Official Title of Study:

A Phase 1/2a Study of BMS-986205 Administered in Combination with Nivolumab (anti-PD-1 Monoclonal Antibody) and in Combination with Both Nivolumab and Ipilimumab (anti-CTLA-4 Monoclonal Antibody) in Advanced Malignant Tumors

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CLINICAL Protocol CA017003

A Phase 1/2a Study of BMS-986205 Administered in Combination with Nivolumab (anti-PD-1 Monoclonal Antibody) and in Combination with Both Nivolumab and Ipilimumab (anti-CTLA-4 Monoclonal Antibody) in Advanced Malignant Tumors

Revised Protocol Number: 05
Incorporates Amendment 14 and Administrative Letter 03, 04, 06, 07, and 08

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

DOCUMENT HISTORY

Document	Date of Issue	Summary of Change
Revised Protocol 05	29-Jun-2018	Incorporates Amendment 14 and Administrative Letters 03 - 08
Amendment 14	29-Jun-2018	This amendment includes: • Updated safety, PK, and efficacy information to support dose selections for Parts 2 and 3, update the risk/benefit assessment, and to establish HLH and DRESS syndrome as adverse events of special interest (AEOSI) requiring expedited reporting • Updated preclinical safety, metabolism, and drug interaction information to support modifications of concomitant medication prohibitions and restrictions (especially regarding CYP1A2) as well as changes to condom requirements for male subjects in light of animal fetal toxicity information • Further evaluation of safety and initial efficacy exploration of nivolumab and ipilimumab on a Q4W/Q8W schedule in combination with BMS-986205 in a mixed tumor type cohort in Part 3. • Alternative dose of BMS-986205 and, if needed, dose and schedule of nivolumab and ipilimumab in the Part 3 cohorts to allow for optimal exploration of tolerability and safety of the triplet combination • Age requirements on tumor tissue blocks and slides (except in subjects who will undergo pre-treatment biopsies) while simultaneously reducing the need for fresh tumor biopsies in subjects in Part 2 • Other changes to align this protocol with the current standards of the BMS-986205 and nivolumab programs and enhance subject safety by: updating exclusion, dose delay, dose reduction, and drug discontinuation criteria, and increasing frequency of methemoglobin monitoring to at least monthly across all protocol parts • Information on the serotonin syndrome as a possible class effect of IDO1 inhibitors and additional exclusion criteria and dose discontinuation criteria to reflect this possiblity • Administrative changes, minor clarifications, typographical corrections, and updates for consistency were made
Administrative Letter 08	09-Nov-2017	BMS-986205 PK [redacted] plasma sample [redacted].
Administrative Letter 07	29-Sep-2017	New study personnel and clarification Flowchart / Time and Events Schedule.
Administrative Letter 06	29-Sep-2017	New study personnel and clarification Flowchart / Time and Events Schedule.
Administrative Letter 04	25-May-2017	Sample day of sample collection description change
Administrative Letter 03	24-May-2017	[redacted]

Document	Date of Issue	Summary of Change
Revised Protocol 04	27-Feb-2017	Incorportates Amendment 08 Global
Amendment 08	27-Feb-2017	• This protocol amendment adds an evaluation of the safety, tolerability, and preliminary anti-tumor activity of the combination of BMS-986205, nivolumab, and ipilimumab in cohorts of melanoma, non-small cell lung cancer (NSCLC), and bladder cancer subjects. Subjects within these tumor-restricted cohorts will receive a selected regimen of nivolumab and ipilimumab based on previous evaluations of safety, tolerability, and anti-tumor activity in those populations, administered together with BMS-986205 given orally daily. The safety and tolerability of the triplet combinations will first be assessed in safety cohorts in each tumor type. After establishing initial safety and tolerability, expansion cohorts will begin enrolling to further assess safety and tolerability, as well as the preliminary anti-tumor activity of each triplet combination. • RCC was added as an expansion cohort in Part 2 based on data showing that RCC expresses high levels of IDO1, as well as translational data showing that RCC subjects treated with nivolumab have increased expression of IDO1. Furthermore, RCC was already previously included as a tumor type for evaluation in Part 1 of this study. • Administrative changes, minor clarifications, typographical corrections, and updates for consistency were made.
Revised Protocol 03	14-Dec-2016	Incorporates Amendment 06 Global
Amendment 06	14-Dec-2016	• This protocol amendment adds multiple dose expansion cohorts with the goal of generating data to further the understanding of which tumor types and specific patient populations will benefit from treatment with the indoleamine 2,3-dioxygenase 1 inhibitor/nivolumab combination. In order to ensure consistent dosing throughout each cohort, nivolumab will be administered at a dose of 240 mg every 2 weeks for the dose escalation (Part 1) and for the dose expansion cohorts (Part 2) that predated Amendment 06. Nivolumab will be administered at a dose 480 mg intravenously every 4 weeks (Q4W) for the dose expansion cohorts added with Amendment 06 (melanoma, non-small cell lung cancer (NSCLC), and additional signal seeking tumors) and the clinical pharmacology substudy (Parts 2 and 3). This amendment eliminates the Food Effect substudy from the global protocol, as this substudy will only open at sites in the United States. Lastly, the duration of study treatment has been changed from 24 weeks to approximately 1 year, with up to 12 cycles. The QTc substudy is modified to utilize Holter monitoring in order to allow for multiple QTc sample collection. Biomarker analysis was removed. Inclusion criteria have been updated to include non-treatment naïve NSCLC subjects and subjects with sarcomas and clarification that pre-treatment biopsies are required for all subjects including the QTc substudy; required period for contraception for men and women of childbearing potential has been changed; and some methods of contraception are no longer considered highly effective due to potential

Document	Date of Issue	Summary of Change
		interaction with BMS-986205. Biopsy time window for Cycle 1 Day 15 (C1D15) in the expansion cohorts has been changed. Supine resting time for electrocardiograms (ECGs) has been changed, and Dose and Schedule rationale for nivolumab has been updated. Guidelines for permanent discontinuation of study drugs have been updated. Administrative changes, minor clarifications, typographical corrections, and updates for consistency were made.
Revised Protocol 02a	19-Sep-2016	Incorporates Amendment 04 U.S. sites only
Revised Protocol 02	13-Jul-2016	Incorporates Amendment 02
Amendment 02	13-Jul-2016	• This amendment corrects typographical errors, updates language for consistency between the synopsis and protocol body, and incorporates a sub-study to perform an early assessment of the effect of BMS-986205 on the QTc interval
Revised Protocol 01	05-Apr-2016	Incorporates Amendment 01
Amendment 01	05-Apr-2016	• This amendment makes changes to the wording describing the DLT period and makes specific changes to the DLT criteria in response to [redacted] received during initial IND review. • Correct typographical errors were updated for consistency. •
Administrative Letter 01	26-Jan-2016	• Provide clarification and correct typographical errors to Time and Events tables 5.1-1 through 5.1-8 for consistency. • Correct typographical errors to lab assessment section 5.3.2.
Original Protocol	24-Nov-2015	Not Applicable

SYNOPSIS

Protocol Title: A Phase 1/2a Study of BMS-986205 Administered in Combination with Nivolumab (anti-PD-1 Monoclonal Antibody) and in Combination with both Nivolumab and Ipilimumab (anti-CTLA-4 Monoclonal Antibody) in Advanced Malignant Tumors

Investigational Product(s), Dose and Mode of Administration, Duration of Treatment with Investigational Product(s): Each subject will be administered a daily oral dose of BMS-986205 in combination with nivolumab (Parts 1 and 2) or in combination with both nivolumab and ipilimumab (Part 3), both administered as an intravenous (IV) infusion per the cohort assignment and the duration of treatment as indicated below.

Study Phase: Phase1/2a

Research Hypothesis: It is anticipated that BMS-986205, administered in combination with nivolumab and in combination with both nivolumab and ipilimumab, will demonstrate adequate safety and tolerability, as well as a favorable benefit/risk profile, to support further clinical testing. No prospective hypotheses are being formally evaluated.

Objectives:

Primary Objectives:

Part 1: Dose Escalation:

To determine the safety, tolerability, dose limiting toxicities (DLTs), and maximum tolerated dose (MTD)/maximum administered dose (MAD)/alternate dose(s) of BMS-986205 administered as monotherapy and in combination with nivolumab in subjects with advanced malignant tumors.

Part 2: Dose Expansion:

To investigate the anti-tumor activity of BMS-986205 administered in combination with nivolumab in distinct cohorts of subjects with advanced malignant tumors.

To evaluate the safety and tolerability of BMS-986205 in combination with nivolumab in subjects with advanced malignant tumors.

Part 3: BMS-986205, Nivolumab and Ipilimumab Combination

To determine the safety, tolerability, dose-limiting toxicities (DLTs), and preliminary anti-tumor activity of BMS-986205 administered in combination with both nivolumab and ipilimumab in subjects with select advanced malignant tumors.

Secondary Objectives:

- To characterize the pharmacokinetics (PK) of BMS-986205 administered alone, in combination with nivolumab, and in combination with both nivolumab and ipilimumab.
- To investigate the anti-tumor activity of BMS-986205 administered in combination with nivolumab in dose escalation and clinical pharmacology substudies.
- To characterize the pharmacodynamic activity of BMS-986205 administered alone, in combination with nivolumab, and in combination with both nivolumab and ipilimumab.
- To characterize the immunogenicity of nivolumab when administered in combination with BMS-986205 and in combination with both BMS-986205 and ipilimumab.
- To characterize the immunogenicity of ipilimumab when administered in combination with nivolumab and BMS-986205

[redacted]

[redacted]

Study Design:

This is a Phase 1/2a, open-label study of BMS-986205 administered as a monotherapy and in combination with nivolumab (Parts 1 and 2), and in combination with nivolumab and ipilimumab (Part 3) in subjects with advanced malignant tumors.

The study will be conducted in 3 parts. A clinical pharmacology QTc substudy will also be performed.

Parts 1 and 2: Dose escalation (Part 1) will start with a lead-in **Cycle 0** whereby BMS-986205 is administered as monotherapy for 2 weeks duration in each dose escalation cohort. Decision to proceed to combination treatment with nivolumab (Cycle 1) for each cohort in dose escalation will be determined after tolerability of the monotherapy lead-in is established in the 2-week Cycle 0 at each dose, as described in Section 3.1.5 in the protocol body. When the decision is made to proceed to Cycle 1, BMS-986205 will be administered concomitantly with nivolumab. The starting dose of BMS-986205 is 25 mg orally daily. Nivolumab will be administered at a dose of 240 mg every 2 weeks (Q2W) for the dose escalation (Part 1) and for the dose expansion (Part 2) cohorts that predated Amendment 06 (cervical, diffuse large B cell lymphoma [DLBCL], squamous cell carcinoma of the head and neck [SCCHN], bladder, and pancreatic cancer). Nivolumab will be administered at a dose 480 mg intravenously every 4 weeks (Q4W) for the dose expansion cohorts added with Amendment 06 (melanoma, NSCLC, and additional signal seeking tumors) and the clinical pharmacology substudy).

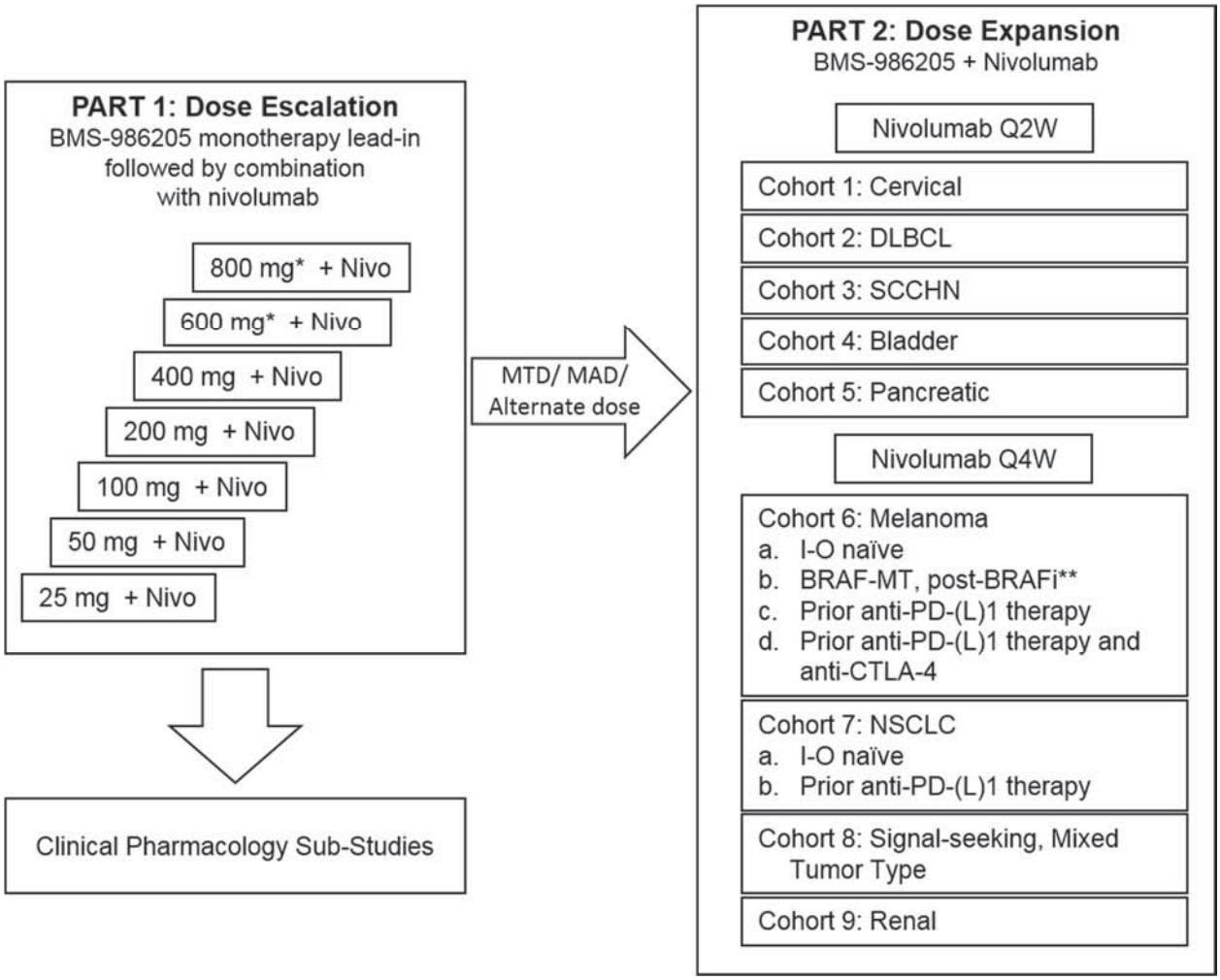
Dose expansion (Part 2) will include 8 disease-restricted expansion cohorts (cervical cancer, DLBCL, SCCHN, bladder cancer, NSCLC, melanoma, renal cell carcinoma, and pancreatic cancer). Various subpopulations of melanoma and NSCLC will be included in separate cohorts to further understand the role of indoleamine 2,3-dioxygenase 1 (IDO1) inhibition in these specific populations. The BRAF mutated, post-BRAF regimen melanoma subjects will be randomized to receive either nivolumab or BMS-986205 in combination with nivolumab in order to order to generate a robust, prospective dataset with nivolumab monotherapy to serve as a basis for understanding the potential added benefit of combination therapy. An additional cohort will be dedicated to tumor types from the escalation inclusion criteria that do not currently have a dedicated expansion cohort or plans for evaluation in other studies.

In addition, a clinical pharmacology substudy will be conducted to characterize the effect of BMS-986205 on QTc intervals.

The starting dose of BMS-986205 is 25 mg orally daily. Nivolumab will be administered at a dose of 240 mg Q2W for the dose escalation (Part 1) and for the dose expansion (Part 2) cohorts that predated Amendment 06. Nivolumab will be administered at a dose 480 mg intravenously Q4W for the dose expansion cohorts added with and after Amendment 06 (melanoma, NSCLC, and additional signal-seeking tumors; renal cell carcinoma) and the clinical pharmacology substudy.

A schematic of Parts 1 and 2 and the pharmacologic substudy is provided in Figure 1.

Figure 1: **Study Design Schematic for Parts 1 and 2 and Clinical Pharmacology Substudy**



*Note: As of Amendment 06, dose escalation beyond 400 mg BMS-986205 may not occur provided that additional pharmacodynamic effect is unlikely.

**Note: The BRAF mutated, post-BRAFi regimen melanoma subjects will be randomized to receive either nivolumab or BMS-986205 + nivolumab.

Abbreviations: CNS = central nervous system; CTLA-4 = cytotoxic T lymphocyte-associated antigen 4; DLBCL = diffuse large B-cell lymphoma; I-O = immuno-oncology; MAD = maximum administered dose; MTD = maximum tolerated dose; Nivo = nivolumab; NSCLC = non-small cell lung cancer; PD-L = programmed cell death; PD-L1 = programmed death receptor-ligand 1; PD-(L)1 = either PD-1 or PD-L1; SCCHN = squamous cell carcinoma of the head and neck.

Please refer to Table 3.1.6-1 in the protocol body for a detailed description of the Part 2 dose expansion cohorts.

Part 3: Part 3 will include the initial safety evaluation and cohorts of the combination of BMS-986205, nivolumab, and ipilimumab in melanoma, NSCLC, and bladder cancer. Subjects with each tumor type will receive BMS 986205 in combination with a different regimen of nivolumab and ipilimumab based on safety and efficacy data observed in previous trials of nivolumab and ipilimumab in that tumor type (see Section 1.1 of the protocol).

For the safety cohorts, the initial dose level of BMS-986205 for each cohort will be based on the available of safety, PK, and PD data for BMS-986205 in combination with nivolumab and any available data from the combination with nivolumab and ipilimumab. The starting dose will not exceed 100 mg in any cohort.

The regimens will consist of:

Melanoma (Ipi 1Q8): BMS 986205 in combination with nivolumab 480 mg Q4W and ipilimumab 1 mg/kg Q8W, all given continuously.

NSCLC (Ipi 1Q6): BMS-986205 in combination with nivolumab 360 mg Q3W and ipilimumab 1 mg/kg Q6W, all given continuously.

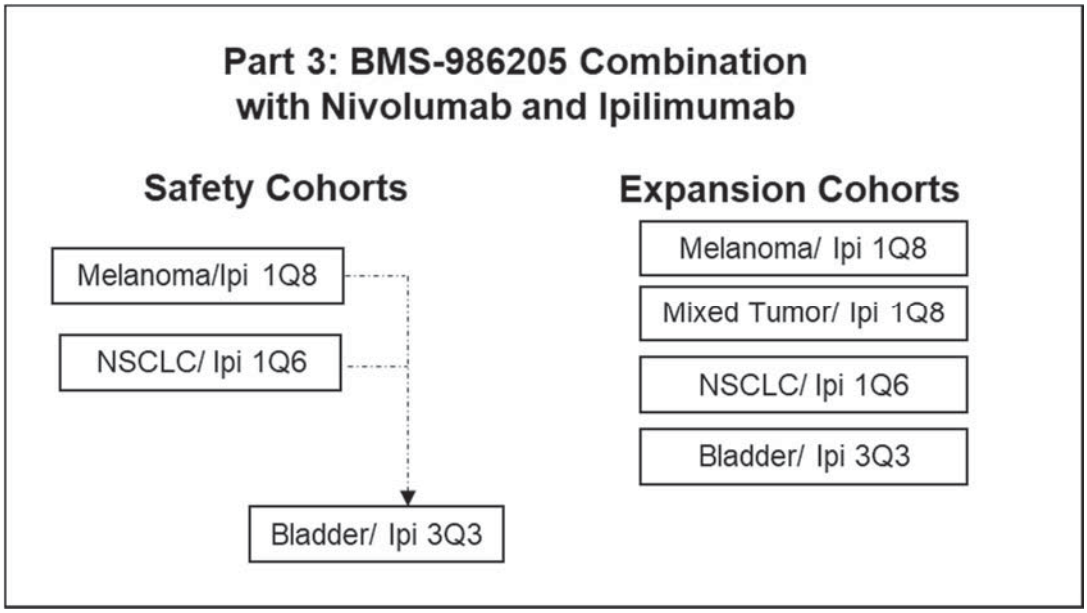
Bladder (Ipi 3Q3): BMS-986205 given continuously, first in combination with nivolumab 80 mg and ipilimumab 3 mg/kg both given Q3W for 4 doses, followed by nivolumab 480 mg Q4W continuously

Evaluation of each regimen will begin with an assessment of safety and tolerability of the triplet combination therapy in a limited number of subjects, including a sentinel subject, in a safety evaluation cohort. The melanoma and NSCLC safety cohorts will begin safety enrollment simultaneously since the dose of ipilimumab is similar between the cohorts. Furthermore, for nivolumab dosing, the 480 mg Q4W and 360 mg Q3W are expected to achieve similar average exposure. The safety evaluation for the bladder regimen will begin enrolling subjects once either the melanoma or NSCLC regimen has been found to be safe and tolerable, as the bladder regimen uses a higher dose (3 mg/kg Q3W) of ipilimumab relative to the melanoma and NSCLC cohorts (1 mg/kg Q6W and Q8W of ipilimumab) during the DLT evaluation period.

Once the initial safety and tolerability have been established independently for each regimen with a given tumor type, subjects will begin enrolling in expansion cohorts for that tumor type Additionally, subjects may be enrolled into a mixed tumor type cohort using the Ipi 1Q8 regimen (nivolumab 480 mg Q4W and ipilimumab 1 mg/kg Q8W) for further evaluation of safety and tolerability, as well as preliminary evaluation of anti-tumor efficacy once the safety of Ipi 1Q8 is established in the melanoma cohort.

The study design schematic for Part 3 is presented in Figure 2.

Figure 2 Study Design Schematic for Part 3



Abbreviations: NSCLC--Non-small cell lung cancer

Study Periods:

Subjects will complete up to 4 periods of the study: Screening, Treatment, Clinical/Safety Follow-up, and Survival/Long-term follow-up, as described below:

Screening (up to 28 days): Subjects will sign consent and be evaluated for study eligibility.

Treatment Phase:

Parts 1 and 2:

Each treatment cycle consists of up to twelve 4-week treatment cycles. For subjects receiving nivolumab on the Q2W regimen, each treatment cycle is composed of a daily oral dose of BMS-986205 and 2 doses of nivolumab administered intravenously Q2W on Days 1 and 15. For subjects receiving nivolumab on the Q4W regimen, each cycle is composed of a daily oral dose of BMS-986205 and 1 dose of nivolumab on Day 1. In addition, Part 1 (dose escalation) and the QTc substudy will start with Cycle 0, a lead-in period of 2 weeks duration, during which monotherapy with BMS-986205 is administered.

Following every 2 treatment cycles (8 weeks), the decision to treat a subject with additional cycles of study drug will be based on radiological tumor assessments (initial evaluation performed at baseline, end of Cycle 2, and every 8 weeks). Assessment of partial response (PR) and complete response (CR) must be confirmed at least 4 weeks following initial assessment. Tumor progression or response endpoints will be assessed using Response Evaluation Criteria In Solid Tumors (RECIST) Version 1.1 criteria for solid tumors or International Working Group [IWG] criteria for Hodgkin's and non-Hodgkin's lymphoma.

Part 3:

For subjects receiving the melanoma/Ipi 1Q8 regimen containing nivolumab 480 mg Q4W and ipilimumab 1 mg/kg Q8W, 1 cycle will consist of 2 doses of nivolumab and 1 dose of ipilimumab (ie, 8 weeks).

For subjects receiving the NSCLC/Ipi 1Q6 regimen containing nivolumab 360 mg Q3W and ipilimumab 1 mg/kg Q6W, 1 cycle will consist of 2 doses of nivolumab and 1 dose of ipilimumab (ie, 6 weeks).

For subjects receiving the bladder/Ipi 3Q3 regimen, during nivolumab and ipilimumab combination dosing, the first 2 cycles will each consist of 2 doses of nivolumab and ipilimumab (each cycle is 6 weeks); after the first 2 cycles, each subsequent cycle will be comprised of 1 dose of nivolumab (ie, 4 weeks).

For subjects receiving the mixed tumor type regimen containing nivolumab 480 mg Q4W and ipilimumab 1 mg/kg Q8W, 1 cycle will consist of 2 doses of nivolumab and 1 dose of ipilimumab (ie, 8 weeks)

Timing of imaging assessments will be based on the regimen the subject is receiving:

Melanoma/Ipi 1Q8: The first imaging assessment will occur at Week 12 (± 1 week); subsequent imaging will be every 8 weeks (± 1 week) thereafter throughout the treatment period.

NSCLC/Ipi 1Q6: The first imaging assessment will occur at Week 6 (± 1 week), and then every 6 weeks (± 1 week) throughout the treatment period.

Bladder/Ipi 3Q3: The first imaging assessment will occur at Week 6 (± 1 week), and then every 6 weeks (± 1 week) during the treatment period up to 24 weeks, after which they will occur every 12 weeks (± 1 week) thereafter throughout the treatment period.

Mixed tumor type/Ipi 1Q8 cohort: The first imaging assessment will occur at Week 8 (± 1 week); subsequent imaging will be every 8 weeks (± 1 week) thereafter throughout the treatment period.

The decision to treat a subject with additional cycles of study drug will be based on the most recent radiological tumor assessment preceding that dose. Assessments of PR and CR must be confirmed at least 4 weeks after the initial assessment. Tumor progression or response endpoints will be assessed using RECIST v1.1 criteria

Treatment beyond progression in all study Parts may be allowed in select subjects with initial RECIST v1.1 or IWG-defined progressive disease (PD) if the benefit/risk assessment favors continued administration of study therapy (eg, subjects are continuing to experience clinical benefit as assessed by the investigator, tolerating treatment, and do not meet treatment discontinuation criteria as specified in Section 3.5 in the protocol body).

Treatment with Additional Cycles beyond 48 weeks: Subjects completing approximately 48 weeks of study therapy in all study Parts with ongoing disease control (CR, PR or stable disease [SD]) may be eligible for an additional 48 weeks of study therapy at the originally assigned dose regimen in all study Parts beyond the initial 48 weeks, on a case-by case basis, after careful evaluation and discussion with the BMS Medical Monitor to determine whether the benefit/risk ratio supports administration of further study therapy. Subjects whose last assessment of the initial 48-week period shows PD will also be eligible to continue to additional cycles (up to a maximum of 2 years from first dose) if they are still deriving clinical benefit, as per the guidance of treatment beyond progression (Section 3.5.1 in the protocol body). For subjects in the bladder triplet combination regimen, ipilimumab will not be re-administered during additional treatment; only BMS-986205 and nivolumab (480 mg Q4W) will continue. Upon completion of 48 weeks of study therapy (or up to a maximum of 96 weeks if applicable), all subjects will enter the Clinical/Safety Follow-up period.

Clinical/Safety Follow-up period: Upon completion of 48 weeks of study therapy (or up to a maximum of 96 weeks if applicable), all subjects will enter the Clinical/Safety Follow-up period once the decision is made to discontinue the subject from treatment (eg, at end of treatment [EOT]).

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

Subjects who discontinue the treatment phase will enter the Clinical/Safety Follow-up period. Subjects must be followed for at least 100 days (representing approximately 5 half-lives for nivolumab) after the last dose of study drug. Follow-up visits should occur at Days 30, 60, and 100 (±10 days) after the last dose of study drug or should coincide with the date of discontinuation (±10 days) if date of discontinuation is greater than 30 days after the last dose of study drug to monitor for AEs. All subjects will be required to complete 3 Clinical/Safety Follow-up visits regardless of whether they start new anti-cancer therapy, except those subjects who withdraw consent for study participation.

Survival/Long-term/Response Follow-up: After completion of the Clinical/Safety Follow-up period, all subjects will then enter the Survival/Long-term Follow-up period. During this period, clinic visits or telephone contact every 3 months will be performed to assess survival status. The duration of the Survival/Long-term Follow-up period will be approximately 2 years following the first dose of study drug, and a minimum of 12 months following the last dose of study drug.

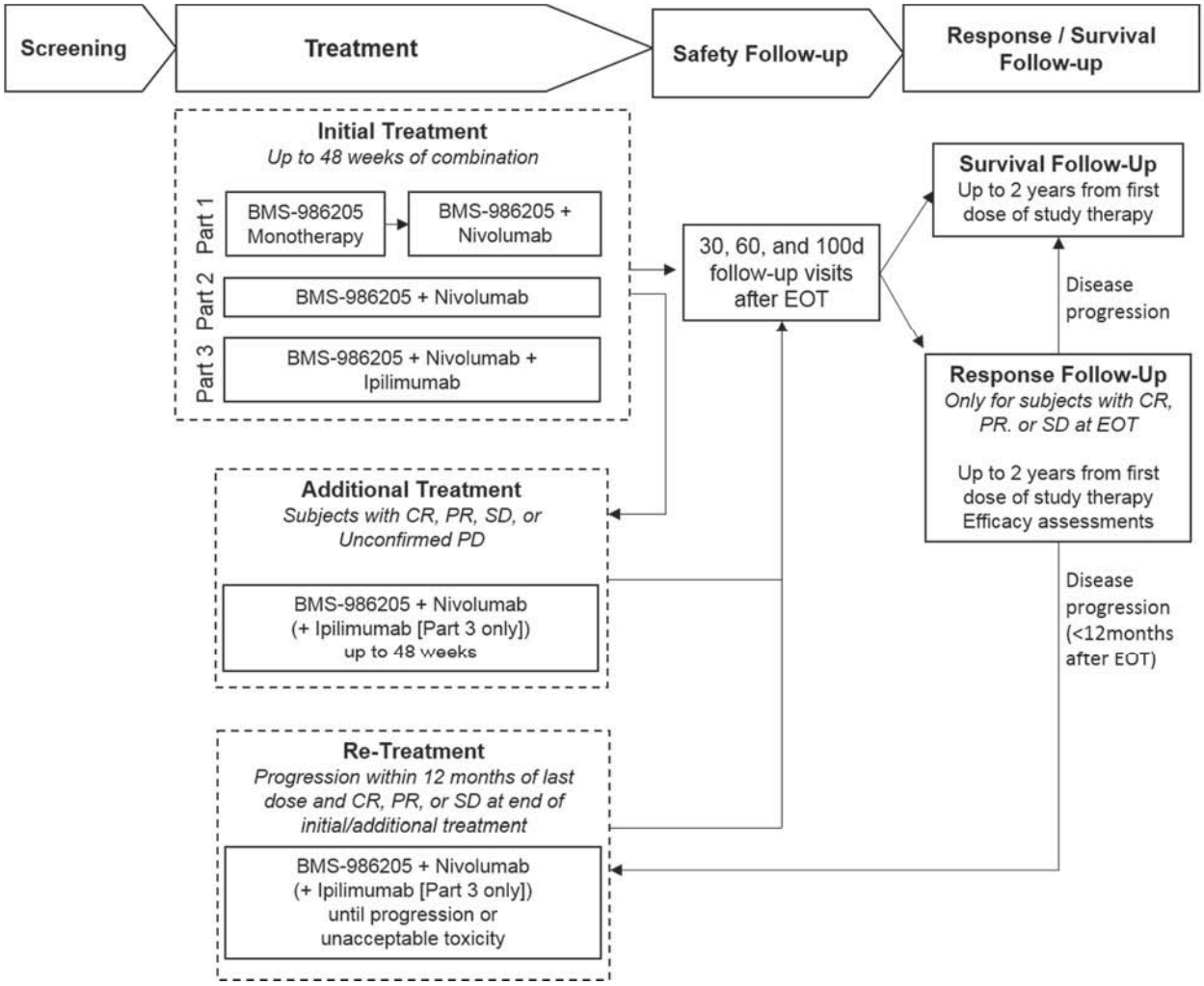
After completion of the Safety Follow-up period, subjects who discontinue study with ongoing SD, PR, or CR at the EOT visit will enter the Response Follow-up period. This period will occur simultaneously with the Survival Follow-up period for these subjects. These subjects will continue to have tumor radiological and clinical tumor assessments every 3 months (every 12 weeks) during the Response Follow-up period or until disease progression or withdrawal of study. Radiological tumor assessments for subjects who have ongoing clinical benefit may continue to be collected after subject complete the survival phase of the study.

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

Data from imaging assessments for subjects who have ongoing clinical benefit may continue to be collected after subjects complete the survival phase of the study.

Re-treatment during Survival/Long-term Follow-up with the originally assigned study therapy regimen (eg, same dose and dose schedule) or modified dose regimen may be permitted within 12 months of last dose of study therapy for subjects who enter Safety/Survival/Long-term Follow-up with ongoing disease control (CR, PR, or SD) for reasons other than drug-related toxicity after discussion and agreement with the BMS Medical Monitor that the benefit/risk assessment favors re-treatment, and the subject continues to meet eligibility criteria for treatment with study therapy as outlined in Section 3.5.1 of the protocol. Subjects meeting criteria for re-treatment will be treated for a maximum of 2 years from the first dose of nivolumab, at the same dose and schedule administered during their initial treatment, unless that dose and scheduled was subsequently found to exceed the MTD, in which case the subject will be treated at the next lower, or alternate dose and schedule (Table 1 in Synopsis). Subjects entering this phase will follow the Time and Events schedule as outlined in Section 5 of the protocol.

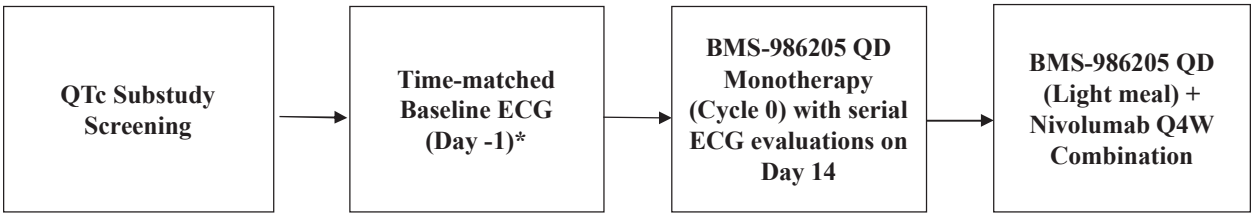
Figure 3: Treatment and Follow-Up Schematic for CA017003



Note: For Part 3 bladder cohort, Additional Treatment will not include ipilimumab

Abbreviations: CR = complete response; EOT= end of treatment; MM = Medical Monitor; PR= partial response; PD = progressive disease; SD = stable disease.

Figure 4: Study Schematic of Clinical Pharmacology QTc Substudy



*: Baseline ECGs should be collected prior to the start of Cycle 0 (Day -1 preferred, up to 5 days prior to Cycle 0 is allowed).

Abbreviations: ECG = electrocardiogram; Q4W = every 4 weeks; QD = once daily.

Part 1: Dose Escalation:

The Part 1 dose escalation phase of the study will evaluate the MTD/MAD/alternate dose of BMS-986205 in combination with nivolumab based on DLTs using a Bayesian Logistic Regression Method (BLRM) model (for BMS-986205 monotherapy lead-in) and BLRM-copula model (for BMS-986205 in combination with nivolumab). The Bayesian models will be used for recommendation of the next dose to be investigated. BLRM (combined with copula) framework with an escalation with overdose control principle will be employed to ensure that safety is not compromised during dose escalation.

The initial dose level of BMS-986205 will be 25 mg administered orally daily. Once initial lead-in monotherapy (Cycle 0) is deemed tolerable, combination with 240 mg flat dose nivolumab at the same dose level with the same subject (Cycle 1) will be initiated.

Dose levels to be considered for the next combination cohort (with monotherapy lead-in) will be based on recommended monotherapy dose from BLRM and recommended combination dose from BLRM-copula. The lower dose from these 2 recommendations will be considered. Potential dose levels for dose escalation are provided in Table 1 in the synopsis. The maximum allowable increase in dose will be 100%. Final dose selection for the next cohort/dose level will be made in conjunction with all data available from PK, and pharmacodynamic assessments, and will be made after discussion and agreement between investigators and BMS Medical Monitor. Accordingly, intermediate or lower doses, or less frequent dosing of BMS-986205 may be tested if none of the planned doses/schedules are found to be tolerated as lead-in phase or in combination with nivolumab.

Approximately 30 subjects will be treated in the dose escalation phase. Depending on the dose recommendation, more than 3 subjects can be treated at each dose level. Increments of approximately 3 subjects will be added to each dose level depending on model recommendation and clinical judgment. Once the safety of any dose level has been established, up to 12 additional subjects may be added to better characterize the PK and pharmacodynamic profile.

Cohort-tolerability assessment and subsequent dose recommendation will occur when 2 DLT-evaluable subjects within a subject cohort have completed the 6-week DLT observation period (see Section 4.5.1 of the protocol for criteria for DLTs). DLTs occurring within the 2 weeks of the lead-in period (DLT observation period for monotherapy) will be used to fit BLRM model for monotherapy. DLTs occurring within the 4 weeks of combination period (DLT observation period for combination) will be used to fit BLRM-copula model. The lower recommended dose from both models will be considered for next dose escalation. Subjects who received ≥ 75% of BMS-986205 doses and 2 doses of nivolumab, and have been followed at least 5 days after second nivolumab dose in the 6-week DLT observation period will be considered as DLT-evaluable subjects. Continuous re-assessment of dose recommendation by BLRM will be carried out at each dose level after each cohort of subjects with consideration of all available DLT information.

The MTD/MAD/alternate dose of BMS-986205 in combination with nivolumab selected cohort will be based on evaluating the recommendation from BLRM-copula and a synthesis of all available data, including clinical and laboratory safety assessments, PK, pharmacodynamic, and efficacy data, from all treated subjects at each dose level up to the MTD/MAD.

No intra-subject dose escalation is allowed, although dose modifications may be permitted (see Section 4.5.3).

Sentinel Subject: During dose escalation, a staggered dosing (sentinel subject) approach will be used for the first subject in the first dose level of both lead-in and combination. The first subject in both lead-in and combination will

receive Cycle 0 Day 1 dose of study drugs, and be observed for 5 days before additional subjects, ie, subject 2 onward in that cohort receive study drug. The first subjects to be dosed in subsequent cohorts will not be required to observe the 5-day interval between treatment start dates.

Table 1: Dose Escalation Schedule

Dose Level	BMS-986205	Nivolumab
-1	DL-1	240 mg IV Q2W
1	25 mg	240 mg IV Q2W
2	50 mg	240 mg IV Q2W
3	100 mg	240 mg IV Q2W
4	200 mg	240 mg IV Q2W
5	400 mg	240 mg IV Q2W
6	600 mg	240 mg IV Q2W
7	800 mg	240 mg IV Q2W

Note: As of Amendment 06, dose escalation beyond 400 mg BMS-986205 may not occur provided that additional pharmacodynamic effect is unlikely.

Note: Up to 12 additional subjects may be added per selected dose levels to provide additional safety, tolerability and PK data. This information will be incorporated into final recommendation for MTD/MAD/alternate dose of BMS-986205.

Abbreviations: DL-1 = dose level-1; IV = intravenous; MAD = maximum administered dose; MTD = maximum tolerated dose; PK = pharmacokinetic; Q2W = every 2 weeks.

Part 2: Dose Expansion:

The purpose of dose expansion is to gather additional safety, tolerability, preliminary efficacy, PK, and pharmacodynamic information regarding BMS-986205 in combination with nivolumab.

Continuous evaluation of toxicity events in the cohort expansions will be performed throughout enrollment in the expansion cohorts. If, at any time, the aggregate rate of treatment-related toxicities meeting DLT criteria exceeds 33% across all subjects treated in cohort expansions, the findings will be discussed and further enrollment may be interrupted. At that time, depending on the nature and grade of the toxicity and after assessing the risk/benefit ratio, a new dose(s) of BMS-986205 for all cohorts may be initiated at a previously tested lower dose level or at a dose level intermediate to previously tested lower dose levels. Additionally, at the discretion of the Sponsor, and in agreement with the investigators, the 480 mg Q4W nivolumab dosing regimen in the designated expansion cohorts and clinical pharmacology substudy may revert back to 240 mg Q2W based on emerging PK, pharmacodynamic, and/or tolerability data from the cohort expansion portion of the study.

Eight disease-restricted populations will be included in cohort expansion. These include cervical cancer, DLBCL, SCCHN, bladder cancer, melanoma, NSCLC, renal cell cancer, and pancreatic cancer. Various subpopulations of melanoma and NSCLC will be included in separate cohorts to further understand the role of IDO1 inhibition in these specific populations (see Table 3.1.5-1 in the protocol body). The BRAF mutated, post-BRAF regimen melanoma subjects will be randomized to receive either nivolumab or BMS-986205 in combination with nivolumab in order to generate a robust, prospective dataset with nivolumab monotherapy to serve as a basis for understanding potential added benefit of combination therapy. An additional cohort will be dedicated to tumor types from the escalation inclusion criteria, which do not currently have a dedicated expansion cohort or plans for evaluation in other studies. The eligible tumor types will be triple negative breast cancer, adenocarcinoma of the endometrium, epithelial cancer of the ovary, and sarcoma. During dose expansion, the Simon 2-stage (optimal) design will be used as a guide for some of the tumor-specific expansion cohorts. Those indications will be classified into 3 categories according to different sample size modeling settings: SCCHN and bladder cancer in a group; cervical cancer, DLBCL, melanoma with prior anti- programmed death receptor-(ligand) 1 (PD-[L]1) therapy, NSCLC with prior anti-PD-(L)1 therapy,

and pancreatic cancer in a different group; and melanoma with prior anti-PD-(L)1 and anti-cytotoxic T lymphocyte-associated antigen 4 (CTLA-4) therapy in another group will be analyzed using a Simon 2-stage design.

Part 3 BMS-986205, Nivolumab, and Ipilimumab Combination

Part 3 of the study will include an initial safety evaluation cohorts of 3 regimens of nivolumab and ipilimumab in combination with BMS-986205 in melanoma, NSCLC, and bladder cancer. Expansion cohorts for each regimen will then be conducted in the tumor type evaluated in the safety cohorts. The Ipi 1Q8W regimen will also be evaluated in a mixed cohort of other tumor types evaluated in Part 1. Each tumor type will receive BMS-986205 in combination with a specific nivolumab and ipilimumab regimen (see Section 3.1.1.2).

For the safety cohorts, the initial dose level of BMS-986205 for each cohort will be based on the available of safety, PK, and PD data for BMS-986205 in combination with nivolumab and any available from the combination with nivolumab and ipilimumab. The starting dose will not exceed 100 mg in any safety cohort. Lower dose levels of BMS-986205 (if required) to be evaluated in each safety cohort will be based on Table 3.1.5-1. Intermediate or lower doses, or less frequent dosing of BMS-986205 may be tested if none of the planned doses/schedules are found to be tolerated. In addition, alternative lower doses and more intermittent schedules of nivolumab and/or ipilimumab may be evaluated if the specified regimen used in each tumor type safety cohort is not found to be tolerable with any of the doses of BMS-986205 outlined in Table 3.1.5-1. Safety will be evaluated independently for each tumor type/regimen combination and treatment regimen based on DLTs using a BLRM-copula model.

All safety cohorts will begin with an assessment of safety and tolerability of the triplet combination regimen in a limited number of subjects. As described in Section 3.1.1.2, the NSCLC/Ipi 1Q6 and melanoma/Ipi 1Q8 regimen cohorts will begin enrollment first, followed by the bladder/Ipi 3Q3 regimen cohort once safety and tolerability have been established in either NSCLC/ Ipi 1Q6 or melanoma/Ipi 1Q8. Initially, approximately 3 subjects will be treated at the selected dose combination of BMS-986205 with nivolumab and ipilimumab. The first subject in each safety cohort will be a sentinel subject who will be observed for 5 days after administration of the first combination dose to ensure safety and tolerability before other subjects can receive treatment within that cohort.

Due to the potential for early discontinuation, an additional subject(s) may be enrolled to ensure approximately 3 DLT-evaluable subjects. Initial safety assessment to allow enrollment in the bladder/ Ipi 3Q3 safety cohort will occur when at least 2 evaluable subjects in either the NSCLC/ Ipi 1Q6 or melanoma/ Ipi 1Q8 safety cohorts have completed a 6-week DLT evaluation period (see Section 4.5.1 for criteria for DLTs). In the melanoma and NSCLC safety evaluation cohorts, if a potential DLT occurring in any third evaluable subject in the specific dose combination does not influence the recommendation by BLRM (-Copula) to open enrollment in the bladder safety cohort, then the bladder safety cohort may proceed with enrollment without waiting for the third subject to complete the corresponding DLT observation period.

