or in Combination with Nivolumab in Subjects with Selected Advanced Solid Tumors or Hematologic Malignancies

**Revised Protocol Number: 07**

[redacted]

**24-hr Emergency Telephone Number**

[redacted]

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

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

## DOCUMENT HISTORY

| Document | Date of Issue | Summary of Change |
|---|---|---|
| Revised Protocol 07 | 18-Mar-2019 | Identifies the dose and schedule for Part 2 and updates the study design for Part 2. Includes revisions to rationales, inclusion/exclusion criteria, T&E tables, sample collection tables and statistics; minor typographical edits, and an update to Appendix 4 RECIST 1.1. [redacted] |
| Revised Protocol 06 | 17-Jul-2018 | Updates schedules for mandatory biopsies during Part 2, updates imaging requirements for tumor assessments; updates inclusion criteria for subjects with NSCLC, corrects dose-limiting toxicity period for Part 2, updates schedules for PK sample collections, includes language to allow for release of IRT codes to facilitate ongoing data review, and added PROSTATE CANCER WORKING GROUP 3 (PCWG3) appendix. |
| Revised Protocol 05 | 01-Mar-2018 | Incorporates Administrative Letter 04 and the following changes:1) clarify the acceptable prior lines of therapy for participants with Non-Small Cell Lung Cancer (NSCLC) in Part 2; 2) update Exclusion Criteria for subjects participating in Part 2; and 3) provide updated contraception and protection requirements based on recent non-clinical reproductive toxicology study. Study design elements including time and events schedules, sample collections, laboratory analyses and additional safety measures have been added to align with these changes. |
| Administrative Letter 04 | 13-Oct-2017 | [redacted] |
| Revised Protocol 04 | 06-Sep-2017 | Adds nivolumab to Part 2 escalation phase and updates to biomarker driven study design with additional tumor types added. Includes revisions to rationales, inclusion/exclusion criteria, T&E table, sample collection tables and statistics; and minor typographical edits. |
| Revised Protocol 03 | 12-Apr-2016 | Incorporates Amendment 05 |
| Amendment 05 | 12-Apr-2016 | Removes Parts 1B & 2B and pertaining language from the protocol; incorporates revisions to the inclusion/exclusion criteria, T&E table, and minor typographical edits. |
| Revised Protocol 02 | 03-Mar-2016 | Incorporates Amendment 04 |
| Amendment 04 | 03-Mar-2016 | Incorporates new dosing regimens, revisions to the inclusion/exclusion criteria, T&E table and minor typographical edits |
| Revised Protocol 01 | 10-Aug-2015 | Incorporates Amendment 01 |
| Amendment 01 | 10-Aug-2015 | Incorporates revisions to the inclusion/exclusion criteria, T&E table, and minor typographical edits |
| Original Protocol | 02-Mar-2015 | Not applicable |

## OVERALL RATIONALE FOR REVISED PROTOCOL 07:

The purpose of this revised protocol is 1) To specify the doses and schedule selected for Part 2; 2) To describe changes in study design for Part 2, including limiting the initial enrollment into Part 2 to subjects with a subset of tumor types and making enrollment to therapy with BMS-986158 in combination with nivolumab contingent upon evaluation of data obtained from subjects treated with monotherapy; 3) To indicate that subjects with castration-resistant prostate cancer are eligible only if they can provide a biopsy sample; 4) To update overdose language to conform to current BMS standards; and 5) To update Appendix 4 to reflect BMS modifications to RECIST 1.1. Study design elements including time and events schedules, sample collections, laboratory analyses and additional safety measures have been modified to align with these changes. Additionally, where applicable, sections in the synopsis have been updated to align with the protocol section changes listed below.

## SUMMARY OF KEY CHANGES FOR REVISED PROTOCOL 07

| Section Number and Title | Description of Change | Brief Rationale |
|---|---|---|
| **Selection of doses and schedule for Part 2** | | |
| Section 1.1.5 Rationale for Dose and Schedule: BMS-986158 | The estimate for the projected human dose has been changed to 2 mg/day. | The estimate was changed based on human PK |
| Section 1.1.5 Rationale for Dose and Schedule: BMS-986158 | Added a rationale for selection of Schedule A | To provide justification for selection of schedule for Part 2 |
| Section 1.1.5 Rationale for Dose and Schedule: Nivolumab | Added text indicating that Schedule A will be used for combination therapy with nivolumab. | To indicate the dosing schedule selected for combination therapy |
| Section 1.1.13 Rationale for Inclusion of Adolescent Subjects | Modified text to indicate that Schedule A was selected for Part 2 and to indicate the doses selected for adolescents | To indicate the dose and schedule selected for adolescents |
| Section 1.4.4.1 Pharmacokinetics of BMS-986158 | Added 4.5 mg as the highest dose tested | To reflect the most recent data available for BMS-986158 |
| Section 3.3.2 Exclusion Criteria | New exclusion criterion<br>2-g Weight of < 40 kg | Insufficient data to support enrollment of patients <40 kg |
| Section 5.5 Pharmacokinetic Assessments | Updated description of PK analysis; Removed PK specimen collection tables for Part 2 Schedules B and C; Updated Table 5.5.1-4 (PK sample collection for Part 2 Schedule A) | To reflect changes in study design and selection of Schedule A for Part 2 |
| **Selection of Tumor Types for Initial Enrollment into Part 2** | | |
| Section 1.1.7: Rationale for Evaluating BMS-986158 in an Initial Monotherapy Expansion Cohort | This is a new section that has been added to provide a rationale for initial enrollment of subjects with a limited subset of tumor types. | To provide a rationale for the change in study design |

## SUMMARY OF KEY CHANGES FOR REVISED PROTOCOL 07

| Section Number and Title | Description of Change | Brief Rationale |
|---|---|---|
| Section 1.1.8: Rationale for Genetically Defined Tumor Cohorts: Amplifications | Added a rationale for including subjects with MYC amplifications in CRPC and non-GC-DLBCL tumor types.<br>Added text indicating which tumor types will be enrolled as part of the initial expansion and which will be enrolled as part of the subsequent expansion in Part 2. | To reflect changes in Part 2 study design |
| Section 1.1.9: Rationale for Specific Patient Populations | Added a rationale for inclusion of subjects with non-GC-DLBCL. | To provide a rationale for inclusion of non-GC-DLBCL patients |
| Section 1.1.9: Rationale for Specific Patient Populations | Described preliminary results of treatment of a CRPC patient with OTX015/MK-8628. | To provide a rationale for inclusion of CRPC patients |
| [redacted] | | |
| Section 1.1.13: Rationale for Inclusion of Adolescent Subjects | Added tumor types from which adolescent subjects may be enrolled. | To align with study design change |
| Section 1.5 Overall Risk/Benefit | Described preliminary results from a study using another BET inhibitor, CPI-0610. | To provide further rationale for enrollment of specific tumor types |
| Section 3.3.1 Inclusion Criteria | Inclusion Criterion 2-a-ix-3: Added the following text: Abiraterone but not enzalutamide may be continued during the study.<br>Inclusion Criterion 2-a-ix-4: Added the following new criterion: Detected MYC amplification in tumor cells (with or without AR amplification) | To clarify inclusion criteria for subjects with CRPC |
| Section 3.3.1 Inclusion Criteria | Inclusion Criterion 2-a-xiii: Added the following text: "DHL"<br>Inclusion Criterion 2-a-xiii-4: Added the following new criterion: "IHC confirmed CD 10-, BCL6-DLBCL, or CD10-, BCL6+ and MUM1+ DLBCL. Gene expression profile may also be used to confirm a diagnosis of non-GC-DLBC." | To add subjects with non-GC DLBCL as eligible for enrollment |
| **To remove mandatory enrollment to therapy with BMS-986158 in combination with nivolumab in Part 2** | | |
| Section 1.1.2 Rationale for combining BMS-986158 with Nivolumab | Added examples from the literature illustrating both proinflammatory and anti-inflammatory actions of BET inhibitors. | Contradictory findings in the literature provide a rationale for deferring combination therapy until |

## SUMMARY OF KEY CHANGES FOR REVISED PROTOCOL 07

| Section Number and Title | Description of Change | Brief Rationale |
|---|---|---|
| | | the effects of BMS-986158 monotherapy have been evaluated. |
| [redacted] | | |
| [redacted]<br>Section 1.2 Research Hypothesis | Changed "monotherapy or in combination with nivolumab" to "monotherapy and/or in combination with nivolumab." | To indicate that combination therapy will only be pursued after an assessment of data obtained from monotherapy |
| Section 4.1 Investigational Product | Added: "BMS-986158 combination with nivolumab will only be pursued on review of safety information and the totality of data obtained from BMS-986158 monotherapy in Parts 1 and 2." | To indicate that combination therapy will only be pursued after an assessment of data obtained from monotherapy |
| **Overall Study Design** | | |
| Section 1.3 Objectives | Modified primary objectives for Parts 1 and 2: there is now one primary objective for all monotherapy and a second primary objective for combination therapy<br>Modified all objectives that refer to combination therapy to indicate that these objectives will only be evaluated if combination is pursued.<br>[redacted] | To reflect the changes in study design |
| Section 3.1 Study Design and Duration | Updated description of overall study design, Part 2 study design, and sample size.<br>Updated Figure 3.1-1 Study Overview and Figure 3.1-2 Expansion Cohort. | To reflect changes in study design |

## SUMMARY OF KEY CHANGES FOR REVISED PROTOCOL 07

| Section Number and Title | Description of Change | Brief Rationale |
|---|---|---|
| Section 3.1.2 Dose Expansion (Part 2) | Updated text describing the study design for Part 2. | To reflect changes in study design |
| Section 3.1.2.1 Safety Evaluation Phase of BMS-986158 Monotherapy | Changed section title from "Parallel and Sequential Evaluation of Monotherapy and Combination Therapy" To "Safety Evaluation Phase of BMS-986158 Monotherapy<br>Removed section contents unrelated to safety. | To better describe the contents of this section |
| Section 3.1.2.3 Safety Evaluation in Adolescents | Updated text describing the study design for Part 2. | To reflect changes in study design |
| Section 3.1.2.4 BMS-986158 Monotherapy and in Combination with Nivolumab Dose Expansion--Number of Participants | Added the text "Number of Participants" to the section title<br>Updated Table 3.1.2.4-1 Planned Sample Size.<br>Updated sample size text. | To reflect change in study design |
| Section 3.6 Treatment Beyond Progression | Updated section to indicate that subjects receiving BMS-986158 monotherapy are not eligible for treatment beyond progression. | Evidence supporting the continuation of BMS-986158 monotherapy beyond progression is lacking. |
| [redacted] | | |
| Section 8.1 Sample Size Determination | Updated section. | To reflect changes in study design |
| **Other changes** | | |
| [redacted] | | |
| Section 1.1.9: Rationale for Specific Patient Populations<br>Section 1.5 Overall Risk/Benefit Assessment | Changed OTX-015 to OTX-015/MK-8626 | To provide both names used in the literature |
| Section 1.1.9: Rationale for Specific Patient Populations | Changed "therapies that maintain a castrate state" to "abiraterone but | Enzalutamide is a moderate-to-strong inducer of CYP enzymes. Because BMS-986158 is a CYP3A |

## SUMMARY OF KEY CHANGES FOR REVISED PROTOCOL 07

| Section Number and Title | Description of Change | Brief Rationale |
|---|---|---|
| | not enzalutamide to maintain a castrate state." | substrate, enzalutamide is excluded in subjects with CRPC. |
| Section 1.1.13: Rationale for Inclusion of Adolescent Subjects | Updated number of subjects treated with BMS-986158. | To reflect the most recent data available for BMS-986158 |
| Section 1.4.3.5 Pharmacokinetic Drug Interactions | Removed text describing BMS-986158 as an OATP3 substrate. | Due to inconsistencies in preclinical data |
| Section 1.4.4 Clinical Pharmacology and Safety | Updated number of subjects treated and AE information to reflect the December 2018 data cut from CA011001. | To reflect the most recent data available for BMS-986158 |
| Section 1.5 Overall Risk/Benefit Assessment | Updated safety information to reflect the December 2018 data cut from CA011001 | To reflect the most recent data available for BMS-986158 |
| Section 3.3.1 Inclusion Criteria | Updated Inclusion Criterion 1-a-i<br>Inclusion Criterion 2-d: the text "only be eligible" has been added | To ensure evaluable biopsies are collected from all subjects |
| Section 4.6 Blinding/Unblinding | Removed text indicating Sponsor may access IRT treatment codes prior to database lock | Part 2 is open-label |
| Section 5.1 Flow Chart/Time and Events Schedule | Table 5.1-1 (Screening): Added PSA screening for CRPC patients added; mandatory archival tumor samples if pretreatment tumor samples not available or sufficient.<br>Table 5.1-3 and Table 5.1-4 (Part 1 Schedule B and C): Targeted Physical Exam, Physical Measurement, Vital Signs may be omitted on Day 8, D8 laboratory tests may be performed at local labs, and tumor assessments should occur every 12 weeks for subjects who have been on study for ≥ 1 year.<br>Table 5.1-5 (Part 2): added PSA screening for CRPC patients; [redacted]. | To simplify visit scheduling for subjects in Part 1 Schedules B and C who have been on study for >1 year and to reflect changes in study design for Part 2. |
| Section 5.3.2 Laboratory Test Assessments | Added PSA screening for CRPC subjects. | To conform with PCWG3 assessment of subjects with CRPC |
| Section 6.1.1 Serious Adverse Event Collection and Reporting | Added SAE reporting period for combination therapy | To align with current reporting standards for nivolumab |
| Section 6.5 Overdose | Updated section. | To align with current BMS standards |

## SUMMARY OF KEY CHANGES FOR REVISED PROTOCOL 07

| Section Number and Title | Description of Change | Brief Rationale |
|---|---|---|
| Appendix 4 RECIST 1.1 | Updated appendix | To align with current BMS standards |

# SYNOPSIS

## Clinical Protocol CA011001

**Protocol Title:** A Phase I/IIa Trial with BMS-986158, a Small Molecule Inhibitor of the Bromodomain and Extra-Terminal (BET) Proteins, as Monotherapy or in Combination with Nivolumab in Subjects with Selected Advanced Solid Tumors or Hematologic Malignancies

**Investigational Product(s), Dose and Mode of Administration, Duration of Treatment with Investigational Product(s)**: BMS-986158 is formulated as a hard gelatin capsule [redacted] to be administered by oral route. Nivolumab is formulated as a solution for injection.

**Part 1 (BMS-986158 monotherapy dose escalation with Schedules A, B, and C enrolling at different dosing schedules,** See Figure 1). Schedule A enrolled first. Each subject in Schedules A, B and C is administered a single dose of BMS-986158 on Cycle 1 Day 1 and no additional doses are administered until Cycle 2 Day 1. For subjects in Schedule A on Cycle 2 Day 1, which must be within approximately 7 days of the Cycle 1 Day 1 dose administration, and on each subsequent cycle, subjects receive once daily dosing for 5 consecutive days of each week, followed by a 2-day rest period, on a 28-day cycle. For subjects in Schedule B on Cycle 2 Day 1, which must be within approximately 7 days of the Cycle 1 Day 1 dose administration, and on each subsequent cycle, subjects receive once daily dosing for 14 consecutive days, followed by a 7-day rest period, on a 21-day cycle. For subjects in Schedule C on Cycle 2 Day 1, which must be within approximately 7 days of the Cycle 1 Day 1 dose administration, and on each subsequent cycle, subjects receive once daily dosing for 7 consecutive days, followed by a 14-day rest period, on a 21-day cycle. In Part 1, the continuous dosing Schedule A enrolled first. Subjects may continue to receive treatment in all 3 dose schedules until disease progression, unacceptable adverse events (AEs) or withdrawal of consent.

**Part 2 expansion (BMS-986158 monotherapy and/or in combination therapy with nivolumab,** See Figure 1). In Part 2, Schedule A (QD dosing for 5 consecutive days on with 2 days off each week of a 28-day cycle) for BMS-986158 administration has been selected for expansion of the 4.5 mg dose, which will be administered for 2 weeks (10 doses) followed by 3.75 mg for the remainder of the treatment period, as agreed upon between the Sponsor/Medical Monitor and investigators considering safety, PK [redacted] data generated during Part 1. This dosing and schedule will be evaluated for up to 2 years in adult and adolescent subjects. Adults and adolescent subjects weighing ≥40 kg will be administered a flat dose of BMS-986158. Using Schedule A and a dosage of 4.5 mg for a 2-week loading period followed by 3.75 mg for the remainder of the treatment period, BMS-986158 will be tested as monotherapy and potentially in combination with nivolumab. If pursued, nivolumab will be administered as a flat dose of 480 mg Q4W. Adolescent subjects will receive nivolumab at 6 mg/kg up to a maximum of 480 mg for Schedule A with the same frequency of administration as adults.

**Study Phase:** Phase I/IIa

**Research Hypothesis**: There is no formal primary research hypothesis for this study to be statistically tested. It is anticipated that BMS-986158 as monotherapy and/or in combination with nivolumab (i pursued) will demonstrate adequate safety and tolerability at pharmacologically relevant doses, so as to permit further clinical development (at a recommended dose range).

**Objectives:**

**Primary**

- To assess the safety and tolerability and to assess the dose limiting toxicities (DLTs), maximum tolerated dose (MTD), and recommended Phase 2 dose (RP2D) of BMS-986158 as monotherapy for subjects with selected advanced solid tumors and hematologic malignancies.
- If combination with nivolumab is pursued, to assess the safety and tolerability at the RP2D of BMS-986158 in combination with nivolumab and to assess the DLT for subjects with advanced solid tumors and hematologic malignancies.

**Secondary**

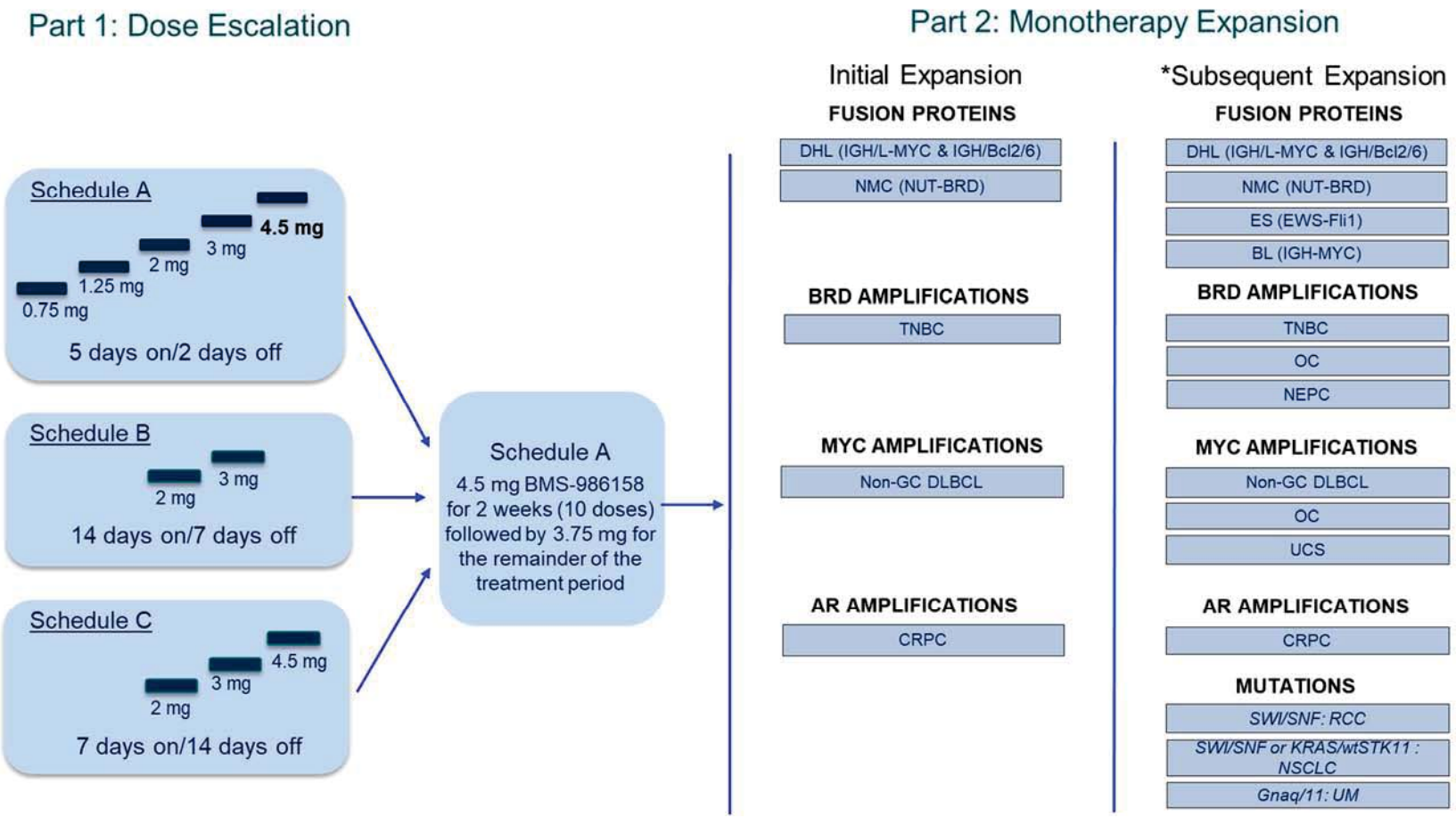
- To assess the preliminary antitumor activity of BMS-986158 monotherapy and, if pursued, in combination with nivolumab as measured by objective response rate (ORR), and response duration based on response evaluation

criteria in solid tumors using criteria from RECIST v1.1, prostate cancers using PCWG3 criteria, or hematologic malignancies using criteria from Lugano 2014.

- To characterize pharmacokinetics of BMS-986158 and metabolite in monotherapy and, if pursued, in combination with nivolumab.
- To assess the dose-response and exposure-response effect of BMS-986158 monotherapy on the ECG (QT interval).

**Study Design:** This is a Phase I/IIa, open-label study of BMS-986158 administered as monotherapy and, if pursued, in combination with nivolumab to subjects with selected advanced solid tumors and hematologic malignancies. The study will be conducted in two parts: a dose escalation phase (**Part 1**) and a dose expansion phase (**Part 2**). Schematics of the study are provided in Figure 1 and Figure 2.

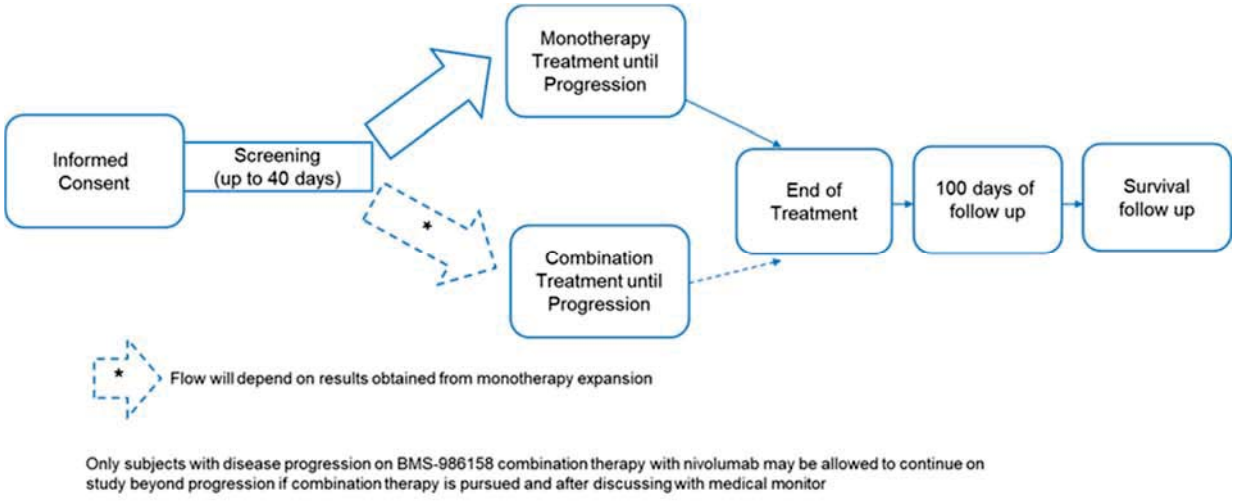
**Figure 1:** **Study Overview**




Abbreviations: BL = Burkitt's lymphoma; CRPC = castrate-resistant prostate cancer; DHL = double-hit lymphoma; ES = Ewing sarcoma; NEPC = neuroendocrine prostate cancer; NMC = NUT-midline carcinoma; NSCLC = non-small cell lung cancer; OC = ovarian cancer; RCC = renal cell carcinoma; Res = response; SOC = standard of care; TNBC = triple negative breast cancer; UCS = uterine carcinosarcoma; UM = uveal melanoma; Non-GC-DLBCL = Non-germinal center diffuse large B-cell lymphoma.

*Up to 45 subjects with a limited set of tumor types will be enrolled in the Initial Expansion. Subsequent enrollment of subjects with an expanded set of tumor types within and across groups (eg, fusion proteins, BRD amplifications, MYC amplifications, AR amplifications, or mutations) as part of the Subsequent Expansion will depend on the totality of data obtained from subjects in the Initial Expansion. If combination therapy with nivolumab is pursued, subjects with any listed tumor type will be eligible.

**Figure 2:** **Expansion Cohorts**




**Part 1** consists of the dose escalation phase with BMS-986158 administered as monotherapy.

**Part 2** consists of cohort expansions in solid tumors and hematologic malignancies (BMS-986158 monotherapy and potentially in combination with nivolumab). Treatment in Part 2 will be initiated when the MTD or maximum administered dose (MAD) if no MTD is reached and dose schedule(s) from Part 1 has been determined. Schedule A (QD dosing for 5 consecutive days of each week, followed by a 2-day rest period, on a 28-day cycle) has been chosen for expansion after starting with 4.5 mg for a 2-week loading period (5 days on/2 days off) followed by the same schedule at a reduced dose level of 3.75 mg for all subjects. The schedule and dosage were chosen based on safety, PK [redacted] data generated during Part 1.

**Part 1: Selection of Dose Levels**

The first cohort of subjects in Schedule A received a starting dose level of 0.75 mg daily for 5 consecutive days per week beginning at Cycle 2. Dose escalation for each subsequent cohort of subjects is guided by the incidence of AEs for which no clear alternative cause is identified, as graded by National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events version 4.03 (NCI CTCAE v4.03) in the first 32-35 days of dosing (DLT evaluation period) of Schedule A, and the first 35 days of dosing (DLT evaluation period) of Schedules B and C. Dose escalation will be in increments of 100% above the previous dose level until the first occurrence of any of the following toxicities that have no alternate cause: any DLT (as described in Section 4.5.1), any ≥ Grade 2 toxicities with the following exceptions: Grade 2 fatigue, Grade 2 alopecia.

Once one or more of the above identified DLTs occurs, a modified Fibonacci dose escalation schema will be employed for any subsequent dose escalations at that schedule, with increments of 67%, 50%, 40%, and 33%. Any further dose escalations will be 33%. In addition, dose modification could also include changes in the dosing interval (e.g. twice weekly), based on available safety and PK data.

Intermediate dose levels may be evaluated if agreed upon by the Sponsor/Medical Monitor and investigators. The next dose level will not exceed 100% of the prior dose level or the dose increment per the modified Fibonacci dose escalation schema.

**Part 1: Dose Escalation Decision Rules**

Enrollment in dose escalation and selection of the maximum tolerated dose (MTD) will adhere to a modified Toxicity Probability Interval (mTPI) design. The design provides a simple algorithm for decisions on escalation, expanding at the same dose level, and de-escalation, depending on the number of observed toxicities after each dose level cohort (see Figure 3). The mTPI method utilizes a target toxicity (DLT) rate and equivalence interval (EI) to guide decisions on escalation after each cohort and to estimate the MTD. For this study the target DLT rate is 27% and the EI is 25%-29%.

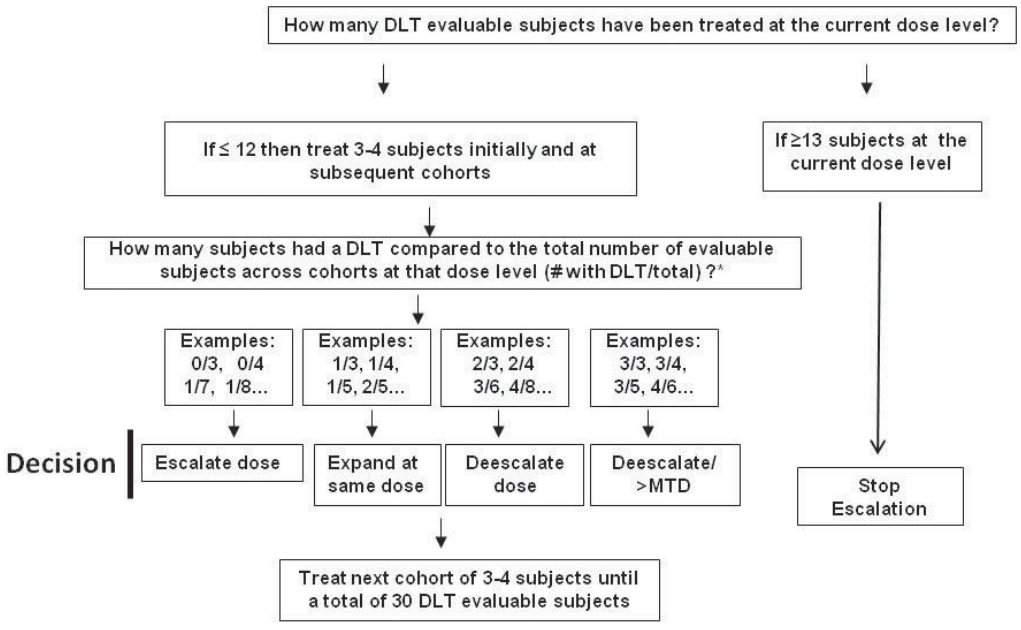
Dose escalation decisions starting with the first dose cohort will be guided by the cumulative number of subjects who are DLT evaluable and who experience a DLT in the DLT evaluation period for all arms (Figure 3). If no DLTs are observed in the first dose cohort, 3-4 subjects will be enrolled at the next dose level. If 1 DLT is observed in 3 or 4 evaluable subjects, this dose level will be expanded by enrolling another cohort of 3-4 at the same dose level. If 2 of 3 or 3 of 4 subjects are observed with DLTs, the next cohort will be enrolled at the lower dose level. Additional decisions are shown in Figure 3. If a decision to treat more subjects at a given dose level is suggested by the mTPI algorithm when there are already at least 13 DLT evaluable subjects treated at the same dose level, a need for further enrollment in the dose escalation phase will be determined by the Sponsor. These same rules will be applied to Schedules B and C. A total of approximately 30 DLT evaluable subjects is expected to be treated per schedule with a total of 90 planned across schedules for the dose escalation phase.

Decisions to escalate, add more subjects to the current dose level, de-escalate (with options to re-escalate), or de-escalate and declare the current dose as unacceptable (exceeding the MTD), will be based on the rate of DLTs in evaluable subjects within the 32 to 35-day DLT evaluation period for Part 1 Schedule A and within the 35-day DLT evaluation period for Part 1 Schedules B and C. At least 3 DLT-evaluable subjects treated at each dose level are required to enable a decision. To account for subjects who may not be able to complete the DLT evaluation period, for reasons other than a DLT, or may not be evaluable for DLT, a fourth subject may be enrolled at this dose level, following agreement between the investigator and Sponsor/Medical Monitor. Subjects must receive at least 16 of the 21 planned doses in Schedule A of Part 1, 17 of the 22 planned doses in Schedule B of Part 1, or 12 of the 15 planned doses in Schedule C of Part 1, during the DLT evaluation period to be considered evaluable for dose escalation decisions. Subjects who developed a DLT during the DLT period are considered evaluable regardless of the number of received doses. Subjects with insufficient data to establish safety during the DLT evaluation period at the dose level tested may be replaced upon agreement of the Sponsor/Medical Monitor and investigators.

There will be no intrasubject dose escalation of BMS-986158.

Figure 3 shows examples of scenarios guiding decisions that may be encountered during dose escalation with respect to the number of DLT evaluable subjects and the number of subjects with a DLT. In addition to escalation or expansion decisions, dose re-escalation is permitted as per Figure 3 after a decision to de-escalate is made, except when a dose level has been identified as exceeding the MTD. Therefore, a dose level could be revisited multiple times under the mTPI design.

**Figure 3: Monotherapy Dose Escalation Decision Guide**




*Complete set of Decision Rules are shown in Appendix 1.

**Part 1A: MTD Determination**

At the end of dose escalation, the MTD or MAD for each evaluated dosing schedule (Schedules A, B, and C) will be selected as the dose with the smaller difference between estimated toxicity and the target DLT rate (27%), among the dose levels used, with an isotonic regression model of the accumulated DLT data based on the mTPI design (Appendix 1).

**Dose Limiting Toxicity for Part 1**

For the purpose of guiding dose escalation decisions, DLTs are defined separately in Protocol Section 4.5.1 and will be determined based on the incidence, intensity, and duration of AEs for which no clear alternative cause is identified. The DLT evaluation period will be within 32 to 35 days (depending on the exact day of the start of Cycle 2) of initiation of study therapy for Schedule A and 35 days for Schedules B and C in Part 1. The DLT period for safety assessment of BMS-986158 and nivolumab combination therapy in Part 2 will match the DLT period for the selected schedule in Part 1 (ie, 32 to 35 days for Schedule A and 35 days for Schedules B and C). AEs will be graded according to NCI CTCAE v4.03. For the purposes of subject management, DLTs will lead to dose interruptions regardless of the cycle in which a DLT occurs. AEs occurring after the above defined DLT evaluation period will be considered for the purposes of defining the RP2D, upon agreement between the Sponsor/Medical Monitor and investigators, if they are determined to have no clear alternative cause and are not related to disease progression.

**Part 2: Dose Expansion**

Treatment in Part 2 can be initiated before Part 1 is completed and when the MTD, or maximum administered dose (MAD) if no MTD is reached for Part 1, has been determined. Schedule A (QD dosing for 5 consecutive days of each week, followed by a 2-day rest period for a 28-day cycle) has been chosen for dosing in expansion to be implemented as follows: The initial dose level of BMS-986158 selected for Part 2 is 4.5 mg with a loading period of 2 weeks (10 doses or half a cycle) with subsequent lower dose of 3.75 mg for the duration of study treatment for each subject. Further dose modification at the subject level is permitted below the dose level of 3.75 mg depending on the observed toxicity and tolerability.

The dose and schedule were selected upon agreement between the Sponsor/Medical Monitor and investigators, considering safety, PK [redacted] data generated during Part 1. Adult and adolescent subjects weighing ≥ 40 kg will be administered a flat dose of BMS-986158.

BMS-986158 will be evaluated in expansion as monotherapy; initially in up to 45 subjects with tumors harboring specific genetic alterations including fusion proteins (NUT-midline carcinoma [NMC], double-hit lymphoma [DHL]), BRD amplifications (triple negative breast cancer [TNBC]), MYC amplifications (non-germinal center diffuse large B-cell lymphoma [non-GC DLBCL]) and AR amplification (castrate resistant prostate cancer [CRPC]). [redacted] Depending on the safety, preliminary efficacy, tolerability [redacted] in these initial cohorts, a subsequent set of monotherapy cohorts in up to 126 subjects with tumor types already evaluated in the initial expansion cohort as well additional tumor types within and across groups of specific genetic alterations may be enrolled. Categories of genetic alterations and tumors under consideration for subsequent enrollment include fusion proteins (NMC, DHL, Ewing sarcoma [ES] and Burkitt's lymphoma [BL]), BRD amplifications (triple negative breast cancer [TNBC], ovarian cancer [OC] and neuroendocrine prostate cancer [NEPC]), MYC amplifications (Non-GC DLBCL, uterine carcinosarcoma [UCS], OC), AR amplification (CRPC) and mutations (renal cell carcinoma [RCC], non-small cell lung cancer [NSCLC] and uveal melanoma [UM]).

The decision to assign new cohorts of subjects to BMS-986158 plus nivolumab combination therapy will be made after review of preliminary efficacy, [redacted] and other available data obtained from both Initial and Subsequent monotherapy expansion subjects upon agreement between the Sponsor/Medical Monitor and investigators. If combination therapy of BMS-986158 and nivolumab is pursued, subjects may be enrolled with any of the tumors types listed in Figure 1.

In Part 2, subjects who have progressive disease after receiving BMS-986158 in combination with nivolumab may have the option of continuing on treatment with the combination, if combination therapy is pursued. Subjects who

have progressive disease after receiving BMS-986158 monotherapy will not have the option of continuing on treatment with BMS-986158 monotherapy or receiving BMS-986158 in combination with of nivolumab.

Clinical safety monitoring of subjects treated with BMS-986158 monotherapy enrolled in Part 2 of the study will be the same as conducted during the dose escalation portion. During Part 2, if in a given tumor cohort the combined incidence of study drug-related AEs that require dose modification exceeds 29% (of treated subjects), then further enrollment to that arm may be interrupted and the findings will be discussed between the Sponsor/Medical Monitor and investigators. An agreement will be reached as to whether a lower dose level or an alternate dose schedule of BMS-986158 should be examined, or whether any additional treatment guidelines should be implemented prior to enrollment of additional subjects on study.

If pursued, the safety of the selected BMS-986158 dose when given in combination with nivolumab within the dose expansion phase will be evaluated by monitoring DLTs in the first 6 to 12 subjects treated across different tumor cohorts receiving combination therapy. The DLT period in Part 2 will be 28 days, which excludes a 7-day single dose period in Part 1 (Cycle 1) to allow appropriate comparison. Once the selected dose of BMS-986158 in combination with nivolumab is deemed safe based on the DLT evaluation, the dose expansion will continue as planned in all cohorts. The guidance for assessing the DLT-related safety and overall safety will be similar to that used in the monotherapy cohorts. The DLT safety monitoring during the dose evaluation phase including potential decision to de-escalate to a lower dose will be based on the mTPI-2 design with target toxicity (DLT) rate of 29% (-2%, +4%).

Duration of Study: The overall duration of the study is expected to be approximately 4 years from the time of the first visit of the first subject to the required survival follow-up of the last subject enrolled. Subjects may discontinue treatment due to disease progression, unacceptable AEs, or withdrawal of consent. Dependent upon treatment, the Clinical Follow-up visits will occur approximately 30 days (for subjects who receive monotherapy) and 60 and 100 days (for subjects who receive combination therapy) after the subject discontinues study treatment. For subjects in partial response (PR) or complete response (CR) who discontinue treatment for AEs, tumor assessments will be performed every 12 weeks for the first year then every 6 months for the second year. If a subject discontinues treatment due to an AE, the subject should be seen in Clinical Follow-up every 30 days until the AEs either resolved to baseline or Grade 1, stabilized, or been deemed irreversible. After completing the Clinical Follow-up Period, subjects will continue on to a Survival Follow-up Period. [redacted] The end of the study will occur after the last treated subject completes their Clinical Follow-up, unless if a subject discontinues prematurely.

**Number of Subjects**: The planned sample size consists of up to approximately 90 subjects for Part 1 and up to approximately 327 subjects for Part 2 for a total of up to approximately 417 subjects in the entire study.

**Study Population:** The study population will include adult men and women who are at least 18 years of age and adolescents ≥ 12 years of age who meet the study eligibility criteria. Adult subjects must have histologic/cytologic confirmation of one of the following malignancies to be eligible: OC, TNBC, NSCLC, RCC, UM, UCS, NEPC, CRPC, NMC, ES, BL, DHL, or non GC-DLBCL. Adolescent subjects must have histologic/cytologic confirmation of NMC, ES, or BL. At least one (1) site of measurable disease as defined by RECIST v1.1 for solid tumors, Lugano 2014 criteria for lymphomas, or PCWG3 for prostate cancers is mandatory. Additionally, in order to be eligible for enrollment to Part 1 of the study, all subjects must have either an archival tumor tissue block or at least twenty (20) unstained cut slides identified and available, and consent to provide this archival tissue. Acquisition of adequate pre-treatment tumor tissue is mandatory for adult subjects in this study. Subjects who do not have archival tissue available may consent to a pre-treatment fresh tumor biopsy to be eligible for this study if it can be performed at acceptable clinical risk as judged by the investigator and if it does not include a target lesion or a lesion in an area treated with prior radiation therapy. All adult subjects enrolled in Part 2 must have tumor lesions that can be biopsied or collected via core needle at acceptable clinical risk (as judged by the investigator) at baseline (pre-treatment), during treatment, and end of treatment (EOT) in case of PD.

Women of childbearing potential (WOCBP) must not be nursing or pregnant and must be using an acceptable method of contraception for at least 4 weeks before dosing and for 5 months following the last dose of study drug. WOCBP must have a negative pregnancy test within 24 hours prior to dosing with study medication. Male participants who are sexually active with a WOCBP should also use an adequate method(s) of contraception, irrespective of vasectomy status or partner's pregnancy status, for up to 7 months following the last dose of study drug.

**Study Drug:** includes Investigational [Medicinal] Products (IP/IMP) as listed:

BMS-986158 is formulated as a hard gelatin capsule [redacted] to be administered by oral route.

Nivolumab is formulated as a solution for injection.

**Study Drug for BMS-986158**

| Medication | Potency | IP/Non-IP |
|---|---|---|
| BMS- 986158 | 0.25 mg and 2 mg | IP |
| Nivolumab | 100 mg/vial (10 mg/mL) | IP |

**Study Assessments:**

**Safety Outcome Measures**: AEs will be assessed continuously during the study and for 30 days after the last treatment of BMS-986158 monotherapy and 100 days post discontinuation of combination therapy. AEs will be coded using the most current version of MedDRA and reviewed for potential significance and importance. AEs will be evaluated according to the NCI CTCAE v4.03. Subjects should be followed until all treatment related AEs have recovered to baseline, or are deemed irreversible by the investigator. Safety assessments will be based on medical review of AE reports and the results of vital sign measurements, ECGs, physical examinations, and clinical laboratory tests.

**Efficacy Measures:** Disease assessment with computed tomography (CT) and/or magnetic resonance imaging (MRI) (solid tumors and lymphoma) or fluorodeoxyglucose - positron emission tomography (hematologic malignancies, when standard of care [SOC]), as appropriate, will be performed at baseline. Disease assessment will occur every 8-9 weeks ±1 week from the start of study therapy. Disease assessment at other time points may be performed at the discretion of the investigator. Tumor assessments will continue until disease progression or until subjects withdraw from the study. Tumor responses will be determined as defined by RECIST v1.1 criteria for solid tumors. For hematologic malignancies, responses will be based on the Lugano 2014 Classification for Initial Evaluation, Staging, and Response for Hodgkin Lymphoma. For prostate cancers (CRPC and NEPC), responses will be defined based on PCWG3. At the Sponsor's discretion, scans and measurements may be reviewed by independent radiologists using RECIST v1.1, Lugano 2014, or PCWG3 criteria at a later date, or at any time during the study.

**Pharmacokinetic Measures:** Pharmacokinetic parameters for BMS-986158 (Cmax, Tmax, AUC(TAU), and AUC(0-T); single dose only if data permits: T-HALF, AUC(INF), CLT/F, Vz/F; multiple dose only: Cmin, Ctau, Ctrough, Accumulation Index (AI) and T-HALFeff), will be derived from parent (BMS-986158) and metabolite plasma concentration versus time data. In addition the metabolite to parent ratios adjusted for molecular weight (MR) will be calculated for Cmax, AUC(0-T), AUC(INF) and AUC(TAU). [redacted]

[redacted]

**Statistical Considerations:**

**Sample Size:**

**Dose Escalation**: In the dose escalation part of the study for monotherapy Part 1, the sample size per dose level cannot be precisely determined and will depend on observed DLTs and the decision rules of the mTPI design. Between 3 and up to 13 DLT evaluable subjects may be enrolled to a given dose level, based on the decision guide by the mTPI design. Treating additional subjects beyond the 13 that are DLT evaluable at a dose level would be unlikely to alter the decision specified by the mTPI algorithm. A total of approximately 30 subjects is expected to be treated per schedule, with a total of 90 planned across schedules for the dose escalation phase. More subjects may be added at a specific schedule if additional dose levels need to be evaluated. Similarly, fewer than 30 subjects may be needed for a different schedule if a smaller number of dose levels are evaluated.

**Cohort Expansion:**

During this part of the study, the efficacy signal assessment will start with initial monotherapy cohorts. This assessment will be guided by a Fleming 2-stage design, to provide the option for early evaluation and planning based on an initial efficacy signal. The sample sizes for each cohort are calculated based on assumptions of true (target) and historic ORR for each tumor type. A 2-stage design provides criteria for the option to stop early for futility, and an understanding of an early signal of preliminary, strong antitumor activity. Approximately 5 to 9 subjects will be treated in each of the cohorts, based on the Fleming (optimal) design criteria; Enrollment may continue after the initial 5 subjects to ensure that sufficient subjects are evaluable (eg, with tumor scans) or in case of early drop outs. There will be no stopping due to an efficacy signal.

[redacted]

In summary, approximately up to 45 subjects are expected to be treated across the Initial monotherapy cohorts, with approximately 5 to 9 subjects per cohort. Based on the totality of data obtained from Initial monotherapy cohorts, up to 126 subjects may be enrolled in Subsequent monotherapy cohorts with an expanded set of tumor types within and across groups.

If the combination of BMS-986158 with nivolumab is pursued, safety will be evaluated across the tumor types in the first 6 to 12 evaluable subjects who receive combination therapy based on the DLT observed. The mTPI-2 design with DLT target of 29% (-2%, +4%) will be used to guide decisions in this setting, including potential de-escalation to a lower dose of BMS-986158 in combination with nivolumab, if warranted by the observed results.

The above sample sizes are based on the assumption that the selected RP2D is deemed safe in combination therapy. If a lower dose level must be evaluated in combination therapy, an additional 6 to 12 subjects may be enrolled to assess safety of BMS-986158 prior to fully expanding in combination therapy.

The potential total for expansion will be approximately up to 201 subjects if only monotherapy is pursued, and approximately up to 327 subjects if all planned expansion cohort subjects in monotherapy and combination therapy groups are pursued.

**Endpoints:**

**Primary Endpoints:** Incidence of AEs at their worst grade, serious adverse events (SAEs) at their worst grade, AEs leading to discontinuations, deaths, and frequency of laboratory test toxicity grade shifting from baseline. Safety will be evaluated from the time that the subject signs the informed consent and for up to 30 days and 100 days after the last dose of BMS-986158 monotherapy or if pursued, BMS-986158 in combination with nivolumab, respectively, or until resolution of any AE for which alternative causes could not be identified resolve to ≤ Grade 1 or baseline or until the event has stabilized, whichever is longer.

**Pharmacokinetics:** Select PK parameters including Cmax, Cmin, Tmax, AUC (TAU), AUC(0-T), will be derived from parent (BMS-986158) and metabolite plasma concentration versus time data for all schedules. In addition parameters specific to single dose only, if data permits, (T-HALF, AUC(INF), CLT/F, Vz/F) or multiple dose only (Cmin, Ctau, Ctrough, AI and T-HALFeff) will be calculated derived from parent (BMS-986158) and metabolite plasma concentration versus time data. The metabolite to parent ratios (MR) will also be calculated for Cmax, AUC(0-T), AUC(INF) and AUC(TAU). [redacted]

**Efficacy:** ORR, Duration of response (DOR), progression-free survival, and Progression Free Survival Rate (PFSR) at select times are efficacy endpoints. ORR is defined as the total number of subjects whose best overall response (BOR) is either a CR or PR, divided by the total number of subjects in the population of interest.

[redacted]

**ECG:** Changes in QTcF (ΔQTcF) from baseline at selected times following monotherapy treatment with BMS-986158 and association measures of QTc changes with BMS-986158 PK exposure.

[redacted]

**Analyses:**

**Safety Analyses:** All recorded AEs will be listed and tabulated by system organ class, preferred term and treatment. Vital signs and clinical laboratory test results will be listed and summarized by treatment. Any significant physical examination findings and clinical laboratory results will be listed. ECG readings by the investigator will be summarized, and abnormalities, if present, will be listed. Safety data may also be presented in adolescent participants based on data availability.

**Efficacy Analyses:** Efficacy results will be presented by tumor type, dose level, dosing schedule and/or regimen. Individual BOR, DOR and PFS using RECIST v1.1 criteria for solid tumors, Lugano 2014 criteria for hematologic malignancies, or PCWG3 for prostate cancers will be listed. BOR outcomes and ORR will be tabulated by dose/dose regimen and across doses for each tumor. For ORR, 95% confidence intervals will be calculated based on the Clopper-Pearson method. The median DOR (mDOR) for responders and median PFS will be estimated by Kaplan-Meier (K-M) methodology. PFS rates (e.g. at 24 weeks) will be similarly estimated, based on K-M methodology, with confidence intervals based on the Greenwood formula and tabulated for each tumor. Individual changes in the tumor burden versus time will be presented graphically by dose level/study arm/dose regimen within a tumor type.

[redacted]

**ECG Analyses:** For subjects with serial ECG measurements and time-matched PK following monotherapy treatment with BMS-986158, changes in the QTcF (ΔQTcF), ECG intervals QRS, and PR, and in heart rate (ΔHR) will be tabulated by treatment and study day. Frequency distributions of max QTcF values, max ΔQTcF, max QRS, max PR, and max heart rate in pre-specified categories will be tabulated by treatment. Scatter plots of heart rate, ΔHR, QTc, and ΔQTcF, vs time-matched BMS-986158 concentrations will be provided. A concentration-response effect of BMS-986158 on QTcF may be assessed by a linear mixed effects regression model for ΔQTcF on PK, by study day, as well as pooled across days.

**Pharmacokinetic Analyses:** PK parameters for BMS-986158 will be calculated using noncompartmental analysis. Summary statistics will be tabulated for the PK parameters by dose level, dose regimen, and study cycle/day for each schedule. To describe the dependency on dose, scatter plots of Cmax and AUC(0-T), AUC(TAU), versus dose will be provided on indicated study cycle for each dose regimen. [redacted] Geometric means and coefficients of variation (CV%) will be reported for Cmax, AUC, Cmin, Ctau, Ctrough, CLT/F, Vz/F, AI, T-HALFeff and MR; Medians and ranges will be reported for Tmax; means and Standard Deviations will be reported for T-Half. PK data may also be summarized separately for adolescent participants depending on data availability. [redacted]

**Interim Analysis:** Because of the exploratory nature of the early phase study, data emerging from each dose level, treatment arm, or each part of the study will be examined prior to the final lock of the study database for timely decisions such as dose level or dose schedule selection, early termination of the study or publications. Analyses will only consist of listings, summaries, and graphs of the available data. In addition, modeling of PK (e.g. exploration of exposure-response and simulations) or key safety data may be utilized to inform dose level or dose schedule selection for subsequent parts of the study, as data permits. No formal inferences requiring any adjustment to statistical significance level will be performed, or adjustment for multiplicity.

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# 1 INTRODUCTION AND STUDY RATIONALE

Patients with relapsed or refractory hematologic and solid tumors have a very poor prognosis[1]. Despite advances in multimodal therapy, increases in overall survival (OS) in these patient populations have been limited. The unmet need resides in the lack of effective treatments to deliver long term survival, hence the need to test compounds that have novel mechanisms of action in clinical studies. This study is focused on BMS-986158, a novel epigenetic drug candidate with direct antitumor effects and immunomodulatory functions, which may be further augmented by nivolumab.

## 1.1 Study Rationale

### *1.1.1 Rationale for targeting bromodomains for cancer therapy*

The bromodomain and extra-terminal (BET) family of adaptor proteins is comprised of 4 members (BRD2, BRD3, BRD4, and BRDT), each of which contain two conserved N-terminal bromodomains (BD1 and BD2) and an extra terminal (ET) protein interaction motif.[2,3] Bromodomain-mediated interactions with acetylated chromatin result in the localization of BET proteins to discrete chromosome regions, where they recruit additional regulatory complexes to influence gene transcription.[4,5,6] BRD4 is dysregulated by chromosomal translocation to form in-frame fusions with the NUT (nuclear protein in testis) gene in NUT-midline carcinoma (NMC);[7] it is also overexpressed in many solid tumors. Early BET inhibitors, JQ1 and I-BET, demonstrated therapeutic effects in multiple tumor models of hematologic malignancies[8,9] including multiple myeloma (MM),[10] as well as in solid tumors.[11] The therapeutic activity of BET inhibitors in hematologic malignancies correlates with transcriptional suppression of key proto-oncogenes, including MYC and BCL2.[12,13] c-MYC is the most frequently amplified oncogene and is deregulated in 40% to 70% of all cancers;[14] however, efforts to target MYC inhibition have not been successful to date.[15,16]

BET inhibitors have the potential to provide an effective strategy for targeting the MYC oncogene in the treatment of cancer.[9] Examination of BRD4 occupancy at genes whose transcription is highly sensitive to JQ1, led to the observation that BRD4 (and potentially other BET family members) localizes to the core promoter regions of many oncogenes.[17] Additionally, BRD4 is enriched in enhancer regions, leading to high expression levels of many growth promoting genes, in addition to MYC.[17] Recent studies demonstrated that key lineage-specific survival genes are regulated by these super-enhancer regions.[18] These enhancers are considerably larger than typical gene enhancer regions and are densely populated by transcription factors, leading to strong activation of gene transcription. Super-enhancers are present in the loci of key oncogenic drivers. BRD4 is particularly enriched in these critical control regions suggesting that inhibition of the bromodomain activity of BRD4 will lead to transcriptional repression of these key oncogenic drivers.[17,18] The greater sensitivity of super-enhancers to perturbation by BRD4 inhibition may explain why cancer cells are specifically sensitive to BRD4 inhibition despite ubiquitous BRD4 expression in a wide range of cells. Because tumor cells are frequently highly reliant on high

oncogene expression for survival, selective disruption of super-enhancers by a BET inhibitor may represent an effective strategy for the treatment of multiple tumor types with an acceptable safety profile.

Preclinical studies using in vitro and in vivo models of various cancer types demonstrated that sensitivity to BET inhibition is higher in tumor cells harboring genetic abnormalities, including gene amplifications (eg, BRD, MYC, or androgen receptor [AR] gene),[19,20,21,22] mutations (eg, Gnaq/11, KRAS, or SWI/SNF),[23,24] and translocations (eg, MYC, BCL2/6, or BRD3/4).[25,26,27] These findings warrant further clinical investigations to understand whether the selected genetic abnormalities can be used as biomarkers for sensitivity of the tumors to treatment with BET inhibitors.

### *1.1.2 Rationale for combining BMS-986158 with Nivolumab*

BET proteins are important in the control of networks of genes, and depending on the context, function as co-activators or co-repressors regulating expression of approximately 3,000 genes. BET inhibitors disrupt the binding interface between the bromodomain and the acteylated lysine groups resulting in pleotropic effects. Several BET inhibitors are currently under investigation as anticancer, anti-inflammatory, and immunomodulatory agents changing a whole field of new epigenetically targeted therapeutics.[28]

Cooperative interactions between BET inhibitors and PD-1 inhibitors may involve different molecular pathways. Inflammatory cytokines, including IFNγ, are expressed within the tumor microenvironment and upregulate PD-L1 levels contributing to immunosuppression.[29,30] Induction of PD-L1 expression in tumor cells, as a downstream effect of canonical IFNγ signaling, is BRD4-dependent.[25] In some tumors, BET inhibitors reduce IFNγ-mediated PD-L1 induction via inhibition of NF-κB activity.[31,32] In mixed lineage leukemia (MLL)-rearranged acute myeloid leukemia (AML) cells, BET inhibition does not induce PD-L1 downregulation,[25] suggesting that the effect of BET inhibitors on PD-L1 expression is not universal and is likely cell-context dependent. JQ1, a BET inhibitor, has been reported to interfere with the production of both pro-inflammatory (IL-12 and TNF) and anti-inflammatory (IL-10 and TGF-β) cytokines from dendritic cells, with lower mRNA expression of IL-12 and TNF but higher expression of IL-10 and TGF-β. At the same time, JQ1 reduced monocyte-derived dendritic cell maturation and T cell proliferation.[33] This finding supports that JQ1 and possibly other BET inhibitors such as BMS-986158 may have immunosuppressive activity in some contexts.[34] However, studies in animal models demonstrated that targeted inhibition of the PD-1/PD-L1 axis by combining anti-PD-1 antibodies and the BET inhibitor JQ1 resulted in synergistic responses in mice bearing MYC-driven lymphomas.[25] These contradictory findings highlight the need to define the effect of BMS-986158 on the immune system before exploring the combination of BMS-986158 with anti-PD-1 agents such as nivolumab. Clinical development of this combination regimen may provide additional options for patients who are currently not effectively treated with anti-PD-1 monotherapy.