DLT-evaluable subjects will be defined as subjects who in the 6-week DLT evaluation period received ≥ 75% of BMS-986205 doses and the following nivolumab and ipilimumab doses for each regimen:

- Melanoma/ Ipi 1Q8: 2 doses of nivolumab and 1 dose of ipilimumab, and followed for at least 5 days after the second dose of nivolumab
- NSCLC/ Ipi 1Q6: 2 doses of nivolumab and 1 dose of ipilimumab, and followed for at least 5 days after the second dose of nivolumab
- Bladder/ Ipi 3Q3: 2 doses of nivolumab and 2 doses of ipilimumab, and followed for at least 5 days after the second dose of each drug

After the initial subjects in each treatment regimen are evaluated, additional increments of approximately 3 to 6 subjects will be treated in the same safety cohort as per the BLRM-copula model recommendation that the dose combination is safe. At least 6 DLT-evaluable subjects will be treated and assessed for a particular BMS-986205 dose in that tumor type/regimen cohort before enrollment in the expansion cohorts for that regimen will begin enrollment. Up to 12 DLT-evaluable subjects in total may be treated in each safety evaluation cohort at the BMS-986205 dose chosen for expansion regimens for further evaluation of safety and pharmacodynamic/PK parameters as required. BLRM (-copula) will be used to monitor the safety of each triplet dose combination on an ongoing basis.

Once the initial safety and tolerability have been established independently for each regimen based on the safety cohorts, enrollment will then begin in expansion cohorts for further evaluation of safety and tolerability, as well as preliminary evaluation of anti-tumor efficacy. In the expansion cohorts, BMS-986205 will be administered at a dose determined to be tolerable in combination with each nivolumab and ipilimumab regimen. Each BMS-986205 and nivolumab/ipilimumab combination regimen will be evaluated in tumor-specific cohorts based on the tumor type evaluated in the safety cohorts. The Ipi 1Q8 regimen will also be evaluated in a mixed tumor-type cohort which may incorporate tumor types evaluated in Part 2 Dose Escalation.

The 3 tumor types for tumor-restricted cohorts will be melanoma, NSCLC, and bladder. As all subjects in these disease-specific cohorts will be receiving agents (nivolumab and ipilimumab) with known anti-tumor activity in those tumor types, a single-stage design will be utilized for each of these tumor types. Approximately 40 subjects will be treated in each of the following expansion cohorts: melanoma PD-L1 positive, melanoma PD-L1 negative, NSCLC PD-L1 positive, NSCLC PD-L1 negative, and bladder; this is to allow for the exploration of early efficacy signals of BMS-986205 in combination with both nivolumab and ipilimumab in relevant subpopulations. In each NSCLC expansion cohort, approximately 10 subjects will be IO-treatment naive, 25 will be treatment-naive, and 5 IO-therapy experienced. In the melanoma cohorts, approximately 35 will be treatment naïve in the advanced setting and 5 will be IO-therapy experienced in each cohort. In the bladder expansion cohort in Part 3, at least 30 subjects will be I-O therapy naive.

A mixed tumor type expansion cohort will also be evaluated, using the same regimen as in the melanoma safety cohort, Ipi 1Q8W. The purpose of this cohort is to obtain preliminary safety, tolerability, and efficacy data in tumor types besides melanoma using the nivolumab 480 mg Q4W/Ipilimumab 1 mg/kg Q8W backbone in combination with BMS-986205 at the dose selected for melanoma expansion cohort. Up to forty subjects may be treated in this cohort. Tumor types included in this cohort may be any previously evaluated in Part 2. All subjects in this cohort will be IO-treatment naive. Selection of tumor types and number of subjects per tumor type will be at the discretion of the Sponsor and based on emerging data from Part 2 of this study as well as other external data (e.g. from studies of nivolumab and ipilimumab in a particular tumor type). For each tumor type enrolled into this cohort, approximately 6 subjects will be initially evaluated for safety and tolerability for 6 weeks each for toxicities meeting the definition of DLT exceeding the threshold defined below prior to enrollment of any other subjects with that tumor type.

Continuous evaluation of toxicity events in the expansion cohorts will be performed throughout enrollment in the expansion cohorts. If, at any time, the aggregate rate of treatment-related toxicities meeting DLT criteria within an individual tumor type/treatment regimen exceeds 33% across all subjects treated in the safety evaluation and dose expansion cohorts, the findings will be discussed and further enrollment may be interrupted. At that time, depending on the nature and grade of the toxicities and after assessing the risk/benefit ratio, a new dose(s) of BMS-986205 for subjects within that cohort may be initiated at a previously tested lower dose level evaluated in Part 1or at a dose level intermediate to previously tested lower dose levels in Part 1.

Duration of Study: The total duration of time for any individual subject is expected to be approximately 2.5 years. The total duration of the study is expected to be 5 years from the onset of the first visit of the first subject to the required Survival/Long-term Follow-up of the last subject enrolled.

Study Population: Male and/or female subjects who are at least 18 years old and satisfy eligibility by medical history, physical examination (PE), 12-lead electrocardiogram (ECG), and clinical laboratory evaluations will be included to participate in the study.

Women of childbearing potential (WOCBP) must not be nursing or pregnant and must be using an acceptable method of contraception. WOCBP must have a negative pregnancy test within 24 hours prior to dosing with study drug.

Study Drug: Includes both investigational [medicinal] products and non-investigational [medicinal] products as listed in Table 2.

Table 2: Study Drugs for CA017003

Medications	Potency	IP/Non-IMP
BMS-986205-04 Capsule	5 mg	IP
BMS-986205-04 Capsule	50 mg	IP
BMS-986205-04 Tablet	25 mg	IP
BMS-986205-04 Tablet	50 mg	IP
BMS-986205-04 Tablet	100 mg	IP
Nivolumab Injection	10 mg/mL (100 mg/vial)	IP
Ipilimumab Injection	5 mg/ml (200 mg/vial)	IP

Abbreviations: IMP = investigational medicinal product; IP = investigational product.

Study Assessments:

- Safety Outcome Measures: Safety assessments will be based on medical review of AE reports and the results of vital sign measurements, ECGs, PEs, and clinical laboratory tests. AEs will be coded using the most current version of Medical Dictionary for Regulatory Activities (MedDRA) and the incidence of observed AEs will be tabulated and reviewed for potential significance and clinical importance. AEs will be assessed continuously during the study and for 100 days after the last dose of nivolumab. Both AEs and laboratory tests will be graded using the NCI CTCAE v4.03.
- Pharmacokinetic Measures: Serial plasma and urinary samples for BMS-986205 [redacted] will be collected from all subjects at specified time points during BMS-986205 monotherapy. PK parameters to be assessed following multiple- and single-dose administration are listed in Section 5.5 of the protocol body. Plasma samples of BMS-986205 will be collected during combination treatment. Plasma concentration data will be tabulated using summary statistics. [redacted]
- Efficacy Measure: Disease assessment with computed tomography and/or magnetic resonance imaging, as appropriate, will be performed at baseline, end of Cycle 2 and every 8 weeks until end of treatment or until subjects withdraw from the study in Part 2, and using the schedules detailed above for Part 3 until end of treatment or until subjects withdraw from the study.. In all Parts, disease assessment will continue every 12 weeks for the first year after the EOT visit, and then every 6 months thereafter, up to 2 years following the EOT visit. until disease progression, at the completion of follow-up, or until subjects withdraw from the study. For subjects with Hodgkin's lymphoma (HL) and non-Hodgkin's lymphoma (NHL), positron emission tomography will be performed at baseline and in order to confirm a CR. Disease assessments at other time points may be performed as clinically indicated. In all study parts, scans will be collected centrally and may be reviewed by a blinded independent central review (BICR) at a later date, or at any time during the study per Sponsor request. Changes in tumor measurements and tumor responses will be assessed by the investigator using RECIST or IWG criteria. Investigators will also report the number and size of new lesions that appear while on study. The tumor assessment time points will be reported on the case report form based on investigators' assessment using RECIST or IWG criteria. Please refer to Appendix 3 for specifics of RECIST v1.1 and Appendix 4 for specifics of the IWG criteria to be utilized in this study.
- For subjects with marrow involvement at screening, a bone marrow biopsy and aspirate will be required to confirm a CR

- Biomarker Measures: Blood and tumor samples will be collected at the times indicated in Section 5.6 of the protocol for the measurement of biomarkers relevant to dose selection [redacted]. Further details of blood and tumor collection and processing will be provided to the site in the procedure manual.
- Immunogenicity Measures: Serum samples to evaluate the development of anti-drug antibody (ADA) response to nivolumab and ipilimumab (where applicable) in combination with BMS-986205 will be collected at specified time points.

Statistical Considerations:

Sample Size Determination:

Part 1 Dose Escalation:

As a Phase 1 dose-escalation trial, the sample size at each dose in these arms depends on observed toxicity and posterior inference. For BMS-986205 in combination with nivolumab (with BMS-986205 lead-in), approximately 30 subjects are expected to be treated during the dose escalation phase. Initially, approximately 3 subjects will be treated at the starting dose levels of BMS-986205 in combination with nivolumab. Due to the potential for early discontinuation, additional subject(s) may be enrolled to ensure approximately 3 evaluable subjects at each dose level. Additional increments of approximately 3 evaluable subjects will be treated in recommended dose levels per BLRM(-Copula) model during the dose escalation phase. At least 6 DLT-evaluable subjects will be treated in the selected dose cohort(s) chosen for expansion. Due to the BMS-986205 lead-in period, more than 3 subjects per cohort may be treated per BMS-986205 dose level considering potential DLTs that may happen within the lead-in period.

Part 2 Dose Expansion:

Eight disease-restricted populations and 1 cohort for various tumors will be included in cohort expansion. These are cervical cancer, DLBCL, SCCHN, bladder cancer, NSCLC, melanoma, renal cell carcinoma and pancreatic cancer. An additional cohort will be dedicated to tumor types from the escalation inclusion criteria, which do not currently have a dedicated expansion cohort or plans for evaluation in other studies. The eligible tumor types will be triple negative breast cancer, adenocarcinoma of the endometrium, epithelial cancer of the ovary, and sarcoma.

A Simon 2-stage (optimal) design will be used as a guide for many of the tumor-specific cohorts (see below for exceptions). The 2-stage design with a reasonable false positive rate (FPR) and false negative rate (FNR), based on assumptions of true (target) and historic objective response rate (ORR) for each indication, will provide guidance for the total sample size for each cohort. The sample sizes are provided in Table 3 although not used for hypothesis testing. Enrollment will be continued during initial efficacy evaluation (ie, with the indicated number of subjects at Stage 1) to ensure that additional subjects are enrolled to account for unexpected trial impact, such as response non-evaluable subjects due to early drop out, design parameter change (eg, historical rate update), and so on.

Table 3: Dose Expansion: Example of the Simon 2-stage Design Characteristics

Expansion Cohort	Historic ORR (%)	Target ORR (%)	Stage 1/ Total N	Stage 1 Responses Futility Boundary	Alpha/ Power (%)	Probability of Early Stopping (%)
Cervical, Melanoma: Prior anti-PD-(L)1, Pancreatic, NSCLC: Prior anti-PD-(L)1, and DLBCL	10	30	12/35	1	10/90	66
Bladder and SCCHN	25	50	10/27	2	10/90	53
Melanoma: Prior anti-PD-(L)1 and anti CTLA-4	5	20	12/37	0	10/90	54

*Note: For the melanoma, prior anti-PD-(L)1 and prior anti-PD-(L)-1/anti-CTLA-4 cohorts, the analysis will be focused on approximately 35 subjects who are BRAF wild-type (WT).

Abbreviations: CTLA-4 = cytotoxic T lymphocyte-associated antigen 4; DLBCL = diffuse large B cell lymphoma; I-O = immuno-oncology; NSCLC = non-small cell lung cancer; PD-1 = programmed cell death; PD-L1 = programmed death receptor-ligand 1; PD-(L)1 = either PD-1 or PD-L1; ORR = objective response rate; SCCHN = squamous cell cancer of the head and neck.

For an expansion cohort of approximately 35 subjects in the cervical, melanoma: prior anti-PD-(L)1, pancreatic, NSCLC: prior anti-PD-(L)1, and DLBCL cohorts, and an assumed true response rate of 30%, there is a 94% chance of observing at least 7 responses (in other words, the FNR is 6%). If the true response rate is only 10% rather than 30%, then there is a 6% chance that there will be at least 7 responses in 35 subjects (in other words, FPR is 6%). Also, if 7 responses are observed (eg, 20% observed response rate), the lower bound of the 80% confidence interval (CI) for the ORR is 11% (higher than historical ORR of 10%). The CI is calculated using Clopper-Pearson method.

For an expansion cohort of approximately 27 subjects in the bladder and SCCHN tumors and assumed true response rate is 50%, there is a 88% chance of observing at least 11 responses (in other words, the FNR is 12%). If the true response rate is only 25% rather than 50%, then there is a 5% chance that there will be at least 11 responses in 27 subjects (in other words, FPR is 5%). If 11 responses are observed (eg, 40% observed response rate), the lower limit of the 80% CI for the ORR is 28% (higher than historical ORR of 25%). The CI is calculated using Clopper Pearson method.

For an expansion cohort of approximately 37 subjects with melanoma with prior anti-PD-(L)1 and anti-CTLA-4 therapy, and an assumed true response rate of 20%, there is a 85% chance of observing at least 5 responses (in other words, the FNR is 15%). If the true response rate is only 5% rather than 20%, then there is a 14% chance that there will be at least 5 responses in 37 subjects (in other words, FPR is 14%). Also, if 5 responses are observed (eg, 14% observed response rate), the lower bound of the 80% CI for the ORR is 7% (higher than historical ORR of 5%). The CI is calculated using the Clopper-Pearson method.

The Simon 2-stage design will not be used for the mixed cohort of additional signal seeking tumor types. Approximately 35 to 40 subjects will be enrolled to allow for the exploration of early efficacy signals seen during the dose escalation portion of the trial as well as potential signals arising from ongoing trials of other IDO1 inhibitors in combination with anti-PD-(L)1. A 2-stage design will also not be utilized for the I-O naive Melanoma, NSCLC, and renal cell carcinoma cohorts, as nivolumab is already an established standard of care. Approximately 40 subjects will be enrolled in each of these cohorts to allow for the exploration of early efficacy signals of BMS-986205 in combination with nivolumab.

Approximately 16 Melanoma IO-naive BRAF mutant subjects post-BRAF regimen therapy will be randomized into two cohorts and will either be treated with nivolumab or nivolumab in combination with BMS 986205, though will not be used for formal statistical comparison.

If there is preliminary evidence of the treatment effect that may represent substantial improvement over available therapies, the protocol may be amended to include sufficient additional subjects who will be treated to demonstrate a substantial and clinically meaningful effect in ORR that is supported by duration of the effect. The total sample size at this stage will be determined based on the ability to produce a CI which would exclude an ORR of the historic response and to provide sufficient information for a reliable understanding of the safety profile.

Part 3 Combination with Nivolumab and Ipilimumab

The combination of BMS-986205 with nivolumab and ipilimumab in Part 3 will be evaluated in 2 parts, the safety evaluation phase and the cohort expansion phase of the combination in melanoma, NSCLC, and bladder cancer as well as a mixed tumor type cohort.

All safety cohorts will begin with an assessment of safety and tolerability of the triplet combination regimen in a limited number of subjects, including a sentinel subject. As described in Section 3.1.1.2, the NSCLC and melanoma regimen cohorts will begin enrollment first, followed by the bladder regimen cohort once safety and tolerability has been established in either NSCLC or melanoma. Initially, approximately 3 subjects will be treated at the selected dose combination of BMS-986205 with nivolumab and ipilimumab. Due to the potential for early discontinuation, an additional subject(s) may be enrolled to ensure approximately 3 DLT evaluable subjects. Initial safety assessment to allow enrollment in the bladder safety cohort will occur when at least 2 evaluable subjects in either the NSCLC or melanoma safety cohorts have completed a 6-week DLT evaluation period (see Section 4.5.1 for criteria for DLTs). In the melanoma and NSCLC safety evaluation cohorts, if the potential DLT occurring in any third evaluable subject regarding the specific dose combination does not influence the recommendation by BLRM (-Copula) to open enrollment in the bladder safety cohort, then the bladder safety cohort may proceed with enrollment without waiting for the third subject to complete the corresponding DLT observation period. After the initial subjects in each treatment regimen are evaluated, additional increments of approximately 3 to 6 subjects will be treated in the same safety cohort as per BLRM-copula model recommendation that the dose combination is safe. At least 6 DLT-evaluable subjects will be treated and assessed in the selected dosing regimen safety cohort before starting enrollment in the expansion cohort for that tumor type/regimen. Up to 12 DLT-evaluable subjects in total may be treated in the safety evaluation cohort for each tumor type at the dose selected for expansion cohorts for evaluation of safety and pharmacodynamic/PK parameters as required. BLRM (-copula) will be used to monitor the safety of the triplet dose combination on an ongoing basis. If, at any time, the aggregate rate of treatment related toxicities meeting DLT criteria within an individual treatment tumor type/regimen exceeds 33% across all subjects treated in the safety evaluation and dose expansion cohorts, the findings will be discussed and further enrollment may be interrupted. At that time, depending on the nature and grade of the toxicities and after assessing the risk/benefit ratio, a new dose(s) of BMS 986205 for subjects within that dosing regimen may be initiated at a previously tested lower dose level or at a dose level intermediate to previously tested lower dose levels.

Once the initial safety and tolerability has been established independently for each regimen based on safety cohort evaluations, enrollment will begin of subjects into expansion cohorts for further evaluation of safety and tolerability, as well as preliminary evaluation of anti-tumor efficacy. In the expansion phase, each BMS-986205 and nivolumab/ipilimumab combination regimen will be evaluated in tumor-specific cohorts based on the tumor type evaluated in the safety cohorts (melanoma, NSCLC, and bladder cancer). The Ipi 1Q8 regimen will also be evaluated in a mixed tumor-type cohorts, which may incorporate tumor types evaluated in Part 2 Dose Expansion. This 40 subject cohort is used to obtain preliminary safety, PK, and PD data for the triplet combination in other tumor types.

As all subjects in the melanoma, NSCLC, and bladder disease-specific cohorts will be receiving agents (nivolumab and ipilimumab) with known efficacy, a single-stage design will be utilized for each of these tumor types. Approximately 40 subjects will be enrolled in each of the following cohorts: melanoma PD-L1 positive, melanoma PD-L1 negative, NSCLC PD-L1 positive, NSCLC PD-L1 negative bladder, and mixed tumor type to allow for the exploration of early efficacy signals of BMS-986205 in combination with both nivolumab and ipilimumab in relevant subpopulations In each NSCLC expansion cohort, approximately 10 subjects will be IO-treatment naive, 25 will be

treatment-naive, and 5 IO-therapy experienced. In the melanoma cohorts, approximately 35 will be treatment naïve in the advanced setting and 5 will be IO-therapy experienced in each cohort. In the bladder expansion cohort in Part 3, at least 30 subjects will be I O therapy naive.

The anti-tumor activity of the expansion cohorts will be continuously monitored in all subjects who are evaluable for response using the measurements described in Section 8.3.1. In the NSCLC cohort, 16 of 25 responses for the treatment naïve subjects would result in 80% CIs for an ORR that is strictly higher than the historical rate of 45.3%.[1] In the melanoma cohort, 22 of 35 responses for the treatment naïve subjects would result in 80% CIs for ORRs that are strictly higher than the historical rates of 580.0%).[2] In the bladder cohort, 16 of 30 responses would result in 80% CI for ORR that is strictly higher than the historical rate of 38.5%.[3] The CIs are calculated using the Clopper-Pearson method.

Endpoints:

Primary Endpoints:

The primary objective of this study is to establish the safety, tolerability, and the MTD/MAD/alternate dose of BMS-986205 as monotherapy, and in combination with nivolumab and with nivolumab and ipilimumab. The assessment of safety will be based on the incidence of AEs, SAEs, AEs leading to discontinuation, and deaths. In addition, clinical laboratory test abnormalities will be examined. AEs and laboratory values will be graded according to the NCI CTCAE v4.03.

The co-primary objective, anti-tumor activity of BMS-986205 in combination with nivolumab in Part 2 (dose expansion) and BMS-986205 in combination with both nivolumab and ipilimumab in Part 3, will be measured by ORR, DoR, and PFSR based on RECIST v1.1 for solid tumors or IWG for blood tumor. For Parts 1 and 2, disease assessment with CT and/or MRI as appropriate will be performed at baseline, end of Cycle 2, and every 8 weeks. For Part 3, in the melanoma cohorts, the first tumor assessment will occur at Week 12; subsequent imaging will be every 8 weeks thereafter during the treatment period; for NSCLC, imaging assessments will occur every 6 weeks during the treatment period; for bladder, imaging assessments will occur every 6 weeks during the treatment period up to 24 weeks, and then occur every 12 weeks thereafter during the treatment period. For all study parts, assessments continue every 12 weeks for the first year after the EOT visit, and then every 6 months thereafter, up to 2 years following the EOT visit until disease progression per RECIST v1.1 or IWG, or until confirmed disease progression for subjects treated beyond progression (defined as an additional 10% or greater increase in tumor burden volume from time of initial progression including all target lesions and new measurable lesions), at the completion of follow-up, or until subjects withdraw from the study.

1) Best overall response (BOR) is defined as the best response designation over the study as a whole, recorded between the dates of first dose until the last tumor assessment prior to subsequent therapy. CR or PR determinations included in the BOR assessment must be confirmed by a second scan performed no less than 4 weeks after the criteria for response are first met. For those subjects who have surgical resection, only presurgical tumor assessments will be considered in the determination of BOR.
2) ORR is defined as the proportion of all treated subjects whose BOR is either a CR or PR.
3) DoR, computed for all treated subjects with a BOR of CR or PR, is defined as the time between the date of first response and the date of disease progression or death, whichever occurs first.
4) PFSR at 24 weeks, 1 year, and 2 years: The proportion of treated subjects remaining progression free and surviving at 24 weeks, 1 year, and 2 years if sufficient data are available. The proportion will be calculated by the Kaplan-Meier estimate, which takes into account censored data.

Secondary endpoints:

Pharmacokinetics: Selected BMS-986205 parameters, such as Cmax, Tmax, AUC(TAU), Ctrough, CLT/F, CLR/F, Vss/F, AI, %UR24, [redacted] from concentration-time data during BMS-986205 monotherapy and concentrations at end of infusion and Ctrough during combination treatment. [redacted]

Pharmacodynamics: Change from baseline for serum and tumor kynurenine and related metabolites and/or percent change from baseline from baseline).

Efficacy: The best overall response, ORR, DoR, and PFSRs at pre-specified time points based on RECIST v1.1 and IWG will be the secondary efficacy endpoints for dose escalation and the clinical pharmacology substudies.

The third secondary objective of immunogenicity will be assessed by the frequency of positive anti-drug antibody (ADA) to nivolumab or ipilimumab.

[redacted]

Analyses:

Safety analysis: All recorded AEs will be listed and tabulated by system organ class, preferred term, treatment arm, and dose level and coded according to the most current version of MedDRA. Vital signs and clinical laboratory test results will be listed. Any significant PE findings and results of clinical laboratory test will be listed.

ECG analysis: Summary statistics will be presented for each ECG parameters (heart rate, QTcF, PR and QRS) and the corresponding changes from baseline by dose and time points. Scatter plots of change from baseline values in each ECG parameters versus the nearest corresponding plasma drug concentrations will be presented. [redacted] The frequency distribution of subjects' maximum recorded postdose QTcF, PR, QRS and ΔQTcF will be tabulated by treatment and summarized

Efficacy analysis: Listing of tumor measurements will be provided by subject and study day in each arm and dose level. Individual subject's best overall response will be listed based on RECIST v1.1 for solid tumor and IWG for blood tumor.

To describe the anti-tumor activity of BMS-986205 in combination with nivolumab and in combination with both nivolumab and ipilimumab, ORR will be calculated. ORR and corresponding 2-sided exact 95% CI by the Clopper and Pearson method will be provided by treatment, and/or dose level and tumor type (if appropriate). Median DoR and corresponding 2 sided 95% CI may be reported by treatment, and/or dose level and tumor type (if appropriate). DoR will be analyzed using the Kaplan-Meier method.

PFSR at 24 weeks, 1 year, and 2 years will be estimated by the Kaplan-Meier methodology, by treatment, tumor type and dose level. The corresponding 90% CI will be derived based on the Greenwood formula.

Pharmacokinetic analysis: PK parameters for BMS-986205 [redacted] will be calculated using noncompartmental analyses.

All individual PK parameters will be listed for each analytic including any exclusions and reasons for exclusion from summaries. Summary statistics will be tabulated for each PK parameters by treatment. Geometric means and coefficients of variation will be presented for Cmax, AUC(TAU), Ctrough, CLT/F, and CLR/F, after multiple dose PK. Medians and ranges will be presented for Tmax. Means and standard deviations will be presented for all other PK parameters.

BMS-986205 dose dependency will be assessed during dose escalation lead-in. To describe the dependency on dose of BMS-986205, scatter plots of Cmax, and AUC(TAU) versus dose may be provided for each day measured. [redacted] Nivolumab and ipilimumab EOI and trough (Ctrough) concentrations and BMS-986205 trough concentration will be tabulated by treatment and study day using summary statistics. These data may also be pooled with other datasets for population PK analysis, which will be presented in a separate report. Urinary recovery data of BMS-986205 will be listed. Cumulative amount and cumulative percent recovered per interval will be summarized. Plots of individual cumulative percent of dose recovered in urine versus end of interval time will be provided. Mean plots of cumulative percent of dose recovered in urine versus end of interval time will also be provided.

Immunogenicity analysis: A listing of all available immunogenicity data will be provided by treatment, dose, and immunogenicity status. The frequency of subjects with a baseline and/or at least 1 positive ADA assessment of nivolumab and/or ipilimumab will be summarized.

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

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3 Sharma P, Callahan MK, Calvo E, et al. Efficacy and Safety of Nivolumab Plus Ipilimumab in Metastatic Urothelial Carcinoma: First Results from the Phase I/II CheckMate 032 Study. Journal of ImmunoTherapy of Cancer. 2016; 4(Suppl 2):O3.

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1 INTRODUCTION AND STUDY RATIONALE

This is a dose escalation and cohort expansion study of BMS-986205, an inhibitor of the indoleamine 2,3-dioxygenase 1 (IDO1) enzyme, in combination with nivolumab (anti-programmed cell death-1 [PD-1]) and in combination with both nivolumab and ipilimumab (anti-cytotoxic T lymphocyte-associated antigen 4 [CTLA-4]) in humans with advanced malignant tumors. This study will be conducted in 3 parts. Part 1 (Dose Escalation) will evaluate the safety profile, tolerability, pharmacokinetics (PK), and pharmacodynamics of escalating oral doses of BMS-986205 in combination with a flat dose of nivolumab in order to identify the maximum tolerated dose (MTD)/recommended Phase 2 dose(s) of BMS-986205 in combination with nivolumab to be used in Part 2. Part 2 (Dose Expansion) will assess the preliminary efficacy of BMS-986205 in combination with nivolumab in specific malignant disease populations and will also serve to generate further data to support dose optimization of the combination. Part 3 will evaluate the safety profile, tolerability, and preliminary efficacy of BMS-986205 in combination with both nivolumab and ipilimumab in specific malignant disease populations. The study also includes a clinical pharmacology substudy designed to evaluate the potential effect of BMS-986205 on the QTc interval.

1.1 Study Rationale

1.1.1 Background and Rationale for Inhibition of IDO

Immunomodulation-based therapies for cancer have become established in recent years and are now one of the most successful and important strategies for treating subjects with hematological malignancies and solid tumors.[1] It is now clear that an anti-cancer antigen-specific immune response is the result of a complex dynamic interplay between antigen-presenting cells (APCs), T lymphocyte cells, and the target cancer cells.[2] The most extensively studied targets of immunotherapy in cancer are the negative regulatory receptors, CTLA-4 and PD-1.[3] Inhibition of these negative regulatory receptors, referred to as immune checkpoint blockade, results in the enhanced activation of T-cell responses and potent anti-tumor activity in preclinical models. Trials with CTLA-4 blockade provided the first clinical evidence of improvement in overall survival with immune modulatory anti-cancer therapy in subjects with metastatic melanoma.[4,5] Following that, Topalian et al showed that anti-PD-1 antibody produced objective responses in subjects with non-small cell lung cancer (NSCLC), melanoma, and renal cell cancer (RCC).[6]

Following on the success of CTLA-4 and anti-PD-1 pathway-targeted agents, the field of tumor immunotherapy is rapidly expanding. In addition to blocking co-inhibitory pathways, targeting the immunosuppressive properties of the cancer cells themselves is considered a promising approach especially in combination with antibody-based immunotherapy. It is possible that combination therapies could potentially lead to greater depth of response and overall survival as has been noted with the combination of anti-PD-1 and anti-CTLA-4 in advanced melanoma subjects.[7,8] Subjects with metastatic or refractory tumors have a very poor prognosis, and despite advances in multimodal therapy, increases in overall survival in this subject population have been limited.

IDO1 catalyzes the degradation of tryptophan to N-formyl-kynurenine, which is the first and rate-limiting step leading to the production of kynurenine and downstream metabolites. The activity of IDO1 causes immune tolerance by inhibiting T-cell function through local depletion of the essential amino acid tryptophan and through generation of inhibitory kynurenine pathway metabolites.[9] In healthy humans, IDO1 is expressed in the placenta, the mucosa of the female genital tract, the lungs, and the lymphoid organs.[10] IDO1 expression in the placenta is believed to play a role in maternal tolerance to allogeneic fetuses[11]; however, its functional roles in the lungs and female genital tract are not as clear, but it may be involved in combating infections or play a role in immune tolerance in those tissues. In the immune system, IDO1 is expressed in dendritic cells and macrophages. It is strongly induced by pro-inflammatory mediators such as interferon-gamma (IFNγ) and endotoxins during the late phase of inflammatory reactions, in which its immunosuppressive role contributes to the physiologic feedback control of the immune response.[12]

IDO1 is highly expressed in several types of human malignancies. High levels or frequencies of IDO1 expression are detected in endometrial, cervical, head and neck, non-small cell lung, kidney, colorectal, bladder/urothelial, and ovarian carcinomas as well as in renal cell carcinoma, melanoma and diffuse large B-cell lymphoma (DLBCL).[10,13] IDO1 expression in tumors is believed to induce immune tolerance as evident by a decrease in tumor infiltration of immune cells and an increase in the proportion of regulatory T cells (Treg) in the tumor infiltrating lymphocytic populations. Increased IDO1 is also correlated with diverse tumor progression parameters and shorter patient-survival time in many cancer indications.[14] In melanoma, IDO1 has been shown to be significantly up-regulated together with the programmed death receptor-ligand 1 (PD-L1).[15] The enzyme is also reported to be a critical resistance mechanism in anti-tumor T-cell immunotherapy targeting CTLA-4.[16] Furthermore, tumor IDO1 transcript is increased in subjects with advanced melanoma and metastatic RCC after treatment with the anti-PD-1 antibody nivolumab.[17,18] These findings suggest that IDO1 is an important regulator of the immunosuppressive mechanisms responsible for tumor escape from host immune surveillance. Inhibition of IDO1 using pharmaceutical agents may alleviate the immunosuppressive properties of the tumor microenvironment and achieve more durable responses and greater subject survival benefits, particularly when used in combination with other cancer immunotherapy agents, such as nivolumab and ipilimumab.

1.1.2 Rationale for BMS-986205 Monotherapy Lead-in Cycle

The totality of the preclinical data with BMS-986205 as well as published clinical data from another IDO1 inhibitor (epacadostat, Incyte corporation) showing no objective responses in approximately 50 subjects with advanced malignancies treated in a monotherapy trial[19], strongly suggest that BMS-986205 will not provide benefit to subjects as a monotherapy. It is, however, expected to broaden and deepen the responses that have been seen with other immune-modulating anti-cancer agents. Thus, this first-in-human Phase 1/2a study has been designed in such a way as to balance the need for sufficient assessment of the short-term clinical profile of BMS-986205 monotherapy prior to allowing the same subjects to receive treatment in

combination with nivolumab (an anti-PD-1 antibody). In Part 1 of this study, subjects will receive 1 monotherapy lead-in cycle with daily oral administration of BMS-986205 for 2 weeks duration in order to characterize the safety, PK, and pharmacodynamic profile of BMS-986205 monotherapy. Based on the predicted human half-life of BMS-986205 of 23 hours, this 2-week interval is expected to cover the anticipated time frame for the occurrence of clinically significant early-onset adverse events (AEs) related to BMS-986205 monotherapy.

1.1.3 Rationale for Combination of BMS-986205 with Nivolumab

PD-1 is a transmembrane protein primarily expressed on activated T cells, B cells, myeloid cells, and APCs.[20] Binding of PD-1 to PD-L1 and PD-L2 has been shown to down-regulate T-cell activation in both murine and human systems.[21,22,23,24] PD-1/PD-L1 interactions may also indirectly modulate the response to tumor antigens through T-cell/APC interactions. Therefore, PD-1 engagement may represent one means by which tumors evade immunosurveillance and clearance.[25] Blockade of the PD-1 pathway by nivolumab has been studied in a variety of preclinical in vitro assays, and anti-tumor activity using a murine analog of nivolumab has been shown in a number of immunocompetent mouse cancer models.[26] Nivolumab has been approved as treatment for melanoma, NSCLC (both non-squamous and squamous histologies), head and neck cancer, RCC, bladder cancer, and Hodgkin's lymphoma (HL) in the United States (US), and is being evaluated extensively across a wide range of other solid tumors and hematological malignancies.

PD-1-blockade enhances T-cell migration to tumors by elevating IFNγ inducible chemokines. IDO1 expression is also known to be strongly regulated by IFNγ. In fact, in clinical trials of subjects with advanced melanoma and metastatic RCC treated with nivolumab, IDO1 gene expression was increased in subjects on treatment[17,18]. These post-treatment increases in the expression of IDO1 are indicative of potential adaptive mechanisms of resistance to counteract the increased anti-tumor immune cell activity potentiated by PD-1/PD-L1 blockade. These data support the hypothesis that combination treatment could result in enhanced anti-tumor activity by providing a second mechanism of alleviating tumor mediated immunosuppression.

1.1.4 Rationale for Combination of BMS-986205 with Both Nivolumab and Ipilimumab

Immunosuppression within tumors is the result of a complex interaction of multiple signaling pathways. Signaling may be accomplished through cell surface-bound proteins such as PD-1 and CTLA-4, as well as through soluble mediators such as kynurenine (produced via IDO1) and others. Therefore, there are multiple points at which immune-directed therapies could act to relieve tumor-induced immune suppression.

Support for the synergistic effects of combining individual immuno-oncology agents with non-overlapping mechanisms of action has been provided by both preclinical and clinical studies. The most well-studied combination to date has been PD-1 and CTLA-4 receptor blockade in improving anti-tumor activity. Preclinically, in vitro combinations of nivolumab and ipilimumab increase IFNγ production 2- to 7-fold over either agent alone in a mixed lymphocyte

reaction. Increased anti-tumor activity of the combination was also observed in 3 of 5 syngeneic murine cancer models. In a murine MEL vaccine model, blockade with either CTLA-4 or PD-1 antibodies increased the proportion of CTLA-4 and PD-1-expressing CD4/CD8 tumor infiltrating T effector cells, and dual blockade increased tumor infiltration of T effector cells and decreased intratumoral Tregs, as compared to either agent alone.

Clinical evidence supporting the combination of immune-modulating therapies has been observed across multiple tumor types in the combination of nivolumab and ipilimumab, as well as other agents targeting PD-1, PD-L1, and CTLA-4. See Section 1.1.5.2 for a discussion of the synergistic clinical effects of combining these agents in specific tumor types. In addition, expression of IDO1 has been found to correlate with that of PD-L1 in tissue from patients with melanoma. Clinically, treatment with anti-PD1 is associated with increases in IDO1 transcript levels in melanoma and RCC[17,18]. Preclinically, there is also evidence that treatment with anti-CTLA-4 therapy leads to an increase in IDO1 transcripts[16].These findings suggest that a combination of therapies targeting PD-1, CTLA-4, and IDO1 may be synergistic and provide additional benefit over therapies targeting only one or two of these immune-regulatory pathways. This in turn may lead to improved clinical outcomes by increasing the number of patients who response to nivolumab and ipilimumab therapies, while also potentially increasing the depth and duration of responses to those therapies.

1.1.5 Rationale for Tumor Selection

IDO1 is overexpressed in several types of human malignancies and is often correlated with poor prognosis. Examination of The Cancer Genome Atlas (TCGA) database reveals that IDO1 exhibits a broad range of gene expression across these various tumor types. In order to address the question of which tumor types will be most likely to respond to IDO1 inhibition, tumors with varying levels of IDO1 expression were selected for further study during cohort expansion in Part 2, including cervical cancer and DLBCL at the high end and pancreatic cancer at the lower end. Published data describing IDO1 protein expression by immunohistochemistry (IHC) across multiple tumor types were used to confirm presence of IDO1 in the tumor indications suggested by the TCGA analysis. Human tumor samples from priority indications were obtained and analyzed for kynurenine levels to confirm that elevated IDO1 expression levels also correlate with elevated IDO1 activity.

1.1.5.1 BMS-986205 and Nivolumab Combination

Given the hypothesis that IDO1 inhibition will increase both the depth and breadth of anti-PD-1 therapy, tumor selection for Parts 1 and 2 was further prioritized based on tumors in which PD-1 blockade has shown activity (ie, melanoma, NSCLC, renal cell carcinoma [RCC], and squamous cell carcinoma of the head and neck [SCCHN]), as well as tumors that to date have shown insensitivity to anti-PD-1 treatment (ie, pancreatic cancer).

As of Nov-2016, there are external data from another IDO1 inhibitor/anti-PD-1 combination (epacadostat/pembrolizumab), showing clinical proof of concept in treatment-naïve advanced melanoma subjects. There was an objective response rate (ORR) of 58% in 19 evaluable advanced melanoma patients, as compared to an ORR of 34% reported for pembrolizumab

monotherapy as per the European Union (EU) Summary of Product Characteristics[27] and the Food and Drug Administration (FDA) prescribing information.[28]

In order to gain understanding of which specific subset(s) of patients with melanoma will benefit from IDO1 inhibition in combination with nivolumab, distinct cohorts of melanoma subjects will be studied during dose expansion in Part 2:

- Immuno-oncology (I-O) naïve, PD-L1 positive and negative: Nivolumab is approved for the treatment of first-line advanced melanoma across PD-L1 status. These cohorts (40 subjects each) are added in order to assess potential synergistic activity of adding IDO1 inhibition to a known standard of care.
- I-O naïve, BRAF mutated, post-BRAF-targeted therapy: Nivolumab is also approved for the treatment of first-line advanced melanoma across BRAF mutation status. Many of the BRAF mutated subjects who were treated in nivolumab trials had received prior BRAF-targeted therapy and still demonstrated clinical benefit with nivolumab. In addition, there is evidence of an increase in tumor infiltrating lymphocytes and an upregulation of PD-L1 following BRAF inhibition,[29] which suggests that the combination of an anti-PD-1 agent with an IDO1 inhibitor may be particularly beneficial in this subset of patients. However, there are not sufficient prospective data on the efficacy of nivolumab monotherapy (40 subjects per arm) in this population. Thus, these subjects will be randomized to receive either BMS-986205 in combination with nivolumab or nivolumab monotherapy in order to generate a robust, prospective dataset with nivolumab monotherapy to serve as a basis for understanding the potential added benefit of combination therapy.
- Prior anti-PD-(L)1 and prior anti-PD-(L)1 + anti-CTLA-4 combination regimen therapy: Recurrent or progressive melanoma following treatment with anti-PD-(L)1 monotherapy or the anti-PD-(L)1 + anti-CTLA-4 combination represents areas of high unmet medical need. These cohorts (approximately 35 subjects each) are added in order to assess whether IDO1 inhibition can act as a mechanism to restore anti-tumor activity in these subjects (refer to Section 1.1.1 for supporting data).

NSCLC will also be evaluated in distinct settings:

- I-O naïve, PD-L1 positive and negative: Nivolumab is an approved therapy for the treatment of advanced NSCLC across PD-L1 status. These cohorts (40 subjects) are added in order to assess potential synergistic activity of adding IDO1 inhibition to a known standard of care.
- I-O experienced: Recurrent or progressive NSCLC following anti-PD-(L)1 therapy represents an area of high unmet medical need. This cohort (35 subjects) is added in order to assess if IDO1 inhibition can act as a mechanism to restore anti-tumor activity in these patients.

Decisions regarding tumor selection were made so that novel combination therapies could potentially bring benefit to subjects with high unmet medical need, as is the case with these subjects with advanced malignancy. Additionally, consideration was given to the inclusion of other tumor types from the dose escalation portion of the trial that do not currently have plans for evaluation in other studies, which will be based on emerging clinical data.

1.1.5.2 BMS-986205, Nivolumab, and Ipilimumab Combinations

The tumors selected for the evaluation of triplet combination in Part 3 are NSCLC, melanoma, and bladder cancer. Selection was based on evidence of high levels of IDO1 expression (see Section 1.1.1); the potential to evaluate BMS-986205 with varying doses and schedules of nivolumab and ipilimumab in tumor types with established safety and tolerability profiles for those regimens (see Section 1.1.6.2); and evidence of increasing clinical benefit with combination immuno-therapy over monotherapy with either agent, described below.

Melanoma

Ipilimumab and nivolumab were both initially evaluated and approved as single agents in metastatic melanoma before being approved in combination.

Ipilimumab was initially approved as monotherapy based on the Phase 3 MDX010-020 study. In this study, compared to melanoma peptide vaccine (gp100), ipilimumab improved OS (10 versus 6 months) and ORR (6 and 11% for ipilimumab-containing arms versus 2% in the gp100 arm).[30] Subsequent to this, nivolumab was approved for the treatment of metastatic melanoma based on the CA209037 and CA209066 studies. In CA209037, compared to investigator's choice of chemotherapy, nivolumab administered at 3 mg/kg every 2 weeks improved both objective response (32% versus 11%) and CR rates (3% versus 0%).[31]

The synergistic combination of the 2 agents was evaluated in the CA209067 and CA209069 studies. In both studies, the combination of nivolumab with ipilimumab improved outcomes compared to ipilimumab. In CA209067[32], the combination demonstrated a response rate of 58%, numerically higher than either single agent (44% for nivolumab, 19% for ipilimumab). In CA209069, the same combination doses achieved a response rate of 61%, significantly greater than that of ipilimumab alone (11%).[33] PD-L1 status appeared to affect response rates in CA209067, as subjects treated with nivolumab and ipilimumab with PD-L1 positive tumors had a response rate of 72.1% versus 54.8% in PD-L1 negative tumors. Based on those initial results, the combination of nivolumab and ipilimumab was approved as therapy in the first-line treatment of metastatic melanoma and became the first combination immuno-oncology regimen approved in any tumor type.

NSCLC

Nivolumab has been approved as monotherapy in patients with squamous NSCLC with progression on or after platinum-based chemotherapy. The approval was based on the results of CA209017, a randomized trial of nivolumab versus docetaxel. The median overall survival (OS) for patients in the nivolumab arm was 9.2 months versus 6 months for those in the docetaxel arm (HR = 0.59). Improvement in survival was observed for nivolumab.[34] A second Phase 3 study, CA209057, lead to the approval in non-squamous histologies with a 27% reduction in risk of death (HR = 0.73; P = 0.0015). Nivolumab also significantly improved ORR versus docetaxel (P = 0.0246), with ORR as high as 36% in subjects with PD-L1 expressing tumors. OS approximately doubled with nivolumab versus docetaxel.[35]

Ipilimumab has been shown to have activity in lung cancer. A Phase 2 study (CA184041) in subjects with NSCLC or small cell lung cancer (SCLC) investigated the addition of ipilimumab to carboplatin and paclitaxel using 2 different schedules (concurrent and phased). The phased schedule demonstrated a significant improvement of immune-related progression-free survival as well as progression-free survival by modified WHO criteria compared to chemotherapy alone, in both NSCLC and SCLC.[32]

Based on data in melanoma, which led to the approval of ipilimumab and nivolumab combination therapy, as well as the activity observed with nivolumab and ipilimumab individually in NSCLC, the nivolumab plus ipilimumab combination has been also evaluated as first-line therapy in patients with advanced NSCLC. In the CA209012 trial, various schedules of nivolumab and ipilimumab were evaluated in treatment-naïve subjects with stage IV or metastatic NSCLC. Promising clinical activity was observed, with response rates for the combinations of nivolumab plus ipilimumab (38% to 47%) at least similar if not improved relative to those observed with platinum-based chemotherapy. Response rates appeared greater in subjects when PD-L1 status was taken into account, with ORR reaching 90% in those subjects with PD-L1 expression greater than 50%.[36]

These data provided proof of concept of combinatorial activity of immunotherapy agents in NSCLC and led to the initiation of CA209227, a randomized, open-label Phase 3 trial evaluating nivolumab monotherapy or nivolumab plus ipilimumab versus platinum doublet chemotherapy in subjects with stage IV or recurrent NSCLC.