### 1.1.3 Rationale for targeting PD-1

Cancer immunotherapy rests on the premise that tumors can be recognized as foreign rather than as self and can be effectively attacked by an activated immune system. An effective immune response in this setting is thought to rely on immune surveillance of tumor antigens expressed on cancer cells that ultimately result in immune responses and cancer cell death. Meanwhile, tumor progression may depend upon acquisition of traits that allow cancer cells to evade immunosurveillance and escape effective innate and adaptive immune responses.[35,36,37] Current immunotherapy efforts attempt to break the apparent tolerance of the immune system to tumor cells and antigens by either introducing cancer antigens by therapeutic vaccination or by modulating regulatory checkpoints of the immune system. T-cell stimulation is a complex process involving the integration of numerous positive as well as negative co-stimulatory signals in addition to antigen recognition by the T-cell receptor.[38] Collectively, these signals govern the balance between T-cell activation and tolerance.

Programmed cell death protein 1 (PD-1) is a member of the CD28 family of T-cell co-stimulatory receptors.[39] PD-1 signaling has been shown to inhibit CD28-mediated upregulation of IL-2, IL-10, IL-13, interferon-γ (IFN-γ), and Bcl-xL. PD-1 expression has also been noted to inhibit T-cell activation and expansion of previously activated cells. Evidence for a negative regulatory role of PD-1 comes from studies of PD-1 deficient mice, which develop a variety of autoimmune phenotypes.[40] These results suggest that PD-1 blockade has the potential to activate anti-self T-cell responses, but these responses are variable and dependent upon various host genetic factors. Thus, PD-1 deficiency or inhibition is not accompanied by a universal loss of tolerance to self-antigens.

In vitro, nivolumab (BMS-936558) binds specifically to PD-1 with high affinity and inhibits the binding of PD-1 to its ligands, programmed cell death-ligand 1 (PD-L1) and programmed cell death-ligand 2 (PD-L2). In vivo blockade of PD-1 by a murine analog of nivolumab enhances the antitumor immune response and result in tumor rejection in several immunocompetent mouse tumor models (MC38, SA1/N, and PAN02).[41]

Clinical studies have been conducted to evaluate safety and efficacy of nivolumab across various tumor types. Nivolumab has been approved as treatment for melanoma, non-small cell lung cancer (NSCLC, both nonsquamous and squamous histologies), head and neck cancer, renal cell carcinoma (RCC), bladder cancer, Hodgkin's lymphoma, and mismatch repair deficient and microsatellite instability-high (MSI-H) colorectal cancer in the US and other countries, and is being evaluated extensively across a wide range of other solid tumors and hematological malignancies.[42,43]

### 1.1.4 Preclinical studies with BMS-986158

BMS-986158 has been tested against a wide-array of cancer cell lines and has demonstrated potent cytotoxicity against multiple hematologic and solid tumors. Many of the most sensitive cancer types are driven by c-MYC including MM, AML and small cell lung carcinoma (SCLC). The on-target mechanism of BMS-986158 is evidenced by its inhibition of c-MYC expression in the JJN3R MM cell line at the same potency (IC50 = 0.8 nM) as its targeted cytotoxicity potency (IC50 = 4 nM). Two other hematologic cell lines, known to be driven by c-MYC, MOLM-13 and OCI-AML3, demonstrated sensitivity with IC50 of 1.7 and 0.7 nM, respectively.

In a panel of 30 human lung cancer cell lines, BMS-986158 demonstrated potent and selective cytotoxic activity (IC50 <10 nM) in 8 lines, intermediate activity (IC50 = 10-100 nM) in 4, and low activity in 18 (IC50 >100 nM). Six of the 8 highly sensitive cell lines were SCLC, further re-enforcing the potential importance of c-MYC in the mechanism of action (MOA) of BMS-986158 BET inhibition.

BMS-986158 was evaluated in a panel of patient-derived xenografts (PDX) in mice. The dose of BMS-986158 (1.6 mg/kg administered BID, 5-days-on-2-days-off for two cycles) was 2-3-fold below its maximum tolerated dose (MTD) in mice (MTD range: 5-10 mg/kg QDx10; 3.2-4.8 mg/kg BIDx10). BMS-986158 demonstrated antitumor activity (tumor growth inhibition [TGI] > 70%) in 8 of 19 (42%) of the PDX models tested. The excellent potency of BMS-986158 against hematologic cancer cell lines in vitro was also reflected in vivo in tumor xenografts in mice; each demonstrated robust sensitivity to BMS-986158 at low, well-tolerated doses. In an ovarian cancer (OC) PDX model that was determined to have amplification of the BRD4 gene, tumor regression was observed during the dosing period (TGI = 126%) suggesting that tumors with BRD4 amplification may be particularly sensitive to BET inhibition. Analysis of human TCGA data also shows that approximately 27% of ovarian tumors of serous histology that are BRCA 1/2 wildtype are also have BRD4 amplification.

### 1.1.5 Rationale for Dose and Schedule

**BMS-986158**

In the pivotal 1-month oral toxicity studies of BMS-986158, the highest non-severely toxic dose (HNSTD) in dogs was 0.15 mg/kg. The MTD in rats was 0.25 mg/kg. The dog was considered the most appropriate species for calculation of the maximum recommended starting dose (MRSD) because a nontolerated dose was attained in dog but not rat and the toxicity profile was similar in both species. The starting dose of 0.75 mg/day was selected based upon the human equivalent dose (HED; scaled by body-surface area) of the HNSTD in dogs (the more sensitive species between dogs and rats) with a safety factor of 1/6 (see Section 1.4.2 for details). The projected human efficacious dose is estimated to be 2 mg/day based on the observed human pharmacokinetics (PK) and a projected human efficacious concentration of 46 ng/mL. This concentration is derived from the minimal efficacious concentration (MEC) established in a mouse xenograft model and corrected for protein binding differences between species. As a patient's disease pathophysiology differs from preclinical animal tumor models, the human efficacious dose will be determined and confirmed in clinical studies.

To assure safety of human subjects, the initial dose of BMS-986158 tested in this study was 0.75 mg/day. Part 1 of this study also evaluates different administration schedules: monotherapy given 5 consecutive days on with 2 days off each week of a 4-week cycle (Schedule A of Part 1); monotherapy given 14 consecutive days on with 7 days off of a 3-week cycle (Schedule B of Part 1); and monotherapy given 7 days on and 14 days off of a 3-week cycle (Schedule C of Part 1). The rationale for the 3 schedules is based on the human half-life of 39 hours. Schedule A effectively provides continuous drug exposure, while Schedules B and C provide intermittent exposure with a break to allow for platelet recovery as needed at higher doses in human trials of other compounds in this class.[44,45,46,47]

For Part 2, Schedule A, has been selected considering the safety, [redacted] and PK obtained during Part 1 (see Section 3.1.2.1). Preliminary analysis of Part 1 showed that Schedule A provided continuous drug exposure with a tolerated safety profile at selected doses above the projected efficacious dose and resulted in sustained targeted gene expression modulation. BMS-986158 will be administered at a starting dose of 4.5 mg for 2 weeks (10 doses) followed by 3.75 mg for the remainder of treatment. A higher dose of 4.5 mg will ensure initial maximal suppression of key oncogenes [redacted]. The subsequent reduction in dose is expected to maintain this gene suppression without compromising tolerability and to mitigate the potential risk for dose interruptions and dose delays. Further dose reduction is permitted beyond the dose de-escalation to 3.75 mg depending on toxicity and tolerability observed in each subject (see guidelines for dose modification in Section 4.5.2).

In addition to adult subjects, adolescent subjects will be included in Part 2 and dosage rationale for these subjects is discussed in Section 1.1.13.

Depending on safety, PK and the totality of data obtained from Part 2, Schedule A with BMS-986158 monotherapy, subjects may also be enrolled in Schedules B or C upon agreement between investigators and the Sponsor/Medical Monitor.

**Nivolumab**

Nivolumab has been extensively studied in a number of tumor types with body weight normalized dosing (mg/kg), and a dose of 3 mg/kg has been approved to be used as monotherapy.[42,43] Population pharmacokinetic (PPK) analyses showed that the PK of nivolumab is linear with dose-proportional exposures over a dose range of 0.1 to 10 mg/kg, similar across tumor types. To evaluate the impact of a flat dosing regimen on the safety and efficacy of nivolumab, simulations were performed using the previously developed, well-characterized PPK model. Based on the simulation results, the range of systemic exposures of nivolumab resulting from either a 3-mg/kg dose or 360 mg every 3 weeks (Q3W) or 480 mg every 4 weeks (Q4W) flat doses is similar. The dosage regimen for nivolumab for the currently approved indications in the US (RCC, metastatic melanoma and NSCLC) has been modified to 240 mg IV every 2 weeks (Q2W) based on FDA approval of the dosing regimen on 13-Sep-2016.

Nivolumab has been shown to be safe and well tolerated up to a dose level of 10 mg/kg, and the relationship between nivolumab exposure produced by 3 mg/kg and efficacy has been found to be

relatively flat.[42,43] Taken together, the PK, safety, and efficacy data indicate that the safety and efficacy profile of 360 mg Q3W or 480 mg Q4W nivolumab will be similar to that of 3 mg/kg Q2W nivolumab. Based on these results, a flat dose of 360 mg Q3W or 480 mg Q4W is recommended for further investigation in adult subjects. A total body-weight dose of 4.5 mg/kg Q3W up to a maximum of 360 mg or 6 mg/kg Q4W up to a maximum of 480 mg is recommended for adolescent subjects.

The decision to pursue combination therapy with nivolumab will be made depending on [redacted] safety and PK results obtained during Part 2 monotherapy. If combination with nivolumab is pursued, Schedule A (5 days on/2 days off for a 4-week cycle) will be used to dose BMS-986158 with a flat dose of 480 mg Q4W nivolumab. The dosage in adolescent subjects is discussed in Section 1.1.13

### 1.1.6 Rationale for Monotherapy Dose Escalation Design and Combination Safety Monitoring.

The increment in the dose levels used in monotherapy dose escalation, especially in the first schedule tested (Schedule A), is guided by the modified Fibonacci to help mitigate the potential risk inherent in the steep dose/toxicity curve and/or the low therapeutic index seen in preclinical studies. Dose escalation decisions will utilize a modified toxicity probability interval (mTPI) design.[48] Rationale for selection of an mTPI over a 3+3 design includes a more accurate determination of MTD, greater flexibility in cohort size, and that it allows de-escalation and re-escalation to a previously tried dose. The design provides a simple dose escalation decision algorithm (Appendix 1), and in addition to the higher accuracy of MTD selection, it treats fewer subjects at suboptimal doses, as seen by simulations described in Appendix 2.

If pursued, the safety monitoring of the selected BMS-986158 dose in combination with nivolumab based on dose limiting toxicities (DLTs) will be guided within the mTPI framework using the more recently available mTPI-2 methodology and taking into account prior information on the safety of monotherapy for nivolumab and BMS-986158 related AEs observed so far. The mTPI-2 design provides better operating characteristics over the 3+3 method (Appendix 8) and has improved performance over the original mTPI design, as it was developed to mitigate some suboptimal decisions by the original mTPI design and to provide a more efficient safety evaluation than the mTPI.[49]

### 1.1.7 Rationale for Evaluating BMS-986158 in an Initial Monotherapy Expansion Cohort

The number of subjects and types of tumors initially enrolled in the Part 2 expansion will be limited to initially focus on tumor types where the greatest signal of activity is expected, based on published preclinical and clinical data.[143,50] Preliminary antitumor activity will be assessed in subjects enrolled during the Initial Expansion, to inform subsequent expansion. [redacted]

[redacted]

### 1.1.8 Rationale for Genetically Defined Tumor Groups

Drug development strategies in oncology continue to evolve with the advent of histology-agnostic biomarkers correlating with the clinical activity of targeted anticancer drugs. For example, recent breakthrough findings led to accelerated approval of pembrolizumab for the treatment of adult and pediatric patients with various solid tumors bearing MSI-H or mismatch repair deficiency.[51,52] Another success of such an approach is a development of larotrectinib, a selective TRK tyrosine kinase inhibitor that demonstrated histology-agnostic efficacy in patients with TRK fusion-positive cancers.[53] Thus, in the light of these novel strategies, tumors with genetic rearrangements that engage molecular pathways regulated by BRD proteins, including gene translocations, mutations, or amplifications, have been selected for Part 2 of this study to identify early clinical activity in these preselected patient populations. The results of this study may help to understand whether the activity of BMS-986158 depends on specific genetic alterations observed in selected histologies or may be tumor agnostic.

**Translocations**

Chromosomal translocations may lead to the formation of fusion proteins with oncogenic properties. Examples of these genetic abnormalities include BRD3,4-NUT fusion (in 75% of cases of NMC), EWS/FLI1 fusion (in 85% of cases of Ewing sarcoma [ES]), and IGH/L-MYC and IGH-BCL-2/6 fusions (in Burkitt's lymphoma [BL] and double-hit lymphoma [DHL]).

- NMC: BRD3 or BRD4, as partners in the BRD3,4-NUT fusion protein, directly contribute to malignant transformation by interfering with cell differentiation,[54,55] and BET inhibitors have been shown to suppress tumor growth in preclinical models as well as in patients.[26,46,56,57]
- ES: BRD proteins function as epigenetic readers regulating the expression of EWS/FLI1.[58,59,60,61,62] BET inhibitors downregulate EWS/FLI1 expression and interfere with tumor cell viability, proliferation, and growth in animal models.[27,63]
- Lymphomas: Pathogenesis of Burkitt's lymphoma (BL) is driven by translocation of MYC,[64,65] and DHL by translocation of both MYC and BLC2 or BCL6.[66] The expression of formed IGH/L-MYC and IGH-BCL-2 fusion proteins is regulated by the BET family,[9,67,68] and BET inhibitors arrested tumor cell growth in vitro as well as in xenograft models.[9,25,69]

Detection of these fusion proteins is required for diagnosis and is a routine clinical practice. Initially, only subjects with NMC carrying BRD3,4-NUT fusion will be selected to participate in Part 2. Subjects with other fusion proteins may be eligible to participate in Part 2 of this study as part of the Subsequent Expansion based on review of the totality of data obtained from subjects in the Initial Expansion in Part 2 (see Section 3.1.2).

**Mutations**

SWI/SNF functions as a tumor suppressing complex and mutations in subunits contribute to malignant transformation.[70] The KRAS protein is required for signaling in normal cells, and the mutation of a KRAS gene contributes to the development of many cancers. Similarly, Gnaq and Gnaq/11 mediate the intracellular signal transduction pathway, and mutations in these genes lead to oncogenesis.

- Renal cell carcinoma (RCC): Approximately 40% of patients with RCC harbor mutations within the SWI/SNF complex, including ARID1A, ARID1B, SMARCA4, SMARCA2, SMARCB1, ARID2, PBRM1 (BAF180) ,[71] and BET inhibitors induced RCC cell apoptosis and repressed tumor growth in vitro and in vivo.[23]
- Non-small cell lung cancer (NSCLC): BMS-986158 suppressed proliferation of NSCLC cell lines with SWI/SNF mutations (BMS, data on file). In vitro and in vivo antitumor activity of other BET inhibitors has also been reported in NSCLC cells harboring KRAS mutations, although this effect was abrogated by concurrent alterations of LKB1, also known as STK11.[72] According to TCGA database, 30% of patients with NSCLC harbor SWI/SNF mutations, and 15% harbor KRAS mutations of which approximately 75% express wild type LKB1.
- Uveal melanoma (UM): BET inhibitor demonstrated cytotoxic activity in UM cells carrying Gnaq/11 mutations and inhibited tumor growth in xenograft models.[24]

Mutations in SWI/SNF complex, KRAS, and Gnaq/11 will be detected in tumor biopsies using the [redacted] diagnostic platform. Mutations in SWI/SNF complex, KRAS, and Gnaq/11 will be detected in tumor biopsies using the [redacted] diagnostic platform. Subjects with tumors carrying these mutations may be eligible to participate in Part 2 of this study as part of the Subsequent Expansion based on review of the totality of data obtained from subjects in the Initial Expansion in Part 2 (see Section 3.1.2 and Figure 3.1-1).

**Amplifications**

- BRD: In patients with OC, BRD amplification is associated with worse overall survival.[19] BRD gene amplification correlates with overexpression of BRD RNA (TCGA database) and is necessary for proliferation and survival of some tumor cell types, including OC[20] and triple negative breast cancer (TNBC).[21] Blocking hyperactivity of BRD proteins with a BET inhibitor results in growth inhibition of xenografts obtained from patients with OC[19] and from patients with TNBC.[21,73,74] Approximately 43% of patients with TNBC, 55% of patients with neuroendocrine prostate cancer (NEPC), and 17% of patients with OC harbor BRD4 amplifications (TCGA database).
- MYC: Forty-one percent of patients with castration-resistant prostate cancer (CRPC) and 47% of OC patients harbor MYC amplifications (TCGA database). BET inhibition results in reduced MYC expression and inhibition of tumor growth in PDX models with high MYC expression and inhibition of AR signaling.[75] High frequency of MYC amplification (approximately 30%) has also been observed in patients with uterine carcinosarcoma (UCS; TCGA database). Also, the non-germinal center subtype of diffuse large B-cell lymphoma (non-GC-DLBCL) is often associated with MYC (and BCL2) overexpression.[76] A recent

Phase I study of a BET inhibitor in patients with relapsed and refractory lymphoma reported objective clinical responses in the non-GC-DLBCL subtype, in particular in patients with activated B cell (ABC)-DLBCL.[77]

- AR: Among other genetic abnormalities sensitive to BET regulation is AR amplification.[22] AR promotes ligand-independent prostate cancer (PC) progression through c-MYC upregulation.[78] BET inhibitors decreased MYC levels and proliferation viability of CRPC cells, and inhibited growth of PC xenografts.[22] Approximately 67% of CRPC patients harbor AR amplification, and 25% to 30% harbor both MYC and AR amplifications (TCGA database).

BRD, MYC, and AR amplifications will be detected in tumor biopsies using [redacted] diagnostic platform. Subjects with TNBC, non-GC-DLBCL and CRPC with any of these gene amplifications/overexpressions will be eligible to participate in Part 2 as part of the Initial Expansion. Subjects with other tumors with these amplifications may be eligible to participate in Part 2 of this study as part of the Subsequent Expansion based on review of the totality of data obtained from all subjects in the Initial Expansion in Part 2 (see Section 3.1.2 and Figure 3.1-1).

### *1.1.9 Rationale for Tumor Specific Patient Populations*

**NMC**: NMC is a rare and aggressive tumor that has a lethal clinical course and no established treatment algorithms.[79] In the absence of guidelines, combinations of different drugs (actinomycin D, alkylating agent, anthracycline, vinca-alkaloid, VP-16, platinum compounds, taxane agents, 5-FU, and cytarabine) have been used as first line (1L) therapy for NMC. On current therapies, patients die of disease with median overall survival (OS) time of 9.7 months from the time of diagnosis.[80] While several complete response (CR) cases following 1L therapy have been reported, the majority of patients relapse with a median time to progression of 9.3 months.[81] Only 8 survivors have been reported to date, and all received surgery in combination with chemotherapy or radiation.[80] Since the vast majority of NMC cases remain refractory to conventional therapy with no 2L options, efforts have been made to develop novel targeted therapeutics. In 75% of cases, NUT (NUTM1) is fused to BRD3 or BRD4 forming a fusion protein that drives oncogenic transformation.[82] Thus, BET inhibitors may directly interfere with molecular mechanisms mediating NMC pathogenesis. In a recent study, 3 of 10 subjects treated with OTX015/MK-8628 achieved (partial response) PR or stable disease (SD),[83] although the genetic rearrangements in responders versus non-responders have not been reported. Because survival with current therapies has been dependent on the possibility of surgical resection, subjects with unresectable NMC harboring BRD3-NUT and BRD4-NUT fusions, regardless of prior treatments, will be eligible to participate in this study.

**ES**: There is a consensus for the ES treatment pathway that VDC/IE interval compression chemotherapy is recommended for 1L therapy.[84,85] Local control includes surgery and radiation. Most ES relapses (approximately 80%) occur within 2 years of the initial diagnosis.[86,87] Chemotherapy is generally recommended for all recurrent ES patients; however, the outcomes remain poor. A combination of irinotecan and temozolomide is the first option after relapse,

primarily because of the favorable toxicity profile. The combined response (CR+PR) rate on this regimen is 53%, and progression-free survival (PFS) at 4 months is approximately 60%. Another regimen is cyclophosphamide and topotecan, and responses to this therapy were correlated with the relapse interval, with no responses when the disease was progressing on prior therapy and with a response rate of approximately 50% when 2 years had passed between the prior therapy and the initiation of therapy. The intensification of conventional therapy or even myeloablative chemotherapy with hematopioetic stem cell transplant (HSCT) has not been reported to be advantageous. In the relapse setting, the response or disease stabilization after all these therapies with median postrecurrence survival ranges from 9 to 17 months dependent on the extent of disease. Thus, the development of novel therapeutic approaches is warranted. ES is associated with translocation of EWS and FLI1 genes resulting in a chimeric fusion transcript EWS/FLI1 in 85% of cases.[58] EWS/FLI1 fusion protein acts as a transcription factor and drives ES cell proliferation and survival by inducing a panel of genes, including GLI1[59,60] and MYC,[61,62] and BET inhibitors have been shown to downregulate EWS/FLi1 expression.[63] Thus, ES patients harboring the EWS/FLI1 fusion that progressed after 1L therapy will be eligible to participate in this study.

**BL**: While BL is among the therapeutic successes in oncology, the optimal initial therapy for BL has not been clearly defined given the paucity of randomized studies and the fact that different, modern BL regimens can all achieve good results.[88] Several chemotherapy regimens have been successfully tested, including CODOX-M/IVAC,[89] LMB 89,[90] R-Hyper-CVAD,[91] and others[88,92,93,94] with CR rates up to 95% and 5-year OS in 70% of patients. Incidence of relapse or refractory disease is approximately 10%, and current results in refractory/relapsed BL are extremely poor.[88] For relapsed or refractory BL in patients who have not received prior cytarabine, regimens such as dexamethasone plus cytarabine plus cisplatin or etoposide plus methylprednisolone plus cytarabine plus cisplatin may be considered. Gemcitabine-based regimens, such as gemcitabine, dexamethasone, and cisplatin, are an option for patients who have received cytarabine. Unfortunately, the vast majority of patients will not respond to additional chemotherapy. Responders are referred for high-dose chemotherapy and HSCT, with a reported 5-year OS of only 21% and 18% for autologous and allogeneic HSCT, respectively.[95] The salvage treatment of relapsed or refractory BL is usually unsuccessful. Median survival for patients with progressive disease (PD) or early relapse is 5 months,[96] and no long-term disease-free survivors after BL relapse have been reported.[88,97] Therefore, novel therapies are needed for this patient population. BL is driven by MYC translocation and formation of an IGH-MYC fusion with the IGH,[98,99] and importantly, translocated MYC locus harbors super enhancers that are sensitive to BET inhibition.[100] In preclinical studies, treatment with the BET inhibitor JQ1 resulted in a 45% tumor volume reduction in Raji cell xenografts as compared to control.[9] In combination with a PD-L1 inhibitor, JQ1 treatment resulted in 100% CR in mice with Eμ-MYC lymphoma,[25] supporting further studies. Therefore, patients with BL that relapsed or are refractory to 1L therapy will be eligible to participate in this study.

**DHL and non-GC-DLBCL:** DHL and non-GC-DLBCL are highly aggressive disease subsets of DLBCL with very poor clinical outcomes and the standard of care (SOC) has not been established for DHL.[101,102] Patients are treated with various chemotherapy regimens, including R-CHOP, R-EPOCH, HyperCVAD, and CODOX-MIVAC as 1L therapy. Retrospective analysis across different studies demonstrated an approximately 57% CR rate for DHL.[103,104] DHL and non-GC-DLBCL are associated with advanced age, therefore, regimens such as CODOX-M/IVAC and HyperCVAD/MA, which are poorly tolerated in elderly patients, are not appropriate for the majority of these patients, whereas R-EPOCH has been suggested as appropriate for most patients with DHL.[105] Overall, the outcome of patients with DHL or non-GC-DLBCL treated with conventional chemotherapy is often poor because, despite the response rate, the majority of patients will experience disease progression after standard treatment with PFS of approximately 9 months and median OS of 15 months.[104,106,107] Regimens used in relapsed/refractory DHL include R-DHAP, R-ESHAP, R-GDP, and R-ICE. However, none of these traditional chemoimmunotherapy regimens produced a significant rate of complete or sustained remissions with a 3-year OS rate from the time of first progression of 7% and median OS of 8 months.[94,104,108,109] Overall, the optimal approach to DHL and non-GC-DLBCL is unknown, and developing optimal therapeutics for DHL and non-GC-DLBCL represents a great unmet clinical need.[110,111] DHL is characterized by translocation of both MYC and BCL2 (IGH-MYC and IGH-BCL2), and both fusion proteins expressed on BRD4-loaded superenhancers may be directly targeted by BET inhibitors.[100,112] Non-GC-DLBCL is characterized by MYC (and BCL2) overexpression, which may be also be targeted by BET inhibitors. Indeed, in combination with other agents (eg, bortezomib, YM-155, or chemotherapy), JQ1 kills DHL cells in vitro.[69] Another BET inhibitor, GS-5829, in combination with venetoclax resulted in broader activity in a DLBCL cell line with greater activity correlating with higher MYC protein levels compared with either agent alone.[113] Thus, subjects with DHL or non-GC-DLBCL that relapsed or are refractory to 1L therapy will be eligible for enrollment in the Initial Expansion in Part 2 of this study.

**OC**: Platinum-containing compounds are recommended as 1L therapy for patients with OC and may be repeated as long as the disease remains platinum sensitive. Platinum refractory disease (RD) is defined as disease progression during the last line of platinum therapy or within 4 weeks from the last platinum dose, and platinum-resistant disease is defined by a platinum free interval (time from last platinum-based chemotherapy to recurrence) of > 1 and < 6 months.[114] A majority (80%) of patients with advanced disease experience a recurrence within 5 years from diagnosis, with 70% of them relapsing within 18 months.[115] Among patients affected by recurrent disease, approximately 23% are platinum resistant, with 5.3% presenting as RD.[116] When single agents like topotecan, paclitaxel, gemcitabine, or pegylated liposomal doxorubicin are used, the PFS across different studies is approximately 5 months with OS approximately 15 months.[117] Recently revised National Comprehensive Cancer Network (NCCN) guidelines recommend the following

combination regimens for patients with platinum-resistant recurrent OC: paclitaxel plus bevacizumab, liposomal doxorubicin plus bevacizumab, and topotecan plus bevacizumab.[118] A combination of bevacizumab with chemotherapy agents resulted in improved PFS of 6.7 months with median OS of 16.6 months.[119] The poly ADP ribose polymerase (PARP) inhibitor, rucaparib, has been recently approved as a single agent for patients with advanced OC harboring BRCA mutations with PFS of 12.8 months.[120,121] Another PARP inhibitor (olaparib) has also been approved for patients with BRCA-mutated progressive OC, and olaparib and niraparib have been approved in the maintenance setting (ongoing complete or partial response to platinum-based chemotherapy). Palliative chemotherapy has been shown only to reduce symptoms in patients with platinum-resistant disease without improving the outcomes.[115,122] Since agents available for patients with platinum-resistant and refractory OC provide only temporary benefit,[119] novel therapeutic approaches are needed.[123] Increased BRD levels are associated with worse PFS and OS in patients with OC,[19] and BRD4 is necessary for proliferation and survival of OC cells[20] providing a basis for testing BET inhibitors in patients harboring BET amplifications. Furthermore, BET inhibitor JQ1 inhibited OC tumor growth with high MYC expression in PDX models.[20] Therefore, subjects with platinum-resistant OC harboring BET and/or MYC amplifications will be eligible to participate in this study; subjects with platinum-resistant OC with BET and/or MYC amplifications and coexisting BRCA1 or BRCA2 mutations will be eligible after treatment with a PARP inhibitor, if available.

**TNBC**: For local disease, surgery and radiotherapy are preferred as 1L therapy. Although, based on NCCN and the European Society for Medical Oncology guidelines, there is no SOC therapy identified as the treatment of choice specifically for TNBC, alkylator plus anthracycline plus taxane-based chemotherapy backbone are frequently used for early stage systemic treatment.[124,125,126] Approximately 30% of patients achieve CR with 5-year disease-free survival of 57% and 5-year OS of 70%.[127] Approximately 36% of patients experience recurrence after the front line neoadjuvant therapy with 25% developing distant metastasis. Survival duration of patients with metastatic TNBC is approximately 15 months.[128] Patients with BRCA1 or BRCA2 mutations (30% of TNBC patients) have above average platinum sensitivity.[129] In patients with metastatic 1L or 2L TNBC treated with carboplatin or docetaxel, objective response rates (ORRs) were observed in 31.4% in the carboplatin arm and 35.6% in the docetaxel arm. The median PFS was 3.1 months in the carboplatin arm and 4.5 months in the docetaxel arm with a median OS of 12.4 months and 12.3 months, respectively. Carboplatin demonstrated significantly increased activity vs docetaxel in BRCA-carriers. ORR was 68% with carboplatin and 33% with docetaxel. In BRCA-negative patients, ORRs were not significantly different at 28.1% with carboplatin and 36.6% with docetaxel. Despite the high ORR to carboplatin, responses were short in both subgroups: BRCA-positive patients had a median PFS of 6.8 months compared with 3.1 months in patients with nonmutated BRCA-receiving carboplatin. For patients with metastatic cancer, sequential single agents are preferred, including taxanes, topoisomerase II inhibitors, platinum-

based drugs, vinca alkaloids, and other antitubulins and antimetabolites, although toxicity profiles should be considered.[126,130] Despite these therapeutic approaches, TNBC remains a lethal disease, thus novel therapeutic approaches are needed. Approximately 34% of TNBC patients harbor BRD amplifications resulting in increased levels of BRD proteins, which control growth and proliferation of cancer cells.[21] BET inhibitors JQ1 and OTX015/MK-8628 inhibit TNBC proliferation in vitro and in vivo[73,74] providing a scientific rationale for testing the effects of BET inhibitors in patients with TNBC harboring BRD amplifications. Thus, subjects with TNBC positive for BRD amplification that progressed after at least 1 therapy in the recurrent/metastatic setting will be eligible to participate in either Part 1 or 2 of this study.

**CRPC:** Most PC-related deaths are results of mCRPC, which progresses and metastasizes after surgical or medical castration.[131] NCCN guidelines recommend use of Sipuleucel-T as 1L therapy in patients with asymptomatic or minimally symptomatic mCRPC. Docetaxel represents the current 1L therapy for symptomatic CRPC patients, and Radium-223 can be used as 1L therapy in patients who are not candidates for docetaxel.[132] Time-to-treatment failure in patients treated with docetaxel is approximately 5 months.[133] Abiraterone or enzalutamide can be used as 2L therapy in patients who progressed on docetaxel, and mitoxantrone and prednisone can used for palliation.[132] Patients with metastatic disease progressing after docetaxel treated with abiraterone acetate plus prednisone achieved median 5.6 months PFS compared to 3.6 months in patients treated with prednisone alone.[134] In patients with mCRPC who progressed on docetaxel, treatment with enzalutamide resulted in median PFS of 8.3 months compared with 2.9 months on placebo.[135] Different guidelines are provided by the European Association of Urology: based on the performance status, symptoms, comorbidities, and extent of disease, the choice of 1L treatment includes abiraterone, cabazitaxel, docetaxel, enzalutamide, Radium 223, and sipuleucel-T. When used as 1L therapy in mCRPC patients, abiraterone plus prednisone treatment resulted in PFS of 16.5 months compared with 8.2 months for prednisone alone.[136] The options for 2L therapy are affected by the treatment chosen as 1L therapy: if either abiraterone or enzalutamide were used as 1L therapy, docetaxel would be offered next; if docetaxel was used as 1L therapy, cabazitaxel, abiraterone plus prednisone, or enzalutamide can be used in patients who had progressed after or during docetaxel-based chemotherapy.[137] It is also recommended that patients who develop CRPC, despite castrate levels of testosterone, should be maintained in a castrate state indefinitely.[138] However, regardless of treatment, life expectancy for CRPC patients is only 15 to 20 months.[137,139,140,141,142] Thus, there is an urgent need to develop novel drugs targeting alternative pathways.[138] Recent studies have shown that BET inhibitors inhibited growth of CRPC in vitro and in vivo, and AR overexpressing cells are more sensitive to BRD inhibitors.[22] OTX015/MK-8628, in a Phase I monotherapy, dose-escalation study, demonstrated clinical activity in an unselected population of advanced solid cancer. One patient with CRPC was reported to have an unconfirmed PR; no details of genetic amplification were given.[143] Therefore, subjects with metastatic CRPC positive for AR amplification that progressed on or after treatment with a

taxane and with an androgen pathway antagonist (eg, abiraterone or enzalutamide) will be eligible to participate in either Part 1 or 2 of this study, and will be permitted to continue abiraterone but not enzalutamide to maintain a castrate state.

**NEPC:** Radical prostatectomy (RP) and radiation therapy (RT) combined with chemotherapy are commonly used as 1L therapy for localized NEPC.[144,145] Metastatic disease is identified in 64% of cases at diagnosis with median survival of 8.5 months.[145,131] Neither RP nor RT improve survival in metastatic patients.[145]. Currently available data suggest that chemo-radiotherapy provides maximal benefit in metastatic patients with ORR of 61%, however, prognosis is poor regardless of histologic subtype and administered treatment due to quick progression (PFS of 5.8 months) and OS of 10.5 months [131,146]. Current 1L treatment generally entails platinum-based chemotherapy.[147,148] Pure small cell carcinoma is frequently treated with platinum plus etoposide combinations, and mixed NEPC is frequently treated with docetaxel.[147] However, the duration of response is transient with a median survival of less than 12 months.[147] In a recent study, patients were treated with cisplatin plus etoposide after disease progression on a carboplatin plus docetaxel regimen, with median OS of 16 months. The trial results suggest that continued platinum-based chemotherapy with the addition of etoposide may be a 2L therapy option in patients with NEPC who experience disease progression on platinum plus taxane combinations.[149] However, others recommend this regimen for palliative purposes due to high toxicity rates.[150,151,152] Other regimens, such as a combination of estrogen and somatostatin analogues, provided symptomatic responses in patients who were refractory to conventional therapy.[153] Palliative benefit of clinical symptom control was also shown for the combination of cyclophosphamide and mitoxantrone with 34.5% ORR and 7.5 months PFS.[154,155] Given the poor outcomes with current options,[144,150,156] studies are needed to identify novel targeted therapies.[147] Approximately 23% of patients with NEPC harbor BRD4 amplifications,[71] and the inhibitory effect of BET inhibitor JQ1 on growth of neuroendocrine tumors in preclinical models has been reported.[157] Thus, subjects with metastatic NEPC harboring BRD amplifications that relapsed or is refractory to 1L therapy will be eligible to participate in this study.

**UCS**: Per NCCN guidelines, carcinosarcoma is now considered and treated as high-grade carcinoma. For UCS, NCCN guidelines include complete surgical staging followed by systemic chemotherapy including ifosfamide/paclitaxel or cisplatin/ifosfamide combinations as 1L therapy.[158] Gynecologic Cancer Intergroup also considers a carboplatin/paclitaxel combination.[159] However, due to the high rate of recurrent tumors (40% to 60%) and the low median OS of 16 to 40 months post-diagnosis, UCS has a poor prognosis.[160] In persistent or recurrent disease, several drugs or combinations (including gemcitabine/docetaxel, thalidomide, imatinib, and sorafenib) have been tested as 2L therapy with no success.[161,162,163,164] For example, patients with recurrent disease who had previously failed 1 regimen of chemotherapy were treated with gemcitabine and

docetaxel with 0% CR, 8.3% PR, and 33.3% SD with PFS of 1.8 months and OS of 4.9 months.[161] Due to the aggressive nature of this disease, rarity, and limited therapeutic options in the relapsed/refractory stage, optimal management of UCS is still not established and novel therapeutic approaches are needed.[165] Approximately 41% of patients with UCS harbor MYC amplifications, and BET inhibitors downregulate NF-κB activity that is required for TGF-β-mediated oncogenic signaling in UCS.[166,167] Thus, subjects with UCS harboring MYC amplifications that relapsed or is refractory to 1L therapy will be eligible to participate in this study.

**NSCLC**: Per NCCN guidelines, 1L treatment largely depends on the stage and histology of NSCLC and includes surgery, radiation, and systemic therapy (eg cisplatin-based chemotherapy combined with other regimens, including etoposide, docetaxel, bevacizumab, etc). For metastatic disease, treatment decisions are also based on molecular profiling of tumors (ie, testing EGFR, ALK, ROS1, BRAF, and PD-L1), which allows the use of targeted therapies as 1L treatment. The 2L treatment options for patients who progress on 1L therapy include systemic therapies (eg, docetaxel, gemcitabine, and ramucirumab/docetaxel) and immune checkpoint inhibitors (eg, nivolumab, pembrolizumab, and atezolizumab). Patients on 2L docetaxel- or pemetrexed-based chemotherapy and erlotinib achieve ORR of approximately 8% to 10%, PFS of 4 months, and median OS of 8 to 10 months, whereas PD-1/PD-L1 inhibitors have shown to prolong OS in pretreated patients.[168,169] Patients with 2L squamous-cell NSCLC treated with nivolumab or docetaxel achieve ORR of 20% or 9%, PFS of 3.5 months or 2.8 months, and OS of 9.2 months or 6.0 months, respectively.[170] In a similar setting, patients with nonsquamous-cell NSCLC treated with nivolumab or docetaxel achieved ORR of 19% or 12%, PFS of 2.3 months or 4.2 months, and OS of 12.2 months or 9.4 months, respectively.[170] Nevertheless, NSCLC remains a lethal disease, and there is a need to investigate novel therapies. In pre-clinical studies, BET inhibitor JQ1 exerts in vitro and in vivo antitumor efficacy in a subset of NSCLC cells harboring KRAS mutation; however, the activity of JQ1 in mutant KRAS NSCLC is abrogated by concurrent alteration or genetic knockdown of LKB1.[171] In addition, BMS-986158 inhibits proliferation of NSCLC cell lines with SWI/SNF mutations (BMS, data on file). Thus, subjects with NSCLC harboring mutations in the SWI/SNF complex or KRAS mutation with wild type LKB1 that progressed on or after 2L therapy will be eligible to participate in this study.

**RCC**: Surgical resection remains an effective therapy for clinically localized RCC. Patients with advanced or stage IV RCC can also be treated with surgery if present with a solitary site of metastasis or solitary recurrence after nephrectomy. For patients with metastatic RCC (mRCC), the prognosis remains poor and median OS ranges from 7.8 to 43.2 months depending on the adverse factor profiling. Treatment for relapsed or Stage IV disease and surgically unresectable mRCC is challenging.[172] For clear cell histology, 1L options include cytokine therapy (eg, interleukin-2 [IL-2] and IFN) and targeted therapy (eg, pazopanib, sunitinib, and temsirolimus).

These drugs showed modest or no improvement in survival and high levels of toxicity. For example, frontline treatment of patients with bevacizumab or interferon alpha resulted in PFS of 10.2 months versus 5.4 months, respectively, with marginal changes in OS (23.3 months versus 21.3 months, respectively).[173] In similar settings, pazopanib provided 9.2 months PFS compared to 4.2 months with best supportive care.[174] As 2L therapy, NCCN recommends checkpoint inhibitors (eg, nivolumab) and anti-VEGF/ VEGFR therapy in addition to cytokines and kinase inhibitors.[175,176,177] In patients with prior cytokine treatment, sorafenib treatment resulted in 5.5 months PFS (compared with 2.8 months for placebo) and 19.3 months OS (compared to 15.5 months for placebo).[178] The best PFS outcome in the 2L setting was observed for lenvatinib, with patients achieving 14.6 months PFS compared with 5.5 months on everolimus.[179] Because metastatic RCC remains a lethal disease and SOC has not been established, there is a need to investigate novel therapeutic approaches.[176,180,181,182] Preclinical studies demonstrated that BET inhibitor JQ1 suppressed RCC cell proliferation, induced cell apoptosis in vitro, and repressed tumor growth in vivo.[23] Notably, SWI/SNF and BET family function as co-regulators of gene transcription machinery.[183] Approximately 50% of patients carry mutations within the SWI/SNF complex.[71] Thus, subjects with metastatic RCC harboring mutations within the SWI/SNF complex that relapsed or is refractory to 2L therapy will be eligible to participate in this study.

**UM**: NCCN guidelines do not provide a recommendation for UM treatment.[184] Currently, local 1L treatment options include transpupillary thermotherapy, photodynamic therapy, plaque radiotherapy, and proton beam radiotherapy for small and medium tumors. For more advanced tumors, enucleation and orbital exenteration are used as 1L treatment options. However, 50% of patients treated locally will develop metastatic disease, with OS approximately 13.4 months and only 8% surviving for 2 years. Several therapies have been tested as 2L treatment, including dacarbazine, BCG, systemic interferon, selumetinib, and fotemustine but have not reported promising results.[185,186,187,188,189] For example, patients with metastatic disease have been treated with the combination of dacarbazine and treosulfan with ORR 0%, median PFS of 12 weeks and median OS of 30 weeks.[186] In another study, patients with metastatic disease were treated with selumetinib or chemotherapy with PFS of 15.9 weeks and 7 weeks, and ORR 49% and 0%, respectively.[189] A number of clinical studies are currently in progress evaluating safety and efficacy of potential 1L and 2L therapies, including sunitinib, valproic acid, dacarbazine/INFα-2b, crizotinib, and ipilimumab, and results have yet to be reported.[190,191] For patients with systemic metastasis, observation is usually chosen because metastatic UM is resistant to treatment, and there is no evidence that current treatment is able to extend survival.[192,193] Because half of patients will develop fatal metastatic disease, there is an urgent need to develop novel therapeutic options.[191,192] Preclinical studies demonstrated that the BET inhibitor JQ1 has cytotoxic activity in cells carrying Gnaq/11 mutations, and inhibits tumor growth in xenografts with Gnaq-mutant UM cells.[24] According to the TCGA database, 85% of patients with UM harbor Gnaq/11 mutations. Thus, subjects with unresectable or metastatic UM harboring Gnaq/11 mutations regardless of prior

number of therapies (including treatment-naive subjects) will be eligible to participate in this study.

[redacted]

### 1.1.12 Rationale for QTc Objective

In this study, the effect of BMS-986158 on the QT interval will be evaluated. Preclinical evaluations did not identify a signal indicating that BMS-986158 may increase the QT interval or affect cardiac conduction. Similar to other drugs in this class, the likelihood BMS-986158 directly or indirectly affects QTc intervals is low. Despite the low risk, such evaluation is required during the development of a therapeutic agent and the design of this study treating subjects across several doses is well suited for this type of evaluation. Serial electrocardiograms (ECGs) (reviewed by a central laboratory) will be collected with matching PK samples from all subjects in dose escalation and at least 20 subjects treated at the MTD or an alternative selected dose in the dose expansion monotherapy cohorts.

### 1.1.13 Rationale for Inclusion of Adolescent Subjects

Exclusion of adolescent subjects from adult trials may slow the investigation of novel therapies in adolescent subjects and delay the delivery of novel efficacious drugs to this patient population. Thus, it has been recommended to consider adolescent subjects for tumor type- and molecular target-appropriate adult oncology trials.[202]

At the time of the clinical cutoff day 21-Dec-2018, BMS-986158 was administered to a total of 81 subjects with various advanced cancers, including rare diseases such as NMC and ES. Some of

these cancers, such as NMC, affect both children and adults. While NMC was initially thought to be a childhood cancer, recent studies have shown that it affects people of all ages with 30% of new cases reported in pediatric patients.[80] Similar to adult patients, NMC is highly lethal in children and adolescent patients with an average of 10 months survival time, despite intensive therapies.[203,80] Thus, there is an unmet medical need for new therapeutic approaches for patients with NMC across all ages. During the dose escalation part of this study, 1 subject with NMC with BRD3-NUT rearrangement responded to 2 mg BMS-986158 treatment by reaching stable disease, characterized by 15% reduction in tumor burden and improved clinical symptoms, including reduced pain. The duration of stable disease in this subject was 9 months.

ES is a rare disease in adults and mostly affects children and adolescents, with a peak of incidence around 15 years.[204] Clinically, most pediatric patients present with lesions arising from the bone, whereas more than 50% of lesions in adults occur in the soft tissue.[205] Early observations suggested an adverse prognosis for patients of older age,[206] whereas recent findings report no effect of age on OS.[207] The lower dose intensity of chemotherapy used to treat adults was discussed as a possible factor.[205] Currently, the treatment of adult patients follows the same principles as for ES in the pediatric age group.[208,209] Approximately 20% to 25% of ES patients are diagnosed with metastatic disease, and with current multimodality treatments, including chemotherapy and radiation, 5-year survival in this patient population is less than 20%.[209] During the dose escalation part of this study, 1 subject with ES responded to BMS-986158 treatment with improved clinical symptoms, including reduced pain and increased overall activity. This observation supports previously published findings that BET inhibitors may affect survival of ES cells in preclinical models.[63]

During the dose expansion part of this study, BMS-986158 will initially be tested in subjects with TNBC, CRPC, DHL, non-GC-DLBCL, NMC and possibly other advanced cancers, including UM, RCC, NSCLC, and BL in the Subsequent Expansion. Except for BL, these cancers are rare in children.[204,210,211,212,213] BL is the most common (approximately 46%) non-Hodgkin's lymphoma in children and adolescents in western countries, and rare in adults with approximately 1,200 cases per year in the US.[214,215] A recent study reported that 5-year relative survival in BL for children, adults, and the elderly were 90.4%, 47.8%, and 28.9%, respectively. Some predictors of poor outcome were shared among all age groups, such as multiple primary tumor sites and advanced stage disease.[216] It was suggested that older patients have inferior outcomes compared with younger patients due to the low intensity therapy, and one of the ways to reduce treatment burden, especially in elderly patients, might be the use of targeted therapy approaches.[214,215] In both adults and children, relapse occurs infrequently but is characterized by a poor prognosis. Pediatric patients who relapse or progress have chemotherapy-resistant disease and can rarely be cured.[217,218,219] In adults, relapsed or refractory BL treated with salvage therapy resulted in median OS of 2.8 months.[220] Because patient numbers are low, there are no randomized trials comparing different relapse regimens. These results provide rationale for development of alternative treatment

approaches focusing on targeted therapy to circumvent chemotherapy-resistant disease by providing alternative therapeutic targets across different ages.

Current experience with BMS-986158 (see Section 1.4.4 and the Investigator's Brochure for details) did not identify drug-related adverse events (AEs) that warrant exclusion of adolescent subjects from this study. Thus, the balance of benefit to risk may be favorable in adolescent subjects with advanced cancers and poor treatment options. Therefore, adolescent subjects with NMC, BL, or ES will be eligible to participate in this study. Additional indications will be allowed at the discretion of the Sponsor if the tumor contains similar genetic abnormalities sensitive to regulation by the BET family proteins.

**Rationale for Adolescent Dose**

**BMS-986158**

Analysis of available PK data indicates dose proportionality and a linear relationship between exposure and body size, allowing for appropriate scaling of dose to younger subjects using allometric scaling of clearance and volume. Current experience with BMS-986158 demonstrates that tested doses are safe in adult subjects. To provide an additional margin of safety, the lower limit of enrollment will be 12 years of age. By 6 years of age, developmental processes related to drug disposition are typically complete, and body weight is the main factor differentiating pediatric and adult drug exposures.[221,222,223] The PK results suggest that BMS-986158 exposure in adolescent subjects ≥40 kg could be similar to adults at the same dose level. Therefore, adolescent subjects ≥ 40 kg will be administered the same doses as adults and receive a starting dose of 4.5 mg for 2 weeks (10 doses) followed by 3.75 mg for the remainder of treatment in Schedule A. Due to the limited PK data collected in Part 1, only adolescents ≥40 kg will be enrolled in Part 2. By enrolling subjects ≥40 kg, it is expected that around 50% of adolescents will be eligible.

**Nivolumab**

Flat doses of nivolumab, 360 mg Q3W or 480 mg Q4W, have been shown to be safe and efficacious in adult subjects. In adolescent subjects, 6 mg/kg dose Q4W up to a maximum of 480 mg will be used for the Schedule A dose expansion. The combination of BMS-986158 with nivolumab will only be pursued if results of the effect of BMS-986158 monotherapy in the tumor microenvironment is favorable for the combination.

## 1.2 Research Hypothesis

There is no formal primary research hypothesis for this study to be statistically tested. It is anticipated that BMS-986158 as monotherapy and/or in combination with nivolumab will demonstrate adequate safety and tolerability at pharmacologically relevant doses, so as to permit further clinical development (at a recommended dose range).

## 1.3 Objectives(s)

### *1.3.1 Primary Objectives*

- To assess the safety and tolerability and to assess the DLTs, MTD, and recommended Phase 2 dose (RP2D) of BMS-986158 as monotherapy for subjects with advanced solid tumors and hematologic malignancies.
- If combination with nivolumab is pursued, to assess the safety and tolerability at the RP2D of BMS-986158 in combination with nivolumab and to assess the DLT for subjects with advanced solid tumors and hematologic malignancies.

### *1.3.2 Secondary Objectives*

- To assess the preliminary antitumor activity of BMS-986158 monotherapy and, if pursued, in combination with nivolumab as measured by ORR, and response duration based on response evaluation criteria in solid tumors using criteria from RECIST v1.1 (Appendix 4), prostate cancers using PCWG3 (Appendix 12) criteria, or hematologic malignancies using criteria from Lugano 2014 (Appendix 9).
- To characterize PK of BMS-986158 and metabolite in monotherapy and, if pursued, in combination with nivolumab.
- To assess the dose-response and exposure-response effect of BMS-986158 monotherapy on the ECG (QT interval).

## 1.4 Product Development Background

### *1.4.1 Pharmacology*

Please refer to the Investigator's Brochure.

### *1.4.2 Toxicity*

BMS-986158 is an inhibitor of the BET reader of acetylated lysine residues on histone tails. The safety profile of BMS-986158 was established in 1-month intermittent dose (5 days on/2 days off; 4 cycles) oral toxicity studies in rats and dogs. The dog data were used to calculate the MRSD for first-in-human clinical studies because a nontolerated dose was attained in the dog but not the rat and the toxicity profiles were considered similar in both species.

In the pivotal 1-month oral study in rats,[224] BMS-986158 was administered by gavage at 0, 0.05, 0.15, or 0.25 mg/kg, followed by a 3-week treatment-free recovery period. In addition to standard toxicologic and toxicokinetic endpoints, pharmacodynamic blood biomarkers (mRNA) were assessed. BMS-986158 was clinically tolerated at doses ≤ 0.25 mg/kg. There were no BMS-986158-related effects on physical (including neurologic and respiratory evaluations) or ophthalmologic examinations. Additionally, there was no increase in micronuclei frequency at ≤ 0.25 mg/kg indicating that BMS-986158 was not genotoxic in the blood micronucleus assay.

BMS-986158-related clinical signs occurred only at the high dose of 0.25 mg/kg beginning on Day 7 and included sporadic incidences of chromorhinorrhea, scant feces, and soiling. Transient, minimal mean body-weight losses at ≥ 0.15 (≤ 1.8%; females only) from Days 1 to 4 and reduced body-weight gain resulted in lower mean body weights (1.7% to 7.5% lower than controls) on Day 25. BMS-986158-related transient decreases in mean food consumption occurred in males at ≥ 0.05 mg/kg and in females at doses ≥ 0.15 mg/kg. These clinical findings were considered nonadverse due to their low small magnitude or transient nature.

BMS-986158-related hematology changes were observed at all doses and those considered notable or toxicologically relevant included decreased white blood cells (0.75 to 0.84× control), lymphocytes (0.74 to 0.85×), and eosinophils (0.54 to 0.61×) and decreased platelets (0.49 to 0.88×) with increased mean platelet volume (1.07 to 1.08×). At ≥ 0.15 mg/kg, BMS-986158-related changes included decreased reticulocytes (0.33 to 0.76×); increased red cell distribution width (1.06 to 1.28×) and mean cell volume (1.04×) and decreased mean cell hemoglobin concentration (0.96 to 0.97×); and decreased segmented neutrophils, monocytes, and basophils (0.48 to 0.77×). At 0.25 mg/kg, additional findings included decreases in red blood cells (RBCs) and hemoglobin (0.92 to 0.93×). The hematology changes were attributed to bone marrow toxicity (with correlative decreased cellularity of the bone marrow; see below) or regenerative responses of the bone marrow to platelet and reticulocyte decreases.

BMS-986158-related decreases in size and weight of the thymus and spleen with lymphoid depletion noted in both organs were observed generally at ≥ 0.15 mg/kg.

The primary BMS-986158-related microscopic changes at all doses included: 1) minimal to moderate bone marrow hypocellularity and minimal lymphoid depletion in the mesenteric or

mandibular (≥ 0.15 mg/kg) lymph nodes accompanied by minimally increased macrophage infiltration in the mesenteric lymph nodes at 0.25 mg/kg; 2) minimal epithelial single-cell necrosis in various segments of the gastrointestinal tract; and 3) minimal to mild degeneration of the mammary gland in males. At the high dose of 0.25 mg/kg, additional microscopic findings included: 1) minimal lymphoid single-cell necrosis in the thymus, 2) minimal decreases in Paneth-cell granules in the jejunum; and 3) minimal erosions, hemorrhage, and mixed-cell or neutrophilic infiltration of the glandular mucosa of stomach.

Day 1 biomarker results at approximately 4 hours after dosing suggested that inhibition of BET pathway resulted in transcriptional modulation including: 1) increases in HEX1M1 and 2) decreases in ZMYND8 and MYC. These generally expected pharmacodynamic biomarker results confirmed that BMS-986158 binds and inhibits bromodomains in rats.

BMS-986158-related adverse target organ effects in rats were dose dependent and occurred in the bone marrow, lymphoid tissues, and gastrointestinal tract, were generally more prominent or severe in females than in males (correlating with higher systemic exposures in females at ≥ 0.15 mg/kg), and were reversible or partially reversible following a 3-week post-dose recovery. The MTD was the high dose of 0.25 mg/kg (area under the concentration-time curve [AUC] ≤ 72.2 ng•h/mL, and a no-observed-adverse-effect level (NOAEL) was not identified.

In the pivotal 1-month oral study in dogs,[225] BMS-986158 was administered in gelatin capsules at 0, 0.07, 0.15, or 0.25 mg/kg, followed by a 3-week treatment-free recovery period. In addition to standard toxicologic and toxicokinetic endpoints, pharmacodynamic blood biomarkers (mRNA) were assessed. BMS-986158 was clinically tolerated at doses ≤ 0.15 mg/kg. There were no BMS-86158-related clinical signs; no physical, ophthalmologic, or electrocardiographic findings; and no effects on food consumption, arterial oxygen saturation, coagulation, or urinalysis parameters at ≤ 0.15 mg/kg. At a dose of 0.25 mg/kg, severe clinical toxicity resulted in early euthanasia of all males and 1 female after 2 cycles of treatment (10 doses). Dosing was discontinued in the remaining 4 female dogs at 0.25 mg/kg. The poor condition of these dogs was attributed to pharmacologically mediated bone-marrow and gastrointestinal toxicities.

At 0.15 mg/kg, minimal body-weight loss (4%) occurred in 1 male over the course of the study. At 0.25 mg/kg, an increased incidence of sporadic fecal changes (mucous, red, dark, black, blood or scant) began on Day 5 and progressed to include: moderate to severe thrombocytopenia, reduced to no food consumption, dehydration, hunched posture, ulceration (mouth and perianal area), hemorrhage (gums), increased body temperature, and body-weight loss in males (6.7% compared to 1% loss in controls) through Day 11.

BMS-986158-related findings at all doses were dose related in incidence and/or severity and included: 1) minimal to moderate seminiferous tubule degeneration in testes with decreased testes weights absolute 14% to 20% at ≤ 0.15 mg/kg; no organ weight data were available at 0.25 mg/kg due to unscheduled euthanasia); 2) minimal to moderate cell debris in the epididymides; and 3) minimal to marked bone-marrow hypocellularity. Decreases in spleen weights (15% to 39%) were noted at ≤ 0.15 mg/kg without any microscopic correlates.

At ≥ 0.15 mg/kg, additional BMS-986158-related findings that were generally dose related in incidence and/or severity included: 1) decreased platelet counts (0.10 to 0.82× most recent pretest) beginning on Day 7; 2) minimal to severe enteropathy of the small and/or large intestines that was characterized by 1 or more of the following: decreased numbers of goblet cells, crypt/gland dilatation, abscesses, and increased mitotic activity, flattening, increased basophilia and/or single-cell necrosis of crypt/gland enterocytes; and/or villous atrophy 3) minimal to mild epithelial cell necrosis, secretory depletion, and marked hypospermia (at 0.15 mg/kg only) in the epididymides; 4) minimal to moderate RBCs in the sinuses of mesenteric lymph nodes that was a consequence of intestinal hemorrhage; 5) increased incidence and severity of lymphoid depletion (mild to severe) in the thymus; and 6) minimal to moderate lymphoid depletion in the mandibular lymph nodes in males.

At the severely toxic dose of 0.25 mg/kg, additional BMS-986158-related findings included: 1) decreased reticulocytes (0.05 to 0.42× most recent pretest) with corresponding decreases in red cell distribution width (0.88 to 0.96×); 2) decreased eosinophils (≤ 0.41×) and lymphocytes (0.16 to 0.41×); 3) mild hemorrhage or acute inflammation in the lungs and pericardium in males; 4) minimal to marked erosions or ulcerations in the oral cavity, tongue, esophagus, stomach (pylorus), and intestines; 5) moderate hemorrhage and/or severe hematomas in the oral cavity and tongue in males; 6) minimal to mild acute inflammation in the esophagus in males; 7) mild hemorrhage in the serosa of the stomach and capsular surface of the spleen and surrounding adipose tissue; 8) mild hemorrhage and/or minimal to moderate single-cell necrosis of lymphocytes (in Peyer's patches) in the small intestines; 9) minimal to moderate lymphoid depletion in the mesenteric lymph nodes and spleen in males; and 10) minimal pancreatic acinar cell necrosis with mild hemorrhage in 1 male.

In general, the decreased circulating reticulocytes, platelets, lymphocytes, and eosinophils were attributable to bone marrow and lymphoid toxicities and correlated microscopically with bone marrow hypocellularity and cellular depletion in lymphoid tissues. Hemorrhage and hematomas in multiple tissues at 0.25 mg/kg with corresponding necropsy findings of dark, brown-black, or red discoloration were related to the moderate to severe thrombocytopenia associated with bone marrow toxicity. Mucosal erosions and ulceration in the gastrointestinal (GI) tract were consequences of BMS-986158-related enteropathy that was considered to be pharmacologically mediated because suppression of the BET protein BRD4 is known to affect intestinal epithelial cell lineage differentiation and reduce stem cell numbers.[226] The degenerative changes in the testes with[227] reduced testicular weights were considered to be pharmacologically mediated as the testes-specific BET protein BRDT is critical in male germ cell differentiation.

On Day 1, blood pharmacodynamic biomarker results at 4 hours post dose indicated generally dose-dependent increases (up to approximately 3× control) in the gene expression markers HEXIM1 and MKNK2 and decreases (down to approximately 0.2× control) in ZMYND8 and MYC expression at all doses of BMS-986158. At 24 hours postdose (Day 1), gene expression parameters generally returned to control levels with the exception of the ZMYND8 gene marker

at 0.25 mg/kg. Transcriptional modulation of these biomarkers confirms that BMS-986158 binds and inhibits bromodomains in dogs.

BMS-986158-related changes observed during or after the 3-week recovery period included: 1) dose-related minimal to severe seminiferous tubule degeneration at 0.07 and 0.15 mg/kg with decreased testes weights (absolute: 26% to 48%) and a correlative bilateral decrease in testes size in 1 male at 0.15 mg/kg; and 2) minimal to mild increases in cell debris, minimal to marked secretory depletion, and moderate hypospermia (0.15 mg/kg only) in the epididymides. The absence of recovery for the testes and epididymal changes was expected given that a full spermatogenic cycle in the dog requires 8-9 weeks. Additional findings at 0.25 mg/kg included: 1) an increase in reticulocytes (3.49× most recent pretest) and a corresponding increase in red cell distribution width (1.17×) in 1 female on Day 35 that was likely a regenerative response to bone-marrow toxicity during the dosing phase; and 2) small increases in serum blood urea nitrogen (1.44×), creatinine (1.52×), and phosphorus (1.57×) in 1 female on Day 26

The primary target organs in dogs were the bone marrow with associated hematology changes and testes/epididymides at all doses and the gastrointestinal tract and lymphoid tissues at doses ≥ 0.15 mg/kg. A dose of 0.15 mg/kg (AUC[0-T] 106 ng•h/mL) was considered the HNSTD for this study and a NOAEL was not identified.

Telemeterized rats demonstrated mild increased heart rate (HR) (~50 bpm) and minimal decreased blood pressure (BP) (~5-10 mmHg) when administered BMS-986158 at 0.5 or 1 mg/kg (AUC[0-24h] ≤ 220 ng•h/mL; maximum observed concentration [Cmax] ≤ 32 ng/mL).[228] These effects were not dose related. Evaluations of potential BMS-986158-related effects on the cardiovascular nervous, and respiratory systems were conducted as part of the pivotal repeat-dose toxicity studies in rats (nervous, respiratory) and dogs (cardiovascular, nervous, respiratory).[224,225] There were no clear BMS-986158-related effects on these systems in these studies after 1-month repeat dosing (5 days on/ 2 days off; 20 doses total) at ≤ 0.25 mg/kg in rats (AUC ≤ 72.2 ng•h/mL; Cmax ≤ 13.8 ng/mL) and ≤ 0.15 mg/kg in dogs (AUC ≤ 106 ng•h/mL; Cmax ≤ 19.5 ng/mL).

The potential effects of BMS-986158 on embryo-fetal development were evaluated in an expanded dose range-finding study in pregnant rats.[229] BMS-986158 was administered daily by oral gavage to timed-mated female rats at 0, 0.05, 0.15, or 0.5 mg/kg from Gestation Days (GD) 6 through 16, the period of organogenesis in this species. BMS-986158 was embryolethal at all tested doses. Specifically, there were profound post-implantation losses (manifested mainly as early resorptions) at all tested doses, 63.6% at 0.05 mg/kg/day and 100% at ≥ 0.15 mg/kg/day. Additionally, in surviving fetuses at 0.05 mg/kg/day, the mean body weight was reduced (28% less than controls) and malformations (affecting tail, anus, and/or viscera) occurred in 4 of 43 (9.3%) fetuses from 2 of 8 (25%) litters. Based on the results from a previous rat toxicity study,[230]maternal AUC values at the lowest observed adverse effect level (LOAEL) of 0.05 mg/kg/day are expected to be 0.002× human exposures following a single dose of 0.75 mg (AUCINF 4.102 µg•h/mL). Increased postimplantation loss has been reported in mouse embryos with BRD2 gene knocked out[231] or nullizygous for BRD4.[232]Moreover, in BRD4 heterozygous

mice, prenatal and postnatal growth retardations, malformations of the eyes and bones, and other pathological abnormalities were noted.[232] Therefore, the developmental toxicity observed in litters of BMS-986158-treated dams is consistent with the pharmacological action of BMS-986158.

BMS-986158 was negative for mutagenicity (exploratory bacterial-reverse mutation and in vitro clastogenicity).[233,234] BMS-986158 was not genotoxic in an oral rat micronucleus assay following intermittent (5 days of dosing followed by a 2-day dosing holiday) dosing for 2 weeks (2 cycles) at doses ≤ 0.25 mg/kg.[224]

BMS-986158 was not phototoxic in rats administered single oral doses ≤ 1 mg/kg (Cmax ≤ 86.5 ng/mL and AUC ≤ 379 ng•h/mL).[235]

BMS-986158 had no meaningful interaction with a broad spectrum of in vitro pharmacologic receptors, transporters, ion channels, nuclear hormone receptors, or enzymes at 5 μg/mL.[236] In subsequent patch-clamp assays, (hERG, calcium, and sodium channels), BMS-986158 produced a mild to moderate inhibition of cardiac hERG/IK2 potassium channel (≤ 51.9% at ≤ 15 μg/mL), SCN5A sodium channel (25.3% to 31.1% at 5.0 μg/mL), and L-type calcium channel (41.7% at 5.0 μg/mL).[237] The in vitro concentrations (up to 15 μg/mL) of BMS-986158 evaluated are substantially higher (2083 to 125,000×) than the free Cmax in humans at the starting and ending Phase 1 doses.

In conclusion, the nonclinical toxicity profile of BMS-986158 has been well characterized and it supports first-in-human dosing in cancer patients.

### *1.4.3 Preclinical Metabolism and Pharmacokinetics*

This section summarizes the data available from a series of in vitro and in vivo PK and metabolism studies that were conducted with BMS-986158 in mice, rats, dogs, and monkeys.

#### *1.4.3.1 Absorption*

The permeability coefficient (Pc) of BMS-986158 was high in both the Caco-2 cell assay (A-to-B Pc: 176 nm/sec, B-to-A Pc: 436 nm/sec) and parallel artificial membrane permeability assay (704 nm/sec at pH 7.4), indicating high membrane permeability. After oral administration of BMS-986158, the time of peak plasma concentration (Tmax) ranged from 1 to 3.7 hours in mice, rats, dogs and monkeys. The absolute oral bioavailability (F) from a solution formulation was ~100% (mouse), 47% (rat), 59% (dog), and 16% (monkey). After intravenous (IV) administration, the apparent elimination half-life (T-HALF) of BMS-986158 was 1.9, 4.2, 5.6 and 2.0 hours for mice, rats, dogs, and monkeys, respectively.

The total plasma clearance (CLTp) of BMS-986158 was 12, 41, 15 and 32 (mL/min/kg) in mice, rats, dogs, and monkeys, respectively.

BMS-986158 exhibited an efflux ratio (B-to-A Pc vs. A-to-B Pc) of ~3 at a nominal concentration of 3 μM, suggesting that BMS-986158 is likely a substrate of efflux transporter(s) such as P-glycoprotein (P-gp) and BCRP. However, based on the existing animal data, efflux transporters do not appear to limit the oral absorption of BMS-986158 to a meaningful extent.

The compound exhibited pH-dependent oral absorption in rats. Coadministration of famotidine (25 mg/kg) reduced, the $C_{max}$ and AUC of BMS-986158 (20 mg/kg administered-orally as a microsuspension), by 46% and 55%, respectively. However, this may represent the worst-case scenario, as the projected clinical dose and exposure are much lower than that used in the rat study.

#### *1.4.3.2 Distribution*

The steady-state volumes of distribution of BMS-986158 in mice, rats, dogs, and monkeys were 1.9, 4.3, 5.3, and 4.2 L/kg, respectively.

At 10 μM, BMS-986158 was 96.1 ± 0.1% bound to human serum proteins and 84.2 to 90.2% bound to the serum proteins of the animal species studied. Consistent with the difference in protein binding between humans and animal species, the blood-to-plasma concentration ratio of BMS-986158 was low (0.57 ± 0.002) in humans, whereas it was close to unity in animal species. The blood-to-plasma concentration ratio of BMS-986158 was about 0.99, 1.08, 1.19, and 1.15 in mouse, rat, dog, and monkey, respectively. These results suggested that the compound was distributed evenly between blood cells and plasma in preclinical species, but not in humans.

#### *1.4.3.3 Metabolism*

The metabolic stability of BMS-986158 in human liver microsomes was lower than that in rat liver microsomes, but similar to that in dog and monkey liver microsomes (predicted intrinsic hepatic clearance [CLint] = 10 mL/min/kg in humans, 12 to 72 mL/min/kg in animals).

Because no quantitative assays were available for most of the metabolites except for Met5 (BMT-161485), no discussion of the relative abundance is possible, other than for parent drug and BMT-161485.

Overall, BMS-986158 was found to be relatively metabolically stable in vitro and in vivo in the animal species tested, except for monkey which exhibited relatively faster turnover in vitro than in vivo. Several metabolites were detected in hepatocyte incubates and in plasma of rat, dog, and monkey. General routes of biotransformation of BMS-986158 included:

- Mono-oxidation at the methyl of the triazole to form Met5 (BMT-161485)
- Glucuronidation at the tertiary alcohol moiety to form Met4
- Mono-oxidation on the benzyl tetrahydropyran moiety to form Met6, Met7
- Mono-oxidation on other parts of the molecule to form Met3, Met12
- Further oxidation of Met5 to form Met8, Met9
- Glucuronidation of Met5, Met6, Met7 to form Met2, Met10, Met11
- Multiple oxidation to form Met1, Met13

The major in vitro oxidative metabolite for BMS-986158 in dog, monkey, and human was BMT-161485, accounting for ~75% of total metabolites in human hepatocytes. In rodents, however, Met6 and Met7 were the major oxidative metabolites. In monkey liver microsomes, BMT-161485 was further oxidized to Met8 and Met9. Met4 was high in monkey and rat

hepatocytes, but was minor in human hepatocytes (~20% of total metabolites). Met4 was not presented in dog hepatocytes. In rat hepatocytes, major metabolites also included Met10/Met11. No glutathione adducts were detected in incubations supplemented with glutathione. There was no human metabolite that was not formed in nonclinical species.

In vivo, BMS-986158 was detected in all 3 animal species as the major circulating drug-related component. BMT-161485 was the major circulating metabolite in dogs and monkeys but not in rats. Met1 and Met3 were detected in dogs and monkeys, and Met6 and Met7 were detected in rats. Overall, the in vivo circulating metabolite profiles were consistent with in vitro profiles.

#### *1.4.3.4 Excretion*

Following a single 0.1-mg/kg IV dose of BMS-986158 to dogs, the fraction of dose recovered as unchanged BMS-986158 in the urine over 48 hours was < 1%, demonstrating that renal clearance is not a meaningful systemic clearance pathway for BMS-986158 in dogs.

#### *1.4.3.5 Pharmacokinetic Drug Interactions*

In vitro metabolic reaction phenotyping studies, using individually expressed recombinant human cytochrome P450 (CYP) enzymes, demonstrated that the oxidative metabolism of BMS-986158 was primarily mediated by CYP3A4 (66%) and CYP3A5 (23%). Furthermore, reaction phenotyping studies with recombinant human uridine diphosphate glucuronosyltransferase (UGT) enzymes demonstrated that the glucuronidation of BMS-986158 is primarily mediated via UGT1A4, with minor contribution by UGT2B17. These data suggest that the potential exists for drug-drug interactions if BMS-986158 is co-administered with an inhibitor or inducer of these enzymes.

Inhibition of CYP enzymes by BMS-986158 in human liver microsomes was minimal (IC50 > 40 μM), except for CYP2C9 (IC50 = 8.4 μM). The IC50 for recombinant hUGT1A1 was 3 μM. In addition, BMS-986158 (up to 40 μM) neither transactivated the human pregnane-X receptor nor induced CYP3A4, CYP2B6, or CYP1A2 mRNA expression and activity in cryopreserved primary human hepatocytes. Therefore, the DDI potential of BMS-986158 as an inhibitor of metabolic enzymes and transporters is minimal, based on the currently projected therapeutic dose and exposure (Cmax 0.082 μM at 11 mg once-a-day).

### *1.4.4 Clinical Pharmacology and Safety*

The current study is a first-in-human study.

At the time of the clinical data cutoff date of 21-Dec-2018, a total of 81 subjects had received at least 1 dose of BMS-986158 in Part 1 of the study under Schedule A, Schedule B or Schedule C. Each subject was administered a single dose of BMS-986158 on Cycle 1 Day 1 (4- to 7-day cycle), and no additional doses were administered until Cycle 2 Day 1. On Cycle 2 Day 1 and each subsequent cycle, subjects in Schedule A received once daily (QD) dosing for 5 consecutive days, followed by a 2-day rest period repeated weekly on a 28-day cycle. Subjects in Schedule B received QD dosing for 14 consecutive days, followed by a 7-day rest period on a 21-day cycle and subjects in Schedule C received QD dosing for 7 consecutive days, followed by a 14-day rest period on a 21-day cycle. In Schedule A, a total of 44 subjects have received QD dosing of 0.75 mg

(n=5), 1.25 mg (n=4), 2 mg (n=13), 3 mg (n=10), or 4.5 mg (n=12) BMS-986158. In Schedule B, 8 subjects have received QD dosing of 2 mg (n=4), 3 mg (n=4). In Schedule C, 29 subjects have received QD dosing of 2 mg (n=6), 3 mg (n=12) or 4.5 mg (n=11) BMS-986158. All clinical data are preliminary and subject to change.

As of 21-Dec-2018, a total of 79 subjects (97.5%) experienced at least 1 AE. The most frequent AEs (occurring in ≥20% of subjects) were diarrhea (49 [60.5%] subjects), nausea (43 [53.1%] subjects), fatigue (41 [50.6%] subjects), decreased appetite (34 [42.0%] subjects), vomiting (34 [42.0%] subjects), thrombocytopenia (32 [39.5%] subjects), dyspnoea (23 [28.4%] subjects), anemia (19 [23.5%] subjects), constipation (19 [23.5%] subjects), and cough (17 [21.0%] subjects). A total of 49 subjects (60.5%) experienced Grade 3 to 4 AEs. Five subjects (6.2%) experienced Grade 5 AEs, all assessed by both Sponsor and investigator to be not related to BMS-986158.

Adverse events evaluated as related to BMS-986158 were experienced by 59 of 81 subjects (72.8%). Thirty-four subjects (42%) experienced diarrhea with none experiencing Grade 3 to 4 diarrhea. Thirty subjects (37%) experienced treatment-related thrombocytopenia including 17 subjects (21.0%) with either Grade 3 or 4 events. Thirteen subjects (16%) were reported to have nausea, including 1 (1.2%) Grade 3 nausea. Other Grade 3 to 4 treatment-related AEs include anemia (3 [3.7%] subjects), vomiting, fatigue, increased bilirubin (2 [2.5%] subjects each), and neutropenia and vertigo (1 [1.2%] subject each). There were no treatment-related AE's of Grade 5 reported.

No treatment-related deaths have been reported in any treatment cohort of Study CA011-001. Nine deaths were reported in participants treated with BMS-986158 monotherapy within 30 days of last dose. Of the 9 deaths, 8 deaths were reported as secondary to disease and 1 due to cerebrovascular accident; all of which were considered not related to BMS-986158 treatment.

A total of 68 subjects were discontinued from study treatment due to disease progression.

A detailed description of BMS-986158 safety is provided in the IB.

#### *1.4.4.1 Pharmacokinetics of BMS-986158*

**BMS-986158**

Interim noncompartmental PK analyses were conducted on BMS-986158 (parent) and BMT-161485 (metabolite) using samples from the monotherapy portion of the study administration of 0.75, 1.25, 2, 3, and 4.5 mg oral doses of BMS-986158 following single and multiple doses using nominal time and examining continuous and intermittent schedules (Schedules A and C, respectively).

Interim PK results indicate that BMS-986158 is moderately to rapidly absorbed (Tmax range: 0.5 to 4 hours) following single dose administration at doses of 0.75 to 4.5 mg. The exposure within the dose range examined appears to increase with increasing dose. From these multiple dosing data, a peak to trough ratio of approximately 2.4 and an accumulation index of approximately 1.97 were determined. The inter- and intra-subject variability was from low to high.

PK parameters of BMS-986158 using nominal sample times show that the overall exposure was significantly higher than predicted. This higher than predicted human exposure may have resulted from, and is consistent with a lower than anticipated clearance and increased serum protein binding in humans. Preclinical determinations of human serum protein binding indicated a 3.9% free fraction for BMS-986158. Interim data from ex vivo plasma samples collected from the 6 subjects at the 2 mg dose on this study showed mean free drug fractions of 0.1% to 0.2% with small to moderate intra- and inter-subject variability that were not concentration dependent. It is postulated that the unexpectedly low free fraction resulted in the low clearance.

The metabolite (BMT-161485) exhibited a similar terminal phase elimination as the parent drug, suggesting formation rate limited PK of BMT-161485. Plasma concentrations of metabolite were low relative to the plasma concentration of the parent drug with exposure ratios less than 30%. The metabolite has potency that is approximately 10-fold weaker than the parent drug.

Preclinical data suggests that BMS-986158 is metabolized in the liver by CYP3A4 mediated oxidation to a hydroxylated metabolite; it also undergoes glucuronidation. BMS-986158 is a substrate of CYP3A4 and an inhibitor of P-gp and transporters.

## 1.5 Overall Risk/Benefit Assessment

Many cancers are driven by MYC pathway and BRD4 super enhancer activation, providing a solid rationale for the trial of BET inhibitors as suppressors of BRD4 and MYC in multiple tumor types.[9,15] Preclinical studies have linked repression of MYC and other oncogenes to tumor cell death and tumor regression in both solid tumors and hematologic cancer models, following BET inhibition.[8,9,10,]BRD4 amplification and overexpression has been correlated with adverse prognostic information.[19]

Sixteen other BET inhibitors have entered Phase 1/2 clinical trials, and 24 studies focused on solid tumors and hematological malignancies are recruiting patients or are completed as listed in clinicaltrials.gov.

Results from most studies have not been reported. Preliminary clinical data is available on the OTX-015/MK-8628 Phase 1 study in leukemia which shows that no DLTs were observed in 28 evaluable subjects with AML, ALL, and refractory anemia (RA) through dose level (DL) 5 (120 mg QD). At DL6 (160 mg QD), MTD was exceeded with 1 patient experiencing grade 3 diarrhea and another grade 3 fatigue and anorexia.[44] The main toxicities were non-cumulative grade 1-2 gastrointestinal events (6 patients diarrhea, 3 dysgueusia, 3 abdominal pain, 3 nausea, 1 anorexia), hyperglycemia (3 patients), coagulation factor VII decrease (6 patients) and direct bilirubin increase (3 patients) (two latter AEs asymptomatic). These toxicities were mainly observed at QD doses above 80 mg and with 40 mg BID. Clinically relevant activity was reported in 5 AML patients treated at 10, 40 and 80 mg, including one sustained CR from cycle 4 to cycle 12 (40 mg QD) and one CR with incomplete platelet recovery (CRp) from cycle 2 to cycle 5 (80 mg QD).[44] Preliminary clinical data is also available on OTX015/MK-8628 Ph 1 study in Non-Leukemic Hematologic Malignancies.[45] In this study, 37 non-leukemic patients (18 diffuse large B-cell lymphoma [DLBCL], 9 other lymphomas, 10 myeloma) were treated over 5 dose levels, 33

of whom were evaluable for DLT. No DLTs were observed through DL4 (80 mg QD). Reversible grade 4 thrombocytopenia was the DLT at DL4 BID (40 mg x2) and 120 mg QD continuous. Sixteen patients experienced Grade 3-4 thrombocytopenia and 3 patients had grade 3-4 neutropenia. Grade 3 non-hematologic toxicities were diarrhea, vomiting, hyperglycemia, and hypernatremia (1 patient each). Other toxicities were non-cumulative grade 1-2 gastrointestinal events (8 patients with diarrhea, 3 dysgueusia, 2 vomiting, 1 nausea, 1 anorexia, 1 abdominal pain), hyperglycemia (7 patients), skin rash (3 patients), asymptomatic coagulation factor VII decrease (2 patients), and direct bilirubin increase (1 patient). Clinically relevant activity was reported in 6 patients treated from 40 to 120 mg, including one CR (120 mg, 17+ weeks [wks]) and 1 PR (80 mg, 28 wks), both in DLBCL patients failing 3-4 prior therapy lines, and both with clinical benefit. Four other patients (two with DLBCL, one follicular, and one lymphoplasmacytic lymphoma) had minor tumor shrinkage with clinical benefit (40 mg, 36+ wks; 80 mg, 14 wks; 120 mg 15 wks; 120 mg, 17 wks). Similarly, a study using another BET inhibitor, CPI-0610, as monotherapy reported objective clinical responses in 5 of 36 subjects with relapsed or refractory DLBCL, specifically in T cell/histocyte-rich and activated B-cell subtypes. Of note was 1 CR and 2 PR in subjects with ABC-DLBCL, 1 PR in follicular lymphoma, and 1 PR in T-cell histocyte rich lymphoma.[77]

The initial assessment of the risk of side effects of BMS-986158 in clinical trials was based on data from nonclinical toxicology studies in rats and dogs. Those studies primarily demonstrated the expected toxicity profile of BET inhibition, with most toxicity shown in the highly proliferative cell populations of the bone marrow and gastrointestinal tract. An additional toxicity observed in the rat but not dog was mammary gland atrophy in males. An additional toxicity observed in the dog but not rat was testicular degeneration. An additional toxicity finding observed in pregnant rats demonstrated embryolethality and teratogenicity. A detailed description of these toxicities is provided in Section 1.4.2 and in the Investigational Brochure. The GI and bone marrow toxicities were reversible upon discontinuation of the drug.

The nonclinical toxicity profile was used to determine the starting dose and to develop appropriate exclusion criteria, contraception measures for male and female participants, and safety monitoring for this study. In addition to frequent complete blood counts (CBCs) and chemistry (including liver enzyme) tests, because of the potential effect of immune system repression, subjects with viral infection (Human immunodeficiency virus [HIV], Hepatitis B or C) are excluded and lymphocyte numbers are monitored regularly. Immunoglobulin levels are also followed routinely to evaluate the potential need for supplementation. Although the nonclinical in vitro and in vivo assessments have not demonstrated any cardiovascular liability, electrocardiograms (ECG) are being monitored frequently. Subjects will be evaluated frequently by physical exam; their weights are being closely monitored, and they are being assessed for the development of diarrhea or other anticipated GI symptoms. Guidelines for the management of diarrhea are provided in Section 4.5.3.

As of the data cutoff date on 21-Dec-2018, preliminary clinical data from the first-in-human CA011001 monotherapy study in subjects with advanced solid tumors have demonstrated that BMS-986158 has an acceptable toxicity profile in 81 subjects treated at all dose levels in Schedule A (0.75, 1.25, 2, 3, and 4.5 mg), Schedule B (2 and 3 mg) and Schedule C (2, 3, and 4.5 mg). All

observed toxicities in the GI or hematopoietic system reversed spontaneously or upon drug withdrawal. To date, the cumulative human safety data are consistent with the non-clinical assessment of toxicity in rats and dogs and support the continued clinical exploration of BMS-986158 for the treatment of a variety of malignancies.

Although BMS-986158 does not demonstrate evidence of genotoxicity, perturbation of cellular differentiation pathways may contribute to development of cancer. Subjects are informed of the potential risk, and are carefully evaluated by the investigators throughout the study. Subjects are counseled on appropriate contraceptive measures, while on study and for at least 3 months after the last dose of BMS-986158. Additionally, subjects are informed of the potential risks to reproductive organs and the option of sperm or egg banking discussed, if appropriate.

The frequent safety assessments are utilized by the Sponsor/Medical Monitor and investigators to determine whether dose modification, additional safety measures, or termination of the study is required at any time. Thorough evaluation of the above-described safety monitoring procedures and of AEs and serious adverse events (SAEs) are reviewed on an ongoing basis by the Sponsor's Medical Monitor and Global Pharmacovigilance and Epidemiology representatives to monitor for any safety signals or trends.

As BMS-986158 is an experimental agent, it is possible that unforeseen, unknown, or unanticipated reactions may occur. Five serious, unexpected serious adverse events have been reported with BMS-986158; 4 of them were assessed to be related to study drug. Two subjects experienced Grade 4 thrombocytopenia, 1 subject experienced Grade 3 vertigo and another subject experienced myocardial infarction. One subject experienced anemia, which was assessed not to be related to BMS-986158.

However, based on the nonclinical safety and toxicity profile of BMS-986158 observed with tested doses in Schedules A, B, and C, the potential safety risks are expected to be minimized, following the planned cautious dose escalation scheme. An urgent need exists for new therapies for subjects with advanced cancer that has progressed or not responded to other treatments. Pharmacologically-active dosing has been achieved at the 4.5 mg dose level in Schedule A. Thus, there may be potential benefits to study subjects with BMS-986158 monotherapy treatment. In addition, based upon potential synergistic effect,[25] a combination of BMS-986158 with nivolumab may provide potential additional benefit but will be pursued only after the effects of BMS-986158 on the tumor microenvironment have been characterized. Furthermore, the substantial nonclinical efficacy profile (see Section 1.4.2) and the growing evidence for MYC and BRD4 targeting in many human cancers (see Section 1.1.3), indicates that the balance of benefit to risk is likely to be favorable for study subjects.

This study may allow the characterization of the safety and clinical activity of nivolumab in combination with BMS-986158 depending on the information obtained in the monotherapy dose expansion cohorts and provide an estimate of the clinical benefit as measured by ORR in subjects with advanced cancers associated with genetic abnormalities, including 1) amplifications of BRD, MYC, or AR genes; or 2) mutations in Gnaq/11, KRAS, or SWI/SNF; or 3) translocations of MYC, BCL2/6, or NUT.

# 2 ETHICAL CONSIDERATIONS

## 2.1 Good Clinical Practice

This study will be conducted in accordance with Good Clinical Practice, as defined by the International Conference on Harmonisation (ICH) and in accordance with the ethical principles underlying European Union Directive 2001/20/EC and the US Code of Federal Regulations, Title 21, Part 50 (21CFR50).

The study will be conducted in compliance with the protocol. The protocol and any amendments and the subject informed consent will receive Institutional Review Board/Independent Ethics Committee (IRB/IEC) approval/favorable opinion prior to initiation of the study.

All potential serious breaches must be reported to BMS immediately. A serious breach is a breach of the conditions and principles of GCP in connection with the study or the protocol, which is likely to affect, to a significant degree, the safety or physical or mental integrity of the subjects of the study or the scientific value of the study.

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

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

## 2.2 Institutional Review Board/Independent Ethics Committee

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

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

## 2.3 Informed Consent

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

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

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

Investigators must:

- Provide a copy of the consent form(s) and written information about the study in the language in which the subject is most proficient prior to clinical study participation. The language must be non-technical and easily understood.
- Allow time necessary for subject or subject's legally acceptable representative to inquire about the details of the study.
- Obtain an informed consent signed and personally dated by the subject or the subject's legally acceptable representative and by the person who conducted the informed consent discussion.
- Obtain the IRB/IEC's written approval/favorable opinion of the written ICF (s) and any other information to be provided to the subjects, prior to the beginning of the study, and after any revisions are completed for new information.
- If informed consent is initially given by a subject's legally acceptable representative or legal guardian, and the subject subsequently becomes capable of making and communicating his or her informed consent during the study, consent must additionally be obtained from the subject.
- Revise the informed consent whenever important new information becomes available that is relevant to the subject's consent. The investigator, or a person designated by the investigator, should fully inform the subject or the subject's legally acceptable representative or legal guardian, of all pertinent aspects of the study and of any new information relevant to the subject's willingness to continue participation in the study. This communication should be documented.

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

The consent form(s) must also include a statement that BMS and regulatory authorities have direct access to subject records.

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

Minors who are judged to be of an age of reason as determined by local requirements should also give their assent. The assent should be documented based on local regulations.

# 3 INVESTIGATIONAL PLAN

## 3.1 Study Design and Duration

This is a Phase 1/2a, open label study to characterize the safety and tolerability of BMS-986158 monotherapy and/or in combination with nivolumab in subjects with advanced solid tumors and hematologic malignancies. The study has two segments: Part 1 (Phase 1 study - dose escalation, with Schedules A, B and C enrolling at different dosing schedules) and Part 2 (Initial Expansion including subjects with a limited set of tumor types followed by Subsequent Expansion including subjects with an expanded set of tumor types) (see Figure 3.1-1). In Part 1, BMS-986158 will be studied as monotherapy, and in Part 2, BMS-986158 will be studied as monotherapy and may be administered in combination with nivolumab depending on [redacted] available data from the monotherapy-treated subjects.

The planned sample size consists of up to approximately 90 subjects for Part 1 and up to approximately 327 subjects for Part 2 for a total of up to approximately 417 subjects in the entire study.

In Part 1, the continuous dosing Schedule A enrolled first. Each subject in Schedules A, B and C of Part 1 is administered a single dose of BMS-986158 on Cycle 1 Day 1 and no additional doses are administered until Cycle 2 Day 1. For subjects in Schedule A on Cycle 2 Day 1, which must be within approximately 7 days of the Cycle 1 Day 1 dose administration, and on each subsequent cycle, subjects receive QD dosing for 5 consecutive days of each week, followed by a 2-day rest period, on a 28-day cycle. For subjects in Schedule B on Cycle 2 Day 1, which must be within approximately 7 days of the Cycle 1 Day 1 dose administration, and on each subsequent cycle, subjects receive QD dosing for 14 consecutive days, followed by a 7-day rest period, on a 21-day cycle. For subjects in Schedule C on Cycle 2 Day 1, which must be within approximately 7 days of the Cycle 1 Day 1 dose administration, and on each subsequent cycle, subjects receive QD dosing for 7 consecutive days, followed by a 14-day rest period, on a 21-day cycle. Subjects may continue to receive treatment until disease progression, unacceptable AEs or withdrawal of consent.

In Part 2, Schedule A for BMS-986158 administration has been selected for expansion of the 4.5 mg dose, which will be administered for 2 weeks (10 doses) followed by 3.75 mg for the remainder of the treatment period. Adult and adolescent subjects weighing ≥ 40 kg will be administered a flat dose of BMS-986158 (see Section 1.1.13). Using Schedule A with a loading period of 2 weeks at 4.5 mg followed by 3.75 mg for the remainder of the treatment period, BMS-986158 will be tested as monotherapy, initially in a limited set of tumor types (NMC, CRPC, DHL, Non-DC-DLBCL, and TNBC; Initial Expansion), with Subsequent Expansion into additional tumor types upon observing signals of antitumor activity or favorable PD effects in the initial set of tumor types. If combination therapy is pursued, nivolumab will be administered as a flat dose of 480 mg Q4W in adults and BMS-986158 will be administered using Schedule A.

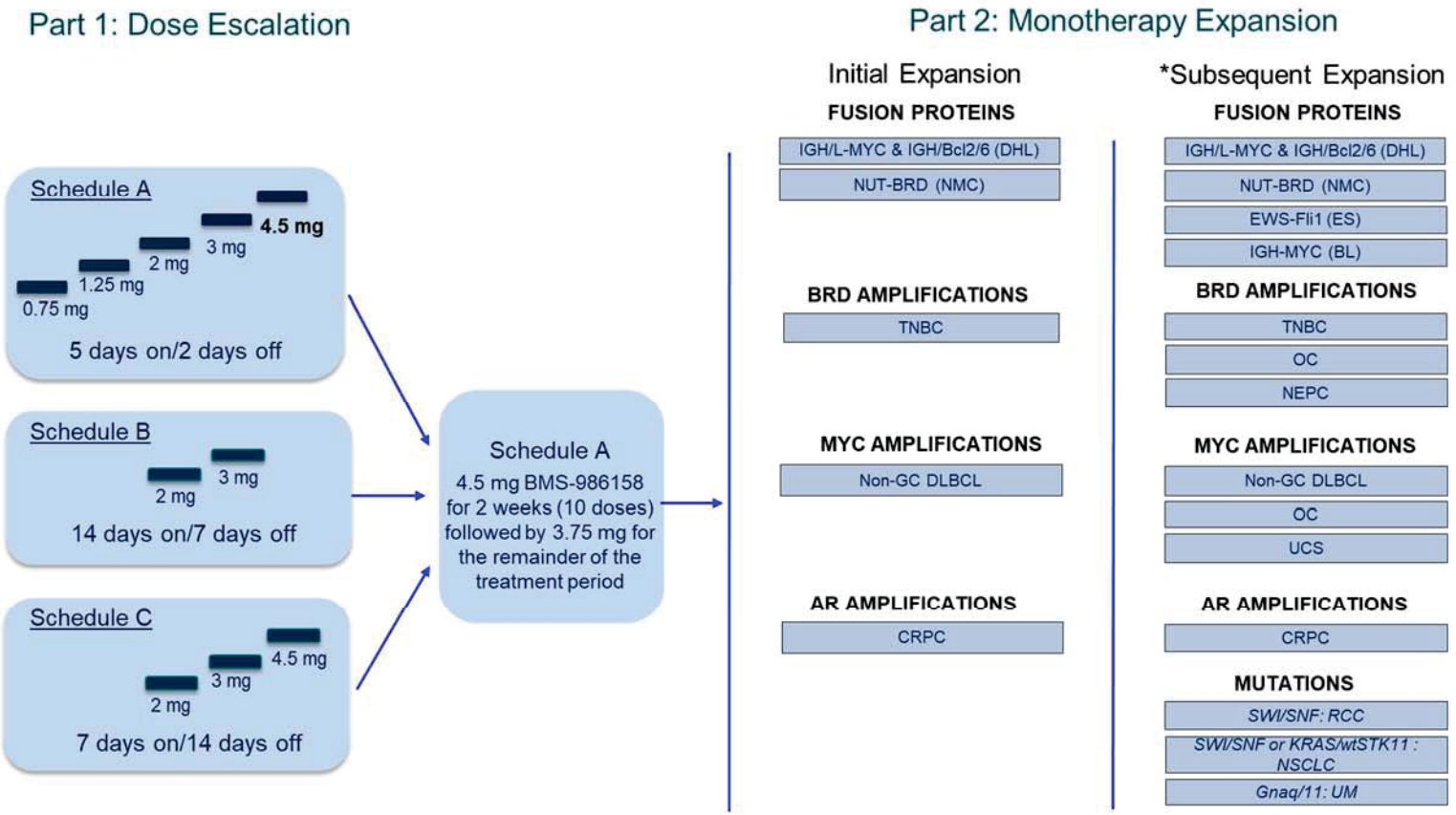
Further dose modification at the subject level is permitted below the dose level of 3.75 mg depending on the observed toxicity and tolerability (see guidelines for dose modification in Section 4.5.2).

Subjects will complete up to 5 study periods (See Figure 3.1-2): Screening (up to 28 days for Part 1 and up to 40 days for Part 2), Treatment (up to 2 years, until disease progression or other protocol-specified criteria), Clinical Follow-up (30 days for BMS-986158 monotherapy and 30 days, 60 days, and 100 days for combination therapy, if pursued), and Survival Follow-up [redacted]. Only subjects who have progressive disease after receiving BMS-986158 in combination with nivolumab may have the option to continue treatment with the combination if combination therapy is pursued. Subjects who have progressive disease after receiving BMS-986158 monotherapy will not have the option to continue treatment with BMS-986158 monotherapy or to receive BMS-986158 in combination with nivolumab.

Safety, PK, [redacted] and efficacy measurements will occur as indicated in Table 5.1-1, Table 5.1-2 Table 5.1-3, Table 5.1-4, Table 5.1-5, and Table 5.1-6. Pre- and on-treatment biopsies will be required for all adult subjects enrolled in Part 2 to allow the assessment of BMS-986158-induced changes in tumor immune infiltration [redacted]

The overall duration of the study is expected to be approximately 4 years from the time of the first visit of the first subject to the required survival follow-up of the last subject enrolled. Subjects may discontinue treatment due to disease progression, unacceptable AEs, or withdrawal of consent. The Clinical Follow-up visits will occur approximately 30 days (for subjects who receive monotherapy), and 60 days and 100 days (for subjects who may receive combination therapy) after the subject discontinues study treatment. For subjects in PR or CR who discontinue treatment for AEs, tumor assessments will be performed every 12 weeks for the first year then every 6 months for the second year. If a subject discontinues treatment due to an AE, the subject should be seen in Clinical Follow-up every 30 days until the AEs either resolved to baseline or Grade 1, stabilized, or been deemed irreversible. After completing the Clinical Follow-up Period, subjects will continue on to a Survival Follow-up Period. [redacted] The end of the study will occur after the last treated subject completes their Clinical Follow-up, unless a subject discontinues prematurely.

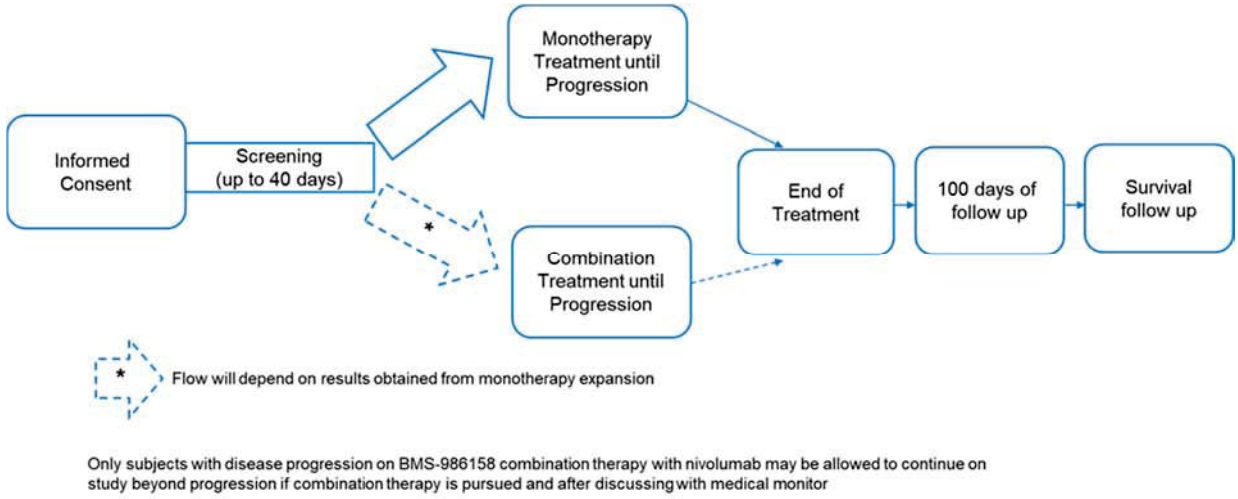
**Figure 3.1-1: Study Overview**




Abbreviations: BL = Burkitt's lymphoma; CRPC = castrate-resistant prostate cancer; DHL = double-hit lymphoma; ES = Ewing sarcoma; NEPC = neuroendocrine prostate cancer; NMC = NUT-midline carcinoma; Non-GC-DLBCL = Non-germinal center diffuse large B-cell lymphoma; NSCLC = non-small cell lung cancer; OC = ovarian cancer; RCC = renal cell carcinoma; Res = response; SOC = standard of care; TNBC = triple negative breast cancer; UCS = uterine carcinosarcoma; UM = uveal melanoma.

*Up to 45 subjects will be enrolled in the Initial Expansion. Subsequent enrollment of subjects with an expanded set of tumor types within and across biomarker groups (eg, fusion proteins, BRD amplifications, MYC amplifications, AR amplifications or mutations) as part of the Subsequent Expansion will depend on the totality of data obtained from subjects in the Initial Expansion. If combination therapy with nivolumab is pursued, subjects with any listed tumor type will be eligible.

**Figure 3.1-2: Expansion Cohorts**




### *3.1.1 Monotherapy Dose Escalation (Part 1)*

In Part 1 (dose escalation), BMS-986158 is administered as monotherapy (Schedules A, B and C). The study design schematics are presented in Figure 3.1-1 and Figure 3.1-2.

To minimize risks to subjects from unanticipated acute toxicities, a waiting period of at least 5 days will occur between administrations of the first dose for the first, second, and third subjects to create an observation period prior to subsequent subject exposures. This waiting period is mandatory only in the first Cohort of Schedule A of Part 1.

**Part 1: Selection of Doses**

In Schedule A of Part 1, the first cohort of subjects received a starting dose of 0.75 mg. In this schedule, each subject was administered a single dose of BMS-986158 on Cycle 1 Day 1 (4-to 7-day cycle) and no additional doses were administered until Cycle 2 Day 1. On Cycle 2 Day 1, which must be within 7 days of the Cycle 1 Day 1 dose administration, and on each subsequent cycle, subjects received QD dosing for 5 consecutive days of each week, followed by a 2-day rest period, on a 28-day cycle. The second cohort of subjects on this schedule received a dose of 1.25 mg. This dose level (a 67% increase) was chosen instead of 1.5 mg dose level (a 100% increase) because of the longer than expected half-life that was calculated based on human exposure data from the first cohort of (n=5) subjects evaluated at the 0.75 mg dose level.

For Schedule B, each subject is administered a single dose of BMS-986158 on Cycle 1 Day 1 (7-day cycle) and no additional doses are administered until Cycle 2 Day 1. On Cycle 2 Day 1, and on each subsequent cycle, subjects receive QD dosing for 14 consecutive days, followed by a 7-day rest period, on a 21-day cycle. For Schedule C, subjects are administered a single dose of BMS-986158 on Cycle 1 Day 1 (7-day cycle) and no additional doses are administered until Cycle 2 Day 1. A schedule of 7 days on, 14 days off may be implemented beginning with Cycle 2 Day 1 and on each subsequent cycle, if agreed upon by the Sponsor/Medical Monitor and investigators. Refer to Figure 3.1-2 and Section 4. Subjects enrolled previously in Part 1 who are still receiving

therapy will continue to be dosed on their original schedule. Subjects may continue to receive treatment until disease progression, unacceptable AEs or withdrawal of consent, or as defined in Section 3.5.

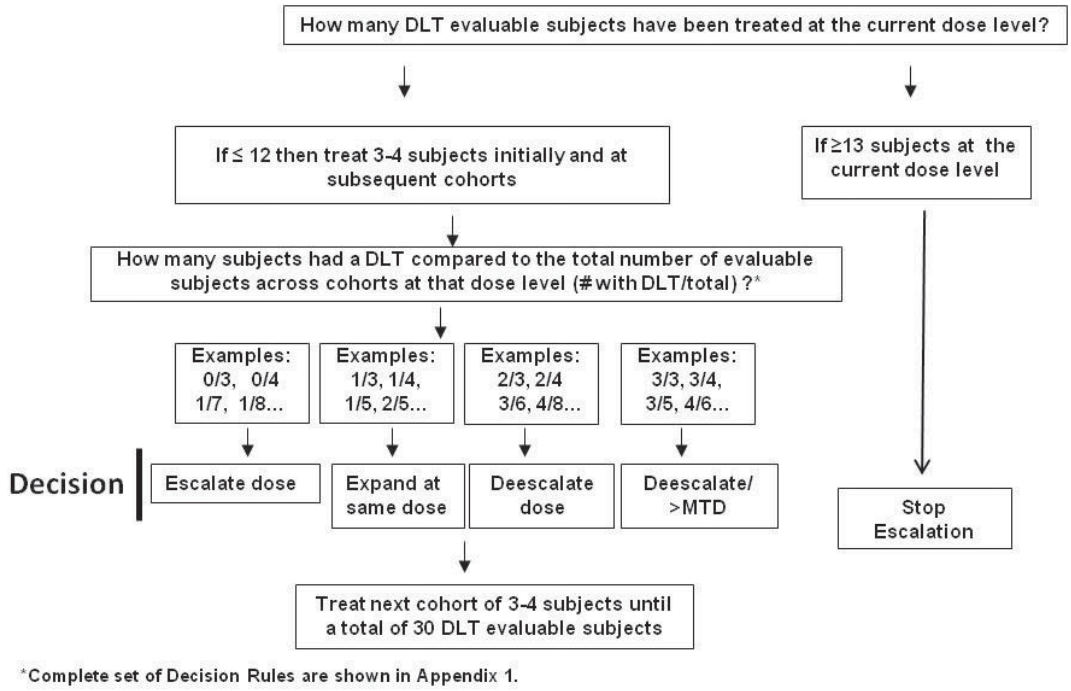
Dose escalation for each subsequent cohort of subjects in each of the schedules will be guided by the incidence of AEs for which no clear alternative cause is identified as graded by National Cancer Institute Common Terminology Criteria for Adverse Events version 4.03 (NCI CTCAE v4.03) in the first 32-35 days of dosing for Schedule A of Part 1. Dose escalation will be in increments of 100% above the previous dose level until the first occurrence of any of the following toxicities that have no alternate cause: any DLT (as described in Section 4.5.1), any ≥ Grade 2 toxicities with the following exceptions: Grade 2 fatigue, Grade 2 alopecia.

Once one or more of the above identified DLTs occurs, a modified Fibonacci dose escalation schema will be employed for any subsequent dose escalations at that schedule, with increments of 67%, 50%, 40%, and 33%. Any further dose escalations will be 33%. In addition, dose modification could also include changes in the dosing interval (e.g. twice weekly) based on available safety and PK data.

Intermediate doses may be evaluated if agreed upon by the Sponsor/Medical Monitor and investigators. The next dose level will not exceed 100% or the dose increment per the modified Fibonacci dose escalation schema.

**Part 1: Monotherapy Dose Escalation Decision Guide**

**Figure 3.1.1-1: Dose Escalation Decision Scheme**




*Complete set of Decision Rules are shown in Appendix 1.

Enrollment in dose escalation and selection of the MTD will adhere to a mTPI design. The design provides a simple algorithm for decisions on escalation, expanding at the same dose, and de-escalation, depending on the number of observed toxicities after each dose cohort (see Figure 3.1.1-1). The mTPI method utilizes a target toxicity (DLT) rate and equivalence interval to guide decisions on escalation after each cohort and to estimate the MTD. For this study, the target DLT rate is 27% and the EI is 25%-29%.

Dose escalation decisions will be guided by the cumulative number of subjects who are DLT evaluable and who experience a DLT in the DLT Evaluation Period for all arms (Figure 3.1.1-1 and Appendix 1). If no DLTs are observed in the first dose cohort of Part 1, 3-4 subjects will be enrolled at the next higher dose level. If 1 DLT is observed in 3 or 4 evaluable subjects, this dose level will be expanded by enrolling another cohort of 3-4 at the same dose level. If 2 of 3 or 3 of 4 subjects are observed with DLTs, the next cohort will be enrolled at the next lower dose level. Additional decisions are shown in Figure 3.1.1-1 and Appendix 1. If a decision to treat more subjects at a given dose level is suggested by the mTPI algorithm when there are already at least 13 DLT evaluable subjects treated at the same dose level, a need for further enrollment in the dose escalation phase will be determined by the Sponsor. These same rules will be applied to Schedules B and C. A total of approximately 30 DLT evaluable subjects is expected to be treated per schedule with a total of 90 planned across schedules for the dose escalation phase.

Decisions to escalate, add more subjects to the current dose, de-escalate (with options to re-escalate), or de-escalate and declare the current dose as unacceptable (exceeding the MTD), will be based on the rate of DLTs in evaluable subjects within the 32-35-day DLT evaluation period of Schedule A for Part 1, and within the 35-day DLT evaluation period of Schedules B and C for Part 1 (Appendix 1). At least 3 DLT-evaluated subjects treated at each dose level are required to enable a decision. To account for subjects who may not be able to complete the DLT evaluation period, for reasons other than a DLT, or may not be evaluable for DLT, a fourth subject may be enrolled at this dose level, following agreement between the investigator and Sponsor/Medical Monitor.

DLT-evaluable subjects are defined as subjects who received at least 16 of 21 doses of BMS-986158 in Schedule A of Part 1; at least 17 of 22 doses of BMS-986158 in Schedule B of Part 1; and at least 12 of 15 doses in Schedule C of Part 1 during the DLT evaluation period and will be considered for dose escalation decisions. Subjects who developed a DLT during the DLT period are considered evaluable regardless of the number of received doses. Subjects with insufficient data to establish safety during the DLT evaluation period at the dose level tested may be replaced upon agreement of the Sponsor/Medical Monitor and investigators.

There will be no intrasubject dose escalation of BMS-986158.

Figure 3.1.1-1 shows examples of scenarios guiding decisions that may be encountered during dose escalation with respect to the number of DLT evaluable subjects and the number of subjects with a DLT. All potential combinations of the number of subjects with DLTs and number of treated subjects evaluable for DLT are shown in Protocol Appendix 1. In addition to escalation or expansion decisions, dose re-escalation is permitted as per Figure 3.1.1-1 and Appendix 1 after a

decision to de-escalate is made, except when a dose level has been identified as exceeding the MTD. Therefore, a dose level could be revisited multiple times under the mTPI design.

In addition to the guide for escalation decisions, to better assess if a dose level is safe given the number of DLTs observed, posterior probabilities of the DLT rate are provided in Section 8.1 to inform decisions regarding dose safety.

**Part 1: MTD Determination**

At the end of dose escalation, the MTD for each evaluated dosing schedule (Schedules A, B, and C) will be selected as the dose with the smaller difference between estimated toxicity and the target DLT rate (27%), among the dose levels used, with an isotonic regression model of the accumulated DLT data based on the mTPI design (Appendix 1).

### *3.1.2 Dose Expansion (Part 2)*

Treatment in Part 2 can be initiated before Part 1 is completed and when the MTD or maximum administered dose (MAD), if no MTD is reached for Part 1, has been determined. Schedule A (QD dosing for 5 consecutive days of each week, followed by a 2-day rest period, on a 28-day cycle) has been chosen for expansion. This regimen was selected after considering safety, PK [redacted] data generated during Part 1 (see Section 1.1.5). The initial dose level of BMS-986158 selected for Part 2 is 4.5 mg with a loading period of 2 weeks (10 doses or half a cycle) with subsequent dose level of 3.75 mg for the duration of study treatment for each subject. Adult and adolescent subjects weighing ≥ 40 kg will be administered a flat dose of BMS-986158. Further dose modification at the subject level is permitted below the dose level of 3.75 mg depending on the observed toxicity and tolerability (see guidelines for dose modification in Section 4.5.2).

BMS-986158 will be first evaluated as monotherapy. The Initial Expansion will enroll a maximum of 45 subjects with tumors harboring specific genetic alterations including fusion proteins (NMC, DHL), BRD amplifications (TNBC), MYC amplifications (Non-GC DLBCL) and AR amplification (CRPC). [redacted] Depending on the safety, preliminary efficacy, tolerability, [redacted] a Subsequent Expansion will enroll up to 126 subjects with tumor types already evaluated in the Initial Expansion as well additional tumor types within and across groups of specific genetic alterations. Categories of genetic alterations and tumors under consideration for the Subsequent Expansion include fusion proteins (NMC, DHL, ES and BL), BRD amplifications (TNBC, OC and NEPC), MYC amplifications (Non-GC DLBCL, UCS, OC), AR amplification (CRPC) and mutations (RCC, NSCLC and UM). See Figure 3.1-1.

The decision to assign new cohorts of subjects to BMS-986158 plus nivolumab combination therapy will be made upon agreement between the Sponsor/Medical Monitor and investigators

after review of [redacted] available data obtained from both initial and subsequently enrolled monotherapy expansion subjects. If combination therapy of BMS-986158 and nivolumab is pursued, subjects may be enrolled with any of the tumors types listed in Figure 3.1-1. The tumor types enrolled will depend on the activity of BMS-986158 monotherapy within and across biomarker groups. Based on the results of Part 2, including PK [redacted], discussion between Sponsor/Medical Monitor and the investigators, and additional considerations, enrollment may be initiated for other indications not listed in Figure 3.1-1 as long as subjects meet the specified inclusion criteria (see Section 3.3.1). Up to approximately 327 subjects will be treated in the dose-expansion phase (Part 2) of this study

#### *3.1.2.1 Safety Evaluation Phase of BMS-986158 Monotherapy Expansion*

Clinical safety monitoring of subjects treated with BMS-986158 monotherapy enrolled in Part 2 of the study will be the same as conducted during the dose escalation portion. During Part 2, if in a given tumor cohort the combined incidence of study drug-related AEs that require dose modification exceeds 29% (of treated subjects), then further enrollment to that arm may be interrupted and the findings will be discussed between the Sponsor/Medical Monitor and investigators. An agreement will be reached as to whether a lower dose level or an alternate dose schedule of BMS-986158 should be examined, or whether any additional treatment guidelines should be implemented prior to enrollment of additional subjects on study in alignment with dose modification criteria (Section 4.5.2), discontinuation criteria, and other safety evaluation criteria.

#### *3.1.2.2 Safety Evaluation Phase of BMS-986158 Combination with Nivolumab*

If combination therapy with nivolumab is pursued, the safety of the selected BMS-986158 dose when given in combination with nivolumab within the dose expansion phase will be evaluated by monitoring DLTs in the first 6 to 12 subjects treated across the different tumor cohorts receiving combination therapy. Once the selected dose of BMS-986158 in combination with nivolumab is deemed safe based on the DLT evaluation, the dose expansion will continue as planned in all cohorts.

The guidance for assessing the DLT-related safety and overall safety will be similar to that used in the monotherapy cohorts. The DLT safety monitoring during the dose evaluation phase including potential decision to de-escalate to a lower dose will be based on the mTPI-2 design[49] with target toxicity (DLT) rate of 29% (-2%, +4%), as presented in Table 3.1.2.2-1. The performance of the design is reported in Appendix 8.

Initially, the first 3 to 4 subjects treated in combination will be evaluated for DLT. If 0 or 1 DLT is observed during the DLT period established for BMS-986158, an additional 3 subjects will be treated at the same BMS-986158 dose level. A decision to stay at the same dose level by treating additional 3 to 4 subjects, to expand (continue enrollment) of all subjects treated with combination therapy across all tumor cohorts (declaring this dose to be safe), or to consider de-escalation will be guided by the number of subjects with DLTs observed during the dose evaluation phase and the posterior probability of DLT. (Table 3.1.2.2-1 and Table 3.1.2.2-2). Subjects who do not complete the DLT observation period for reasons other than DLTs will not contribute to this safety evaluation and can be replaced. De-escalation may be considered if the safety and tolerability

profile for the selected BMS-986158 dose is evaluated as not acceptable, after discussion between the investigator(s) and the Sponsor/Medical Monitor.