Bladder Cancer

High levels of programmed death 1 (PD-1) ligand 1 (PD-L1) expression have been noted in bladder/urothelial carcinoma (UC), suggesting tumor-associated immune tolerance and escape from immune surveillance. PD-L1 expression has been reported in approximately 20% (5% cutoff) and 30% (1% cutoff) of tumor tissue sample.[37,38,39] PD-1 and PD-L1 immune checkpoint inhibitors appear to show benefit in patients with disease progression on platinum-based therapy.[37] In an open-label, multicenter Phase 1/2 expansion cohort in patients with metastatic UC, nivolumab elicited a response rate of 24.4% with acceptable safety, regardless of tumor PD-L1 expression, in patients who had received 1 or more prior lines of chemotherapy (CA209032).[38] In a larger study in unresectable or metastatic UC, CA209275, nivolumab had clinically meaningful efficacy and a manageable safety profile.[39] At 7 months of median follow-up, 24.4% of patients remain on therapy. Confirmed overall response rate (ORR) was 19.6% (95% CI: 15.0, 24.9). Nivolumab was granted accelerated approval in 2017 as monotherapy in bladder cancer based on these results.

Ipilimumab has been explored precystectomy in a pilot trial of patients with clinically localized bladder cancer. In this trial, 12 patients were treated with 2 doses of ipilimumab (n = 6 treated with 3 mg/kg and n = 6 treated with 10 mg/kg).[40] Most drug-related adverse events (AEs) were Grade 1 or 2, all patients demonstrated an increase in CD4+ ICOShi T cells in tumor tissue and systemic circulation, and 8/12 patients had down-staging of their disease on final pathology

review. The efficacy and safety of first-line gemcitabine, cisplatin plus ipilimumab for metastatic UC is being investigated in a Phase 2 trial (NCT01524991).

The CA209032 study has evaluated the combination of nivolumab and ipilimumab in bladder cancer after first-line chemotherapy. Preliminary results from that study revealed overall response rates of 36% to 38.5% for a nivolumab and ipilimumab combinations in this patient population.[41] To evaluate this further, a Phase 3 trial of nivolumab and ipilimumab in recurrent or platinum refractory bladder cancer has been initiated. The potential for increasing clinical activity with the combination of immunotherapy agents in bladder cancer supports the evaluation of the combination of BMS-986205, nivolumab, and ipilimumab.

1.1.6 Rationale for Dose and Schedule

1.1.6.1 Dose and Schedule for BMS-986205

Selection of FIH Starting Dose

The selection of BMS-986205 starting dose and schedule is based on the pivotal 1-month toxicology studies in rats and dogs and the extrapolation of in vivo data from preclinical efficacy models in mice.

In the pivotal 1-month oral repeat-dose toxicity study in rats, the dose of 20 mg/kg once daily (QD) was established as the MTD and the dose that produces severe toxicity to 10% (STD10) of rats. A dose of 5 mg/kg/day was considered to be the no-observed adverse effect level (NOAEL) in the 1-month rat study. In the 1-month dog study, a dose of 30 mg/kg/day was the highest nonseverely toxic dose (HNSTD) and also the NOAEL. Using body surface area conversion, a human equivalent dose (HED) of 3.2 mg/kg was determined based on the rat STD10, one-tenth of which will suggest a starting dose of 0.32 mg/kg in humans. Similarly, based on the dog HNSTD and scaled by body surface area, a HED of 16.2 mg/kg can be calculated, one-sixth of which would suggest a starting dose of 2.7 mg/kg. The rat was considered the most appropriate species to determine the maximum recommended starting dose because, although the toxicity profiles were generally similar in both rats and dogs, the rat was the most sensitive species with a lower projected starting dose. The maximum starting dose of 0.32 mg/kg (25 mg based on a median body weight of 80 kg) was therefore selected for this study. Based on the observed exposure in rats and predicted human PK, the starting dose of 25 mg would project an exposure (area under the concentration-time curve from time zero to 24 hours postdose [AUC(0-24h)]) margin of 65 relative to the MTD/STD10 and 15 relative to the NOAEL. At the HNSTD/NOAEL in dogs, the exposure margin was 33 relative to the projected AUC at the starting dose of 25 mg in humans.

In preclinical models in mice (M109), administration of BMS-986205 QD resulted in significant reduction in kynurenine levels in both serum and in tumor tissues in a dose-dependent manner. Given the projected human half-life of ~23 hours, a QD dosing schedule was selected for this initial study.

In preclinical studies in dogs, approximately 2- to 3-fold higher exposures were observed when dosing with food compared to under fasting condition (see Section 1.4.3). BMS-986205 will be administered after a light meal (see Section 4.2) in order to optimize the systemic exposure.

Selection of Dose for Dose Expansion (Part 2), Combination with Nivolumab and Ipilimumab (Part 3)

Based on the preliminary clinical safety, pharmacokinetic, and pharmacodynamic data observed to date, cohort expansion in Part 2 was opened using both 100 and 200 mg doses in combination with nivolumab. This initial selection of two doses for cohort expansion in Part 2 allowed for the continued accrual of data at both doses to support a final dose decision. After review of safety, PK, and PD data, 100 mg was selected as the dose to be used for remaining subject enrollment in Part 2. See Section 1.4.4.4, for the description of clinical safety and tolerability of 100 and 200 mg and Section 1.4.4.1 for a discussion of the preliminary pharmacokinetic profile.

For Part 3 of this study, the maximum initial dose of BMS-986205 evaluated will be 100 mg daily. The selection of 100 mg was based on the aggregate safety and PK data in combination with nivolumab across doses of BMS-986205 found to be safe and tolerable, as well as to provide an additional safety margin since the safety profile of BMS-986205 at 200 mg is acceptable in combination with nivolumab. Lower doses may be evaluated based on emerging safety, PK, and PD data.

1.1.6.2 Dose and Schedule for Nivolumab in Combination with BMS-986205

Nivolumab 240 mg every 2 weeks (Q2W) has been approved for use as monotherapy in patients with melanoma, RCC, and NSCLC, and will be administered in combination with BMS-986205 for the dose escalation portion of the study (Part 1), as well as for the dose expansion cohorts that were included in the protocol prior to Amendment 06. Nivolumab 480 mg every 4 weeks (Q4W) will be administered in combination with BMS-986205 for the dose expansion cohorts that are added with Amendment 06 (Part 2) [melanoma, NSCLC, and additional signal-seeking tumors] and the clinical pharmacology substudy (Part 3). This change in dosing interval as of Amendment 06 will provide a more convenient regimen for the patients. The expansion cohorts that predated Amendment 06 will continue with the nivolumab 240 mg Q2W dosing regimen in order to ensure consistent dosing within each cohort.

The safety and efficacy of the 480 mg Q4W flat dose of nivolumab are expected to be similar to the approved nivolumab dose of 240 mg flat doses or 3 mg/kg Q2W. The nivolumab dose of 480 mg Q4W was selected based on clinical data and modeling and simulation approaches using population PK (PPK) and exposure-response analyses of data from studies in multiple tumor types (melanoma, NSCLC, and RCC) where body weight normalized dosing (mg/kg) has been used. The PPK analyses have shown that exposure to nivolumab increased dose proportionally over the dose range of 0.1 to 10 mg/kg administered Q2W, and no clinically meaningful differences in PK across ethnicities and tumor types were observed. Nivolumab clearance and volume of distribution were found to increase as the body weight increases, but less than proportionally with increasing weight, indicating that milligram per kilogram dosing represents an over-adjustment for the effect of body weight on nivolumab PK. Using the PPK model, the

overall distributions of nivolumab average steady-state exposures are comparable after treatment with either nivolumab 3 mg/kg Q2W or nivolumab 480 mg Q4W, although the flat dose regimen of 480 mg Q4W is predicted to result in approximately 40% higher steady-state peak concentration (Cmaxss) and approximately 20% lower steady-state trough concentrations compared to the reference regimen of 3 mg/kg Q2W. Across the various tumor types in the clinical program, 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 and safety has been found to be relatively flat. Although nivolumab Cmaxss is predicted to be higher following 480 mg Q4W, these exposures are predicted to be lower than or within the exposure ranges observed at doses up to 10 mg/kg Q2W used in the nivolumab clinical program and are not considered to put subjects at increased risk. The exposures predicted following administration of nivolumab 480 mg Q4W are on the flat part of the exposure-response curves for previously investigated tumors (melanoma and NSCLC) and are not predicted to affect efficacy. Based on these data, nivolumab 480 mg Q4W is expected to have similar efficacy and safety profiles to nivolumab 3 mg/kg Q2W.

Of note, as an immunoglobulin G4 (IgG4) monoclonal antibody, nivolumab does not interact directly with cytochrome P450 (CYP) enzyme systems. Systemic cytokine modulation data indicated that there were no meaningful changes in cytokines known to have indirect effects on CYP enzymes across all dose levels of nivolumab (0.3, 2, and 10 mg/kg) during the course of treatment. Therefore, it is unlikely that nivolumab administered at either 240 mg Q2W or 480 mg Q4W will affect the systemic exposures of BMS-986205.

At the discretion of the Sponsor, and in agreement with the investigators, the 480 mg Q4W nivolumab dosing regimen in the designated expansion cohorts and clinical pharmacology substudy may revert back to 240 mg Q2W based on emerging PK, pharmacodynamic, and/or tolerability data from the cohort expansion portion of the trial.

1.1.6.3 Doses and Schedules for Nivolumab and Ipilimumab in Combination with BMS-986205

The safety profile of nivolumab and ipilimumab is well characterized from a large safety database at different dose and schedules as monotherapy or in combination in different tumor indications. Consistent with the mechanism of action of nivolumab and ipilimumab, the most frequently reported drug-related AEs observed in clinical trials are those associated with activation of the immune system. The most common types of immune-mediated AEs include endocrinopathies, diarrhea/colitis, hepatitis, pneumonitis, nephritis, and rash. In combination regimens, the frequency and intensity of these events vary and appear to depend on the specific dose and schedule used as well as the patient population/tumor type being treated. As described below, while the overall pattern of AEs observed with the combination of nivolumab and ipilimumab remains relatively consistent across doses and schedules evaluated, the incidence and severity of immune-mediated AEs varies across tumor types. Therefore, evaluation of safety and tolerability of specific dose/schedule combinations of nivolumab and ipilimumab with BMS-986205 in Part 3 will be evaluated in tumor types in which that nivolumab/ipilimumab regimen has evidence of both tolerability and efficacy (see Section 1.1.5.2).

Melanoma

The regimen selected for evaluation of triplet therapy in melanoma is BMS-986205 in combination with nivolumab 480 mg Q4W and ipilimumab 1 mg/kg Q8W.

The currently approved combination of nivolumab and ipilimumab in metastatic melanoma is nivolumab 1 mg/kg with ipilimumab 3 mg/kg Q3W (N1I3) for 4 doses, followed by nivolumab 3 mg/kg Q2W ongoing. Two large randomized trials (CA209069 and CA209067) utilized this same dose regimen N1I3. In CA209067, Grade 3 and 4 adverse events were: nivolumab alone 43.5%, ipilimumab alone 55.6%, and nivolumab plus ipilimumab (N1I3) 68.7%. Discontinuation as a result of treatment was also highest in the combination group, 36.4%, as compared to 7.7% with nivolumab alone group and 14.8% of those in the ipilimumab alone group.[33] While the safety of N1I3 ratio was considered acceptable and majority of the AEs were managed with recommended treatment algorithms, there is rationale that lowering the dose of ipilimumab from 3 mg/kg to 1 mg/kg could potentially reduce the incidence of high grade AEs. This led to the initiation of the CA209511 study, which is comparing N1I3 to a nivolumab 3 mg/kg and ipilimumab 1 mg/kg Q3W (N3I1) regimen. In addition, a separate cohort consisting ipilimumab 1 mg/kg Q8W together with nivolumab 6 mg/kg (alternating with 480-mg flat dose) Q4W, all continuing until unacceptable toxicity is being evaluated.

The rationale for a regimen with Q8W ipilimumab dosing is to potentially optimize safety and efficacy while also extending the dosing intervals for the convenience of patients and health care providers. From a safety perspective, this extended schedule of ipilimumab is predicted to lead to reduced incidence of high grade adverse events compared to regimens utilizing more frequent and/or higher doses of ipilimumab, while simultaneously allowing for an increase in the dose of nivolumab used in combination with ipilimumab.

Regarding PK, nivolumab dosing at 480 mg Q4W is expected to result in similar time averaged concentrations at steady state (Cavgss) as nivolumab 3 mg/kg Q2W. In addition, nivolumab exposures following 480 mg are predicted to be below the those observed at doses up to 10 mg/kg Q2W (used in the Phase 1 nivolumab clinical program) that have been shown to be safe and well tolerated[26].

Efficacy may also be improved through the addition of BMS-986205 to the use nivolumab 480 mg plus ipilimumab 1 mg/kg regimen. Combination regimens in which ipilimumab is continued beyond 4 doses until progression or intolerability have not been assessed in patients with advanced melanoma. Furthermore, it is possible that patients receiving lower and less frequent ipilimumab doses will stay on the combination longer by reducing high grade AEs and thereby increasing the number of combination doses administered. This may result in improved efficacy.

Lastly, the proposed regimen may provide convenience to patients and health care providers, due to the increased interval between doses (i.e. every 4 weeks instead of every 3 weeks).

NSCLC

The regimen selected for evaluation of triplet therapy in NSCLC is BMS-986205 in combination with nivolumab 360 mg Q3W and ipilimumab 1 mg/kg Q6W.

Previous evaluations of nivolumab and ipilimumab combinations in NSCLC were based on the success of combination therapy in melanoma as well as the evidence of monotherapy activity of nivolumab in NSCLC. Data from these cohorts demonstrate nivolumab 3 mg/kg Q2W given with ipilimumab at 1 mg/kg Q6W is tolerable. Of particular note, the rate of discontinuation for this combination due to drug-related AEs was 11% compared to 10% in the nivolumab monotherapy arm; fatigue was the most commonly reported AE related to study therapy in the combination arm (23.1%).[36] This combination regimen is being evaluated currently in the CA209227 study in first-line treatment of NSCLC.

A flat dose of nivolumab has been selected for the current study. From a PK perspective, using the PPK model, the overall distributions of nivolumab average steady-state exposures (Cavgss) are predicted to be comparable after treatment with either nivolumab 3 mg/kg Q2W or 360 mg Q3W. Although nivolumab Cmaxss is predicted to be higher (23%) following 360 mg Q3W, these exposures are predicted to be within the exposure ranges observed at doses up to 10 mg/kg Q2W used in the nivolumab clinical program, and are not considered to put subjects at increased risk. The exposures predicted following administration of nivolumab 360 mg Q3W are on the flat part of the exposure-response curves for previously investigated tumors, melanoma and NSCLC, and are not predicted to affect efficacy. Based on these data, nivolumab 360 mg Q3W is expected to have similar efficacy and safety profiles to nivolumab 3 mg/kg Q2W. Therefore the combination dosing schedule selected for this study (nivolumab 360 mg Q3W plus ipilimumab 1 mg/kg Q6W) provides a combination regimen where the immune-mediated AEs were mostly low grade and manageable with prompt use of corticosteroids.

Bladder Cancer

The regimen selected for evaluation of triplet therapy in bladder cancer is BMS-986205 in combination with nivolumab 80 mg Q3W and ipilimumab 3 mg/kg Q3W for four doses, followed by nivolumab 480 mg Q4W.

Nivolumab and ipilimumab combinations have been evaluated in advanced bladder cancer in the CA209032 trial. Subjects were treated with either nivolumab 1 mg/kg and ipilimumab 3 mg/kg (N1I3) or nivolumab 3 mg/kg and ipilimumab 1 mg/kg (N3I1), both given Q3W for 4 cycles and then followed by nivolumab monotherapy. In contrast to the experience with nivolumab and ipilimumab combinations evaluated in other tumor types such as melanoma and NSCLC, treatment with higher doses of ipilimumab in bladder cancer were not associated with increased toxicity. Preliminary analysis of 24 subjects in the N1I3 (median follow-up: 7.8 months) and 104 subjects in N3I1 (median follow-up: 16.7 months) showed that discontinuations due to study drug toxicity were approximately equal between the groups (8% for N1I3, 14% for N3I1) as were the rates of Grade 3 or 4 toxicity (30.8% for N1I3 and 31.7% for N3I1).[41] As higher doses of ipilimumab may provide additional clinical activity, and taking into consideration the equal

safety to date between the N1I3 and N3I1 arms in CA209032, the N1I3 regimen was selected for evaluation in combination with BMS-986205 in the current trial.

1.1.7 Rationale for Nivolumab and Ipilimumab 30-minute Infusion

Long infusion times place a burden on subjects and treatment centers. Establishing that nivolumab can be safely administered using shorter infusion times of 30 minutes duration in subjects will diminish the burden provided no change in safety profile. Both nivolumab and ipilimumab have been administered safely at doses ranging up to 10 mg/kg over these treatment durations. Overall, infusion reactions including high-grade hypersensitivity reactions have been uncommon across multiple clinical studies, and all have been managed by following the safety algorithms. Infusion duration of 30 minutes for 3 mg/kg nivolumab (30% of the dose provided at 10 mg/kg) is not expected to present any safety concerns compared with the prior experience at 10 mg/kg nivolumab dose infused over the 60-minute duration. Similarly, shortened infusion duration of 30 minutes for ipilimumab is not expected to present additional safety concerns.[42]

1.1.8 Rationale for the Use of Tablet Formulation

A capsule formulation was used in the dose escalation (Part 1) and in patients participating the dose expansion (Part 2) of the study prior to Amendment 8. A tablet formulation has been developed to help reduce the pill burden and with its smaller size, provide ease of administration. The tablet formulation became available for use for subjects in Part 2 (after implementation of Amendment 7), Part 3 and in the QTc clinical pharmacology substudy.

Biopharmaceutics studies (in vitro biorelevant dissolution and non-clinical pharmacokinetic studies) were conducted to investigate the in vitro and in vivo performance of the two dosage forms.

Biorelevant dissolution of the two dosage forms were compared in a non-sink, 2-stage USP-II apparatus (fed state gastric fluid, pH 5 → fed-state simulated intestinal fluid (FeSSIF), pH 5, transitioned at 20 min). At a representative human dose of 100 mg, the dissolution profiles showed that both dosage forms disintegrate and dissolve rapidly, reaching a solubility indicative of complete drug release and dissolution in the intestinal fluid. To confirm the finding, a pharmacokinetic study was conducted in the dog model using 4 male dogs, pentagastrin-treated, as a cross-over between the tablet and capsule dosage form (50 mg) in the fed-state. The 50 mg dog dose is equivalent to roughly 150 mg human effective dose based on body surface area dose adjustment. The mean PK profiles for the two dosage forms were similar. The tablet was 80% bioavailable relative to the capsule formulation. The Cmax was 85% of the capsule, while the Tmax was the same[43].The mean values for Cmax and AUC were not statistically different ($p>0.05$, Student's t-test). The comparative PK parameters are listed in Table 1.1.8-1.

Table 1.1.8-1: Comparative Pharmacokinetic Parameters

PK Parameters	Capsule (50 mg)	Tablet (25 mg x 2)
Cmax (ng/mL)	332.12 ± 98.04	282.67 ± 99.88
Tmax (h)	2	2

Table 1.1.8-1: Comparative Pharmacokinetic Parameters

PK Parameters	Capsule (50 mg)	Tablet (25 mg x 2)
AUC (ng·h/mL)	1252.91 ± 392.91	1000.48 ± 416.89
AUC variability (%CV)	31.34	41.67

Cmax and AUC are mean values ± standard deviation (n=4 dogs), Tmax is the median value

Preliminary results from the dose escalation cohorts indicated potentially significant biomarker (peripheral kynurenine inhibition) over a wide dose/exposure range (See Section 1.4.4.1). Given the significant overlap in the in vitro and in vivo performance of the dose forms, the tablet is expected to perform similarly compared to the capsule while improving subject convenience and compliance.

1.1.9 Rationale for Clinical Pharmacology Substudy

1.1.9.1 QTc Substudy

In this substudy, the effect of BMS-986205 on the QTc interval will be evaluated. Preclinical evaluations did not identify a signal indicating that BMS-986205 may increase the QTc interval or have an adverse effect on cardiac conduction (Section 1.4.2). Despite the low risk, such evaluation is required during the development of a therapeutic agent and the design of this study (treating subjects across a wide range of doses, the inclusion of a 2-week BMS-986205 monotherapy leading-in period) is well suited for the evaluation of QTc risk, in particular, the characterization of the impact of BMS-986205 exposure on QTc changes. Serial electrocardiograms (ECGs; reviewed by a core laboratory) will be collected with matching PK samples during the BMS-986205 monotherapy at steady state in subjects participating in the substudy. To minimize the potential effects of intrinsic factors such as food ingestion and circadian patterns on QTc intervals, time-matched baseline ECGs will be collected prior to the start of BMS-986205 treatment.

As nivolumab is known not to affect the QTc interval, only routine ECG monitoring will be collected during combination treatment in both dose escalation and dose expansion phase of the study.

1.1.10 Rationale for Use of Blood and Tumor Tissue in Biomarker Studies

Biomarkers are increasingly playing a key role in the development of cancer therapeutics. By tracking treatment-induced changes in molecular markers measured in tissue and body fluids, the activity of experimental agents may be assessed and the details of their mechanisms of action may be elucidated. Such pharmacodynamic measures may be instrumental also for identifying appropriate doses and treatment schedules and may provide supporting information for future regimens.

This study includes fresh pre- and on-treatment biopsies as well as collection of archival tissue. Fresh biopsies will allow for assessment of key biomarker correlates which require contemporaneous tissue and specific processing (eg tumor kynurenine). Age limits on archival

tissues from subjects not providing fresh biopsies are required to allow for accurate interpretation of key biomarkers (eg PDL1) which may become compromised with age of sample.

The evaluation of pre- and on-treatment biopsies in this study is particularly critical for understanding biological consequences and clinical effects of combining therapies targeting multiple mechanisms simultaneously. The collection of both pre-treatment tumor biopsies and archival tumor tissue will provide important insight into questions related to mechanism of action and response to therapy. [redacted]

Identification and validation of critical markers in archival tissue will potentially enable diagnostic test development for future selection of patients most likely to respond to therapy based on archival tissue alone and obviate the need for fresh biopsies in larger groups of patients.

Blood and tumor tissue samples will be collected in this study at baseline and on treatment to identify molecular markers associated with clinical activity and mechanism of action of BMS-986205 in the lead-in phase or in combination with nivolumab ± ipilimumab. This information will be used to identify appropriate doses and treatment schedules of BMS-986205 in combination with nivolumab and in combination with both nivolumab and ipilimumab. Additionally, examination of biomarkers in samples obtained prior to treatment may provide information that allows identification of subjects with specific characteristics that will respond best to these agents. Information gained from tumor samples will not be used to make individual subject treatment decisions, but may inform pursuit of a validated marker to inform optimized treatment decisions in future protocol amendments or separate studies.

[redacted]

[redacted]

1.2 Research Hypothesis

It is anticipated that BMS-986205, administered in combination with nivolumab and in combination with both nivolumab and ipilimumab, will demonstrate adequate safety and tolerability, as well as a favorable benefit/risk profile, to support further clinical testing. No prospective hypotheses are being formally evaluated.

1.3 Objectives(s)

1.3.1 Primary Objectives

Part 1: Dose Escalation

To determine the safety, tolerability, dose-limiting toxicities (DLTs), and MTD/maximum administered dose (MAD)/alternate dose(s) of BMS-986205 administered as monotherapy and in combination with nivolumab in subjects with advanced malignant tumors.

Part 2: Dose Expansion

To investigate the anti-tumor activity of BMS-986205 administered in combination with nivolumab in distinct cohorts of subjects with advanced malignant tumors.

To evaluate the safety and tolerability of BMS-986205 in combination with nivolumab in subjects with advanced malignant tumors.

Part 3: BMS-986205, Nivolumab and Ipilimumab Combination

To determine the safety, tolerability, dose-limiting toxicities (DLTs), and preliminary anti-tumor activity of BMS-986205 administered in combination with both nivolumab and ipilimumab in subjects with select advanced malignant tumors.

1.3.2 Secondary Objectives

1) To characterize the PK of BMS-986205 administered alone, in combination with nivolumab, and in combination with both nivolumab and ipilimumab.
2) To investigate the anti-tumor activity of BMS-986205 administered in combination with nivolumab in dose escalation and clinical pharmacology substudies.
3) To characterize the pharmacodynamic activity of BMS-986205 administered alone, in combination with nivolumab, and in combination with both nivolumab and ipilimumab.
4) To characterize the immunogenicity of nivolumab when administered in combination with BMS-986205 and in combination with both BMS-986205 and ipilimumab.
5) To characterize the immunogenicity of ipilimumab when administered in combination with nivolumab and BMS-986205

1.4 Product Development Background

1.4.1 Pharmacology

BMS-986205

BMS-986205 is a small molecule inhibitor of IDO1 with half maximal inhibitory concentration (IC50) biochemical potency of 13.3 ± 1.8 nM and inhibitory constant (Ki) value of 21 ± 3 nM. Cellular potency as measured by the IC50 inhibition of kynurenine production was determined to be 1.11 ± 0.93 nM in human embryonic kidney 293 (HEK293) cells transiently expressing IDO1 and 1.71 ± 0.07 nM in HeLa cells stimulated with IFNγ. In addition, BMS-986205 inhibited kynurenine production in human whole blood (hWB) stimulated with IFNγ and LPS with an IC50 value of 33 ± 4.2nM. In an allogeneic mixed lymphocyte reaction (MLR) using IDO1 expressing dendritic cells, BMS-986205 restored T-cell proliferation with a half maximal effective concentration (EC50) value of 1.2 ± 0.4 nM.

BMS-986205 also exhibited significant pharmacodynamic effects in reducing tumor and serum kynurenine levels in at least 2 different murine syngeneic tumor models. The maximal reduction in tumor kynurenine levels was observed between 6 and 7 hours after dosing and the effects were sustained for 24 hours.

More detailed information can be found in the current version of the BMS-986205 Investigator Brochure (IB).

Nivolumab

Nivolumab is a fully human, IgG4 (kappa) isotype monoclonal antibody that binds to PD-1 with nanomolar affinity (dissociation constant [K_d], 3.06 nM) and a high degree of specificity. Nivolumab blocks binding of PD-1 to its ligands PD-L1 and PD-L2. Nonclinical in vitro testing of nivolumab demonstrated that binding to PD-1 results in enhanced T-cell proliferation and release of IFNγ in vitro in MLR and cytomegalovirus assays. Additional details are provided in the current version of the nivolumab IB.

Ipilimumab

Ipilimumab is a fully human IgG1 (kappa) monoclonal antibody that has specificity and a high affinity for human CTLA-4. The calculated dissociation constant value from an average of several studies was 5.25 nM. Binding of ipilimumab to purified, recombinant human CTLA-4 antigen was also demonstrated by enzyme-linked immunosorbent assay with half-maximal binding at 15 ng/mL, whereas saturation was observed at approximately 0.1 μg/mL. No cross-reactivity was observed against human CD28. Ipilimumab completely blocked binding of B7.1 and B7.2 to human CTLA-4 at concentrations higher than 6 and 1 μg/mL, respectively. Additional details are provided in the current version of the ipilimumab IB.

1.4.2 Toxicity

The safety profile of BMS-986205 was evaluated in single- and repeat-dose oral toxicity studies up to 3 months in duration (rats and dogs) and in genetic toxicity, phototoxicity, and safety pharmacology assessments. Rats and dogs were used as the main species for toxicologic evaluation and unless otherwise stated, all animal studies were dosed daily by the oral route. Dogs were considered an appropriate nonrodent species for nonclinical evaluation because of greater oral bioavailability (39%) compared to monkeys (10%) and consequently higher systemic exposure to BMS-986205. The rat data was used to calculate the maximum recommended starting dose because the rat was more sensitive to BMS-986205 toxicity on a mg/m^2 basis, although the toxicity profiles in the rat and dog were generally similar. Animal-to-human exposure multiples were calculated relative to either the preliminary mean Cmax or AUC in humans at the clinical dose of 100 mg (Cmax 0.476 μg/mL, AUC [0-24h] 4.85 μg•h/mL).

BMS-986205 is not phototoxic or genotoxic in vitro, and demonstrated no significant in vitro interactions with a broad spectrum of pharmacologic receptors, transporters, ion channels, nuclear hormones, or enzymes at ≥ 30 μM except for moderate inhibition at the α7 nicotinic cholinergic receptor (IC50 of 0.7 μM to 0.9 μM). In patch-clamp ion channel assays, BMS-986205 produced low to moderate inhibitory effects on the cardiac human ether-à-go-go-related gene (hERG) rapid delayed rectifier (IKr) potassium channel current (75% inhibition at 3 μM and IC50 1.1 μM), on the cardiac SCN5A sodium channel (≤ 13% inhibition at 10 μM), and on the L-type calcium channel (83% inhibition at 10 μM). In addition, similar testing of BMT-238450, a pharmacologically inactive metabolite of BMS-986205, demonstrated no significant off target receptor, ion channel, or transporter interactions (including cardiac ion channels) at ≥ 10 μM. The in vitro concentrations tested

above (≥ 0.7 μM) are substantially higher (≥ 580×) than the preliminary free Cmax (1.2 nM or 0.5 ng/mL) at the current Phase 3 dose of 100 mg. Additionally, there were no clinically significant effects on cardiovascular, respiratory, or central nervous system (CNS) endpoints evaluated in the 1- and 3-month pivotal repeat-dose toxicity studies in rats and dogs. In particular, no BMS-986205-related hemodynamic or electrocardiogram (ECG) changes were observed in dogs at doses up to 100 mg/kg with associated Cmax values up to 3.6 μg/mL (8.8 μM; safety multiple of 8× relative to preliminary Cmax of 0.476 μg/mL at the clinical dose of 100 mg).

The results from the pivotal 1-month toxicity studies in rats and dogs were generally similar to those from the pivotal 3-month studies and are detailed in Section 4.3 of the Investigator Brochure. However, as higher doses were administered in the 1-month studies, there were some adverse findings highlighted below that were not observed in the 3-month studies. In the 1-month rat study, doses were 5, 20, and 80 mg/kg/day. BMS-986205 was not tolerated at 80 mg/kg/day with signs of overt toxicity that included decreased activity, coolness to touch, hunched posture, piloerection, partially closed eyelids, recumbency, abnormal gait, aggressiveness, chromorhinorrhea, dehydration, body weight loss, and/or reduced food consumption resulting in death or early euthanasia; at ≥ 20 mg/kg/day, adverse findings included minimal hepatocellular necrosis with correlative increases in serum alanine aminotransferase (ALT: ~2× control) and minimal bile duct hyperplasia/fibroplasia in the liver. The severely toxic dose in 10% of animals (STD10) in rats was 20 mg/kg/day (mean combined-sex AUC ≤ 11.1 μg•h/mL) and the no-observed adverse effect level (NOAEL) was 5 mg/kg/day (AUC: 2.5 μg•h/mL). Relative to the preliminary human AUC values at the 100 mg clinical dose, the corresponding AUC exposure multiples are 2.3× and 0.5× at the STD10 and NOAEL, respectively. In the 1-month dog study, doses were 10, 30, and 100 mg/kg/day. At 100 mg/kg/day, BMS-986205 was not tolerated (body weight loss), and there were adverse findings in the liver (hepatocellular necrosis, centrilobular rarefaction, and bile stasis) with associated increases in serum transaminases (up to 18×) and total bilirubin (TBIL) (up to 4.3×). The dose of 30 mg/kg/day (mean combined-sex AUC: 5.6 μg•h/mL) was considered the highest non-severely toxic dose (HNSTD) and also the NOAEL for this study. At the current Phase 3 dose of 100 mg the dose multiple is 24× and, relative to preliminary human AUC values, the corresponding AUC exposure multiple is 1× at the HNSTD/NOAEL.

In the 3-month Good Laboratory Practice (GLP) oral toxicity study in rats doses were 0 (vehicle control), 1, 3, or 10 mg/kg/day (0, 6, 18, and 60 mg/m^2), respectively. BMS-986205 was well tolerated at doses ≤ 10 mg/kg/day (mean AUC ≤ 9.66 μg•h/mL). At ≥ 1 mg/kg/day, BMS-986205-related findings included dose-dependent increases in minimal to marked tubular regeneration in the kidney of male rats that lacked increased cellular stratification and nuclear or cellular pleomorphism seen with atypical hyperplasia. This finding was considered adverse at ≥ 3 mg/kg/day due to the extensive change that was accompanied by circumferential basement thickening and/or mononuclear infiltrates in the adjacent interstitium. At ≥ 3 mg/kg/day, there were additional generally dose-related changes that reflected oxidative injury to erythrocytes by

the BMS-986205 metabolite, p-chloroaniline,[44,45] with subsequent accelerated red blood cell (RBC) turnover and active hematopoiesis. These included minimal to mild increases in methemoglobin (metHb) concentrations (1.41× to 8.81× control); minimal decreases in RBC count (0.88× to 0.93×), hemoglobin (0.90× to 0.95×), and hematocrit in females (0.91× to 0.96×); minimal to moderate increased hematopoiesis and pigment accumulation in the spleen that correlated with increases in absolute and/or relative (to body and/or to brain) spleen weights (13% to 32%); minimal to moderate increases in reticulocyte counts in females (1.16× to 2.00×); transient and minimal increase in red blood cell distribution width (RDW) in females (1.05× to 1.06×); and increased incidence of females showing minimal degree of acanthocytes and/or echinocytes; and at 10 mg/kg/day, minimal increases in mean corpuscular volume (MCV) (1.05× to 1.06×); in mean corpuscular hemoglobin concentration (MCHC) (1.04× to 1.07×); increases in absolute and/or relative (to body and/or to brain) spleen weights that correlated microscopically with minimal to moderate pigment accumulation and increased hematopoiesis in the spleen; and presence of RBCs with crystallized hemoglobin-like structures in 1 female. In females at 10 mg/kg/day, the magnitude of increases in metHb and changes in RBC parameters (including morphology) together were considered adverse as these changes are expected to collectively result in decreased total functional oxygen-carrying capacity, paralleling the occurrence of clinical symptoms in humans (cyanosis, headache, and dizziness) with low-grade methemoglobinemia (~8%) and concurrent anemia. Although a recovery period was not included in this study, there was evidence of a regenerative process in the kidney that was likely a response to previous BMS-986205-related renal tubular injury in male rats and would be expected to recover once the insult was removed. In addition, the changes associated with p-chloroaniline formation would be expected to recover once the insult was removed. The NOAEL was considered to be 1 mg/kg/day (mean sex-combined AUC ≤ 0.666 μg•h/mL) and the STD10 was considered to be 10 mg/kg/day (mean sex combined AUC ≥ 9.66 μg•h/mL). Relative to the preliminary human AUC values at the 100 mg clinical dose, the corresponding AUC exposure multiples are 2× and 0.14× at the STD10 and NOAEL, respectively. Dose multiples are 8× and 0.8× at the STD10 and NOAEL, respectively.

In the 3-month GLP oral toxicity study in dogs doses were 0 (vehicle control) 10, 30, or 60 mg/kg/day (0, 60, 180, and 360 mg/m^2), respectively. BMS-986205 was well tolerated at doses ≤ 60 mg/kg/day (mean AUC ≤ 18.6 μg•h/mL). At all doses, there was a spectrum of generally dose-related changes that reflected oxidative injury to erythrocytes by the p-chloroaniline metabolite,[44,45] with subsequent accelerated RBC turnover and active hematopoiesis. These changes included the following: 1) minimal to mild, reversible increases in metHb concentration at ≥ 10 mg/kg/day (1.63× to 6.3× pretest); 2) minimal decreases in red cell mass at ≥ 30 mg/kg/day in females only (0.94× to 0.86×) and 60 mg/kg/day in both sexes (0.97× to 0.82×); 3) poikylocytosis (abnormal RBC shape) with crystallized hemoglobin-like structures in 3 animals at 60 mg/kg/day; 4) changes consistent with an erythroid regenerative response including minimal to moderate increases in reticulocyte counts (1.73× to 2.76×), minimal increases in platelet counts (1.30× to 1.76×) at ≥ 30 mg/kg/day, and minimal decreases in MCHC

(0.94× to 0.98×) at 60 mg/kg/day; 5) in the liver, minimal to mild increased hematopoiesis and increased incidence and/or severity of minimal to mild pigment (likely hemosiderin) accumulation in Kupffer cells, consistent with hemolysis (extravascular), and minimal bile stasis at ≥ 30 mg/kg/day; 6) in the kidney, increased incidence and/or severity of minimal to moderate pigment accumulation in kidney tubules (likely hemosiderin [a breakdown pigment of hemoglobin]); and 7) minimal to mild increased hematopoiesis in the bone marrow and spleen at all doses. The magnitude of increases in metHb and decreases in red cell mass together were considered adverse at 60 mg/kg/day as these changes are expected to collectively result in decreased total functional oxygen-carrying capacity, paralleling the occurrence of clinical symptoms in humans (cyanosis, headache, and dizziness) with low-grade methemoglobinemia (~8%) and concurrent anemia. All other findings were considered nonadverse, adaptive, or regenerative changes. Although a recovery period was not included in this study, the changes associated with p-chloroaniline formation would be expected to recover once the insult was removed. The NOAEL was considered to be 30 mg/kg/day (mean sex-combined AUC ≤ 8.47 μg•h/mL), and the HNSTD was considered to be 60 mg/kg/day (mean sex-combined AUC ≤ 18.6 μg•h/mL). Relative to preliminary human AUC values at the current Phase 3 clinical dose of 100 mg QD, the corresponding AUC multiples are 2× and 4× at the NOAEL and HNSTD, respectively. Dose multiples are 24× and 48× at the NOAEL and HNSTD, respectively.

BMS-986205 was associated with fetal loss and fetal malformations in an embryofetal development study in rats. In this study, oral doses of 20 and 50 mg/kg/day (only doses tested) were administered over the relevant period of organogenesis in rats and were associated with exposure multiples of 5× and 14×, respectively, compared to the exposures at the current Phase 3 clinical dose of 100 mg. There was a dose-dependent increase in the incidence of fetal loss and fetal malformations. Thus, exposure to BMS-986205 poses a potential risk to human pregnancy. BMS-986205 should not be administered to pregnant women.

Overall, the nonclinical toxicology profile of BMS-986205 has been well characterized, supporting clinical use in oncology subjects.

1.4.3 Preclinical Metabolism and Pharmacokinetics

The PK and metabolism of BMS-986205 were characterized in a series of in vitro studies in animal species and human models and in vivo studies that were conducted in mice, rats, dogs, and monkeys.[46,47] After IV administration, the apparent elimination half-life (T-HALF) of BMS-986205 ranged from 1.8 hours to 6.6 hours and total plasma clearance (CLTp) was equivalent to ≤ 48% of the respective reported liver blood flows in animals[48], suggesting that the compound has low to moderate systemic clearance. The volume of distribution at steady-state (Vss) indicated that BMS-986205 is distributed extravascularly, with low brain distribution observed in rats following IV dosing. BMS-986205 (10 μM, 4.1 μg/mL)was > 99.9% bound to serum proteins in humans and in the animal species studied.

After oral administration of BMS-986205, the time of maximum observed concentration (Tmax) ranged from 0.5 hours to 1.7 hours and absolute oral bioavailability (F) of BMS-986205 given as

a solution or suspension formulation was 29% to 55%, 64%, 39%, and 10% in mice, rats, dogs, and monkeys, respectively. Preliminary data showed that following a single 5 mg/kg and 25 mg/kg oral dose of BMS-986205 in pentagastrin-treated dogs, BMS-986205 AUC(0-24h) increased by approximately 2.2× and 3.0×, respectively, under fed conditions compared to fasting conditions, indicating that there was a food effect, but the observed food effect was not dose related. Following a single oral dose of BMS-986205 (5 mg/kg oral dose) to famotidine pretreated dogs under fasted condition, there was no reduction in AUC(0-24h) or maximum plasma concentration (Cmax) and the values were within PK experimental variability, compared to pentagastrin pretreated dogs.

The biotransformation of BMS-986205 was characterized by the production of numerous metabolites; biotransformation reactions included mono- and di-oxidation to form various oxidative metabolites including BMT-269044 (hydroxylation) and BMT-303671 (N-oxide), oxidation followed by glutathione (GSH) conjugation, and amide hydrolysis to an acid metabolite, M9 (BMT-238450) and p-chloroaniline. In vitro incubations of [^{14}C]BMS-986205 in rat, dog, monkey, and human hepatocytes demonstrated that p-chloroaniline was further metabolized to form an aniline sulfate (M1, BMT-242377) and 4-chloroacetanilide (M3, BMS-215753). The rank order of the extent of hydrolysis was rat (21%) > dog (13%) > human (4%) ~ monkey (4%). In addition, GSH adducts of oxidative metabolites were detected in hepatocyte incubations from rat, dog, and monkey, but were not observed in humans. No unique human metabolite was observed in hepatocytes. The primary in vivo biotransformation pathways in intact rats and dogs, and in bile duct-cannulated (BDC) rats administered [^{14}C]BMS-986205 were mono- and di-oxidation and hydrolysis of BMS-986205 to form BMT-238450 and p-chloroaniline. Subsequent metabolism of p-chloroaniline formed BMT-242377 and BMS-215753. Unchanged parent drug was a prominent circulating component in intact rat and dog. Other circulating drug-related materials included aniline-derived metabolites (BMT-242377 and BMS-215753), acid metabolite M9 (BMT-238450), and oxidative metabolites (BMT-269044 and BMT-303671). Preliminary reaction phenotyping studies in human liver microsomes demonstrated that cytochrome P450 (CYP) 3A4 was the major enzyme responsible for the oxidative metabolism of BMS-986205.

Preliminary data suggest that BMT-303671 blocked kynurenine production in hWB, with an IC50 value comparable to BMS-986205. BMT-269044 was also active in inhibiting kynurenine production in hWB, but was ~ 5-fold less potent than BMS-986205, while BMT-238450 was pharmacologically inactive under the same conditions.

A few selected metabolites including BMT-269044, BMT-303671, BMT-238450, and those derived from p-chloroaniline are being monitored in the ongoing, first-in-human (FIH), Phase1/2a Study CA017-003. Preliminary results suggest that plasma concentrations of BMT-269044 and BMT-303671 were approximately 30% to 40% of BMS-986205 levels. In the 3-month rat oral toxicity study, the AUC(0-24h) exposures of BMT-303671, BMT-269044, and BMT-238450 measured at the STD10 dose of 10 mg/kg/day were 11.2 µg•h/mL, -8.26 µg•h /mL and 18.4 µg•h /mL, respectively. At these exposures, the multiples over the AUC(0-24h) for BMT-303671 (2.10 µg•h /mL), BMT-269044 (1.88 µg•h /mL), and BMT-238450 (0.498 µg•h

/mL) at the 100 mg clinical dose are 5×, 4×, and 37×, respectively. In the 3-month dog oral toxicity study, the AUC(0-24h) exposures of BMT-303671, BMT-269044, and BMT-238450 measured at the HNSTD of 60 mg/kg/day were 0.728 µg•h /mL, 0.483 µg•h /mL, and 17.4 µg•h /mL, respectively, with associated exposure multiples at the 100 mg clinical dose of 0.35×, 0.26×, and 35×, respectively.

In human liver microsomes, BMS-986205 inhibited CYP1A2, CYP2B6, CYP2C8, CYP2C9, and CYP2C19 with IC50 values ranging from 1.0 µM to 26.5 µM. BMS-986205 also inhibited CYP3A4 with IC50s of 13.3 µM and 7.5 µM using midazolam and testosterone as the probe substrates, respectively. Additionally, BMS-986205 appeared to be a time-dependent inhibitor of CYP3A4, which had a 5× shift in IC50 values. However, the inhibitor concentration corresponding to the half-maximal rate of inactivation (KI) was determined to be greater than 20 µM, indicating that time-dependent inhibition of CYP3A4 by BMS-986205 is not anticipated. BMS-986205 also inhibited recombinant human uridine diphosphate glucuronosyltransferase(UGT) 1A1 (IC50 = 3.5 µM). BMT-269044 and BMT-303671 exhibited inhibition of CYP2B6, CYP2C8, CYP2C9, CYP2C19, and CYP3A4. BMT-238450 was not a CYP or UGT1A1 inhibitor. BMS-986205 inhibited digoxin and cladribine transport, as well as organic anion transporting polypeptide (OATP)1B1, OATP1B3, bile salt export pump (BSEP), organic cation transporter (OCT)1, and multidrug and toxin extrusion protein 1 (MATE1) (IC50 = 2.1 µM to 19.0 µM). In human hepatocytes, BMS-986205 did not cause any meaningful increase in CYP1A2, CYP2B6, and CYP3A4 enzyme activity, but did show some increase in corresponding CYP2B6 and CYP3A4 mRNA levels, indicating a potential for drug-drug interaction (DDI) with substrates of CYP2B6 and CYP3A4 through CYP induction.

Based on the preliminary human Cmax concentration (1.2 µM [0.5 µg/mL) at the current Phase 3 clinical dose (100 mg), using a 1% free fraction, the potential for BMS-986205 and its metabolites to cause DDIs by inhibition of CYP enzymes or UGT1A1 is low. However, drugs that inhibit or induce CYP3A4 may alter the plasma concentrations of BMS-986205. The potential to inhibit the human drug transporters OATP1B1, OATP1B3, BSEP, MATE1, and OCT1 is low, but BMS-986205 has been shown to inhibit P-glycoprotein (P-gp)/breast cancer resistance protein (BCRP), suggesting that BMS-986205 could affect the absorption and distribution of compounds that are P-gp/BCRP substrates. Additional details can be found in the IB for BMS-986205.

1.4.4 Clinical Pharmacology and Safety

1.4.4.1 Pharmacokinetics of BMS-986205

Preliminary PK for BMS-986205 are evaluated based on results from the dose escalation cohorts. Following BMS 986205 administration with a light meal, the exposures of BMS-986205 appear to increase in a dose proportional manner when the dose was increased from 50 mg to 400 mg. The time to reach peak plasma concentrations (Tmax) varied in a wide range with median about 3 hours to 5 hours. Following 100 mg QD doses, the geometric mean (CV%) accumulation ratio based on AUC(0 24h) between Day 1 and Day 14 was estimated to be 2 (79%), which corresponded to an estimated effective half-life of 37 hours, supportive of QD dosing of BMS-

986205. The geometric mean BMS-986205 concentration at the end of the dosing interval on Day 14 exceeded the in vitro hWB IC50 value (7.4 ng/mL) for all dose levels and exceeded the in vitro hWB IC90 (92 ng/mL) at dose levels of 100 mg and above. Main circulating metabolites (> 10% metabolite to parent AUC ratio based on AUC[0-24h] on Day 14) following the 100 mg QD doses were 12% for BMT-238450, 34% for BMS-269044, and 39% for BMS 303671. Preliminary results indicated BMT-303671 blocked kynurenine production in hWB with similar IC50 as BMS-986205 whereas BMS-269044 was~5-fold less potent and BMT-238450 was pharmacologically inactive (Section 1.4.3). Thus, it is possible that BMT-303671 contributes to the overall pharmacological activity. Additionally, preliminary data from an ADME study (Study CA017-052A) in healthy subjects suggest that unlike non-clinical toxicology species (rats and dogs), the hydrolysis pathway, which forms the p chloroaniline metabolite, represents a minor pathway in humans, accounting for ~7% of the total clearance.

Effect of food on the PK of BMS-986205 was evaluated in healthy subjects in Study CA017-053. Preliminary PK data indicate that following a single 100 mg dose, BMS-986205 geometric mean Cmax and AUC(0-168h) are 114% (90% CI 75.4% to 161.1%) and 52.8% (37.2% to 70.3%) higher, respectively, when dosed after a high fat meal compared to under fasting condition. BMS-986205 Cmax and AUC(0-168h) are 96.5% (71.7% to 124.8%) and 42.6% (28.0% to 58.8%) higher respectively, when dosed after a light meal compared to under fasting condition. Tmax ranged from 2 hours to 4 hours when dosing fasted and from 2 hours to 5 hours when dosed after a meal. PK variabilities are generally smaller when dosed after a meal. The terminal half-life averaged from 52 hours to 62 hours across the treatment groups.

1.4.4.2 Pharmacokinetics of Nivolumab

Single-dose PK of nivolumab was evaluated in 39 subjects with multiple tumor types in CA209001 in the dose range of 0.3 to 10 mg/kg. The median Tmax across dose levels ranged from 1.6 to 3.1 hours with individual values ranging from 0.9 to 7 hours. The PK of nivolumab was linear in the range of 0.3 to 10 mg/kg with dose-proportional increase in Cmax and AUC(INF). Geometric mean clearance after a single IV dose ranged from 0.13 to 0.19 mL/h/kg, while mean volume of distribution of terminal phase (Vz) varied between 83 to 113 mL/kg across doses. The mean terminal T-HALF of nivolumab was 17 to 25 days, consistent with half-life of endogenous IgG4, indicating that the elimination mechanism of nivolumab may be similar to IgG4. Both elimination and distribution of nivolumab appeared to be independent of dose within the dose range studied.

The multiple dose PK of nivolumab given Q2W in subjects with multiple tumor types was determined from the CA209003 study as well as PPK analyses using data from 909 subjects across nivolumab studies. Multiple-dose PK of nivolumab following Q2W dosing was linear with dose-proportional increase in Cmax and AUC(TAU) in the studied range of 0.1 to 10 mg/kg. The geometric mean of terminal T-HALF was 26.7 days and the typical clearance was 8.7 mL/h, which are consistent with those of full human immunoglobulin antibodies.

Nivolumab 480 mg Q4W is currently under active clinical evaluation across multiple tumor types. Using a PPK model, nivolumab 480 mg Q4W is predicted to provide average steady-state concentrations (Cavgss) similar to nivolumab 3 mg/kg Q2W. Nivolumab 480 mg Q4W is predicted to provide greater (approximately 40%) Cmaxss and lower (approximately 20%) trough steady-state concentrations (Cminss). Nivolumab has been shown to be safe and well tolerated up to doses of 10 mg/kg Q2W and has not demonstrated a clear dose response or exposure-response safety relationship. Based on these safety findings, the predicted Cmaxss at 480 mg Q4W is not considered to put subjects at increased risk for AEs. The approved dose of 3 mg/kg Q2W has shown survival benefit across multiple tumor types compared to respective standards of care. Nivolumab exposure was not a predictor of survival in exposure-response efficacy analyses conducted for multiple tumor types. The Cminss values following nivolumab 480 mg Q4W are predicted to be in the range of those on the flat part of the exposure-response efficacy curves and are not expected to impact efficacy.

As of Nov-2016, approximately 50 subjects in the nivolumab clinical development programs have received at least 1 dose of nivolumab 480 mg Q4W, either as the starting therapy or as maintenance treatment following nivolumab 240 mg Q2W. Bristol-Myers Squibb (BMS) has a clinical safety program that monitors symptoms potentially related to infusion-related reactions reported on the day of infusion and the following day. For the approximately 50 subjects treated with 30-minute infusions of nivolumab 480 mg, there have been no reports of any symptoms that may potentially be linked to infusion reactions on the day of infusion or the following day. There have been no new safety signals identified during routine clinical and pharmacovigilance monitoring of these studies. Clinical evaluation of this dose regimen is ongoing; as such, summaries of safety information, PK, and immunogenicity are not currently available.

Additional details are provided in the current version of the nivolumab IB.

1.4.4.3 Pharmacokinetics of Ipilimumab

The PK of ipilimumab has been extensively studied in subjects with melanoma at the 3- and 10-mg/kg doses administered as a 1.5-hour IV infusion. The PK of ipilimumab was characterized by population PK (PPK) analysis and determined to be linear and time invariant in the dose range of 0.3 to 10 mg/kg. The mean CL (± standard deviation) value after IV administration of 10 mg/kg was 18.3 ± 5.88 mL/h, and the mean Vss (± standard deviation) value was 5.75 ± 1.69 L. The PPK of ipilimumab was studied in 785 subjects (3,200 serum concentrations) with advanced MEL in 4 Phase 2 studies (CA184004, CA184007, CA184008, and CA184022),36 1 Phase 3 study (CA184024), and 1 Phase 1 study (CA184078). The PPK analysis demonstrated that the PK of ipilimumab is linear, the exposures are dose proportional across the tested dose range of 0.3 to 10 mg/kg, and the model parameters are time invariant, similar to that determined by non-compartmental analyses. Volume of central compartment (Vc) and peripheral compartment were found to be 4.35 and 3.28 L, respectively, suggesting that ipilimumab first distributes into plasma volume and, subsequently, into extracellular fluid space. CL of ipilimumab and Vc were found to increase with increase in body weight. However, there was no significant increase in exposure with increase in body weight when dosed on a milligram per kilogram basis, supporting dosing of ipilimumab based on a weight-normalized regimen. The PK

of ipilimumab is not affected by age, gender, race, and immunogenicity (anti-drug antibody [ADA] status); concomitant use of chemotherapy; prior therapy; body weight; performance status; or tumor type. Other covariates had effects that were either not statistically significant or were of minimal clinical relevance.

1.4.4.4 Clinical Safety

The information provided below is a general summary of safety. Please refer to the BMS-986205 Investigator Brochure for full safety information.

Safety of BMS-986205 as Monotherapy and in Combination with Nivolumab

The overall safety experience with BMS-986205 is based on treatment of 477 subjects as of a 15-Nov-2017 database lock, the majority of whom have been treated with BMS-986205 and nivolumab in this study.

As monotherapy and in combination with nivolumab, BMS-986205 overall has been well tolerated in both subjects with malignancies and healthy volunteers in other studies, with treatment-related adverse events (TRAEs) that were generally low grade and manageable. The safety profile of combination therapy with nivolumab and BMS-986205 has been largely comparable to that of nivolumab given as monotherapy. The most commonly reported TRAEs (in > 10% of subjects) during combination therapy with nivolumab were fatigue (14.1%) and nausea (11.1%). Grade 3 TRAEs have been reported in approximately 11% of subjects receiving the combination and treatment-related SAEs in approximately 7%. There has been 1 treatment-related death due to myocarditis prior to the clinical data cutoff date (15-Nov-2017), which occurred during combination with nivolumab. In addition, there was one treatment-related death due to Stevens-Johnson syndrome and one treatment-related death due to hepatic failure which occurred after the clinical data cutoff date.

With regard to p-chloroaniline, there have been no clinically significant metHb events at the 100 mg dose level, and the highest reported metHb value was 16% in a subject receiving 200 mg of BMS-986205; no other subjects had reported metHb levels over 10%, none have required specific treatment for methemoglobinemia, and there have been no treatment discontinuations due to methemoglobinemia. Anemia and hemolytic anemia have also occurred infrequently (2.5% and 0.3% of subjects receiving combination therapy with nivolumab, respectively) and responded to dose holding, reductions, and other standard clinical measures.

Based on the available safety data,100 and 200 mg dose levels were opened in cohort expansion to allow for further evaluation of safety, PK, and PD data in order to ultimately allow for a final selection of dose for cohort expansion.

Safety of BMS-986205 in Combination with both Nivolumab and Ipilimumab

Preliminary safety information for the combination of BMS-986205, nivolumab, and ipilimumab is available as of 3-May-2018 for the 13 subjects treated in Part 3 to date. This data is preliminary and subject to change.

In melanoma, 8 subjects have been treated: 4 at 100 mg BMS-986205 and 4 at 50 mg. In the 100 mg group, 2 DLTs (G3 autoimmune hepatitis in both) were reported out of 4 DLT evaluable subjects. While further enrollment was permitted at this dose per BLRM, given the observed DLTs in melanoma subjects as well as those in NSCLC (see below), the dose was reduced to 50 mg. With 50 mg, there have been no DLTs reported in 3 DLT-evaluable subjects. Enrollment at 50 mg is ongoing.

In NSCLC, 3 subjects were treated at 100 mg. Two discontinued due to disease progression and were not evaluable for DLTs. The third subject experienced a DLT of Grade 3 transaminase elevations. In consideration of the DLTs observed in melanoma at 100 mg described above, further enrollment at 100 mg in NSCLC was held and subjects were then treated with 50 mg. In the 50 mg cohort, both DLT-evaluable subjects experienced DLTs (Gr 3 transaminase elevations in both). Per the BLRM analysis, further enrollment at 50 mg was held and enrollment at 25 mg opened.

As described above, among all subjects in Part 3, hepatic events have been the most commonly observed toxicities. These events have resolved with interruption or discontinuation of study drugs and administration of immunosuppressive treatments. No deaths have been reported in either cohort.

1.5 Overall Risk/Benefit Assessment

1.5.1 Risk/Benefit for BMS-986205

As of 15-Nov-2017, 90 subjects have been treated with BMS-986205 monotherapy in this and other studies. TRAEs have been infrequent and generally mild. As BMS-986205 is not anticipated to have monotherapy antitumor activity, it is being developed as a combination agent, primarily with other immune-modulatory agents. Monotherapy treatment periods in this protocol are used primarily to provide preliminary safety and PK information..

Metabolism of BMS-986205 produces a p-chloroaniline (PCA) metabolite, which is associated with the formation of methemoglobin as well as with hemolytic anemia, as was observed in animal studies using BMS-986205. As of 15-Nov-2017, the peak metHb reported was 16% in a subject receiving BMS-986205 at 200 mg this study, below the commonly accepted threshold for the development of clinically significant symptoms (20%).[49]. This level was not associated with clinical sequelae, and the subject continued therapy at 100 mg of BMS-986205 with resolution of the methemoglobinemia. No other subjects had a metHb value of > 10% reported. No subject on study has required specific treatment for methemoglobinemia or had BMS-986205 discontinued due to methemoglobinemia. Drug-related Grade 3 anemia was reported in approximately 1% of subjects and hemolytic anemia in 0.3% during combination therapy with nivolumab.

Based on the findings from animal studies, entry criteria and monitoring parameters were developed in an attempt to reduce the risk of methemoglobinemia and hemolytic anemia. Subjects with cytochrome b5 reductase and glucose-6-phosphate dehydrogenase (G6PD) deficiencies are excluded due to the increased risk of methemoglobinemia and hemolysis, respectively. Guidance for detection and management of methemoglobinemia as well as guidelines for dose interruptions, reductions, and discontinuation are provided in Section 4.5.7

for the management of treatment-related hematological adverse events. In addition, complete physical examinations (PEs) will be conducted on Day 1 of each cycle, with symptom-directed PEs weekly during monotherapy and Q2W during combination. With regard to animal findings of hepatocyte damage, subjects with viral hepatitis or other liver disease, such as nonalcoholic fatty liver disease (NAFLD), will be excluded to minimize the potential for hepatotoxicity; frequent monitoring of liver function tests and guidance for dose modification and treatment interruptions have also been implemented. Similarly, subjects with inadequate renal function will be excluded to minimize the potential for nephrotoxicity due to renal findings in animals. While there was an in vitro hERG inhibition (IC50 at ~1.2 uM), high (> 99%) serum protein binding, projected human free Cmax of 0.018 uM at the highest dose planned, and lack of in vivo ECG findings in dogs suggest low cardiovascular risk to human subjects. Nevertheless, subjects with QTc prolongation at baseline will be excluded, medications known to cause prolonged QT will be restricted, and ECGs will be monitored during the study.

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

The International Agency for Research on Cancer classifies p-chloroaniline as Group 2B, or possibly carcinogenic to humans (1993),[50] but the human relevance of this classification is questionable since it does not take into account dose/exposure multiples, mechanism, and species differences. The secondary mechanism of carcinogenicity (following hematologic toxicity) in rats is not considered a significant issue for patients. This conclusion is further supported by the dose multiple of 52× when considering the NOEL for rat tumors and the daily exposure of patients to p-chloroaniline at the 100 mg clinical dose. Using ICH M7 principles, the less-than-lifetime exposures are calculated for p-chloroaniline, then the associated, theoretical cancer risks are the following: For 1 year of p-chloroaniline exposure associated with the 100 mg BMS-986205 dose, the risk is < 1 in 100,000; for 2 years of exposure, the risk is 1.83 in 100,000, both of which approximate the acceptable risk of 1 in 100,000 (per ICH M7) for drugs of any therapeutic class that may provide clinical benefit.

Since BMS-986205 is an experimental agent, it is possible that unforeseen, unknown, or unanticipated reactions may occur. However, the safety profile has been manageable thus far at doses of up to 200 mg.

1.5.2 Risk/Benefit for Combination with Nivolumab

As of 15-Nov-2017, 397 subjects have received BMS-986205 in combination with nivolumab (n=303 BMS-986205 100 mg + nivolumab 240 mg Q2W; n = 92 BMS-986205 100 mg + 480 mg Q4W) in this study. The MTD of BMS-986205 in combination with nivolumab was established at 200 mg based on the safety and tolerability profile and incidence of dose-limiting toxicities. Full information regarding the clinical safety information available as of the 15-Nov-2017 cut off can be found in the most recent version of the BMS-986205 Investigator Brochure

Nivolumab has demonstrated a manageable safety profile. The overall safety experience, when used either as a monotherapy or in combination with another therapeutic, is based on experience in approximately 12,300 subjects treated to date. There is no pattern in the incidence, severity, or causality of AEs to nivolumab dose level. The most common AEs include fatigue, rash, pruritus, diarrhea, and nausea. Side effects of nivolumab therapy may include those associated with immune-mediated activation, such as pneumonitis, thyroiditis, and hepatitis. Most of these events resolved with immune-modulating medication. To mitigate risk from serious immune-mediated AEs, subject management algorithms for nivolumab-related AEs from prior collective nivolumab experience have been included.

There is potential for overlapping toxicity between the preclinical toxicology findings of BMS-986205 involving the liver and nivolumab-related hepatotoxicity. However, the incidence of nivolumab-related hepatitis is quite low (~ 1%) and thus the liver-related exclusion criteria and the monitoring of liver function specified in the protocol will help to minimize the risk of hepatotoxicity. The immuno-oncology AE management algorithms also provide guidance for management of hepatic events.

The overall safety profile of BMS-986205 and nivolumab observed to date in Study CA017-003 has shown that the safety of the combination is largely consistent with that of nivolumab monotherapy and that the combination is well tolerated. The most common TRAEs (occurring in > 5% of subjects) occurring during treatment with this combination were fatigue (14.1%),nausea (11.1%), decreased appetite (9.1%), AST increased (7.6%), and ALT increased (7.1%). Grade 3 TRAEs have been reported in approximately 11% and Grade 4 TRAEs in 1.5% of subjects receiving the combination (n=397 in CA017-003), with treatment-related SAEs in approximately 7% and TRAEs leading to discontinuation in approximately 4%. Three treatment-related deaths have been reported: myocarditis, Stevens-Johnson syndrome, and hepatic failure; the latter two occurred after the data cut-off date (15-Nov-2017).

Nivolumab has demonstrated clinical activity in subjects with advanced NSCLC, RCC, melanoma, head and neck cancer, and lymphomas, as well as in subjects with other tumors. As outlined in Section 1.1.3, there is a mechanistic rationale that combination of an IDO1 inhibitor with checkpoint blockade will bring enhanced benefit to patients. Preliminary evidence of clinical activity for BMS-986205 plus nivolumab has been observed in the current study in both cervical and bladder cancers.[51]

1.5.3 Risk/Benefit for Combination with Both Nivolumab and Ipilimumab

Nivolumab and ipilimumab combinations have a well-defined toxicity profile based on a safety database of patients treated with the combination across multiple tumor types. Multiple dosing regimens have been evaluated. While the pattern and immune-mediated nature of toxicities remains relatively consistent, the severity and incidence of the toxicities does appear to differ by tumor type in each regimen evaluated. Therefore, within this protocol, the selection of each tumor type to be evaluated in safety lead-in Part 3 has been linked to a particular nivolumab and ipilimumab combination regimen known to have acceptable tolerability within that tumor type.

This should help to minimize the impact that the addition of BMS-986205 will have on the safety and tolerability of the nivolumab and ipilimumab regimens being evaluated.

As described in Section 1.5.2, preliminary data from the combination of BMS-986205 with nivolumab have not revealed any unforeseen toxicities to date. BMS-986205 has not been previously evaluated in combination with ipilimumab. Preliminary safety data are available from 11 subjects treated in Part 3 of this study. In those subjects, treatment-related hepatic events have been the most commonly observed TRAEs/DLTs. These events have been manageable with treatment interruption or discontinuation as well as administration of immunosuppressive therapies. While preliminary, these data also suggest that the dose of BMS-986205 may be related to the observed hepatic toxicities in this combination regimen, as 0/3 DLTs have been observed in melanoma at 50 mg versus 2/4 at 100 mg.

Similar to this, the IDO1 inhibitor epacadostat has been previously evaluated with ipilimumab in patients with metastatic melanoma. Initial doses of 300 mg BID in combination with ipilimumab 3 mg/kg Q3W led to unacceptable rates of Grade 3 to 4 ALT elevations, although these were reversible with treatment discontinuation and corticosteroid administration.[52] When lower doses of epacadostat up to 50 mg BID were evaluated with the same ipilimumab regimen, treatment-related toxicity rates were acceptable.

To address the potential for hepatotoxicity with triplet combinations of BMS-986205, nivolumab, and ipilimumab, initial safety of the triplet combination will be evaluated in NSCLC and melanoma cohorts using an ipilimumab dose of 1 mg/kg Q6-8W; only after safety is established with the 1 mg/kg dose of ipilimumab will the higher dose of 3 mg/kg ipilimumab Q3W be evaluated in a bladder cohort (see Section 1.1.6.3). Careful safety monitoring will be undertaken with frequent assessment of liver chemistries in addition to other safety laboratories and physical exams. During the first 6 weeks of the DLT evaluation period for the safety cohorts, liver chemistries will be checked on a more frequent, weekly basis. Rules for dose modification and discontinuation have been created to allow for rapid identification of toxicities requiring intervention, and investigators will be provided with algorithms for management of immune related adverse events that have been developed to address toxicity associated with immuno-oncology therapies, including combination regimens.

Nivolumab and ipilimumab combinations have demonstrated clinical activity in melanoma, NSCLC, and bladder cancer that exceed the clinical activity of each agent alone. Subjects receiving the triplet therapy regimens will therefore be receiving active combinations for their individual tumor types, with the addition of BMS-986205, which may lead to increasing benefit. Furthermore, the combinations of IDO1 inhibition with nivolumab and ipilimumab separately have been shown to have clinical activity and are actively being investigated in other trials.

1.5.4 Summary

Despite innovations in cancer treatment, alternative therapies are needed for subjects with advanced cancer. The emerging role of combination immune-modulating therapies in producing deep and durable responses in a variety of tumor types, as well as emerging clinical data from trials studying the combination of an IDO1 inhibitor with PD-(L)1-targeted therapies, suggest

that there may be a potential benefit of IDO1 inhibition with BMS-986205 when used in combination with nivolumab. Furthermore, there are preliminary clinical data showing possibly clinical activity of the combination of BMS-986205 with nivolumab in cervical and bladder cancers.[51] This together with the known improvement in clinical activity of nivolumab and ipilimumab combinations over monotherapy treatments support the evaluation of combination therapies with BMS-986205, nivolumab, and ipilimumab. Overall, the safety profile of BMS-986205 has been manageable both as monotherapy and in combination with nivolumab. It is expected that the addition of BMS-986205 (in doses already shown to be safe in combination with nivolumab) to nivolumab and ipilimumab backbone regimens with known tolerability in specific tumor types will be safe. The incidence of immune-related events will continue to be monitored across all combinations in the study as more subjects are treated in order to assess the impact of IDO1 inhibition on the known toxicity of nivolumab monotherapy and nivolumab and ipilimumab combination regimens. The benefit/risk ratio supports continued evaluation of BMS-986205 as monotherapy, in combination with nivolumab, and in combination with both nivolumab and ipilimumab in subjects with advanced cancer.

2 ETHICAL CONSIDERATIONS

2.1 Good Clinical Practice

This study will be conducted in accordance with Good Clinical Practice (GCP), as defined by the International Conference on Harmonisation (ICH) and in accordance with the ethical principles underlying EU 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) (ICFs) 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:

1) 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 nontechnical and easily understood.
2) Allow time necessary for subject or subject's legally acceptable representative to inquire about the details of the study.
3) 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.
4) 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.
5) 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.
6) 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 HIPAA Authorization.

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

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

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

3 INVESTIGATIONAL PLAN

3.1 Study Design and Duration

This is a Phase 1/2a, open-label study of BMS-986205 administered as a monotherapy, in combination with nivolumab (Parts 1 and 2), and in combination with both nivolumab and ipilimumab (Part 3) in subjects with advanced malignant tumors. A clinical pharmacology QTc substudy will also be conducted.

3.1.1 Screening and Treatment

3.1.1.1 Parts 1 and 2 (BMS-986205 Monotherapy and Combination with Nivolumab)

Dose escalation (Part 1) will start with a lead-in Cycle 0 whereby BMS-986205 is administered as monotherapy of 2 weeks duration in each dose escalation subject. Decision to proceed to combination treatment with nivolumab (Cycle 1) for each subject in dose escalation will be determined after tolerability of the monotherapy lead-in is established in the 2-week Cycle 0 (see Section 3.1.4). The starting dose of BMS-986205 is 25 mg orally daily. Nivolumab will be administered at a dose of 240 mg Q2W for the dose escalation (Part 1) and for the dose expansion (Part 2) cohorts that predated Amendment 06 (cervical, DLBCL, SCCHN, bladder, and pancreatic cancer). Nivolumab will be administered at a dose 480 mg intravenously Q4W for the dose expansion cohorts in Part 2 added with Amendment 06 (melanoma, NSCLC, and additional signal-seeking tumors) and Amendment 08 (RCC), as well as for the clinical pharmacology substudy. In the event the 25 mg dose of BMS-986205 is determined to exceed the MTD in monotherapy or in combination with nivolumab, a lower BMS-986205 dose (DL-1) may be explored based on available safety, PK, and biomarker information. Please refer to Appendix 1. At no point will the dose of BMS-986205 administered in combination with nivolumab exceed doses of BMS-986205 that have been demonstrated previously to be safe in the monotherapy lead-in Cycle 0 (Section 3.1.4). Subjects with select malignant tumor types will be enrolled per the inclusion criteria in Section 3.3.1.

Each Part 1 dose escalation subject will start with Cycle 0, which is a 2-week BMS-986205 monotherapy lead-in. If there are no DLTs (see Section 4.5.1), subjects will proceed to receive the combination of nivolumab and BMS-986205 (Cycle 1). In addition to the defined DLTs, the following AEs will also prohibit a subject from proceeding to combination with nivolumab:

- Grade 2 or higher immune-related AEs considered related to BMS-986205 (eg, immune-mediated pneumonitis, colitis, hepatitis, nephritis, and renal dysfunction) with the exception of immune-mediated hypothyroidism and hyperthyroidism
- Grade 2 AST and ALT elevations that do not resolve to Grade 1 or baseline within 1 week

Dose expansion (Part 2) will be carried out at the combination dose of BMS-986205 selected from dose escalation in combination with nivolumab 240 mg Q2W (cohorts 1 to 5) or 480 mg Q4W (cohorts 6 to 9), and may represent the MTD, MAD, or an alternate dose for the combination.

Study drug consisting of BMS-986205 daily and nivolumab will be administered in 4-week cycles, for up to 12 cycles. Subjects in 8 disease-restricted populations and subjects in 1 mixed signal-seeking cohort of additional tumors will be enrolled as follows: SCCHN, RCC, bladder cancer, cervical cancer, DLBCL, melanoma, NSCLC, and pancreatic cancer. The mixed signal-seeking cohort will include triple-negative breast cancer, adenocarcinoma of the endometrium, epithelial cancer of the ovary, and sarcoma. The doses selected for dose expansion will not exceed the MTD or MAD determined in dose escalation.

Clinical Pharmacology Substudy:

QTc Substudy

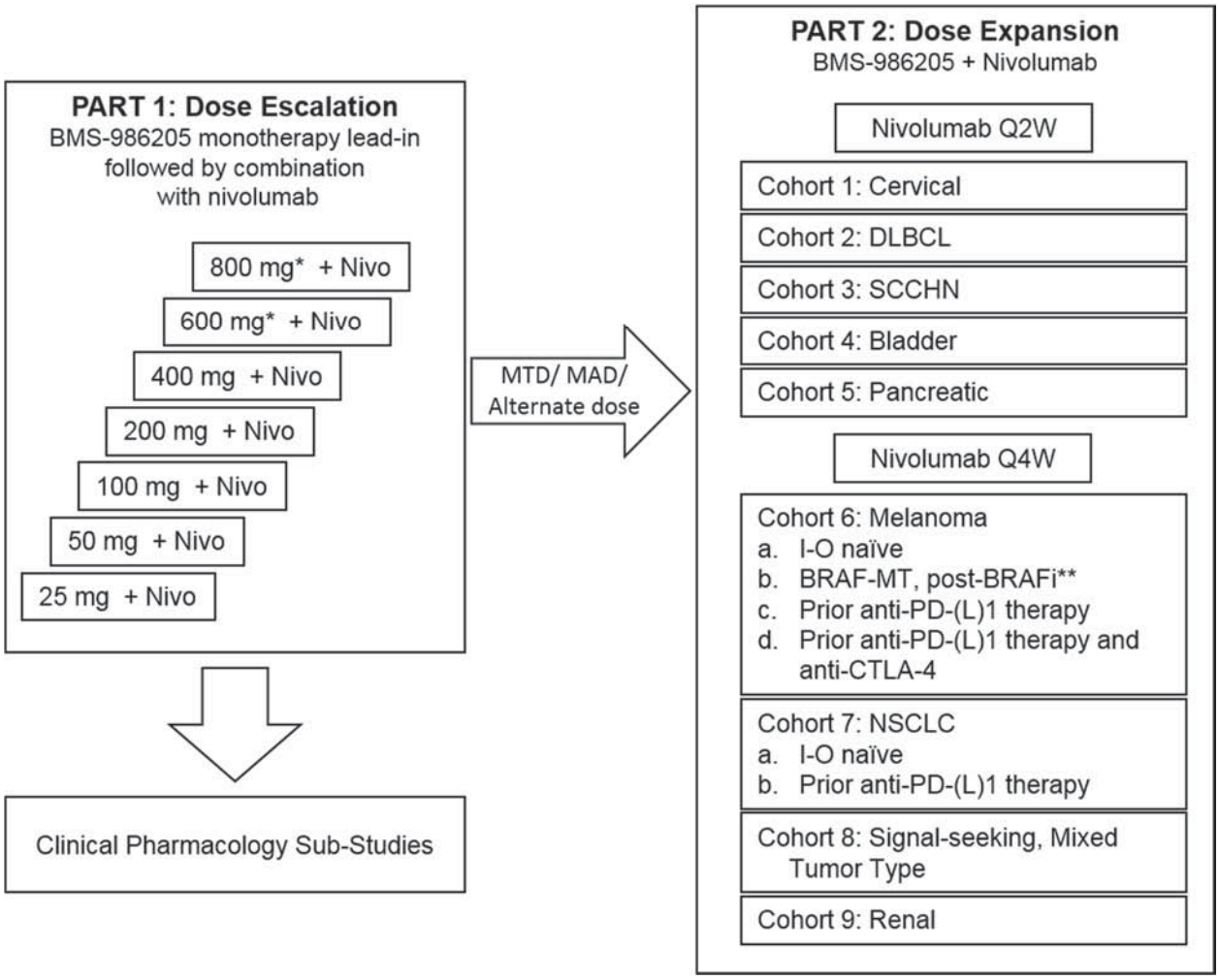
A clinical pharmacology substudy will be conducted in parallel with dose expansion to characterize the effect of BMS-986205 on the QTc intervals.

To minimize the influence of intrinsic factors such as food ingestion and circadian patterns on the QTc evaluation, time-matched baseline ECGs following a light meal will be collected prior to the start of BMS-986205 treatment cycles. During Cycle 0, subjects will receive BMS-986205 QD monotherapy with a light meal on Days 1 to 14 (see Table 5.1-14). Serial ECG samples in addition to the matched PK samples will be collected on Day 14 (Table 5.5.4.3-1). Subjects will then receive BMS-986205 in combination with nivolumab on Cycle 1 Day 1 and will follow all assessments as per Table 5.1-15.

The inclusion criteria (Section 3.3.1) used in the dose escalation phase will apply to subjects participating in the QTc substudy. At least 3 dose levels (below, at, and above the expected clinical dose) will be evaluated in at least 6 subjects per dose level in the substudy. Additional doses at supratherapeutic level may be evaluated in the substudy if warranted to allow for characterization of concentrations/QTc relationship at exposures that may exceed expected therapeutic levels due to extrinsic or intrinsic factors such as drug interactions, food effect, or organ dysfunction. The doses to be evaluated in the substudy will be determined based on available safety, PK, and biomarker data.

The study design schematic for Parts 1 and 2, and the Clinical Pharmacology Substudy is presented in Figure 3.1.1.1-1.

Figure 3.1.1.1-1: Parts 1, 2, and Clinical Pharmacology Substudy Study Design Schematic



*Note: As of Amendment 06, dose escalation beyond 400 mg BMS-986205 may not occur provided that additional pharmacodynamic effect is unlikely.

**Note: The BRAF-mutated, post-BRAFi regimen melanoma subjects will be randomized to receive either nivolumab or BMS-986205 + nivolumab.

Abbreviations: CTLA-4 = cytotoxic T lymphocyte-associated antigen 4; DLBCL = diffuse large B-cell lymphoma; I-O = immuno-oncology; MAD = maximum administered dose; MTD = maximum tolerated dose; Nivo = nivolumab; NSCLC = non-small cell lung cancer; PD1 = programmed cell death-1; PD-L1 = programmed death receptor-ligand 1; PD-(L)1 = either PD-1 or PD-L1; SCCHN = squamous cell carcinoma of the head and neck.

Please refer to Table 3.1.6-1 for a detailed description of the Part 2 dose expansion cohorts.

Subjects will complete up to 4 phases of the study: Screening, Treatment, Clinical/Safety Follow-up and Survival/Long-term Follow-up, as described below:

Screening:

The screening phase will last for up to 28 days. The screening phase begins by establishing the subject's initial eligibility and signing of the ICF. Subjects will be enrolled using the Interactive Voice Response System (IVRS).

Treatment Phase:

The treatment phase consists of up to twelve 4-week treatment cycles. For subjects receiving nivolumab on the Q2W regimen, each treatment cycle is composed of a daily oral dose of BMS-986205 and 2 doses of nivolumab administered intravenously Q2W on Days 1 and 15. For subjects receiving nivolumab on the Q4W regimen, each cycle is composed of a daily oral dose of BMS-986205 and 1 dose of nivolumab on Day 1. In addition, the dose escalation (Part 1) and the QTc substudy will start with Cycle 0, a lead-in period of 2 weeks duration, during which monotherapy with BMS-986205 is administered.

Following every 2 treatment cycles (8 weeks), the decision to treat a subject with additional cycles of study drug will be based on radiological tumor assessments (initial evaluation performed at baseline, end of Cycle 2, and every 8 weeks). Assessments of partial response (PR) and complete response (CR) must be confirmed at least 4 weeks following initial assessment. Tumor progression or response endpoints will be assessed using Response Evaluation Criteria in Solid Tumors (RECIST) v1.1 for solid tumors and International Working Group (IWG) criteria for HL and non-Hodgkin's lymphoma (NHL; Appendices 3 and 4).

Treatment beyond progression may be allowed in select subjects with initial RECIST v1.1 or IWG-defined progressive disease (PD) if the benefit/risk assessment favors continued administration of study drug (eg, subjects are continuing to experience clinical benefit as assessed by the investigator, tolerating treatment, and meeting other criteria specified in Section 3.5.1).

Subjects with a response of stable disease (SD), PR, or CR at the end of a given cycle will continue to the next treatment cycle. Subjects will generally be allowed to continue study drug until the first occurrence of either 1) completion of the maximum number of cycles, 2) PD, 3) clinical deterioration suggesting that no further benefit from treatment is likely, 4) intolerability to therapy, or 5) the subject meets criteria for discontinuation of study drug as outlined in Section 4.5.3. Individual subjects with confirmed CR will be given the option to discontinue study drug on a case-by-case basis after specific consultation and agreement between the investigator and BMS Medical Monitor in settings where benefit/risk justifies the discontinuation of study drug.

3.1.1.2 Part 3 (Combination with Both Nivolumab and Ipilimumab)

Part 3 is the safety evaluation and cohort expansion of the combination of BMS-986205, nivolumab, and ipilimumab. Initial safety evaluations will be performed in subjects with melanoma, NSCLC, and bladder cancer. Subjects with each tumor type will receive

BMS-986205 in combination with a different regimen of nivolumab and ipilimumab based on safety and efficacy data observed in previous trials of nivolumab and ipilimumab in that tumor type (see Section 1.1). After this initial safety evaluation, dosing regimens will then be evaluated in expansion cohorts, which may include subjects with other types of malignancies.

Subjects in safety evaluation cohorts will receive BMS-986205 at a dose which was shown to be tolerable in combination with nivolumab (from Parts 1 and 2) and nivolumab plus ipilimumab (from Part 3), as applicable. The dose of BMS-986205 will not exceed 100 mg daily.

The regimens will consist of:

- **Melanoma (Ipi 1Q8 regimen)**: BMS-986205 in combination with nivolumab 480 mg Q4W and ipilimumab 1 mg/kg Q8W, all given continuously.
- **NSCLC (Ipi 1Q6 regimen)**: BMS-986205 in combination with nivolumab 360 mg Q3W and ipilimumab 1 mg/kg Q6W, all given continuously.
- **Bladder (Ipi 3Q3 regimen)**: BMS-986205 given continuously, first in combination with nivolumab 80 mg and ipilimumab 3 mg/kg both given Q3W for 4 doses, followed by nivolumab 480 mg Q4W continuously

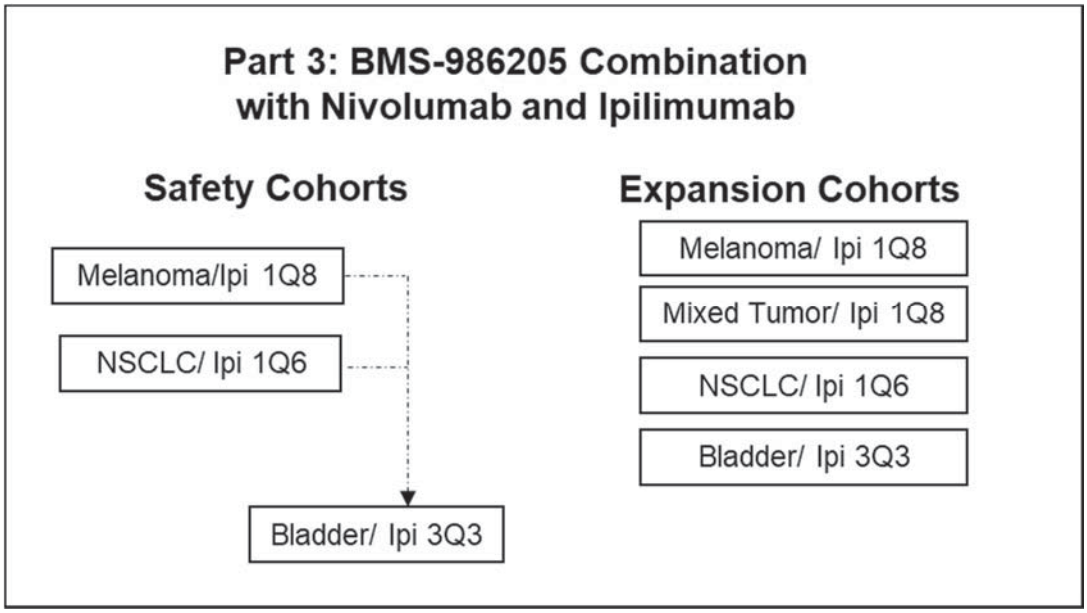
Evaluation of each regimen will begin with an assessment of safety and tolerability of the triplet combination therapy in a limited number of subjects, including a sentinel subject (see Section 3.1.7), in a safety evaluation cohort. The melanoma and NSCLC safety cohorts will begin safety enrollment simultaneously since the dose of ipilimumab is similar between the cohorts. Furthermore, for nivolumab dosing, the 480 mg Q4W and 360 mg Q3W are expected to achieve similar average exposure. The safety evaluation for the bladder regimen will begin enrolling subjects once either the melanoma or NSCLC regimen has been found to be safe and tolerable, as the bladder regimen uses a higher dose (3 mg/kg Q3W) of ipilimumab relative to the melanoma and NSCLC cohorts (1 mg/kg Q6W and Q8W of ipilimumab) during the DLT evaluation period.

Once the initial safety and tolerability have been established independently for each regimen (see Section 3.1.7) within a given tumor type, subjects will begin enrolling in expansion cohorts for that tumor type.

Additionally, subjects may be enrolled into a mixed tumor type cohort using the Ipi 1Q8 regimen for further evaluation of safety and tolerability, as well as preliminary evaluation of anti-tumor efficacy once the safety of Ipi 1Q8 is established in the melanoma cohort.

The study design schematic for Part 3 is presented in Figure 3.1.1.2-1.

Figure 3.1.1.2-1: Part 3



Screening:

The screening phase will last for up to 28 days. The screening phase begins by establishing the subject's initial eligibility and signing of the ICF. Subjects will be enrolled using the Interactive Voice Response System (IVRS).

Treatment Phase:

For subjects receiving the melanoma/Ipi 1Q8regimen containing nivolumab 480 mg Q4W and ipilimumab 1 mg/kg Q8W, 1 cycle will consist of 2 doses of nivolumab and 1 dose of ipilimumab (ie, 8 weeks). For subjects receiving the NSCLC/Ipi 1Q6 regimen containing nivolumab 360 mg Q3W and ipilimumab 1 mg/kg Q6W, 1 cycle will consist of 2 doses of nivolumab and 1 dose of ipilimumab (ie, 6 weeks). For subjects receiving the bladder/Ipi 3Q3 regimen, during the nivolumab and ipilimumab lead-in, the first 2 cycles will each consist of 2 doses of nivolumab and ipilimumab (each cycle is 6 weeks); after the first 2 cycles, each subsequent cycle will be comprised of 1 dose of nivolumab (ie, 4 weeks).

Timing of imaging assessments will be based on the regimen the subject is receiving:

- **Melanoma/ Ipi 1Q8**: The first imaging assessment will occur at Week 12 (± 1 week); subsequent imaging will be every 8 weeks (± 1 week) thereafter throughout the treatment period.
- **NSCLC/ Ipi 1Q6**: The first imaging assessment will occur at Week 6 (± 1 week), and then every 6 weeks (± 1 week) throughout the treatment period.
- **Bladder/ Ipi 3Q3**: The first imaging assessment will occur at Week 6 (± 1 week), and then every 6 weeks (± 1 week) during the treatment period up to 24 weeks, after which they will occur every 12 weeks (± 1 week) thereafter throughout the treatment period.

- **Mixed tumor type/ Ipi 1Q8**: The first imaging assessment will occur at Week 8 (± 1 week); subsequent imaging will be every 8 weeks (± 1 week) thereafter throughout the treatment period.

The decision to treat a subject with additional cycles of study drug will be based on the most recent radiological tumor assessment preceding that dose. Assessments of PR and CR must be confirmed at least 4 weeks after the initial assessment. Tumor progression or response endpoints will be assessed using RECIST v1.1 criteria.

Treatment beyond progression may be allowed in select subjects with initial RECIST v1.1 or IWG-defined progressive disease (PD) if the benefit/risk assessment favors continued administration of study drug (eg, subjects are continuing to experience clinical benefit as assessed by the investigator, tolerating treatment, and meeting other criteria other criteria specified in Section 3.5.1).

Subjects with a response of stable disease (SD), PR, or CR at the most recent imaging assessment will continue to receive study treatment. Subjects will generally be allowed to continue study drug until the first occurrence of either 1) completion of the maximum duration of study therapy (2 years from first dose), 2) PD, 3) clinical deterioration suggesting that no further benefit from treatment is likely, 4) intolerability to therapy, or 5) the subject meets criteria for discontinuation of study drug as outlined in Section 4.5.3. Individual subjects with confirmed CR will be given the option to discontinue study drug on a case-by-case basis after specific consultation and agreement between the investigator and BMS Medical Monitor in settings where benefit/risk justifies discontinuation of study drug.

3.1.2 Treatment with Additional Cycles Beyond 48 Weeks

In all Parts of this study, all subjects will be treated for 48 weeks of BMS-986205 in combination with nivolumab or both nivolumab and ipilimumab unless criteria for study drug discontinuation are met earlier (Section 3.4.3). All subjects completing approximately 48 weeks of study therapy with ongoing disease control (CR, PR, or SD) may be eligible for up to an additional 48 weeks (a maximum of 2 years from first dose of study therapy) of treatment at the originally assigned dose regimen (except for the bladder triplet regimen) beyond the initial 48 weeks, on a case-by-case basis, after careful evaluation and discussion with the BMS Medical Monitor to determine whether the benefit/risk ratio supports administration of further study drug. For the bladder triplet combination, the additional 48 weeks of study treatment will include nivolumab and BMS-986205 but not ipilimumab; nivolumab will be given as 480 mg Q4W starting with the first cycle of additional treatment. Subjects whose last assessment of the initial 48-week period shows PD will also be eligible to continue to additional cycles if they are still deriving clinical benefit, as per the guidance of treatment beyond progression (Section 3.5.1). Upon completion of 48 weeks of study drug (or up to a maximum of 96 weeks [2 years] if applicable), all subjects will enter the Clinical/Safety Follow-up period.

3.1.3 Follow-up

3.1.3.1 Clinical/Safety Follow-up

Upon completion of 48 weeks of study drug (or up to a maximum of 96 weeks if applicable), all subjects will enter the Clinical/Safety Follow-up period once the decision is made to discontinue the subject from treatment (eg, at end of treatment [EOT]).

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

Subjects who discontinue the treatment phase will enter the Clinical/Safety Follow-up period. Subjects must be followed for at least 100 days (representing approximately 5 half-lives for nivolumab) after the last dose of study drug. Follow-up visits should occur at Days 30, 60, and 100 (±10 days) after the last dose of study drug or should coincide with the date of discontinuation (±10 days) if date of discontinuation is greater than 30 days after the last dose of study drug to monitor for AEs. All subjects will be required to complete 3 Clinical/Safety Follow-up visits regardless of whether they start a new anti-cancer therapy, except those subjects who withdraw consent for study participation.