**Table 3.1.2.2-1: Combination Safety Monitoring Guidance for DLT during Safety Evaluation Phase by mTPI-2**

| | Number of DLT Evaluable Participants Treated | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| Number of participants with a DLT | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 | 11 | 12 |
| 0 | E | E | E | E | E | E | E | E | E | E |
| 1 | E | E | E | E | E | E | E | E | E | E |
| 2 | D | D | D | S | E | E | E | E | E | E |
| 3 | DU | D | D | D | D | D | S | S | E | E |
| 4 | - | DU | DU | D | D | D | D | D | D | S* |
| 5 | - | - | DU | DU | DU | DU | D | D | D | D |
| 6 | - | - | - | DU | DU | DU | DU | DU | D | D |
| 7 | - | - | - | - | DU | DU | DU | DU | DU | DU |

Source: Target Toxicity (DLT) Rate used is 29% (-2%, +4%).

D = de-escalate to lower dose; DLT = dose limiting toxicity; E = expand at this dose in each tumor type; DU = de-escalate to lower dose and the current dose will never be used again in the trial; mTPI = modified Toxicity Probability Interval; S = stay at the same dose.

*Additional considerations including information from Table 3.1.2.2-2 below will be used.

In the case where 4 DLTs are observed out of 12 evaluable subjects as shown in Table 3.1.2.2-1, the design recommends the decision to stay at the same dose level (S), indicating that more subjects need to be evaluated to determine whether the dose level is safe. After considering additional information such as provided in Table 3.1.2.2-2, a lower dose may be considered for evaluation based on discussion between Sponsor/Medical Monitor and investigators.

In addition to the above guidance, the following posterior probabilities may be utilized to make a more informed decision on the safety based on DLT findings prior to the decision to expand. Assuming a 33% acceptable DLT rate in a combination therapy setting, which corresponds to a Beta(1,2) distribution, Table 3.1.2.2-2 shows the risk of selecting a BMS-986158 dose level as safe based on the observed DLTs and expressed as a posterior probability of toxicity given the number of DLTs observed during the combination safety evaluation phase.

**Table 3.1.2.2-2: Posterior Probability of a DLT in Combination Therapy Assuming Observed Data**

| Number of Subjects at a Dose Level | Number of Subjects with an Observed DLT | Probability of DLT Rate >33% | Probability of DLT Rate >40% |
|---|---|---|---|
| 6 | 0 | 4% | 2% |
| 6 | 1 | 20% | 11% |
| 6 | 2 | 47% | 32% |

**Table 3.1.2.2-2: Posterior Probability of a DLT in Combination Therapy Assuming Observed Data**

| Number of Subjects at a Dose Level | Number of Subjects with an Observed DLT | Probability of DLT Rate >33% | Probability of DLT Rate >40% |
|---|---|---|---|
| 9 | 1 | 8% | 3% |
| 9 | 2 | 24% | 12% |
| 9 | 3 | 48% | 30% |
| 12 | 2 | 11% | 4% |
| 12 | 3 | 27% | 12% |
| 12 | 4 | 48% | 28% |

Posterior probabilities are calculated using a Beta(1,2) prior corresponding to 33% DLT rate (ie, 1 of 3 evaluable subjects has a DLT).

DLT = dose limiting toxicity.

Based on the above, if 0 out of 6, 1 out of 9, or 2 out of 12 subjects experience a DLT, the dose level may be considered sufficiently safe to open enrollment to the additional subjects in the expansion phase of the study.

### *3.1.2.3 Safety Evaluation in Adolescents*

Adolescent subjects will be treated with a dose and schedule selected from Part 1 (dose escalation) in adult subjects. The safety of this selected BMS-986158 dose will be evaluated in adolescents (≥12 to <18 years of age) as part of the dose expansion phase (Part 2) in subjects with NMC, BL, ES, or other tumors with genetic abnormalities in BRD proteins (Section 1.1.7 and Section 1.1.13). Initially, 3 to 4 adolescent subjects across different tumor types may be enrolled in the Initial Expansion and monitored for DLT. Further enrollment of adolescent subjects into the Subsequent Expansion will depend on the totality of data, including safety, PK and PD data obtained from all subjects in the initial expansion. Based on safety and other available data, the Sponsor may consider decreasing the dose level of BMS-986158 for adolescent subjects. The selected dose may be further evaluated in adolescent subjects in combination with nivolumab, if combination therapy is pursued, depending on the review of pharmacodynamics results and other data from BMS-986158 monotherapy. If pursued, 3 to 4 subjects ≥12 to <18 years of age across any eligible tumor types (eg, NMC, BL, and ES), will be treated with BMS-986158 in combination with nivolumab to establish safety of the combination treatment in this adolescent population. Subjects will be observed for DLT, and if safety is considered acceptable, additional adolescent subjects will be treated with combination therapy.

### *3.1.2.4 BMS-986158 Monotherapy and in Combination with Nivolumab Dose Expansion--Number of Subjects*

Once the safety and tolerability profile is established at the selected dose of BMS-986158 alone or in combination with nivolumab during the dose evaluation phase, the tested dose level will be enrollment in the expansion phase will initiate at this dose level to to assess a preliminary efficacy

signal, and to obtain additional data, such as [redacted] safety information across the selected tumors.

Enrollment in the Part 2 expansion will start in the initial BMS-986158 monotherapy cohorts. Although a 2-stage (Fleming) design will be used to guide assessment of preliminary anti-tumor activity in each of the monotherapy cohorts (and in combination therapy with nivolumab, if pursued), up to 9 subjects may be enrolled in each of the initial cohorts to better characterize the PK, safety, [redacted] and inform enrollment in both the subsequent monotherapy and potential combination expansion cohorts. The decision to open subsequent cohorts (monotherapy or in combination) will take into acount the totality of the available data and upon agreement of the Sponsor/Medical Monitor, in consultation with the investigators. The decision to continue or discontinue enrollment in one or more cohorts or discontinue treatment in existing cohorts will be made by the Sponsor/Medical Monitor based on a comprehensive assessment of the accruing on-treatment evidence (see Section 3.1.2.1 and Section 3.5).

Clinical safety monitoring of subjects during dose expansion phase will continue throughout the study. If at a selected BMS-986158 dose level, the combined incidence exceeds 33% for study drug related toxicity requiring treatment discontinuation, further enrollment to that dose level may be interrupted and a decision to continue dosing will be based on discussions of the observed aggregate (acute and chronic) toxicities between the investigator(s) and the Sponsor, if needed.

Table 3.1.2.4-1 shows the planned number of subjects per tumor type and setting (monotherapy or combination therapy and Initial or Subsequent) in the expansion phase.

**Table 3.1.2.4-1: Dose Expansion Planned Sample Size**

| Tumor Cohort and Group | Initial Monotherapy | Subsequent Monotherapy | Combination Therapy | Total |
|---|---|---|---|---|
| **FUSION PROTEINS** | | | | |
| DHL | 5 to 9 | 5 to 9 | 5 to 9 | 15 to 27 |
| NMC | 5 to 9 | 5 to 9 | 5 to 9 | 15 to 27 |
| ES | | 5 to 9 | 5 to 9 | 10 to 18 |
| BL | | 5 to 9 | 5 to 9 | 10 to 18 |
| **BRD AMPLIFICATIONS** | | | | |
| TNBC | 5 to 9 | 5 to 9 | 5 to 9 | 15 to 27 |
| OC w BRD amplifications | | 5 to 9 | 5 to 9 | 10 to 18 |
| NEPC | | 5 to 9 | 5 to 9 | 10 to 18 |
| **MYC AMPLIFICATIONS** | | | | |
| Non-GC-DLBCL | 5 to 9 | 5 to 9 | 5 to 9 | 15 to 27 |
| OC w MYC amplifications | | 5 to 9 | 5 to 9 | 10 to 18 |
| UCS | | 5 to 9 | 5 to 9 | 10 to 18 |

**Table 3.1.2.4-1: Dose Expansion Planned Sample Size**

| Tumor Cohort and Group | Initial Monotherapy | Subsequent Monotherapy | Combination Therapy | Total |
|---|---|---|---|---|
| **AR AMPLIFICATIONS** | | | | |
| CRPC | 5 to 9 | 5 to 9 | 5 to 9 | 15 to 27 |
| **MUTATIONS** | | | | |
| RCC | | 5 to 9 | 5 to 9 | 10 to 18 |
| NSCLC | | 5 to 9 | 5 to 9 | 10 to 18 |
| UM | | 5 to 9 | 5 to 9 | 10 to 18 |
| **All Cohorts** | **25 to 45** | **70 to 126** | **70 to 126** | **165 to 297** |

The minimum overall planned sample sizes are based on Stage 1 initial enrollment, subsequent enrollment, and combination therapy enrollment subject counts per cohort. The maximums are determined similarly. The above assumes that the selected dose level administered in combination is deemed safe; alternately an additional 6 to12 subjects may need to be treated to assess safety at a lower dose level and to continue enrolling all combination therapy cohorts.

An additional 6 to 12 subjects may be enrolled to evaluate a lower dose of BMS-986158 in combination therapy as well as another 18 subjects may be enrolled to evaluate target gene engagement in tumors, and additional PK and safety characteristics in up to 2 cohorts at a different dose or schedule. Therefore, the potential total for expansion will be approximately up to 201 subjects if only monotherapy is pursued, and approximately up to 327 subjects if all planned expansion cohort subjects in monotherapy and combination therapy groups are pursued.

**Administration of Additional Treatment Cycles:**

Subjects may discontinue treatment due to disease progression, unacceptable AEs, or at the subject's request. Treatment decisions related to subject management will be based exclusively on RECIST version 1.1 (Appendix 4), the Lugano 2014 criteria (Appendix 9), or PCWG3 criteria (including PSA assessments) (Appendix 12). Subjects with an objective response of CR, partial response (PR) or stable disease, will continue therapy until they develop progressive disease (PD, unless in case of treatment beyond progression as detailed in Section 3.6), experience clinical deterioration, develop AEs requiring discontinuation of treatment or withdraw consent. Subjects who developed disease progression on BMS-986158 monotherapy in Part 2 will not be allowed to switch to combination therapy.

Subjects who develop toxicity requiring discontinuation of treatment will enter the Clinical Follow-up Period. The subject should be seen in follow-up at least every 30 days, until the AE has resolved to baseline, stabilized, or been deemed irreversible. After completion of the Clinical Follow-up Period, subjects will then enter the Survival Follow-up Period. During this period, clinic visits or telephone contact every 3-4 months will be performed to assess survival status. [redacted]

[redacted] The end of the study will occur after the last treated subject completes their Clinical Follow-up unless if a subject discontinues prematurely. Subjects in Survival Follow-up Period who have progression of disease will be eligible to receive anticancer therapy as appropriate.

## 3.2 Post Study Access to Therapy

At the end of the study, BMS will not continue to provide BMS supplied study drugs to subjects/investigators unless BMS chooses to extend the study. The investigator should ensure that the subject receives appropriate SOC to treat the condition under study.

## 3.3 Study Population

Subjects will undergo screening evaluations to determine eligibility within 28 days for Part 1 and up to 40 days for Part 2 prior to first administration of study medication. For entry into the study, the subject MUST fulfill the required eligibility data prior to dosing on Day 1. No exceptions will be granted.

### *3.3.1 Inclusion Criteria*

**1) Signed Written Informed Consent**

a) The subject must sign the informed consent form prior to the performance of any study related procedures that are not considered part of standard of care.

**i)** Part 2 only: Subjects must consent and will be required to undergo mandatory pretreatment and on-treatment biopsies. Adolescent subjects with genetic alterations detected as SOC (eg, IGH/MYC fusion) are exempt from this requirement. Subjects must have a lesion that can be biopsied at acceptable clinical risk as judged by the investigator. Subjects whose pre-treatment biopsy yields inadequate tissue quantity or quality will be eligible if sufficient archival tissue is available, after discussion with the Medical Monitor. For subjects with adequate pretreatment biopsy and available archival tissue, both specimens should be submitted. Existing formalin-fixed paraffin-embedded (FFPE) tumor tissue, either a block or unstained slides (minimum 20 slides are required) for performance of correlative studies, should also be collected if available. Additional information concerning the number of tissue cores and preparation are provided in the Laboratory Manual.

**2) Target Population**

a) Subjects must have a confirmed histologic or cytologic diagnosis of one of the following malignancies for participation in the study and meet the other criteria listed (a specific exception for disease diagnosis criteria is noted in inclusion criterion k and requirements for the [redacted] test are noted in inclusion criterion m)

**i)** Ovarian **cancer (OC)**

(1) Histological or cytological documented epithelial ovarian cancer, primary peritoneal carcinoma, or fallopian tube cancer

(2) Received at least one prior Platinum Based Therapy (PBT) regimen

(3) Have platinum-resistant/refractory disease (progression or recurrence within 6 months), be intolerant of platinum-containing compounds, and/or have hypersensitivity to platinum-containing compounds.

(4) Must have known BRCA1/2 mutation status, and if BRCA1/2 mutation is present, must have received treatment with a PARP inhibitor, if available

(5) **For Part 2 Expansion only**: All OC subjects must have BRD and/or MYC amplification in tumor cells

**ii) Triple negative breast cancer (TNBC)**

(1) Males and females with histologically or cytologically confirmed triple negative breast carcinoma as defined by ASCO/CAP guidelines.

(2) Had progression or refractory disease during or after at least 1 chemotherapy regimen for the treatment of metastatic or locally advanced disease.

(3) Part 2 only: all subjects with TNBC must have BRD amplification in tumor cells

**iii) Part 1 only: Small cell lung cancer (SCLC)**

(1) Histologically or cytologically documented SCLC, limited or extensive stage disease.

(2) Received at least 1 prior Platinum Based Therapy (PBT) regimen.

**iv) Part 2 only: Non-Small cell lung cancer (NSCLC)**

(1) Histologically or cytologically documented NSCLC

(2) Had progression during or after at least 2 lines of therapy in the advanced metastatic setting

(3) Subjects must have mutations in SWI/SNF complex in tumor cells or detected KRAS mutation with wild type STK11 in tumor cells

(4) Subjects must have received at least 1 prior checkpoint inhibitor immunotherapy

(5) Subjects with known abnormalities of EGFR, ALK, ROS1, BRAF must have received appropriate targeted therapies

(6) Subjects should be ineligible for or received a platinum-based chemotherapy for NSCLC in the adjuvant, neoadjuvant, or recurrent setting

**v) Part 2 only: Renal cell carcinoma (RCC)**

(1) Histologically or cytologically confirmed metastatic RCC

(2) Detected mutations in SWI/SNF complex in tumor cells

(3) Had progression or refractory disease during or after at least 2 lines of therapy

**vi) Part 2 only: Uveal melanoma (UM)**

(1) Histologically or cytologically confirmed unresectable or metastatic UM

(2) Detected Gnaq/11 mutations in tumor cells

(3) Untreated or had progression or refractory disease during or after any line of therapy

**vii) Part 2 only: Uterine carcinosarcoma (UCS)**

(1) Women with histologically or cytologically confirmed UCS

(2) Detected MYC amplifications in tumor cells

(3) Had progression or refractory disease during or after at least 1L treatment regimen

**viii) Part 2 only: Neuroendocrine prostate cancer (NEPC)**

(1) Men with histologically or cytologically confirmed unresectable or metastatic NEPC

(2) Detected BRD amplification in tumor cells

(3) Had progression or refractory disease during or after at least 1L treatment regimen

**ix) Part 2 only: Castration-resistant prostate cancer (CRPC)**

(1) Men with histologically or cytologically confirmed unresectable or metastatic CRPC

(2) Detected AR amplification in tumor cells (with or without MYC amplification)

(3) Had progression or refractory disease during or after at least 1 treatment with a taxane and with an androgen pathway antagonist (eg, abiraterone or enzalutamide). Abiraterone but not enzalutamide may be continued during the study.

(4) Detected MYC amplification in tumor cells (with or without AR amplification)

**x) Part 2 only: NUT-midline carcinoma (NMC)**

(1) Adult and adolescent subjects with Fluorescence in situ hybridization (FISH)-confirmed fusion of NUT with BRD3 or BRD4

(2) Unresectable, or had progression or refractory disease during or after any line of therapy

**xi) Part 2 only: Ewing sarcoma (ES)**

(1) Adult and adolescent subjects with FISH-confirmed fusion of EWS with FLI1

(2) Had progression or refractory disease during or after at least 1L chemotherapy regimen

**xii) Part 2 only: Burkitt's lymphoma/leukemia (BL)**

(1) Adult and adolescent subjects with FISH-confirmed rearrangement of MYC

(2) Had progression or refractory disease during or after at least 1L chemotherapy regimen

(3) Confirmed presence or absence of bone marrow involvement before enrollment.

**xiii) Part 2 only: Double-hit lymphoma (DHL) or non-germinal center subtype of diffuse large B-cell lymphoma (non-GC-DLBCL)**

(1) FISH-confirmed rearrangement of MYC and of BCL2 or BCL6 DHL

(2) Had progression or refractory disease during or after at least 1 chemotherapy regimen

(3) Confirmed presence or absence of bone marrow involvement before enrollment

(4) IHC confirmed CD 10-, BCL6- DLBCL, or CD10-, BCL6+ and MUM1+ DLBCL. Gene expression profile may also be used to confirm a diagnosis of non-GC-DLBCL

**xiv)** **Part 2 only**: adolescent subjects with malignancies harboring genetic abnormalities likely sensitive to BET inhibition who have progressive disease with no effective therapeutic options may be enrolled after discussion and agreement between the Sponsor/Medical Monitor and Investigator.

b) Subjects with controlled, treated brain metastasis fulfilling all the following criteria may be screened: no radiographic progression for at least 2 weeks following radiation and/or surgical treatment, off steroids for at least 2 weeks, without new or progressing neurological signs or symptoms.

c) All subjects must have at least one measurable lesion at baseline by computed tomography (CT) or magnetic resonance imaging (MRI) as per RECIST v1.1 for solid tumors or Lugano 2014 criteria for lymphomas.

d) For Part 1, all subjects must have archival tumor tissue identified and available [redacted] (if slides are provided, a minimum of 10 (ten) unstained slides with at least 5 micron thick tissue sections are required) **unless a fresh biopsy is provided.** All subjects not providing a fresh biopsy must consent to provide tumor blocks or slides to the sponsor and the availability of the tissue must be confirmed prior to subjects receiving study medication. If an archived tumor specimen is unavailable or unsuitable [redacted], subjects may consent to a pre-treatment fresh tumor biopsy to be eligible for this study if it can be performed at minimal acceptable clinical risk as judged by the investigator and if it does not include a target lesion or lesion in an area treated with prior radiation therapy.

**For Part 2, both a pre-treatment and on-treatment fresh biopsy must be provided.** EOT biopsies must be collected for subjects experiencing PD. For adolescent subjects, fresh biopsies pre- and post-treatment are preferred but not mandated. If a fresh biopsy is not provided, archival tumor tissue is required. The screening tumor tissue for the expansion cohorts enrolled in Part 2 of the study must be shipped as described in the laboratory manual for biomarker testing including identification of select pre-defined genetic biomarkers prior to treatment, with the exception of samples from subjects with NMC, ES, BL, and DHL for which the characterization of fusion proteins is a part of SOC. Subjects whose pre-treatment biopsy yields inadequate tissue quantity or quality will only be eligible if sufficient archival tissue is available, after discussion with the Medical Monitor. If there is only 1 measureable lesion and a core needle biopsy is done (instead of excisional), the lesion may be used as a measureable lesion. If there are more than 1 measureable lesions, the lesion being biopsied should not be a target lesion. Fine needle biopsies are not allowed.

e) Subjects must have a life expectancy of at least 3 months.

f) Subjects must have an Eastern Cooperative Oncology Group (ECOG) Performance Status of 0 to 1 (Appendix 5).

g) Subjects who have undergone any major surgery within 4 weeks of study drug administration are excluded. Subjects must have recovered from the effects of major surgery at least 14 days before the first dose of the study drug.

h) Prophylactic anticoagulation for venous access devices with low-dose heparin or similar (e.g. heparin catheter flush) will be permitted.

i) For antiplatelet agents, prophylactic doses are permitted (e.g. aspirin < 300 mg daily, clopidogrel < 75 mg daily).

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

k) Subjects with solid tumor types that are not included in the preferred target population may also be enrolled after a minimum of 2 subjects with the preferred tumor types have been enrolled at a single dose level during escalation, or during monotherapy expansion after discussion with the Sponsor/Study Director. These subjects must have progressed on or had refractory disease to at least one prior anticancer regimen, not be eligible for additional effective standard of care therapy for their disease, and must have the possibility of being positively impacted by the treatment offered in this study.

l) Androgen Receptor Deprivation (ARD) therapy is permitted for subjects with prostate cancer at doses defined by the investigator if the therapeutic agent is not a strong inducer or inhibitor of CYP3A4 activity.

m) If biomarker result from the [redacted] test is inconclusive, [redacted] will repeat the test. If there is not enough tumor material, the tumor biopsy must be repeated. Subjects who have had prior tumor biopsy and analysis by [redacted] conducted < 6 months prior to enrollment and have data available do not need to provide additional sample for [redacted] testing at screening.

**3) Previous Treatment**

a) Prior anticancer therapy treatments such as chemotherapy, radiotherapy, biological immunotherapy, or investigational agents (therapeutic or diagnostic) are permitted.

**i)** For cytotoxic agents, at least 4 weeks must have elapsed from last dose of prior cytotoxic anticancer therapy and the initiation of study drug administration.

**ii)** For non-cytotoxic agents, at least 4 weeks or 5 half-lives (whichever is shorter) must have elapsed from the last dose of prior non-cytotoxic anticancer therapy and the initiation of study drug administration. If 5 half-lives is shorter than 4 weeks, agreement with Sponsor/Medical Monitor is mandatory.

b) *Not applicable; removed per Revised Protocol 03*. If subject had stem cell transplantation, the procedure must have occurred at least 3 months prior to treatment initiation (for autologous SCT) or 4 months (for allogeneic SCT) and without evidence of active graft-versus-host disease (GVHD).

c) All acute toxicities, from any prior therapy (radiotherapy, chemotherapy, or surgical procedures) must have resolved to Grade ≤ 1, NCI CTCAE, version 4.03 or to baseline if irreversible.

d) Concomitant therapy with bisphosphonates is acceptable as per American Society of Clinical Oncology (ASCO) guidelines. Doses of bisphosphonates must be stable for at least 30 days prior to treatment initiation, as per ASCO guidelines.

**4) Age and Reproductive Status**

a) Males and Females, 12 years of age or greater at the time of informed consent.

**i)** For subjects < 18 years of age, age-adjusted normal ranges for all assessments shall be used, as appropriate, for inclusion, exclusion, and dose modification criteria. In addition, an alternate pediatric assessment (eg, left ventricular shortening fraction rather than left ventricular ejection fraction [LVEF]) with an institutionally defined normal range may be used as appropriate.

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

c) Women must not be breastfeeding

d) WOCBP must agree to follow instructions for method(s) of contraception for the duration of treatment plus 5 half-lives of study treatments plus 30 days (duration of ovulatory cycle) for a total of 5 months post-treatment completion (see Appendix 11). In addition, female participants must be willing to refrain from donation of oocytes during this time.

e) Males who are sexually active with WOCBP must agree to follow instructions for method(s) of contraception (Appendix 11) for the duration of treatment with study treatments plus 5 half-lives of study treatments plus 90 days (duration of sperm turnover) for a total of 7 months post-treatment completion. In addition, male participants must be willing to refrain from sperm donation during this time (see Appendix 11).

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

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

One of the highly effective methods of contraception listed in Appendix 11 is required during study duration and until the end of relevant systemic exposure, which is defined as 5 months for females and 7 months for males.

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

### *3.3.2 Exclusion Criteria*

**1) Medical History and Concurrent Diseases**

a) Evidence of uncontrolled, active infection, requiring parenteral anti-bacterial, anti-viral or anti-fungal therapy < 7 days prior to administration of study medication

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

c) Subjects with concomitant second malignancies (except adequately treated non-melanomatous skin cancers or in situ bladder, breast or cervical cancers) are excluded unless a complete remission was achieved at least 3 years prior to study entry and no additional therapy is required or anticipated to be required during the study period

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

e) History of medically significant thromboembolic events or bleeding diathesis within the past 6 months, such as cerebrovascular accident (including transient ischemic attacks), pulmonary embolism, pulmonary hemorrhage > 2 teaspoonfuls/24hrs or repeated pulmonary hemorrhage, gastrointestinal hemorrhage requiring transfusion or procedural intervention

f) Uncontrolled or significant cardiovascular disease including:

   **i)** Congestive heart failure New York Heart Association [NYHA] Class 3 or greater within 3 months (Appendix 6)

   **ii)** History of congenital long QT syndrome or clinically significant ventricular arrhythmias (such as ventricular tachycardia, ventricular fibrillation or Torsade de Pointes). Controlled atrial fibrillation is not an exclusion criterion

   **iii)** Active coronary artery disease, unstable or newly diagnosed angina or myocardial infarction in the past 6 months

g) Inability to tolerate oral medication.

h) HIV-related disease or known positivity for human immunodeficiency virus (HIV).

i) History of and chronic hepatitis evidenced by:

   **i)** Positive Test for hepatitis B surface antigen

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

   Note: Participants with positive hepatitis C antibody and negative quantitative hepatitis C by PCR are eligible. History of resolved hepatitis A virus infection is not an exclusion criterion.

j) Not *applicable; removed per Revised Protocol 02*. NCI CTCAE v4.03 Grade 2 or higher peripheral neuropathy (sensory or motor).

k) Any other sound medical, psychiatric and/or social reason as determined by the investigator.

l) Use of strong inhibitors of CYP3A4 or P-gp within 1 week or 5 half-lives (whichever is longer) or strong inducers of CYP3A4 or P-gp within 2 weeks or 5 half-lives (whichever is longer). See Appendix 3

m) Current uncontrolled autoimmune pneumonitis

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

o) Uncontrolled endocrine disorder including thyroid disease

p) Prior organ allograft or allogenic hematopoietic stem cell transplantation (HSCT)

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

**2) Physical and Laboratory Test Findings**

a) Inadequate bone marrow function defined as:

**i)** Absolute neutrophil count (ANC) < 1,500 cells/$mm^3$ for solid tumors and <1,000 cells/$mm^3$ for hematologic malignancies

**ii)** Platelet count < 100,000 cells/$mm^3$ for solid tumors and <75,000 cells/$mm^3$ for hematologic malignancies

**iii)** Hemoglobin < 8 g/dL

b) Abnormal blood coagulation parameters:

**i)** PT such that international normalized ratio (INR) is > 1.5x ULN (or > 2.5 x baseline, if a subject is on a stable dose of therapeutic warfarin) or a PTT > 1.2x upper limit of normal (ULN).

c) Inadequate hepatic function defined as:

**i)** Aspartate aminotransferase (AST) > 3x ULN

**ii)** Alanine aminotransferase (ALT) > 3x ULN

**iii)** Total bilirubin > 1.5 x ULN (except known Gilbert's syndrome, direct bilirubin > 1.5x ULN);

d) Inadequate renal function defined as:

**i)** Creatinine clearance (CrCl) ≤ 50 mL/minute (either measured or calculated using a standard formula such as Cockcroft and Gault) within 14 days prior to randomization

e) Any of the following on 12-lead electrocardiogram (ECG) prior to study drug administration, confirmed by repeat.

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

**ii)** QTcF > 450 msec, except right bundle branch block

f) Inadequate thyroid function

Note: Subclinical hypothyroidism (thyroid-stimulating hormone < 10 mIU/mL) or controlled hypothyroidism on appropriate thyroid supplementation are acceptable if negative for thyroglobulin, thyroid peroxidase antibodies, and thyroid stimulating immunoglobulin.

g) Weight of < 40 kg.

**3)** ***Not applicable; removed per Revised Protocol 03.*** Allergies and Adverse Drug Reaction - history of significant allergy or severe drug toxicity to one of the mandatory chemotherapeutic agents or their diluents (e.g. Cremaphor) excludes a subject from that particular arm, except a Grade ≤2 infusion reaction to paclitaxel, with successful subsequent retreatment with premedication.

**4) Other Exclusion Criteria**

a) Prisoners or subjects who are involuntarily incarcerated

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

c) Inability to comply with restrictions and prohibited activities/treatments as listed in Section 3.4

d) Women who are pregnant

e) Adolescents who provide active dissent

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

### *3.3.3 Women of Childbearing Potential*

Women of childbearing potential (WOCBP) is defined as any female who has experienced menarche and who has not undergone surgical sterilization (hysterectomy or bilateral oophorectomy) and is not postmenopausal. Menopause is defined as 12 months of amenorrhea in a woman over age 45 in the absence of other biological or physiological causes. In addition, females under the age of 55 years must have a documented serum follicle stimulating hormone, (FSH) level > 40mIU/mL to confirm menopause.

Females treated with hormone replacement therapy, (HRT) are likely to have artificially suppressed FSH levels and may require a washout period in order to obtain a physiologic FSH level. The duration of the washout period is a function of the type of HRT used. The duration of the washout period below are suggested guidelines and the investigators should use their judgement in checking serum FSH levels. If the serum FSH level is >40 mIU/ml at any time during the washout period, the woman can be considered postmenopausal.

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

Other parenteral products may require washout periods as long as 6 months.

## 3.4 Concomitant Treatments

Glucocorticoids may be administered for treatment of infusion reactions and as premedication to prevent infusion reactions.

Palliative radiation therapy to a limited field (eg, painful bone metastasis, painful lumps), if it is not the sole site of measurable and/or assessable disease, is allowed any time during study participation with prior approval of the Sponsor/Medical Monitor.

Subjects with prostate cancer (CRPC and NEPC) are allowed to continue ARD therapy during this trial if the therapeutic agent(s) is (are) not prohibited due to CYP3A4 interactions (eg, enzalutamide is prohibited). Other agents without strong CYP3A4 interactions, such as androgen synthesis inhibitors, gonadotropin realizing hormone analogs, or AR antagonists may be continued if the subject is already on a stable dose.

Subjects are permitted to use topical, ocular, intra-articular, intranasal, and inhalational corticosteroids (with minimal systemic absorption). Adrenal replacement steroid doses > 10 mg daily prednisone are permitted. A brief (<3 weeks) course of corticosteroids for prophylaxis (eg, contrast dye allergy) or for treatment of non-autoimmune conditions (eg, delayed-type hypersensitivity reaction caused by a contrast allergen) is permitted.

Any concomitant therapies within 4 weeks prior to study drug administration and until the final follow-up visit must be recorded on the CRF.

### *3.4.1 Prohibited and/or Restricted Treatments*

Prohibited and/or restricted medications taken prior to study drug administration in the study are described in Section 3.3.2. Medications taken within 4 weeks prior to study drug administration and until the end of the Clinical Follow-up Period must be recorded on the case report form (CRF). The following medications are prohibited during the study (unless utilized to treat a drug-related AE):

- Concurrent anti-neoplastic therapy (ie, chemotherapy, immunotherapy regimens, or radiation therapy, standard or investigational). However, the maintenance of the castrate state by ARD therapy is allowed in subjects with CRPC.
- Prior exposure to BET inhibitors
- Exposure to any investigational drug within 4 weeks of or concurrent with study drug administration
- Concomitant use of strong inhibitors of CYP3A4 or strong inducers of CYP3A4.
- Prophylactic use of myeloid growth factors to support neutrophil counts may NOT be used before completion of DLT evaluation period. After the completion of the DLT period, the use

of hematopoietic growth factors is at the discretion of the treating physician, as per institutional guidelines. Subjects with neutropenic fever or infection should be treated promptly and may receive therapeutic colony-stimulating factors if appropriate.

- Immunosuppressive agents
- Immunosuppressive doses of systemic corticosteroids (except as stated in Section 3.3.2)
- Live virus vaccine during the study and for a period of three months after the last dose of study treatment.

### *3.4.2 Other Restrictions and Precautions*

Subjects may take the study drug with or without food, however it must be documented whether the drug was taken with or without (no food approximately1 hour prior and 2 hours after dose) food.

- Grapefruit and Seville oranges and their juices can inhibit CYP3A4 and should not be consumed while on study.
- Because of the potential for reproductive adverse effects, options for sperm and egg banking should be discussed with the subject, if appropriate.
- Subjects should be provided loperamide or lomotil at the first dosing visit, instructed on its use and counseled to contact their clinician at the first occurrence of diarrhea or loose stools.

**Anti-Emetic and Anti-Diarrheal Medications**

Supportive care may include premedication with anti-emetics to limit treatment-related nausea and vomiting. Subjects should receive medications for treatment-induced diarrhea, as outlined in Section 4.5.3.

**Other Concomitant Medications**

Anti-inflammatory or narcotic analgesics may be offered as needed. Packed RBC and platelet transfusions should be administered as clinically indicated.

## 3.5 Discontinuation of Subjects following any Treatment with Study Drug

Subjects MUST discontinue BMS-986158 if receiving monotherapy and both BMS-986158 and nivolumab if receiving combination therapy (and non-IP at the discretion of the investigator) for any of the following reasons:

- Subject's request to stop study treatment and/or participation in the study
- Any clinical AE, laboratory abnormality or intercurrent illness which, in the opinion of the investigator, indicates that continued participation in the study is not in the best interest of the subject
- Termination of the study by BMS
- Loss of ability to freely provide consent through imprisonment or involuntarily incarceration for treatment of either a psychiatric or physical (eg, infectious disease) illness
- Inability to comply with protocol

- Discretion of the investigator
- AEs requiring discontinuation as outlined in the Dose Modification section (See Section 4.5.2)
- Pregnancy
- Documented and confirmed PD as defined by RECIST v1.1 (for solid tumors, see Appendix 04), or Lugano 2014 (for hematoligic tumors see Appendix 09), or PCWG3 (for CRPC and NEPC see Appendix 12) unless participant meets criteria for treatment beyond progression (Section 3.6)

All subjects who discontinue investigational product (IP) should comply with protocol specified follow-up procedures as outlined in Section 5. The only exception to this requirement is when a subject withdraws consent for all study procedures including post-treatment study follow-up or loses the ability to consent freely (ie, is imprisoned or involuntarily incarcerated for the treatment of either a psychiatric or physical illness).

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

## 3.6 Treatment Beyond Progression

Evidence supporting the continuation of BMS-986158 monotherapy in subjects with solid or hematologic malignancies beyond progression of their disease is lacking and therefore monotherapy treatment beyond progression will not be allowed. If combination therapy is pursued, subjects receiving BMS-986158 in combination with nivolumab will be permitted to continue on combination therapy beyond initial RECIST v1.1, Lugano 2014 (Appendix 9), or PCWG (Appendix 12) defined PD, as long as they meet the following criteria:

- Investigator-assessed clinical benefit and not having rapid disease progression
- Continue to meet all other study protocol eligibility criteria
- Tolerance of study drug
- Stable performance status
- Treatment beyond progression will not delay an imminent intervention to prevent serious complications of disease progression (eg, CNS metastases)
- Subject provides written informed consent prior to receiving any BMS-986158 plus nivolumab treatment using an ICF describing any reasonably foreseeable risks, discomforts, or other alternative treatment options

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

## 3.7 Post Study Drug Follow-up

In this study, safety is a key endpoint of the study. Post study follow-up is of critical importance and is essential to preserving subject safety and the integrity of the study. Subjects who discontinue study drug must continue to be followed for collection of outcome and/or survival follow-up data as required and in line with Section 5 until death or the conclusion of the study.

### *3.7.1 Withdrawal of Consent*

Subjects who request to discontinue study drug will remain in the study and must continue to be followed for protocol specified follow-up procedures. The only exception to this is when a subject specifically withdraws consent for any further contact with him/her or persons previously authorized by subject to provide this information. Subjects should notify the investigator of the decision to withdraw consent from future follow-up **in writing**, whenever possible. The withdrawal of consent should be explained in detail in the medical records by the investigator, as to whether the withdrawal is from further treatment with study drug only or also from study procedures and/or post treatment study follow-up, and entered on the appropriate CRF page. In the event that vital status (whether the subject is alive or dead) is being measured, publicly available information should be used to determine vital status only as appropriately directed in accordance with local law.

### *3.7.2 Lost to Follow-Up*

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

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

# 4 STUDY DRUG

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

- All products, active or placebo, being tested or used as a comparator in a clinical trial.
- Study required premedication, and
- Other drugs administered as part of the study that are critical to claims of efficacy (eg, background therapy, rescue medications)

BMS-986158 will be administered orally. The appropriate number of capsules, based on the assigned dose level, will be administered.

Doses should be taken at approximately the same time each day. Dose can be taken with or without food (defined as no food approximately 1 hour prior and 2 hours after dose) and this information should be recorded in the study diary and the CRF. If a dose is missed on a dosing day, the dose should be skipped and dosing should be resumed at the next scheduled dose. Subjects may be dosed on the regularly scheduled day in the following week. Doses of BMS-986158 should not be repeated if the subject vomits more than 2 hours after taking the dose. Missed dosing information should be recorded in the study diary, the CRF, and medical record along with a description of the reason for the missed dose. The next dosing day should be kept on schedule. If the subject misses a dose, BMS must be notified. Subjects should bring all drug containers to each study visit for drug reconciliation. Empty drug containers should be collected at each visit (or reconciled at least once a month, whichever is prior). Table 4-1 indicates the dose and dosage form to be administered in this study.

**Table 4-1: Treatment Administration**

| Product Description Class and Dosage Form | Potency | Primary Packaging (Volume)/ Label Type | Secondary Packaging / Label Type | Appearance | Storage Conditions (per label) |
|---|---|---|---|---|---|
| BMS-986158-01 | 0.25 mg | Bottle/Open Label | N/A | Capsule | Refer to label on the container |
| BMS-986158-01 | 2.0 mg | Bottle/Open Label | N/A | Capsule | Refer to label on the container |
| Nivolumab (BMS-936558) solution for injection | 100 mg/vial (10 mg/mL) | Vial/Open Label | Box | Vial | Refer to label on the container |

The time of dose administration will be called “0” hour.

Product description and storage information is described in Table 4-1.

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

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

IP documentation must be maintained that includes all processes required to ensure drug is accurately administered. This includes documentation of drug storage, administration and, as

applicable, storage temperatures, reconstitution, and use of required processes (eg, required diluents, administration sets).

Infusion-related supplies (eg, IV bags, in-line filters, 0.9% NaCl solution) will not be supplied by the Sponsor and should be purchased locally if permitted by local regulations.

Please refer to the current version of the IB and/or pharmacy reference sheets for complete storage, handling, dispensing, and infusion information for nivolumab.

## 4.1 Investigational Product

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

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

In this protocol the IP are BMS-986158 and nivolumab. BMS-986158 in combination with nivolumab will only be pursued on review of safety information and the totality of data obtained from BMS-986158 monotherapy in Parts 1 and 2.

**Nivolumab (Part 2)**

Nivolumab infusions should start approximately 30 minutes following BMS-986158 administration. Nivolumab should be infused over 30 minutes in adults and adolescents. Further details regarding preparation and administration will be provided separately in site pharmacy training materials.

**Guidelines for Nivolumab-related Infusion Reactions**

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

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

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

- Stop the nivolumab infusion, begin an IV infusion of normal saline, and treat the subject with diphenhydramine 50 mg IV (or equivalent) and/or acetaminophen/paracetamol 325 to 1000

mg; remain at bedside and monitor subject until resolution of symptoms. Corticosteroid and/or bronchodilator therapy may also be administered as appropriate. If the infusion is interrupted, then restart the infusion at 50% of the original infusion rate when symptoms resolve; if no further complications ensure after 30 minutes, the rate may be increased to 100% of the original infusion rate. Monitor subject closely. If symptoms recur then no further nivolumab will be administered at that visit.

- For future infusions, the following prophylactic premedications are recommended: diphenhydramine 50 mg IV (or equivalent) and/or acetaminophen/paracetamol 325 to 1,000 mg should be administered at least 30 minutes before nivolumab infusions. If necessary, corticosteroids (up to 25 mg of hydrocortisone or equivalent) may be used.

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

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

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

## 4.2 Non-investigational Product

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

## 4.3 Storage and Dispensing

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

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

IP documentation (whether supplied by BMS or not) must be maintained that includes all processes required to ensure drug is accurately administered. This includes documentation of drug storage,

administration and, as applicable, storage temperatures, reconstitution, and use of required processes (eg, required diluents, administration sets).

## 4.4 Method of Assigning Subject Identification

This is an open-label study. Enrolled subjects, including those not dosed, will be assigned sequential subject numbers starting with 00001, eg, 00001, 00002, 00003.... 00010. Those enrolled subjects meeting eligibility criteria will be eligible to be dosed. Sequential numbering may restart at 00001 for each participating site as the distinct subject identification number (PID) will ultimately be comprised of the site number and subject number, eg, 0002 00001.

During Part 1, once informed consent has been obtained, the investigator (or designee) will register the subject by transmitting a copy of the completed enrollment worksheet (registration form) to the Sponsor.

The following information is required for registration:

- Subject's date of birth (month and year only are acceptable if required by local regulation)
- Gender
- Diagnosis
- Statement that subject is eligible
- Date of informed consent
- Planned date of first dose

Treatment groups and/or dose levels will be provided to the site study team after the subject has registered and eligibility for the study confirmed. Site personnel/investigator will receive a receipt confirming treatment assignment. A copy of this documentation should remain in the subject's chart.

In the dose escalation phase, if a subject discontinues treatment with BMS-986158 during the DLT Evaluation period for reasons other than DLT, the subject may be replaced if necessary for safety assessments. Replacement subjects will receive the same treatment but will be assigned a new subject number.

Subjects may be permitted to rescreen for the study following agreement between the Sponsor/Medical Monitor and investigators.

In Part 2, during the screening visit, the investigative site will call into the enrollment option of the interactive response technology (IRT) designated by BMS. Enrolled participants, including those not dosed, will be assigned sequential participant numbers for their site starting with 00001, (eg, 00001, 00002, 00003.... 00010). The patient identification number (PID) will ultimately be comprised of the site number and participant number. Once it is determined that the participant meets the eligibility criteria following the screening visit, the investigative site will call the IRT to centrally assign the participant into the appropriate monotherapy or combination therapy cohort. If both monotherapy and combination cohorts are open for a tumor type, the assignment of subjects will alternate between the 2 regimens.

## 4.5 Selection and Timing of Dose for Each Subject

In each dose escalation part (Part 1) of the study, subjects will be assigned to a specific dose level (see Section 3.1.1). Subjects in the expansion cohorts (Part 2) will be enrolled at or below the MTD or alternative dose as agreed upon by the Sponsor/Medical Monitor and investigators (Section 3.1.2).

### *4.5.1 Dose Limiting Toxicities*

For the purpose of guiding dose escalation, DLTs will be defined based on incidence, intensity, and duration of AEs for which no clear alternative cause is identified. The DLT evaluation period for dose escalation in Part 1 Schedule A is 32 to 35 days (depending on the exact day of the start of Cycle 2); for Schedules B and C it is 35 days. For Part 1 Schedule A, subjects must receive at least 16 of 21 doses of BMS-986158; for Schedule B at least 17 of the 22 doses; and for Schedule C at least 12 of 15 doses to be considered DLT evaluable for dose escalation decisions. The DLT period for safety assessment of BMS-986158 and, if pursued, nivolumab combination therapy in Part 2 will be 28 days for all schedules which excludes a 7-day period for a single dose as in Cycle 1 in Part 1, to allow similar drug exposure and appropriate comparison of the safety profile between Part 1 and Part 2. For Part 2 safety assessment of the combination therapy (if pursued), subjects must receive at least 15 of 20 doses on Schedule A. If alternate schedules are explored, subjects must receive 16 of 21 doses on Schedule B, and 11 of 14 doses on Schedule C. AEs will be graded according to the NCI CTCAE v4.03. For the purpose of subject management, any AE that meets DLT criteria, regardless of the cycle in which it occurs, will lead to dose interruption. Subjects who withdraw from the study during the DLT evaluation interval for reasons other than a DLT may be replaced at the same dose level. The incidence of DLT(s) during the first cycles of treatment (the DLT evaluation period) will be used in dose escalation decisions and to define the MTD. AEs occurring after the DLT period will be considered for the purposes of defining the recommended Phase 2 dose, upon agreement between the Sponsor/ Medical Monitor and investigators, if the AEs are determined to have no clear alternative cause and are not related to disease progression.

DLT(s) will be defined as any of the following events unless a clear alternative cause is identified:

Non-Hematologic DLT:

Any of the following events will be considered a Non-Hematologic DLT:

- ≥ Grade 3 Non-Hematologic toxicity, with the following exceptions.
  - ♦ ≥ Grade 3 electrolyte abnormalities that are not complicated by associated clinical AEs, are not clinically significant, last < 72 hours and either resolve spontaneously or respond to conventional medical intervention
  - ♦ ≥ Grade 3 elevations in serum transaminases (AST, ALT), total bilirubin, alkaline phosphatase that last < 5 days and are not associated with clinical symptoms.
  - ♦ Isolated Grade 3 elevation of amylase or lipase not associated with clinical or radiographic evidence of pancreatitis

- ♦ Grade 3 nausea, vomiting or diarrhea that lasts < 48 hours and either resolves spontaneously or responds to conventional medical intervention
- ♦ Isolated Grade 3 fever not associated with hemodynamic compromise (ie hypotension, clinical or laboratory evidence of impaired end-organ perfusion)
- ♦ Grade 3 endocrinopathy that is well controlled by hormone replacement
- ♦ Grade 3 fatigue

Alopecia of any grade is not considered a DLT

Hematologic DLT:

- Grade 4 neutropenia ≥ 5 days in duration
- Grade 3 febrile neutropenia that lasts > 48 hours
- Grade 4 thrombocytopenia or Grade 3 thrombocytopenia associated with clinically significant bleeding

### *4.5.2 Guidelines for Dose Modifications*

Subjects will be monitored continuously for AEs while on study therapy. Subjects will be instructed to notify their physician immediately for any and all AEs. The criteria presented in this section and Table 4.5.2-1 for dose modifications and delays for BMS-986158 are meant as general guidelines.

- Subjects will continue to receive therapy as long as they have not had disease progression or an AE requiring dose modification, as described below.
- Dose modifications, interruptions, or delays may occur in the setting of lower grade AEs and/or be more conservative than indicated in Table 4.5.2-1 based on the clinical judgment of the investigator, and in consultation with the Sponsor/Medical Monitor.
- For BMS-986158, dose reductions should be to the previous lower dose level, or to a dose level in between the previous dose level and the current dose level, after discussion between Sponsor/Medical Monitor. A decision to remain at the current dose level requires a discussion and an agreement between the investigator and the Sponsor/Medical Monitor.
- If several AEs of varying grade or severity occur simultaneously, the dose modification applied should be the greatest reduction applicable based on the worse grade (or severity) observed among the AEs reported.
- Assessment of causality (chronology, confounding factors such as disease, concomitant medications, diagnostic tests and previous experience with the agent) must be determined and documented by the investigator, prior to dose modification.
- If the same Grade 3 non-hematologic AE recurs despite a dose reduction, a second dose reduction versus discontinuation of the subject from further protocol therapy will be discussed and agreed upon by the Sponsor/Medical Monitor and investigators.
- Subjects who experience a Grade 4 non-hematologic AE will not receive additional protocol-related therapy and will be removed from study unless discussed and agreed upon by the

Sponsor/Medical Monitor and investigators that it is in the best interest of the subject to receive additional therapy with BMS-986158 (for example, if the subject has demonstrated a response to therapy).

- No more than 2 dose level reductions of BMS-986158 will be allowed per subject. If a third dose reduction is required, the subject must discontinue BMS-986158 (and nivolumab, if receiving combination therapy based on response to therapy). Dose re-escalation after a dose reduction may occur in limited circumstances (such as a change in attribution of an AE, or if re-escalation is in the best interest of the subject) after discussion and agreement of the Sponsor/Medical Monitor and investigators. The number of dose modifications needed for a subject should be discussed and agreed between the investigator and the Sponsor/Medical Monitor.
- Skipped doses will not be administered within the same cycle.
- For an AE requiring dose modification, BMS-986158 (and nivolumab for subjects receiving combination therapy) should be interrupted to allow recovery from the AE. Re-initiation of study drug cannot occur until AE decreases to ≤ Grade 1 or baseline assessment. In case of delayed recovery to ≤ Grade 1 or baseline (except for alopecia) from treatment-related AEs that results in a delay of treatment for > 30 days, the subject will not receive additional protocol-related therapy and will be removed from study unless discussed and agreed upon by the Sponsor/Medical Monitor and investigators that it is in the best interest of the subject to receive additional therapy with BMS-986158 (for example, if the subject has demonstrated a response to therapy).
- For patients receiving combination therapy, if 1 study drug must be discontinued, the other study drug may be continued as single agent therapy based on discussion with Sponsor/Medical Monitor and the investigator.
- For subjects in Part 2 monotherapy expansion or (if pursued) combination expansion who report an AE requiring dose modification, the dose of BMS-986158 should be reduced from 3.75 mg to 3 mg. See Table 4.5.2-1.

For data collection and analysis purposes, all subjects will continue to be classified by the original treatment arm.

**Table 4.5.2-1: Dose Modification Criteria for BMS-986158 Drug-Related Adverse Events**

| Adverse Event | Initial Action | Dose Modification |
|---|---|---|
| Grade 4 febrile neutropenia | Discontinue BMS-986158 | Discontinue BMS-986158 |
| Grade 3 febrile neutropenia | Hold BMS-986158 until return to baseline or Grade 1 | 1st event: Consider reduction by 1 dose level.<br>2nd event: Reduce by 1 dose level |
| ≥ Grade 4 hematologic toxicity (neutropenia or thrombocytopenia) | Hold BMS-986158 until returns to baseline or Grade 1. | 1st event: Consider reduction by 1 dose level.<br>2nd event: Reduce by 1 dose level. |
| Grade 3 thrombocytopenia with clinically significant bleeding | Hold BMS-986158 until return to baseline or Grade 1 | 1st event: Consider reduction by 1 dose level.<br>2nd event: Reduce by 1 dose level |
| ≥ Grade 3 non-hematologic AE in subjects receiving maximum medical management. | Hold BMS-986158 until resolves to baseline or Grade 1. | 1st event: Consider reduction by 1 dose level.<br>2nd event: Reduce by 1 dose level. |
| QTcF > 500 msec confirmed by at least one repeat ECG | Discontinue BMS-986158 | Discontinue BMS-986158 |
| ≥ Grade 3 diarrhea not adequately controlled with medication at maximum doses | Hold BMS-986158 until resolves to baseline or Grade 1. | 1st event: Consider reduction by 1 dose level.<br>2nd event: Reduce by 1 dose level. |

If needed, based on the occurrence of DLTs or other AEs, an individual subject enrolled on any arm may have the BMS-986158 schedule revised to match the alternate schedule on an another arm, at the agreement of the investigator and Sponsor/Medical Monitor, in order to better manage the overall tolerability of study treatment. This schedule change may be in lieu of dose modification shown in Table 4.5.2-1. At the agreement of the investigator and Sponsor/Medical Monitor, subjects who have already had dose reduction may be restarted at the original dose under the revised schedule. For data collection and analysis purposes, all subjects will continue to be classified by the original treatment arm.

Reasons for dose modifications or delays, the supportive measures taken and the outcome must be documented in the subject's chart and recorded in the CRF.

Subjects will be monitored continuously for AEs while on study therapy. Subjects will be instructed to notify their physician immediately for any and all toxicity. The criteria presented in this section for dose modifications and delays are meant as general guidelines.

Assessment of causality (chronology, confounding factors such as disease, concomitant medications, diagnostic tests and previous experience with the agent) must be determined and documented by the investigator, prior to modifying any drugs.

### 4.5.3 Management of Diarrhea for BMS-986158

For symptoms of diarrhea that occur at any time during treatment with BMS-986158, dose interruption is recommended until diarrhea resolves. After recovery, dose reduction or discontinuation should follow the criteria in Section 4.5.2 depending on the severity of the diarrhea. The following are guidelines for the management of diarrhea and are not intended to replace the clinical judgment of the treating physician(s):

For Grade 3 or higher events of diarrhea that are not controlled (ie, to Grade 1 or baseline) with loperamide or lomotil, dosing of BMS-986158 should be interrupted, as continued dosing will likely result in increased severity of diarrhea. In addition, evaluation of infectious causes should be considered. After recovery, dose reduction or discontinuation should follow the criteria in the protocol, depending on the severity of the diarrhea. The following are guidelines for the management of diarrhea, and should be used along with the clinical judgment of the treating physician(s).

- Diet: Recommendations should include eating small, frequent meals, diet modification (avoiding milk products, spicy and/or fatty foods, alcohol, and caffeine), and aggressive oral hydration.
- Treatment with Loperamide: Loperamide should be started at the earliest sign of (1) a poorly formed or loose stool, (2) the occurrence of 1 to 2 more bowel movements than usual in 1 day, or (3) an increase in stool volume or liquidity. Loperamide may be taken in the following manner: 4 mg at the first onset of diarrhea, then 2 mg every 2 hours around the clock until diarrhea-free for at least 12 hours. Subjects may take loperamide 4 mg every 4 hours during the night. This dose regimen is higher than the standard dose of loperamide but is typical for the treatment of diarrhea caused by anticancer therapy. Subjects should be provided with loperamide and instructed in its use at the initial treatment visit so that they have sufficient supply on hand in case antidiarrheal support is required. It is important that loperamide is taken as instructed. For subjects who cannot tolerate loperamide or who do not get adequate relief with maximum doses, standard doses of Lomotil® (diphenoxylate/atropine) may be added or used instead of loperamide.
- Additional antidiarrheal measures, such as octreotide, may be used at the discretion of the investigator or treating physician.
- Increase Fluid Intake and, if applicable, consider stopping anti-hypertensive therapy and nonsteroidal anti-inflammatory drugs (NSAIDs): Hypotension and/or renal insufficiency can occur in the setting of volume depletion from severe diarrhea. At the onset of any diarrhea, subjects should be instructed to increase fluid intake to help maintain fluid and electrolyte balance during episodes of diarrhea. Parenteral hydration should be started if oral hydration is not sufficient. The investigator should consider interrupting anti-hypertensive therapy and NSAIDs, if medically appropriate.

### 4.5.4 Management Algorithms for Immuno-oncology Agents

Immuno-oncology agents are associated with AEs that can differ in severity and duration from AEs caused by other therapeutic classes. Nivolumab is considered an immuno-oncology agent in this protocol. Early recognition and management of AEs associated with immuno-oncology agents

may mitigate severe toxicity. Management algorithms have been developed form extensive experience with nivolumab and ipilimumab to assist investigators in assessing and managing the following groups of AEs:

- Gastrointestinal
- Renal
- Pulmonary
- Hepatic
- Endocrinopathies
- Skin
- Neurological

The clinical nature of AEs noted with nivolumab (in combination with BMS-986158) will determine the role of the above algorithms for use in toxicities related to its use in this study. The algorithms recommended for utilization in this protocol are included in Appendix 10.

In addition, nivolumab therapy can be associated with visual complaints. Inflammation of components within the eye is an uncommon, but clinically important, event. An ophthalmologist should evaluate visual complaints with examination of the conjunctiva, anterior and posterior chambers, and retina. Topical corticosteroids may be used to manage low-grade events. Low-grade events that do not resolve and high-grade events should be managed with systemic corticosteroids. Consultation with a BMS Medical Monitor should be sought for all cases of ocular inflammatory events. Complaints of double vision should also prompt medical evaluation.

Cases of rare events, some with fatal outcome, have been reported with nivolumab (see the Investigator Brochure for Nivolumab for details). If a participant develops signs and symptoms of myositis, myocarditis or rhabdomyolysis or other rare event, the case should be discussed with BMS Medical Monitor, close monitoring should be implemented, and the patient referred to a specialist for assessment and treatment without delay. Based on the severity of the event, nivolumab should be withheld or discontinued, and appropriate treatment instituted. For Grade 3 myocarditis, nivolumab should be permanently discontinued.

## 4.6 Blinding/Unblinding

This study is a non-randomized open-label study for Part 1 and Part 2. Interactive Response Technology (IRT) will be used in Part 2 for treatment assignment. Data emerging from this exploratory study may be necessary to inform timely decisions for adjusting procedures in subsequent portions of the study, including early termination of the study. Additionally, availability of the open label treatment assignments may facilitate optimization of the bioanalytical analysis of samples.

## 4.7 Treatment Compliance

At scheduled PK sample collections laboratory evaluation days, BMS-986158 will be administered to the subject in the clinical facility. At all other times throughout the study, BMS-986158 will be

administered on an outpatient basis. The investigator and the study personnel will ensure that each subject receives the calculated dose of the study drug. Treatment compliance will be monitored by drug accountability, as well as recording BMS-986158 administration in subjects' medical records and CRF. Subjects must keep a diary of study medication doses and any missed doses (see Section 4). Subjects should bring all drug containers to each study visit for drug reconciliation. Drug supplies will be inventoried and accounted for throughout the study. The Drug Accountability Log will be reviewed by the study monitor during site visits and at the completion of the study. Any discrepancy should be brought to the attention of the Sponsor.