3.1.3.2 Survival/Long-term/Response Follow-up

After completion of the Clinical/Safety Follow-up period, all subjects will then enter the Survival/Long-term Follow-up period. During this period, clinic visits or telephone contact every 3 months will be performed to assess survival status. The duration of the Survival/Long-term Follow-up period will be approximately 2 years following the first dose of study drug, and a minimum of 12 months following the last dose of study drug.

After completion of the Safety Follow-up period, subjects who discontinue study with ongoing SD, PR, or CR at the EOT visit will enter the Response Follow-up period. This period will occur simultaneously with the Survival Follow-up period for these subjects. These subjects will continue to have radiological and clinical tumor assessments every 3 months (12 weeks) during the Response Follow-up period or until disease progression or withdrawal of study. Radiological tumor assessments for subjects who have ongoing clinical benefit may continue to be collected after subjects complete the survival phase of the study.

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

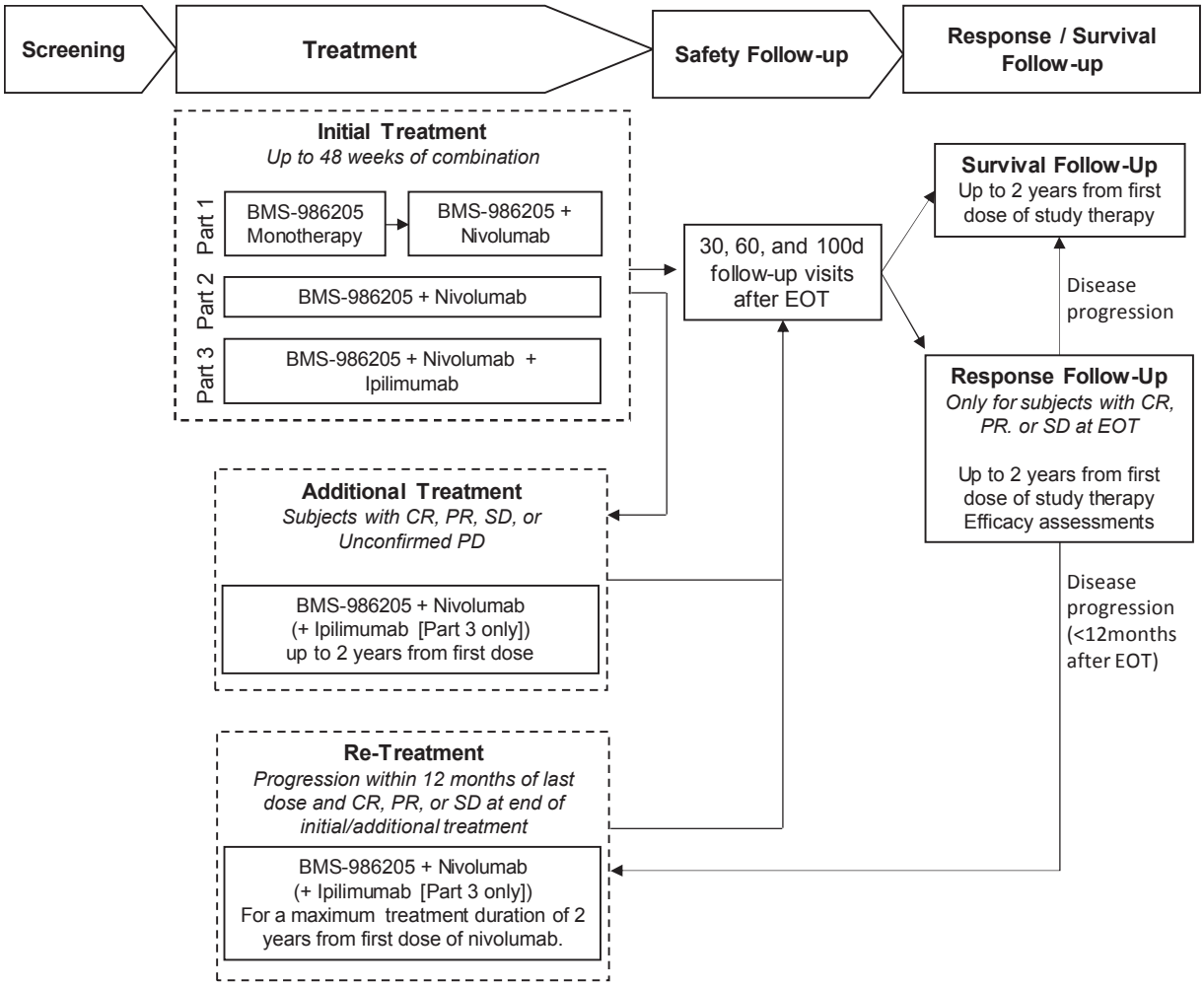
Data from imaging assessments for subjects who have ongoing clinical benefit may continue to be collected after subjects complete the survival phase of the study.

3.1.4 Re-treatment during Safety/Survival/Long-term Follow-up

Re-treatment may be allowed in this study with disease progression during follow-up. Subjects completing approximately 48 weeks of study treatment or who discontinue therapy due to a CR, who enter Safety/Survival/Long-term Follow-up with ongoing disease control (CR, PR, or SD) for reasons other than drug-related toxicity, may be eligible for re-treatment upon subsequent confirmed disease progression within 12 months of the last dose of study drug, on a case-by-case basis, after careful evaluation and discussion with the BMS Medical Monitor to determine whether the benefit/risk ratio supports administration of further study drug. Subjects meeting criteria for re-treatment will be treated for a maximum duration of 2 years from first dose of nivolumab, with the originally assigned dose regimen (eg, same dose and dose schedule administered during the initial treatment period) or modified dose regimen, unless that dose and schedule were subsequently found to exceed the MTD, in which case the subject will be treated at the next lower or alternate dose and schedule (see Table 4.5.3-1). Subjects entering this phase will follow the same Time and Events schedule as outlined in Section 5. Samples for PK will be collected less frequently. During re-treatment, pharmacodynamic biomarker samples obtained from blood will be collected as outlined in Section 5.7.

The treatment and follow-up schematic for Parts 1, 2, and 3, and the pharmacology substudy is presented in Figure 3.1.4-1. The study design schematic for the clinical pharmacology substudy is presented in Figure 3.1.4-2.

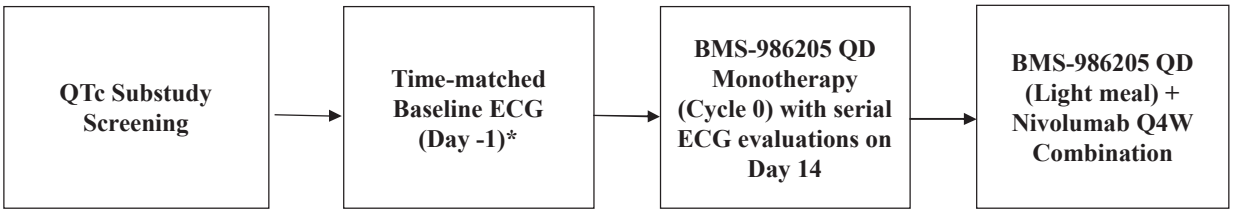
Figure 3.1.4-1: Treatment and Follow-Up Schematic for CA017003--All Study Parts



Note: For Part 3 bladder cohort, Additional Treatment will not include ipilimumab

Abbreviations: CR = complete response; EOT= end of treatment; PD = progressive disease; PI = principal investigator; PR= partial response; SD = stable disease.

Figure 3.1.4-2: Study Schematic of Clinical Pharmacology QTc Substudy



*: Baseline ECGs should be collected prior to the start of Cycle 0 (Day -1 preferred, up to 5 days prior to Cycle 0 is allowed).

Abbreviations: ECG = electrocardiogram; Q4W = every 4 weeks; QD = once daily.

3.1.5 Part 1: Dose Escalation

The dose escalation phase of the study will evaluate the MTD/MAD/alternate dose of BMS-986205 in combination with nivolumab based on DLTs using a BLRM model (for BMS-986205 monotherapy lead-in) and BLRM-copula model (for BMS-986205 in combination with nivolumab). The Bayesian models will be used for recommendation of the next dose to be investigated. A BLRM (combined with copula) framework with an escalation with overdose control principle will be employed to ensure that safety is not compromised during dose escalation.

The initial dose level of BMS-986205 will be 25 mg administered orally daily. Once initial lead-in monotherapy (Cycle 0) is deemed tolerable, combination with a 240-mg flat dose of nivolumab at the same dose level with the same subject (Cycle 1) will be initiated.

Dose levels to be considered for the next combination cohort of the subject (with monotherapy lead-in) will be based on recommended monotherapy dose from the BLRM and recommended combination dose from the BLRM-copula. The lower dose from these 2 recommendations will be considered. Potential dose levels for dose escalation are provided in Table 3.1.5-1. The maximum allowable increase in dose will be 100%. Final dose selection for the next cohort/dose level will be made in conjunction with all data available from PK and pharmacodynamic assessments, and will be made after discussion and agreement between investigators and the BMS Medical Monitor. Accordingly, intermediate or lower doses, or less frequent dosing of BMS-986205 may be tested if none of the planned doses/schedules are found to be tolerated as lead-in phase or in combination with nivolumab.

Approximately 30 subjects will be treated in the dose escalation phase. Depending on the dose recommendation, more than 3 subjects can be treated at each dose level. Increments of approximately 3 subjects will be added to each dose level depending on model recommendation and clinical judgment. Once the safety of any dose level has been established, up to 12 additional subjects may be added to better characterize the PK and pharmacodynamic profile.

Cohort-tolerability assessment and subsequent dose recommendation will occur when 2 DLT-evaluable subjects within a subject cohort have completed the 6-week DLT observation period (see Section 4.5.1 for criteria for DLTs). DLTs occurring within the 2 weeks of the lead-in period (DLT observation period for monotherapy) will be used to fit the BLRM model for monotherapy. DLTs occurring within the 4 weeks of combination period (DLT observation period for combination) will be used to fit the BLRM-copula model. The lower recommended dose from both models will be considered for next dose escalation. Subjects who received ≥ 75% of BMS-986205 doses and 2 doses of nivolumab, and have been followed at least 5 days after the second nivolumab dose, in the 6-week DLT observation period will be considered as DLT-evaluable subjects. Continuous re-assessment of dose recommendation by BLRM will be carried out at each dose level after each cohort of subjects with consideration of all available DLT information.

The MTD/MAD/alternate dose of BMS-986205 in combination with nivolumab selected for the cohort will be based on evaluating the recommendation from the BLRM-copula and a synthesis

of all available data, including clinical and laboratory safety assessments, PK, pharmacodynamic, and efficacy data, from all treated subjects at each dose level up to the MTD/MAD.

Up to 12 additional subjects may be added per selected dose levels to provide additional safety, tolerability, and PK data. This information will be incorporated into the final recommendation for the MAD/MTD/alternate dose of BMS-986205.

No intra-subject dose escalation is allowed, although dose modifications may be permitted (see Table 4.5.3-1).

Sentinel Subject: During dose escalation, a staggered dosing (sentinel subject) approach will be used for the first subject in the first dose level of both lead-in and combination. The first subject in both lead-in and combination will receive Cycle 0 Day 1 dose of study drugs and will be observed for 5 days before additional subjects (ie, subject 2 onward) in that cohort receive study drug. The first subjects to be dosed in subsequent cohorts will not be required to observe the 5-day interval between treatment start dates.

Table 3.1.5-1: Dose Escalation Schedule

Dose Level	BMS-986205	Nivolumab
-1	DL-1	240 mg IV Q2W
1	25 mg	240 mg IV Q2W
2	50 mg	240 mg IV Q2W
3	100 mg	240 mg IV Q2W
4	200 mg	240 mg IV Q2W
5	400 mg	240 mg IV Q2W
6	600 mg	240 mg IV Q2W
7	800 mg	240 mg IV Q2W

Note: As of Amendment 06, dose escalation beyond 400 mg BMS-986205 may not occur provided that additional pharmacodynamic effect is unlikely.

Note: Up to 12 additional subjects may be added per selected dose levels to provide additional safety, tolerability, and PK data. This information will be incorporated into the final recommendation for the MTD/MAD/alternate dose of BMS-986205.

Abbreviations: DL-1 = dose level-1; IV = intravenous; MAD = maximum administered dose; MTD = maximum tolerated dose; PK = pharmacokinetic; Q2W = every 2 weeks.

3.1.6 Part 2: Dose Expansion

The purpose of dose expansion is to gather additional safety, tolerability, preliminary efficacy, PK, and pharmacodynamic information regarding BMS-986205 in combination with nivolumab.

Eight disease-restricted populations will be included in dose expansion. These include cervical cancer, DLBCL, SCCHN, bladder cancer, melanoma, NSCLC, RCC, and pancreatic cancer. Various subpopulations of melanoma and NSCLC will be included in separate cohorts to further

understand the role of IDO1 inhibition in these specific populations as described in Section 1.1.5 and Table 3.1.6-1). An additional cohort will be dedicated to tumor types from the escalation inclusion criteria that do not currently have a dedicated expansion cohort or plans for evaluation in other studies. The eligible tumor types will be triple negative breast cancer, adenocarcinoma of the endometrium, epithelial cancer of the ovary, and sarcoma. Enrollment to this additional cohort will not exceed approximately 35 to 40 subjects. It will allow for the exploration of early efficacy signals seen during the dose escalation portion of the trial as well as potential signals arising from ongoing trials of other IDO1 inhibitors in combination with anti-PD-(L)1.

During dose expansion, the Simon 2-stage (optimal) design will be used as a guide for some of the tumor-specific expansion cohorts , although not used for hypothesis testing. Enrollment will continue for these tumor-specific expansion cohorts while evaluation of efficacy at stage 1 is ongoing. The 2-stage design with a reasonable false-positive rate (FPR) and false-negative rate (FNR) will provide guidance for the total sample size for these cohorts based on assumptions of true (target) and historic ORR for these indications. The sample sizes for each expansion cohort are provided in Table 3.1.5-1.

Initially, guided by, a minimum of 10 subjects in the SCCHN and bladder tumor cohorts; 12 subjects in the cervical, pancreatic, DLBCL, melanoma with prior anti-PD-(L)1 therapy, and NSCLC with prior anti-PD-(L)1 therapy cohorts; and 12 subjects in the melanoma with prior anti-PD-(L)1 and anti-CTLA-4 therapy cohort will be treated in Stage 1 for an initial evaluation of efficacy.

Table 3.1.6-1: Part 2 Expansion Cohorts

Cohort	BMS-986205 + Nivolumab	Total Subjects (Approximately)
1	Cervical	**35**
2	DLBCL	**35**
3	SCCHN	**27**
4	Bladder	**27**
5	Pancreatic	**35**
6	Melanoma	
6a	Melanoma, I-O naïve, PD-L1 positive	**40**
6b	Melanoma, I-O naïve, PD-L1 negative	**40**
6c*	BRAF-MT Melanoma, I-O naïve, post BRAFi	**8**
6d*	BRAF-MT Melanoma, I-O naïve, post BRAFi (nivolumab therapy)	**8**
6e	Melanoma, prior anti-PD-(L)1	**35**
6f	Melanoma, prior anti-PD-(L)1 and anti-CTLA-4	**37**
7	NSCLC	
7a	NSCLC, I-O naïve, PD-L1 positive	**40**
7b	NSCLC, I-O naïve, PD-L1 negative	**40**
7c	NSCLC, prior anti-PD-(L)1	**35**
8	Additional signal-seeking tumors	**35**
9	Renal cell carcinoma	**40**

NOTE: The BRAF-mutated, post-BRAF regimen melanoma subjects will be randomized to receive either nivolumab or BMS-986205 + nivolumab.

Abbreviations: BRAFi = BRAF inhibitor; CTLA-4 = cytotoxic T lymphocyte-associated antigen 4; DLBCL = diffuse large B-cell lymphoma; I-O = immuno-oncology; NSCLC = non-small cell lung cancer, PD-1 = programmed cell death-1; PD-L1 = programmed death receptor-ligand 1; PD-(L)1 = either PD-1 or PD-L1; SCCHN = squamous cell carcinoma of the head and neck.

Continuous evaluation of toxicity events in the dose expansions will be performed throughout enrollment in the expansion cohorts. If, at any time, the aggregate rate of treatment-related toxicities meeting DLT criteria exceeds 33% across all subjects treated in the dose expansions, the findings will be discussed and further enrollment may be interrupted. At that time, depending on the nature and grade of the toxicities and after assessing the risk/benefit ratio, a new dose(s) of BMS-986205 for all cohorts may be initiated at a previously tested lower dose level or at a dose level intermediate to previously tested lower dose levels. Additionally, at the discretion of the Sponsor, and in agreement with the investigators, the nivolumab 480 mg Q4W dosing

regimen in the designated expansion cohorts and clinical pharmacology substudy may revert back to 240 mg Q2W based on emerging PK, pharmacodynamic, and/or tolerability data from the cohort expansion portion of the study.

3.1.7 Part 3: BMS-986205, Nivolumab, and Ipilimumab Combination

Part 3 of the study will include a initial safety evaluation cohorts of 3 regimens of nivolumab and ipilimumab in combination with BMS-986205 in melanoma, NSCLC, and bladder cancer. Expansion cohorts for each regimen will then be conducted in the tumor type evaluated in the safety cohorts. The Ipi 1Q8W regimen will also be evaluated in a mixed cohort of other tumor types evaluated in Part 2. Each tumor type will receive BMS-986205 in combination with a specific nivolumab and ipilimumab regimen (see Section 3.1.1.2).

For the safety cohorts, the initial dose level of BMS-986205 for each cohort will be based on the available of safety, PK, and PD data for BMS-986205 in combination with nivolumab and any available from the combination with nivolumab and ipilimumab. The starting dose will not exceed 100 mg in any safety cohort. Lower dose levels of BMS-986205 (if required) to be evaluated in each safety cohort will be based on Table 3.1.5-1. Intermediate or lower doses, or less frequent dosing of BMS-986205 may be tested if none of the planned doses/schedules are found to be tolerated. In addition, alternative lower doses and more intermittent schedules of nivolumab and/or ipilimumab may be evaluated if the specified regimen used in each tumor type safety cohort is not found to be tolerable with any of the doses of BMS-986205 outlined in Table 3.1.5-1. Safety will be evaluated independently for each tumor type/regimen combination and treatment regimen based on DLTs using a BLRM-copula model.

All safety cohorts will begin with an assessment of safety and tolerability of the triplet combination regimen in a limited number of subjects. As described in Section 3.1.1.2, the NSCLC/Ipi 1Q6 and melanoma/Ipi 1Q8 regimen cohorts will begin enrollment first, followed by the bladder/Ipi 3Q3 regimen cohort once safety and tolerability have been established in either NSCLC/ Ipi 1Q6 or melanoma/Ipi 1Q8. Initially, approximately 3 subjects will be treated at the selected dose combination of BMS-986205 with nivolumab and ipilimumab. The first subject in each safety cohort will be a sentinel subject who will be observed for 5 days after administration of the first combination dose to ensure safety and tolerability before other subjects can receive treatment within that cohort.

Due to the potential for early discontinuation, an additional subject(s) may be enrolled to ensure approximately 3 DLT-evaluable subjects. Initial safety assessment to allow enrollment in the bladder/ Ipi 3Q3 safety cohort will occur when at least 2 evaluable subjects in either the NSCLC/ Ipi 1Q6 or melanoma/ Ipi 1Q8 safety cohorts have completed a 6-week DLT evaluation period (see Section 4.5.1 for criteria for DLTs). In the melanoma and NSCLC safety evaluation cohorts, if a potential DLT occurring in any third evaluable subject in the specific dose combination does not influence the recommendation by BLRM (-Copula) to open enrollment in the bladder safety cohort, then the bladder safety cohort may proceed with enrollment without waiting for the third subject to complete the corresponding DLT observation period.

DLT-evaluable subjects will be defined as subjects who in the 6-week DLT evaluation period received ≥ 75% of BMS-986205 doses and the following nivolumab and ipilimumab doses for each regimen:

- Melanoma/ Ipi 1Q8: 2 doses of nivolumab and 1 dose of ipilimumab, and followed for at least 5 days after the second dose of nivolumab
- NSCLC/ Ipi 1Q6: 2 doses of nivolumab and 1 dose of ipilimumab, and followed for at least 5 days after the second dose of nivolumab
- Bladder/ Ipi 3Q3: 2 doses of nivolumab and 2 doses of ipilimumab, and followed for at least 5 days after the second dose of each drug

After the initial subjects in each treatment regimen are evaluated, additional increments of approximately 3 to 6 subjects will be treated in the same safety cohort as per the BLRM-copula model recommendation that the dose combination is safe. At least 6 DLT-evaluable subjects will be treated and assessed for a particular BMS-986205 dose in that tumor type/regimen cohort before enrollment in the expansion cohorts for that regimen will begin. Up to 12 DLT-evaluable subjects in total may be treated in each safety evaluation cohort at the BMS-986205 dose chosen for expansion regimens for further evaluation of safety and pharmacodynamic/PK parameters as required. BLRM (-copula) will be used to monitor the safety of each triplet dose combination on an ongoing basis.

Once the initial safety and tolerability have been established independently for each regimen based on the safety cohorts, enrollment will then begin in expansion cohorts for further evaluation of safety and tolerability, as well as preliminary evaluation of anti-tumor efficacy. In the expansion cohorts, BMS-986205 will be administered at a dose determined to be tolerable in combination with each nivolumab and ipilimumab regimen. Each BMS-986205 and nivolumab/ipilimumab combination regimen will be evaluated in tumor-specific cohorts based on the tumor type evaluated in the safety cohorts. The Ipi 1Q8 regimen will also be evaluated in a mixed tumor-type cohorts which may incorporate tumor types evaluated in Part 2.

The 3 tumor types for tumor-restricted cohorts will be melanoma, NSCLC, and bladder. As all subjects in these disease-specific cohorts will be receiving agents (nivolumab and ipilimumab) with known anti-tumor activity in those tumor types, a single-stage design will be utilized for each of these tumor types. Approximately 40 subjects will be treated in each of the following expansion cohorts: melanoma PD-L1 positive, melanoma PD-L1 negative, NSCLC PD-L1 positive, NSCLC PD-L1 negative, and bladder; this is to allow for the exploration of early efficacy signals of BMS-986205 in combination with both nivolumab and ipilimumab in relevant subpopulations. In each NSCLC expansion cohort, approximately 10 subjects will be IO-treatment naive, 25 will be treatment-naive, and 5 IO-therapy experienced. In the melanoma cohorts, approximately 35 will be treatment naïve in the advanced setting and 5 will be IO-therapy experienced in each cohort. In the bladder expansion cohort in Part 3, at least 30 subjects will be I-O therapy naive.

A mixed tumor type expansion cohort will also be evaluated, using the same regimen as in the melanoma safety cohort, Ipi 1Q8W. The purpose of this cohort is to obtain preliminary safety,

tolerability, and efficacy data in tumor types besides melanoma using the nivolumab 480 mg Q4W/Ipilimumab 1 mg/kg Q8W backbone in combination with BMS-986205 at the dose selected for the melanoma expansion cohort. Up to forty subjects may be treated in this cohort. Tumor types included in this cohort may be any previously evaluated in Part 2. All subjects in this cohort will be IO-treatment naive. Selection of tumor types and number of subjects per tumor type will be at the discretion of the Sponsor and based on emerging data from Part 2 of this study as well as other external data (e.g. from studies of nivolumab and ipilimumab in a particular tumor type). For each tumor type enrolled into this cohort, approximately 6 subjects will be initially evaluated for safety and tolerability for 6 weeks each for toxicities meeting DLT criteria exceeding the threshold defined below prior to enrollment of any other subjects with that tumor type.

Continuous evaluation of toxicity events in the expansion cohorts will be performed throughout enrollment in the expansion cohorts. If, at any time, the aggregate rate of treatment-related toxicities meeting DLT criteria within an individual tumor type/treatment regimen exceeds 33% across all subjects treated in the safety evaluation and dose expansion cohorts, the findings will be discussed and further enrollment may be interrupted. At that time, depending on the nature and grade of the toxicities and after assessing the risk/benefit ratio, a new dose(s) of BMS-986205 and/or dose and schedule of nivolumab and/or ipilimumab (as described above) for subjects within that cohort may be initiated.

3.2 Post Study Access to Therapy

At the conclusion of the study, subjects who continue to demonstrate clinical benefit may be eligible to receive BMS-supplied study drug. Study drug may be provided via an extension of the study, a rollover study requiring approval by responsible health authority and ethics committee, or through another mechanism at the discretion of BMS. BMS reserves the right to terminate access to BMS-supplied study drug if any of the following occur: a) the marketing application is rejected by responsible health authority; b) the study is terminated due to safety concerns; c) the subject can obtain medication from a government-sponsored or private health program; or d) therapeutic alternatives become available in the local market.

3.3 Study Population

For entry into the study, the following criteria MUST be met 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 ICF prior to the performance of any study-related procedures that are not considered part of standard of care.

b) Consent for tumor biopsy samples

2) Target Population

a) Subjects must be at least 18 years old and have histologic or cytological confirmation of a malignancy that is advanced (metastatic and/or unresectable) with measureable disease per RECIST v1.1 or revised IWG criteria for lymphomas (see Appendices 3 and 4).

1) Dose Escalation (Part 1 only): Subjects must have received, and then progressed or been intolerant to, at least 1 standard treatment regimen in the advanced or metastatic setting, if such a therapy exists, EXCEPT for subjects with melanoma, who can be treatment naïve, as they will be given concomitant nivolumab, which constitutes standard of care.

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

a) Melanoma: BRAF mutation status must be known.

b) NSCLC (squamous and non-squamous histology): Subjects' epidermal growth factor receptor (EGFR), anaplastic lymphoma kinase (ALK), and KRAS mutational status will be recorded if available.

c) Head and neck cancer restricted to squamous cell carcinoma: Human papillomavirus (HPV) status must be documented.

i) Confirmation of tumor human papillomavirus (HPV) status for subjects with oropharyngeal SCCHN: Prior testing results are acceptable if known.

(1) If tumor HPV status is unknown, subjects must consent to allow their submitted archived tumor tissue sample in the form of block or unstained slides to be tested for confirmation of tumor HPV status.

d) Transitional cell carcinoma of the genitourinary tract

e) RCC

f) Pancreatic adenocarcinoma

g) Colorectal neoplasm: Microsatellite Instability (MSI) status must be documented.

h) HL

i) B cell NHL excluding Burkett's lymphoma and precursor B-lymphoblastic leukemia/lymphoma

j) Cervical cancer

k) Triple negative breast cancer

l) Adenocarcinoma of the endometrium

m) Ovarian epithelial cancer

n) Sarcoma: Limited to the following histologies:

i) Undifferentiated pleomorphic sarcoma

ii) Liposarcoma: dedifferentiated and myxoid

iii) Angiosarcoma

iv) Alveolar soft part sarcoma

v) Synovial sarcoma

vi) Ewing's sarcoma

vii) Osteosarcoma

viii) Chondrosarcoma

ix) Gastrointestinal stromal tumor

2) Dose Expansion (Part 2 Only):

The following tumor types will be permitted:

a) Cervical Cancer

i) Persistent, recurrent, or metastatic cervical cancer with documented disease progression.

ii) Squamous, adenosquamous, or adenocarcinoma histology-confirmation of the original primary tumor is required.

iii) Must have had 1 prior systemic chemotherapeutic regimen (eg, paclitaxel/cisplatin, paclitaxel/cisplatin/bevacizumab) for persistent, recurrent, or metastatic disease. Chemotherapy administered concurrently with primary radiation (eg, weekly cisplatin), adjuvant chemotherapy given following completion of radiation therapy or as concurrent chemotherapy, and radiation therapy (eg, paclitaxel and carboplatin for up to 4 cycles) is not counted as a systemic chemotherapy regimen.

iv) Confirmation of tumor human papillomavirus (HPV) status: Prior testing results are acceptable if known.

(1) If tumor HPV status is unknown, subjects must consent to allow their submitted fresh or archived tumor tissue sample in the form of block or unstained slides to be tested for confirmation of tumor HPV status.

b) Diffuse Large B-cell lymphoma

i) Subjects must have received and then progressed or become refractory to at least 1 prior standard systemic therapy such as cytotoxic chemotherapy and anti-CD-20 targeted immunotherapy. The following are not considered separate lines of treatment: addition of a compound to an ongoing regimen, restarting the same regimen after a drug holiday, or switching from IV to oral therapy.

ii) Subjects must have received high-dose chemotherapy with autologous stem cell transplant (ASCT), if eligible. Ineligibility for ASCT will be determined using local institutional criteria.

iii) Subjects must be more than 100 days post autologous transplant.

iv) Prior allogeneic stem-cell transplantation is excluded.

v) Not a candidate for potentially curative therapy.

c) SCCHN-Oral Cavity, Pharynx, Larynx

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

ii) Must have evidence of progression or recurrence after platinum therapy in the adjuvant (ie, with radiation after surgery), primary (ie, with radiation), recurrent, or metastatic setting.

iii) Radiation therapy must have been completed at least 4 weeks prior to study drug administration.

iv) Documentation of p16-positive or p16-negative disease to determine HPV status of tumor for SCC of the oropharynx.[53]

(1) Confirmation of tumor human papillomavirus (HPV) status: Prior testing results are acceptable if known. If tumor HPV status is unknown, subjects must consent to allow their submitted fresh or archived tumor tissue sample in the form of block or unstained slides to be tested for confirmation of tumor HPV status.

d) Bladder Cancer

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

ii) Progression or recurrence after treatment:

- With at least 1 platinum-containing chemotherapy regimen for metastatic or surgically unresectable locally advanced urothelial cancer OR
- Within 12 months of peri-operative (neo-adjuvant or adjuvant) treatment with a platinum agent in the setting of cystectomy for localized muscle-invasive urothelial cancer.

e) Pancreatic Cancer

i) Documented locally advanced, unresectable, or metastatic pancreatic cancer that has progressed on, or after, or been intolerant to (or are not candidates for) at least 1 line of standard therapy.

f) Melanoma, I-O Naïve, PD-L1 Positive (Number 6a in Table 3.1.6-1)

i) Histologically confirmed, unresectable Stage III or Stage IV melanoma, as specified in the American Joint Committee on Cancer (AJCC) staging system.

ii) PD-L1 positive subjects, defined as PD-L1 ≥ 1%, are eligible for this cohort. PD-L1 status will be determined using tissue acquired from the mandatory pre-treatment biopsy. Results of previous PD-L1 status testing must be documented if available.

iii) Must not have received prior systemic therapy in the unresectable or metastatic setting.

iv) BRAF (V600) mutation status must be known. Both BRAF-mutated and WT subjects are permitted in this cohort.

g) Melanoma, I-O Naïve, PD-L1 Negative (Number 6b in Table 3.1.6-1)

i) Histologically confirmed, unresectable Stage III or Stage IV melanoma, as specified in the American Joint Committee on Cancer (AJCC) staging system.

ii) PD-L1 negative subjects, defined as PD-L1 < 1%, are eligible for this cohort. PD-L1 status will be determined using tissue acquired from the mandatory pre-treatment biopsy. Results of previous PD-L1 status testing must be documented if available.

iii) iii. Must not have received prior systemic therapy in the unresectable or metastatic setting.

iv) BRAF (V600) mutation status must be known. Both BRAF-mutated and WT subjects are permitted in this cohort.

**Note for the melanoma I-O naïve cohorts: If the PD-L1 status from the pre-treatment biopsy is not available prior to the start of treatment, subjects will be retrospectively assigned to the correct cohort once the result is available.

h) Melanoma: I-O Naïve, BRAF Mutated, Post-BRAF Inhibitor Therapy (Nivolumab with and without BMS-986205) [Numbers 6c and 6d in Table 3.1.6-1]

i) Histologically confirmed, unresectable Stage III or Stage IV melanoma, as specified in the American Joint Committee on Cancer (AJCC) staging system. Subjects must have documented BRAF (V600) mutation and have had progressive or recurrent disease either during or after BRAF-targeted therapy in the unresectable or metastatic setting.

ii) PD-L1 status must be documented if available. PD-L1 status will also be re-tested using tissue acquired from the mandatory pre-treatment biopsy.

iii) Subjects must not have received prior systemic treatment in the unresectable or metastatic setting, except for BRAF- or BRAF/MEK-targeted therapy as stated above.

i) Melanoma, Prior Anti-PD-(L)1 Therapy (Number 6e in Table 3.1.6-1)

i) Histologically confirmed, unresectable Stage III or Stage IV melanoma, as specified in the American Joint Committee on Cancer (AJCC) staging system.

ii) PD-L1 status must be documented if available. PD-L1 status will also be re-tested using tissue acquired from the mandatory pre-treatment biopsy.

iii) Must have had progressive or recurrent disease either during or within 6 months after anti-PD-(L)1 monotherapy. Subjects may have received other systemic therapies for their disease; however anti-PD-(L)1 targeted therapy must have been the most recent therapy administered.

iv) BRAF (V600) mutation status must be known. Both BRAF-mutated and WT subjects are permitted in this cohort.

j) Melanoma, Prior Anti-PD-(L)1 and Anti-CTLA-4 Therapy (Number 6f in Table 3.1.6-1)

i) Histologically confirmed, unresectable Stage III or Stage IV melanoma, as specified in the American Joint Committee on Cancer (AJCC) staging system.

ii) PD-L1 status must be documented if available. PD-L1 status will also be re-tested using tissue acquired from the mandatory pre-treatment biopsy.

iii) Must have had progressive or recurrent disease either during or within 6 months after anti-PD-(L)1 component of the combination therapy. Subjects may have received other systemic therapies for their disease; however, anti-PD-(L)1 and anti-CTLA-4 therapy must have been the most recent therapies administered.

iv) BRAF (V600) mutation status must be known. Both BRAF-mutated and WT subjects are permitted in this cohort.

k) NSCLC, I-O Naïve, PD-L1 Positive (Number 7a in Table 3.1.6-1)

i) Histologically or cytologically confirmed, advanced (ie, unresectable or metastatic) NSCLC of either squamous or non-squamous histology.

ii) Subjects must have received platinum-based chemotherapy.

iii) EGFR and ALK status must be known. KRAS mutational status should be documented if available.

(1) EGFR and ALK may be unknown for subjects with squamous cell histology.

iv) Subjects with a sensitizing EGFR mutation or ALK rearrangement must have received EGFR-directed or ALK-directed therapy, respectively.

v) Prior anti-PD-(L)1 or anti-CTLA-4 therapy is not permitted.

vi) PD-L1 positive subjects, defined as PD-L1 ≥ 1%, are eligible for this cohort. PD-L1 status will be determined using tissue acquired from the mandatory pre-treatment biopsy. Results of previous PD-L1 status testing must be documented if available.

l) NSCLC, I-O Naïve, PD-L1 Negative (Number 7b in Table 3.1.6-1)

i) Histologically or cytologically confirmed, advanced (ie, unresectable or metastatic) NSCLC of either squamous or non-squamous histology.

ii) Subjects must have received platinum-based chemotherapy.

iii) Prior treatment of an I-O agent is not permitted.

iv) EGFR and ALK status must be known. KRAS mutational status should be documented if available.

(1) EGFR and ALK may be unknown for subjects with squamous cell histology.

v) Subjects with a sensitizing EGFR mutation or ALK rearrangement must have received EGFR-directed or ALK-directed therapy, respectively.

vi) PD-L1 negative subjects, defined as PD-L1 < 1%, are eligible for this cohort. PD-L1 status will be determined using tissue acquired from the mandatory pre-treatment biopsy. Results of previous PD-L1 status testing must be documented if available.

**Note for the NSCLC I-O naïve cohorts: If the PD-L1 status from the pre-treatment biopsy is not available prior to the start of treatment, subjects will be retrospectively assigned to the correct cohort once the result is available.

m) NSCLC, Prior Anti-PD-(L)1 Therapy (Number 7c in Table 3.1.6-1)

i) Histologically or cytologically confirmed, advanced (ie, unresectable or metastatic) NSCLC of either squamous or non-squamous histology.

ii) Must have had progressive or recurrent disease either during or within 6 months after anti-PD-(L)1 therapy (administered as monotherapy or as part of a combination). No intervening systemic therapy is permitted between anti-PD-(L)1 treatment and enrollment on this trial.

iii) PD-L1 status must be documented if available. PD-L1 status will also be re-tested using tissue acquired from the mandatory pre-treatment biopsy.

iv) Subjects must have received platinum-based chemotherapy in the recurrent or metastatic setting.

v) EGFR and ALK status must be known. KRAS mutational status should be documented if available.

(1) EGFR and ALK may be unknown for subjects with squamous cell histology.

vi) Subjects with a sensitizing EGFR mutation or ALK rearrangement must have received EGFR-directed or ALK-directed therapy, respectively.

n) Mixed Cohort of Signal-seeking Tumors

Subjects must have histologically documented:

i) Triple negative breast cancer
ii) Adenocarcinoma of the endometrium
iii) Epithelial cancer of the ovary
iv) Sarcoma (as outlined in Target Population, Dose Escalation)
v) Subjects must have completed, or been intolerant to, at least 1 standard chemotherapy regimen in the advanced or metastatic setting (eg, platinum-based therapy for ovarian cancer), if such therapy exists. Subjects must also have been considered for all other potentially efficacious therapies.
vi) Subjects with ovarian cancer should have a platinum-free interval of < 9 months.

o) Renal cell carcinoma

i) Advanced or metastatic RCC with a clear cell component.
ii) Must have received at least 1 but not more than 2 prior anti-angiogenic therapy regimens (including but not limited to sunitinib, sorafenib, pazopanib, axitinib, tivozanib, and bevacizumab) in the advanced or metastatic setting. Prior cytokine therapy (eg, IL-2 IFN-α), vaccine therapy, or treatment with cytotoxics is allowed.
iii) Must have received no more than 3 total prior systemic treatment regimens in the advanced or metastatic setting and must have evidence of progression on or after the last treatment regimen received and within 6 months prior to study enrollment.

3) Part 3: Combination with both Nivolumab and Ipilimumab (Safety and Expansion Cohorts)

a) Melanoma, PD-L1 positive

i) Histologically confirmed, unresectable Stage III or Stage IV melanoma, as specified in the American Joint Committee on Cancer (AJCC) staging system.
ii) Subjects must be either I-O therapy naïve, or may have received and then had disease progression after 1 prior I-O therapy in the advanced or metastatic setting. For subjects who have received prior immuno-oncology therapy, prior treatment with only 1 agent is permitted; subjects who have received combination I-O therapy are excluded. At least 35 subjects in this cohort will be I-O treatment naïve.
iii) PD-L1 positive subjects, defined as PD-L1 $\geq$ 1%, are eligible for this cohort. PD-L1 status will be determined using tissue acquired from the mandatory pre-treatment biopsy. Results of previous PD-L1 status testing must be documented if available. (Note: If the PD-L1 status from the pre-treatment biopsy is not available prior to the start of treatment, subjects will be retrospectively assigned to the correct cohort once the result is available.)
iv) BRAF (V600) mutation status must be known. Both BRAF-mutated and WT subjects are permitted in this cohort

b) Melanoma, PD-L1 negative

i) Histologically confirmed, unresectable Stage III or Stage IV melanoma, as specified in the American Joint Committee on Cancer (AJCC) staging system.

ii) Subjects must be either I-O therapy naïve, or may have received and then had disease progression after 1 prior I-O therapy in the advanced or metastatic setting. For subjects who have received prior immuno-oncology therapy, prior treatment with only 1 agent is permitted; subjects who have received combination I-O therapy are excluded. At least 20 subjects in this cohort will be I-O treatment naïve

iii) PD-L1 negative subjects, defined as PD-L1 <1%, are eligible for this cohort. PD-L1 status will be determined using tissue acquired from the mandatory pre-treatment biopsy. Results of previous PD-L1 status testing must be documented if available. (Note: If the PD-L1 status from the pre-treatment biopsy is not available prior to the start of treatment, subjects will be retrospectively assigned to the correct cohort once the result is available.)

iv) BRAF (V600) mutation status must be known. Both BRAF-mutated and WT subjects are permitted in this cohort

c) NSCLC PD-L1 positive

i) Histologically or cytologically confirmed, advanced (ie, unresectable or metastatic) NSCLC of either squamous or non-squamous histology.

ii) Subjects must be either treatment naïve in the advanced setting or may have received and then had disease progression after at least one line of prior therapy. For subjects who received chemotherapy or a TKI as first line therapy, no subsequent therapy is permitted. For subjects who received PD-(L)1 targeted therapy as first line treatment, this may have been given either as monotherapy or in combination with chemotherapy only; no prior I-O combination therapy is permitted. Subjects who received PD-(L)1 targeting monotherapy as first-line treatment may also have received chemotherapy or TKI therapy after disease progression. At least 25 subjects in this cohort will be treatment naïve in the advanced setting and at least 10 subjects IO-therapy naive.

iii) EGFR and ALK status must be known. KRAS mutational status should be documented if available.

(1) EGFR and ALK may be unknown for subjects with squamous cell histology.

(2) Subjects with a sensitizing EGFR mutation or ALK/ROS1 rearrangement must have received appropriate therapy directed at the mutation or rearrangement

iv) PD-L1 positive subjects, defined as PD-L1 ≥ 1%, are eligible for this cohort. PD-L1 status will be determined using tissue acquired from the mandatory pre-treatment biopsy. Results of previous PD-L1 status testing must be documented if available. (Note: If the PD-L1 status from the pre-treatment biopsy is not available prior to the start of treatment, subjects will be retrospectively assigned to the correct cohort once the result is available.)

d) NSCLC PD-L1 negative

i) Histologically or cytologically confirmed, advanced (ie, unresectable or metastatic) NSCLC of either squamous or non-squamous histology.

ii) Subjects must be either treatment naïve in the advanced setting or may have received and then had disease progression after at least one line of prior therapy. For subjects who received chemotherapy or a TKI as first line therapy, no subsequent therapy is permitted. For subjects who received PD-(L)1 targeted therapy as first line treatment,

this may have been given either as monotherapy or in combination with chemotherapy only; no prior I-O combination therapy is permitted. Subjects who received PD-(L)1 targeting monotherapy as first-line treatment may also have received chemotherapy or TKI therapy after disease progression. At least 25 subjects in this cohort will be treatment naïve in the advanced setting and at least 10 subjects IO-therapy naive.

iii) EGFR and ALK status must be known. KRAS mutational status should be documented if available.

(1) EGFR and ALK may be unknown for subjects with squamous cell histology.

(2) Subjects with a sensitizing EGFR mutation or ALK/ROS1 rearrangement must have received appropriate therapy directed at the mutation or rearrangement.

iv) PD-L1 negative subjects, defined as PD-L1 < 1%, are eligible for this cohort. PD-L1 status will be determined using tissue acquired from the mandatory pre-treatment biopsy. Results of previous PD-L1 status testing must be documented if available. (Note: If the PD-L1 status from the pre-treatment biopsy is not available prior to the start of treatment, subjects will be retrospectively assigned to the correct cohort once the result is available.)

e) Bladder cancer

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

ii) Progression or recurrence after treatment with:

– At least 1 platinum-containing chemotherapy regimen for metastatic or surgically unresectable locally advanced urothelial cancer OR

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

iii) Subjects may have received prior I-O therapies, but at least 30 subjects in this cohort will be I-O therapy naive.

f) **Mixed Tumor Type Cohort (Ipi 1Q8)**

i) Subjects must have tumor types included in Part 2 and meet inclusion criteria defined for each tumor type in Part 2

ii) All subjects must be I-O therapy naive.

3) General Inclusion Criteria:

a) Eastern Cooperative Oncology Group performance status of ≤ 1

b) Ability to swallow pills or capsules.

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

d) Subjects with prior exposure to therapy with any agent specifically targeting checkpoint pathway inhibition (such as anti-PD-[L]1, anti-PDL-2, anti-LAG-3, and anti-CTLA-4 antibodies) are permitted after a washout period of any time greater than 4 weeks from

the last treatment.**Note that certain expansion cohorts do not allow prior treatment with immunotherapy agents, including I-O naïve melanoma and NSCLC. See tumor-specific eligibility criteria above. In addition, the 4-week washout period is not required for the following Part 2 expansion cohorts: Melanoma, prior anti-PD-(L)1 and prior anti-PD-(L)1/anti-CTLA-4 combination and NSCLC, prior anti-PD-(L)1 or for subjects in Part 3 Melanoma and NSCLC cohorts with prior IO-treatment.**

Note: *(i) Subjects who experienced prior Grade 1 to 2 checkpoint therapy-related immune-mediated AEs must have confirmed recovery from these events at the time of study entry, **other than endocrinopathies treated with supplementation**, as documented by resolution of all related clinical symptoms, abnormal findings on PE, and/or associated laboratory abnormalities. Where applicable, these subjects must also have completed steroid tapers for treatment of these AEs by a minimum of 14 days prior to commencing treatment with study drug.*

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

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

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

g) All subjects must have archival FFPE tumor tissue available. This must be a block or 20 FFPE unstained slides (fewer slides may be acceptable with the approval of the medical monitor, but generally at least 15 will be required). With Amendment 14, archival tissues from subjects in Parts 1 and 3 may be of any age, while for all other subjects blocks must have been obtained less than 1 year prior to enrollment, and FFPE slides must have been cut less than 4 months prior to enrollment; if archival tissue meeting these age requirements is not available, subjects must undergo fresh biopsies as detailed below. Tumor samples for archival tissue obtained by fine needle aspirate/biopsy or from bone lesion are not acceptable. Subjects must consent to the acquisition of this archival tissue. In limited circumstances, subjects with newly diagnosed, untreated melanoma and NSCLC without archival tissue available may be permitted to enroll after permission is obtained from the Medical Monitor or Study Director, but will be required to undergo fresh biopsy.

h) All subjects in Parts 1 and 3 (as well as subjects in other parts without archival tissue meeting the requirements above) will be required to undergo mandatory pre-treatment biopsies. All subjects will be required to undergo an on-treatment biopsy, unless considered to pose unacceptable clinical risk, as judged by the investigator and in consultation with the medical monitor/study director.

i) Pre-treatment tissue must be collected prior to first dose of study drug. Recent fresh samples (frozen and FFPE) obtained prior to start of screening that meet biomarker requirements (Section 5.7.2) of the study as determined by the Study Director or Medical Monitor may be substituted for fresh biopsies, after permission from the Study Director or Medical Monitor is obtained.

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

iii) Where possible, the biopsied lesion should be distinct from target lesions being evaluated for radiologic response, and the same lesion should be used for both the baseline and on-treatment sampling.

i) Blood methemoglobin levels within the ULN

j) Adequate marrow function for subjects with solid tumor histologies as defined by the following:

i. White blood cell (WBC) ≥ 2000/μL (stable off any growth factor within 4 weeks of first study drug administration)

ii. Neutrophils ≥ 1500/μL (stable off any growth factor within 4 weeks of first study drug administration)

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

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

k) Adequate marrow function for subjects with B-cell NHL and HL malignancies as defined by the following:

i. Absolute neutrophil count ≥ 750/μL (no WBC growth factors for prior 14 days)

ii. Platelets ≥ 50× 10^3/μL (no platelet transfusions for prior 14 days)

iii. Hemoglobin > 8.0 g/dL (no RBC transfusions for prior 7 days)

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

i. ALT and AST ≤ 3× institutional ULN

ii. Total bilirubin ≤ 1.5× institutional ULN (except subjects with Gilbert's Syndrome who must have normal direct bilirubin)

iii. [This criterion is no longer applicable]

iv. Normal thyroid function, subclinical hypothyroidism (thyroid-stimulating hormone [TSH] < 10 mIU/mL), or have controlled hypothyroidism on appropriate thyroid supplementation

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

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

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

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

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

4) Age and Reproductive Status

a) Men and women, ages ≥ 18 years at the time of informed consent

b) Women of childbearing potential (WOCBP) must have a negative serum or urine pregnancy test (urine pregnancy test: minimum sensitivity 25 IU/L or equivalent units of human chorionic gonadotropin) 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 with study drug(s) plus an additional 5 months (approximately 23 weeks) post-treatment completion.

e) Males who are sexually active with WOCBP must agree to use a synthetic or latex condom during sexual activity for the duration of treatment with study treatment plus an additional 7 months after the last dose of the study treatment (ie, 90 days [the duration of sperm turnover] plus the time required for nivolumab to undergo approximately 5 half-lives). This criterion applies to azoospermic males as well. In addition, male subjects must be willing to refrain from sperm donation during this time.

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

Investigators shall counsel WOCBP and male subjects who are sexually active with WOCBP on the importance of pregnancy prevention and the implications of an unexpected pregnancy. Investigators shall advise WOCBP and male subjects who are sexually active with WOCBP on the use of highly effective methods of contraception (Appendix 11). Highly effective methods of contraception have a failure rate of < 1% when used consistently and correctly. **Hormonal contraceptives are not highly effective methods of contraception for subjects receiving BMS-986205 in this study who are WOCBP.**

3.3.2 Exclusion Criteria

1) Target Disease Exceptions

a) Subjects with known or suspected CNS metastases, untreated CNS metastases, or with the CNS as the only site of disease are excluded. However, subjects with controlled brain metastases will be allowed to enroll. Controlled brain metastases are defined as no radiographic progression for at least 4 weeks following radiation and/or surgical treatment (or 4 weeks of observation if no intervention is clinically indicated), off of steroids for at least 2 weeks, and no new or progressive neurological signs and symptoms. Please note: SCCHN subjects with direct extension of tumor through the base of skull will not be excluded, as they are considered distinct from hematogenously spread parenchymal brain metastasis.

b) Ocular melanoma

c) [This criterion is no longer applicable]

2) Medical History and Concurrent Diseases

a) Subjects with a history or presence of G6PD deficiency, cytochrome b5 reductase deficiency, or other diseases that put them at risk of methemoglobinemia.

b) History of congenital or autoimmune hemolytic disorders.

If subject has history of transient acquired hemolytic anemia, discuss with Medical Monitor for study eligibility.

c) History or presence of hypersensitivity or idiosyncratic reaction to methylene blue.

d) Subjects with a prior malignancy are excluded (except non-melanoma skin cancers and in situ cancers such as the following: bladder, colorectal, cervical/dysplasia, melanoma, or breast). Subjects with other second malignancies diagnosed more than 2 years ago who have received therapy with curative intent with no evidence of disease during the interval who are considered by the investigator to present a low risk for recurrence will be eligible.

e) Other active malignancy requiring concurrent intervention.

f) Prior organ allograft or allogeneic bone marrow transplantation.

g) Any anti-cancer therapy (eg, chemotherapy, biologics, vaccines, or hormonal treatment) including investigational drugs within 4 weeks prior to the first dose of study drug administration, except for non-cytotoxic therapies, for which at least 4 weeks or 5 half-lives (whichever is shorter) must have elapsed between last dose and first treatment with any study drugs; if 5 half-lives is shorter than 4 weeks, agreement with the Medical Monitor must be obtained. ****Note that this criterion does not apply for anti-PD-(L)1 therapy in the following Part 2 expansion cohorts: Melanoma, prior anti-PD-(L)1 and anti-PD-(L)1/anti-CTLA-4 combination and NSCLC, prior anti-PD-(L)1.**

h) Prior therapy with an IDO inhibitor.

i) Subjects with active, known or suspected autoimmune disease. Subjects with vitiligo, type I diabetes mellitus, residual hypothyroidism due to autoimmune condition only requiring hormone replacement, euthyroid subjects with a history of Grave's disease

(subjects with suspected autoimmune thyroid disorders must be negative for thyroglobulin and thyroid peroxidase antibodies and thyroid stimulating immunoglobulin prior to first dose of study drug), psoriasis not requiring systemic treatment, or conditions not expected to recur in the absence of an external trigger are permitted to enroll.

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

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

k) Requirement for daily supplemental oxygen.

l) Uncontrolled or significant cardiovascular disease including, but not limited to, any of the following:

i) Myocardial infarction or stroke/transient ischemic attack within the past 6 months

ii) Uncontrolled angina within the past 3 months

iii) Any history of clinically significant arrhythmias (such as ventricular tachycardia, ventricular fibrillation, or torsades de pointes)

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

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

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

m) History of any chronic hepatitis as evidenced by the following:

i) Positive test for hepatitis B surface antigen

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

Note: *Subjects 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*

n) History of other preexisting liver disease (eg, NAFLD).

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

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

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

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

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

t) Subjects with history of life-threatening toxicity related to prior immune therapy (eg. anti-CTLA-4 or anti-PD-1/PD-L1 treatment or any other antibody or drug specifically targeting T-cell co-stimulation or immune checkpoint pathways) except those that are unlikely to re-occur with standard countermeasures (eg, hormone replacement after adrenal crisis)

u) Concomitant use of strong inhibitors of CYP3A4 or strong inducers of CYP3A4 (see Appendix 7).

   i) Per Amendment 14, also includes strong inhibitors/inducers of CYP1A2

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

w) Use of packed red blood cells or platelet transfusion within 2 weeks prior to the first dose of study drug as specified in Section 3.3.1, j and k.

x) A known or underlying medical condition that, in the opinion of the investigator or Sponsor, could make the administration of study drug hazardous to the subjects or could adversely affect the ability of the subject to comply with or tolerate the study.

y) Subjects with confirmed or suspected serotonin syndrome

z) Subjects with active ILD/pneumonitis or with recent history of ILD/ pneumonitis requiring steroids (excluding radiation pneumonitis)

aa) Subjects with impairment of gastrointestinal function or gastrointestinal disease, or other conditions known to interfere significantly with the absorption of oral medication, per investigator judgement

3) Physical and Laboratory Test Findings

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

   i) [This criterion is no longer applicable]

ii) [This criterion is no longer applicable]

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

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

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

c) Second or third degree heart block at Screening (QTc substudy only)

4) Allergies and Adverse Drug Reaction

a) History of allergy to nivolumab (all study parts) or ipilimumab (Part 3 only).

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

5) Other Exclusion Criteria

a) Prisoners or 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.

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

WOCBP is defined as any female who has experienced menarche, who has not undergone surgical sterilization (hysterectomy or bilateral oophorectomy), and who 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 durations of the washout periods below are suggested guidelines, and the investigators should use their judgment in checking serum FSH levels.

- 1 week minimum for vaginal hormonal products (eg, rings, creams, gels)
- 4 weeks 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.

3.4 Concomitant Treatments

3.4.1 Prohibited and/or Restricted Treatments

Prohibited and/or restricted medications taken prior to and during study drug administration in the study are described below. Medications taken within 2 weeks prior to study drug administration must be recorded on the case report form (CRF).

The following medications are prohibited during the study:

- Prior exposure to BMS-986205 or other IDO inhibitor.
- Concurrent administration of any anti-cancer therapies (investigational or approved) with the exception of subjects in the follow up and survival period of the study.
- Concomitant use of strong inhibitors of CYP3A4 and/or CYP1A2 or strong inducers of CYP3A4 and/or CYP1A2 (see Appendix 7).
- Immunosuppressive agents (except as stated in Section 3.4.3), unless they are utilized to treat an AE.
- Use of any medicinal herbal preparations within 2 weeks of the first dose of study drug and during study treatment unless prescribed by a treating physician. Please see restrictions on the use of marijuana in Section 3.4.2.
- Palliative radiotherapy is permitted only under certain conditions as described in Section 3.3.1.

  Any concomitant therapies must be recorded on the CRF.

3.4.2 Other Restrictions and Precautions

Restricted therapies are not prohibited but are not recommended; consult BMS medical monitor if the following are clearly medically indicated:

1) Grapefruit and Seville oranges and their juices can inhibit CYP3A4 and should not be consumed while on study.
2) Concurrent use of moderate inhibitors or inducers of CYP3A4 and/or CYP1A2 may affect the systemic exposure of BMS-986205. See Appendix 7 for a list of CYP3A4 and/or CYP1A2 modulators.
3) Concurrent smoking (tobacco, marijuana, etc.) may induce CYP1A2 and decrease the systemic exposure of BMS-986205.
4) Caution is warranted when consuming marijuana by means other than smoking as it may lead to increased exposure of BMS-986205 through interaction with metabolic enzymes.
5) Caution is warranted when administering BMS-986205 to subjects taking drugs that are highly dependent on CYP3A4 or CYP2B6 for metabolism. See Appendix 7 for a list of sensitive CYP3A4 and CYP2B6 substrates.
6) Caution is warranted when administering BMS-986205 to subjects taking drugs that may be associated with QT prolongation. Drugs that may prolong QT intervals are prohibited during

Cycle 0 of the QTc substudy. See Appendix 8 for a list of common medications associated with QT prolongation.

7) Caution is warranted when administering BMS-986205 to subjects taking drugs that are subject to extensive intestinal efflux by P-gp/BCRP. See Appendix 9 for a list of common P-gp/BCRP substrates.
8) In vitro solubility data indicate that BMS-986205 has decreased solubility with increasing pH. Until further data are available, subjects should try to avoid taking proton pump inhibitors. H_2 antagonists and short-acting antacid agents, such as Maalox® or TUMS®, may be taken, but it is recommended that these not be taken 4 hours before or 4 hours after dosing of BMS-986205.
9) Caution is warranted when using other agents known to cause methemoglobinemia (see Appendix 10). Dapsone, topical anesthetics, and antimalarial drugs are the most likely agents, and thus these drugs should only be used after discussion with the Study Director/Medical Monitor.
10) Preclinical studies suggest potential effect of food on BMS-986205 absorption (see Section 1.4.3). BMS-986205 should be administered following a light meal (see Table 4-2 for a sample light meal). Subjects should avoid heavy meals with high fat content 4 hours prior until 4 hours post BMS-986205 dose.

The development of serotonin syndrome has been associated with exposure to another investigational agent that inhibits the IDO1 enzyme. No case of serotonin syndrome has been observed with administration of BMS-986205. Given the possibility of a class effect, there is a theoretical risk that BMS-986205 could cause an increase in serotonin levels in the brain that might trigger serotonin syndrome when administered in combination with serotonergic agents or tryptophan supplements. Use caution and monitor for symptoms of serotonin syndrome in subjects receiving concurrent serotonergic psychiatric medications and/or tryptophan supplements.

3.4.3 Permitted Therapy

- Subjects are permitted the use of topical, ocular, intra-articular, intranasal, and inhalational corticosteroids (with minimal systemic absorption). Treatment with a short course of steroids (< 5 days) up to 7 days prior to initiating study drug is permitted. A brief course of corticosteroids for prophylaxis (eg, contrast dye allergy) or for treatment of nonautoimmune conditions (eg, delayed-type hypersensitivity reaction caused by a contact allergen) is permitted.
- Inhaled or intranasal corticosteroids (with minimal systemic absorption may be continued if the subject is on a stable dose) and adrenal replacement steroid doses > 10 mg daily prednisone equivalent are permitted in the absence of active autoimmune disease. Nonabsorbed intra-articular steroid injections will be permitted.
- Immunosuppressive agents and the use of systemic corticosteroids are permitted in the context of treating AEs. Subjects receiving corticosteroids for treatment of drug-related AEs must be at < 10 mg/day prednisone or equivalent prior to re-initiation of study drug. Subjects may continue to receive HRT.

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

3.4.3.1 Palliative Local Therapy

Palliative and supportive care for disease-related symptoms may be offered to all subjects on the trial; however, investigators should consult with the BMS Medical Monitor prior to initiating palliative radiation in subjects who have not yet completed the DLT evaluation period. Limited radiation therapy or surgery to control isolated lesions is permitted for subjects who have investigator-assessed clinical benefit following consultation with the BMS Medical Monitor.

Subjects should not receive study drug during radiation as the potential for overlapping toxicities with radiotherapy and BMS-986205 or with radiotherapy and the combination of BMS-986205 and nivolumab is currently not known. Anecdotal data suggest that radiotherapy administered to subjects while receiving nivolumab therapy is tolerable. However, because concurrent radiotherapy and immunotherapies in cancer have not been formally evaluated, in cases where palliative radiotherapy is required for a tumor lesion, then BMS-986205 alone or BMS-986205 in combination with nivolumab (and ipilimumab, where applicable) should be withheld for at least 1 week before, during, and 1 week after radiation. Subjects should be closely monitored for any potential toxicity during and after receiving radiotherapy, and AEs related to radiotherapy should resolve to Grade 1 prior to resuming study drug.

3.5 Discontinuation of Subjects Following any Treatment with Study Drug

Subjects MUST discontinue investigational product (and non-investigational product 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 that 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
- Pregnancy
- Completion of study-required procedures.
- Documented and confirmed disease progression as defined by RECIST v1.1 or IWG (see Appendix 3 and 4) unless subject meets criteria for treatment beyond progression (Section 3.5.1)
- Clinical deterioration while receiving active study drug that in the opinion of the investigator indicates that continued participation in the study is not in the best interest of the subject
- Protocol-defined reasons for discontinuation (see Sections 3.5.1 and 4.5.6).

In the case of pregnancy, the investigator must immediately, within 24 hours of the event, notify the BMS Medical Monitor/designee of this event. In most cases, the study drug will be permanently discontinued in an appropriate manner. If the investigator determines a possible favorable benefit/risk ratio that warrants continuation of study drug, a discussion between the investigator and the BMS Medical Monitor/designee must occur.

All subjects who discontinue investigational product 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.

3.5.1 Treatment Beyond Progression

A subset of subjects with solid tumors treated with immunotherapy may derive clinical benefit despite initial evidence of PD. Subjects will be permitted to continue on treatment beyond initial RECIST v1.1 (see Appendix 3) or IWG-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 additional nivolumab, ipilimumab, or BMS-986205 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 documented in the study records. Subjects will be re-consented to explain the rationale for this ongoing treatment.

3.5.2 Discontinuation Due to Further Progression (Confirmed Progression)

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

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

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

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

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

3.5.3 Assessment Schedule for Subjects with Postprogression Treatment

Subjects should continue to receive monitoring according to the On-Treatment Assessments in Section 5.4. Radiographic assessment by computed tomography (CT; preferred) or magnetic resonance imaging (MRI) described in Section 5 is required when subjects continue postprogression treatment. For subjects who discontinue postprogression treatment with study drug, no additional radiographic assessments will be required.

3.6 Post Study Drug Follow-up

[redacted] 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 3.1.3 until death or the conclusion of the study.

3.6.1 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 the 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.

3.6.2 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 3 documented phone calls, faxes, texts, or emails as well as lack of response by subject to 1 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 AND STUDY DRUG ADMINISTRATION

All protocol-specified investigational and non-investigational products are considered study drug.

Study Drug:

Product description and storage information is described in Table 4-1. Preparation and administration instructions will be provided separately via site training materials.

For study drugs not provided by BMS and obtained commercially by the site, storage should be in accordance with the package insert, summary of product characteristics, or similar documentation.

Table 4-1: Study Drugs for CA017003

Product Description Class and Dosage Form	Potency	IP/ Non-IMP	Blinded or Open Label	Packaging/ Appearance	Storage Conditions (per label)
BMS-986205-04	5 mg	IP	Open	Capsule	Refer to the label on container and/or pharmacy manual
BMS-986205-04	25 mg	IP	Open	Tablet	Refer to the label on container and/or pharmacy manual
BMS-986205-04	50 mg	IP	Open	Capsule/Tablet	Refer to the label on container and/or pharmacy manual
BMS-986205-04	100 mg	IP	Open	Tablet	Refer to the label on container and/or pharmacy manual
Nivolumab (BMS-936558-01) Solution for Injection	100 mg (10 mg/mL)	IP	Open	Vial	Refer to the label on container and/or pharmacy manual
Ipilimumab (BMS-734016) Solution for Injection	200 mg (5 mg/mL)	IP	Open	Vial	Refer to the label on container and/or pharmacy manual

Abbreviations: IP = investigational product.

Study drugs not provided by BMS and obtained commercially by the site should be stored in accordance with the product label. Compounding instructions will be provided separately to the site.

Study Drug Administration:

BMS-986205

At scheduled PK sample collection as well as on laboratory evaluation days, BMS-986205 will be administered to the subject in the clinical facility. At all other times throughout the study, BMS-986205 will be administered on an out-subject basis, except when subjects are seen in the clinic for administration of nivolumab, assessment of AEs, and laboratory evaluation.

Restrictions related to food and fluid intake are described in Section 3.4.2.

Dose Escalation (Part 1)

BMS-986205 should be administered using the capsule formulation in Part 1.

BMS-986205 should be administered in the morning following a light meal approximately 24 hours apart. On the morning of Days 1 and 14 when serial PK samples are collected, after fasting for at least 10 hours, each subject will receive a single oral dose of BMS-986205 within approximately 5 minutes of completing a light meal. At the time of dosing, approximately 240 mL of water will be administered to the subject along with BMS-986205. The time of BMS-986205 administration will be called "0" hour. A description of a sample light breakfast meal is provided in Table 4-2.

Table 4-2: Representative Light Breakfast Meal

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

Source: US Department of Agriculture Nutrient Database for Standard Reference, Release 28 (September 2015)[54]

QTc Substudy

BMS-986205 should be administered using the tablet formulation in QTc Substudy, unless the Sponsor specifies that the capsule formulation should be used.

On ECG baseline day, after fasting for at least 10 hours, subjects should receive a light meal at approximately the same time as they would on Cycle 0 Day 14. Within approximately 5 minutes of completing the light meal, approximately 240 mL of water will be administered, although no BMS-986205 will be given. Time-matched baseline ECG will be collected (taken at the same time-points on the baseline day as on Cycle 0 Day 14). During Cycle 0 of the QTc substudy, subjects will receive BMS-986205 QD following a light meal on Days 1-14. On Day 14, following an overnight fast of at least 10 hours, each subject will receive BMS-986205 within approximately 5 minutes of completing a light meal. At the time of dosing, approximately 240 mL of water will be administered to the subject along with BMS-986205. Serial ECGs and PK samples will be collected as indicated in Table 5.5.4.3-1.

Dose Expansion (Part 2) and Dose Escalation/Expansion (Part 3)

BMS-986205 should be administered using the tablet formulation in Parts 2 and 3, unless the Sponsor specifies that the capsule formulation should be used. Patients enrolled prior to Amendment 8 should continue to use the capsule formulation unless otherwise specified by the Sponsor.

BMS-986205 should be administered following light meals approximately 24 hours apart.

Nivolumab (Part 2)

Nivolumab infusions should start approximately 30 minutes following BMS-986205. Nivolumab should be infused over 30 minutes. After the first nivolumab infusion, subjects should be monitored per local/institutional guidelines. If no such guidelines exist, an observation period of 2 hours after the end of the nivolumab infusion is suggested.

Further details regarding preparation and administration will be provided separately in site/pharmacy training materials.

Nivolumab and Ipilimumab (Part 3)

Nivolumab infusions should start approximately 30 minutes following BMS-986205. For all doses used within Part 3, Nivolumab should be infused over 30 minutes. Further details regarding preparation and administration will be provided separately in site/pharmacy training materials.

The second infusion in the combination cohort will always be ipilimumab, and will start approximately 30 minutes after completion of the nivolumab infusion and the infusion line has been flushed, filters changed and the patient has been observed to ensure no infusion reaction has occurred. Subjects should receive ipilimumab as a 30-minute IV infusion. Further details regarding preparation and administration will be provided separately in site/pharmacy training materials.

After the first nivolumab infusion, subjects should be monitored per local/institutional guidelines. If no such guidelines exist, an observation period of 2 hours after the end of the nivolumab infusion is suggested.

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

4.1 Investigational Product

An investigational product, 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 that are used or assembled (formulated or packaged) differently than the authorized form, used for an unauthorized indication, or used to gain further information about the authorized form.

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

In this protocol, investigational products are BMS-986205, nivolumab, and ipilimumab.

4.2 Non-investigational Product

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

4.3 Storage and Dispensing

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

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

Investigational product documentation (whether supplied by BMS or not) must be maintained and include 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).

Storage facilities for controlled substances must be securely locked and substantially constructed, with restricted access to prevent theft or diversion, as applicable by local regulations.

4.4 Method of Assigning Subject Identification

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

If the clinical pharmacology substudy and dose escalation cohort are open at the same time, subjects will be assigned to the dose escalation cohort first. If no escalation cohort is open, subjects will be assigned to the clinical pharmacology substudy. If the clinical pharmacology substudy and dose expansion are open at the same time, subjects with the specific tumor type for dose expansion will be assigned to the dose expansion. All other subjects will be assigned to the clinical pharmacology substudy.

For the QTc substudy, subjects will be assigned to one of the 3 doses within the substudy. The doses or assignments may be adjusted based on future findings. Subjects who did not finish Day 14 of the QTc substudy will be replaced.

During dose escalation in Part 1 and safety cohort evaluation in Part 3, subjects who are not evaluable for DLT determination may be replaced. Replacement subjects will be assigned to the same treatment but will be assigned a new subject number.

4.5 Selection and Timing of Dose for Each Subject

BMS-986205 will be administered orally daily at the doses listed in Section 3.1.5

Each subject will be assigned to a specific dose level as listed in Section 4 in sequential order during dose escalation Part 1. Subjects in dose expansion Part 2 will be treated at the MTD, the MAD, or at an alternate dose determined from Part 1, if agreed upon by the investigators and the Sponsor. Subjects treated in Part 3 will receive BMS-986205 at 100 mg daily and will receive doses and schedules of nivolumab and ipilimumab selected for each tumor-specific expansion cohort as detailed in Section 3.1.7.

In Parts 1 and 2, Nivolumab will be administered intravenously as flat doses; either 240 mg Q2W for the Part 1 dose escalation and for the Part 2 dose expansion cohorts that predated Amendment 06, or 480 mg Q4W for the Part 2 dose expansion cohorts added with or after Amendment 06 (melanoma, NSCLC, RCC, and additional signal-seeking tumors) and the clinical pharmacology substudy. In Part 3, nivolumab will also be administered in flat doses for all cohorts at the specified doses for those cohorts.

There will be no dose escalations or reductions of nivolumab allowed once assigned. Subjects receiving nivolumab Q2W will be dosed no less than 12 days from the previous dose and no more than 3 days from the scheduled dose. Subjects receiving nivolumab Q3W may be dosed 21 days (± 3 days) from the previous dose. Subjects receiving nivolumab Q4W may be dosed 28 days (± 3 days) from the previous dose.

For subjects receiving ipilimumab, the dosing calculations should be based on the body weight. If the subject's weight on the day of the dosing differs by > 10% from the weight used to calculate the dose, the dose must be recalculated. All doses should be rounded up or to the nearest milligram per institutional standard. There will be no dose modifications of ipilimumab allowed. Subjects receiving ipilimumab Q3W may be dosed no less than 19 days from the previous dose and no more than 3 days from the scheduled dose. Subjects receiving ipilimumab Q6W may be dosed every 42 days (± 3 days). Subjects receiving ipilimumab Q8W may be dosed every 56 days (± 3 days).

When nivolumab and ipilimumab are scheduled to be dosed on the same day, if dosing is delayed, both nivolumab and ipilimumab must be delayed together. If dosing is resumed after a dose delay, both nivolumab and ipilimumab must be resumed on the same day if the next scheduled day includes both nivolumab and ipilimumab administration.

There are no premedications recommended for nivolumab or ipilimumab (where applicable) on the first cycle. If an acute infusion reaction is noted, the subjects should be managed according to Section 4.7.1.

4.5.1 Dose-limiting Toxicities

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

Part 1: Cycle 0 (BMS-986205 monotherapy lead-in) will have a 2-week DLT evaluation period (DLT 1). The combination regimen will have 4-week DLT evaluation period (DLT 2). Therefore, the total DLT assessment period is 6 weeks in Part 1. Subjects may proceed from Cycle 0 to Cycle 1 at each cohort unless any of the following events are observed: any DLT, Grade 2 or higher immune-related AEs considered related to BMS-986205 (eg, immune-mediated pneumonitis, colitis, hepatitis, nephritis, renal dysfunction) with the exception of immune-mediated hypothyroidism and hyperthyroidism, or Grade 2 AST or ALT elevation that does not resolve to Grade 1 within 1 week. For Grade 2 AST or ALT elevations that resolve to Grade 1 or baseline within 1 week, subjects can be rechallenged with BMS-986205 monotherapy for a minimum of 5 days before proceeding to combination with nivolumab provided there is not a recurrence of Grade 2 event.

The DLT-evaluation interval begins on the first day of treatment and continues for 6 weeks. The DLT 1 period is 14 days, and subjects must receive 75% of the BMS-986205 monotherapy doses to be considered evaluable for combination with nivolumab. The DLT 2 period is 4 weeks during which subjects will receive daily dosing of BMS-986205 and 2 doses of nivolumab. The total DLT period is 6 weeks, and subjects must have received at least 75% of BMS-986205 doses and 2 doses of nivolumab with observation for a minimum of 5 days following the second combination therapy dose to be considered evaluable for dose escalation decisions. Based on the predicted human half-life of BMS-986205 of 23 hours, this interval is expected to cover the anticipated time frame for the occurrence of clinically significant immediate and early onset AEs related to BMS-986205 monotherapy during Cycle 0 and repeat dosing of BMS-986205 in combination with nivolumab in Cycle 1.

Part 3: The DLT-assessment period is 6 weeks in Part 3 for all treatment regimens evaluated. The DLT-evaluation interval begins on the first day of treatment and continues for 6 weeks.

DLT-evaluable subjects will be defined as subjects who in the 6 week DLT evaluation period received ≥ 75% of BMS-986205 doses and the following nivolumab and ipilimumab doses for each regimen:

- Melanoma/Ipi 1Q8: 2 doses of nivolumab and 1 dose of ipilimumab, and followed for at least 5 days after the second dose of nivolumab

- NSCLC/Ipi 1Q6: 2 doses of nivolumab and 1 dose of ipilimumab, and followed for at least 5 days after the second dose of nivolumab
- Bladder/Ipi 3Q3: 2 doses of nivolumab and 2 doses of ipilimumab, and followed for at least 5 days after the second dose of each drug

The incidence of DLTs that occur within 6 weeks following the start of study drug will guide dose escalation decisions. AEs will be graded according to the NCI CTCAE v4.03. For the purposes of subject management, drug-related AEs occurring at any time that meet the DLT definition will lead to dose interruption, dose modifications, and/or permanent discontinuation of study drug as defined in Section 4.5.3 and Section 4.5.6. 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 DLT evaluation period will be used in dose escalation decisions and to define the MTD. AEs occurring after the DLT period will be considered for the purposes of defining the MTD, upon agreement between the Sponsor/Medical Monitor and investigators, if they are determined to have no clear alternative cause and are not related to disease progression.

AEs will be graded according to the NCI CTCAE v4. For the purpose of guiding dose escalation, DLTs are defined below based on the incidence and grade of AEs for which no alternative cause can be identified.

In addition to the criteria listed below, any drug-related toxicity that results in a subject not being able to receive at least 75% of the doses of BMS-986205 and all pre-specified doses (see above) of nivolumab and ipilimumab (where applicable) during the DLT evaluation period or causing greater than 2 weeks of dose delay may be classified as a DLT.

DLTs for DLT1 and DLT2 Periods in Part 1 and the entire DLT evaluation period in Part 3

Nonhematologic Dose-limiting Toxicity (DLT):

A. Hepatic Nonhematologic DLT

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

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

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

B. Nonhepatic Nonhematologic DLT

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

- Grade 2 or greater episcleritis, uveitis, or iritis
- Any other Grade 2 eye pain or blurred vision that does not respond to topical therapy and does not improve to Grade 1 severity within 2 weeks OR requires systemic treatment
- Grade 2 myocarditis
- Grade 3 pneumonitis, bronchospasm, neurologic toxicity, hypersensitivity reaction, or infusion reaction of any duration requires discontinuation
- Any Grade 3 or greater nondermatologic, nonhepatic, nonhematologic toxicity will be considered a DLT with the following specific EXCEPTIONS:
  - Grade 3 or Grade 4 electrolyte abnormalities that are not complicated by associated clinical adverse experiences, last less than 48 hours and either resolve spontaneously or respond to conventional medical intervention
  - Grade 3 nausea, vomiting, or diarrhea that lasts less than 48 hours and either resolves spontaneously or responds to conventional medical intervention
  - Isolated Grade 3 elevation of amylase or lipase not associated with clinical or radiographic evidence of pancreatitis
  - Isolated Grade 3 fever not associated with hemodynamic compromise (eg, hypotension, clinical or laboratory evidence of impaired end-organ perfusion)
  - Grade 3 endocrinopathy that is well-controlled by hormone replacement
  - Grade 3 tumor flare (defined as pain, irritation, or rash that localizes to site of known or suspected tumor)
  - Grade 3 fatigue
  - Grade 3 infusion reaction that returns to Grade 1 in less than 6 hours

C. Dermatologic DLT

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

D. Hematologic DLT

- Methemoglobin levels ≥ 15%
- Grade 4 neutropenia ≥ 5 days in duration
- Grade 4 thrombocytopenia or Grade 3 thrombocytopenia with bleeding, or any requirement for platelet transfusion
- Grade ≥ 3 febrile neutropenia for 48 hours
- Grade ≥ 3 hemolysis (ie, requiring transfusion or medical intervention such as steroids)
- Grade 4 anemia not explained by underlying disease

4.5.2 Management Algorithms for Immuno-oncology Agents

I-O agents are associated with AEs that can differ in severity and duration from AEs caused by other therapeutic classes. Nivolumab, ipilimumab, and BMS-986205 are considered I-O agents in this protocol. Early recognition and management of AEs associated with I-O agents

may mitigate severe toxicity. Management algorithms have been developed from 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 BMS-986205 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 5.

4.5.3 Guidelines for Dose Modification

Subjects will be monitored continuously for AEs while on study drug. Subjects will be instructed to notify their physician immediately for any and all AEs. The criteria presented in this section and Table 4.5.3-1 for dose modifications for BMS-986205 are meant as general guidelines.

Dose modification may occur in the setting of lower grade AE and/or be more conservative than indicated in Table 4.5.3-1 based on the clinical judgment of the investigator and in consultation with the Sponsor/Medical Monitor.

- Dose reductions of BMS-986205 should be to the previous lower dose level; subjects receiving 25 mg of BMS-986205 will not undergo any (further) dose reductions.
- If several AEs of varying grade or severity occur simultaneously, the dose modification applied should be the greatest reduction applicable.
- Assessment of causality (ie, chronology, confounding factors such as disease, concomitant medications, diagnostic tests, and previous experience with the agent) must be determined and documented by the investigator prior to dose modification.
- If the same AE recurs despite a dose reduction, a second dose reduction versus discontinuation of BMS-986205 will be discussed and agreed upon by the Sponsor/Medical Monitor and investigators, if criteria for discontinuation are otherwise not met.
- No more than 2 dose reductions of BMS-986205 will be allowed per subject. Dose re-escalation after a dose reduction may occur in limited circumstances (such as a change in attribution of an AE) after discussion and agreement of the Sponsor/Medical Monitor and investigators.
- Skipped doses will not be administered within the same cycle.
- For an AEs leading to dose modification, BMS-986205, nivolumab, and ipilimumab (where applicable) should be interrupted to allow recovery from the AE; see Section 4.5.4for delay criteria. Re-initiation of study drug cannot occur until AE decreases to ≤ Grade 1 or baseline assessment. See Section 4.5.5 for resumption after dose delays.
- During the DLT evaluation period, if the dose is reduced and a subject experiences a DLT at the lower dose, this DLT will be attributed to the highest dose level administered.

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

Table 4.5.3-1: Dose Modifications

Dose Modification Criteria for Drug-related Adverse Events	BMS-986205 Monotherapy Modification at the Next Dose (Part 1 Only)	BMS-986205 Combination Modification at the Next Dose (Parts 1, 2 and 3)
Methemoglobin ≥ 15%	Decrease 1 level of BMS-986205	Interrupt dosing until improvement and decrease 1 level of BMS-986205 in combination with same dose of nivolumab or nivolumab and ipilimumab.
Methemoglobinemia with Grade 3 AEs such as hypoxia and hemolysis	Interrupt BMS-986205. Continuation of BMS-986205 after recovery at a lower dose level may be considered after discussion with the Study Director/Medical Monitor. Subjects may proceed to get nivolumab monotherapy.	Interrupt BMS-986205. Continuation of BMS-986205 after recovery at a lower dose level may be considered after discussion with the Study Director/Medical Monitor. Subjects may proceed to get nivolumab monotherapy or nivolumab and ipilimumab.
Methemoglobinemia with Grade 4 AEs such as hypoxia and hemolysis	Permanent discontinuation of BMS-986205. Subjects may proceed to get nivolumab monotherapy.	Permanent discontinuation of BMS-986205. However, treatment with nivolumab or nivolumab and ipilimumab may continue after discussion between PI and Medical Monitor.
QTcF > 500 msec confirmed by at least 1 repeat ECG and at least 60 msec above baseline	Interrupt if needed to optimize electrolyte management. If persists after electrolyte optimization (including dose modification of BMS-986205, if necessary), discontinue. Subjects may proceed to get nivolumab monotherapy.	Interrupt if needed to optimize electrolyte management. If persists after electrolyte optimization (including dose modification of BMS-986205, if necessary), discontinue. However, treatment with nivolumab or nivolumab and ipilimumab may continue after discussion between PI and Medical Monitor.
Any other drug-related ≥ Grade 3 adverse event that does not meet permanent discontinuation criteria (Section 4.5.6)	Decrease 1 level of BMS-986205	Decrease 1 level of BMS-986205 in combination with same dose of nivolumab or nivolumab and ipilimumab.
Grade 2 LFT abnormalities that do not resolve within 1 week	Interrupt BMS-986205. Continuation of BMS-986205 after recovery at a lower dose level may be considered after discussion with the Study Director/Medical Monitor. Subjects may proceed to get nivolumab monotherapy.	NA
Grade 2 LFT abnormalities	Interrupt dosing until improvement to	NA

Table 4.5.3-1: Dose Modifications

Dose Modification Criteria for Drug-related Adverse Events	BMS-986205 Monotherapy Modification at the Next Dose (Part 1 Only)	BMS-986205 Combination Modification at the Next Dose (Parts 1, 2 and 3)
that resolve in 1 week	Grade 1 or baseline and resume at same dose. If recurrence of Grade 2 LFT elevations, decrease 1 level.	

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

4.5.4 Dose Delays due to Toxicity

- Subjects who experience a DLT must have study drug held. Subjects who are required to permanently discontinue all study drugs are listed in Section 4.5.6. In addition, all Grade 2 hepatic, pulmonary, renal, gastrointestinal, and neurological AEs should be evaluated and managed per the toxicity management algorithms (Appendix 5). Subjects not meeting guidelines for permanent discontinuation will be permitted to resume therapy based on the criteria specified below in Section 4.5.5. Subjects eligible to resume study drug will resume study drug at the treatment visit following their last received study drug dose.
- The scheduled tumor assessments (ie, CT/MRI, positron emission tomography [PET], etc.) will continue on the specified schedule relative to the subject's first dose regardless of any treatment delay incurred.

Study treatment (BMS-986205, nivolumab and ipilimumab [where applicable]) administration should be delayed for the following:

- Grade 2 non-skin, drug-related AE, with the exception of fatigue, nausea, vomiting and anemia
- Grade 2 drug-related creatinine, AST, ALT and/or Total Bilirubin abnormalities
- Grade 3 skin, drug-related AE
- Grade 3 drug-related fatigue, nausea, vomiting, and anemia
- Grade 3 drug-related laboratory abnormality, with the following exceptions:
  - Grade 3 lymphopenia or asymptomatic amylase or lipase elevations do not require dose delay
  - Grade ≥ 3 AST, ALT, Total Bilirubin will require dose discontinuation in most cases (see Section 4.5.6 for details)
- Any AE, laboratory abnormality, or intercurrent illness which, in the judgment of the investigator, warrants delaying the dose of study medication

In addition, **only BMS-986205** should be delayed for the following:

- Methemoglobin ≥ 15%
- Clinically significant elevations in methemoglobin (generally 10% with a normal hemoglobin level[55]) with any associated Grade 3 AE (hypoxia, dyspnea, confusion, etc) attributable to sustained elevations of methemoglobin and not attributable to another etiology

- QTcF > 500 msec confirmed by at least 1 repeat ECG and at least 60 msec above baseline (See Appendix 8).

If nivolumab or (and ipilimumab in Part 3) dosing is delayed for reasons other than study drug toxicity (eg, administrative issues, holidays, etc), BMS-986205 dosing should continue uninterrupted.

Participants may continue to receive nivolumab (and ipilimumab in Part 3) during dose delays of BMS-986205 for elevations of methemoglobin and associated events, as well as QTcF prolongations.

For participants with methemoglobin elevations with associated Grade 3 AEs, if contribution of nivolumab (and ipilimumab in Part 3) to the associated AE cannot be ruled out (eg, a participant with dyspnea in whom pneumonitis has not yet been ruled out), nivolumab (and ipilimumab in Part 3) dosing should be delayed as well. See Section 4.5.7 for management of methemoglobinemia.

If BMS-986205 dosing is delayed, dose reduction may be necessary. See Section 4.5.3.

If dosing is resumed after a delay, BMS-986205 may be resumed as soon as the criteria to resume treatment are met (see Section 4.5.5). Nivolumab (and ipilimumab in Part 3) should be resumed as soon as possible after criteria to resume treatment are met but may be resumed later than BMS-986205 given the differences in each drug's administration.

Participants who require delay of any study treatment should be re-evaluated weekly or more frequently if clinically indicated and resume dosing when criteria to resume are met.

4.5.5 Criteria to Resume Treatment

- Subjects experiencing AEs not meeting criteria for permanent discontinuation as outlined in Section 4.5.6 may resume treatment with study drug under the following criteria:
- Subjects may resume treatment with study drug when the drug-related AE(s) resolve to Grade ≤ 1 or baseline value with the following EXCEPTIONS:
  - Subjects may resume treatment in the presence of Grade 2 fatigue.
  - Subjects who have not experienced a Grade 3 drug-related skin AE may resume treatment in the presence of Grade 2 skin toxicity.
- Grade 2 eye pain or blurred vision not meeting DLT criteria (Section 4.5.1) must resolve to baseline prior to resuming study drug.
- Drug-related pulmonary toxicity, diarrhea, or colitis must have resolved to baseline before treatment is resumed.
- Subjects with drug-related endocrinopathies adequately controlled with only physiologic hormone replacement may resume treatment.
- If the criteria to resume treatment are met, the subject should restart treatment at the next scheduled time point per protocol.
- The consideration to re-initiate study drug under these exceptions will be made on a case-by-case basis after considering the overall benefit/risk profile and in consultation between the

investigator and the BMS Medical Monitor. Any AE with clinical risk will be assessed on a case-by-case basis with the investigator and the BMS Medical Monitor to determine the risks and benefits of continuing therapy following resolution versus discontinuing therapy permanently.

- If treatment with study drug is delayed > 6 weeks from the last dose of BMS-986205 and /or nivolumab (and ipilimumab, where applicable), the subject must be permanently discontinued from study drug, except as specified in Section 4.5.3.

4.5.6 Guidelines for Permanent Discontinuation

Subjects will be required to permanently discontinue all study drugs for the following AEs:

- Clinical deterioration, as assessed by the investigator
- Any occurrence of serotonin syndrome
- Any Grade 3 non-skin, drug-related AE lasting > 7 days, or recurs with the following exceptions for laboratory abnormalities, neurologic toxicity, drug-related uveitis, pneumonitis, bronchospasm, hypersensitivity reactions, infusion reactions, endocrinopathies (and diarrhea and colitis for subjects receiving ipilimumab):
  - Grade 3 drug-related neurologic toxicity, uveitis, pneumonitis, bronchospasm, myocarditis, hypersensitivity reaction, or infusion reaction of any duration requires discontinuation; for subjects receiving ipilimumab, Grade 3 diarrhea and colitis of any duration also require discontinuation
  - Grade 3 drug-related endocrinopathies, adequately controlled with only physiologic hormone replacement do not require discontinuation. Adrenal insufficiency requires discontinuation regardless of control with hormone replacement.
  - Grade 3 drug-related laboratory abnormalities do not require treatment discontinuation except:
    - Grade 3 drug-related thrombocytopenia > 7 days or associated with bleeding requires discontinuation
    - Any drug-related liver function test (LFT) abnormality that meets the following criteria require discontinuation:
      - Grade ≥ 3 drug-related AST, ALT or Total Bilirubin requires discontinuation*
      - Concurrent AST or ALT > 3 x ULN and total bilirubin > 2x ULN

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

- Any Grade 4 drug-related adverse event or laboratory abnormality (including but not limited to creatinine, AST, ALT, or Total Bilirubin), except for the following events which do not require discontinuation:
  - Grade 4 neutropenia ≤ 7 days
  - Grade 4 lymphopenia or leukopenia or asymptomatic amylase or lipase

  - Isolated Grade 4 electrolyte imbalances/abnormalities that are not associated with clinical sequelae and are corrected with supplementation/appropriate management within 72 hours of their onset
  - Grade 4 drug-related endocrinopathy adverse events, such as, hyper- or hypothyroidism, or glucose intolerance, which resolve or are adequately controlled with physiologic hormone replacement (corticosteroids, thyroid hormones) or glucose-controlling agents, respectively, may not require discontinuation after discussion with and approval from the BMS Medical Monitor.
- Any dosing delay lasting > 6 weeks will be cause for permanent discontinuation. Extensions to the period of dose delays may be granted for individual subjects on a case-by-case basis after specific consultation and agreement between the investigator and BMS Medical Monitor in settings where benefit/risk may justify continued study drug (eg, subject deriving clinical benefit who requires prolonged steroid taper for management of non-DLT immune-related AEs or experiences delays for management of a non-drug-related AE).
- Accordingly, dosing delays to allow for prolonged steroid tapers to manage drug-related AEs are allowed. Additionally, dosing delays > 6 weeks that occur for non-drug-related reasons may be allowed if approved by the BMS Medical Monitor.
- Prior to re-initiating treatment in a subject with a dosing delay lasting > 6 weeks, the BMS Medical Monitor must be consulted.
- Tumor assessments should continue as per protocol even if dosing is delayed.