## 4.8 Destruction of Study Drug

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

Any unused study drugs can only be destroyed after being inspected and reconciled by the responsible BMS Study Monitor unless study drug containers must be immediately destroyed as required for safety, or to meet local regulations (eg, cytotoxics or biologics).

On-site destruction is allowed provided the following minimal standards are met:

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

If conditions for destruction cannot be met, the responsible BMS Study Monitor will make arrangements for return of study drug.

It is the investigator's responsibility to arrange for disposal of all empty containers, provided that procedures for proper disposal have been established according to applicable federal, state, local, and institutional guidelines and procedures, and provided that appropriate records of disposal are kept.

## 4.9 Return of Study Drug

If study drug will not be destroyed upon completion or termination of the study, all unused and/or partially used study drug that was supplied by BMS must be returned to BMS. The return of study drug will be arranged by the responsible Study Monitor.

Arrangements for the return of study drug will be made by the responsible Study Monitor.

# 5 STUDY ASSESSMENTS AND PROCEDURES

## 5.1 Flow Chart/Time and Events Schedule

Study assessments and procedures are presented in Table 5.1-1, Table 5.1-2, Table 5.1-3, Table 5.1-4, Table 5.1-5, and Table 5.1-6.

**Table 5.1-1: Screening Procedural Outline (Study Days -40 to -1) (CA011001)**

| Procedure | Screening Visit | Notes |
|---|---|---|
| **Eligibility Assessments** | | |
| Informed Consent | X | A subject is considered enrolled only when a protocol specific informed consent is signed. Minors judged to be of an age of reason as determined by local requirements should also give their assent. |
| Inclusion/Exclusion Criteria | X | All eligibility criteria must be met for subjects to participate in the study. |
| Medical History | X | Include any toxicities or allergy related to previous treatments, smoking history, and alcohol use. |
| Prior Treatments | X | Including prior cancer treatment regimens and medications administered within 4 weeks of dosing |
| **Safety Assessments** | | |
| Physical Examination (PE) | X | If the screening PE is performed within 48 hours prior to dosing on Cycle 1 Day 1 then a single exam may count as both the screening and predose evaluation. To include breast examination if clinically indicated. |
| Physical Measurements | X | Includes height and weight. |
| Vital Signs | X | Includes body temperature, respiratory rate, blood pressure and heart rate. Blood pressure and heart rate should be measured after the subject has been resting quietly for at least 5 minutes. |
| ECOG | X | See Appendix 5 for scale. |
| Electrocardiogram (ECGs) | X | A single 12-lead ECG. QTcF assessments ≥450 msec must be confirmed on repeat ECG. ECGs should be recorded after the subject has been supine for at least 5 minutes. |
| Laboratory Tests | X | Includes blood samples and urinalysis. See Section 5.3.2 |
| Thyroid Function Tests | X | TSH with reflex testing to free T3 and free T4 if TSH is abnormal. Results should be reviewed by the investigator or appropriate designee within 48 hours of dose administration. |
| Coagulation Panel | X | aPTT, PT and/or INR. See Section 5.3.2 |
| Serology | X | Includes HIV, Hepatitis B and Hepatitis C. See Section 5.3.2 |
| MUGA/ECHO | X | Must include a quantitative assessment of LVEF and utilize the same modality for any subsequent assessments |
| Pregnancy Test | X | For WOCBP only. WOCBP must have a negative test during screening. Test must be repeated within 24 hours prior to the start of study drug. Sensitivity of test must be at least 25 IU/L or equivalent units of HCG. |

**Table 5.1-1: Screening Procedural Outline (Study Days -40 to -1) (CA011001)**

| Procedure | Screening Visit | Notes |
|---|---|---|
| FSH | X | If needed to document post-menopausal status as defined in Section 3.3.3. |
| PSA for CRPC patients only | X | |
| **Adverse Event Reporting** | | |
| Clinical Complaints | X | Clinical complaints related to the disease under study must be collected within 14 days of the first dose of study drug. |
| Monitor for Serious Adverse Events | X | All SAEs must be collected from the date of subject's written consent until 30 days post discontinuation of monotherapy dosing or 100 days post discontinuation of combination dosing or subject's participation in the study if the last scheduled visit occurs at a later time. |
| **Baseline Assessments** | | |
| Archived tumor block or unstained slides/Biopsy | X | Study personnel must ensure that paraffin tissue block or FFPE unstained slides physically exist prior to initiating therapy. However, if archived tumor tissue is unavailable, subject must have fresh pre-treatment biopsy. Archival tumor samples are mandatory if pretreatment biopsies are not available or sufficient for adult subjects enrolled in Part 2. Adolescent subjects must provide archived tumor tissue unless a fresh treatment biopsy is provided (preferred). Slides/tissue block are to be sent to central lab after performing specified tests locally (see "Laboratory tests" in this table below). See Section 3.3.1. |
| Fresh Tumor Biopsy | X | **For Part 2**, a pre-treatment biopsy [redacted] is mandatory for adult subjects. Pre-treatment biopsies should be conducted during the screening period after all other eligibility criteria have been met. See Section 5.6 for details on biopsy collection and specimen handling. |
| Tumor Assessments | X | Contrast enhanced CT of the chest, CT/MRI of the abdomen, pelvis, and all other known and/or suspected sites of disease or fluorodeoxyglucose - positron emission tomography (FDG-PET) for hematologic malignancies should occur within 28 days (Part 1) or 40 days (Part 2) prior to date of first dose. See Section 5.3.1 for further details. For participants with CRPC and NEPC, whole body scans are required. |
| MRI Brain | X | MRI of the brain without and with contrast is required for participants with known or suspected brain metastases, unless participant has completed an imaging study of the brain within 30 days of study drug administration. |

**Table 5.1-1: Screening Procedural Outline (Study Days -40 to -1) (CA011001)**

| Procedure | Screening Visit | Notes |
|---|---|---|
| | | Participants with a history of brain metastasis or symptoms should have a surveillance MRI study per standard of care (approximately every 12 weeks), or sooner if clinically indicated. CT of the brain without and with contrast can be performed if MRI is contraindicated. See Section 5.3.1for further details. |
| Bone Scan | X | Required for participants with prostate cancer (NEPC and CRPC). Others as clinically indicated (ie, subjects with a history or symptoms of bone metastases), but bone scans will not be considered a modality for assessments for measurable disease. |
| MRI Breast Imaging | X | For participants with TNBC without measurable lesions outside the breast, contrast enhanced MRI of the breasts should also be performed.<br>If performed at screening, should be continued at same frequency as body imaging. Additional imaging may be performed as clinically indicated. See Section 5.3.1 for further details. |
| [redacted] | | |
| [redacted] Testing | X | Required for adult subjects in Part 2. Subjects who have undergone this testing within 6 months of screening and have data available do not need to be tested again. Subjects with NMC, ES, BL, and DHL are excluded from this testing. |
| **Clinical Drug Supplies** | | |
| Dose level assignment | X | At the completion of screening procedures and eligibility determined. |
| IRT participant assignment | X | For Part 2 only, after participants meet all eligibility criteria, sites will use IRT for participant assignment. Subsequent visits will be entered into the IRT system for drug supply (see Section 4.4). |

**Table 5.1-2: On Treatment Outline (CA011001)- Part 1 Escalation - Schedule A - 5 days on / 2 days off dosing schedule**

| Procedure | Cycle 1(7 Days) | | | | Cycle 2 (28 Days) | | | | | | | | | Cycle 3 (28 Days) | | | | Cycle 4 and beyond (28 days) | | EOT[a] | Notes |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | D 1 | D 2 | D 3 | D 4 | D 1 | D2 | D 5 | D 8 | D12 | D 15 | D 19 | D 22 | D26 | D 1 | D 8 | D 15 | D 22 | D 1 | D 15 | | |
| **Safety Assessments** | . | | | | | | | | | | | | | | | | | | | | |
| Physical Examination (PE) | X | | | | | | | | | | | | | X | | | | X | | X | See Screening notes. Include breast exam if clinically indicated. |
| Targeted Physical Exam | | | | | X | | | X | | X | | X | | | X | X | X | | X | | Targeted physical exam involves a visual and physical assessment of the body area causing feeling of discomfort to the subject (eg, local pain, rash, or swelling) |
| Physical Measurements | X | | | | X | | | X | | X | | X | | X | X | X | X | X | X | X | Weight only |
| Vital Signs | X | | | | X | | | X | | X | | X | | X | X | X | X | X | X | X | See Section 5.3 for details |
| ECOG | X | | | | | | | | | | | | | X | | | | X | | X | See Appendix 5 for details |

**Table 5.1-2: On Treatment Outline (CA011001)- Part 1 Escalation - Schedule A - 5 days on / 2 days off dosing schedule**

| Procedure | Cycle 1(7 Days) | | | | Cycle 2 (28 Days) | | | | | | | | | Cycle 3 (28 Days) | | | | Cycle 4 and beyond (28 days) | | EOT[a] | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | D 1 | D 2 | D 3 | D 4 | D 1 | D2 | D 5 | D 8 | D12 | D 15 | D 19 | D 22 | D26 | D 1 | D 8 | D 15 | D 22 | D 1 | D 15 | | Notes |
| Electrocardiogram (ECGs)[b] | X | X | | | X | X | X | X | | | | | | X | | | | X | | X | Triplicate 12-lead ECGs will be collected prior to the first BMS-986158 dose during Cycle 1, Day 1(0 hour), 2 and 4 hours post BMS dose. A single 12 lead ECG will be collected thereafter. Refer to Table 5.5.1-1 for details. |
| Laboratory Tests | X[c] | | | | X | | | X | | X | | X | | X | X | X | X | X | X | X | Includes blood and urinalysis samples. Fasting Glucose taken predose C1D1, C3D1 and on additional days, if clinically indicated. IgG levels are taken on Day 1 of every other cycle only, starting with Cycle 1. Creatinine Clearance taken on Day 1 of each cycle. See Section 5.3.2 for details. |

**Table 5.1-2: On Treatment Outline (CA011001)- Part 1 Escalation - Schedule A - 5 days on / 2 days off dosing schedule**

| Procedure | Cycle 1(7 Days) | | | | Cycle 2 (28 Days) | | | | | | | | | Cycle 3 (28 Days) | | | | Cycle 4 and beyond (28 days) | | EOT[a] | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | D 1 | D 2 | D 3 | D 4 | D 1 | D2 | D 5 | D 8 | D12 | D 15 | D 19 | D 22 | D26 | D 1 | D 8 | D 15 | D 22 | D 1 | D 15 | | Notes |
| Coagulation Panel | X | | | | X | | | X | | X | | X | | X* | | | | | | X* | aPTT, PT and INR. *Cycle 3 and beyond to be done if clinically indicated (e.g. signs of bleeding, especially GI bleeding). See 5.3.2 for details |
| MUGA/ECHO | X | | | | | | | | | | | | | | | | | | | | Only if clinically indicated with the same assessment used at screening. See notes in screening. |
| Pregnancy Test | X | | | | X | | | | | | | | | X | | | | X | | X | For WOCBP only. Sensitivity of test must be at least 25 IU/L or equivalent units of HCG. Pregnancy test must be done within 24 hours prior to starting study drug |

**Table 5.1-2: On Treatment Outline (CA011001)- Part 1 Escalation - Schedule A - 5 days on / 2 days off dosing schedule**

| Procedure | Cycle 1(7 Days) | | | | Cycle 2 (28 Days) | | | | | | | | | Cycle 3 (28 Days) | | | | Cycle 4 and beyond (28 days) | | EOT[a] | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | D 1 | D 2 | D 3 | D 4 | D 1 | D2 | D 5 | D 8 | D12 | D 15 | D 19 | D 22 | D26 | D 1 | D 8 | D 15 | D 22 | D 1 | D 15 | | Notes |
| **Adverse Event Reporting** | . | | | | | | | | | | | | | | | | | | | | |
| Monitor for Non-Serious Adverse Events | X | | | | | | | | | | | | | | | | | | | | See Section 6.2. Non-serious AE will be collected from first dose of study drug until 30 days post discontinuation of dosing. AEs reported during this time period should be followed until resolved to baseline, stabilized or deemed irreversible |
| Monitor for Serious Adverse Events | X | | | | | | | | | | | | | | | | | | | | All SAEs must be collected from the date of subject's written consent until 30 days post discontinuation of dosing or subject's participation in the study if the last scheduled visit occurs at a later time. |

**Table 5.1-2: On Treatment Outline (CA011001)- Part 1 Escalation - Schedule A - 5 days on / 2 days off dosing schedule**

| Procedure | Cycle 1(7 Days) | | | | Cycle 2 (28 Days) | | | | | | | | | Cycle 3 (28 Days) | | | | Cycle 4 and beyond (28 days) | | EOT[a] | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | D 1 | D 2 | D 3 | D 4 | D 1 | D2 | D 5 | D 8 | D12 | D 15 | D 19 | D 22 | D26 | D 1 | D 8 | D 15 | D 22 | D 1 | D 15 | | Notes |
| **Sample Collection** | | | | | | | | | | | | | | | | | | | | | |
| Pharmacokinetic (PK) Sampling | X[redacted] | | | | | | | | | | | | | | | | | | | | See Section 5.5. |
| [redacted] | | | | | | | | | | | | | | | | | | | | | |
| **Efficacy Assessments** | | | | | | | | | | | | | | | | | | | | | |
| Tumor Assessments[e] | X | | | | | | | | | | | | | | | | | | | X* | Tumor Assessments should occur every 8 weeks (± 7 days) from date of first dose until PD or treatment discontinuation, whichever occurs later.<br>For subjects who have been on study for ≥ 1 year, tumor assessments should occur every 12 weeks (± 7 days) until PD or treatment discontinuation. |

**Table 5.1-2: On Treatment Outline (CA011001)- Part 1 Escalation - Schedule A - 5 days on / 2 days off dosing schedule**

| Procedure | Cycle 1(7 Days) | | | | Cycle 2 (28 Days) | | | | | | | | | Cycle 3 (28 Days) | | | | Cycle 4 and beyond (28 days) | | EOT[a] | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | D 1 | D 2 | D 3 | D 4 | D 1 | D2 | D 5 | D 8 | D12 | D 15 | D 19 | D 22 | D26 | D 1 | D 8 | D 15 | D 22 | D 1 | D 15 | | Notes |
| | | | | | | | | | | | | | | | | | | | | | *EOT if not assessed within the last 9 weeks |
| [redacted] | | | | | | | | | | | | | | | | | | | | | |
| **Clinical Drug Supplies** | | | | | | | | | | | | | | | | | | | | | |
| BMS 986158 Administration | Dosing regimen is 5 days on, 2 days off. Refer to Section 4 | | | | | | | | | | | | | | | | | | | | Those supplied by BMS or sourced by the investigator. |

Abbreviations: D = Day; EOT = End of treatment; FDG-PET = fluorodeoxyglucose - positron emission tomography

[a] Refer to Table 5.1-6 for Clinical Follow-up and Survival Follow-up Periods

[b] QTcF assessments ≥450 msec must be confirmed on repeat ECG. ECGs should be recorded after the subject has been supine for at least 5 minutes. Serial time matched ECGs will also occur on specific days and time points.

[c] For cycle 1only, assessments may be performed up to 72 hours prior to dosing.

[redacted]

[e] Contrast enhanced CT of the chest, CT/MRI of the abdomen, pelvis, and all other known and/or suspected sites of disease (see Section 5.3.1 for further details).

[redacted]

**Table 5.1-3: On Treatment Outline (CA011001) - Part 1 Escalation - Schedule B - 14 days on / 7 days off dosing schedule**

| Procedure | Cycle 1 (7 Days) | | Cycle 2 (21 Days) | | | | | | | Cycle 3 (21 Days) | | | | | Cycle 4 and beyond (21 days) | | | EOT[a] | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | D 1 | D 7 | D 1 | D2 | D 4 | D 8 | D14 | D15 | D16 | D 1 | D 4 | D8 | D14 | D18 | D 1 | D8 | D 15 | | Notes |
| **Safety Assessments** | | | | | | | | | | | | | | | | | | | |
| Physical Examination (PE) | X | | | | | | | | | X | | | | | X | | | X | See Screening notes. Include breast exam if clinically indicated. |
| Targeted Physical Exam | | | X | | | X | X | | | | | X | X | | | X* | X | | *Beginning with cycle 4, Day 8 assessments may be done between day 8-11. This assessment may be omitted on Day 8 for subjects who have been on study for ≥ 1 year. |

**Table 5.1-3: On Treatment Outline (CA011001) - Part 1 Escalation - Schedule B - 14 days on / 7 days off dosing schedule**

| Procedure | Cycle 1 (7 Days) | | Cycle 2 (21 Days) | | | | | | | Cycle 3 (21 Days) | | | | | Cycle 4 and beyond (21 days) | | | EOT[a] | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | D 1 | D 7 | D 1 | D2 | D 4 | D 8 | D14 | D15 | D16 | D 1 | D 4 | D8 | D14 | D18 | D 1 | D8 | D 15 | | Notes |
| Physical Measurements | X | | X | | | X | X | | | X | | X | X | | X | X* | X | X | Weight only. *Beginning with cycle 4, Day 8 assessments may be done between day 8-11. This assessment may be omitted on Day 8 for subjects who have been on study for ≥ 1 year. |
| Vital Signs | X | | X | | | X | X | | | X | | X | X | | X | X* | X | X | *Beginning with cycle 4, Day 8 assessments may be done between day 8-11. See Section 5.3 for details. This assessment may be omitted on Day 8 for subjects who have been on study for ≥ 1 year. |
| ECOG | X | | | | | | | | | X | | | | | X | | | X | See Appendix 5 for details |

**Table 5.1-3: On Treatment Outline (CA011001) - Part 1 Escalation - Schedule B - 14 days on / 7 days off dosing schedule**

| Procedure | Cycle 1 (7 Days) | | Cycle 2 (21 Days) | | | | | | | Cycle 3 (21 Days) | | | | | Cycle 4 and beyond (21 days) | | | EOT[a] | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | D 1 | D 7 | D 1 | D2 | D 4 | D 8 | D14 | D15 | D16 | D 1 | D 4 | D8 | D14 | D18 | D 1 | D8 | D 15 | | Notes |
| Electrocardiogram (ECGs)[b] | X | | | | | | X | X | | | | | | | | X[c] | | X | Triplicate 12-lead ECGs will be collected prior to the first BMS-986158 dose during Cycle 1, Day 1(0 hour), 2 and 4 hours post BMS dose. A single 12 lead ECG will be collected thereafter. Refer to Section 5.5.1 for details. |
| Laboratory Tests | X[d] | | X | | | X* | X | | | X | | X* | X | | X | X* | X | X | Includes blood and urinalysis samples. Fasting Glucose taken predose C1D1, C3D1 and on additional days, if clinically indicated. IgG levels are taken on Day 1 of every other cycle only, starting with Cycle 1. |

**Table 5.1-3: On Treatment Outline (CA011001) - Part 1 Escalation - Schedule B - 14 days on / 7 days off dosing schedule**

| Procedure | Cycle 1 (7 Days) | | Cycle 2 (21 Days) | | | | | | | Cycle 3 (21 Days) | | | | | Cycle 4 and beyond (21 days) | | | EOT[a] | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | D 1 | D 7 | D 1 | D2 | D 4 | D 8 | D14 | D15 | D16 | D 1 | D 4 | D8 | D14 | D18 | D 1 | D8 | D 15 | | Notes |
| | | | | | | | | | | | | | | | | | | | Creatinine Clearance taken on Day 1 of each cycle. See Section 5.3.2 for details. Beginning with cycle 3, the day 14 assessment has a ±2 day window<br>*CBC only. For subjects on study ≧ 1 year, D8 assessments may be done at local labs. |
| Coagulation Panel | X | | X | | | X | | | | X* | | | | | | | | X* | aPTT, PT and INR. *Cycle 3 and beyond to be done if clinically indicated (e.g. signs of bleeding, especially GI bleeding). See Section 5.3.2 for details |
| MUGA/ECHO | X | | | | | | | | | | | | | | | | | | Only if clinically indicated with the same assessment used at screening. |

**Table 5.1-3: On Treatment Outline (CA011001) - Part 1 Escalation - Schedule B - 14 days on / 7 days off dosing schedule**

| Procedure | Cycle 1 (7 Days) | | Cycle 2 (21 Days) | | | | | | | Cycle 3 (21 Days) | | | | | Cycle 4 and beyond (21 days) | | | EOT[a] | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | D 1 | D 7 | D 1 | D2 | D 4 | D 8 | D14 | D15 | D16 | D 1 | D 4 | D8 | D14 | D18 | D 1 | D8 | D 15 | | Notes |
| | | | | | | | | | | | | | | | | | | | See notes in screening. |
| Pregnancy Test | X | | X | | | | | | | X | | | | | X | | | X | For WOCBP only. Sensitivity of test must be at least 25 IU/L or equivalent units of HCG. Pregnancy test must be done within 24 hours prior to starting study drug |

**Table 5.1-3: On Treatment Outline (CA011001) - Part 1 Escalation - Schedule B - 14 days on / 7 days off dosing schedule**

| Procedure | Cycle 1 (7 Days) | | Cycle 2 (21 Days) | | | | | | | Cycle 3 (21 Days) | | | | | Cycle 4 and beyond (21 days) | | | EOT[a] | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | D 1 | D 7 | D 1 | D2 | D 4 | D 8 | D14 | D15 | D16 | D 1 | D 4 | D8 | D14 | D18 | D 1 | D8 | D 15 | | Notes |
| **Adverse Event Reporting** | | | | | | | | | | | | | | | | | | | |
| Monitor for Non-Serious Adverse Events | X | | | | | | | | | | | | | | | | | | See Section 6.2. Non-serious AE will be collected from first dose of study drug until 30 days post discontinuation of dosing. AEs reported during this time period should be followed until resolved to baseline, stabilized or deemed irreversible |

**Table 5.1-3: On Treatment Outline (CA011001) - Part 1 Escalation - Schedule B - 14 days on / 7 days off dosing schedule**

| Procedure | Cycle 1 (7 Days) | | Cycle 2 (21 Days) | | | | | | | Cycle 3 (21 Days) | | | | | Cycle 4 and beyond (21 days) | | | EOT[a] | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | D 1 | D 7 | D 1 | D2 | D 4 | D 8 | D14 | D15 | D16 | D 1 | D 4 | D8 | D14 | D18 | D 1 | D8 | D 15 | | Notes |
| Monitor for Serious Adverse Events | X | | | | | | | | | | | | | | | | | | All SAEs must be collected from the date of subject's written consent until 30 days post discontinuation of dosing or subject's participation in the study if the last scheduled visit occurs at a later time. |
| **Sample Collection** | | | | | | | | | | | | | | | | | | | |
| Pharmacokinetic (PK) Sampling | X[redacted] | | | | | | | | | | | | | | | X[redacted] | | | See Section 5.5. There will be no PK collection after cycle 8. |
| [redacted] | | | | | | | | | | | | | | | | | | | |

**Table 5.1-3: On Treatment Outline (CA011001) - Part 1 Escalation - Schedule B - 14 days on / 7 days off dosing schedule**

| Procedure | Cycle 1 (7 Days) | | Cycle 2 (21 Days) | | | | | | | Cycle 3 (21 Days) | | | | | Cycle 4 and beyond (21 days) | | | EOT[a] | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | D 1 | D 7 | D 1 | D2 | D 4 | D 8 | D14 | D15 | D16 | D 1 | D 4 | D8 | D14 | D18 | D 1 | D8 | D 15 | | Notes |
| **Efficacy Assessments** | | | | | | | | | | | | | | | | | | | |
| Tumor Assessments[f] | | | X | | | | | | | | | | | | | | | X* | Tumor Assessments should occur every 9 weeks (+/- 7 days) from date of first dose until PD or treatment discontinuation, whichever occurs later. For subjects who have been on study for ≥ 1 year, tumor assessments should occur every 12 weeks (± 7 days) until PD or treatment discontinuation.<br>*EOT if not assessed within the last 9 weeks |
| [redacted] | | | | | | | | | | | | | | | | | | | |

**Table 5.1-3: On Treatment Outline (CA011001) - Part 1 Escalation - Schedule B - 14 days on / 7 days off dosing schedule**

| Procedure | Cycle 1 (7 Days) | | Cycle 2 (21 Days) | | | | | | | Cycle 3 (21 Days) | | | | | Cycle 4 and beyond (21 days) | | | EOT[a] | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | D 1 | D 7 | D 1 | D2 | D 4 | D 8 | D14 | D15 | D16 | D 1 | D 4 | D8 | D14 | D18 | D 1 | D8 | D 15 | | Notes |
| [redacted] | | | | | | | | | | | | | | | | | | | |
| **Clinical Drug Supplies** | | | | | | | | | | | | | | | | | | | |
| BMS 986158 Administration | Dosing regimen is 14 days on, 7 days off. Refer to Section 4 | | | | | | | | | | | | | | | | | | Those supplied by BMS or sourced by the investigator. |

Abbreviations: D = Day; EOT = End of treatment;

[a] Refer to Table 5.1-6 for Clinical Follow-up and Survival Follow-up Periods

[b] QTcF assessments ≥450 msec must be confirmed on repeat ECG. ECGs should be recorded after the subject has been supine for at least 5 minutes. Serial time matched ECGs will also occur on specific days and time points.

[c] ECGs will be collected on C4D8, C6D8 and C8D8. ECGs will not be collected after cycle 8.

[d] For cycle 1only, assessments may be performed up to 72 hours prior to dosing.

[redacted]

[f] Contrast enhanced CT of the chest, CT/MRI of the abdomen, pelvis, and all other known and/or suspected sites of disease. See Section 5.3.1 for further details.

[redacted]

[redacted]

**Table 5.1-4: On Treatment Outline (CA011001)- Part 1 Escalation - Schedule C - 7 days on/14 days off dosing schedule**

| Procedure | Cycle 1(7 Days) | Cycle 2 (21 Days) | | | | | Cycle 3 (21 Days) | | | | Cycle 4 and beyond (21 days) | | | EOT[a] | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | D 1 | D 1 | D2 | D 4 | D 7 | D10 | D 1 | D4 | D 8 | D15 | D 1 | D8 | D15 | | Notes |
| **Safety Assessments** | | | | | | | | | | | | | | | |
| Physical Examination (PE) | X | | | | | | X | | | | X | | | X | See Screening notes. Include breast exam if clinically indicated. |
| Targeted Physical Exam | | X | | | X | | | | X | | | | X | | C2D14 has a ±1 day window. |
| Physical Measurements | X | X | | | X | | X | | X | | X | | X | X | Weight only |
| Vital Signs | X | X | | | X | | X | | X | | X | | | X | See Section 5.3 for details |
| ECOG | X | | | | | | X | | | | X | | | X | See Appendix 5 for details |

**Table 5.1-4: On Treatment Outline (CA011001)- Part 1 Escalation - Schedule C - 7 days on/14 days off dosing schedule**

| Procedure | Cycle 1(7 Days) | Cycle 2 (21 Days) | | | | | Cycle 3 (21 Days) | | | | Cycle 4 and beyond (21 days) | | | EOT[a] | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | D 1 | D 1 | D2 | D 4 | D 7 | D10 | D 1 | D4 | D 8 | D15 | D 1 | D8 | D15 | | Notes |
| Electrocardiogram (ECGs)[b] | X | | | | X | X | | | | | | X[c] | | X | Triplicate 12-lead ECGs will be collected prior to the first BMS-986158 dose during Cycle 1, Day 1(0 hour), 2 and 4 hours post BMS dose. A single 12 lead ECG will be collected thereafter. Refer to Section 5.5.1for details. |
| Laboratory Tests | X[d] | X | | | X | X* | X | | X | X* | X | X | X* | X | Includes blood and urinalysis samples. Fasting Glucose taken predose C1D1, C3D1 and on additional days, if clinically indicated. IgG levels are taken on Day 1 of every other cycle only, starting with Cycle 1. Creatinine Clearance taken on Day 1 of each cycle. See Section 5.3.2 for details. C3D15 and C3D18 has a ±2 day window. For subjects on study ≧ 1 year, D8 assessments may be done at local labs.<br>* CBC only (±24hours) |
| Coagulation Panel | X | X | | | X | | X* | | | | | | | X* | aPTT, PT and INR. *Cycle 2 and beyond to be done if clinically indicated (e.g. signs of bleeding, especially GI bleeding). See Section 5.3.2 for details |

**Table 5.1-4: On Treatment Outline (CA011001)- Part 1 Escalation - Schedule C - 7 days on/14 days off dosing schedule**

| Procedure | Cycle 1(7 Days) | Cycle 2 (21 Days) | | | | | Cycle 3 (21 Days) | | | | Cycle 4 and beyond (21 days) | | | EOT[a] | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | D 1 | D 1 | D2 | D 4 | D 7 | D10 | D 1 | D4 | D 8 | D15 | D 1 | D8 | D15 | | Notes |
| MUGA/ECHO | X | | | | | | | | | | | | | | Only if clinically indicated with the same assessment used at screening. See notes in screening. |
| Pregnancy Test | X | X | | | | | X | | | | X | | | X | For WOCBP only. Sensitivity of test must be at least 25 IU/L or equivalent units of HCG. Pregnancy test must be done within 24 hours prior to starting study drug |
| **Adverse Event Reporting** | | | | | | | | | | | | | | | |
| Monitor for Non-Serious Adverse Events | X | | | | | | | | | | | | | | See Section 6.2. Non-serious AE will be collected from first dose of study drug until 30 days post discontinuation of dosing. AEs reported during this time period should be followed until resolved to baseline, stabilized or deemed irreversible |
| Monitor for Serious Adverse Events | X | | | | | | | | | | | | | | All SAEs must be collected from the date of subject's written consent until 30 days post discontinuation of dosing or subject's participation in the study if the last scheduled visit occurs at a later time. |

**Table 5.1-4: On Treatment Outline (CA011001)- Part 1 Escalation - Schedule C - 7 days on/14 days off dosing schedule**

| Procedure | Cycle 1(7 Days) | Cycle 2 (21 Days) | | | | | Cycle 3 (21 Days) | | | | Cycle 4 and beyond (21 days) | | | EOT[a] | Notes |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | D 1 | D 1 | D2 | D 4 | D 7 | D10 | D 1 | D4 | D 8 | D15 | D 1 | D8 | D15 | | |
| **Sample Collection** | | | | | | | | | | | | | | | |
| Pharmaco-kinetic (PK) Sampling | X[■] | | | | | | | | | | X[■] | | | | See Section 5.5. There will be no PK collection after cycle 8. |
| [redacted] | | | | | | | | | | | | | | | |
| **Efficacy Assessments** | | | | | | | | | | | | | | | |
| Tumor Assessments[f] | | X | | | | | | | | | | | | X* | Tumor Assessments should occur every 9 weeks (± 7 days) from date of first dose until PD or treatment discontinuation, whichever occurs later. For subjects who have been on study for ≥ 1 year, tumor assessments should occur every 12 weeks (± 7 days) until PD or treatment discontinuation.<br>*EOT if not assessed within the last 9 weeks |
| Optional Tumor Biopsy[e] | | X[g] | | | | | | | | | | | | | See Section 5.6 for details on biopsy collection and specimen handling. |
| [redacted] | | | | | | | | | | | | | | | |

**Table 5.1-4: On Treatment Outline (CA011001)- Part 1 Escalation - Schedule C - 7 days on/14 days off dosing schedule**

| Procedure | Cycle 1(7 Days) | Cycle 2 (21 Days) | | | | | Cycle 3 (21 Days) | | | | Cycle 4 and beyond (21 days) | | | EOT[a] | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | D 1 | D 1 | D2 | D 4 | D 7 | D10 | D 1 | D4 | D 8 | D15 | D 1 | D8 | D15 | | Notes |
| [redacted] | | | | | | | | | | | | | | | |
| **Clinical Drug Supplies** | | | | | | | | | | | | | | | |
| BMS 986158 Administration | Dosing regimen is 7 days on, 14 days off. Refer to Section 4 | | | | | | | | | | | | | | Those supplied by BMS or sourced by the investigator. |

Abbreviations: D = Day; EOT = End of treatment

[a] Refer to Table 5.1-6 for Clinical Follow-up and Survival Follow-up Periods

[b] QTcF assessments ≥450 msec must be confirmed on repeat ECG. ECGs should be recorded after the subject has been supine for at least 5 minutes. Serial time matched ECGs will also occur on specific days and time points.

[c] ECGs will be collected on C4D8, C6D8 and C8D8. ECGs will not be collected after cycle 8.

[d] For cycle 1only, assessments may be performed up to 72 hours prior to dosing.

[redacted]

[f] Contrast enhanced CT of the chest, CT/MRI of the abdomen, pelvis, and all other known and/or suspected sites of disease. See Section 5.3.1 for further details.

[redacted]

**Table 5.1-5: On Treatment & Follow-Up Outline (CA011001)- Part 2 BMS-986158 Monotherapy and/or in Combination with Nivolumab Expansion - Schedule A - 5 days on/2 days off dosing schedule**

| Procedure | Cycle 1 (28 Days) | | | | Cycle 2 (28 Days) | | | | Cycle 3 and beyond (28 Days) | | EOT[a] | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| ± 3 days (for all visits except C1D1 and mandatory tumor biopsy) | D 1 | D 8 | D 15 | D 22 | D 1 | D 8 | D 15 | D 22 | D 1 | D 15 | | Notes |
| **Safety Assessments** | | | | | | | | | | | | |
| Physical Examination (PE) | X | | | | X | | | | X | | X | See Screening notes. Include breast exam if clinically indicated. |
| Target Physical Exam | | X | X | X | | X | X | X | X | X | | Targeted to signs and symptoms |
| Physical Measurements | X | X | X | X | X | X | X | X | X | X | X | Weight only |
| Vital Signs | X | X | X | X | X | X | X | X | X | X | X | See Section 5.3 for details |
| ECOG | X | | | | X | X | | | X | | X | See Appendix 5 for details |
| Electrocardiogram (ECGs)[b,c] | X | | | | X | X | | | X | | X | 12-lead ECG should be recorded after the participant has been supine for at least 5 minutes. A single ECG must be collected at predose on Day 1 of each cycle and at EOT. For the ECG/QTc assessment in participants treated with BMS-986158 monotherapy only, refer to Section 5.5.1 for details. |
| Laboratory Tests[d] | X | X* | X | X* | X | X* | X | X* | X | X | X | Includes blood and urinalysis samples. Fasting Glucose taken predose C1D1, C3D1 and on additional days, if clinically indicated. . IgG levels are taken on Day 1 of every other cycle only, starting with Cycle 1. Creatinine Clearance taken on Day 1 of each cycle. See Section 5.3.2 for details. |

**Table 5.1-5: On Treatment & Follow-Up Outline (CA011001)- Part 2 BMS-986158 Monotherapy and/or in Combination with Nivolumab Expansion - Schedule A - 5 days on/2 days off dosing schedule**

| Procedure | Cycle 1 (28 Days) | | | | Cycle 2 (28 Days) | | | | Cycle 3 and beyond (28 Days) | | EOT[a] | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| ± 3 days (for all visits except C1D1 and mandatory tumor biopsy) | D 1 | D 8 | D 15 | D 22 | D 1 | D 8 | D 15 | D 22 | D 1 | D 15 | | Notes |
| | | | | | | | | | | | | * CBC only (±24hours) |
| Thyroid Function Tests [e] | X | | | | X | | | | X | | X | Collect on Day 1 every cycle, predose, beginning with Cycle 1 Day 1 and at EOT.<br>To include TSH with reflex testing (free T3 and free T4) if TSH is abnormal. Results should be examined by the investigator or appropriate designee within 48 hours of dose administration |
| PSA for CRPC subjects only | X | | | | X | | | | X | | X | Collect on Day 1 every cycle, predose, beginning with Cycle 1 Day 1 and at EOT. |
| Coagulation Panel | X | X | X | X | X* | | | | | | X* | aPTT, PT and INR. * Cycle 2 and beyond to be done if clinically indicated (e.g. signs of bleeding, especially GI bleeding). See Section 5.3.2 for details |
| MUGA/ECHO | X | | | | | | | | | | | Only if clinically indicated with the same assessment used at screening. See notes in screening. |
| Pregnancy Test | X | | | | X | | | | X | | X | For WOCBP only. Sensitivity of test must be at least 25 IU/L or equivalent units of HCG. Pregnancy test must be done within 24 hours prior to starting study drug |
| **Adverse Event Reporting** | . | | | | | | | | | | | |

**Table 5.1-5: On Treatment & Follow-Up Outline (CA011001)- Part 2 BMS-986158 Monotherapy and/or in Combination with Nivolumab Expansion - Schedule A - 5 days on/2 days off dosing schedule**

| Procedure | Cycle 1 (28 Days) | | | | Cycle 2 (28 Days) | | | | Cycle 3 and beyond (28 Days) | | EOT[a] | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| ± 3 days (for all visits except C1D1 and mandatory tumor biopsy) | D 1 | D 8 | D 15 | D 22 | D 1 | D 8 | D 15 | D 22 | D 1 | D 15 | | Notes |
| Monitor for Non-Serious Adverse Events | X | | | | | | | | | | | See Section 6.2. Non-serious AE will be collected from first dose of study drug until 30 days post discontinuation of dosing. AEs reported during this time period should be followed until resolved to baseline, stabilized or deemed irreversible |
| Monitor for Serious Adverse Events | X | | | | | | | | | | | All SAEs must be collected from the date of subject's written consent until 30 days post discontinuation of dosing or subject's participation in the study if the last scheduled visit occurs at a later time. |
| **Sample Collection** | | | | | | | | | | | | |
| Pharmacokinetic (PK) Sampling | X[■] | | | | | | | | | | | See Section 5.5. Patients who crossover from monotherapy to combination therapy will not be required to provide samples for PK. |
| [redacted] | | | | | | | | | | | | |
| **Efficacy Assessments** | | | | | | | | | | | | |
| Tumor Assessments[g] | X | | | | | | | | | | X* | Tumor Assessments should occur every 8 weeks (± 7 days) from date of first dose until PD or treatment discontinuation, whichever occurs later. |

**Table 5.1-5: On Treatment & Follow-Up Outline (CA011001)- Part 2 BMS-986158 Monotherapy and/or in Combination with Nivolumab Expansion - Schedule A - 5 days on/2 days off dosing schedule**

| Procedure | Cycle 1 (28 Days) | | | | Cycle 2 (28 Days) | | | | Cycle 3 and beyond (28 Days) | | EOT[a] | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| ± 3 days (for all visits except C1D1 and mandatory tumor biopsy) | D 1 | D 8 | D 15 | D 22 | D 1 | D 8 | D 15 | D 22 | D 1 | D 15 | | Notes |
| | | | | | | | | | | | | For participants with CRPC and NEPC, whole body bone scans should also be performed.<br>For participants with TNBC without measurable lesions outside the breast, contrast enhanced MRI of the breasts should also be performed.<br>*EOT if not assessed within the last 9 weeks. |
| [redacted] | | | | | | | | | | | | |

**Table 5.1-5: On Treatment & Follow-Up Outline (CA011001)- Part 2 BMS-986158 Monotherapy and/or in Combination with Nivolumab Expansion - Schedule A - 5 days on/2 days off dosing schedule**

| Procedure | Cycle 1 (28 Days) | | | | Cycle 2 (28 Days) | | | | Cycle 3 and beyond (28 Days) | | EOT[a] | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| ± 3 days (for all visits except C1D1 and mandatory tumor biopsy) | D 1 | D 8 | D 15 | D 22 | D 1 | D 8 | D 15 | D 22 | D 1 | D 15 | | Notes |
| [redacted] | | | | | | | | | | | | |
| **Clinical Drug Supplies** | | | | | | | | | | | | |
| BMS 986158 Administration | Dosing regimen is 5 days on, 2 days off. Refer to Section 4 | | | | | | | | | | | Those supplied by BMS or sourced by the investigator. Refer to Section 4 |
| Nivolumab Administration | Nivolumab will be administered on a 480 mg Q4W schedule beginning on Cycle 1 Day 1. Adolescent doses will be administered at 6 mg/kg Q4W up to a maximum of 480 mg. Refer to Section 4 | | | | | | | | | | | For subjects assigned to combination therapy only. |

Abbreviations: CRPC = castrate resistant prostate cancer; D = Day; EOT = End of treatment; FDG-PET = fluorodeoxyglucose - positron emission tomography; PSA = prostate specific antigen; Q2W = every 2 weeks

[a] Refer to Table 5.1-6 for Clinical Follow-up and Survival Follow up Periods

[b] QTcF assessments ≥450 msec must be confirmed on repeat ECG. ECGs should be recorded after the subject has been supine for at least 5 minutes. Serial time matched ECGs will also occur on specific days and time points.

[c] ECG collection instructions: For monotherapy treatment ECGs are to be collected at all timepoints indicated in Table 5.1-5 and Table 5.5.1-4. For combination therapy treatment ECGs are to be collected at timepoints indicated in Table 5.1-5 only

[d] For cycle 1only, assessments may be performed up to 72 hours prior to dosing

[e] Thyroid function testing only required for Part 2 Combination treatment with Nivolumab

[redacted]

[g] Contrast enhanced CT of the chest, CT/MRI of the abdomen, pelvis, and all other known and/or suspected sites of disease. FDG-PET for hematologic malignancies. See Section 5.3.1 for further details. Bone scan for prostate cancer.

Note: Patients who crossover from monotherapy to combination therapy will begin at Cycle 1.

**Table 5.1-6: Clinical Follow-up and Survival Follow-up Phase Procedural Outline (CA011001)**

| Procedure | Clinical Follow-up | Clinical Follow-up | Clinical Follow-up | Survival Follow-up | |
|---|---|---|---|---|---|
| | 30 days (+/- 5 days) | 60 days[a] (+/- 5 days) | 100 days[a] (+/- 5 days) | every 12 weeks (+/- 2 weeks) | Notes |
| **Safety Assessments** | | | | | |
| Physical Examination (PE) | X | X | X | | See Screening notes. Include breast exam if clinically indicated. |
| Vital Signs | X | X | X | | Includes body temperature, blood pressure and heart rate |
| Performance Status (ECOG) | X | X | X | | ECOG score (se Appendix 5) |
| Laboratory Tests | X | X | X | | See Section 5.3.2 on "Hematology" and "Serum Chemistry" for specific tests to be included. |
| Thyroid Function Tests[b] | X | X | X | | To include TSH with reflex testing (free T3 and free T4) if TSH is abnormal b |
| PSA for CRCP subjects only | X | X | X | X | |
| Tumor Assessment | | | | X | For the first year of survival follow-up for subjects who do not already have PD.<br>For participants with CRPC and NEPC, whole body bone scans should also be performed.<br>For participants with TNBC without measurable lesions outside the breast, contrast enhanced MRI of the breasts should also be performed. |
| **Adverse Event Reporting** | | | | | |
| Monitor for non-Serious Adverse Events | X | X | X | | Non-serious AEs will be collected starting with the first dose of study medication and through 30 days after discontinuation of dosing for subjects receiving BMS-986158 monotherapy, |

**Table 5.1-6: Clinical Follow-up and Survival Follow-up Phase Procedural Outline (CA011001)**

| Procedure | Clinical Follow-up | Clinical Follow-up | Clinical Follow-up | Survival Follow-up | |
|---|---|---|---|---|---|
| | 30 days (+/- 5 days) | 60 days[a] (+/- 5 days) | 100 days[a] (+/- 5 days) | every 12 weeks (+/- 2 weeks) | Notes |
| | | | | | and through 100 days for subjects receiving combination therapy. |
| Monitor for Serious Adverse Events | X | X | X | | All SAEs must be collected starting at the time a subject signs informed consent and through 30 days after discontinuation of dosing for subjects receiving BMS-986158 monotherapy, and through 100 days for subjects receiving combination therapy. |
| **Sample Collection** | | | | | |
| Pharmacokinetic (PK) Sampling | X | | X | | See Section 5.5.1; For subjects receiving combination therapy only |
| [redacted] | | | | | |

**Table 5.1-6: Clinical Follow-up and Survival Follow-up Phase Procedural Outline (CA011001)**

| Procedure | Clinical Follow-up | Clinical Follow-up | Clinical Follow-up | Survival Follow-up | |
|---|---|---|---|---|---|
| | 30 days (+/- 5 days) | 60 days[a] (+/- 5 days) | 100 days[a] (+/- 5 days) | every 12 weeks (+/- 2 weeks) | Notes |
| [redacted] | | | | | |

[a] Clinical follow-up for patients who receive BMS-986158 in combination with nivolumab will be 60 days and 100 days following the last dose of study drugs

[b] Thyroid function testing only required for Part 2 participants Combination treatment with Nivolumab

### *5.1.1 Retesting During Screening*

Retesting of laboratory parameters and/or other assessments during the Screening or Lead-in period will be permitted (in addition to any parameters that require a confirmatory result).

Any new result will override the previous result (ie, the most current result prior to treatment) and is the value by which study inclusion will be assessed, as it represents the subject's most current, clinical state.

## 5.2 Study Materials

The site will provide all required materials for the tests performed locally (ie, relevant clinical laboratory tests and urine drug screens). The site will have available a well-calibrated scale for recording body weight, a 12-lead ECG machine, and a calibrated sphygmomanometer and thermometer for vital signs assessments. A current and fully-stocked [advanced cardiac life support (ACLS) or basic cardiac life support (BCLS) cart will be immediately available on the premises. The site will have urine collection containers, a refrigerated centrifuge, a monitored and alarmed refrigerator, and freezer (-20°C or below), as well as containers and dry ice for shipment and storage of blood and urine samples. The site will provide all materials required for accurate source documentation of study activities and for housing the subjects during the study.

BMS will provide a BMS-approved protocol and any amendments or administrative letters (if required), and IB. CRFs (electronic or hard copy) will be provided by BMS. The Central Laboratory will provide labels and tubes for the collection of blood samples for PK [redacted]. Enrollment registration worksheets will be provided to the study sites. Sites will fax/e-mail enrollment worksheets to BMS at the time of informed consent. NCI CTCAE criteria will be provided to study sites prior to site initiation. BMS will also provide subject diaries to collect oral dosing, missed dosing information including a description of the reason for the missed dose, PID number, date and time of dosing, number of stools, doses of loperamide, etc will also be captured in the diary. The subject must record any incidence of vomiting 2 hours post ingestion of BMS-986158 dose. Sites may use their own IRB approved subject diaries as long as it captures all the information required by the protocol. Subject diaries should be kept on-site and should only be provided to BMS upon request. The subjects must bring their diaries to every office visit (or at least once a month) so that it can be reviewed by the site staff. Additional instructions will be provided along with the subject diary.

## 5.3 Safety Assessments

All subjects who receive at least one dose of BMS-986158 will be evaluated for safety parameters. Additionally, any occurrence of an SAE from the time of consent until 30 days post discontinuation of BMS-986158 monotherapy and 100 days post discontinuation of combination therapy will be documented. Any occurrence of non-serious AEs will be collected from first dose of study drug until 30 days post discontinuation of BMS-986158 monotherapy and 100 days post discontinuation of combination therapy. AEs will be coded using the most current version of MedDRA. Safety will be evaluated for all treated subjects using the NCI CTCAE v4.03. Safety assessments will be based on medical review of AE reports and the results of vital sign measurements (body temperature, respiratory rate, heart rate, and blood pressure (heart rate and blood pressure should

be measured after subject has been resting quietly for at least 5 minutes), physical examinations and clinical laboratory tests. Subjects should be followed until all AEs for which no clear alternative cause is identified other than to BMS-986158 have recovered to baseline or are deemed irreversible by the investigator. The incidence of AEs will be tabulated and reviewed for potential significance and clinical importance.

The schedule of required visits, tests, procedures and assessments are described Table 5.1-1, Table 5.1-2 Table 5.1-3, Table 5.1-4, Table 5.1-5, and Table 5.1-6.

In limited instances, scheduled events (including events other than safety assessments) can occur outside of the indicated timeframes but the Sponsor should first be notified.

If a subject has a delay in study drug administration for any reason, then assessments and laboratory tests (with the exception of any tests needed to ensure subject safety) should be correspondingly delayed with the exception of tumor assessments (continue scans every 8-9 weeks ± 7 days regardless of dosing delays). At baseline, a medical history will be obtained to capture relevant underlying conditions. Baseline signs and symptoms are those that are assessed within 2 weeks prior to subject enrollment. The baseline physical examination should include weight, height, heart rate, blood pressure, respiratory rate, temperature, and ECOG status and should be performed within 28 days of treatment arm assignment (see Table 5.1-1, Table 5.1-2. Table 5.1-3, Table 5.1-4, Table 5.1-5, and Table 5.1-6). If any vital sign is abnormal, the subject must be observed further for a period of time, as clinically indicated. Any new or worsening clinically significant changes must be reported on the appropriate non-serious or serious AE page.

Additional measures including non-study required laboratory tests should be performed as clinically indicated.

Only data for the procedures and assessments specified in this protocol (see Table 5.1-1, Table 5.1-2. Table 5.1-3, Table 5.1-4, Table 5.1-5, and Table 5.1-6) should be submitted to BMS. Additional procedures and assessments may be performed as part of SOC; however, data for these assessments should remain in the subject's medical record and should not be provided to BMS unless specifically requested by BMS.

Clinical laboratories will be assessed (see Table 5.1-1, Table 5.1-2. Table 5.1-3, Table 5.1-4, Table 5.1-5, and Table 5.1-6.). Sites should collect samples between -28 to -1 days from enrollment in Part 1 and -40 to -1 days in Part 2 to insure that results required for eligibility purposes are verified prior to registration. Pregnancy testing must be performed within 24 hours prior to the initial administration of IP at baseline and then prior to administration of either study medication during study therapy and at the clinical follow-up visit. CBC plus differential and serum chemistry panel should be drawn within 24 hours prior to each subsequent scheduled cycle. Fasting (no food or drink for at least 8 hours) glucose samples are to be taken predose on C1D1 and C3D1 for Schedules A, B and C of Part 1 and Part 2. On-study laboratory tests will be performed on site/locally. Laboratory tests may be obtained more frequently if indicated. Additional laboratory tests should be performed as per SOC.

Laboratory toxicities (eg, suspected drug induced liver enzyme elevations) will be monitored during the Clinical Follow-up period via on site/local labs until all study drug toxicities for which

no clear alternative cause is identified other than to BMS-986158 resolve, return to baseline, or are deemed irreversible.

In case of dose interruption for any reason, assessments and laboratory tests (with the exception of any tests needed to ensure subject safety) should be correspondingly delayed with the exception of tumor assessments (ie, continue scans every 8-9 weeks ± 7 days regardless of dosing delays).

### *5.3.1 Imaging Assessment for the Study*

Any incidental findings of potential clinical relevance that are not directly associated with the objectives of the protocol should be evaluated and handled by the Study Investigator as per standard medical/clinical judgment.

Images will be submitted to a central imaging vendor and may undergo blinded independent central review (BICR) at any time during the study. Prior to scanning first participant, sites should be qualified and understand the image acquisition guidelines and submission process as outlined in the CA011-001 Imaging Manual provided by the central imaging vendor.

Every attempt should be made to image each subject using an identical acquisition protocol on the same scanner for all imaging time points.

**CT/MRI**

Contrast-enhanced CT scans acquired on dedicated CT equipment is preferred for this study. CT with contrast of the chest, abdomen, pelvis, and all other known and/or suspected sites of disease or FDG-PET (for hematologic malignancies) are to be performed for tumor assessments as indicated in Table 5.1-1, through Table 5.1-6. CT scans should be acquired with ≤5mm slices with no intervening gap (contiguous).

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

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

If a participant has a contraindication for CT IV contrast, a non-contrast CT of the chest and a contrast enhanced MRI of the abdomen, pelvis, and other known and/or suspected sites of disease may be obtained. MRI's should be acquired with slice thickness of ≤5 mm with no gap (contiguous).

If a patient has only 1 measurable lesion, which will be subjected to a core needle biopsy, the CT scan should be conducted after the biopsy to establish a baseline.

**Use of CT component of a PET-CT scanner:** Combined modality scanning such as with PET CT is increasingly used in clinical care, and is a modality/technology that is in rapid evolution; therefore, the recommendations outlined here may change rather quickly with time. At present, low dose or attenuation correction CT portions of a combined PET-CT are of limited use in

anatomically-based efficacy assessments and it is therefore suggested that they should not be substituted for dedicated diagnostic contrast enhanced CT scans for anatomically-based lesion measurements. However, if a site can document that the CT performed as part of a PET-CT is of identical diagnostic quality to a diagnostic CT (with IV and oral contrast), then the CT portion of the PET-CT can be used for target lesion measurements. Note, however, that the PET portion of the CT introduces additional data which may bias an investigator if it is not routinely or serially performed.

Participants with prostate cancer (CRPC or NEPC) should have bone lesions assessed using technetium-99m radionuclide bone scans at each imaging assessment. Anterior and posterior whole body planar images should be acquired. Additional (including spot views and SPECT) images should be submitted if acquired. For other participants, bone scans may be obtained if clinically indicated.

For participants with TNBC who do not have measurable lesions outside the breasts, contrast enhanced MRI of the breasts should also be performed as outlined in Section 5.1 (Flow Chart/Time and Events Schedule).

### *5.3.2 Laboratory Test Assessments*

A local laboratory will perform the safety analyses and will provide reference ranges for these tests. A central laboratory will also be utilized for protocol requirements.

Results of clinical laboratory tests performed on Day -1 must be available prior to dosing. Unless otherwise specified, analysis may be performed within the 72 hours prior to dosing for cycle 1 only.

The following clinical laboratory tests will be performed:

**Hematology**

Hemoglobin
Hematocrit
Total leukocyte count, including differential
Platelet count
Absolute neutrophil count (ANC)/absolute lymphocyte count (ALC) determination

**Serum Chemistry**

Aspartate aminotransferase (AST)
Alanine aminotransferase (ALT)
GGT
Amylase
Lipase
Total bilirubin
Direct bilirubin
Alkaline phosphatase
Lactate dehydrogenase (LDH)
Creatinine
Blood Urea Nitrogen (BUN) or UREA
Uric acid
Glucose (Fasting on predose on C1D1 and C3D1 for Schedules A, B and C of Part 1 and for Part 2)
Prostate-specific antigen (PSA) in CRPC patients only
Total Protein
Albumin
Sodium
Potassium
Chloride
Calcium
Phosphorus
Magnesium
Bicarbonate
Thyroid Stimulating Hormone

**Thyroid Stimulating Hormone**

Thyroid-stimulating hormone (TSH) with reflex testing to free T3 and free T4 if TSH is abnormal.

**Urinalysis**

Protein
Glucose
Blood
Leukocyte esterase
Specific gravity
pH
Microscopic examination of the sediment if blood, protein or leukocytes esterase are positive on the dipstick

**Serology**

Total immunoglobulin (IgG) levels - Day 1 of every other cycle only
Hepatitis C antibody (HCV Ab), Hepatitis C RNA (when HCV Ab is not available), hepatitis B surface antigen, HIV-1, -2 antibody (screening only)

**Other Analyses**

Pregnancy test (WOCBP only: screening, predose, discharge).
FSH
aPTT, PT and INR (Coagulation Panel)
Creatinine Clearance (CLcr) for Cockcroft and Gault calculation

Results of all laboratory tests required by this protocol must be provided to BMS, either recorded on the laboratory pages of the CRF or by another mechanism (eg, provided electronically). If the units of a test result differ from those printed on the CRF, the recorded laboratory values must specify the correct units. Any abnormal laboratory test result considered clinically significant by the investigator must be recorded on the appropriate AE page of the CRF (see Section 6.3 Laboratory Test Result Abnormalities).

## 5.4 Efficacy Assessments

### *5.4.1 Primary Efficacy Assessment*

Disease assessment with CT and/or MRI (solid tumors and lymphomas), or FDG-PET (hematologic malignancies, when SOC), or as appropriate, will be performed at baseline. Disease assessment will occur every 8-9 weeks ±7 days from the date of first dose. Disease assessment at other time points may be performed if the investigator is concerned about tumor progression. Tumor assessments will continue until there is disease progression (unless treatment beyond progression in which case imaging should continue as per schedule), or until subjects withdraw from the study. Responses will be based on RECIST v1.1 (Appendix 4) for solid tumors. For hematologic malignancies, responses will be based on the Lugano 2014 Classification for Initial Evaluation, Staging, and Response for Hodgkin Lymphoma (Appendix 9). For prostate cancer (NEPC and CRPC), responses will be based on PCWG3 (including PSA assessments; Appendix 12). At the sponsor's discretion, scans and measurements may be reviewed by independent radiologists using RECIST v1.1, Lugano 2014, or PCWG3 criteria at a later date, or at any time during the study.

### *5.4.2 Secondary Efficacy Assessments*

Not applicable.

[redacted]

## 5.5 Pharmacokinetic Assessments

The pharmacokinetics of BMS-986158 monotherapy in Part 1 will be characterized by non-compartmental data analysis methods and population PK modeling approaches with plasma drug and metabolite concentrations collected at predetermined times. In Part 2, sparse PK samples will be collected with BMS-986158 monotherapy and in combination with nivolumab will be characterized with population PK modeling approaches. [redacted]

[redacted] Validated assays will be used to measure BMS-986158 and metabolite(s) in plasma [redacted].