All subjects who discontinue investigational product should comply with protocol-specified follow-up procedures as outlined in Section 3.1.2. 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 (eg, 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

4.5.7 Detection and Management of Methemoglobinemia

BMS-986205 may produce a p-chloroaniline metabolite. P-chloroaniline has been associated with the production of methemoglobin. Symptoms of methemoglobinemia are related to the lack of oxygen delivery to tissues and are proportional to the fraction of methemoglobin, as described below for subjects with normal hemoglobin levels.

Symptoms associated with elevations of methemoglobin are as follows:

- 0% to 10% - Usually asymptomatic
- 10% to 20% - Cyanosis without other symptoms
- 20% to 50% - Headache, dyspnea, lightheadedness (possibly syncope), weakness, confusion, palpitations, chest pain
- 50% to 70% - Coma, seizures, arrhythmias; acidosis
- > 70% - Usually death

Note that subjects with anemia may experience symptoms at lower methemoglobin percentages than listed above, depending on the degree of anemia.

Increasing levels of methemoglobin may confound the results of standard pulse oximeters, with values of around 85% reported consistently as methemoglobin levels increase, regardless of the true oxygen saturation.

When methemoglobinemia is suspected, part of the diagnostic work-up includes evaluation for other disorders that can present with a similar clinical picture, including cardiac and pulmonary disease. A fresh peripheral blood sample (either venous or arterial) should be sent for evaluation of methemoglobin levels; methemoglobin levels may vary with storage of blood.

Testing is done at Screening, at least once each treatment cycle, and as clinically indicated.

The following management recommendations are intended as guidelines for the investigator and may be modified based on institutional practices or local standard of care, as appropriate.

Initial care includes supportive measures and the administration of supplemental oxygen. In mild cases, recovery often occurs simply by interrupting the administration of the offending medication. Concomitant medication lists should be reviewed for medications besides study treatment which can cause methemoglobinemia (see Appendix 10).

Further treatment is generally indicated when the methemoglobin level is above 20% or is associated with symptoms.

Intravenous methylene blue is the first-line antidotal agent and works by restoring the oxygen carrying capacity of hemoglobin by reduction of methemoglobin from its oxidized state. It is given as a 1% solution at a dose of 1 to 2 mg/kg. Most subjects require only 1 dose, and symptoms should resolve within 1 hour. Methylene blue may confound the interpretation of methemoglobin levels detected by co-oximetry; alternative methods should be used after treatment with methylene blue if methemoglobin level monitoring is required. Methylene blue should be used with caution in subjects with concurrent use of serotonergic psychiatric medications, as this could increase the risk of serotonin syndrome.

Exchange transfusion and hyperbaric oxygen treatment are second-line options for subjects with severe methemoglobinemia whose condition does not respond to methylene blue or who cannot be treated with methylene blue. Subject transfer should occur when life-threatening methemoglobinemia that is refractory to treatment occurs in a facility that cannot provide the appropriate critical care.

4.6 Blinding/Unblinding

Not applicable.

4.7 Treatment Compliance

At scheduled PK sample collection as well as on laboratory evaluation days, BMS-986205 will be administered to the subject in the clinical facility. At all other times throughout the study,

BMS-986205 will be administered on an out-subject basis, except when subjects are seen in the clinic for administration of nivolumab, assessment of AEs, and laboratory evaluation. Trained medical personnel will dispense BMS-986205 to the subjects. Treatment compliance will be monitored by drug accountability, as well as by recording BMS-986205 administration in the subject pill diary, medical record, and CRF. Subjects should bring all drug containers to each study visit for drug reconciliation.

4.7.1 Treatment of Drug-related Infusion Reactions

Since nivolumab and ipilimumab contain only human immunoglobulin protein sequences, they are unlikely to be immunogenic and induce infusion or hypersensitivity reactions. However, if such a reaction were to occur, it might manifest with fever, chills, rigors, headache, rash, pruritus, arthralgias, hypo- or hypertension, bronchospasm, or other symptoms. All Grade 3 or 4 infusion reactions should be reported within 24 hours to the BMS Medical Monitor and reported as an SAE if criteria are met. Infusion reactions should be graded according to NCI CTCAE v4.03 guidelines.

Treatment recommendations are provided below and may be modified based on local treatment standards and guidelines as appropriate:

For Grade 1 symptoms: Mild reaction; infusion interruption not indicated; intervention not indicated.

Remain at bedside and monitor 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 study drug administrations.

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

- Stop the nivolumab or ipilimumab infusion, begin an IV infusion of normal saline, and treat the subject with diphenhydramine 50 mg IV (or equivalent) and/or paracetamol 325 to 1000 mg (acetaminophen); monitor subject until resolution of symptoms.
- Bronchodilator or corticosteroid therapy may also be administered as appropriate.
- The infusion may be restarted at 50% of the original infusion rate when symptoms resolve; if no further complications ensue after 30 minutes, the rate may be increased to 100% of the original infusion rate. Monitor subject closely.
- The amount of study drug infused must be recorded on the CRF.
- If symptoms recur, then no further ipilimumab or nivolumab, as the case may be, will be administered at that visit.
- The following prophylactic premedications are recommended for future infusions: diphenhydramine 50 mg (or equivalent) and/or paracetamol 325 to 1000 mg (acetaminophen) should be administered at least 30 minutes before additional nivolumab or ipilimumab

administrations. If necessary, corticosteroids (up to 25 mg of SoluCortef or equivalent) may be used.

Late-occurring 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).

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

Immediately discontinue study drug infusion. Begin an IV infusion of normal saline and treat the subject as follows: recommend bronchodilators, epinephrine 0.2 to 1 mg of a 1:1,000 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. Study drug 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).

4.8 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 standard operating procedures 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.

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.

4.10 Retained Samples for Bioavailability/Bioequivalence

Not applicable.

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, Table 5.1-6, Table 5.1-7, Table 5.1-8, Table 5.1-9, Table 5.1-10, Table 5.1-11, Table 5.1-12, Table 5.1-13, Table 5.1-14, and Table 5.1-15. In limited instances, scheduled events can occur outside of the indicated timeframes but BMS should be notified.

Table 5.1-1: Screening Procedural Outline (CA017003)

Procedure	Screening Visit 28 days	Day-14 to -1 Visit	Day-1 Visit	Notes
Eligibility Assessments				
Informed Consent	X			A subject is considered enrolled only when a protocol-specific informed consent is signed. Obtain subject number from IVRS.
Inclusion/Exclusion Criteria	X			
Medical History	X			Also include any toxicities or allergies related to previous treatments as well as any history of cytochrome b5 reductase deficiency or G6PD deficiency, and also record any vaccination received within 30 days of first dose of study medication.
Prior Systemic Therapies	X			Including prior cancer treatment regimens and medications administered within 4 weeks of dosing.
Tobacco History/Status	X			
Archive Tumor Tissue Samples	X			A block or 20 FFPE unstained slides (generally at least 15 required). With Amendment 14, archival tissues from subjects in Parts 1 and 3 may be of any age, while for all other subjects blocks must have been obtained less than 1 year prior to enrollment, and FFPE slides must have been cut less than 4 months prior to enrollment
Fresh Pre-treatment Tumor Biopsy	X			All subjects in Parts 1 and 3 (as well as subjects in other parts without archival tissue meeting the requirements above) will be required to undergo mandatory pretreatment biopsies Tumor tissue is to be sent to the central laboratory.
[redacted]				
Safety Assessments				
Physical Examination	X			If the screening PE is performed within 24 hours prior to dosing on Day 1, then a single examination may count as both the screening and predose evaluation.
Physical Measurements	X			Includes height and weight.
ECOG Performance Status	X			ECOG Performance Status (see Appendix 2).

Table 5.1-1: Screening Procedural Outline (CA017003)

Procedure	Screening Visit 28 days	Day-14 to -1 Visit	Day-1 Visit	Notes
Vital Signs	X			Includes body temperature, seated 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.
Oxygen Saturation	X			Pulse oximetry collected at rest.
Revised International Prognostic Index at Time of Initial Diagnosis	X			For subjects with lymphoma only. Refer to Appendix 6.
Electrocardiogram	X			12-lead ECGs should be recorded after the subject has been supine for at least 5 minutes.
Laboratory Tests				*Laboratory tests listed below must be completed within 2 weeks of Day 1, unless otherwise noted.*
Chemistry (Excluding LFTs)		X		Includes assessments for sodium, potassium, chloride, total serum calcium, magnesium, bicarbonate/carbon dioxide, phosphorus, BUN, creatinine, creatinine clearance, fasting glucose, total protein, albumin, amylase, lipase, uric acid, ferritin, and LDH.
Methemoglobin		X		Methemoglobin levels to be assessed on arterial or venous blood sample (performed locally).
G6PD Deficiency Testing	X			To be performed locally; may be performed at any time during screening
CBC with Differential and Platelets		X		
LFT Assessments		X		Includes AST, ALT, total bilirubin, direct bilirubin (only if total bilirubin is elevated), alkaline phosphatase, and GGT (only when alkaline phosphatase increases to ≥ Grade 2).
PT/PTT		X		
Urinalysis		X		Urine to be checked for protein, glucose, blood, leukocyte esterase, specific gravity, and pH. Microscopic examination of sediment will be done if blood, protein, or leukocyte esterase is significantly positive on dipstick.
Thyroid Function Tests		X		TSH with free T3 and T4.

Table 5.1-1: Screening Procedural Outline (CA017003)

Procedure	Screening Visit 28 days	Day-14 to -1 Visit	Day-1 Visit	Notes
Genetic Mutation	X			See Section 5.7. Collected as part of the medical history on appropriate CRFs.
Mutational and Viral Status	X			Document histology, EGFR, ALK, and PD-L1 status for subjects with **NSCLC**. Document BRAF and PD-L1 status for subjects with **Melanoma.** **SCCHN (oropharyngeal) and cervical cancer subjects only**: Sites must submit and document prior HPV status within 28 days of dosing. See Inclusion Criteria (Section 3.3.1). **Lymphoma subjects only**: Results of previous molecular analysis must be recorded in the CRFs, if available. - Document prior EBV status if available. - For subjects with DLBCL: May include, but are not limited to, BCL2, MYC, BCL6, CD10, MUM1, Ki67, BCL2 14:18 translocation, and MYC break-apart. **CRC subjects only**: Sites must submit and document prior MSI testing and results. See Inclusion Criteria (Section 3.3.1).
Serology	X			Within 28 days of dosing: hepatitis B surface antigen, hepatitis C antibody (if hepatitis C antibody is positive reflex to hepatitis C RNA) or hepatitis C RNA. **Note:** Testing for HIV-1 and HIV-2 must be performed at sites where mandated by local requirements.
Pregnancy Test			X	WOCBP only **at screening and within 24 hours prior to dosing.** The serum pregnancy test may be completed on the first day of treatment, provided the results are available before the start of study drug. If performed within 24 hours of dosing on Cycle 0 Day 1, then Cycle 0 Day 1 pregnancy test is not required.
Follicle Stimulating Hormone	X			If needed to document postmenopausal status as defined in Section 3.3.3.
Concomitant Medications		X		Collected during the 2 weeks prior to Cycle 1 Day 1.
Clinical Complaints		X		Collected during the 2 weeks prior to Cycle 1 Day 1.

Table 5.1-1: Screening Procedural Outline (CA017003)

Procedure	Screening Visit 28 days	Day-14 to -1 Visit	Day-1 Visit	Notes
Adverse Event Reporting				
Monitor for Serious Adverse Events	X			All SAEs must be collected from the date of subject's written consent until 100 days post discontinuation of nivolumab or subject's participation in the study if the last scheduled visit occurs at a later time. eSAEs should be approved in the BMS EDC tool within 5 business days of entry.
Baseline Efficacy Assessments	See Section 5.4			

Abbreviations: ALK = anaplastic lymphoma kinase; ALT = alanine aminotransferase; AST = aspartate aminotransferase; BMS EDC = Bristol-Myers Squibb Electronic Data Capture; BUN = blood urea nitrogen; CBC = complete blood count; CRC = colorectal cancer; CRF = case report form; CT = computed tomography; DLBCL = diffuse large B-cell lymphoma; ECG = electrocardiogram; ECOG = Eastern Cooperative Oncology Group; EGFR = epidermal growth factor receptor; GGT = gamma-glutamyl transferase; HIV = human immunodeficiency virus; HL = Hodgkin's lymphoma; HPV = human papillomavirus; IVRS = Interactive Voice Response System; LDH = lactate dehydrogenase; LFT = liver function test; MRI = magnetic resonance imaging; MSI = microsatellite instability; NHL = non-Hodgkin's lymphoma; NSCLC = non-small cell lung cancer; PD-L1 = programmed death receptor-ligand 1; PE = physical examination; PET = positron emission tomography; PT = prothrombin time; PTT = partial thromboplastin time; RNA = ribonucleic acid; SAE = serious adverse event; SCCHN = squamous cell carcinoma of the head and neck; TSH = thyroid-stimulating hormone; WOCBP = women of childbearing potential.

Table 5.1-2: On-treatment Procedure Outline (BMS-986205 Monotherapy in Part 1 Dose Escalation)

Procedure	Cycle 0				Notes
	Day 1	Day 2	Day 8	Day 14	
IVRS Assignment	X				Cycle 0 only. BMS-985205 IP assignment. Once subject eligibility has been confirmed, IVRS assignment can be performed within 3 days prior to first study drug administration. (Discuss with Sponsor if institutional policies and procedures require additional lead-time.)
Complete Physical Examination	X[b]				Predose.
Symptom-directed PE		X	X	X	Predose.
Vital Signs and Oxygen Saturations	X				Includes temperature, seated blood pressure, and heart rate. Blood pressure and heart rate should be measured after the subject has been seated quietly for at least 5 minutes.
12-lead ECG	X			X	Collect triplicate ECGs on Cycle 0 Day 1 and Cycle 0 Day 14 at -1 hour pre-dose and 2 and 4 hours post dose. All ECG tests during Cycle 0 will be performed in triplicates (eg, 1 ECG test equals 3 consecutive individual 12-lead ECGs performed allowing a 5-minute window between ECGs). ECGs should be performed after the subject has been resting supine for at least 5 minutes and should be completed prior to any PK/PD sample blood collections when assessments occur at the same time points.
Laboratory Test[a]					
Chemistry (Excluding LFTs)	X[b]		X	X	Predose; includes assessments for sodium, potassium, chloride, total serum calcium, magnesium, bicarbonate/carbon dioxide, phosphorus, BUN, creatinine, glucose, total protein, albumin, amylase,

Table 5.1-2: On-treatment Procedure Outline (BMS-986205 Monotherapy in Part 1 Dose Escalation)

Procedure	Cycle 0				Notes
	Day 1	Day 2	Day 8	Day 14	
					lipase, and LDH.
Methemoglobin	X	X*	X	X	If elevated, draw reticulocyte count, LDH, and haptoglobin. Collect predose and at 2 and 4 hours postdose on Day 1; if elevated see Section 4.5.7. Predose on Day 4 (±1 day). Predose on Days 8 and 14. *Only collect predose on Day 2 if elevated either 2 or 4 hours postdose evaluation on Day 1. Additional samples as clinically indicated.
CBC with Differential and Platelets	X[b]	X*	X	X	Collect predose. If methemoglobin is elevated, collect at 2 and 4 hours postdose on Day 1. Predose on Day 4 (±1 day). *Only collect on Day 2 only if methemoglobin is elevated.
LFT Assessments	X[b]		X	X	Collect predose. Includes AST, ALT, total bilirubin, direct bilirubin (only if total bilirubin is elevated), alkaline phosphatase, and GGT (only when alkaline phosphatase is increased to ≥ Grade 2).
Pregnancy Test (WOCBP)	X				Serum or urine pregnancy test must be performed (urine pregnancy test: minimum sensitivity 25 IU/L or equivalent units of hCG) within 24 hours prior to administration of study drug. If pregnancy test is positive, hold all study drugs and perform confirmatory testing. If pregnancy is confirmed, permanently discontinue all study drugs

Table 5.1-2: On-treatment Procedure Outline (BMS-986205 Monotherapy in Part 1 Dose Escalation)					
Procedure	**Cycle 0**				**Notes**
	Day 1	**Day 2**	**Day 8**	**Day 14**	
					and immediately notify Sponsor per Section 6.5.
Concomitant Medication Assessments	X	X	X	X	Review prior to dosing.
Monitor for Nonserious Adverse Events	X	X	X	X	Nonserious AEs will be collected starting with the first dose of study drug and through 100 days after completion of study drugs (or 30 days if subject only received BMS-986205).
Monitor for Serious Adverse Events	X	X	X	X	All SAEs must be collected from the date of subject's written consent until 100 days after completion of study drugs (or 30 days if subject only received BMS-986205) or subject's participation in the study if the last scheduled visit occurs at a later time. eSAEs should be approved in the BMS EDC tool within 5 business days of entry.
Pharmacokinetic (PK) Assessments	See Section 5.5.4				Performed in all subjects.
Immunogenicity Assessments	See Section 5.5.4.				Performed in all subjects.
Biomarker Assessments	See Section 5.6 and Table 5.6-1.				See Section 5.6.
Urine for p-chloroaniline	See Section 5.4.				Urine (0 to 24 hours) collection start after first dose. An approximately 50 mL aliquot of each urine collection (0 to 8 hours, 8 to 24 hours) will be frozen for shipment.
[redacted]					
Study Drug Administration	Details regarding preparation and administration are provided in the site training materials				

Table 5.1-2: On-treatment Procedure Outline (BMS-986205 Monotherapy in Part 1 Dose Escalation)

Procedure	Cycle 0				Notes
	Day 1	Day 2	Day 8	Day 14	
BMS-986205 Administration	X	Continuous daily dosing during all cycles			BMS-986205 administration must be performed daily. BMS-986205 must be administered with a light meal approximately the same time each day.
Pill Diary	X	Pill diary must be completed with each administered daily dose of BMS-986205.			Review pill diary during each visit for compliance of daily administration of BMS-986205. Collect pill diary at the completion of each cycle.

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

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

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

Table 5.1-3: On-treatment Procedural Outline (BMS-986205 + Nivolumab Part 1 Dose Escalation and Part 2 Dose Expansion)

Procedure	Cycle 1 (4 weeks)				Cycles 2+ (4 weeks)			End of Treatment[a,b,c]	Notes
	Day 1	Day 8	Day 15	Day 22	Day 1	Day15 (±2 days)	Day 22 (+7 days)[d]		
IVRS Assignment									
IVRS Assignment	X		Q2W Nivo dosing only		X	Q2W Nivo dosing only			Once subject eligibility has been confirmed, IVRS assignment can be performed within 3 days prior to first study drug administration. (Discuss with Sponsor if institutional policies and procedures require additional lead-time.)
Safety Assessments									
Complete Physical Examination	X				X				
Symptom-directed PE			X			Q2W Nivo dosing only		X	

Table 5.1-3: On-treatment Procedural Outline (BMS-986205 + Nivolumab Part 1 Dose Escalation and Part 2 Dose Expansion)

Procedure	Cycle 1 (4 weeks)				Cycles 2+ (4 weeks)			End of Treatment[a,b,c]	Notes
	Day 1	Day 8	Day 15	Day 22	Day 1	Day15 (±2 days)	Day 22 (+7 days)[d]		
Vital Signs and Oxygen Saturations	X	X	X	X	X	Q2W Nivo dosing only		X	Includes temperature, seated blood pressure, and heart rate. Blood pressure and heart rate should be measured after the subject has been seated quietly for at least 5 minutes. For nivolumab, VS should be obtained prior to the infusion and then every 30 minutes (± 10 minutes) until 1 hour following completion of the infusion, except on Cycle 1 Days 1 and 15 (for subjects receiving nivolumab 240 mg Q2W) and on Cycle 1 Day 1 (for subjects receiving nivolumab 480 mg Q4W) when VS will be obtained until 4 hours following completion of the infusion. If any vital sign is abnormal (based upon clinician assessment) at the final check, the subject must be observed further for a period of time, as clinically indicated.
12-lead ECG	X				X				12-lead ECGs should be recorded after the subject has been supine for at least 5 minutes. ECGs must be collected predose on Day 1 of each cycle.

Table 5.1-3: On-treatment Procedural Outline (BMS-986205 + Nivolumab Part 1 Dose Escalation and Part 2 Dose Expansion)

Procedure	Cycle 1 (4 weeks)				Cycles 2+ (4 weeks)			End of Treatment[a,b,c]	Notes
	Day 1	Day 8	Day 15	Day 22	Day 1	Day15 (±2 days)	Day 22 (+7 days)[d]		
Laboratory Tests	**On-study laboratory tests (including pregnancy testing) to be done on site/local. Laboratory tests do not need to be repeated on Day 1 for Cycles 1 and onward, if completed within the last 72 hours.** **All laboratory testing will be done weekly for Cycle 1 only, unless otherwise specified.**								
Chemistry (Excluding LFTs)	X	X	X	X	X	Q2W Nivo dosing only		X	Predose; includes assessments for sodium, potassium, chloride, total serum calcium, magnesium, bicarbonate/carbon dioxide, phosphorus, BUN, creatinine, glucose, total protein, albumin, amylase, lipase, and LDH.
Methemoglobin	X	X	X	X	X			X	Collect predose. Collected once per cycle from Cycle 2 on, or more frequently as clinical indicated. If elevated, draw reticulocyte count, LDH, and haptoglobin.
CBC with Differential and Platelets	X	X	X	X	X	Q2W Nivo dosing only		X	Predose.
LFT Assessments	X	X	X	X	X	Q2W Nivo dosing only		X	Predose; includes AST, ALT, total bilirubin, direct bilirubin (only if total bilirubin is elevated), alkaline phosphatase, and GGT (only when alkaline phosphatase is increased to ≥ Grade 2).

Table 5.1-3: On-treatment Procedural Outline (BMS-986205 + Nivolumab Part 1 Dose Escalation and Part 2 Dose Expansion)

Procedure	Cycle 1 (4 weeks)				Cycles 2+ (4 weeks)			End of Treatment[a,b,c]	Notes
	Day 1	Day 8	Day 15	Day 22	Day 1	Day15 (±2 days)	Day 22 (+7 days)[d]		
Thyroid Function Tests	X				X			X	If collected at screening do not repeat on Cycle 1 Day 1. Collect every 2 cycles, predose, beginning with Cycle 3 Day 1 and at the end of treatment. To include TSH with reflex testing to free T3 and free T4 if TSH abnormal. Results should be examined by the investigator or appropriate designee within 48 hours of dose administration.
Pregnancy Test (WOCBP)	X		Q2W Nivo dosing only		X	Q2W Nivo dosing only		X	Serum or urine pregnancy test must be performed (urine pregnancy test: minimum sensitivity 25 IU/L or equivalent units of hCG) within 24 hours prior to administration of study drug. If pregnancy test is positive, hold all study drugs and perform confirmatory testing. If pregnancy is confirmed, permanently discontinue all study drug and immediately notify Sponsor per Section 6.5.
Adverse Event Reporting and Concomitant Medication Assessments									
Concomitant Medication Assessments	X	X	X	X	X	Q2W Nivo dosing only	X	X	Review prior to dosing.

Table 5.1-3: On-treatment Procedural Outline (BMS-986205 + Nivolumab Part 1 Dose Escalation and Part 2 Dose Expansion)

Procedure	Cycle 1 (4 weeks)				Cycles 2+ (4 weeks)			End of Treatment[a,b,c]	Notes
	Day 1	Day 8	Day 15	Day 22	Day 1	Day15 (±2 days)	Day 22 (+7 days)[d]		
Monitor for Nonserious Adverse Events	X	X	X	X	X	Q2W Nivo dosing only	X	X	Nonserious AEs will be collected starting with the first dose of study drug and through 100 days after discontinuation of nivolumab.
Monitor for Serious Adverse Events	X	X	X	X	X	Q2W Nivo dosing only	X	X	All SAEs must be collected from the date of subject's written consent until 100 days post discontinuation of nivolumab or subject's participation in the study if the last scheduled visit occurs at a later time. eSAEs should be approved in the BMS EDC tool within 5 business days of entry.
Sample Collection									
Pharmacokinetic Assessments	See Section 5.5.4.								
Immunogenicity Assessments	See Section 5.5.4.								
Biomarker Assessments	See Section 5.6 and Table 5.6-2.								Biopsy window for C1D15 is C1D15 to C1D28.
[redacted]									
Efficacy Assessments	See Section 5.4								
Imaging							X		See Section 5.4

Table 5.1-3: On-treatment Procedural Outline (BMS-986205 + Nivolumab Part 1 Dose Escalation and Part 2 Dose Expansion)

Procedure	Cycle 1 (4 weeks)				Cycles 2+ (4 weeks)			End of Treatment[a,b,c]	Notes
	Day 1	Day 8	Day 15	Day 22	Day 1	Day15 (±2 days)	Day 22 (+7 days)[d]		
Study Drug Administration									Details regarding preparation and administration are provided in the site training materials.
BMS-986205 Administration	X	**Continuous daily dosing during all cycles**							BMS-986205 should be dispensed once every cycle. BMS-986205 administration must be performed daily. BMS-986205 must be administered with a light meal approximately the same time each day.
Nivolumab Administration	X		Q2W Nivo dosing only		X	Q2W Nivo dosing only			For subjects receiving nivolumab 240 mg Q2W, nivolumab should be dispensed at Cycle 1 Day 1 and Cycle 1 Day 15. Every 14 days during Cycles 2+. For subjects receiving nivolumab 480 mg Q4W, nivolumab should be dispensed at Day 1 of each cycle. After the first nivolumab infusion, subjects should be monitored per local/institutional guidelines. If no such guidelines exist, an observation period of 2 hours after the end of the nivolumab infusion is suggested.

Table 5.1-3: On-treatment Procedural Outline (BMS-986205 + Nivolumab Part 1 Dose Escalation and Part 2 Dose Expansion)

Procedure	Cycle 1 (4 weeks)				Cycles 2+ (4 weeks)			End of Treatment[a,b,c]	Notes
	Day 1	Day 8	Day 15	Day 22	Day 1	Day15 (±2 days)	Day 22 (+7 days)[d]		
Pill Diary	X	**Pill diary must be completed with each administered daily dose of BMS-986205**						X	Review pill diary during each visit for compliance of daily administration of BMS-986205. Collect pill diary at the completion of each cycle and EOT.

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

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

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

[d] Concomitant medication assessment and monitoring for nonserious AEs from Days 22 to 28 must be recorded on the next subject visit. for SAE, the guidance provided in Section 6.1 must be followed.

Abbreviations: AE = adverse event; ALT = alanine aminotransferase; AST = aspartate aminotransferase; BMS EDC = Bristol-Myers Squibb Electronic Data Capture; BUN = blood urea nitrogen; CBC = complete blood count; CR = complete response; ECG = electrocardiogram; EOT = end of treatment; GGT = gamma-glutamyl transferase; hCG = human chorionic gonadotropin; IVRS = Interactive Voice Response System; IWG = International Working Group; LDH = lactate dehydrogenase; LFT = liver function test; PE = physical examination; Q2W = every 2 weeks; Q4W = every 4 weeks; RECIST = Response Evaluation Criteria In Solid Tumors; SAE = serious adverse event; TSH = thyroid-stimulating hormone; VS = vital signs; WOCBP = women of childbearing potential.

Table 5.1-4: On-treatment Procedural Outline--Part 3 (BMS-986205, Nivolumab, and Ipilimumab): Melanoma and Mixed Tumor Type

Procedure	Cycle 1 (8 weeks)							Cycles 2+ (8 weeks)			End of Treatment [a,b,c]	Notes
	Day 1	Day 8	Day 15	Day 22 (±2 days)	Day 29	Day 36 (±2 days)	Day 43 (±2 days)	Day 1	Day 15 (±2 days)	Day 29		
IVRS Assignment												
IVRS Assignment	X				X			X		X		Once subject eligibility has been confirmed, IVRS assignment can be performed within 3 days prior to first study drug administration. (Discuss with Sponsor if institutional policies and procedures require additional lead-time.)
Safety Assessments												
Complete Physical Examination	X				X			X		X		Predose
Symptom-directed PE		X	X	X		X	X		C2 only		X	Predose
Vital Signs and Oxygen Saturations	X	X	X	X	X	X	X	X	C2 only	X	X	Includes temperature, seated blood pressure, and heart rate. Blood pressure and heart rate should be measured after the subject has been seated quietly for at least 5 minutes. For nivolumab and ipilimumab, VS should be obtained prior to the first infusion and then every 30 minutes (± 10 minutes)

Table 5.1-4: On-treatment Procedural Outline--Part 3 (BMS-986205, Nivolumab, and Ipilimumab): Melanoma and Mixed Tumor Type

Procedure	Cycle 1 (8 weeks)							Cycles 2+ (8 weeks)			End of Treatment [a,b,c]	Notes
	Day 1	Day 8	Day 15	Day 22 (±2 days)	Day 29	Day 36 (±2 days)	Day 43 (±2 days)	Day 1	Day 15 (±2 days)	Day 29		
												until 1 hour following completion of the last infusion except on Cycle 1 Day 1 when VS will be obtained until 4 hours following completion of both infusions. If any vital sign is abnormal (based upon clinician assessment) at the final check, the subject must be observed further for a period of time, as clinically indicated.
12-lead ECG	X							X				12-lead ECGs should be recorded after the subject has been supine for at least 5 minutes. ECGs must be collected at predose on Day 1 of each cycle.

Table 5.1-4: On-treatment Procedural Outline--Part 3 (BMS-986205, Nivolumab, and Ipilimumab): Melanoma and Mixed Tumor Type

Procedure	Cycle 1 (8 weeks)							Cycles 2+ (8 weeks)			End of Treatment [a,b,c]	Notes
	Day 1	Day 8	Day 15	Day 22 (±2 days)	Day 29	Day 36 (±2 days)	Day 43 (±2 days)	Day 1	Day 15 (±2 days)	Day 29		
Laboratory Tests	**On-study laboratory tests (including pregnancy testing) to be done on site/local. Laboratory tests do not need to be repeated on Day 1 if completed within the last 72 hours.**											
Chemistry (Excluding LFTs)	X	X	X	X	X	X	X	X	C2 only	X	X	Predose; includes assessments for sodium, potassium, chloride, total serum calcium, magnesium, bicarbonate/carbon dioxide, phosphorus, BUN, creatinine, glucose, total protein, albumin, amylase, lipase, and LDH.
Methemoglobin	X	X	X	X	X	X	X	X	C2 only	X	X	Predose; additional assessments as clinically indicated. If elevated, draw reticulocyte count, LDH, and haptoglobin.
CBC with Differential and Platelets	X	X	X	X	X	X	X	X	C2 only	X	X	Predose.
LFT Assessments	X	X	X	X	X	X	X	X	C2 only	X	X	Predose; includes AST, ALT, total bilirubin, direct bilirubin (only if total bilirubin is elevated), alkaline phosphatase, and GGT (only when alkaline phosphatase is increased

Table 5.1-4: On-treatment Procedural Outline--Part 3 (BMS-986205, Nivolumab, and Ipilimumab): Melanoma and Mixed Tumor Type

Procedure	Cycle 1 (8 weeks)							Cycles 2+ (8 weeks)			End of Treatment [a,b,c]	Notes
	Day 1	Day 8	Day 15	Day 22 (±2 days)	Day 29	Day 36 (±2 days)	Day 43 (±2 days)	Day 1	Day 15 (±2 days)	Day 29		
												to ≥ Grade 2).
Thyroid Function Tests	X				X			X		X	X	If collected at screening do not repeat on Cycle 1 Day 1. To include TSH with reflex testing to free T3 and free T4 if TSH abnormal. Results should be examined by the investigator or appropriate designee within 48 hours of dose administration.
Pregnancy Test (WOCBP)	X				X			X		X	X	Serum or urine pregnancy test must be performed (urine pregnancy test: minimum sensitivity 25 IU/L or equivalent units of hCG) within 24 hours prior to administration of study drug. If pregnancy test is positive, hold all study drugs and perform confirmatory testing. If pregnancy is confirmed, permanently discontinue all study drug and immediately notify Sponsor per Section 6.5.

Table 5.1-4: On-treatment Procedural Outline--Part 3 (BMS-986205, Nivolumab, and Ipilimumab): Melanoma and Mixed Tumor Type

Procedure	Cycle 1 (8 weeks)							Cycles 2+ (8 weeks)			End of Treatment [a,b,c]	Notes
	Day 1	Day 8	Day 15	Day 22 (±2 days)	Day 29	Day 36 (±2 days)	Day 43 (±2 days)	Day 1	Day 15 (±2 days)	Day 29		
Adverse Event Reporting and Concomitant Medication Assessments												
Concomitant Medication Assessments	X	X	X	X	X	X	X	X	C2 only	X	X	Review prior to dosing.
Monitor for Nonserious Adverse Events	X	X	X	X	X	X	X	X	C2 only	X	X	Nonserious AEs will be collected starting with the first dose of study drug and through 100 days after discontinuation of nivolumab.
Monitor for Serious Adverse Events	X	X	X	X	X	X	X	X	C2 only	X	X	All SAEs must be collected from the date of subject's written consent until 100 days post discontinuation of nivolumab or subject's participation in the study if the last scheduled visit occurs at a later time. eSAEs should be approved in the BMS EDC tool within 5 business days of entry.
Sample Collection												
Pharmacokinetic Assessments	See Section 5.5.4											
Immunogenicity Assessments	See Section 5.5.4											

Table 5.1-4: On-treatment Procedural Outline--Part 3 (BMS-986205, Nivolumab, and Ipilimumab): Melanoma and Mixed Tumor Type

Procedure	Cycle 1 (8 weeks)							Cycles 2+ (8 weeks)			End of Treatment [a,b,c]	Notes
	Day 1	Day 8	Day 15	Day 22 (±2 days)	Day 29	Day 36 (±2 days)	Day 43 (±2 days)	Day 1	Day 15 (±2 days)	Day 29		
Biomarker Assessments	See Section 5.6 and Table 5.6-2											Mandatory on-treatment biopsies required for all subject. Biopsy window for C1D15 is C1D15-C1D28. EOT biopsy is optional.
[redacted]												
Efficacy Assessments	See Section 5.4											
Study Drug Administration												Details regarding preparation and administration are provided in the site training materials.
BMS-986205 Administration	X	**Continuous daily dosing during all cycles**										BMS-986205 should be dispensed on Day 1 and Day 29 of each cycle. BMS-986205 administration must be performed daily. BMS-986205 must be administered with a light meal approximately the same time each day.
Nivolumab Administration	X				X			X		X		Nivolumab should be dispensed at Day 1 and D29 of each cycle.

Table 5.1-4: On-treatment Procedural Outline--Part 3 (BMS-986205, Nivolumab, and Ipilimumab): Melanoma and Mixed Tumor Type

Procedure	Cycle 1 (8 weeks)							Cycles 2+ (8 weeks)			End of Treatment [a,b,c]	Notes
	Day 1	Day 8	Day 15	Day 22 (±2 days)	Day 29	Day 36 (±2 days)	Day 43 (±2 days)	Day 1	Day 15 (±2 days)	Day 29		
												After the first nivolumab infusion, subjects should be monitored per local/institutional guidelines. If no such guidelines exist, an observation period of 2 hours after the end of the nivolumab infusion is suggested.
Ipilimumab Administration	X							X				Ipilimumab should be dispensed on Day 1 of each cycle.
Pill Diary	X	**Pill diary must be completed with each administered daily dose of BMS-986205**									X	Review pill diary during each visit for compliance of daily administration of BMS-986205. Collect pill diary at the completion of each cycle and EOT.

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

[b] For subject who complete all scheduled cycles of therapy, the EOT visit will be the same as the last scheduled and completed on-treatment visit and the start of the Week 1 Clinical/Safety Follow-up visit.

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

Abbreviations: Abbreviations: AE = adverse event; ALT = alanine aminotransferase; AST = aspartate aminotransferase; BMS EDC = Bristol-Myers Squibb Electronic Data Capture; BUN = blood urea nitrogen; CBC = complete blood count; CR = complete response; ECG = electrocardiogram; EOT = end of treatment; GGT = gamma-glutamyl transferase; hCG = human chorionic gonadotropin; IVRS = Interactive Voice Response System; IWG = International Working Group; LDH = lactate dehydrogenase; LFT = liver function test; PE = physical examination; Q2W = every 2 weeks; Q4W = every 4 weeks; RECIST =

Response Evaluation Criteria In Solid Tumors; SAE = serious adverse event; TSH = thyroid-stimulating hormone; VS = vital signs; WOCBP = women of childbearing potential

Table 5.1-5: On-treatment Procedural Outline--Part 3 (BMS-986205, Nivolumab, and Ipilimumab): NSCLC

Procedure	Cycle 1 (6 weeks)						Cycles 2+ (6 weeks)			End of Treatment[a,b,c]	Notes
	Day 1	Day 8	Day 15	Day 22	Day 29 (±2 days)	Day 36 (±2 days)	Day 1	Day 15 (±2 days)	Day 22		
IVRS Assignment											
IVRS Assignment	X			X			X		X		Once subject eligibility has been confirmed, IVRS assignment can be performed within 3 days prior to first study drug administration. (Discuss with Sponsor if institutional policies and procedures require additional lead-time.)
Safety Assessments											
Complete Physical Examination	X			X			X		X		
Symptom-directed PE		X	X		X	X		C2 only		X	
Vital Signs and Oxygen Saturations	X	X	X	X	X	X	X	C2 only	X	X	Includes temperature, seated blood pressure, and heart rate. Blood pressure and heart rate should be measured after the subject has been seated quietly for at least 5 minutes. For nivolumab and ipilimumab, VS should be obtained prior to the first infusion and then every 30 minutes (± 10 minutes) until 1 hour following completion of the last infusion except on Cycle 1 Day 1 when VS will be obtained until 4 hours following completion of both infusions.

Table 5.1-5: On-treatment Procedural Outline--Part 3 (BMS-986205, Nivolumab, and Ipilimumab): NSCLC

Procedure	Cycle 1 (6 weeks)						Cycles 2+ (6 weeks)			End of Treatment[a,b,c]	Notes
	Day 1	Day 8	Day 15	Day 22	Day 29 (±2 days)	Day 36 (±2 days)	Day 1	Day 15 (±2 days)	Day 22		
											If any vital sign is abnormal (based upon clinician assessment) at the final check, the subject must be observed further for a period of time, as clinically indicated.
12-lead ECG	X						X				12-lead ECGs should be recorded after the subject has been supine for at least 5 minutes. ECGs must be collected at predose on Day 1 of each cycle.
Laboratory Tests	**On-study laboratory tests (including pregnancy testing) to be done on site/local. Laboratory tests do not need to be repeated on Day 1 if completed within the last 72 hours.**										
Chemistry (Excluding LFTs)	X	X	X	X	X	X	X	C2 only	X	X	Predose; includes assessments for sodium, potassium, chloride, total serum calcium, magnesium, bicarbonate/carbon dioxide, phosphorus, BUN, creatinine, glucose, total protein, albumin, amylase, lipase, and LDH.
Methemoglobin	X	X	X	X	X	X	X		X	X	Predose; additional assessments as clinically indicated. If elevated, draw reticulocyte count, LDH, and haptoglobin.
CBC with Differential and Platelets	X	X	X	X	X	X	X	C2 only	X	X	Predose.

Table 5.1-5: On-treatment Procedural Outline--Part 3 (BMS-986205, Nivolumab, and Ipilimumab): NSCLC

Procedure	Cycle 1 (6 weeks)						Cycles 2+ (6 weeks)			End of Treatment[a,b,c]	Notes
	Day 1	Day 8	Day 15	Day 22	Day 29 (±2 days)	Day 36 (±2 days)	Day 1	Day 15 (±2 days)	Day 22		
LFT Assessments	X	X	X	X	X	X	X	C2 only	X	X	Predose; includes AST, ALT, total bilirubin, direct bilirubin (only if total bilirubin is elevated), alkaline phosphatase, and GGT (only when alkaline phosphatase is increased to ≥ Grade 2).
Thyroid Function Tests	X			X			X			X	If collected at screening do not repeat on Cycle 1 Day 1. To include TSH with reflex testing to free T3 and free T4 if TSH abnormal. Results should be examined by the investigator or appropriate designee within 48 hours of dose administration.
Pregnancy Test (WOCBP)	X			X			X		X	X	Serum or urine pregnancy test must be performed (urine pregnancy test: minimum sensitivity 25 IU/L or equivalent units of hCG) within 24 hours prior to administration of study drug. If pregnancy test is positive, hold all study drugs and perform confirmatory testing. If pregnancy is confirmed, permanently discontinue all study drug and immediately notify Sponsor per Section 6.5.

Table 5.1-5: On-treatment Procedural Outline--Part 3 (BMS-986205, Nivolumab, and Ipilimumab): NSCLC

Procedure	Cycle 1 (6 weeks)						Cycles 2+ (6 weeks)			End of Treatment[a,b,c]	Notes
	Day 1	Day 8	Day 15	Day 22	Day 29 (±2 days)	Day 36 (±2 days)	Day 1	Day 15 (±2 days)	Day 22		
Adverse Event Reporting and Concomitant Medication Assessments											
Concomitant Medication Assessments	X	X	X	X	X	X	X	C2 only	X	X	Review prior to dosing.
Monitor for Nonserious Adverse Events	X	X	X	X	X	X	X	C2 only	X	X	Nonserious AEs will be collected starting with the first dose of study drug and through 100 days after discontinuation of nivolumab.
Monitor for Serious Adverse Events	X	X	X	X	X	X	X	C2 only	X	X	All SAEs must be collected from the date of subject's written consent until 100 days post discontinuation of nivolumab or subject's participation in the study if the last scheduled visit occurs at a later time. eSAEs should be approved in the BMS EDC tool within 5 business days of entry.
Sample Collection											
Pharmacokinetic Assessments	See Section 5.5.4										
Immunogenicity Assessments	See Section 5.5.4										
Biomarker Assessments	See Section 5.6 and Table 5.6-2										Mandatory on-treatment biopsies required for all subject. Biopsy window for C1D15 is C1D15 to C1D28. EOT biopsy is optional.

Table 5.1-5: On-treatment Procedural Outline--Part 3 (BMS-986205, Nivolumab, and Ipilimumab): NSCLC

Procedure	Cycle 1 (6 weeks)						Cycles 2+ (6 weeks)			End of Treatment[a,b,c]	Notes
	Day 1	Day 8	Day 15	Day 22	Day 29 (±2 days)	Day 36 (±2 days)	Day 1	Day 15 (±2 days)	Day 22		
[redacted]											
Efficacy Assessments	See Section 5.4										
Study Drug Administration											Details regarding preparation and administration are provided in the site training materials.
BMS-986205 Administration	X	**Continuous daily dosing during all cycles**									BMS-986205 should be dispensed on Day 1 and Day 22 of every cycle BMS-986205 administration must be performed daily. BMS‑986205 must be administered with a light meal approximately the same time each day.
Nivolumab Administration	X			X			X		X		Nivolumab should be dispensed on Days 1 and 22 of each cycle. After the first nivolumab infusion, subjects should be monitored per local/institutional guidelines. If no such guidelines exist, an observation period of 2 hours after the end of the nivolumab infusion is suggested.
Ipilimumab Administration	X						X				Ipilimumab should be dispensed on Day 1 of each cycle.
Pill Diary	X	**Pill diary must be completed with each administered daily dose of BMS-986205**								X	Review pill diary during each visit for compliance of daily

Table 5.1-5: On-treatment Procedural Outline--Part 3 (BMS-986205, Nivolumab, and Ipilimumab): NSCLC

Procedure	Cycle 1 (6 weeks)						Cycles 2+ (6 weeks)			End of Treatment[a,b,c]	Notes
	Day 1	Day 8	Day 15	Day 22	Day 29 (±2 days)	Day 36 (±2 days)	Day 1	Day 15 (±2 days)	Day 22		
											administration of BMS-986205. Collect pill diary at the completion of each cycle and EOT.

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

[b] For subject who complete all scheduled cycles of therapy, the EOT visit will be the same as the last scheduled and completed on-treatment visit and the start of the Week 1 Clinical/Safety Follow-up visit.