The PK parameters to be assessed for BMS-986158 following single dose administration include but are not limited to:

| | |
|---|---|
| Cmax | Maximum observed plasma concentration |
| Tmax | Time of maximum observed plasma concentration |
| AUC(0-T) | Area under the plasma concentration-time curve from time zero to time of last quantifiable concentration |
| AUC(TAU) | Area under the concentration-time curve in one dosing interval |

If data permits, the following single dose PK parameters may also be assessed:

| | |
|---|---|
| T-HALF | Apparent terminal phase half-life |
| AUC(INF) | Area under the plasma concentration-time curve from time zero extrapolated to infinite time |
| CLT/F | Apparent total body clearance, reported only for parent, not for metabolite |
| Vz/F | Apparent volume of distribution of terminal phase, reported only for parent, not for metabolite |

The PK parameters to be assessed for BMS-986158 following multiple dose administration in Part 1 include but are not limited to:

| | |
|---|---|
| Cmax | Maximum observed plasma concentration |
| Tmax | Time of maximum observed plasma concentration |
| AUC(0-T) | Area under the plasma concentration-time curve from time zero to time of last quantifiable concentration |
| AUC(TAU) | Area under the concentration-time curve in one dosing interval |
| Cmin | The minimum observed concentration within a dosing interval (ie, occurring no matter when over the dosing interval) |
| Ctau | Concentration at the end of a dosing interval. |
| Ctrough | Trough observed plasma concentration (this includes predose concentrations (C0) and concentrations at the end of dosing interval (Ctau)). |

| | |
|---|---|
| AI | Accumulation Index; ratio of an exposure measure at steady-state 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 and Ctau). |

In addition, the following PK parameters may also be assessed after single and multiple dose administrations in Part 1, if data permit:

| | |
|---|---|
| MR_Cmax | Ratio of metabolite Cmax to parent Cmax, corrected for molecular weight |
| MR_AUC(0-T) | Ratio of metabolite AUC(0-T) to parent AUC(0-T), corrected for molecular weight |
| MR_AUC(INF) | Ratio of metabolite AUC(INF) to parent AUC(INF), corrected for molecular weight (following single dose only) |
| MR_AUC(TAU) | Ratio of metabolite AUC(TAU) to parent AUC(TAU), corrected for molecular weight |

[redacted]

### 5.5.1 Pharmacokinetics [redacted] Collection and Processing

Table 5.5.1-1, Table 5.5.1-2, and Table 5.5.1-3 list the sampling schedules to be followed for the assessment of pharmacokinetics in Part 1. Table 5.5.1-4 lists the sampling schedules to be followed for the assessment of PK for BMS-986158 monotherapy in Part 2 and Table 5.5.1-5 lists the sampling schedules for BMS-986158 and nivolumab combination therapy in Part 2. Further details of blood collection and processing will be provided to the site in the procedure manual.

**Table 5.5.1-1: Pharmacokinetic Specimen Collection & ECG Schedule for BMS-986158 Monotherapy for Schedule A (5 days on / 2 days off) of Part 1**

| Study Cycle of Sample Collection (Cycle 1= 7 days, Subsequent cycles are 28 days each) | Study Day of Sample Collection | Event | Time (post BMS-986158 Dose) Hour: Min | BMS-986158 Blood Sample for Plasma Analysis | ECG QTc[a] |
|---|---|---|---|---|---|
| 1 | 1 | predose | 00:00 | X[b] | X |
| 1 | 1 | | 00:30 | X | |
| 1 | 1 | | 01:00 | X | |

**Table 5.5.1-1: Pharmacokinetic Specimen Collection & ECG Schedule for BMS-986158 Monotherapy for Schedule A (5 days on / 2 days off) of Part 1**

| Study Cycle of Sample Collection (Cycle 1= 7 days, Subsequent cycles are 28 days each) | Study Day of Sample Collection | Event | Time (post BMS-986158 Dose) Hour: Min | BMS-986158 Blood Sample for Plasma Analysis | ECG QTc[a] |
|---|---|---|---|---|---|
| 1 | 1 | | 02:00 | X | X |
| 1 | 1 | | 04:00 | X | X |
| 1 | 1 | | 08:00(±2hr) | X | X |
| 1 | 2 | | 24:00[c] | X | X |
| 1 | 3 | | 48:00[c] | X | |
| 1 | 4 | | 72:00[c] | X | |
| 2 | 1 | | 00:00 | X | X |
| 2 | 1 | | 00:30 | X | |
| 2 | 1 | | 01:00 | X | |
| 2 | 1 | | 02:00 | X | |
| 2 | 1 | | 04:00 | X | |
| 2 | 1 | | 08:00(±2hr) | X | |
| 2 | 2 | | 24:00[d] | X | X |
| 2 | 5 | predose | 00:00 | X[redacted] | X |
| 2 | 5 | | 00:30 | X | |
| 2 | 5 | | 01:00 | X | |
| 2 | 5 | | 02:00 | X | X |
| 2 | 5 | | 04:00 | X | X |
| 2 | 5 | | 08:00(±2hr) | X | X |
| 2 | 6 | | 24:00[e] | X | X |
| 2 | 8 | predose | 00:00 | X[redacted] | X |
| 2 | 8 | | 04:00 | X | |
| 4 | 8 (+3 days)[f] | | 24:00 | X[redacted] | |

[a] Triplicate 12-lead ECGs will be collected prior to the first BMS-986158 dose during Cycle 1, Day 1(0 hour), 2 and 4 hours post BMS dose. A single 12 lead ECG will be collected thereafter. The single 12-lead ECG. QTcF assessments ≥450 msec must be confirmed on repeat ECG

[redacted]

[c] Time represents hours after Cycle 1 Day 1 dose of BMS-986158

[d] Time represents approximate hours after the Cycle 2 Day 1 dose of BMS-986158

[e] Time represents approximate hours after the Cycle 2 Day 5 dose of BMS-986158

[f] Sample may be collected at any time from Cycle 4 Day 8 through Cycle 4 Day 11

**Table 5.5.1-2: Pharmacokinetic Specimen Collection & ECG Schedule for BMS-986158 - Monotherapy for Schedule B (14 days on/7 days off) of Part 1**

| Study Cycle of Sample Collection (Cycle 1= 7 days, Subsequent cycles are 21 days each) | Study Day of Sample Collection | Event | Time (post BMS-986158 Dose) Hour:Min | BMS-986158 Blood Sample for Plasma Analysis | ECG QTc'[a] |
|---|---|---|---|---|---|
| 1 | 1 | predose | 00:00 | X[redacted] | X |
| 1 | 1 | | 00:30 | X | |
| 1 | 1 | | 01:00 | X | |
| 1 | 1 | | 02:00 | X | X |
| 1 | 1 | | 04:00 | X | X |
| 1 | 1 | | 08:00 (±2hr) | X | X |
| 1 | 2 | | 24:00[c] | X | X |
| 1 | 3 | | 48:00[c] | X | |
| 1 | 4 | | 72:00[c] | X | |
| 1 | 5 | | 96:00[c] | X | |
| 2 | 1 | predose | 00:00 | X | |
| 2 | 14 | predose | 00:00 | X[redacted] | X |
| 2 | 14 | | 00:30 | X | |
| 2 | 14 | | 01:00 | X | |
| 2 | 14 | | 02:00 | X | X |
| 2 | 14 | | 04:00 | X | X |
| 2 | 14 | | 08:00 (±2hr) | X | X |
| 2 | 15 | | 24:00[d] | X | X |
| 2 | 16 | | 48:00[d] | X | |
| 2 | 17 | | 72:00[d] | X | |
| 2 | 18 | | 96:00[d] | X[redacted] | |

**Table 5.5.1-2: Pharmacokinetic Specimen Collection & ECG Schedule for BMS-986158 - Monotherapy for Schedule B (14 days on/7 days off) of Part 1**

| Study Cycle of Sample Collection (Cycle 1= 7 days, Subsequent cycles are 21 days each) | Study Day of Sample Collection | Event | Time (post BMS-986158 Dose) Hour:Min | BMS-986158 Blood Sample for Plasma Analysis | ECG QTc'[a] |
|---|---|---|---|---|---|
| 4 | 8 (+3 days)[e] | predose | 00:00 | X[redacted] | X |
| 6 | 8 (+3 days)[e] | predose | 00:00 | X | X |
| 8 | 8 (+3 days)[e] | predose | 00:00 | X | X |

[a] Triplicate 12-lead ECGs will be collected prior to the first BMS-986158 dose during Cycle 1, Day 1(0 hour), 2 and 4 hours post BMS dose. A single 12 lead ECG will be collected thereafter. QTcF assessments ≥450 msec must be confirmed on repeat ECG.

[redacted]

[c] Time represents approximate hours after Cycle 1 Day 1 dose of BMS-986158

[d] Time represents approximate hours after the Cycle 2 Day 14 dose of BMS-986158

[e] Sample may be collected at any time from Cycle Day 8 through Cycle Day 11

**Table 5.5.1-3: Pharmacokinetic Specimen Collection & ECG Schedule for BMS-986158 Monotherapy for Schedule C (7 days on / 14 days off ) of Part 1**

| Study Cycle of Sample Collection (Cycle 1= 7 days, Subsequent cycles are 21 days each) | Study Day of Sample Collection | Event | Time (post BMS-986158 Dose) Hour: Min | BMS-986158 Blood Sample for Plasma Analysis | ECG QTc[a] |
|---|---|---|---|---|---|
| 1 | 1 | predose | 00:00 | X[redacted] | X |
| 1 | 1 | | 00:30 | X | |
| 1 | 1 | | 01:00 | X | |
| 1 | 1 | | 02:00 | X | X |
| 1 | 1 | | 04:00 | X | X |
| 1 | 1 | | 08:00(±2hr) | X | X |
| 1 | 2 | | 24:00[c] | X | X |
| 1 | 3 | | 48:00[c] | X | |
| 1 | 4 | | 72:00[c] | X | |
| 2 | 1 | predose | 00:00 | X | |

**Table 5.5.1-3: Pharmacokinetic Specimen Collection & ECG Schedule for BMS-986158 Monotherapy for Schedule C (7 days on / 14 days off ) of Part 1**

| Study Cycle of Sample Collection (Cycle 1= 7 days, Subsequent cycles are 21 days each) | Study Day of Sample Collection | Event | Time (post BMS-986158 Dose) Hour: Min | BMS-986158 Blood Sample for Plasma Analysis | ECG QTc[a] |
|---|---|---|---|---|---|
| 2 | 7 | predose | 00:00 | X[redacted] | X |
| 2 | 7 | | 00:30 | X | |
| 2 | 7 | | 01:00 | X | |
| 2 | 7 | | 02:00 | X | X |
| 2 | 7 | | 04:00 | X | X |
| 2 | 7 | | 08:00 | X | X |
| 2 | 8 | | 24:00[d] | X | X |
| 2 | 9 | | 48:00[d] | X | X |
| 2 | 10 | | 72:00[d] | X | X |
| 2 | 11 | | 96:00[d] | X[redacted] | X |
| 4 | 8 (+3 days)[e] | | 24:00 | X[redacted] | X |
| 6 | 8 (+3 days)[e] | | 24:00 | X | X |
| 8 | 8 (+3 days)[e] | | 24:00 | X | X |

[a] Triplicate 12-lead ECGs will be collected prior to the first BMS-986158 dose during Cycle 1, Day 1(0 hour), 2 and 4 hours post BMS dose. A single 12 lead ECG will be collected thereafter. QTcF assessments ≥450 msec must be confirmed on repeat ECG.

[redacted]

[c] Time represents approximate hours after Cycle 1 Day 1 dose of BMS-986158

[d] Time represents approximate hours after the Cycle 2 Day 7 dose of BMS-986158

[e] Sample may be collected at any time from Cycle Day 8 through Cycle Day 11

**Table 5.5.1-4: Pharmacokinetic Specimen Collection Schedule for BMS-986158 Monotherapy for Schedule A in Part 2 (5 days on / 2 days off) Expansion Cohorts**

| Study Cycle of Sample Collection (1 Cycle = 28 days) | Study Day of Sample Collection | Event | Time (post BMS-986158 Dose) Hour: Min | BMS-986158 Blood Sample for Plasma Analysis |
|---|---|---|---|---|
| 1 | 1 | predose | 00:00 | X |
| 1 | 1 | | 00:30[a] | X |
| 1 | 1 | | 01:00[a] | X |
| 1 | 1 | | 02:00 | X |
| 1 | 1 | | 04:00 | X |
| 1 | 1 | | 06:00[a] | X |
| 1 | 2 | predose | 00:00 | X |
| 1 | 5 | predose | 00:00 | X |
| 1 | 5 | | 00:30[a] | X |
| 1 | 5 | | 01:00[a] | X |
| 1 | 5 | | 02:00 | X |
| 1 | 5 | | 04:00 | X |
| 1 | 5 | | 06:00[a] | X |
| 1 | 12 | predose | 00:00 | X |
| 1 | 12[b] | | 04:00 – 12:00 | X |
| 2 | 1 | predose | 00:00 | X |
| 2 | 1 | | 00:30[a] | X |
| 2 | 1 | | 01:00[a] | X |
| 2 | 1 | | 02:00 | X |
| 2 | 1 | | 04:00 | X |
| 2 | 1 | | 06:00[a] | X |
| 2 | 2 | predose | 00:00 | X |
| 2 | 5 | predose | 00:00 | X |
| Every 3 cycles from cycle 3 | 1 | predose | 00:00 | X |
| Progression (EOT) | | | | X |

[a] Sample collection only applies for adolescent subjects

[b] Sample is preferably taken the same day of biopsy. If biopsy is rescheduled to another time, PK sample day should be moved accordingly

Note: Blood sample collection for adolescent subjects will occur at the same frequency but 50% of the volume as that for adult subjects.

**Table 5.5.1-5: Pharmacokinetic Specimen Collection Schedule for BMS-986158 in Combination with Nivolumab 480 mg Q4W for Schedule A (5 days on / 2 days off) of Part 2 Expansion Cohorts**

| Study Cycle of Sample Collection (1 Cycle = 28 days) | Study Day of Sample Collection | Event | Time Post Dose[a] Hour: Min | BMS-986158 Blood Sample for Plasma Analysis |
|---|---|---|---|---|
| 1 | 1 | predose | 00:00 | X |
| 1 | 1 | | 00:30[c] | X |
| 1 | 1 | | 01:00 | X |
| 1 | 1 | | 02:00[c] | X |
| 1 | 1 | | 04:00 | X |
| 1 | 1 | | 06:00[c] | X |
| 1 | 2 | predose | 00:00 | X |
| 1 | 5 | predose | 00:00 | X |
| 1 | 5 | | 00:30[c] | X |
| 1 | 5 | | 01:00 | X |
| 1 | 5 | | 02:00[c] | X |
| 1 | 5 | | 04:00 | X |
| 1 | 5 | | 06:00[c] | X |
| 1 | 12 | predose | 00:00 | X |
| 1 | 12[d] | | 04:00 – 12:00 | X |
| 2 | 1 | predose | 00:00 | X |
| 2 | 1 | | 00:30[c] | X |
| 2 | 1 | | 01:00 | X |
| 2 | 1 | | 02:00[c] | X |
| 2 | 1 | | 04:00 | X |
| 2 | 1 | | 06:00[c] | X |

**Table 5.5.1-5: Pharmacokinetic Specimen Collection Schedule for BMS-986158 in Combination with Nivolumab 480 mg Q4W for Schedule A (5 days on / 2 days off) of Part 2 Expansion Cohorts**

| Study Cycle of Sample Collection (1 Cycle = 28 days) | Study Day of Sample Collection | Event | Time Post Dose[a] Hour: Min | BMS-986158 Blood Sample for Plasma Analysis | [redacted] |
|---|---|---|---|---|---|
| 2 | 5 | predose | 00:00 | X | |
| Every 3 cycles from cycle 3 | 1 | predose | 00:00 | X | |
| Progression (EOT) | | | | X | |
| FU1 (30 days) | | | | | |
| FU2 (100 days) | | | | | |

Note: Blood sample collection for adolescent subjects will occur at the same frequency but 50% of the volume as that for adult subjects.

[a] All BMS-986158 sample collection times are with reference to the time of BMS-986158 oral dose administration.

[redacted]

[c] Sample collection only applies to adolescent patients.

[d] Sample is preferably taken the same day of biopsy. If biopsy is rescheduled to another time, PK sample day should be moved accordingly

### *5.5.2 Pharmacokinetic Sample Analyses*

The plasma samples will be analyzed for BMS-986158 and metabolite, BMT-161485 by a validated LC-MS/MS assay.

[redacted]

Pharmacokinetic analyses will be performed on the tumor tissue.

[redacted]

In addition, plasma samples will be archived for potential metabolite analysis, if the need arises and to the extent possible.

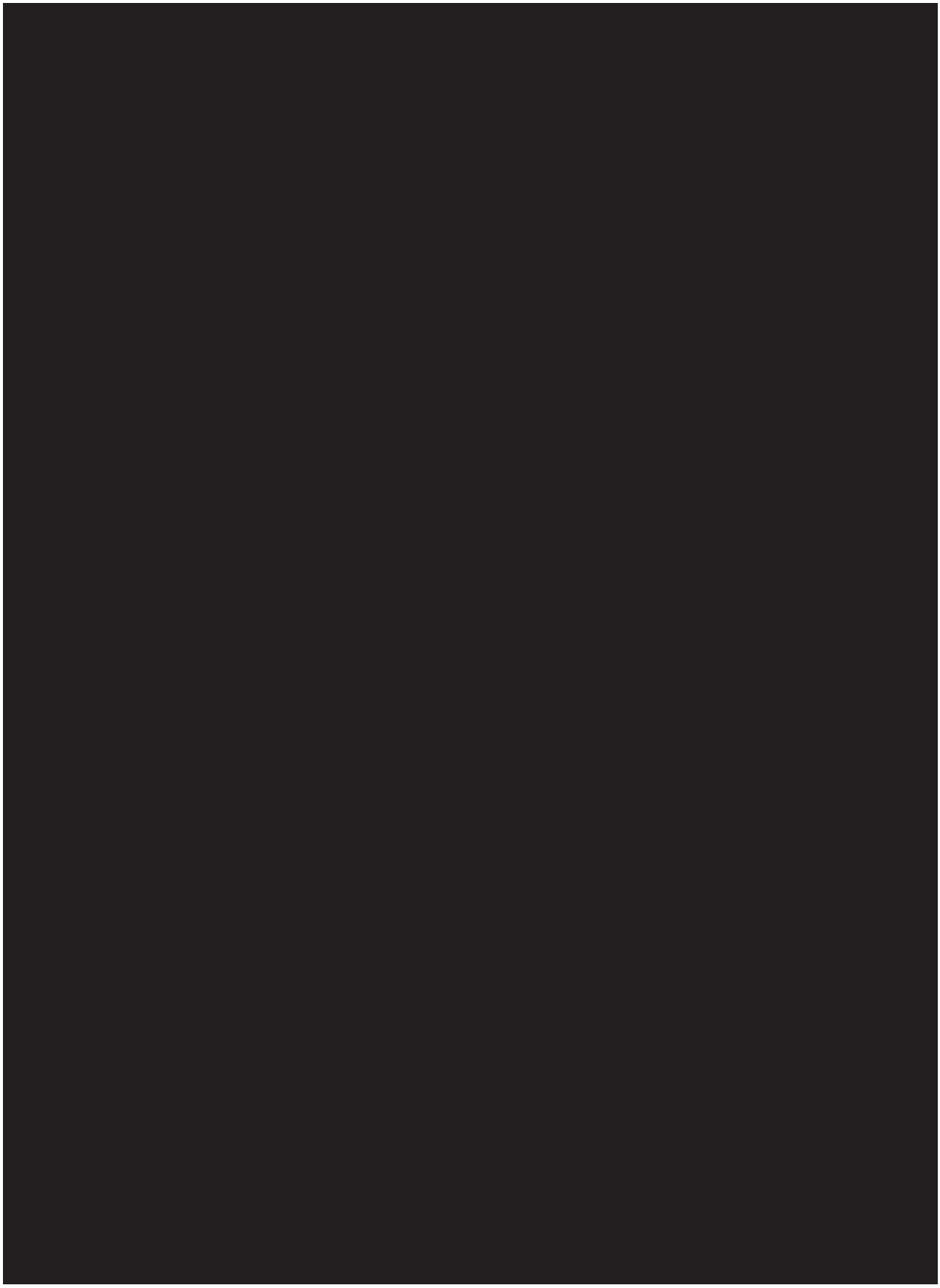
[redacted]

### *5.5.4 Labeling and Shipping of Biological Samples*

Detailed instructions for the pharmacokinetic blood collection, labeling, processing, storage, and shipping will be provided to the site in the procedure manual.

## 5.6 Biomarker Assessments

[redacted]



[redacted]

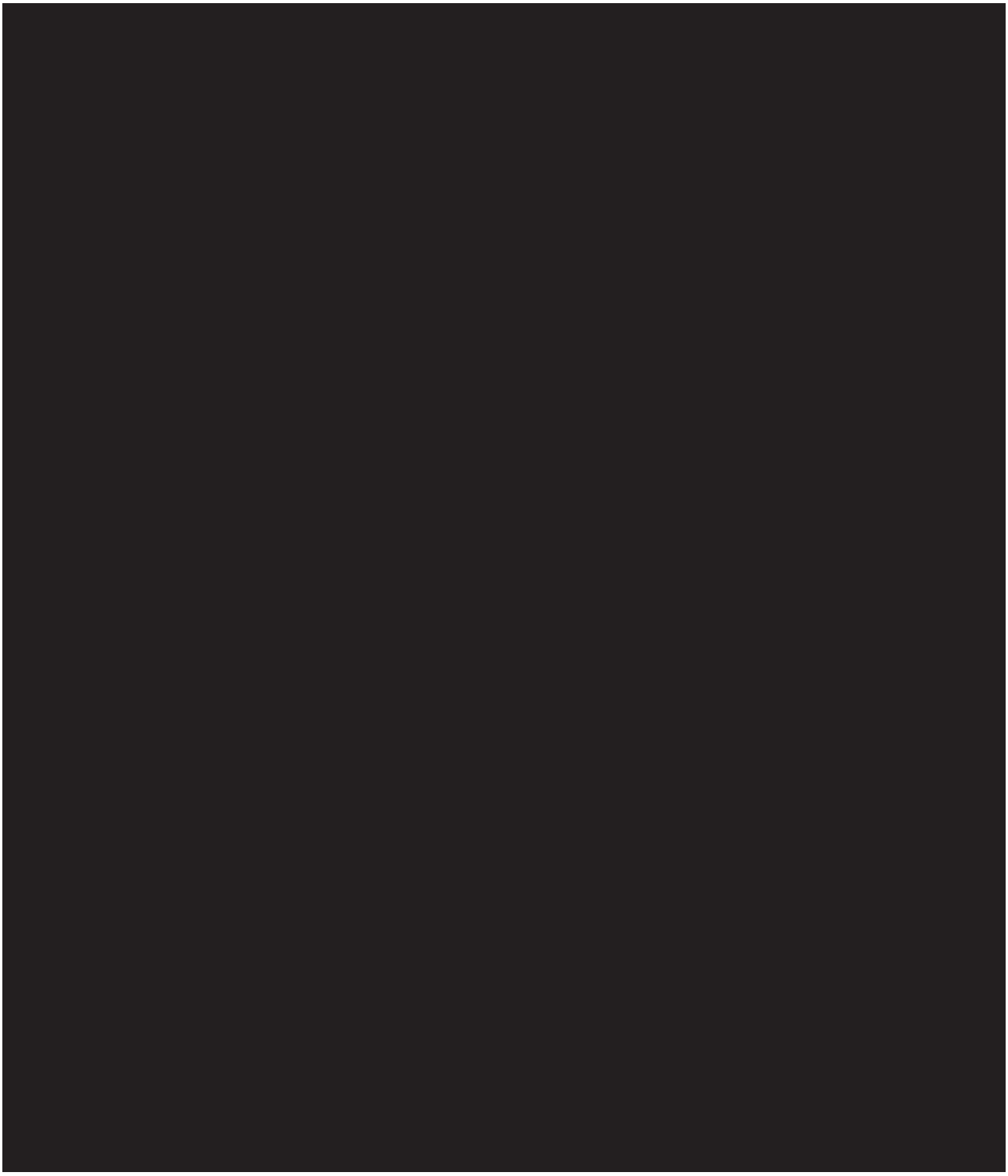
**Tumor Biopsy Collection Details**

A minimum of 1 FFPE tumor tissue block (preferred) OR a minimum of 3-4 core biopsies are required for biomarker evaluations in adult subjects. Specimens should contain a minimum of 100 evaluable tumor cells.

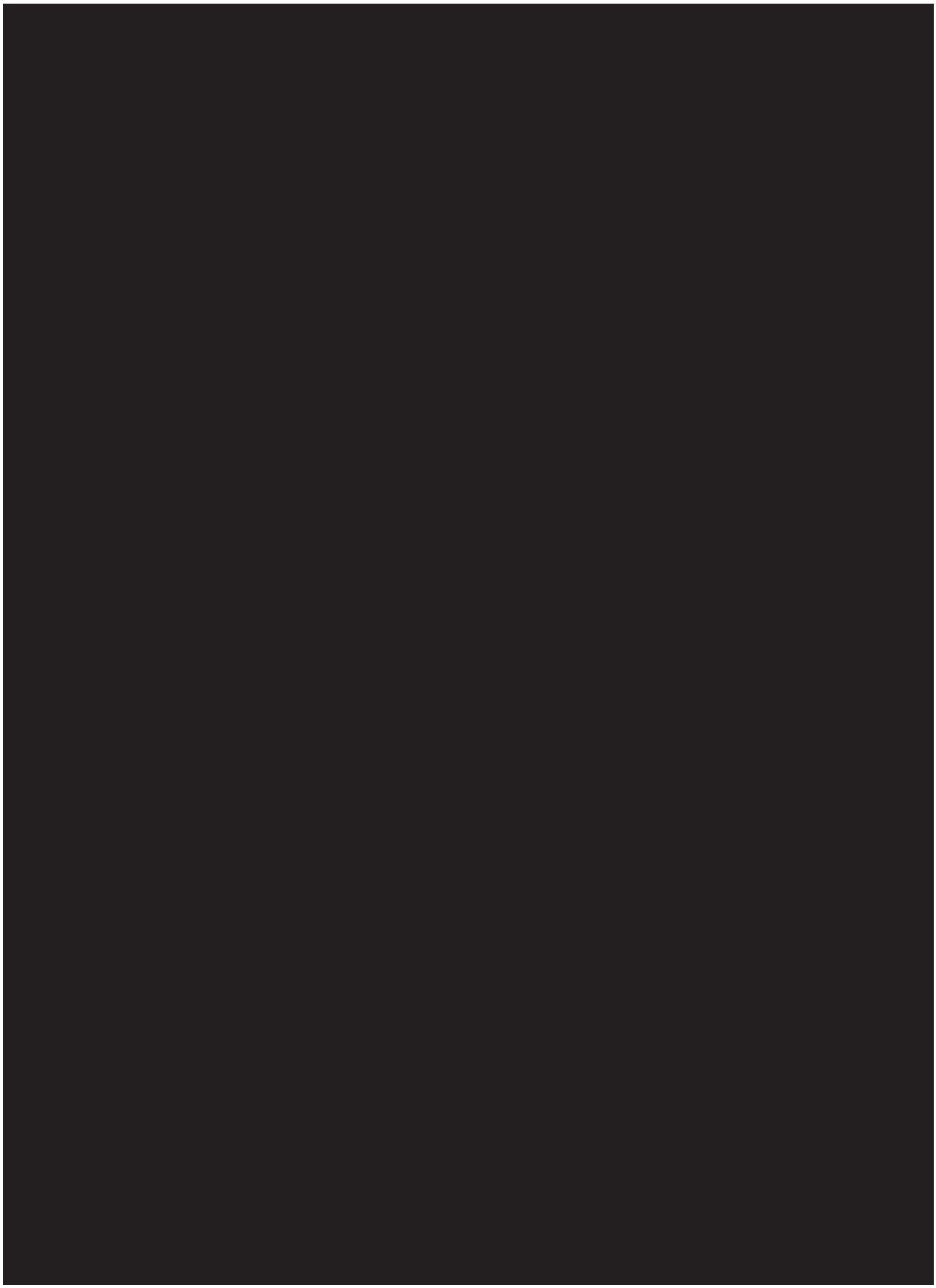
Complete instructions on tissue collection, processing, handling, and shipment of all biopsy samples will be provided in a separate procedure manual. Collection procedures at baseline and during treatment should be completed on a single, appropriately-assessable lesion when possible. Immediate confirmation for presence of viable tumor cells from collected tissue samples is strongly recommended. If core needle biopsies are collected, 3 cores plus one additional core is required at screening in cases where prospective testing is required by [redacted] (16 gauge is preferred if feasible), and 3 cores should be collected during treatment and at the EOT in subjects with PD. All cores will be formalin fixed for FFPE block preparation, 1 will be for [redacted] testing (at screening only, and subjects with NMC, ES, BL, and DHL are exempted [redacted] If adequate tissue is not obtained following initial passages of the needle, repeat passages may be completed.

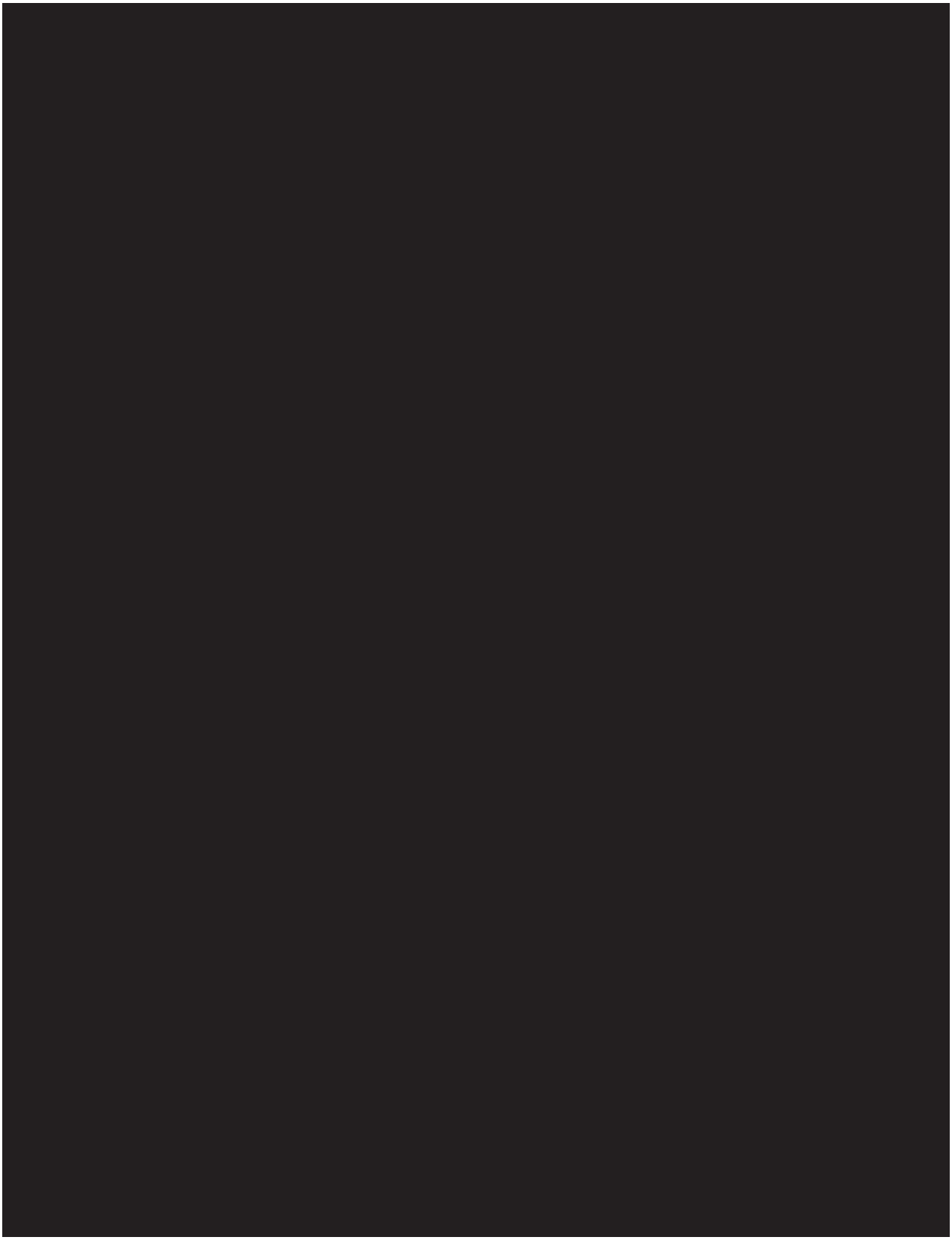
The investigator, in consultation with the radiology staff, must determine the degree of risk associated with the biopsy procedure and find it acceptable. Biopsies may be done with local anesthesia or conscious sedation. Institutional guidelines for the safe performance of biopsies should be followed. Excisional biopsies may be performed to obtain tumor biopsy samples. Invasive procedures that require general anesthesia should not be performed to obtain a biopsy

specimen. [redacted]



[redacted]





## 5.7 Outcomes Research Assessments

Not applicable.

[redacted]

## 5.9 Results of Central Assessments

Not applicable

[redacted]

[redacted]

# 6 ADVERSE EVENTS

An AE is defined as any new untoward medical occurrence or worsening of a preexisting medical condition in a clinical investigation subject administered study drug and that does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (such as an abnormal laboratory finding), symptom, or disease temporally associated with the use of study drug, whether or not considered related to the study drug.

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

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

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

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

BMS will be reporting AEs to regulatory authorities and ethics committees according to the local applicable laws including European Directive 2001/20/EC and FDA Code of Federal Regulations 21 CFR Parts 312 and 320.

## 6.1 Serious Adverse Events

A ***Serious Adverse Event (SAE)*** is any untoward medical occurrence that at any dose:

- results in death
- is life-threatening (defined as an event in which the subject was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe)

- requires inpatient hospitalization or causes prolongation of existing hospitalization (see **NOTE** below)
- results in persistent or significant disability/incapacity
- is a congenital anomaly/birth defect
- is an important medical event (defined as a medical event(s) that may not be immediately life-threatening or result in death or hospitalization but, based upon appropriate medical and scientific judgment, may jeopardize the subject or may require intervention [eg, medical, surgical] to prevent one of the other serious outcomes listed in the definition above.) Examples of such events include, but are not limited to, intensive treatment in an emergency room or at home for allergic bronchospasm; blood dyscrasias or convulsions that do not result in hospitalization.) Potential drug induced liver injury (DILI) is also considered an important medical event. (See Section 6.6 for the definition of potential DILI.)

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

Although pregnancy, overdose, cancer, and potential drug induced liver injury (DILI) are not always serious by regulatory definition, these events must be handled as SAEs. (See Section 6.1.1 for reporting pregnancies).

Any component of a study endpoint that is considered related to study therapy (eg, death is an endpoint, if death occurred due to anaphylaxis, anaphylaxis must be reported) should be reported as SAE (see Section 6.1.1 for reporting details.

**NOTE**:

The following hospitalizations are NOT considered SAEs in BMS clinical studies:

- a visit to the emergency room or other hospital department < 24 hours, that does not result in admission (unless considered an important medical or life-threatening event)
- elective surgery, planned prior to signing consent
- admissions as per protocol for a planned medical/surgical procedure
- routine health assessment requiring admission for baseline/trending of health status (eg, routine colonoscopy)
- medical/surgical admission other than to remedy ill health and planned prior to entry into the study. Appropriate documentation is required in these cases
- admission encountered for another life circumstance that carries no bearing on health status and requires no medical/surgical intervention (eg, lack of housing, economic inadequacy, caregiver respite, family circumstances, administrative reason).
- Admission for administration of anticancer therapy in the absence of any other SAEs (applies to oncology protocols)

### *6.1.1 Serious Adverse Event Collection and Reporting*

Sections 5.6.1 and 5.6.2 in the Investigator Brochure (IB) represent the Reference Safety Information to determine expectedness of serious adverse events for expedited reporting. Following the subject's written consent to participate in the study, all SAEs, whether related or not related to study drug, must be collected, including those thought to be associated with protocol-specified procedures. All SAEs must be collected that occur during the screening period and within 30 days of discontinuation of dosing for subjects receiving BMS-986158 monotherapy and within 100 days of discontinuation for subjects receiving BMS-986158 in combination with nivolumab.

The investigator should report any SAE that occurs after these time periods and that is believed to be related to study drug or protocol-specified procedure.

An SAE report should be completed for any event where doubt exists regarding its seriousness.

If the investigator believes that an SAE is not related to study drug, but is potentially related to the conditions of the study (such as withdrawal of previous therapy or a complication of a study procedure), the relationship should be specified in the narrative section of the SAE Report Form.

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

**SAE Email Address:** Refer to Contact Information list.

**SAE Facsimile Number:** Refer to Contact Information list.

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

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

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

If an ongoing SAE changes in its intensity or relationship to study drug or if new information becomes available, a follow-up SAE report should be sent within 24 hours to the BMS (or designee) using the same procedure used for transmitting the initial SAE report.

All SAEs should be followed to resolution or stabilization.

## 6.2 Nonserious Adverse Events

A ***nonserious adverse event*** is an AE not classified as serious.

### 6.2.1 Nonserious Adverse Event Collection and Reporting

The collection of nonserious AE information should begin at initiation of study drug until the time points specified in the Schedule of Activities (Section 5). Nonserious AE information should also be collected from the start of the screening period or other observational period intended to establish a baseline status for the subjects.

Nonserious AEs should be followed to resolution or stabilization, or reported as SAEs if they become serious (see Section 6.1.1). Follow-up is also required for nonserious AEs that cause interruption or discontinuation of study drug and for those present at the end of study treatment as appropriate. All identified nonserious AEs must be recorded and described on the nonserious AE page of the CRF (paper or electronic).

Completion of supplemental CRFs may be requested for AEs and/or laboratory abnormalities that are reported/identified during the course of the study.

## 6.3 Laboratory Test Result Abnormalities

The following laboratory test result abnormalities should be captured on the nonserious AE CRF page or SAE Report Form (paper or electronic) as appropriate:

- Any laboratory test result that is clinically significant or meets the definition of an SAE
- Any laboratory test result abnormality that required the subject to have study drug discontinued or interrupted
- Any laboratory test result abnormality that required the subject to receive specific corrective therapy.

It is expected that wherever appropriate, the clinical rather than laboratory term would be used by the reporting investigator (eg, thrombocytopenia versus decreased platelet count, anemia versus low hemoglobin value, etc.).

## 6.4 Pregnancy

If, following initiation of the investigational product, it is subsequently discovered that a study subject is pregnant or may have been pregnant at the time of study exposure, including during at least 5 half-lives after product administration, the investigator must immediately notify the BMS Medical Monitor/designee of this event and complete and forward a Pregnancy Surveillance Form to BMS Designee within 24 hours and in accordance with SAE reporting procedures described in Section 6.1.1.

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

Protocol-required procedures for study discontinuation and follow-up must be performed on the subject unless contraindicated by pregnancy (eg, x-ray studies). Other appropriate pregnancy follow-up procedures should be considered if indicated.

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

Any pregnancy that occurs in a female partner of a male study participant should be reported to BMS. Information on this pregnancy will be collected on the Pregnancy Surveillance Form.

## 6.5 Overdose

An overdose is defined as the accidental or intentional administration of any dose of a product that is considered both excessive and medically important. Overdose, as a verbatim term (as reported by the investigator), should not be reported as an AE/SAE unless it is an intentional overdose taken with possible suicidal/self-harming intent. Such overdoses should be reported regardless of sequelae and should specify "intentional overdose" as the verbatim term. See Section 6.1.1 for reporting details.

## 6.6 Potential Drug Induced Liver Injury (DILI)

Wherever possible, timely confirmation of initial liver-related laboratory abnormalities should occur prior to the reporting of a potential DILI event. All occurrences of potential DILIs, meeting the defined criteria, must be reported as SAEs (see Section 6.1.1 for reporting details).

Potential drug induced liver injury is defined as:

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

AND

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

AND

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

## 6.7 Other Safety Considerations

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

# 7 DATA MONITORING COMMITTEE AND OTHER EXTERNAL COMMITTEES

Not applicable

# 8 STATISTICAL CONSIDERATIONS

## 8.1 Sample Size Determination

**Dose Escalation (Part 1)**:

In the dose escalation part of the study for monotherapy Part 1, the sample size per dose level cannot be precisely determined but depends on the observed DLT and the decision rule of mTPI. Between 3 and up to 13 DLT evaluable subjects may be enrolled to a given dose level, based on the decision guide by the mTPI design. Treating additional subjects beyond the 13 at a dose level would be unlikely to alter the decision specified by the mTPI algorithm. A total of approximately 30 subjects is expected to be treated per schedule, with a total of 90 planned across schedules for the dose escalation phase. More subjects may be added at a specific schedule if additional dose levels need to be evaluated. Similarly, fewer than 30 subjects may be needed for a different schedule if a smaller number of dose levels are evaluated.

Assuming a 27% acceptable DLT rate, which corresponds to a Beta(1,2.7) distribution, the following table shows the risk associated with selecting a dose level as safe given the number of DLTs observed at that dose level based on the posterior probability associated with an observed DLT.

**Table 8.1-1: Posterior Probability of DLT in Monotherapy Assuming Observed DLTs**

| Number of Subjects DLT Evaluable at a Dose Level | Number of Subjects with Observed DLT | Probability DLT Rate >33% | Probability DLT Rate >40% |
|---|---|---|---|
| 6 | 1 | 16% | 8% |
| | 2 | 41% | 25% |
| 9 | 2 | 20% | 9% |
| | 3 | 43% | 25% |
| 12 | 2 | 9% | 3% |
| | 3 | 23% | 10% |
| 13 | 3 | 19% | 7% |
| | 4 | 37% | 18% |

Assuming a 27% target DLT (± 2%) rate for the mTPI DLT target, a prior Beta distribution used is Beta(1,2. 7)

**Cohort Expansion (Part 2):**

**Initial Monotherapy Expansion:**

During this part of the study, the efficacy signal assessment will start with initial monotherapy cohorts. This assessment will be guided by a Fleming 2-stage design, to provide the option for early evaluation and planning based on an initial efficacy signal. The sample sizes for each cohort are calculated based on assumptions of true (target) and historic ORR for each tumor type. A 2-stage design provides criteria for the option to stop early for futility, and an understanding of an early signal of preliminary, strong antitumor activity. Approximately 5 to 9 subjects will be treated

in each of the cohorts, based on the Fleming (optimal) design criteria. Enrollment may continue after the initial 5 subjects to ensure that sufficient subjects are evaluable (eg, with tumor scans) or in case of early drop outs. In addition to futility, an efficacy boundary is shown (Table 8.1-2); however there will be no stopping due to an efficacy signal.

[redacted]

In summary, approximately up to 45 subjects are expected to be treated across the Initial monotherapy cohorts, with approximately 5 to 9 subjects per cohort (Table 8.1-2).

**Table 8.1-2: Characteristics for Initial Monotherapy Expansion Cohorts Signal assessment when guided by a Two-Stage Design**

| Tumor Cohort and Group | Target ORR % | SOC ORR % | Stage 1 / Total N | Stage 1 Res Futility/ Efficacy Boundary | Stage 2 Res Futility/ Efficacy Boundary | FPR/FNR (%) |
|---|---|---|---|---|---|---|
| **FUSION PROTEINS** | | | | | | |
| NMC | 50 | 10 | 5/9 | 0/2 | 2/3 | 10/10 |
| DHL | 50 | 10 | 5/9 | 0/2 | 2/3 | 10/10 |
| **BRD AMPLIFICATIONS** | | | | | | |
| TNBC | 50 | 10 | 5/9 | 0/2 | 2/3 | 10/10 |
| **MYC AMPLIFICATIONS** | | | | | | |
| Non-GC-DLBCL | 35 | 10 | 5/9 | 0/2 | 1/2 | 20/20 |
| **AR AMPLIFICATIONS** | | | | | | |
| CRPC | 35 | 10 | 5/9 | 0/2 | 1/2 | 20/20 |

Abbreviations: CRPC = castrate-resistant prostate cancer; DHL = double-hit lymphoma; FNR = false negative rate; FPR = false positive rate; N = number of subjects; NMC = NUT-midline carcinoma; ORR = objective response rate; RCC = renal cell carcinoma; Res = response; SOC = standard of care; TNBC = triple negative breast cancer; Non-GC-DLBCL = Non-germinal center diffuse large B-cell lymphoma;

Note: Tumor ORR assumptions will also be used when assessing a signal across tumors within a group,

### Subsequent Monotherapy Expansion

Based on totality of data obtained from the Initial Expansion, up to 126 subjects may be enrolled in the Subsequent Expansion cohorts with an expanded set of tumor types within and across groups (Table 8.1-3).

**Table 8.1-3: Characteristics for Subsequent Monotherapy Expansion Cohorts signal assessment when guided by a 2-stage design**

| Tumor Cohort and Group | Target ORR % | SOC ORR % | Stage 1 / Total N | Stage 1 Res Futility/ Efficacy Boundary | Stage 2 Res Futility/ Efficacy Boundary | FPR/FNR (%) |
|---|---|---|---|---|---|---|
| **FUSION PROTEINS** | | | | | | |
| DHL | 50 | 10 | 5/9 | 0/2 | 2/3 | 10/10 |
| NMC | 50 | 10 | 5/9 | 0/2 | 2/3 | 10/10 |
| ES | 35 | 10 | 5/9 | 0/2 | 1/2 | 20/20 |
| BL | 50 | 10 | 5/9 | 0/2 | 2/3 | 10/10 |
| **BRD AMPLIFICATIONS** | | | | | | |
| TNBC | 50 | 10 | 5/9 | 0/2 | 2/3 | 10/10 |
| OC w BRD amplifications | 50 | 10 | 5/9 | 0/2 | 2/3 | 10/10 |
| NEPC | 50 | 10 | 5/9 | 0/2 | 2/3 | 10/10 |
| **MYC AMPLIFICATIONS** | | | | | | |
| Non-GC-DLBCL | 35 | 10 | 5/9 | 0/2 | 1/2 | 20/20 |
| OC w MYC amplifications | 35 | 10 | 5/9 | 0/2 | 1/2 | 20/20 |
| UCS | 35 | 10 | 5/9 | 0/2 | 1/2 | 20/20 |
| **AR AMPLIFICATIONS** | | | | | | |
| CRPC | 35 | 10 | 5/9 | 0/2 | 1/2 | 20/20 |
| **MUTATIONS** | | | | | | |
| RCC | 35 | 10 | 5/9 | 0/2 | 1/2 | 20/20 |
| NSCLC | 35 | 10 | 5/9 | 0/2 | 1/2 | 20/20 |
| UM | 35 | 10 | 5/9 | 0/2 | 1/2 | 20/20 |

Abbreviations: BL = Burkitt's lymphoma; CRPC = castrate-resistant prostate cancer; DHL = double-hit lymphoma; ES = Ewing sarcoma; FNR = false negative rate; FPR = false positive rate; N = number of subjects; NEPC = neuroendocrine prostate cancer; NMC = NUT-midline carcinoma; NSCLC = non-small cell lung cancer; OC = ovarian cancer; ORR = objective response rate; RCC = renal cell carcinoma; Res = response; SOC = standard of care; TNBC = triple negative breast cancer; UCS = uterine carcinosarcoma; UM = uveal melanoma; Non-GC-DLBCL = Non-germinal center diffuse large B-cell lymphoma;

Note: Tumor ORR assumptions will also be used when assessing a signal across tumors within a group.

### Combination Therapy:

If the combination of BMS-986158 with nivolumab is pursued, the safety of combination treatment will be evaluated across the tumor types in the first 6 to 12 evaluable subjects who receive combination therapy based on the DLT observed. The mTPI-2 design with DLT target of 29% (-2%, +4%) will be used to guide decisions in this setting, including potential de-escalation to a lower dose of BMS-986158 in combination with nivolumab, if warranted by the observed results

(see Table 3.1.2.2-1). In addition, calculations related to the risk of selecting a BMS-986158 dose level as safe based on the observed DLTs are shown expressed as a posterior probability of toxicity in Section 3.1.2 (Table 3.1.2.2-2).

The sample sizes are based on the assumption that the selected dose level is deemed safe in combination therapy. If a lower dose level must be evaluated in combination therapy, an additional 6 to 12 subjects may be enrolled to assess safety of BMS-986158 prior to fully expanding in combination therapy.

**Table 8.1-4: Two-Stage Design Characteristics for Combination Therapy for Dose Expansion Cohorts**

| Tumor Cohort and Group | Target ORR % | SOC ORR % | Stage 1 / Total N | Stage 1 Res Futility/ Efficacy Boundary | Stage 2 Res Futility/ Efficacy Boundary | FPR/FNR (%) |
|---|---|---|---|---|---|---|
| **FUSION PROTEINS** | | | | | | |
| DHL | 50 | 10 | 5/9 | 0/2 | 2/3 | 10/10 |
| NMC | 50 | 10 | 5/9 | 0/2 | 2/3 | 10/10 |
| ES | 35 | 10 | 5/9 | 0/2 | 1/2 | 20/20 |
| BL | 50 | 10 | 5/9 | 0/2 | 2/3 | 10/10 |
| **BRD AMPLIFICATIONS** | | | | | | |
| TNBC | 50 | 10 | 5/9 | 0/2 | 2/3 | 10/10 |
| OC w BRD amplifications | 50 | 10 | 5/9 | 0/2 | 2/3 | 10/10 |
| NEPC | 50 | 10 | 5/9 | 0/2 | 2/3 | 10/10 |
| **MYC AMPLIFICATIONS** | | | | | | |
| Non-GC-DLBCL | 35 | 10 | 5/9 | 0/2 | 1/2 | 20/20 |
| OC w MYC amplifications | 35 | 10 | 5/9 | 0/2 | 1/2 | 20/20 |
| UCS | 35 | 10 | 5/9 | 0/2 | 1/2 | 20/20 |
| **AR AMPLIFICATIONS** | | | | | | |
| CRPC | 35 | 10 | 5/9 | 0/2 | 1/2 | 20/20 |
| **MUTATIONS** | | | | | | |
| RCC | 35 | 10 | 5/9 | 0/2 | 1/2 | 20/20 |
| NSCLC | 35 | 10 | 5/9 | 0/2 | 1/2 | 20/20 |
| UM | 35 | 10 | 5/9 | 0/2 | 1/2 | 20/20 |

Abbreviations: BL = Burkitt's lymphoma; CRPC = castrate-resistant prostate cancer; DHL = double-hit lymphoma; ES = Ewing sarcoma; FNR = false negative rate; FPR = false positive rate; N = number of subjects; NEPC = neuroendocrine prostate cancer; NMC = NUT-midline carcinoma; NSCLC = non-small cell lung cancer; OC = ovarian cancer; ORR = objective response rate; RCC = renal cell carcinoma; Res = response; SOC = standard of care; TNBC = triple negative breast cancer; UCS = uterine carcinosarcoma; UM = uveal melanoma; Non-GC-DLBCL = Non-germinal center diffuse large B-cell lymphoma;

Note: Tumor ORR assumptions will also be used when assessing a signal across tumors within a group,

Additionally, another 18 subjects may be enrolled in the expansion, in order to evaluate target gene engagement in tumors, and additional PK and safety characteristics in 1-2 cohorts at a second dose and schedule.

The potential total for expansion will be approximately up to 201 subjects if only monotherapy is pursued, and approximately up to 327 subjects if all planned expansion cohort subjects in monotherapy and combination therapy groups are pursued.

## 8.2 Populations for Analyses

- All Enrolled Subjects: All subjects who provide an ICF.
- All Treated Subjects: All subjects who receive at least one dose of study medication
- Pharmacokinetic Subjects: All subjects who receive at least one dose of BMS-986158 as monotherapy or in combination with nivolumab if the combination is pursued and who have available serum and plasma concentration data for the corresponding analyte

[redacted]

- Response Evaluable Population: All treated subjects who have baseline tumor measurement and at least one other tumor measurement after treatment, clinical progression, or death prior to the first on-treatment tumor assessment.

[redacted]

All subjects who receive study medication will be included in the safety data set.

## 8.3 Endpoints

### *8.3.1 Primary Endpoint(s)*

The primary objective (to assess the safety and tolerability and to define the DLTs and MTD of BMS-986158) will be measured by the primary endpoints of: Incidence of AEs at their worst grade, SAEs at their worst grade, AEs leading to discontinuations, deaths, and frequency of laboratory test toxicity grade shifting from baseline. Safety will be evaluated from the time that the subject signs the informed consent, and for up to 30 days and 100 days after the last dose of BMS-986158 monotherapy or BMS-986158 in combination with nivolumab, respectively, or until resolution of any AE for which alternative causes could not be identified resolve to ≤ Grade 1 or baseline or until the event has stabilized, whichever is longer.

### *8.3.2 Secondary Endpoint(s)*

The endpoint(s) used to measure efficacy, PK, and ECG objectives are described below:

#### *8.3.2.1 Efficacy*

The first secondary objective (efficacy) will be based on RECIST v1.1 for solid tumors (Appendix 4), Lugano 2014 criteria for hematologic malignancies (Appendix 9), or PCWG3

criteria for prostate cancer (CRPC or NEPC) (Appendix 12) using the following secondary endpoints:

- Best overall response (BOR): defined as the best response designation, recorded between the dates of first dose and the date of first objectively documented progression (per RECIST v1.1 for solid tumors, Lugano 2014 criteria for hematologic malignancies or PCWG3 for prostate cancer) or the date of subsequent therapy, whichever occurs first. CR or PR determinations included in the BOR for solid tumor assessments must be confirmed by a second scan performed no less than 4 weeks, and for hematologic malignancies, no less than 2 weeks after the criteria for response are first met. For subjects without documented progression or subsequent therapy, all available response designations will contribute to the BOR assessment. For subjects who continue treatment beyond progression or begin subsequent therapy, the BOR should be determined based on response designations recorded up to the time of the initial evaluation (RECIST v1.1 for solid tumors, Lugano 2014 criteria for hematologic malignancies or PCWG3 criteria for prostate cancer [CRPC or NEPC]) defined progression or subsequent therapy, whichever occurs first. For those subjects who have surgical resection, only pre-surgical tumor assessments will be considered in the determination of BOR. A BOR of SD requires a minimum of 49 days on study from date of first dose to the date of the first imaging assessment.
- ORR: defined as the total number of subjects whose BOR is either a CR or PR divided by the total number of subjects in the population of interest
- Duration of Response (DOR): defined for a subject with confirmed response as the time between the date of first response and the date of the first objectively documented disease progression (as determined by RECIST v1.1 for solid tumors, Lugano 2014 criteria for hematologic malignancies, or PCWG3 (including PSA assessments) for prostate cancer [CRPC or NEPC]), or death due to any cause, whichever occurs first. For those subjects who remain alive and have not progressed, duration of response will be censored on the date of last tumor assessment. Subjects who started subsequent therapy without a prior reported progression will be censored at the last tumor assessment prior to initiation of the subsequent anticancer therapy. Response duration will only be evaluated in subjects with a BOR of CR or PR.
- PFS: defined as the time from the first dose of study medication to the date of the first objective documentation of tumor progression or death due to any cause. Clinical deterioration in the absence of radiographic evidence is not considered progression for the purpose of determining PFS. Subjects who neither progressed nor died will be censored on the date of their last tumor assessment. Subjects who did not have any on-study tumor assessments will be censored on the date of the first dose of study medication. Subjects who started subsequent therapy without a prior reported progression will be censored at the last tumor assessment prior to initiation of the subsequent anticancer therapy.
- Progression Free Survival Rate (PFSR) at week 't': defined as the proportion of subjects who remain progression free and surviving at 't' weeks (t=12, 24). The proportion will be calculated by the product-limit method (Kaplan-Meier estimate) which takes into account censored data.

#### *8.3.2.2 Pharmacokinetics*

PK of BMS-986158 monotherapy and in combination with nivolumab (parent and metabolite, as data permits) will be derived from plasma concentration versus time.

The PK parameters to be assessed following single dose administration include:

| | |
|---|---|
| Cmax | Maximum observed plasma concentration |
| Tmax | Time of maximum observed plasma concentration |
| AUC(0-T) | Area under the plasma concentration-time curve from time zero to time of last quantifiable concentration |
| AUC(TAU) | Area under the concentration-time curve in one dosing interval |

If data permits, the following single dose PK parameters may also be assessed:

| | |
|---|---|
| T-HALF | Apparent terminal phase half-life |
| AUC(INF) | Area under the plasma concentration-time curve from time zero extrapolated to infinite time |
| CLT/F | Apparent total body clearance, reported only for parent, not for metabolite |
| Vz/F | Apparent volume of distribution of terminal phase, reported only for parent, not for metabolite |

The PK parameters to be assessed following multiple dose administration include:

| | |
|---|---|
| Cmax | Maximum observed plasma concentration |
| Tmax | Time of maximum observed plasma concentration |
| AUC(0-T) | Area under the plasma concentration-time curve from time zero to time of last quantifiable concentration |
| AUC(TAU) | Area under the concentration-time curve in one dosing interval |
| Cmin | The minimum observed concentration within a dosing interval |
| Ctau | Concentration at the end of a dosing interval |
| Ctrough | Trough observed plasma concentration (this includes predose concentrations (C0) and concentrations at the end of dosing interval (Ctau)); |

| | |
|---|---|
| AI | Accumulation Index; ratio of an exposure measure at steady-state 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 |

In addition, the following PK parameters may also be assessed after single and multiple dose administrations, if data permit:

| | |
|---|---|
| MR_Cmax | Ratio of metabolite Cmax to parent Cmax, corrected for molecular weight |
| MR_AUC(0-T) | Ratio of metabolite AUC(0-T) to parent AUC(0-T), corrected for molecular weight |
| MR_AUC(INF) | Ratio of metabolite AUC(INF) to parent AUC(INF), corrected for molecular weight (following single dose only) |
| MR_AUC(TAU) | Ratio of metabolite AUC(TAU) to parent AUC(TAU), corrected for molecular weight |

[redacted]

Individual subject pharmacokinetic parameter values will be derived by non-compartmental methods by a validated pharmacokinetic program. Actual times will be used for the analyses.

[redacted]

#### *8.3.2.4 ECG/QTc*

Changes in QTcF, ( $\Delta$ QTcF) from baseline, at selected times following monotherapy treatment with BMS-986158, and association measures of QTc changes with BMS-986158 PK exposure.

[redacted]

## 8.4 Analyses

### *8.4.1 Demographics and Baseline Characteristics*

A description of the participant population will be included in the statistical output reported, including subgroups of age, gender, and race. Prior cancer therapy (types and number) and other baseline characteristics will be tabulated for each tumor type.

### *8.4.2 Efficacy Analyses*

Efficacy results will be presented by tumor type, dose level, dosing schedule and/or regimen. Individual BOR, duration of response and PFS using RECIST v1.1 criteria (Appendix 4) for solid tumors, Lugano 2014 criteria for hematologic malignancies (Appendix 9), or PCWG3 (including PSA assessments) for prostate cancer (CRPC or NEPC Appendix 12) will be listed. BOR outcomes and ORR will be tabulated by dose / dose regimen and across doses for each tumor. For ORR, 95% confidence intervals (CIs) will be calculated based on the Clopper-Pearson method. The median DOR (mDOR) (for responders) and median PFS will be estimated by Kaplan-Meier (K-M) methodology. PFS rates (e.g. at 24 weeks) will be similarly estimated, based on K-M methodology, with confidence intervals based on the Greenwood formula and tabulated for each tumor. Individual changes in the tumor burden versus time will be presented graphically by dose

level/study arm/dose regimen within a tumor type. Depending on the purpose of the analysis efficacy may be reported for all treated subjects, or for response-evaluable subjects. Additional details will be presented in the Statistical Analysis Plan (SAP), as necessary.

[redacted]

### 8.4.3 Safety Analyses

All recorded AEs will be listed and tabulated by system organ class, preferred term and treatment. Vital signs and clinical laboratory test results will be listed and summarized by treatment. Any significant PE findings, and clinical laboratory results will be listed. ECG readings will be evaluated by the investigator and abnormalities, if present, will be listed. Safety data may also be presented in adolescent participants based on data availability.

### 8.4.4 Pharmacokinetic Analyses

PK parameters for BMS-986158 will be calculated using noncompartmental analysis. Summary statistics will be tabulated for the PK parameters by dose level, dose regimen, and study cycle/day, for each schedule. To describe the dependency on dose, scatter plots of Cmax and AUC(0-T), AUC(TAU) versus dose will be provided on indicated study cycle for each dose regimen. [redacted] Geometric means and coefficients of variation will be reported for Cmax, AUC, Cmin, Ctau, Ctrough, CLT/F, Vz/F, AI, T-HALFeff and MR; Medians and ranges will be reported for Tmax; means and SD will be reported for T-HALF. PK data may also be summarized separately for adolescent participants depending on data availability.

[redacted]

In addition, PK data obtained from this study may be used to perform population PK analysis and exposure response analysis for selected endpoints, as appropriate and as the data permits. These analyses will be described in a separate report.

### 8.4.5 ECG Analyses

For subjects with serial ECG measurements and time-matched PK following monotherapy treatment with BMS-986158, changes in the QTcF ( $\Delta$ QTcF), ECG intervals QRS, and PR, and in heart rate ( $\Delta$ HR) will be tabulated by treatment and study day. Frequency distributions of max QTcF values, max $\Delta$ QTcF, and of max HR in pre-specified categories will be tabulated by treatment. Scatter plots of heart rate, $\Delta$ HR, QTc, and $\Delta$ QTcF, vs time-matched BMS-986158 concentrations will be provided. A concentration-response effect of BMS-986158 on QTcF may be assessed by a linear mixed effects regression model for $\Delta$ QTcF on plasma and serum concentrations, stratified by study day, as well as pooled across days.

[redacted]

### *8.4.7 Outcomes Research Analyses*

Not applicable.

[redacted]

## 8.5 Interim Analyses

Because the exploratory nature of the early phase study, data emerging from each dose level, treatment arm, or each part of the study will be examined prior to the final lock of the study database for timely decisions such as dose level or dose schedule selection, early termination of the study or publications. Analyses will consist of listings, summaries, and graphs of the available data. In addition, modeling of PK (eg, exploration of exposure-response and simulations) or key

safety data may be utilized to inform dose or dose schedule selection, for subsequent parts of the study as data permits. No formal inferences requiring any adjustment to statistical significance level will be performed, or adjustment for multiplicity.

# 9 STUDY MANAGEMENT

## 9.1 Compliance

### *9.1.1 Compliance with the Protocol and Protocol Revisions*

The study shall be conducted as described in this approved protocol. All revisions to the protocol must be discussed with, and be prepared by, BMS. The investigator should not implement any deviation or change to the protocol without prior review and documented approval/favorable opinion from the IRB/IEC of an amendment, except where necessary to eliminate an immediate hazard(s) to study subjects.

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

- IRB/IEC for review and approval/favorable opinion
- BMS
- Regulatory Authority(ies), if required by local regulations

Documentation of approval signed by the chairperson or designee of the IRB(s)/IEC(s) must be sent to BMS.

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

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

### *9.1.2 Monitoring*

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

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

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

#### 9.1.2.1 Source Documentation

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

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

### 9.1.3 Investigational Site Training

Bristol-Myers Squibb will provide quality investigational staff training prior to study initiation. Training topics will include but are not limited to: GCP, AE reporting, study details and procedure, electronic CRFs, study documentation, informed consent, and enrollment of WOCBP.

## 9.2 Records

### 9.2.1 Records Retention

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

BMS will notify the investigator when the study records are no longer needed.

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

### 9.2.2 Study Drug Records

It is the responsibility of the investigator to ensure that a current disposition record of study drug (inventoried and dispensed) is maintained at the study site to include IP and non-investigational product(s). Records or logs must comply with applicable regulations and guidelines and should include:

- amount received and placed in storage area
- amount currently in storage area
- label identification number or batch number
- amount dispensed to and returned by each subject, including unique subject identifiers
- amount transferred to another area/site for dispensing or storage

- nonstudy disposition (eg, lost, wasted)
- amount destroyed at study site, if applicable
- amount returned to BMS
- retain samples for bioavailability/bioequivalence, if applicable
- dates and initials of person responsible for Investigational Product dispensing/accountability, as per the Delegation of Authority Form.

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

### *9.2.3 Case Report Forms*

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

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

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

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

The completed CRF, including any paper or electronic SAE/pregnancy CRFs, must be promptly reviewed, signed, and dated by the investigator or qualified physician who is a subinvestigator and who is delegated this task on the Delegation of Authority Form. For electronic CRFs, review and approval/signature is completed electronically through the BMS electronic data capture tool. The investigator must retain a copy of the CRFs including records of the changes and corrections.

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

## 9.3 Clinical Study Report and Publications

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

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

- Other criteria (as determined by the study team)

The data collected during this study are confidential and proprietary to BMS. Any publications or abstracts arising from this study require approval by BMS prior to publication or presentation and must adhere to BMS's publication requirements as set forth in the approved clinical trial agreement (CTA). All draft publications, including abstracts or detailed summaries of any proposed presentations, must be submitted to BMS at the earliest practicable time for review, but at any event not less than 30 days before submission or presentation unless otherwise set forth in the CTA. BMS shall have the right to delete any confidential or proprietary information contained in any proposed presentation or abstract and may delay publication for up to 60 days for purposes of filing a patent application.

# 10 GLOSSARY OF TERMS

| Term | Definition |
|---|---|
| Complete Abstinence | Complete abstinence as defined as complete avoidance of heterosexual intercourse is an acceptable form of contraception for all study drugs. This also means that abstinence is the preferred and usual lifestyle of the subject. This does not mean periodic abstinence (eg, calendar, ovulation, symptothermal, profession of abstinence for entry into a clinical trial, post-ovulation methods) and withdrawal, which are not acceptable methods of contraception. Women must continue to have pregnancy tests. Acceptable alternate methods of highly or less effective contraception must be discussed in the event that the subject chooses to forego complete abstinence. |
| [redacted] | |

# 11 LIST OF ABBREVIATIONS

| Term | Definition |
|---|---|
| 1L | first line |
| 2L | second line |
| [redacted] | |
| ACLS | advanced cardiac life support |
| [redacted] | |
| AE | adverse event |
| AI | accumulation index |
| ALT | alanine aminotransferase |
| AML | acute myeloid leukemia |
| ANC | absolute neutrophil count |
| aPTT | activated partial thromboplastin time |
| AR | androgen receptor |
| ARD | androgen receptor deprivation |
| ASCO | American Society for Clinical Oncology |
| AST | aspartate aminotransferase |
| AT | aminotransaminases |
| AUC | area under the concentration-time curve |
| AUC(0-T) | area under the concentration-time curve from time zero to the time of the last quantifiable concentration |
| AUC(INF) | area under the concentration-time curve from time zero extrapolated to infinite time |
| AUC(TAU) | area under the concentration-time curve in one dosing interval |
| BCRp | breast cancer resistant protein |
| BET | bromodomain and extra terminal |
| BID | twice a day |
| BL | Burkitt's lymphoma |
| BMS | Bristol-Myers Squibb |
| BOR | best overall response |
| BP | blood pressure |
| BRD | bromodomain |

| Term | Definition |
|---|---|
| BRD4 | bromodomain containing protein 4 |
| B-to-A | basolateral to apical |
| CAP | College of American Pathologists |
| CBC | complete blood count |
| CFR | Code of Federal Regulations |
| CI | confidence interval |
| CLT | total body clearance of drug from plasma |
| Cmax, CMAX | maximum observed concentration |
| CNS | central nervous system |
| CR | complete response |
| CRF | case report form |
| CrCl | creatinine clearance |
| CRPC | castration-resistant prostate cancer |
| CSR | Clinical Study Report |
| CT | computed tomography |
| CTA | clinical trial agreement |
| CTC | circulating tumor cells |
| CTCAE | Common Terminology Criteria for Adverse Events |
| [redacted] | |
| Ctrough, CTROUGH | trough observed concentration |
| CV | coefficient of variation |
| CYP | cytochrome p-450 |
| DDI | drug-drug interaction |
| DHL | double-hit lymphoma |
| DILI | drug induced liver injury |
| DLBCL | diffuse large B-cell lymphoma |
| DLT | dose limiting toxicity |
| DNA | deoxyribonucleic acid |
| DOR | duration of response |
| EC | Ethics Committee |

| Term | Definition |
|---|---|
| ECG | electrocardiogram |
| ECHO | echocardiogram |
| ECOG | Eastern Cooperative Oncology Group |
| eCRF | electronic case report form |
| EDC | electronic data capture |
| EOT | end of treatment |
| ES | Ewing sarcoma |
| ET | extra terminal |
| FDG-PET | fluorodeoxyglucose - positron emission tomography |
| FFPE | formalin fixed paraffin embedded |
| [redacted] | |
| FISH | fluorescence in situ hybridization |
| FSH | follicle stimulating hormone |
| GCP | Good Clinical Practice |
| [redacted] | |
| GI | gastrointestinal |
| GLP | Good Laboratory Practice |
| HCG | human chorionic gonadotropin |
| HCV | hepatitis C virus |
| HED | human equivalent dose |
| HIV | human immunodeficiency virus |
| HNSTD | highest non-severely toxic dose |
| HR | heart rate |
| HRT | hormone replacement therapy |
| HSCT | hematopioetic stem cell transplant |
| IB | Investigator's Brochure |
| ICF | Informed Consent Form |
| ICH | International Conference on Harmonisation |
| IEC | Independent Ethics Committee |
| IFNγ | interferon gamma |
| IgG | immunoglobulin G |

| Term | Definition |
|---|---|
| IHC | immunohistochemistry |
| IL | interleukin |
| INR | international normalized ratio |
| IP | investigational product |
| IRB | Institutional Review Board |
| IUD | intrauterine device |
| IV | intravenous |
| IVRS | interactive voice response system |
| K | slope of the terminal phase of the log concentration-time curve |
| LVEF | left ventricular ejection fraction |
| MLL | mixed lineage leukemia |
| MM | multiple myeloma |
| MOA | mechanism of action |
| MRI | magnetic resonance imaging |
| mRNA | messenger RNA |
| MRSD | maximum recommended starting dose |
| MSI-H | microsatellite instability-high |
| MTD | maximum tolerated dose |
| mTPI | modified toxicity probability interval. |
| MUGA | multiple gated acquisition scan |
| N/A | not applicable |
| NCCN | National Comprehensive Cancer Network |
| NEPC | neuroendocrine prostate cancer |
| NMC | NUT-midline carcinoma |
| NOAEL | no-observed adverse effect level |
| Non-GC-DLBCL | non-germinal center diffuse large B-cell lymphoma |
| NSAIDs | non-steroidal anti-inflammatory drugs |
| NSCLC | non-small cell lung cancer |
| NUT | nuclear protein in testis |

| Term | Definition |
|---|---|
| OC | ovarian cancer |
| ORR | objective response rate |
| OS | overall survival |
| PARP | poly ADP ribose polymerase |
| PBT | platinum based therapy |
| P-gp | P-glycoprotein |
| Pc | permeability coefficient |
| PC | prostate cancer |
| PCWG3 | Prostate Cancer Working Group 3 |
| PD | progressive disease |
| PD-1 | programmed cell death protein 1 |
| PD-L1 | programmed cell death-ligand 1 |
| PD-L2 | programmed cell death-ligand 2 |
| p-DILI | potential drug induced liver injury |
| PDX | patient-derived xenografts |
| PE | physical examination |
| PFS | progression free survival |
| PFSR | progression free survival rate |
| PID | patient identification number |
| PK | pharmacokinetic(s) |
| PPK | population pharmacokinetics |
| PR | partial response |
| [redacted] | |
| PSA | prostate specific antigen |
| PTT | partial thromboplastin time |
| Q2W | every 2 weeks |
| Q3W | every 3 weeks |
| Q4W | every 4 weeks |
| QD | once daily |
| RBC | red blood cell |

| Term | Definition |
|---|---|
| RCC | renal cell carcinoma |
| RD | refractory disease |
| RECIST | response evaluation criteria in solid tumors |
| RNA | ribonucleic acid |
| RP | radical prostatectomy |
| RP2D | recommended Phase 2 dose |
| RR | response rate |
| r/r | relapsed or refractory |
| SAE | serious adverse event |
| SAP | statistical analysis plan |
| SCLC | small cell lung cancer |
| SD | standard deviation |
| SNP | single nucleotide polymorphism |
| SOC | standard of care |
| TB | total bilirubin |
| TCGA | The Cancer Genome Atlas |
| [redacted] | |
| T-HALF | apparent elimination half-life |
| Tmax, TMAX | time of maximum observed concentration |
| TNBC | triple negative breast cancer |
| UCS | uterine carcinosarcoma |
| UGT | uridine diphosphate glucuronosyltransferase |
| ULN | upper limit of normal |
| UM | uveal melanoma |
| US | United States |
| [redacted] | |
| WOCBP | women of childbearing potential |

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# APPENDIX 1 DOSE ESCALATION ALGORITHM BASED ON MODIFIED TOXICITY PROBABILITY INTERVAL (MTPI) DESIGN

**Table 1:[a] mTPI Design[b] Decision Rule with up to 15 Subjects at a Dose**

| Number of subjects with DLT | Number of subjecs treated at current dose | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 | 11 | 12 | 13 | 14 | 15 |
| 0 | E | E | E | E | E | E | E | E | E | E | E | E | E | E | E |
| 1 | D | S | S | S | S | S | E | E | E | E | E | E | E | E | E |
| 2 | | DU | D | D | S | S | S | S | S | S | S | S | E | E | E |
| 3 | | | DU | DU | DU | D | S | S | S | S | S | S | S | S | S |
| 4 | | | | DU | DU | DU | DU | D | S | S | S | S | S | S | S |
| 5 | | | | | DU | DU | DU | DU | DU | DU | D | S | S | S | S |
| 6 | | | | | | DU | DU | DU | DU | DU | DU | DU | D | S | S |
| 7 | | | | | | | DU | DU | DU | DU | DU | DU | DU | DU | DU |
| 8 | | | | | | | | DU | DU | DU | DU | DU | DU | DU | DU |
| 9 | | | | | | | | | DU | DU | DU | DU | DU | DU | DU |
| 10 | | | | | | | | | | DU | DU | DU | DU | DU | DU |
| 11 | | | | | | | | | | | DU | DU | DU | DU | DU |
| 12 | | | | | | | | | | | | DU | DU | DU | DU |
| 13 | | | | | | | | | | | | | DU | DU | DU |
| 14 | | | | | | | | | | | | | | DU | DU |
| 15 | | | | | | | | | | | | | | | DU |

[a] **E** = Escalate to next higher dose, S = Stay at the current dose, **D** = De-escalate to the next lower dose, **U** = The current dose is unacceptably toxic

[b] Target DLT at MTD = 27% (+/-2%), flexible cohort size

# APPENDIX 2 SIMULATION OF MTPI VS 3 + 3 DOSE ESCALATION DESIGNS WITH 6 DOSE LEVELS

Simulations of mTPI and 3+3 designs, shown below, demonstrate that the mTPI design has a greater chance of selecting the correct MTD than the 3+3 design, and treating fewer subjects at sub-optimal doses.

The mTPI uses a set of decision rules guided by simple Bayesian models and requires a clinically relevant pre-determined target DLT rate and an equivalence interval (EI), within which any dose is considered close to the true maximum tolerated dose (MTD). For this study, the selected target toxicity (DLT) rate is 27% and EI [25%, 29%].

The mTPI design makes decisions using the same two observed numbers as the traditional 3+3 design, the number of DLT evaluable subjects and the number of subjects with DLT. Based on these two numbers, unit probability mass is calculated within each of three regions as stated above, and decision is based on which region has the largest unit probability mass:

- E: escalating to the higher dose if interval (0, 25%) has the largest unit probability mass,
- S: staying at the same dose if interval [25, 29%] has the largest unit probability mass,
- D: de-escalating to the lower dose if interval (29, 100%) has the largest unit probability mass.

At the end of the trial, MTD will be picked, by isotonic regression estimation method, to be the dose whose estimated toxicity rate is closest to the target toxicity rate among all the tried doses.

Simulations were performed to examine the operating characteristics of mTPI and 3 + 3 designs for this study. Escalation decisions based on the mTPI are shown in the protocol. Decisions based on the 3+3 design are shown below:

- E: no subject with DLT out of 3 DLT evaluable subjects initially, or at most 1 subject with DLT out of 6 DLT evaluable subjects after adding 3 more subjects.
- S: 1 subject with DLT out of 3 DLT evaluable subjects initially.
- D: at least 2 subjects with DLT out of 3 DLT evaluable subjects initially, or at least 2 subjects with DLT out of 6 DLT evaluable subjects after adding 3 more subjects at this dose

**Settings for simulation:**

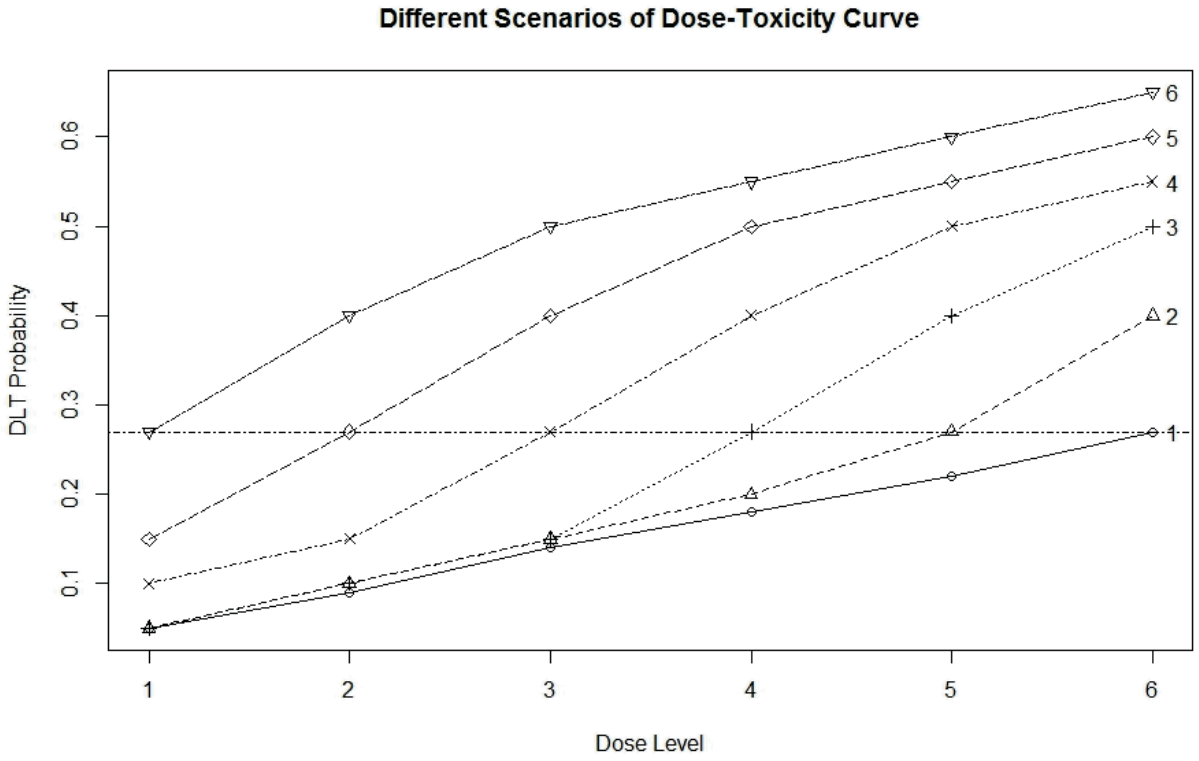
- 6 dose-toxicity scenarios, each of which with a number of 6 (expected) dose levels
- 1000 trials per scenario
- Target toxicity (Pt) for mTPI design: 27% with Equivalence Interval (EI) = [25, 29%]
- mTPI: Cohort sizes of 3-4 at all dose levels, requiring a min of 3 per cohort for escalation decisions. Therefore 4 subjects per cohort and 25% dropout rate were used in simulations.
- Stopping rule for mTPI: When there are already 13 DLT evaluable subjects treated at a dose level, and mTPI suggested decision is to treat more subjects at this dose level, dose escalation can be stopped.

- Maximum number of DLT evaluable subjects for the study is 30.
- A nominal dose level of -1 is added in the tables to account for the case when de-escalation decision is made from dose level 1. However, the dose level -1 is not used in the simulations.

**Dose-Toxicity Curve Scenarios**

Six (6) scenarios of dose-toxicity (DLT) curves are selected to cover various possibilities and presented in the following figure with scenario ID shown at the end of line. The target toxicity rate of 0.27 is also superposed in the figure as a horizontal dashed line. The exact numeric values of DLT probability are available in each of the simulation results.

**Figure -1: Dose-Toxicity Probability Scenarios**




**Simulation Results**

Simulation results are summarized from all the simulated trials per scenario, and include the following statistics:

- MTD Selected: Frequency of each dose level being selected as MTD.
- Subjects Allocated: Number of subjected being allocated to each dose level.
- DLT rate: The average number of subjects who have DLT across all dose levels.
- Average Sample Size: The average number of subjects across all dose levels.

- Early Stop Prob: mTPI only. The frequency of triggering the mTPI stopping rule during the trial.

| Scenario 1 | | Dose Level | | | | | | | DLT Rate | Average Sample Size | Early Stop Prob. |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | -1 | 1 | 2 | 3 | 4 | 5 | **6** | | | |
| True DLT rate | | | 0.05 | 0.09 | 0.14 | 0.18 | 0.22 | **0.27** | | | |
| MTD Selected (%) | 3+3 | 3 | 7 | 16 | 18 | 19 | 16 | **21** | 15.3 | | |
| | mTPI | 1 | 2 | 12 | 23 | 26 | 22 | **15** | 12.3 | | 16 |
| Subjects Allocated (n) | 3+3 | | 3.6 | 4.0 | 4.0 | 3.5 | 2.8 | **1.7** | | 19.7 | |
| | mTPI | | 5.0 | 5.8 | 5.5 | 3.5 | 1.6 | **0.4** | | 21.8 | |
| Note: The true MTD is dose level 6, the highest dose level, and all dose levels can be considered to be tolerated. In this case, mTPI has a somewhat lower chance of picking the highest dose level (15% vs. 21% for 3+3) but greater chance of picking doses closer to the top dose, compared to the 3+3 and lower chance (15% vs. 26% for 3+3) of picking the 2 lowest doses or dose level -1. | | | | | | | | | | | |

| Scenario 2 | | Dose Level | | | | | | | DLT Rate | Average Sample Size | Early Stop Prob. |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | -1 | 1 | 2 | 3 | 4 | **5** | 6 | | | |
| True DLT rate | | | 0.05 | 0.10 | 0.15 | 0.20 | **0.27** | 0.40 | | | |
| MTD Selected (%) | 3+3 | 3 | 9 | 17 | 23 | 22 | **18** | 9 | 17.1 | | |
| | mTPI | 1 | 2 | 13 | 27 | 27 | **19** | 12 | 13.6 | | 18 |
| Subjects Allocated (n) | 3+3 | | 3.6 | 4.0 | 4.0 | 3.5 | **2.8** | 1.7 | | 19.1 | |
| | mTPI | | 4.8 | 6.1 | 5.7 | 3.6 | **1.3** | 0.3 | | 21.8 | |
| Note: The true MTD is dose level 5, the second highest dose level, and there is one over-toxic dose. In this scenario. mTPI picks the correct MTD about as often as the 3+3 , and it picks the 2 lowest doses or dose level -1 less often (29% vs. 16% for the 3+3). The top dose level is selected 3% more frequently by mTPI compared to 3+3. | | | | | | | | | | | |

| Scenario 3 | | Dose Level | | | | | | | DLT Rate | Average Sample Size | Early Stop Prob. |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | -1 | 1 | 2 | 3 | **4** | 5 | 6 | | | |
| True DLT rate | | | 0.05 | 0.10 | 0.15 | **0.27** | 0.40 | 0.50 | | | |
| MTD Selected (%) | 3+3 | 2 | 9 | 15 | 35 | **27** | 9 | 2 | 18.4 | | |
| | mTPI | 2 | 1 | 11 | 34 | **35** | 14 | 4 | 15.2 | | 16 |
| Subjects Allocated (n) | 3+3 | | 3.6 | 4.0 | 4.3 | **3.8** | 2.0 | 0.6 | | 18.4 | |
| | mTPI | | 4.7 | 6.1 | 6.3 | **3.8** | 0.8 | 0 | | 21.7 | |
| Note: The true MTD is dose level 4, and as such, there are three sub-optimal dose levels and two over toxic dose levels. mTPI chooses the correct MTD with 35% rate, vs. 27% for 3+3. Selection of over-toxic dose levels is more frequent by mTPI, (18% chance vs. 11% for 3+3), while selection of the 2 lowest doses or dose level -1 is less likely for mTPI (14% vs. 26% for 3+3). | | | | | | | | | | | |

| Scenario 4 | | Dose Level | | | | | | | DLT Rate | Average Sample Size | Early Stop Prob. |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | -1 | 1 | 2 | 3 | 4 | **5** | 6 | | | |
| True DLT rate | | | 0.10 | 0.15 | **0.27** | 0.40 | 0.50 | 0.55 | | | |
| MTD Selected (%) | 3+3 | 10 | 20 | 32 | **28** | 9 | 1 | 0 | 23.5 | | |
| | mTPI | 4 | 7 | 31 | **40** | 14 | 4 | 0 | 20.3 | | 31 |
| Subjects Allocated (n) | 3+3 | | 4.2 | 4.4 | **3.7** | 2.1 | 0.6 | 0.1 | | 15.1 | |
| | mTPI | | 5.9 | 7.1 | **5.6** | 1.6 | 0.2 | 0 | | 20.3 | |
| Note: The true MTD is dose level 3. Under this scenario, there are two sub-optimal doses and three over-toxic dose levels. mTPI picks the correct MTD 12% more often than 3+3 does, and picks doses higher than the MTD 8% more often. Selection of sub-optimal dose levels (lower than MTD or level -1) by mTPI is 20% less frequent (42% vs. 62% for 3+3). | | | | | | | | | | | |

| Scenario 5 | | Dose Level | | | | | | | DLT Rate | Average Sample Size | Early Stop Prob. |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | -1 | 1 | **2** | 3 | 4 | **5** | 6 | | | |
| True DLT rate | | | 0.15 | **0.27** | 0.40 | 0.50 | 0.55 | 0.60 | | | |
| MTD Selected (%) | 3+3 | 23 | 37 | **29** | 10 | 2 | 0 | 0 | 29.0 | | |
| | mTPI | 9 | 26 | **47** | 15 | 3 | 1 | 0 | 26.8 | | 52 |
| Subjects Allocated (n) | 3+3 | | 4.9 | **4.1** | 2.2 | 0.6 | 0.1 | 0 | | 12.0 | |
| | mTPI | | 7.9 | **7.7** | 2.5 | 0.3 | 0 | 0 | | 18.4 | |
| Note: The true MTD is dose level 2, the second lowest dose level. In this case of one sub-optimal dose level and four over-toxic dose levels mTPI picks the correct MTD almost 20% more often (47% vs. 29% for 3+3). Selection of sub-optimal doses by the mTPI is much less frequent (35% vs. 60% by the 3+3) while over-toxic dose selection is 7% more likely for mTPI than by 3+3. | | | | | | | | | | | |

| Scenario 6 | | Dose Level | | | | | | | DLT Rate | Average Sample Size | Early Stop Prob. |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | -1 | **1** | 2 | 3 | 4 | **5** | 6 | | | |
| True DLT rate | | | **0.27** | 0.40 | 0.50 | 0.55 | 0.60 | 0.65 | | | |
| MTD Selected (%) | 3+3 | 51 | **36** | 11 | 1 | 0 | 0 | 0 | 40 | | |
| | mTPI | 30 | **48** | 19 | 2 | 1 | 0 | 0 | 38.7 | | 54 |
| Subjects Allocated (n) | 3+3 | | **5.2** | 2.7 | 0.7 | 0.1 | 0 | 0 | | 8.7 | |
| | mTPI | | **9.3** | 4.0 | 0.5 | 0 | 0 | 0 | | 13.8 | |
| Note: The true MTD is dose level 1, the lowest dose, which represents an unlikely case when only the lowest dose level is considered to be tolerated. mTPI selects the correct MTD more often (48% vs. 36% for the 3+3). mTPI picks no dose (dose level -1) at a much lower rate (30% vs. 51% for 3+3), but also chooses high dose levels more frequently (22% vs. 12% for 3+3). | | | | | | | | | | | |

## APPENDIX 3 CYP3A4 GUIDANCE

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

http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/DrugInteractionsLabeling/ ucm080499.htm.

**Table 1: Classification of In Vivo Inhibitors of CYP Enzymes**

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

Please note that this is not an exhaustive list.

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

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

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

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

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

[f] Herbal product.

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

**Table 2: Classification of In Vivo Inducers of CYP Enzymes**

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

Please note that this is not an exhaustive list.

[a] Not a marketed drug.

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

[c] Herbal product.

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

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

| CYP Enzymes | Sensitive Substrates[a] | Substrates with Narrow Therapeutic Range[b] |
|---|---|---|
| CYP3A(6) | Alfentanil, aprepitant, budesonide, buspirone, conivaptan, darifenacin, darunavir, dasatinib, dronedarone, eletriptan, eplerenone, everolimus, felodipine, indinavir, fluticasone, lopinavir, lovastatin, lurasidone, maraviroc, midazolam, nisoldipine, quetiapine, saquinavir, sildenafil, simvastatin, sirolimus, tolvaptan, tipranavir, triazolam, vardenafil | Alfentanil, astemizole,[c] cisapride,[c] cyclosporine, dihydroergotamine, ergotamine, fentanyl, pimozide, quinidine, sirolimus, tacrolimus, terfenadine[c] |

Please note that this is not an exhaustive list.

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

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

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

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

# APPENDIX 4 RESPONSE EVALUATION CRITERIA IN SOLID TUMORS GUIDELINES (VERSION 1.1) [redacted]

## 1 EVALUATION OF LESIONS

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

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

### 1.1 Measurable

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

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

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

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

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

### 1.2 Non-Measurable

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

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

## 1.3 Special considerations regarding lesion measurability

### *1.3.1 Bone lesions*

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

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

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

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

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

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

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

# 2 RESPONSE CRITERIA

## 2.1 Evaluation of Target Lesions

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

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

### *2.1.1 Special Notes on the Assessment of Target Lesions*

#### *2.1.1.1 Lymph nodes*

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

#### *2.1.1.2 Target lesions that become 'too small to measure'*

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

or progressions based upon measurement error. To reiterate, however, if the radiologist is able to provide an actual measure, that should be recorded, even if it is below 5 mm.

#### *2.1.1.3 Lesions that split or coalesce on treatment*

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

### 2.2 Evaluation of Non-Target Lesions

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

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

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

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

#### *2.2.1.1 When the patient also has measurable disease*

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

#### *2.2.1.2 When the patient has only non-measurable disease*

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

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

### *2.2.2 New Lesions*

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

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

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

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

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

## 2.3 Response Assessment

### *2.3.1 Evaluation of Best Overall Response*

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

### *2.3.2 Time Point Response*

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

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

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

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

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

| Non-Target Lesions | New Lesions | Overall Response |
|---|---|---|
| CR | No | CR |
| Non-CR/non-PD | No | Non-CR/non-PD[a] |
| Not all evaluated | No | NE |

| Table 2.3.2-2: Time Point Response: Patients with Non-target Disease Only | | |
|---|---|---|
| **Non-Target Lesions** | **New Lesions** | **Overall Response** |
| Unequivocal PD | Yes or No | PD |
| Any | Yes | PD |
| CR = complete response, PD = progressive disease and NE = inevaluable | | |

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

### *2.3.3 Best Overall Response*

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

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

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

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

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

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

### *2.3.4 Confirmation Scans*

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

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

REFERENCES

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

# APPENDIX 5 ECOG PERFORMANCE STATUS

| ECOG PERFORMANCE STATUS[1] | |
|---|---|
| **Grade** | **ECOG** |
| 0 | Fully active, able to carry on all predisease performance without restriction. |
| 1 | Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light house work, office work. |
| 2 | Ambulatory and capable of all self-care but unable to carry out any work activities. Up and about more than 50% of waking hours. |
| 3 | Capable of only limited selfcare, confined to bed or chair more than 50% of waking hours. |
| 4 | Completely disabled. Cannot carry on any selfcare. Totally confined to bed or chair. |
| 5 | Dead |

[1] Oken MM, Creech RH, Tormey DC, Horton J, Davis TE, McFadden ET, and Carbone PP. Toxicity and Response Criteria of the Eastern Cooperative Oncology Group. Am J Clin Oncol 1982;5:649-655.

## APPENDIX 6 NYHA CLASSIFICATION

**NYHA Classification**

| | |
|---|---|
| **Class I** | Subjects with no limitation of physical activity; ordinary physical activity does not cause undue fatigue, palpitation, or dyspnea (shortness of breath). |
| **Class II** | Subjects with slight limitation of physical activity; they are comfortable at rest, but ordinary physical activity results in fatigue, palpitation, or dyspnea. |
| **Class III** | Subjects with marked limitation of physical activity; they are comfortable at rest, but less than ordinary activity causes fatigue, palpitation, or dyspnea. |
| **Class IV** | Subjects who are unable to carry out any physical activity without discomfort; they have symptoms of cardiac insufficiency at rest; if any physical activity is undertaken, discomfort is increased. |

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

# APPENDIX 8 SIMULATION OF MTPI-2 VS 3+3 DOSE ESCALATION DESIGNS WITH 2 DOSE LEVELS

Simulations of mTPI-2 and 3+3 designs, shown below, demonstrate that the mTPI-2 design has a greater chance of selecting the correct MTD than the 3+3 design, and of treating fewer subjects at sub-optimal doses.

The mTPI-2 design, similarly to the mTPI, uses a pre-determined relevant target toxicity (DLT) rate (Pt) and an equivalence interval (EI) defined as [Pt-e1, Pt+e2], within which any dose level is considered close to the true maximum tolerated dose (MTD). It recommends decisions to either Stay (S) at the current dose, Escalate (E), or de-escalate (D), guided by simple Bayesian probability models. These decisions are related to the unit probability mass (UMP) under the posterior probability distribution of a DLT rate in the intervals [0,Pt-e1), [Pt-e1, Pt+e2], and (Pt+e2,1] of the [0,1] sample space corresponding to decisions of E, S, and D (or DU), respectively.

As an escalation decision is not of interest in the combination dose safety evaluation of this study, a design recommendation to escalate will be used as an indication to Expand more broadly at this dose level, (as this dose level is deemed safe to escalate). Therefore the symbol E will be used to indicate a decision to Expand in this setting. In contrast the decision S (Stay) indicates that this dose level needs to be evaluated further for safety before treating at this dose level in all expansion cohorts. For the BMS-986158 combination with nivolumab treatment, the target DLT rate was set to 29%, and the EI is: [27%, 33%], based on known toxicity of nivolumab and adverse events rate of BMS-986158 to date.

The mTPI-2 design, similarly to the 3+3 design, provides a decision guide using the number of DLT-evaluable subjects and the number of subjects with a DLT observed at each dose level.

The mTPI-2 design framework mitigates some suboptimal decisions and makes more efficient dose finding as compared to the original mTPI. This is achieved by subdividing each of the three decision intervals into equal length subintervals of length e1+e2 and calculating UMP for each of the subintervals within each interval. The decision will be based on the interval in which any of these subintervals has the largest UMP, under the posterior probability density, given the observed DLT data, as follows:

- E: Expanding at this dose (Escalate if relevant) if any sub-interval within (0, 27%) has the largest unit probability mass
- S: staying at the same dose if any subinterval within [27%, 33%] has the largest unit probability mass,
- D: de-escalating to the lower dose if any subinterval within (33%, 100%) has the largest unit probability mass.

At the end of the trial, MTD will be picked by isotonic regression estimation method to be the dose level whose estimated toxicity rate is closest to the target toxicity rate among all the evaluated dose levels.

Simulations were performed to examine the operating characteristics of mTPI-2 and 3+3 designs for this study. Escalation decisions based on the mTPI2 are shown in the protocol. Decisions based on the 3+3 design are shown below:

- E: no subject with DLT out of 3 DLT evaluable subjects initially, or at most 1 subject with DLT out of 6 DLT evaluable subjects after adding 3 more subjects.
- S: 1 subject with DLT out of 3 DLT evaluable subjects initially.
- D: at least 2 subjects with DLT out of 3 DLT evaluable subjects initially, or at least 2 subjects with DLT out of 6 DLT evaluable subjects after adding 3 more subjects at this dose

**Settings for simulation:**

- 6 dose-toxicity scenarios, each of which with a number of 2 (expected) dose levels
- 1000 trials per scenario
- Target toxicity (Pt) for mTPI-2 design: 29% with Equivalence Interval (EI) = [27, 33%]
- The mTPI-2: initial cohort size of 3 (or 4) followed by cohort size of 3 (or 4) for the remaining cohorts at the same (or lower if needed) dose level, requiring a minimum of 3 for a dose decision; Therefore cohorts of size 4 and a 25% dropout rate were used in the simulations.
- Stopping rule for mTPI-2: When there are already 12 DLT evaluable subjects treated at a dose level, and mTPI-2 suggested decision is to treat more subjects at this dose level, dose escalation can be stopped.
- Maximum number of DLT evaluable subjects for the study is 12.
- A nominal dose level of -1 is added in the tables to account for the case when de-escalation decision is made from dose level 1. However, the dose level -1 is not used in the simulations.
- A Beta(1,2) prior probability distribution is used which corresponds to a 33% expected DLT rate assumed for the combination of nivolumab with BMS-986158.

**Dose-Toxicity Curve Scenarios**

Six (6) scenarios of dose-toxicity (DLT) curves are selected to cover various possibilities and presented in the following figure with scenario ID shown at the end of line.

| Scenario | DLT Rate at Dose Level 1 | DLT Rate at Dose Level 2* |
|---|---|---|
| 1 | 0.15 | 0.25 |
| 2 | 0.20 | 0.27 |
| 3 | 0.15 | 0.30 |
| 4 | 0.25 | 0.35 |
| 5 | 0.30 | 0.35 |

| | | |
|---|---|---|
| 6 | 0.35 | 0.45 |

*Starting dose level

**Simulation Results**

Simulation results are summarized from all the simulated trials per scenario, and include the following statistics:

- MTD Selected: Frequency of each dose level being selected as MTD.
- Subjects Allocated: Number of subjected being allocated to each dose level.
- DLT rate: The average number of subjects who have DLT across all dose levels.
- Average Sample Size: The average number of subjects across all dose levels.
- Early Stop Prob: mTPI-2 only. The frequency that mTPI-2 stopping rule was triggered during the trial.

| Scenario 1 | | Dose Level | | | DLT Rate | Average Sample Size | Early Stop Prob. |
|---|---|---|---|---|---|---|---|
| True DLT Rate | | -1 | 1 / 15% | 2 / 25% | | | |
| MTD Selected (%) | 3+3 | 20% | 31% | 49% | | | |
| | mTPI-2 | 9.5% | 36% | 54% | | | |
| Subjects Allocated (n) | 3+3 | | 4.7 | 3.5 | | 8.2 | |
| | mTPI-2 | | 4.1 | 4.4 | | 8.5 | |
| Note: The mTPI-2 selects the MTD more frequently than does the 3+3, and the 3+3 selects no dose 10.5% more frequently than does the mTPI-2. | | | | | | | |

| Scenario 2 | | Dose Level | | | DLT Rate | Average Sample Size | Early Stop Prob. |
|---|---|---|---|---|---|---|---|
| True DLT Rate | | -1 | 1 / 20% | 2 / 27% | | | |
| MTD Selected (%) | 3+3 | 32% | 28% | 41% | | | |
| | mTPI-2 | 17% | 43% | 40% | | | |
| Subjects Allocated (n) | 3+3 | | 4.8 | 3.0 | | 7.8 | |
| | mTPI-2 | | 4.2 | 3.9 | | 8.1 | |
| Note: The correct MTD is selected about as often by both designs but the 3+3 selects no dose as the MTD 15% more frequently than does the mTPI-2. | | | | | | | |

| Scenario 3 | | Dose Level | | | DLT Rate | Average Sample Size | Early Stop Prob. |
|---|---|---|---|---|---|---|---|
| True DLT Rate | | -1 | 1 / 15% | 2 / 30% | | | |
| MTD Selected (%) | 3+3 | 22% | 36% | 42% | | | |
| | mTPI-2 | 11% | 46% | 43% | | | |
| Subjects Allocated (n) | 3+3 | | 4.9 | 3.5 | | 8.3 | |
| | mTPI-2 | | 4.2 | 4.3 | | 8.5 | |
| Note: The correct MTD is selected as often by both designs, but the 3+3 selects no dose (-1) twice as frequently (22% vs. 11%) than does the mTPI-2. | | | | | | | |

| Scenario 4 | | Dose Level | | | DLT Rate | Average Sample Size | Early Stop Prob. |
|---|---|---|---|---|---|---|---|
| True DLT Rate | | -1 | 1 / 25% | 2 / 35% | | | |
| MTD Selected (%) | 3+3 | 42% | 33% | 25% | | | |
| | mTPI-2 | 24% | 51% | 25% | | | |
| Subjects Allocated (n) | 3+3 | | 5.0 | 2.7 | | 7.7 | |
| | mTPI-2 | | 4.4 | 3.5 | | 7.9 | |
| Notes: The higher dose is selected 25% of the times by both designs, the mTPI-2 selects the correct MTD 18% more often than does the 3+3. The 3+3 selects no dose more frequently (18% more) than does the mTPI-2. | | | | | | | |

| Scenario 5 | | Dose Level | | | DLT Rate | Average Sample Size | Early Stop Prob. |
|---|---|---|---|---|---|---|---|
| True DLT Rate | | -1 | 1 / 30% | 2 / 35% | | | |
| MTD Selected (%) | 3+3 | 54% | 25% | 21% | | | |
| | mTPI-2 | 30% | 49% | 22% | | | |
| Subjects Allocated (n) | 3+3 | | 5.0 | 2.2 | | 7.2 | |
| | mTPI-2 | | 4.3 | 3.4 | | 7.7 | |
| Notes: The mTPI-2 design selects the correct dose as the MTD almost twice as often as the 3+3 (24% more frequently) and the 3+3 selects no dose 24% more frequently than does the mTPI-2. | | | | | | | |

| Scenario 6 | | Dose Level | | | DLT Rate | Average Sample Size | Early Stop Prob. |
|---|---|---|---|---|---|---|---|
| True DLT Rate | | -1 | 1 / 35% | 2 / 45% | | | |
| MTD Selected (%) | 3+3 | 69% | 22% | 8.2% | | | |
| | mTPI-2 | 44% | 46% | 11% | | | |
| Subjects Allocated (n) | 3+3 | | 4.9 | 1.6 | | 6.5 | |
| | mTPI-2 | | 4.4 | 2.6 | | 7.0 | |
| Notes: The mTPI-2 design selects the dose with 35% toxicity more than twice as often as the 3+3 (24% more frequently) and selects the top toxic dose 3% more often than the 3+3. The 3+3 selects no dose 25% more frequently than does the mTPI-2. | | | | | | | |

# APPENDIX 9 LUGANO 2014 CLASSIFICATION FOR INITIAL EVALUATION, STAGING, AND RESPONSE FOR HODGKIN LYMPHOMA

## Table 1: Revised Criteria for Response Assessment

| Response and Site | PET-CT–Based Response | CT-Based Response |
|---|---|---|
| Complete | Complete metabolic response | Complete radiologic response (all of the following) |
| Lymph nodes and extralymphatic sites | Score 1, 2, or 3* with or without a residual mass on 5PS† | Target nodes/nodal masses must regress to ≤ 1.5 cm in LDi |
| | It is recognized that in Waldeyer's ring or extranodal sites with high physiologic uptake or with activation within spleen or marrow (eg, with chemotherapy or myeloid colony-stimulating factors), uptake may be greater than normal mediastinum and/or liver. In this circumstance, complete metabolic response may be inferred if uptake at sites of initial involvement is no greater than surrounding normal tissue even if the tissue has high physiologic uptake | No extralymphatic sites of disease |
| Nonmeasured lesion | Not applicable | Absent |
| Organ enlargement | Not applicable | Regress to normal |
| New lesions | None | None |
| Bone marrow | No evidence of FDG-avid disease in marrow | Normal by morphology; if indeterminate, IHC negative |
| Partial | Partial metabolic response | Partial remission (all of the following) |
| Lymph nodes and extralymphatic sites | Score 4 or 5† with reduced uptake compared with baseline and residual mass(es) of any size | ≥ 50% decrease in SPD of up to 6 target measurable nodes and extranodal sites |
| | At interim, these findings suggest responding disease | When a lesion is too small to measure on CT, assign 5 mm × 5 mm as the default value |
| | At end of treatment, these findings indicate residual disease | When no longer visible, 0 × 0 mm |
| | | For a node > 5 mm × 5 mm, but smaller than normal, use actual measurement for calculation |
| Nonmeasured lesions | Not applicable | Absent/normal, regressed, but no increase |
| Organ enlargement | Not applicable | Spleen must have regressed by > 50% in length beyond normal |
| New lesions | None | None |
| Bone marrow | Residual uptake higher than uptake in normal marrow but reduced compared with baseline (diffuse uptake compatible with reactive changes from chemotherapy allowed). If there are persistent focal changes in the marrow in the context of a nodal response, consideration should be given to further evaluation with MRI or biopsy or an interval scan | Not applicable |
| No response or stable disease | No metabolic response | Stable disease |
| Target nodes/nodal masses, extranodal lesions | Score 4 or 5 with no significant change in FDG uptake from baseline at interim or end of treatment | < 50% decrease from baseline in SPD of up to 6 dominant, measurable nodes and extranodal sites; no criteria for progressive disease are met |
| Nonmeasured lesions | Not applicable | No increase consistent with progression |
| Organ enlargement | Not applicable | No increase consistent with progression |
| New lesions | None | None |
| Bone marrow | No change from baseline | Not applicable |
| Progressive disease | Progressive metabolic disease | Progressive disease requires at least 1 of the following |
| Individual target nodes/nodal masses | Score 4 or 5 with an increase in intensity of uptake from baseline and/or | PPD progression: |
| Extranodal lesions | New FDG-avid foci consistent with lymphoma at interim or end-of-treatment assessment | An individual node/lesion must be abnormal with:<br>LDi > 1.5 cm and<br>Increase by ≥ 50% from PPD nadir and<br>An increase in LDi or SDi from nadir<br>0.5 cm for lesions ≤ 2 cm<br>1.0 cm for lesions > 2 cm<br>In the setting of splenomegaly, the splenic length must increase by > 50% of the extent of its prior increase beyond baseline (eg, a 15-cm spleen must increase to > 16 cm). If no prior splenomegaly, must increase by at least 2 cm from baseline<br>New or recurrent splenomegaly |
| Nonmeasured lesions | None | New or clear progression of preexisting nonmeasured lesions |
| New lesions | New FDG-avid foci consistent with lymphoma rather than another etiology (eg, infection, inflammation). If uncertain regarding etiology of new lesions, biopsy or interval scan may be considered | Regrowth of previously resolved lesions<br>A new node > 1.5 cm in any axis<br>A new extranodal site > 1.0 cm in any axis; if < 1.0 cm in any axis, its presence must be unequivocal and must be attributable to lymphoma<br>Assessable disease of any size unequivocally attributable to lymphoma |
| Bone marrow | New or recurrent FDG-avid foci | New or recurrent involvement |

Abbreviations: 5PS, 5-point scale; CT, computed tomography; FDG, fluorodeoxyglucose; IHC, immunohistochemistry; LDi, longest transverse diameter of a lesion; MRI, magnetic resonance imaging; PET, positron emission tomography; PPD, cross product of the LDi and perpendicular diameter; SDi, shortest axis perpendicular to the LDi; SPD, sum of the product of the perpendicular diameters for multiple lesions.

*A score of 3 in many patients indicates a good prognosis with standard treatment, especially if at the time of an interim scan. However, in trials involving PET where de-escalation is investigated, it may be preferable to consider a score of 3 as inadequate response (to avoid undertreatment). Measured dominant lesions: Up to six of the largest dominant nodes, nodal masses, and extranodal lesions selected to be clearly measurable in two diameters. Nodes should preferably be from disparate regions of the body and should include, where applicable, mediastinal and retroperitoneal areas. Non-nodal lesions include those in solid organs (eg, liver, spleen, kidneys, lungs), GI involvement, cutaneous lesions, or those noted on palpation. Nonmeasured lesions: Any disease not selected as measured, dominant disease and truly assessable disease should be considered not measured. These sites include any nodes, nodal masses, and extranodal sites not selected as dominant or measurable or that do not meet the requirements for measurability but are still considered abnormal, as well as truly assessable disease, which is any site of suspected disease that would be difficult to follow quantitatively with measurement, including pleural effusions, ascites, bone lesions, leptomeningeal disease, abdominal masses, and other lesions that cannot be confirmed and followed by imaging. In Waldeyer's ring or in extranodal sites (eg, GI tract, liver, bone marrow), FDG uptake may be greater than in the mediastinum with complete metabolic response, but should be no higher than surrounding normal physiologic uptake (eg, with marrow activation as a result of chemotherapy or myeloid growth factors).

†PET 5PS: 1, no uptake above background; 2, uptake ≤ mediastinum; 3, uptake > mediastinum but ≤ liver; 4, uptake moderately > liver; 5, uptake markedly higher than liver and/or new lesions; X, new areas of uptake unlikely to be related to lymphoma.

# APPENDIX 10 MANAGEMENT ALGORITHMS FOR IMMUNO-ONCOLOGY AGENTS

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

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

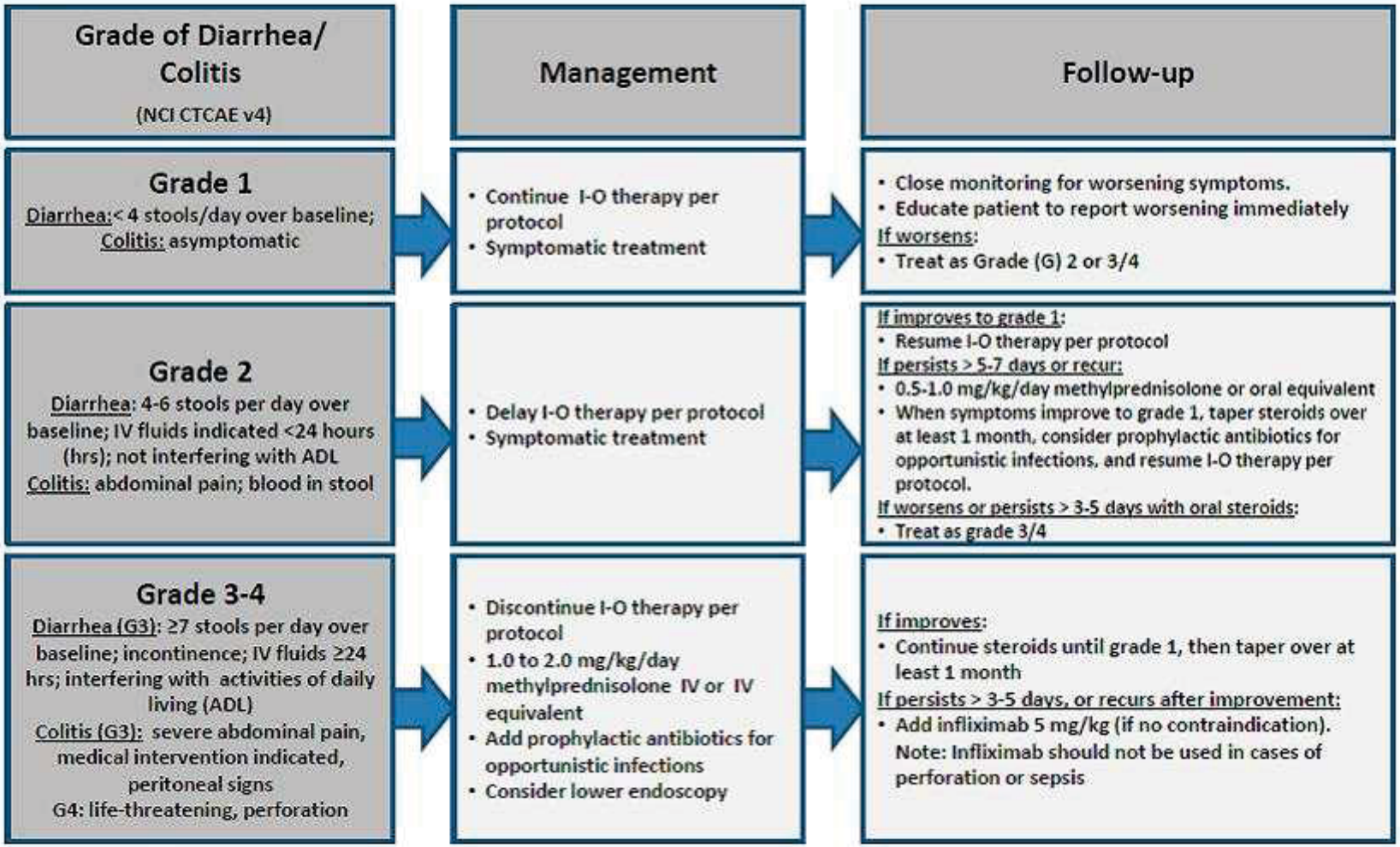
Corticosteroids are a primary therapy for immuno-oncology drug-related adverse events. The oral equivalent of the recommended intravenous (IV) doses may be considered for ambulatory patients with low-grade toxicity. The lower bioavailability of oral corticosteroids should be taken into account when switching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

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

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

# GI Adverse Event Management Algorithm

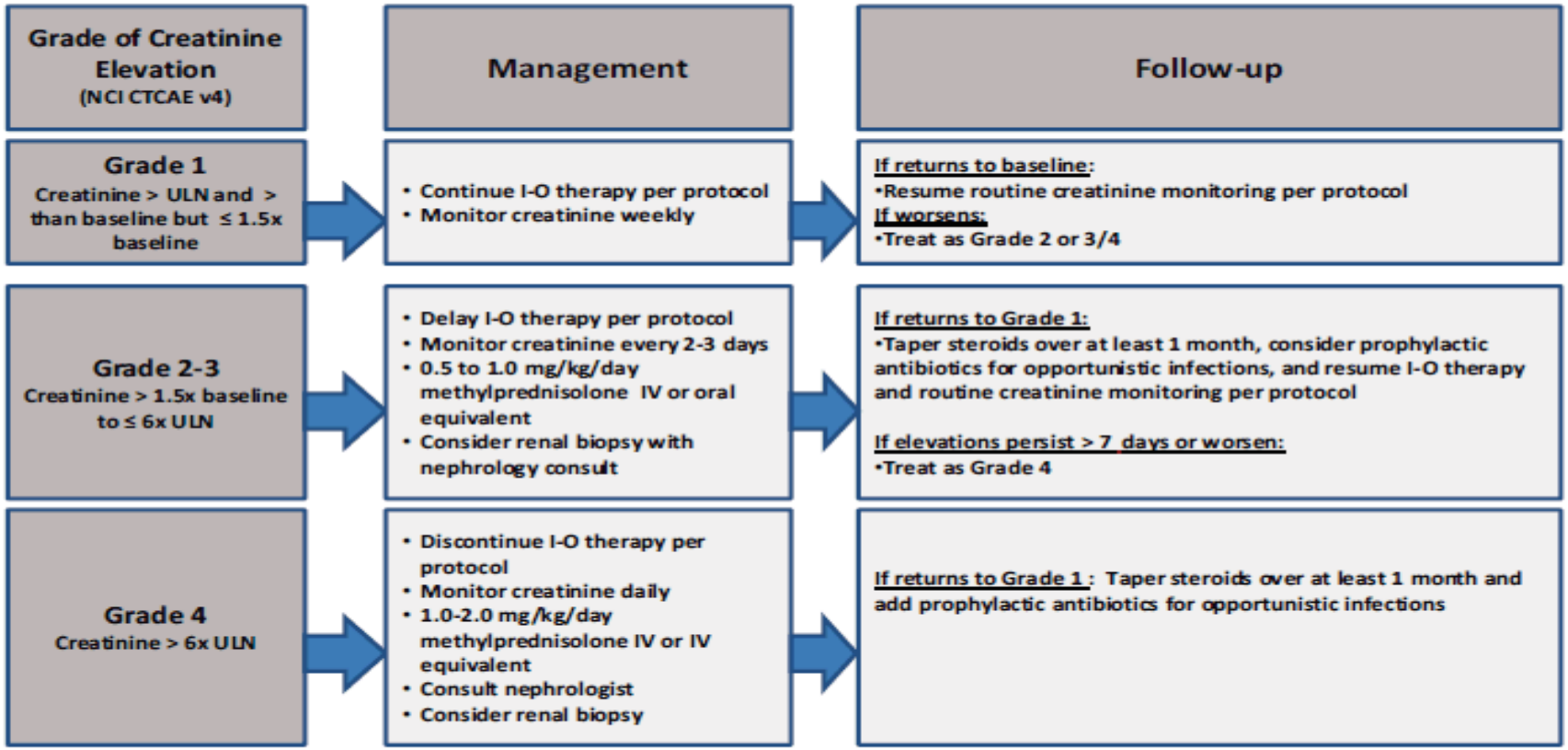
Rule out non-inflammatory causes. If non-inflammatory cause is identified, treat accordingly and continue I-O therapy. Opiates/narcotics may mask symptoms of perforation. Infliximab should not be used in cases of perforation or sepsis.




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

# Renal Adverse Event Management Algorithm

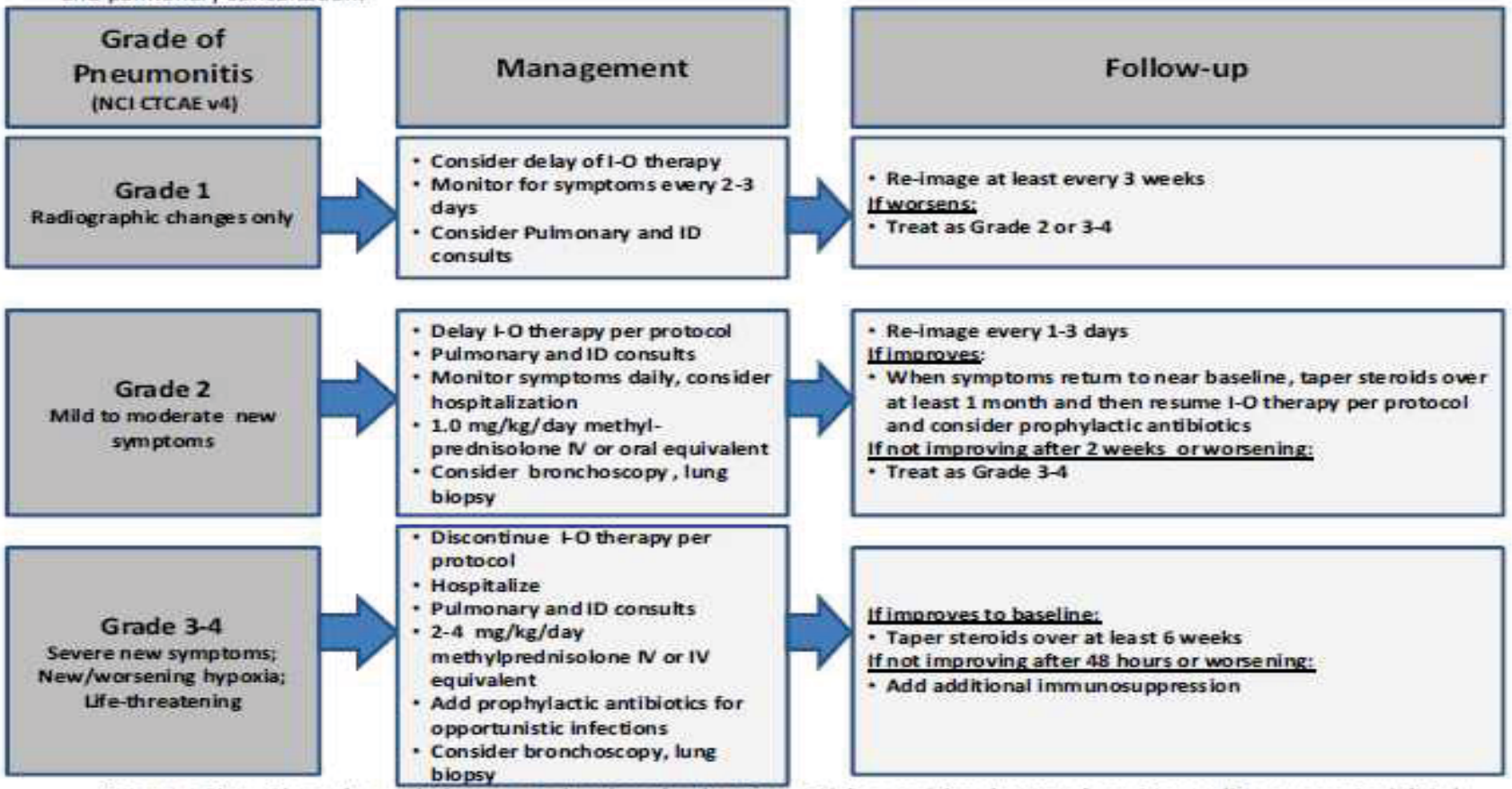
Rule out non-inflammatory causes. If non-inflammatory cause, treat accordingly and continue I-O therapy




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

# Pulmonary Adverse Event Management Algorithm

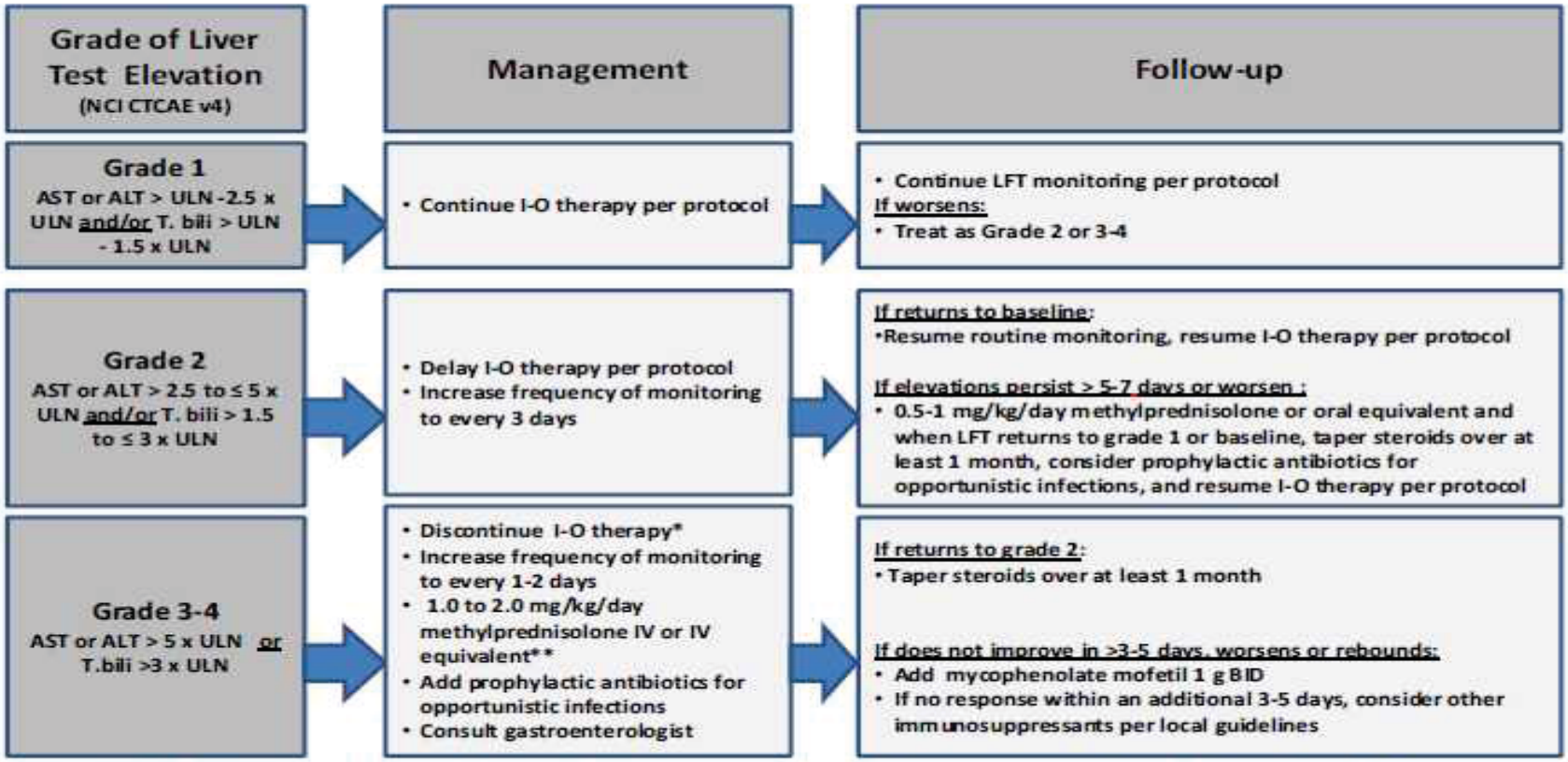
Rule out non-inflammatory causes. If non-inflammatory cause, treat accordingly and continue I-O therapy. Evaluate with imaging and pulmonary consultation.




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

# Hepatic Adverse Event Management Algorithm

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




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

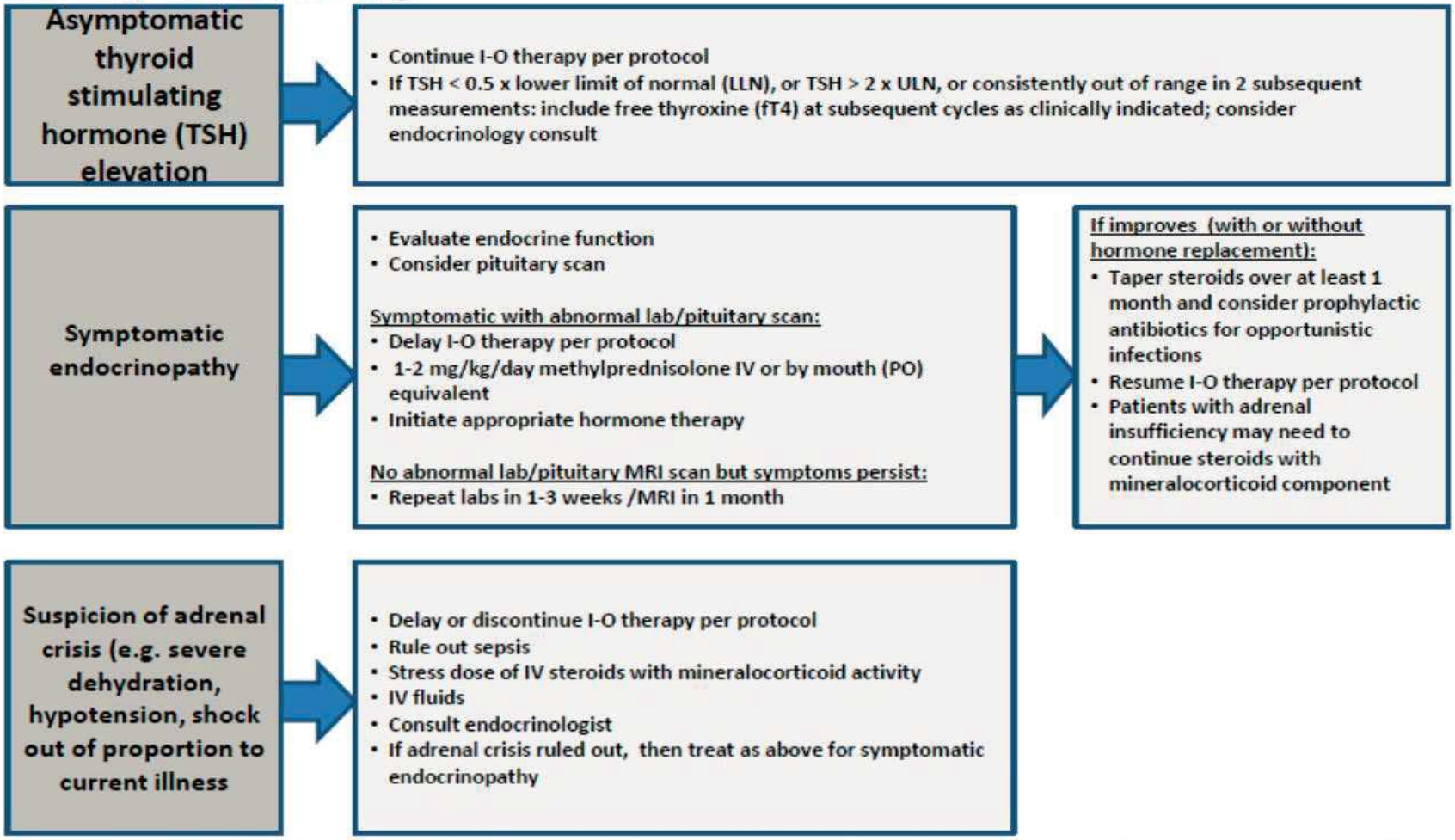
***I-O therapy may be delayed rather than discontinued if AST/ALT ≤ 8 x ULN or T.bili ≤ 5 x ULN.**

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

Refer to http://livertox.nih.gov/ for a compendium of agents that may cause liver injury

# Endocrinopathy Management Algorithm

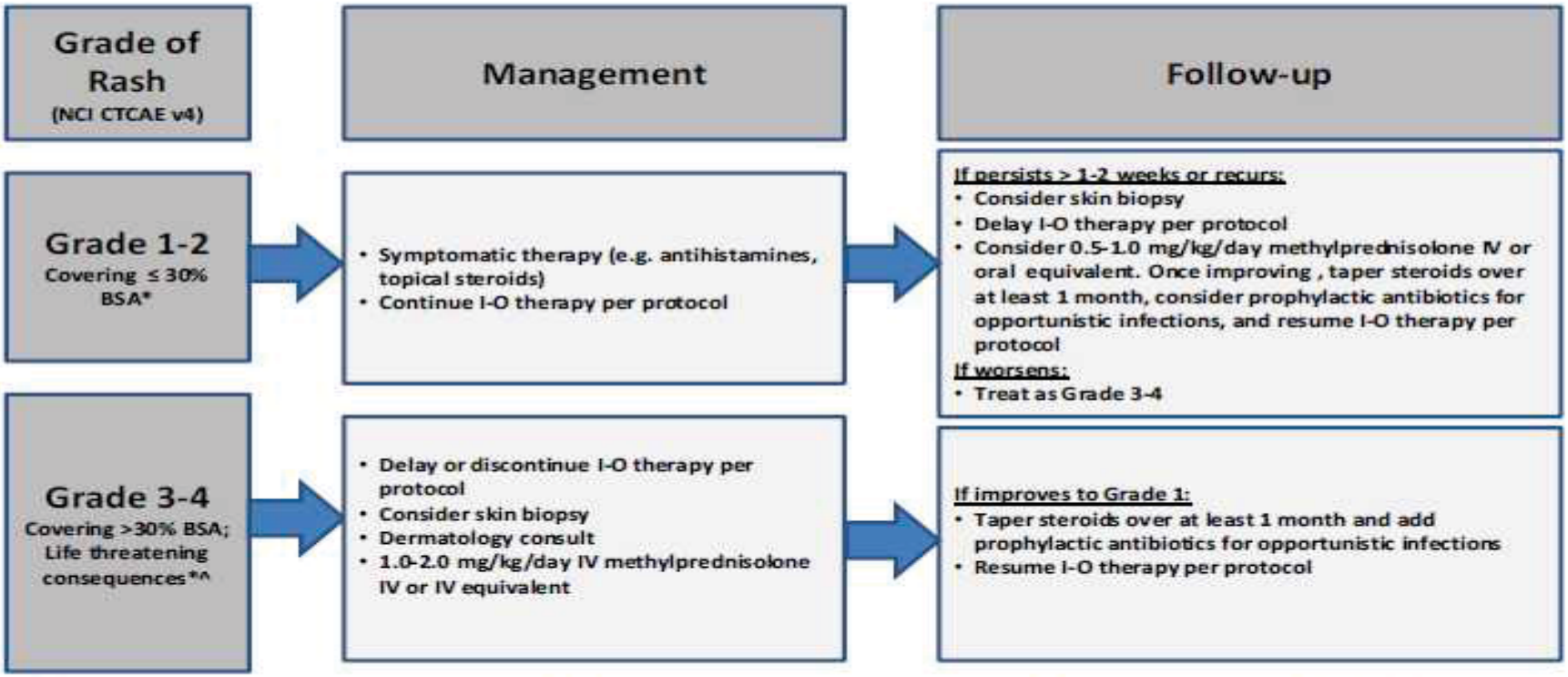
Rule out non-inflammatory causes. If non-inflammatory cause, treat accordingly and continue I-O therapy. Consider visual field testing, endocrinology consultation, and imaging.




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

# Skin Adverse Event Management Algorithm

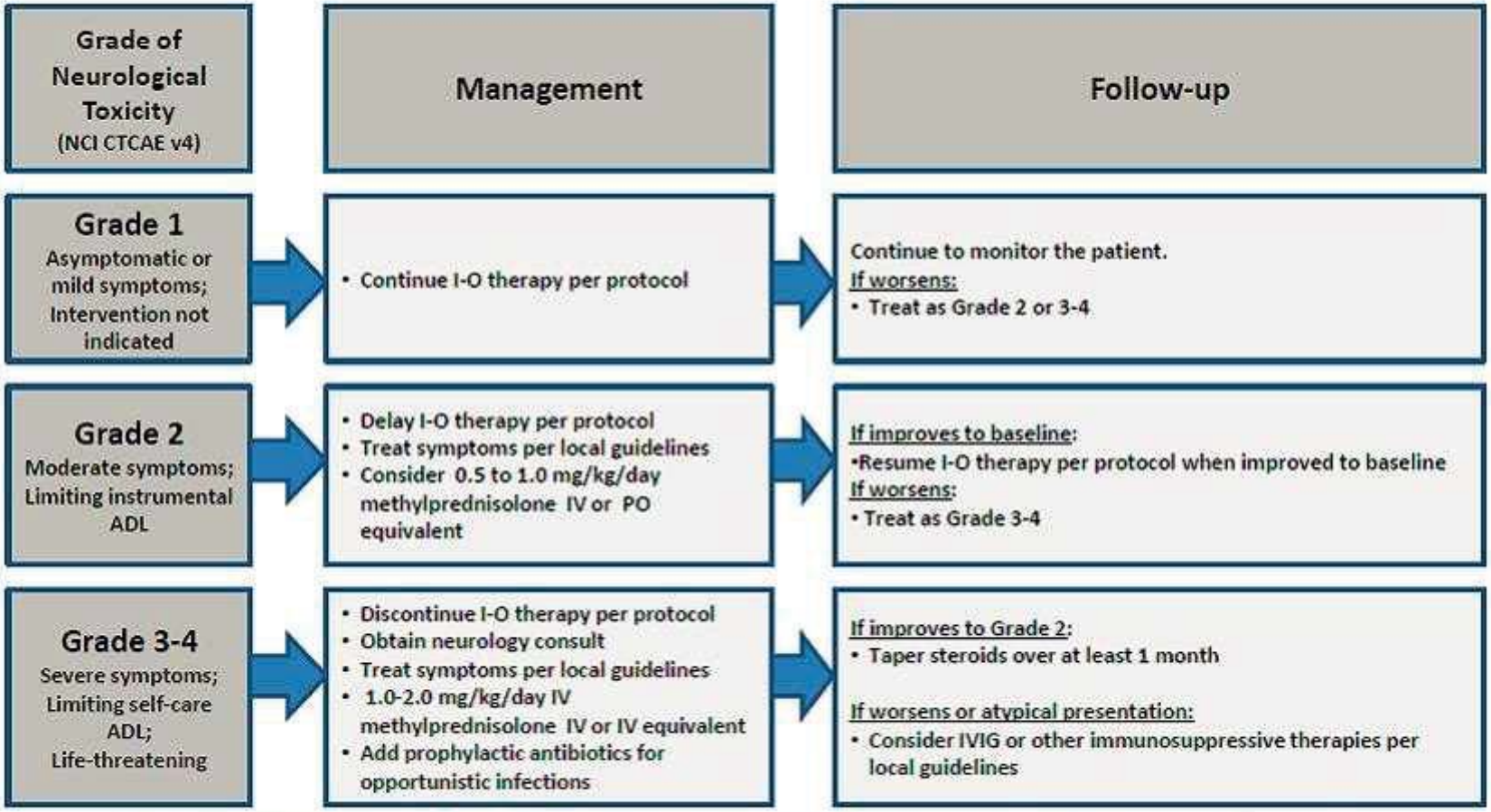
Rule out non-inflammatory causes. If non-inflammatory cause, treat accordingly and continue I-O therapy.




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

# Neurological Adverse Event Management Algorithm

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




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

# APPENDIX 11 WOMEN OF CHILDBEARING POTENTIAL DEFINITIONS AND METHODS OF CONTRACEPTION

## DEFINITIONS

### Woman of Childbearing Potential (WOCBP)

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

**Women in the following categories are not considered WOCBP**

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

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

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

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

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

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

## CONTRACEPTION GUIDANCE FOR FEMALE PARTICIPANTS OF CHILD BEARING POTENTIAL

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

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

| **Highly Effective Contraceptive Methods That Are User Dependent**<br><br>*Failure rate of <1% per year when used consistently and correctly.*[a] |
|---|
| • Combined (estrogen- and progestogen-containing) hormonal contraception associated with inhibition of ovulation[b]<br>– oral<br>– intravaginal<br>– transdermal |
| • Progestogen-only hormonal contraception associated with inhibition of ovulation[b]<br>– oral<br>– injectable |
| **Highly Effective Methods That Are User Independent** |
| • Implantable progestogen-only hormonal contraception associated with inhibition of ovulation[b]<br>• Intrauterine device (IUD)[c]<br>• Intrauterine hormone-releasing system (IUS)[c]<br>• Bilateral tubal occlusion |
| • Vasectomized partner<br><br>*A vasectomized partner is a highly effective contraception method provided that the partner is the sole male sexual partner of the WOCBP and the absence of sperm has been confirmed. If not, an additional highly effective method of contraception should be used.* |
| • Sexual abstinence<br><br>*Sexual abstinence, defined as complete absence of heterosexual intercourse, is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the study treatment. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the study and the preferred and usual lifestyle of the participant.*<br><br>• It is not necessary to use any other method of contraception when complete abstinence is elected. |

| |
|---|
| • WOCBP participants who choose complete abstinence must continue to have pregnancy tests, as specified in Section 2.<br>• Acceptable alternate methods of highly effective contraception must be discussed in the event that the WOCBP participants chooses to forego complete abstinence |
| NOTES:<br>[a] Typical use failure rates may differ from those when used consistently and correctly. Use should be consistent with local regulations regarding the use of contraceptive methods for participants participating in clinical studies.<br>[b] Hormonal contraception may be susceptible to interaction with the study treatment, which may reduce the efficacy of the contraceptive method. Hormonal contraception is permissible only when there is sufficient evidence that the IMP and other study medications will not alter hormonal exposures such that contraception would be ineffective or result in increased exposures that could be potentially hazardous. In this case, alternative methods of contraception should be utilized.<br>[c] Intrauterine devices and intrauterine hormone releasing systems are acceptable methods of contraception in the absence of definitive drug interaction studies when hormone exposures from intrauterine devices do not alter contraception effectiveness |

Listed below are the Less Than Highly Effective and Unacceptable Contraceptive Methods that are **NOT** acceptable methods of contraception or protection for participants in this study.

| **Less Than Highly Effective Contraceptive Methods That Are User Dependent**<br>*Failure rate of >1% per year when used consistently and correctly.* |
|---|
| • Male or female condom with or without spermicide. Male and female condoms cannot be used simultaneously<br>• Diaphragm with spermicide<br>• Cervical cap with spermicide<br>• Vaginal Sponge with spermicide<br>• Progestogen-only oral hormonal contraception, where inhibition of ovulation is not the primary mechanism of action |
| **Unacceptable Methods of Contraception** |
| • Periodic abstinence (calendar, symptothermal, post-ovulation methods)<br>• Withdrawal(coitus interruptus).<br>• Spermicide only<br>• Lactation amenorrhea method (LAM) |

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

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

- Inform any and all partner(s) of their participation in a clinical drug study and the need to comply with contraception instructions as directed by the investigator.
- All male participants will be required to always use a latex or other synthetic condom during any sexual contact with WOCBP; even if the participants have undergone a successful vasectomy or if their partner is already pregnant or breastfeeding. Males should continue to use a condom while on study and until the end of relevant systemic exposure defined as 7 months after the end of study treatment.
- Female partners of males participating in the study to consider use of effective methods of contraception until the end of relevant systemic exposure, defined as 7 months after the end of treatment in the male participant.
- Male participants with a pregnant or breastfeeding partner must agree to remain abstinent from penile vaginal intercourse or use a male condom during each episode of penile penetration during the treatment and until 7 months after the end of treatment.
- Refrain from donating sperm for the duration of the study treatment and until 7 months after the end of treatment.
-

## COLLECTION OF PREGNANCY INFORMATION

Guidance for collection of Pregnancy Information and outcome of pregnancy on the Pregnancy Surveillance Form is provided in Section 6.1.1.

# APPENDIX 12 PROSTATE CANCER WORKING GROUP 3 (PCWG3) GUIDELINES (WITH MODIFIED RESPONSE EVALUATION CRITERIA IN SOLID TUMORS (RECIST) CRITERIA FOR SOFT TISSUE LESION ASSESSMENT)

## 1 EVALUATION OF LESIONS

Bone lesions should be evaluated with Technecium-99m based radionuclide bone scan as per PCWG3[1].

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

### 1.1 Measurable

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

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

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

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

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

### 1.2 Non-Measurable

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

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

### 1.3 Special considerations regarding bone lesions

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

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

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

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

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

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

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

## 2 RESPONSE CRITERIA

### 2.1 Evaluation of Target Lesions

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

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

### *2.1.1 Special Notes on the Assessment of Target Lesions*

#### *2.1.1.1 Lymph nodes*

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

#### *2.1.1.2 Target lesions that become 'too small to measure'*

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

#### *2.1.1.3 Lesions that split or coalesce on treatment*

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

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

## 2.2 Evaluation of Non-Target Lesions

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

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

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

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

#### *2.2.1.1 When the patient also has measurable disease*

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

#### *2.2.1.2 When the patient has only non-measurable disease*

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

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

### 2.2.2 New Lesions

New bone lesions

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

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

New soft tissue lesions

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

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

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

## 2.3 Response Assessment

### *2.3.1 Evaluation of Best Overall Response*

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

### *2.3.2 Time Point Response*

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

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

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

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

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

| Non-Target Lesions | New Lesions | Overall Response |
|---|---|---|
| CR | No | CR |
| Non-CR/non-PD | No | Non-CR/non-PD[a] |
| Not all evaluated | No | NE |
| Unequivocal PD | Yes or No | PD |
| Any | Yes | PD |
| CR = complete response, PD = progressive disease and NE = inevaluable | | |

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

### *2.3.3 Best Overall Response*

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

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

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

**Table 2.3.3-1: Best Overall Response (Confirmation of CR&PR Required)**

| Overall Response First Time Point | Overall Response Subsequent Time Point | BEST Overall Response |
|---|---|---|
| CR | CR | CR |
| CR | PR | SD, PD OR PR[a] |
| CR | SD | SD provided minimum criteria for SD duration met, otherwise, PD |
| CR | PD | SD provided minimum criteria for SD duration met, otherwise, PD |
| CR | NE | SD provided minimum criteria for SD duration met, otherwise, NE |
| PR | CR | PR |
| PR | PR | PR |
| PR | SD | SD |
| PR | PD | SD provided minimum criteria for SD duration met, otherwise, PD |
| PR | NE | SD provided minimum criteria for SD duration met, otherwise, NE |
| NE | NE | NE |

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

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

### *2.3.4 Confirmation Scans*

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

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

REFERENCES

[1] Trial Design and Objectives for Castration-Resistant Prostate Cancer: Updated Recommendations From the Prostate Cancer Clinical Trials Working Group 3. Scher et al. J Clin Oncol 2016, 34(12):1402-1418

# APPENDIX 13 REVISED PROTOCOL SUMMARY OF CHANGE HISTORY

**Overall Rationale for Revised Protocol 06, 17-Jul-2018**

The purpose of this revised protocol is 1) to update schedules for mandatory on-treatment biopsies during Part 2 (Cohort Expansion); [redacted] 3) to update imaging requirements for tumor assessments; 4) to update Inclusion criteria for subjects with NSCLC, 5) to correct DLT period for Part 2, 6) to update schedules for PK sample collections, 7) to include language to allow for release of IRT codes and allow for data review while the study is ongoing, and 8) to include the PROSTATE CANCER WORKING GROUP 3 (PCWG3) appendix. Study design elements including time and events schedules, sample collections, laboratory analyses and additional safety measures have been added to align with these changes. Additionally, where applicable, sections in the synopsis have been updated, to align with the protocol section changes listed below.

## SUMMARY OF KEY CHANGES FOR REVISED PROTOCOL 06

| Section Number and Title | Description of Change | Brief Rationale |
|---|---|---|
| [redacted] | | |
| Sections 3.1 Study Design and Duration, 3.1.2.1 Sequential or Parallel Evaluation of Monotherapy and Combination Therapy, 3.1.2.4 BMS-986158 Monotherapy and in Combination with Nivolumab Dose Expansion, 8.1 Sample Size Determination | Updated the planned sample size | To include additional 18 subjects which may be enrolled for target gene engagement in tumors, and additional PK and safety characteristics in 1 or 2 cohorts. |
| Section 3.3.1 Inclusion Criteria, Previous Treatment, 3 b) | Clarified that Inclusion Criterion 3 b) no longer applicable as per Revised Protocol 03 | To align with BMS formatting guidelines on removed text. |
| Section 3.3.2 Exclusion Criteria: Medical History and Concurrent Diseases | Updated numbering of criteria related to history of chronic hepatitis (Criterion i). | Numbering of criteria regarding hepatitis was incorrectly formatted. |
| | Clarified that Exclusion Criterion j is no longer applicable as per Revised Protocol 02. | To align with BMS formatting guidelines on removed text. |
| | Updated exclusion criteria 2 q) to include the word “not” in the last sentence “...conditions expected not to recur”. | Typographical correction |
| | Clarified that Exclusion Criterion 3 no longer applicable as per Revised Protocol 03. | To align with BMS formatting guidelines on removed text |
| | Clarified that in regard of prior therapies, subjects with NSCLC | To address a request from health Authorities |

## SUMMARY OF KEY CHANGES FOR REVISED PROTOCOL 06

| Section Number and Title | Description of Change | Brief Rationale |
|---|---|---|
| | should be "ineligible" instead of "offered". | |
| Sections 3.5 Discontinuation of Subjects following any Treatment with Study Drug, 3.6 Treatment Beyond Progression, 8.3.2.1 Efficacy, 8.4.2 Efficacy Analysis | Added PCWG3 Criteria for tumor assessment in subjects with prostate cancers | To update imaging guidelines for subjects with prostate cancers. |
| Section 4.6 Blinding/Unblinding | Added text to provide IRT treatment codes to be released during Part 2. | In order to allow access to data for review while the study is ongoing. |
| Section 4.5.1 Dose Limiting Toxicities | Changed the DLT period from 35 to 28 days in Part 2 and added the number of doses required for the safety assessment in Part 2. | To allow similar drug exposure and appropriate comparison of the safety profile between Part 1 and Part 2. |
| Section 5.1, Table 5.1-1 Study Assessments and Procedures: Screening Procedural Outline | Added an "X" to the screening visit column for Thyroid Function Test. | Typographical correction. |
| Section 5.1, Tables 5-1-1 through 5.1-8 | Clarified activities and provided more details related to TSH, ECG, imaging assessments, and tumor biopsies. | To align with updates in safety and tumor assessments. |
| Section 5.3.1, Imaging Assessment for the Study | Clarified activities and provided more details related to imaging assessments. | To implement current BMS guidelines on tumor assessment using imaging. |
| Section 5.4.1 Primary Efficacy Assessment | Updated activities related to imaging assessments | To implement current BMS guidelines on tumor assessment using imaging. |
| Section 5.5.1 Pharmacokinetics [redacted] Collection and Processing, Tables 5.5.1-7, 5.5.1-8 , and 5.5.1-9 | Clarified nivolumab dose in table title [redacted] | To align with updated schedule of PK sample collection. |
| [redacted] | | |

## SUMMARY OF KEY CHANGES FOR REVISED PROTOCOL 06

| Section Number and Title | Description of Change | Brief Rationale |
|---|---|---|
| [redacted] | | |
| Section 6.3 Laboratory Test Result Abnormalities | Added "Thrombocytopenia versus decreased platelet count". | For reporting AEs, an example added to illustrate a preferred use of a clinical term instead of a laboratory parameter. |
| Section 8.1 Sample Size Determination, Cohort Expansion (Part 2) | Added that sample size may be adjusted if more than one dose/schedule are tested in Part 2 | To allow additional biomarker evaluation for a selection of optimal dose/schedule in Part 2 |
| 8.3.2.1 Efficacy | Updated text to include the PCWG3 criteria for prostate cancers. | |
| Appendix 12 PROSTATE CANCER WORKING GROUP 3 (PCWG3)GUIDELINES(WITH MODIFIED RESPONSE EVALUATION CRITERIA IN SOLID TUMORS (RECIST)CRITERIA FOR SOFT TISSUE LESION ASSESSMENT) | Added the following appendix:<br>PROSTATE CANCER WORKING GROUP 3 (PCWG3)GUIDELINES(WITH MODIFIED RESPONSE EVALUATION CRITERIA IN SOLID TUMORS (RECIST)CRITERIA FOR SOFT TISSUE LESION ASSESSMENT) | To provide additional details for tumor assessment in subjects with prostate cancers. |

**Overall Rationale for Revised Protocol 05, 01-Mar-2018:**

The purpose of this revised protocol is to 1.) To clarify the acceptable prior lines of therapy for participants with Non-Small Cell Lung Cancer (NSCLC) in Part 2; 2) to update Exclusion Criteria for subjects participating in Part 2; and 3) To provide updated contraception and protection requirements based on recent non-clinical reproductive toxicology study. Study design elements including time and events schedules, sample collections, laboratory analyses and additional safety measures have been added to align with these changes.

[redacted]

**SUMMARY OF KEY CHANGES FOR REVISED PROTOCOL 05**

| Section Number and Title | Description of Change | Brief Rationale |
|---|---|---|
| Synopsis | Synopsis was updated. | Synopsis was updated to reflect the changes made in the protocol. |
| 1.4.2 Toxicity | Added new data from pre-clinical rat reproductive toxicology study | To describe recent findings of selective developmental toxicity in pregnant rats. |
| 1.5 Overall Risk/Benefit Assessment | Added the toxicity finding of embryolethality and teratogenicity in pregnant rats. | To interpret recent findings of selective developmental toxicity in pregnant rats. |
| 3.1 Study Design and Duration, | Added that more than one dosing schedule for BMS-986158 administration may be considered in Part 2 | To reflect a potential for evaluating multiple dosing schedules in Part 2. |
| 3.1.2 Dose Expansion (Part 2) | Allowing treatment in Part 2 to be initiated before Part 1 is completed. | To allow timely evaluation of the selected doses/schedules in Part 2 |
| 3.3.1, Inclusion Criteria, 2) Target Population a), iv) | Added 3 inclusion criteria to Part 2 NSCLC<br>• Subjects must have received at least 1 prior checkpoint inhibitor immunotherapy<br>• Subjects with known abnormalities of EGFR, ALK, ROS1, BRAF must have received appropriate targeted therapies<br>• Subjects should have been offered or received a platinum-based chemotherapy for NSCLC in the adjuvant, neoadjuvant, or recurrent setting | To assure that the selected subjects have received appropriate prior therapies, inclusion criteria were added providing details on the 2 lines of prior therapy. |

## SUMMARY OF KEY CHANGES FOR REVISED PROTOCOL 05

| Section Number and Title | Description of Change | Brief Rationale |
|---|---|---|
| Inclusion Criteria 4) Age and Reproductive Status d) | Added that female participants must be willing to refrain from donation of oocytes 5 months post-treatment. | To implement recent findings of selective developmental toxicity in pregnant rats. |
| Inclusion Criteria 4) Age and Reproductive Status f) | Removed the exemption that azoospermic males are exempt from contraception. | To implement recent findings of selective developmental toxicity in pregnant rats. |
| 3.3.2 Exclusion Criteria Medical History and Concurrent Diseases 1), i), ii) | Revised the hepatitis criteria for Hepatitis B and Hepatitis C. | Updates were made on diagnostic tests for hepatitis. |
| 3.3.2 Exclusion Criteria Medical History and Concurrent Diseases 1), l), m), n), o) p) | Added additional exclusion criteria: current uncontrolled autoimmune pneumonitis, use of non-oncology vaccines, uncontrolled endocrine disorder, prior organ allograft or HSCT, and active or known or suspected autoimmune disease. | Updates were made to reduce a potential for toxicity in response to treatment with Nivolumab. |
| 3.3.2 Exclusion Criteria Physical and Laboratory Test Findings 2), f) | Added the following exclusion criteria: Inadequate thyroid function | New criterion excludes subjects with inadequate thyroid function to limit a potential for toxicity in response to Nivolumab treatment. |
| 3.4.1 Prohibited and/or Restricted Treatments | Added a prohibited/ restricted treatment: .Live virus vaccine during the study and for a period of three months after the last dose of study treatment | New restriction limits subjects with a potential for toxicity in response to treatment with Nivolumab. |
| 3.5 Discontinuation of Subjects following any Treatment with Study Drug | Added to the list of discontinuation of study treatment: Documented and confirmed PD as defined by RECIST v1.1 or Lugano 2014 unless participant meets criteria for treatment beyond progression. | Updated to clarify conditions for discontinuation of treatment. |
| 4.5.4 Management Algorithms for Immuno-oncology Agents | Added that nivolumab therapy can be associated can be associated with visual, cardiac and other rare events. | Updated to reflect potential AEs related to treatment with Nivolumab |
| Schedule of Events Tables 5.1-1, 5.1-5 , 5.1-6, 5.1-7, 5.1-8, Section 5.3.2 Laboratory Test Assessments | Added the requirement for thyroid testing at screening and while on study. | New criterion excludes subjects with inadequate thyroid function to limit a potential for toxicity in response to Nivolumab treatment. |
| Schedule of Events Tables 5.1-5, 5.1-6, 5.1-7 | Added that a +/- 3 day window is allowed for all visits except C1D1 | Updated to reflect a 3 day window for visits that can be performed in a window of time |

## SUMMARY OF KEY CHANGES FOR REVISED PROTOCOL 05

| Section Number and Title | Description of Change | Brief Rationale |
|---|---|---|
| [redacted] | | |
| Appendix 11 | Updated the contraception language including the requirements for acceptable methods of contraception and duration of contraception. | To implement recent findings of selective developmental toxicity in pregnant rats |
| All | Minor formatting and typographical corrections | Minor, therefore have not been summarized |

**Overall Rationale for the Revised Protocol 04, 06-Sep-2017:**

The purpose of this amendment is to add treatment in combination with Nivolumab, as well as define the biomarker-driven tumor population for Part 2 (dose expansion) of the study. One of the treatment arm schedules (updated from "arm" to "schedule") from Part 1 (monotherapy dose escalation) and the corresponding MTD will become the dose and selected dosing schedule for Part 2. In Part 2, a small safety cohort of 6 to 12 subjects will be administered BMS-986158 in combination with nivolumab to ensure safety and tolerability. Once determined safe and tolerable, expansion of combination therapy will occur in parallel to the BMS-986158 monotherapy expansion. Subjects with selected tumor types who demonstrate specified genetic profiles (via [redacted] genetic testing) will be enrolled to the expansion phase to maximize potential efficacy of monotherapy and combination therapy: ovarian, TNBC, NSCLC, RCC, UM, UCS, NEPC, CRPC, NMC, ES, BL and DHL. All of the study design elements, including the objectives, DLT assessments, time and events schedules and sample collections, sample size, dose modifications, statistical considerations, and supporting appendices have been added or updated to align with these changes. In addition, the expansion phase was updated to include adolescent subjects.

**SUMMARY OF KEY CHANGES FOR REVISED PROTOCOL 04**

| Section Number and Title | Description of Change | Brief Rationale |
|---|---|---|
| Title Page | Updated the revised date, revised protocol number and incorporation of amendments, and document history. Updated title to align with the new study design. | Updates were made to align with the new study design and for administrative reasons. |
| Synopsis | Updated to align with the changes made in the protocol body | Updates were made to align with the new study design |
| Section 1.1.1 Rationale for targeting bromodomains for cancer therapy | Rationale for targeting genetic abnormalities associated with BET inhibition has been added. | Provides rationale for the selected BET-associated biomarkers. |
| Section 1.1.2 Rationale for combining BMS-986158 with Nivolumab | New section has been added to support rationale for combining BMS-986158 and nivolumab | Provides rationale for BET inhibitor plus PD-L1 inhibitor in combination therapy. |
| Section 1.1.3 Rationale for targeting PD-1 | Language regarding potential benefit of targeting PD-1 has been added. | Provides rationale for BMS-986158 to be administered in combination with Nivolumab. |
| Section 1.1.5 Rationale for Dose and Schedule | Updated data in BMS-986158 subsection. Details regarding potential addition of Nivolumab to each arm has been added. | Most recent data from the current study were added for BMS-986158. Nivolumab will be administered at a different dose and schedule depending on which schedule is chosen for Part 2. |
| Section 1.1.6, Rationale for Monotherapy Dose Escalation | Updated safety monitoring rationale for combination therapy | Updates were made to reflect the new study design. |

## SUMMARY OF KEY CHANGES FOR REVISED PROTOCOL 04

| Section Number and Title | Description of Change | Brief Rationale |
|---|---|---|
| Design and Combination Safety Monitoring | | |
| Section 1.1.7 Rationale for Genetically Defined Tumor Cohort [redacted] | Rationale for targeting tumors based on genetic rearrangements regulated by BRD proteins was added. | New section provides background information on specific tumor types and mutations/amplifications for expansion enrollment. |
| Section 1.1.8 Rationale for Specific Patient Populations | New section has been added. | New section provides detailed rationale for tumor types to be enrolled during expansion. |
| [redacted] | | |
| Section 1.1.12 Rationale for Inclusion of Adolescent Subjects | New Section has been added. | Provides BET data, dose, and rationale for enrollment of adolescent subjects for participation in the expansion phase of the study (Part 2). |
| Section 1.2 Research Hypothesis | Added combination therapy. | Updated to reflect the new study design. |
| Section 1.3 Objectives | Primary, Secondary, [redacted] Objectives have been updated. | Language regarding combination with Nivolumab and biomarker driven strategy information has been added. |
| Section 1.4.4 Clinical Pharmacology and Safety | Language updated with most recent adverse event data and to align with the Investigator Brochure. | Most recent safety and pharmacology data have been provided. |
| Section 1.4.4.1 Pharmacokinetics of BMS-986158 | Analysis performed on dose cohorts explored thus far is included. | Pharmacokinetic information for the BMS-986158 compound provided to align with pharmacokinetic information of Nivolumab. |
| Section 1.5 Overall Risk/Benefit Statement | Section updated with most recent clinical data available. Updated with language for the new study design. | Language provided to align with Investigator Brochure. Updated to reflect the new study design. |

## SUMMARY OF KEY CHANGES FOR REVISED PROTOCOL 04

| Section Number and Title | Description of Change | Brief Rationale |
|---|---|---|
| Section 2.3 Informed Consent | Statement added regarding adolescent assent. | Adolescents who meet eligibility criteria may participate in dose expansion. |
| Section 3.1 Study Design and Duration; Section 3.1.1 Monotherapy Dose Escalation; Section 3.1.2 Dose Expansion (Part 2) | Section updated with new study design, including BMS-986158 monotherapy and in combination with nivolumab dose administration information. Study schematics have been updated to reflect the new study design. | Escalation and expansion details regarding tumor population, selection of dose, and dose administration schedule, have been provided for monotherapy and combination therapy. |
| Section 3.1.2.1 Sequential or Parallel Evaluation of Monotherapy and Combination Therapy | Section added to provide expansion details regarding method for assigning monotherapy and/or combination therapy. | Dependent on tumor type, specific tumor populations will begin in monotherapy or combination therapy, or be allowed to cross over. |
| Section 3.1.2.2 Safety Evaluation Phase of BMS-986158 Combination with Nivolumab | Language surrounding the dose evaluation phase and selection of dose of BMS-986158 in combination with Nivolumab, has been added. | Details regarding the dose evaluation phase, which will dose up to 12 subjects, and subsequently determine the dose/schedule for expansion, are provided. |
| Section 3.1.2.3 Safety Evaluation in Adolescents | Language regarding the safety cohort of dosing in adolescents during expansion has been added. | The number of adolescents and the method for selecting the dose of BMS-986158 are provided. |
| Section 3.1.2.4 BMS-986158 Monotherapy and in Combination with Nivolumab Dose Expansion | Language added regarding number of subjects to be enrolled, and the design to be utilized to determine efficacy. Language added to allow for crossover from monotherapy to combination therapy for subjects enrolled in Part 2. | Language updated to align with new Part 2 design and to provide patients on BMS-986158 monotherapy another option for therapy after disease progression. |
| Section 3.3.1 Inclusion Criteria and Appendix 11. | Specific information updated regarding the following criteria: enrollment of adolescent subjects, biopsy requirements, Foundation One genetic testing, reproductive and WOCBP requirements, and the following tumor populations: OC, TNBC, SCLC, NSCLC, RCC, UM, UCS, NEPC, CRPC, NMC, ES, BL and DHL. | Specific procedures are now required for enrollment; the tumor population has been defined for Part 2. WOCBP requirements were moved into the new standard appendix (Appendix 11). |
| Section 3.3.2 Exclusion Criteria | Clarifications made to the following criterion:<br>1) Medical History and Concurrent Disease<br>2) Physical and Laboratory Test Findings<br>4) Other Exclusion Criteria | Criteria have been aligned with updated tumor population; adolescent information has been added. |

## SUMMARY OF KEY CHANGES FOR REVISED PROTOCOL 04

| Section Number and Title | Description of Change | Brief Rationale |
|---|---|---|
| Section 3.4 Concomitant Treatments; Section 3.4.1 Prohibited and/or Restricted Treatments; Section 3.4.2 Other Restrictions and Precautions | Concomitant treatment regarding specific therapies has been updated. | Administration of specific treatments updated to align with expansion tumor population and the requirements for nivolumab. |
| Section 3.5 Discontinuation of Subjects following any Treatment with Study Drug | Language added to include monotherapy and combination therapy. | Section clarifies reasons for discontinuation from the study whether subjects receive BMS-986158 monotherapy or in combination with nivolumab. |
| Section 3.6 Treatment Beyond Progression | Section added clarifying that specific subjects, meeting specified criteria, may continue therapy beyond progression. | Due to some subjects deriving clinical benefit despite initial evidence of progressive disease, criteria has been added for those that may be treated after progression. |
| Section 4 Study Drug; Section 4.1 Investigational Product | Nivolumab language has been added, and product information for BMS-986158 has been updated. | Product information for BMS-986158 and nivolumab and guidelines regarding infusion reactions for nivolumab have been added. |
| Section 4.4 Method of Assigning Subject Identification | Language for PID assignment utilizing IRT for Part 2 has been added. | An IRT will be utilized during expansion to aid with cohort assignment of specific tumor types. |
| Section 4.5 Selection and Timing of Dose For Each Subject | Preliminary safety data summary language has been removed. | As additional data are now available, preliminary BMS-986158 and competitor data have been removed. |
| Section 4.5.1 Dose Limiting Toxicities | The DLT period for combination therapy in Part 2 has been added. Updates were made to hematologic DLTs. | The DLT period for combination therapy for subjects in Part 2 will match the length of the DLT period in Part 1. Neutropenia and thrombocytopenia DLTs were further defined based on clinical data observed thus far. |
| Section 4.5.2 Guidelines for Dose Modifications | Clarifications have been added to the third and eighth bullet points; Grade 4 neutropenia and thrombocytopenia AEs have been clarified in Table 4.5.2-1 | Dose reduction and escalation for BMS-986158, in certain cases, can be discussed with the Sponsor. Dose modifications suggestions for hematologic toxicities were updated based on current clinical data. |
| Section 4.5.3 Management of Diarrhea | Language has been clarified that suggested methods for management of diarrhea is management of BMS-986158. Algorithms for managing adverse events associated with nivolumab have been added | Diarrhea management for BMS-986158 is provided in the protocol; language and an Appendix have been added for the management of nivolumab adverse events. |

## SUMMARY OF KEY CHANGES FOR REVISED PROTOCOL 04

| Section Number and Title | Description of Change | Brief Rationale |
|---|---|---|
| Section 5.1 Flow Chart/Time and Events Schedule | Table 5.1-1: Length of screening window for Part 2, consent, biopsy, [redacted] and IRT procedures updated. Table 5.1-5: Title updated to include nivolumab, physical exam, [redacted] and treatment administration procedures updated. Table 5.1-6 and Table 5.1-7: Title updated to include nivolumab, [redacted] and treatment administration procedures updated. Table 5.1-8: 60-day and 100-day clinical follow-up visits added; procedures further clarified. | Screening procedures and Part 2 Tables (for monotherapy and combination therapies in expansion) have been further clarified. Clinical Follow-up visits clarified to extend time needed to monitor those subjects who were administered combination therapy. |
| Section 5.3 Safety Assessments | Clinical follow-up language of 60 and 100 days for those on combination therapy has been added. Length of screening period was extended to 40 days for subjects in Part 2. | Assessments updated to align with Part 2 participation requirements. |
| Section 5.3.1 Imaging Assessment for the Study | Statement added that if subject has only 1 measureable lesion, a CT scan should be performed after biopsy to establish a baseline. | Core needle biopsies will be allowed in this instance to ensure that baseline values are available. |
| Section 5.4 Efficacy Assessments; Section 5.4.1 Primary Efficacy Assessment | Language added regarding acceptable modalities for assessing solid tumors and lymphomas and methods for assessing tumor response/progression. | Assessment language was updated to align with enrollment of specific tumor types and inclusion of subjects with lymphoma. |
| Section 5.5 Pharmacokinetic Assessments; 5.5.1, Pharmacokinetics [redacted] Collection and Processing, Section 8.3.2.2 Pharmacokinetics | [redacted] Sample collection for adolescents was added to Tables 5.5.1-4, 5.5.1-5, and 5.5.1-6, and Tables 5.5.1-7 through 5.5.1-9 were for subjects receiving combination therapy. | Language and tables updated to clarify general time points for PK sample collection, including collection for adolescents and for those that receive BMS-986158 in combination with nivolumab. |
| [redacted] | | |

## SUMMARY OF KEY CHANGES FOR REVISED PROTOCOL 04

| Section Number and Title | Description of Change | Brief Rationale |
|---|---|---|
| [redacted] | | |
| Section 8.1 Sample Size Determination; Section 8.2 Populations for Analyses | Population, and sample size for Parts 1 and 2 of the study, and incidence rate of DLTs have been updated. | Information has been updated to include nivolumab combination, tumor population and biomarker-driven strategy for Part 2. |
| Section 8.3.1, Primary Endpoint(s) | Follow-up for safety evaluation has been updated to include combination therapy cohorts. | Updated to reflect the addition of BMS-986158 and nivolumab combination therapy. |
| Section 8.3.2.1 Efficacy; Section 8.4.2 Efficacy Results | BOR, DoR, and PFS endpoints clarified due to biomarker driven population of Part 2. | Criteria for efficacy determination were updated to include Lugano 2014 for hematologic malignancies, and efficacy measurements for endpoints were clarified. |
| Synopsis, Section 8.3.2.2 Pharmacokinetics and Section 8.3.2.4, ECG/QTc | Updated to include the combination cohorts for PK and to clarify the ECG/QTc assessment is for BMS-986158 monotherapy treatment only. | Updated to reflect addition of BMS-986158 and nivolumab combination therapy for PK assessments and to clarify ECG/QTc assessments. |
| [redacted] | | |

## SUMMARY OF KEY CHANGES FOR REVISED PROTOCOL 04

| Section Number and Title | Description of Change | Brief Rationale |
|---|---|---|
| Section 8.4.3 Safety Analyses; Section 8.4.4 Pharmacokinetic Analyses | Language added confirming methods for analysis in adolescent subjects. | Adolescent subjects may be enrolled to Part 2. |
| Section 8.4.5 ECG Analyses | Language added to clarify that time-matched ECGs (with PK) will be performed for monotherapy only. | No time-matched ECG will be performed for subjects receiving combination therapy. |
| Section 12 References | Updated. | Updated to align with new text. |
| Appendix 3 , CYP3A4 Guidance | Added enalutamide to the strong in vivo inducers of CYP enzymes that cause ≥ 80% decrease in area under the concentration-time curve. | BMS-986158 is a substrate of CYP3A4. Enalutamide is contraindicated for CYP3A4 substrates per package insert, thus was added to the guidance. |
| Appendices 8, 9, and 10 | New appendices include:<br>Appendix 8, Simulation of MTPI-2 vs 3+3 Dose Escalation Designs With 2 Dose Levels<br>Appendix 9, Lugano 2014 Classification for Initial Evaluation Staging, and Response for Hodgkin Lymphoma<br>Appendix 10, Management Algorithms for Immuno-oncology Agents | Added to support the new study design. |
| Appendix 11 | Added Appendix 11, Women of Childbearing Potential Definitions and Methods of Contraception | Details for women of childbearing potential and the use of highly effective methods of contraception were moved from Inclusion Criteria 4d and 4e to Appendix 11. |
| All | Minor formatting, clarifications, and typographical corrections. | Minor, therefore have not been summarized. |