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

Abbreviations: AE = adverse event; ALT = alanine aminotransferase; AST = aspartate aminotransferase; BMS EDC = Bristol-Myers Squibb Electronic Data Capture; BUN = blood urea nitrogen; CBC = complete blood count; CR = complete response; ECG = electrocardiogram; EOT = end of treatment; GGT = gamma-glutamyl transferase; hCG = human chorionic gonadotropin; IVRS = Interactive Voice Response System; IWG = International Working Group; LDH = lactate dehydrogenase; LFT = liver function test; PE = physical examination; Q2W = every 2 weeks; Q4W = every 4 weeks; RECIST = Response Evaluation Criteria In Solid Tumors; SAE = serious adverse event; TSH = thyroid-stimulating hormone; VS = vital signs; WOCBP = women of childbearing potential

Table 5.1-6: On-treatment Procedural Outline--Part 3 (BMS-986205, Nivolumab, and Ipilimumab): Bladder

Procedure	Cycles 1 and 2 (each 6 weeks)						Cycles 3+ (4 weeks		End of Treatment[a,b,c]	Notes
	Day 1	Day 8	Day 15	Day 22	Day 29 (±2 days)	Day 36 (±2 days)	Day 1	Day 15 (±2 days)		
IVRS Assignment										
IVRS Assignment	X			X			X			Once subject eligibility has been confirmed, IVRS assignment can be performed within 3 days prior to first study drug administration. (Discuss with Sponsor if institutional policies and procedures require additional lead-time.)
Safety Assessments										
Complete Physical Examination	X			X			X			
Symptom-directed PE		C1 only	X		C1 only	C1 only		C3 only	X	

Table 5.1-6: On-treatment Procedural Outline--Part 3 (BMS-986205, Nivolumab, and Ipilimumab): Bladder

Procedure	Cycles 1 and 2 (each 6 weeks)						Cycles 3+ (4 weeks		End of Treatment[a,b,c]	Notes
	Day 1	Day 8	Day 15	Day 22	Day 29 (±2 days)	Day 36 (±2 days)	Day 1	Day 15 (±2 days)		
Vital Signs and Oxygen Saturations	X	C1 only	X	X	C1 only	C1 only	X	C3 only	X	Includes temperature, seated blood pressure, and heart rate. Blood pressure and heart rate should be measured after the subject has been seated quietly for at least 5 minutes. For nivolumab and ipilimumab, VS should be obtained prior to the first infusion and then every 30 minutes (± 10 minutes) until 1 hour following completion of the last infusion except on Cycle 1 Day 1 when VS will be obtained until 4 hours following completion of both infusions. If any vital sign is abnormal (based upon clinician assessment) at the final check, the subject must be observed further for a period of time, as clinically indicated.
12-lead ECG	X						X			12-lead ECGs should be recorded after the subject has been supine for at least 5 minutes. ECGs must be collected at predose on Day 1 of each cycle.

Table 5.1-6: On-treatment Procedural Outline--Part 3 (BMS-986205, Nivolumab, and Ipilimumab): Bladder

Procedure	Cycles 1 and 2 (each 6 weeks)						Cycles 3+ (4 weeks		End of Treatment[a,b,c]	Notes
	Day 1	Day 8	Day 15	Day 22	Day 29 (±2 days)	Day 36 (±2 days)	Day 1	Day 15 (±2 days)		
Laboratory Tests	**On-study laboratory tests (including pregnancy testing) to be done on site/local. Laboratory tests do not need to be repeated on Day 1 for Cycles 1 and onward if completed within the last 72 hours.**									
Chemistry (Excluding LFTs)	X	C1 only	X	X	C1 only		X	C3 only	X	Predose; includes assessments for sodium, potassium, chloride, total serum calcium, magnesium, bicarbonate/carbon dioxide, phosphorus, BUN, creatinine, glucose, total protein, albumin, amylase, lipase, and LDH.
Methemoglobin	X	C1 only	X	X	X		X		X	Predose; additional assessments as clinically indicated. If abnormal, draw LDH, reticulocyte count, and haptoglobin
CBC with Differential and Platelets	X	C1 only	X	X	C1 only		X	C3 only	X	Predose.
LFT Assessments	X	C1 only	X	X	C1 only		X	C3 only	X	Predose; includes AST, ALT, total bilirubin, direct bilirubin (only if total bilirubin is elevated), alkaline phosphatase, and GGT (only when alkaline phosphatase is increased to ≥ Grade 2).

Table 5.1-6: On-treatment Procedural Outline--Part 3 (BMS-986205, Nivolumab, and Ipilimumab): Bladder

Procedure	Cycles 1 and 2 (each 6 weeks)						Cycles 3+ (4 weeks		End of Treatment[a,b,c]	Notes
	Day 1	Day 8	Day 15	Day 22	Day 29 (±2 days)	Day 36 (±2 days)	Day 1	Day 15 (±2 days)		
Thyroid Function Tests	X			X			X		X	If collected at screening, do not repeat on Cycle 1 Day 1. To include TSH with reflex testing to free T3 and free T4 if TSH abnormal. Results should be examined by the investigator or appropriate designee within 48 hours of dose administration.
Pregnancy Test (WOCBP)	X			X			X		X	Serum or urine pregnancy test must be performed (urine pregnancy test: minimum sensitivity 25 IU/L or equivalent units of hCG) within 24 hours prior to administration of study drug. If pregnancy test is positive, hold all study drugs and perform confirmatory testing. If pregnancy is confirmed, permanently discontinue all study drug and immediately notify Sponsor per Section 6.5.
Adverse Event Reporting and Concomitant Medication Assessments										
Concomitant Medication Assessments	X	X	X	X	X	X	X	C3 only	X	Review prior to dosing.
Monitor for Nonserious Adverse Events	X	X	X	X	X	X	X	C3 only	X	Nonserious AEs will be collected starting with the first dose of study drug and through 100 days after discontinuation of nivolumab.

Table 5.1-6: On-treatment Procedural Outline--Part 3 (BMS-986205, Nivolumab, and Ipilimumab): Bladder

Procedure	Cycles 1 and 2 (each 6 weeks)						Cycles 3+ (4 weeks		End of Treatment[a,b,c]	Notes
	Day 1	Day 8	Day 15	Day 22	Day 29 (±2 days)	Day 36 (±2 days)	Day 1	Day 15 (±2 days)		
Monitor for Serious Adverse Events	X	X	X	X	X	X	X	C3 only	X	All SAEs must be collected from the date of subject's written consent until 100 days post discontinuation of nivolumab or subject's participation in the study if the last scheduled visit occurs at a later time. eSAEs should be approved in the BMS EDC tool within 5 business days of entry.
Sample Collection										
Pharmacokinetic Assessments	See Section 5.5.4									
Immunogenicity Assessments	See Section 5.5.4									
Biomarker Assessments	See Section 5.6 and Table 5.6-2									Mandatory on-treatment biopsies required for all subject. Biopsy window for C1D15 is C1D15-C1D28. EOT biopsy is optional.
[redacted]										
Efficacy Assessments	See Section 5.4									
Study Drug Administration										Details regarding preparation and administration are provided in the site training materials. If additional treatment beyond 48 weeks is given, additional cycles should follow the schedule and events

Table 5.1-6: On-treatment Procedural Outline--Part 3 (BMS-986205, Nivolumab, and Ipilimumab): Bladder

Procedure	Cycles 1 and 2 (each 6 weeks)						Cycles 3+ (4 weeks		End of Treatment[a,b,c]	Notes
	Day 1	Day 8	Day 15	Day 22	Day 29 (±2 days)	Day 36 (±2 days)	Day 1	Day 15 (±2 days)		
										of Cycle 3+ of initial treatment
BMS-986205 Administration	X	**Continuous daily dosing during all cycles**								BMS-986205 should be dispensed on Day 1 and Day 22 of Cycles 1 and 2, and the Day 1 of Cycle 3 and beyond. BMS-986205 administration must be performed daily. BMS‑986205 must be administered with a light meal approximately the same time each day.
Nivolumab Administration	80 mg			80 mg			480 mg			Nivolumab should be dispensed at Days 1 and 22 of Cycles 1 and 2 and Day 1 of Cycle 3 and beyond. After the first nivolumab infusion, subjects should be monitored per local/institutional guidelines. If no such guidelines exist, an observation period of 2 hours after the end of the nivolumab infusion is suggested.
Ipilimumab Administration	X			X						Ipilimumab should be dispensed on Days 1 and 22 of Cycles 1 and 2 only.
Pill Diary	X	**Pill diary must be completed with each administered daily dose of BMS-986205**							X	Review pill diary during each visit for compliance of daily administration of BMS-986205. Collect pill diary at the completion of each cycle and EOT.

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

[b] For subject who complete all scheduled cycles of therapy, the EOT visit will be the same as the last scheduled and completed on-treatment visit and the start of the Week 1 Clinical/Safety Follow-up visit

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

Abbreviations: AE = adverse event; ALT = alanine aminotransferase; AST = aspartate aminotransferase; BMS EDC = Bristol-Myers Squibb Electronic Data Capture; BUN = blood urea nitrogen; CBC = complete blood count; CR = complete response; ECG = electrocardiogram; EOT = end of treatment; GGT = gamma-glutamyl transferase; hCG = human chorionic gonadotropin; IVRS = Interactive Voice Response System; IWG = International Working Group; LDH = lactate dehydrogenase; LFT = liver function test; PE = physical examination; Q2W = every 2 weeks; Q4W = every 4 weeks; RECIST = Response Evaluation Criteria In Solid Tumors; SAE = serious adverse event; TSH = thyroid-stimulating hormone; VS = vital signs; WOCBP = women of childbearing potential.

Table 5.1-7: Follow-up Procedural Outline (CA017003)

Procedure	Clinical/Safety Follow-up			Survival/Long-term Follow-up	Response Follow-up[c]	Notes
	FU 1 30 days[a] (± 10 days)	FU 2 60 days (± 10 days)	FU 3 100 days (± 10 days)	All Subjects Begins After Completion of Clinical/Safety Follow-up Every 12 Weeks (± 2 weeks) Until 2 years After FIRST Dose of Study Drug and a Minimum of 12 months after LAST Dose of Study Drug[b]	Begins After Completion of Safety Follow-up (±2weeks) Until End of Survival Follow-up	
Safety Assessments						
Physical Examination	X	X	X			Symptom-directed only.
Vital Signs	X	X	X			Includes body temperature, seated blood pressure, and heart rate. Blood pressure and heart rate should be measured after the subject has been seated quietly for at least 5 minutes.
Laboratory Tests						
Chemistry (Excluding LFTs)	X	X	X			Includes assessments for sodium, potassium, chloride, total serum calcium, magnesium, bicarbonate/carbon dioxide, phosphorus, BUN, creatinine, glucose, total protein, albumin, amylase, lipase, and LDH.

Table 5.1-7: Follow-up Procedural Outline (CA017003)

Procedure	Clinical/Safety Follow-up			Survival/Long-term Follow-up	Response Follow-up[c]	Notes
	FU 1 30 days[a] (± 10 days)	FU 2 60 days (± 10 days)	FU 3 100 days (± 10 days)	All Subjects Begins After Completion of Clinical/Safety Follow-up Every 12 Weeks (± 2 weeks) Until 2 years After FIRST Dose of Study Drug and a Minimum of 12 months after LAST Dose of Study Drug[b]	Begins After Completion of Safety Follow-up (±2weeks) Until End of Survival Follow-up	
Methemoglobin	X	X	X			Only to be drawn if above ULN at last assessment; not required during follow-up. If elevated, draw reticulocyte count, LDH, and haptoglobin.
CBC with Differential and Platelets	X	X	X			If methemoglobin is elevated, collect this assessment at same time point(s) as methemoglobin collection.
LFT Assessment	Collect at 30, 60, and 100 days following the last dose of study drug. For subjects with LFT abnormalities following the last dose of study drug, consider collecting weekly until normalized.					Includes AST, ALT, total bilirubin, direct bilirubin (only if total bilirubin is elevated), alkaline phosphatase, and GGT (only when alkaline phosphatase is increased to ≥ Grade 2).
Thyroid Function Tests	X	X	X			To include TSH with reflex testing to free T3 and free T4 if TSH abnormal.

Table 5.1-7: Follow-up Procedural Outline (CA017003)

Procedure	Clinical/Safety Follow-up			Survival/Long-term Follow-up	Response Follow-up[c]	Notes
	FU 1 30 days[a] (± 10 days)	FU 2 60 days (± 10 days)	FU 3 100 days (± 10 days)	All Subjects Begins After Completion of Clinical/Safety Follow-up Every 12 Weeks (± 2 weeks) Until 2 years After FIRST Dose of Study Drug and a Minimum of 12 months after LAST Dose of Study Drug[b]	Begins After Completion of Safety Follow-up (±2weeks) Until End of Survival Follow-up	
Pregnancy Test	X	X	X			For WOCBP; serum or urine pregnancy test may be performed (clinic urine pregnancy test: minimum sensitivity 25 IU/L or equivalent units of hCG). If positive, perform confirmatory testing. If pregnancy is confirmed, immediately notify Sponsor per Section 6.5.
Adverse Event Reporting and Concomitant Medication Assessments						
Monitor for Nonserious Adverse Events	X	X	X			Nonserious AEs will be collected starting with the first dose of study drug and through 100 days after completion of study drugs (or 30 days if subject only received BMS-986205).

Table 5.1-7: Follow-up Procedural Outline (CA017003)

Procedure	Clinical/Safety Follow-up			Survival/Long-term Follow-up	Response Follow-up[c]	Notes
	FU 1 30 days[a] (± 10 days)	FU 2 60 days (± 10 days)	FU 3 100 days (± 10 days)	All Subjects Begins After Completion of Clinical/Safety Follow-up Every 12 Weeks (± 2 weeks) Until 2 years After FIRST Dose of Study Drug and a Minimum of 12 months after LAST Dose of Study Drug[b]	Begins After Completion of Safety Follow-up (±2weeks) Until End of Survival Follow-up	
Monitor for Serious Adverse Events	X	X	X			All SAEs must be collected from the date of subject's written consent until 100 days after completion of study drugs (or 30 days if subject only received BMS-986205) or subject's participation in the study if the last scheduled visit occurs at a later time. eSAEs should be approved in the BMS EDC tool within 5 business days of entry.
Concomitant Medication Assessments	X	X	X			
Sample Collection						
Pharmacokinetic Assessments	See Section 5.4					
Immunogenicity (ADA) Assessments	See Section 5.4.					
Efficacy Assessments						
Diagnostic Imaging			X		X	See Section 5.4

Table 5.1-7: Follow-up Procedural Outline (CA017003)

Procedure	Clinical/Safety Follow-up			Survival/Long-term Follow-up	Response Follow-up[c]	Notes
	FU 1 30 days[a] (± 10 days)	FU 2 60 days (± 10 days)	FU 3 100 days (± 10 days)	All Subjects Begins After Completion of Clinical/Safety Follow-up Every 12 Weeks (± 2 weeks) Until 2 years After FIRST Dose of Study Drug and a Minimum of 12 months after LAST Dose of Study Drug[b]	Begins After Completion of Safety Follow-up (±2weeks) Until End of Survival Follow-up	
Assessment of Subject Survival Status				X		Subject status will be assessed by either a clinic visit or telephone contact.
New Subsequent Anti-cancer Therapies	X	X	X	X		Any new anti-cancer therapies (including surgery and radiotherapy) will be recorded.

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

[b] Follow up after first dose of combination therapy, not monotherapy lead-in.

[c] Only for subjects with CR, PR, or SD at end of treatment.

Abbreviations: ADA = anti-drug antibody; AE = adverse event; ALT = alanine aminotransferase; AST = aspartate aminotransferase; BUN = blood urea nitrogen; CBC = complete blood count; CR = complete response; ECOG = Eastern Cooperative Oncology Group; FU = follow-up; GGT = gamma-glutamyl transferase; hCG = human chorionic gonadotropin; IWG = International Working Group; LDH = lactate dehydrogenase; LFT = liver function test; PR = partial response; RECIST = Response Evaluation Criteria In Solid Tumors; SAE = serious adverse event; TSH = thyroid-stimulating hormone; WOCBP = women of childbearing potential.

Table 5.1-8: Re-treatment Day 0 Procedural Outline (CA017003)

Procedure	Day 0[a]	Notes
Safety Assessments		
Informed Consent	X	Subjects must re-consented.
Complete Physical Examination	X	If the screening PE is performed within 1 day of dosing on Cycle 1 Day 1, then a single examination may count as both the screening and predose evaluation.
ECOG Performance Status	X	ECOG Performance Status (Appendix 2).
Physical Measurements	X	Weight
Vital Signs	X	Includes body temperature, respiratory rate, seated blood pressure, and heart rate. Blood pressure, respiratory rate, and heart rate should be measured after the subject has been seated quietly for at least 5 minutes.
Oxygen Saturation	X	Pulse oximetry collected at rest.
Electrocardiogram	X	12-lead ECG should be recorded after the subject has been supine for at least 5 minutes if not done within the last 30 days.
Laboratory Tests		**Laboratory tests listed below must be completed within 2 weeks of re-treatment Day 1 unless otherwise noted.**
Chemistry (Excluding LFTs)	X	Includes assessments for sodium, potassium, chloride, total serum calcium, magnesium, bicarbonate/carbon dioxide, phosphorus, BUN, creatinine, creatinine clearance, fasting glucose, total protein, albumin, amylase, lipase, uric acid, ferritin, and LDH.
Methemoglobin	X	Methemoglobin levels to be assessed on arterial or venous blood sample (performed locally).
CBC with Differential and Platelets	X	
LFT Assessments	X	Includes AST, ALT, total bilirubin, direct bilirubin (only if total bilirubin is elevated), alkaline phosphatase, and GGT (only when alkaline phosphatase is increased to ≥ Grade 2).

Table 5.1-8: Re-treatment Day 0 Procedural Outline (CA017003)

Procedure	Day 0[a]	Notes
Urinalysis	X	Urine to be checked for protein, glucose, blood, leukocyte esterase, specific gravity, and pH. Microscopic examination of sediment will be done if blood, protein, or leukocyte esterase is significantly positive on dipsticks.
Serology Tests	X	Repeat the following if > 6 months since last treatment: hepatitis B surface antigen, hepatitis C antibody (if hepatitis C antibody is positive reflex to hepatitis C RNA), or hepatitis C RNA. Note: Testing for HIV-1 and HIV-2 must be performed at sites where mandated by local requirements.
Thyroid Function Tests	X	TSH with free T3 and free T4.
Pregnancy Test	X	WOCBP only, at screening and within 24 hours prior to dosing. The serum pregnancy test may be completed on the first day of treatment provided the results are available before the start of study drug. If performed within 24 hours of dosing on Cycle 1 Day 1, then Cycle 1 Day 1 pregnancy test is not required.
Follicle Stimulating Hormone	X	If needed to document postmenopausal status as defined in Section 3.3.3.
Efficacy Assessments		
Diagnostic Imaging	X	CT with contrast is the preferred modality (MRI if CT is not feasible). Assessment should include the chest/abdomen/pelvis at a minimum; and should include other anatomic regions as indicated by individual subject disease histories.
Brain Imaging	X	Brain imaging (CT/MRI) only required for subjects with history or symptoms of brain metastases and have not had brain imaging within 30 days of anticipated first study drug administration.
Bone Scan Imaging	X	As clinical indicated (eg, subjects with history or symptoms of bone metastases), but bone scans will not be considered a modality for assessment for measurable disease.
Clinical Drug Supplies		
Subject Registration via IVRS	X	Ensure subject continues to meet eligibility for protocol treatment.

[a] All procedures for re-treatment eligibility will be performed within 28 days of re-treatment Day 1 dosing unless noted otherwise.

Abbreviations: ALT = alanine aminotransferase; AST = aspartate aminotransferase; BUN = blood urea nitrogen; CBC = complete blood count; CRP = C-reactive protein; CT = computed tomography; ECG = electrocardiogram; ECOG = Eastern Cooperative Oncology Group; GGT = gamma-glutamyl transferase; HIV = human immunodeficiency virus; LDH = lactate dehydrogenase; LFT = liver function test; MRI = magnetic resonance imaging; PE = physical examination; RNA = ribonucleic acid; TSH = thyroid-stimulating hormone; WOCBP = women of childbearing potential.

Table 5.1-9: Re-treatment Procedural Outline (CA017003 Dose Escalation Part 1 and Dose Expansion Part 2)

Procedure	Cycle 1			Cycles 2+				
	Day 1	Day 15 (± 2 days)	Day 22-28 (± 2 days)	Day 1	Day 15 (± 2 days)	Day 22 (± 7 days)[d]	End of Treatment[a,b,c]	Notes
Safety Assessments								
IVRS	X	Q2W Nivo Dosing Only		X	Q2W Nivo Dosing Only			Once subject eligibility has been confirmed, IVRS assignment can be performed within 3 days prior to first study drug administration. (Discuss with Sponsor if institutional policies and procedures require additional lead-time.)
Complete Physical Examination	X			X				Predose
Symptom-directed PE		X			Q2W Nivo Dosing Only		X[a]	Predose
Vital Signs	X	Q2W Nivo Dosing Only		X	Q2W Nivo Dosing Only		X	Includes temperature, seated blood pressure, and heart rate. Blood pressure and heart rate should be measured after the subject has been seated quietly for at least 5 minutes. Vital signs will be obtained at predose If any vital sign is abnormal (based upon clinician assessment) at the final check, the subject must be observed further for a period of time, as clinically indicated.

Table 5.1-9: Re-treatment Procedural Outline (CA017003 Dose Escalation Part 1 and Dose Expansion Part 2)

Procedure	Cycle 1			Cycles 2+				
	Day 1	**Day 15 (± 2 days)**	**Day 22-28 (± 2 days)**	**Day 1**	**Day 15 (± 2 days)**	**Day 22 (± 7 days)[d]**	**End of Treatment[a,b,c]**	**Notes**
Laboratory Tests	**On-study laboratory testing (including pregnancy testing) to be done on site/local, within 24 hours prior to dosing**							
Chemistry (Excluding LFTs)	X	Q2W Nivo Dosing Only		X	Q2W Nivo Dosing Only		X	Includes assessments for sodium, potassium, chloride, total serum calcium, magnesium, bicarbonate/carbon dioxide, phosphorus, BUN, creatinine, glucose, total protein, albumin, amylase, lipase, and LDH.
Methemoglobin	X			X				Once per cycle, or more frequently as clinically indicated.
CBC with Differential and Platelets	X	Q2W Nivo Dosing Only		X	Q2W Nivo Dosing Only		X	Predose. Collect if methemoglobin is elevated when measurement is taken.
LFT Assessments	X	Q2W Nivo Dosing Only		X	Q2W Nivo Dosing Only		X	Predose; includes AST, ALT, total bilirubin, direct bilirubin (only if total bilirubin is elevated), alkaline phosphatase, and GGT (only when alkaline phosphatase is increased to ≥ Grade 2).
Thyroid Function Tests	X			C2 and every other cycle			X	To include TSH with reflex testing to free T3 and free T4 if TSH abnormal. Results should be examined by the investigator or appropriate designee within 48 hours of dose administration. During re-treatment, collect thyroid function tests every 2 cycles.

Table 5.1-9: Re-treatment Procedural Outline (CA017003 Dose Escalation Part 1 and Dose Expansion Part 2)

Procedure	Cycle 1			Cycles 2+				
	Day 1	**Day 15 (± 2 days)**	**Day 22-28 (± 2 days)**	**Day 1**	**Day 15 (± 2 days)**	**Day 22 (± 7 days)[d]**	**End of Treatment[a,b,c]**	**Notes**
Pregnancy Test (WOCBP)	X	Q2W Nivo Dosing Only		X	Q2W Nivo Dosing Only		X	Serum or urine pregnancy test must be performed (urine pregnancy test: minimum sensitivity 25 IU/L or equivalent units of hCG) within 24 hours prior to administration of study drug. If the pregnancy test is positive, hold all study drugs and perform confirmatory testing. If pregnancy is confirmed, permanently discontinue all study drug and immediately notify Sponsor per Section 3.5.
Adverse Event Reporting and Concomitant Medication Assessments								
Concomitant Medication Assessments	X	Q2W Nivo Dosing Only	X	X	Q2W Nivo Dosing Only	X	X	Review prior to dosing.
Monitor for Nonserious Adverse Events	X	Q2W Nivo Dosing Only	X	X	Q2W Nivo Dosing Only	X	X	Nonserious AEs will be collected starting with the first dose of study drug and through 100 days after completion of study drugs.
Monitor for Serious Adverse Events	X	Q2W Nivo Dosing Only	X	X	Q2W Nivo Dosing Only	X	X	All SAEs must be collected from the date of subject's written consent until 100 days after completion of study or subject's participation in the study if the last scheduled visit occurs at a later time. eSAEs should be approved in

Table 5.1-9: Re-treatment Procedural Outline (CA017003 Dose Escalation Part 1 and Dose Expansion Part 2)

Procedure	Cycle 1			Cycles 2+				
	Day 1	**Day 15 (± 2 days)**	**Day 22-28 (± 2 days)**	**Day 1**	**Day 15 (± 2 days)**	**Day 22 (± 7 days)[d]**	**End of Treatment[a,b,c]**	**Notes**
								the BMS EDC tool within 5 business days of entry.
Sample Collection								
Pharmacokinetic Assessments	See Section 5.5.4							
Immunogenicity Assessments	See Section 5.5.4							
[redacted]								
Efficacy Assessments	See Section 5.4							
Imaging Assessments						C2 and then every 2 cycles		See Section 5.4
Study Drug Administration								Details regarding preparation and administration are provided in site training materials.
BMS-986205 Administration	X	**Daily continuous dosing**						BMS-986205 should be dispensed once every cycle. BMS-986205 administration must be performed daily. BMS-986205 must be administered with a light meal at approximately the same time each day.

Table 5.1-9: Re-treatment Procedural Outline (CA017003 Dose Escalation Part 1 and Dose Expansion Part 2)

Procedure	Cycle 1			Cycles 2+				
	Day 1	**Day 15 (± 2 days)**	**Day 22-28 (± 2 days)**	**Day 1**	**Day 15 (± 2 days)**	**Day 22 (± 7 days)[d]**	**End of Treatment[a,b,c]**	**Notes**
Nivolumab Administration	X	Q2W nivolumab only		X	Q2W nivolumab only			For subjects receiving nivolumab 240 mg Q2W, nivolumab should be dispensed at Cycle 1 Day 1 and Cycle 1 Day 15. Every 14 days during Cycles 2+. For subjects receiving nivolumab 480 mg Q4W, nivolumab should be dispensed at Day 1 of each cycle. After the first nivolumab infusion, subjects should be monitored per local/institutional guidelines. If no such guidelines exist, an observation period of 2 hours after the end of the nivolumab infusion is suggested.
Pill Diary	X	**Pill diary must be completed with each administered daily dose of BMS-986205.**					X	Review pill diary during each visit for compliance of daily administration of BMS-986205. Collect pill diary at the completion of each cycle and EOT.

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

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

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

[d] Concomitant medication assessment and monitoring for nonserious AEs from Days 22 to 28 must be recorded on the next subject visit. for SAE, the guidance provided in Section 6.1 must be followed.

Abbreviations: AE = adverse event; ALT = alanine aminotransferase; AST = aspartate aminotransferase; BMS EDC = Bristol-Myers Squibb Electronic Data Capture; BUN = blood urea nitrogen; CBC = complete blood count; CRP = C-reactive protein; ECOG = Eastern Cooperative Oncology Group; EOT = end of treatment; GGT = gamma-glutamyl transferase; hCG = human chorionic gonadotropin; IVRS = Interactive Voice Response System; IWG = International Working Group; LDH = lactate dehydrogenase; LFT = liver function test; PE = physical examination; Q2W = every 2 weeks; Q4W = every 4 weeks; RECIST = Response Evaluation Criteria In Solid Tumors; SAE = serious adverse event; TSH = thyroid-stimulating hormone; WOCBP = women of childbearing potential.

Table 5.1-10: Re-treatment Procedural Outline Part 3: Melanoma

Procedure	Cycle 1				Cycles 2+		End of Treatment[a,b,c]	Notes
	Day 1	Day 15 (±2 days)	Day 29	Day 43 (±2 days)	Day 1	Day 29		
IVRS Assignment								
IVRS Assignment	X		X		X	X		Once subject eligibility has been confirmed, IVRS assignment can be performed within 3 days prior to first study drug administration. (Discuss with Sponsor if institutional policies and procedures require additional lead-time.)
Safety Assessments								
Complete Physical Examination	X		X		X	X		
Symptom-directed PE		X		X			X	
Vital Signs and Oxygen Saturations	X	X	X	X	X	X	X	Includes temperature, seated blood pressure, and heart rate. Blood pressure and heart rate should be measured after the subject has been seated quietly for at least 5 minutes. For nivolumab and ipilimumab, VS should be obtained prior to the first infusion and then every 30 minutes (± 10 minutes) until 1 hour following completion of the last infusion except on Cycle 1 Day 1 when VS will be obtained until 4 hours following completion of both infusions. If any vital sign is abnormal (based upon clinician assessment) at the final check, the subject must be observed further for a period of time, as clinically indicated.
12-lead ECG	X				X			12-lead ECGs should be recorded after the subject has been supine for at least 5 minutes. ECGs must be collected at predose on Day 1 of each cycle.

Table 5.1-10: Re-treatment Procedural Outline Part 3: Melanoma

Procedure	Cycle 1				Cycles 2+		End of Treatment[a,b,c]	Notes
	Day 1	Day 15 (±2 days)	Day 29	Day 43 (±2 days)	Day 1	Day 29		
Laboratory Tests	**On-study laboratory tests (including pregnancy testing) to be done on site/local. Laboratory tests do not need to be repeated on Day 1 if completed within the last 72 hours.**							
Chemistry (Excluding LFTs)	X	X	X	X	X	X	X	Predose; includes assessments for sodium, potassium, chloride, total serum calcium, magnesium, bicarbonate/carbon dioxide, phosphorus, BUN, creatinine, glucose, total protein, albumin, amylase, lipase, and LDH.
Methemoglobin	X	X	X	X	X	X	X	Predose; additional assessments as clinically indicated. If elevated, draw reticulocyte count, LDH, and haptoglobin.
CBC with Differential and Platelets	X	X	X	X	X	X	X	Predose.
LFT Assessments	X	X	X	X	X	X	X	Predose; includes AST, ALT, total bilirubin, direct bilirubin (only if total bilirubin is elevated), alkaline phosphatase, and GGT (only when alkaline phosphatase is increased to ≥ Grade 2).
Thyroid Function Tests	X		X		X	X	X	If collected at screening do not repeat on Cycle 1 Day 1. To include TSH with reflex testing (free T3 and free T4). Results should be examined by the investigator or appropriate designee within 48 hours of dose administration.
Pregnancy Test (WOCBP)	X		X		X	X	X	Serum or urine pregnancy test must be performed (urine pregnancy test: minimum sensitivity 25 IU/L or equivalent units of hCG) within 24 hours prior to administration of study drug. If pregnancy test is positive, hold all study drugs and perform confirmatory testing. If pregnancy is confirmed, permanently discontinue all study drug and immediately notify Sponsor per Section 6.5.

Table 5.1-10: Re-treatment Procedural Outline Part 3: Melanoma

Procedure	Cycle 1				Cycles 2+		End of Treatment[a,b,c]	Notes
	Day 1	Day 15 (±2 days)	Day 29	Day 43 (±2 days)	Day 1	Day 29		
Adverse Event Reporting and Concomitant Medication Assessments								
Concomitant Medication Assessments	X	X	X	X	X	X	X	Review prior to dosing.
Monitor for Nonserious Adverse Events	X	X	X	X	X	X	X	Nonserious AEs will be collected starting with the first dose of study drug and through 100 days after discontinuation of nivolumab.
Monitor for Serious Adverse Events	X	X	X	X	X	X	X	All SAEs must be collected from the date of subject's written consent until 100 days post discontinuation of nivolumab or subject's participation in the study if the last scheduled visit occurs at a later time. eSAEs should be approved in the BMS EDC tool within 5 business days of entry.
Sample Collection								
Pharmacokinetic Assessments	See Section 5.5.4							
Immunogenicity Assessments	See Section 5.5.4							
Biomarker Assessments	See Section 5.6 and Table 5.6-2.							
[redacted]								
Efficacy Assessments	See Section 5.4							

Table 5.1-10: Re-treatment Procedural Outline Part 3: Melanoma

Procedure	Cycle 1				Cycles 2+		End of Treatment[a,b,c]	Notes
	Day 1	Day 15 (±2 days)	Day 29	Day 43 (±2 days)	Day 1	Day 29		
Study Drug Administration	Details regarding preparation and administration are provided in the site training materials.							
BMS-986205 Administration	X	**Continuous daily dosing during all cycles**						BMS-986205 administration must be performed daily. BMS‑986205 must be administered with a light meal approximately the same time each day.
Nivolumab Administration	X		X		X	X		Nivolumab should be dispensed at Day 1 and D29 of each cycle. After the first nivolumab infusion, subjects should be monitored per local/institutional guidelines. If no such guidelines exist, an observation period of 2 hours after the end of the nivolumab infusion is suggested.
Ipilimumab Administration	X				X			Ipilimumab should be dispensed on Day 1 of each cycle.
Pill Diary	X	**Pill diary must be completed with each administered daily dose of BMS-986205**					X	Review pill diary during each visit for compliance of daily administration of BMS-986205. Collect pill diary at the completion of each cycle and EOT.

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

[b] For subject who complete all scheduled cycles of therapy, the EOT visit will be the same as the last scheduled and completed on-treatment visit and the start of the Week 1 Clinical/Safety Follow-up visit.

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

Abbreviations: AE = adverse event; ALT = alanine aminotransferase; AST = aspartate aminotransferase; BMS EDC = Bristol-Myers Squibb Electronic Data Capture; BUN = blood urea nitrogen; CBC = complete blood count; CR = complete response; ECG = electrocardiogram; EOT = end of treatment; GGT = gamma-glutamyl transferase; hCG = human chorionic gonadotropin; IVRS = Interactive Voice Response System; IWG = International Working Group; LDH = lactate dehydrogenase; LFT = liver function test; PE = physical examination; Q2W = every 2 weeks; Q4W = every 4 weeks; RECIST = Response Evaluation Criteria In Solid Tumors; SAE = serious adverse event; TSH = thyroid-stimulating hormone; VS = vital signs; WOCBP = women of childbearing potential.

Table 5.1-11: Re-treatment Procedural Outline Part 3: NSCLC

Procedure	Cycle 1				Cycles 2+		End of Treatment[a,b,c]	Notes
	Day 1	Day 8 (±2 days)	Day 22	Day 29 (±2 days)	Day 1	Day 22		
IVRS Assignment								
IVRS Assignment	X		X		X	X		Once subject eligibility has been confirmed, IVRS assignment can be performed within 3 days prior to first study drug administration. (Discuss with Sponsor if institutional policies and procedures require additional lead-time.) BMS-986205 should be dispensed once every cycle.
Safety Assessments								
Complete Physical Examination	X		X		X	X		Predose
Symptom-directed PE		X		X			X	
Vital Signs and Oxygen Saturations	X	X	X	X	X	X	X	Includes temperature, seated blood pressure, and heart rate. Blood pressure and heart rate should be measured after the subject has been seated quietly for at least 5 minutes. For nivolumab and ipilimumab, VS should be obtained prior to the first infusion and then every 30 minutes (± 10 minutes) until 1 hour following completion of the last infusion except on Cycle 1 Day 1 when VS will be obtained until 4 hours following completion of both infusions. If any vital sign is abnormal (based upon clinician assessment) at the final check, the subject must be observed further for a period of time, as clinically indicated.

Table 5.1-11: Re-treatment Procedural Outline Part 3: NSCLC

Procedure	Cycle 1				Cycles 2+		End of Treatment[a,b,c]	Notes
	Day 1	Day 8 (±2 days)	Day 22	Day 29 (±2 days)	Day 1	Day 22		
12-lead ECG	X				X			12-lead ECGs should be recorded after the subject has been supine for at least 5 minutes. ECGs must be collected at predose on Day 1 of each cycle.
Laboratory Tests	**On-study laboratory tests (including pregnancy testing) to be done on site/local. Laboratory tests do not need to be repeated on Day 1 if completed within the last 72 hours.**							
Chemistry (Excluding LFTs)	X	X	X	X	X	X	X	Predose; includes assessments for sodium, potassium, chloride, total serum calcium, magnesium, bicarbonate/carbon dioxide, phosphorus, BUN, creatinine, glucose, total protein, albumin, amylase, lipase, and LDH.
Methemoglobin	X	X	X	X	X	X	X	Predose; additional assessments as clinically indicated. If elevated, draw reticulocyte count, LDH, and haptoglobin.
CBC with Differential and Platelets	X	X	X	X	X	X	X	Predose.
LFT Assessments	X	X	X	X	X	X	X	Predose; includes AST, ALT, total bilirubin, direct bilirubin (only if total bilirubin is elevated), alkaline phosphatase, and GGT (only when alkaline phosphatase is increased to ≥ Grade 2).
Thyroid Function Tests	X		X		X		X	If collected at screening, do not repeat on Cycle 1 Day 1. To include TSH with reflex testing (free T3 and free T4). Results should be examined by the investigator or appropriate designee within 48 hours of dose administration.
Pregnancy Test (WOCBP)	X		X		X	X	X	Serum or urine pregnancy test must be performed (urine pregnancy test: minimum sensitivity 25 IU/L or equivalent units of hCG) within 24 hours prior to administration of study drug.

Table 5.1-11: Re-treatment Procedural Outline Part 3: NSCLC

Procedure	Cycle 1				Cycles 2+		End of Treatment[a,b,c]	Notes
	Day 1	Day 8 (±2 days)	Day 22	Day 29 (±2 days)	Day 1	Day 22		
								If pregnancy test is positive, hold all study drugs and perform confirmatory testing. If pregnancy is confirmed, permanently discontinue all study drug and immediately notify Sponsor per Section 6.5.
Adverse Event Reporting and Concomitant Medication Assessments								
Concomitant Medication Assessments	X	X	X	X	X	X	X	Review prior to dosing.
Monitor for Nonserious Adverse Events	X	X	X	X	X	X	X	Nonserious AEs will be collected starting with the first dose of study drug and through 100 days after discontinuation of nivolumab.
Monitor for Serious Adverse Events	X	X	X	X	X	X	X	All SAEs must be collected from the date of subject's written consent until 100 days post discontinuation of nivolumab or subject's participation in the study if the last scheduled visit occurs at a later time. eSAEs should be approved in the BMS EDC tool within 5 business days of entry.
Sample Collection								
Pharmacokinetic Assessments	See Section 5.5.4							
Immunogenicity Assessments	See Section 5.5.4							
Biomarker Assessments	See Section 5.6 and Table 5.6-2.							
[redacted]								
Efficacy	See Section 5.4							

Table 5.1-11: Re-treatment Procedural Outline Part 3: NSCLC

Procedure	Cycle 1				Cycles 2+		End of Treatment[a,b,c]	Notes
	Day 1	Day 8 (±2 days)	Day 22	Day 29 (±2 days)	Day 1	Day 22		
Assessments								
Study Drug Administration								Details regarding preparation and administration are provided in the site training materials.
BMS-986205 Administration	X	**Continuous daily dosing during all cycles**						BMS-986205 administration must be performed daily. BMS‑986205 must be administered with a light meal approximately the same time each day.
Nivolumab Administration	X		X		X	X		Nivolumab should be dispensed at Day 1 and D22 of each cycle. After the first nivolumab infusion, subjects should be monitored per local/institutional guidelines. If no such guidelines exist, an observation period of 2 hours after the end of the nivolumab infusion is suggested.
Ipilimumab Administration	X				X			Ipilimumab should be dispensed on Day 1 of each cycle.
Pill Diary	X	**Pill diary must be completed with each administered daily dose of BMS-986205**					X	Review pill diary during each visit for compliance of daily administration of BMS-986205. Collect pill diary at the completion of each cycle and EOT.

[a] EOT is defined as the visit where decision is made to discontinue the subject from treatment0.

[b] For subject who complete all scheduled cycles of therapy, the EOT visit will be the same as the last scheduled and completed on-treatment visit and the start of the Week 1 Clinical/Safety Follow-up visit.

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

Abbreviations: AE = adverse event; ALT = alanine aminotransferase; AST = aspartate aminotransferase; BMS EDC = Bristol-Myers Squibb Electronic Data Capture; BUN = blood urea nitrogen; CBC = complete blood count; CR = complete response; ECG = electrocardiogram; EOT = end of treatment; GGT = gamma-glutamyl transferase; hCG = human chorionic gonadotropin; IVRS = Interactive Voice Response System; IWG = International Working Group; LDH =

lactate dehydrogenase; LFT = liver function test; PE = physical examination; Q2W = every 2 weeks; Q4W = every 4 weeks; RECIST = Response Evaluation Criteria In Solid Tumors; SAE = serious adverse event; TSH = thyroid-stimulating hormone; VS = vital signs; WOCBP = women of childbearing potential.

Table 5.1-12: Re-treatment Procedural Outline Part 3: Bladder

Procedure	Cycles 1 and 2				Cycles 3+		End of Treatment a,b,c	Notes
	Day 1	Day 8 (±2 days)	Day 22	Day 29 (±2 days)	Day 1	Day 15		
IVRS Assignment	X		X		X	X		Once subject eligibility has been confirmed, IVRS assignment can be performed within 3 days prior to first study drug administration. (Discuss with Sponsor if institutional policies and procedures require additional lead-time.)
Safety Assessments								
Complete Physical Examination	X		X		X			Predose
Symptom-directed PE		X		X		C3	X	
Vital Signs and Oxygen Saturations	X	X	X	X	X	C3	X	Includes temperature, seated blood pressure, and heart rate. Blood pressure and heart rate should be measured after the subject has been seated quietly for at least 5 minutes. For nivolumab and ipilimumab, VS should be obtained prior to the first infusion and then every 30 minutes (± 10 minutes) until 1 hour following completion of the last infusion except on Cycle 1 Day 1 when VS will be obtained until 4 hours following completion of both infusions. If any vital sign is abnormal (based upon clinician assessment) at the final check, the subject must be observed further for a period of time, as clinically indicated.
12-lead ECG	X				X			12-lead ECGs should be recorded after the subject has been supine for at least 5 minutes. ECGs must be collected at predose on Day 1 of each cycle.

Table 5.1-12: Re-treatment Procedural Outline Part 3: Bladder

Procedure	Cycles 1 and 2				Cycles 3+		End of Treatment a,b,c	Notes
	Day 1	Day 8 (±2 days)	Day 22	Day 29 (±2 days)	Day 1	Day 15		
Laboratory Tests	**On-study laboratory tests (including pregnancy testing) to be done on site/local. Laboratory tests do not need to be repeated on Day 1 if completed within the last 72 hours.**							
Chemistry (Excluding LFTs)	X	X	X	X	X	C3	X	Predose; includes assessments for sodium, potassium, chloride, total serum calcium, magnesium, bicarbonate/carbon dioxide, phosphorus, BUN, creatinine, glucose, total protein, albumin, amylase, lipase,, and LDH.
Methemoglobin	X	X	X	X	X		X	Predose; additional assessments as clinically indicated. If elevated, draw reticulocyte count, LDH, and haptoglobin.
CBC with Differential and Platelets	X	X	X	X	X	C3	X	Predose.
LFT Assessments	X	X	X	X	X	C3	X	Predose; includes AST, ALT, total bilirubin, direct bilirubin (only if total bilirubin is elevated), alkaline phosphatase, and GGT (only when alkaline phosphatase is increased to ≥ Grade 2).
Thyroid Function Tests	X		X		X		X	If collected at screening, do not repeat on Cycle 1 Day 1. To include TSH with reflex testing to free T3 and free T4 if TSH abnormal. Results should be examined by the investigator or appropriate designee within 48 hours of dose administration.

Table 5.1-12: Re-treatment Procedural Outline Part 3: Bladder

Procedure	Cycles 1 and 2				Cycles 3+		End of Treatment a,b,c	Notes
	Day 1	Day 8 (±2 days)	Day 22	Day 29 (±2 days)	Day 1	Day 15		
Pregnancy Test (WOCBP)	X		X		X		X	Serum or urine pregnancy test must be performed (urine pregnancy test: minimum sensitivity 25 IU/L or equivalent units of hCG) within 24 hours prior to administration of study drug. If pregnancy test is positive, hold all study drugs and perform confirmatory testing. If pregnancy is confirmed, permanently discontinue all study drug and immediately notify Sponsor per Section 6.5.
Adverse Event Reporting and Concomitant Medication Assessments								
Concomitant Medication Assessments	X	X	X	X	X	C3	X	Review prior to dosing.
Monitor for Nonserious Adverse Events	X	X	X	X	X	C3	X	Nonserious AEs will be collected starting with the first dose of study drug and through 100 days after discontinuation of nivolumab.
Monitor for Serious Adverse Events	X	X	X	X	X	C3	X	All SAEs must be collected from the date of subject's written consent until 100 days post discontinuation of nivolumab or subject's participation in the study if the last scheduled visit occurs at a later time. eSAEs should be approved in the BMS EDC tool within 5 business days of entry.
Sample Collection								
Pharmacokinetic Assessments	See Section 5.5.4							
Immunogenicity Assessments	See Section 5.5.4							
Biomarker Assessments	See Section 5.6 and Table 5.6-2.							

Table 5.1-12: Re-treatment Procedural Outline Part 3: Bladder

Procedure	Cycles 1 and 2				Cycles 3+		End of Treatment a,b,c	Notes
	Day 1	Day 8 (±2 days)	Day 22	Day 29 (±2 days)	Day 1	Day 15		
[redacted]								
Efficacy Assessments	See Section 5.4							
Study Drug Administration								Details regarding preparation and administration are provided in the site training materials.
BMS-986205 Administration	X	**Continuous daily dosing during all cycles**						BMS-986205 administration must be performed daily. BMS-986205 must be administered with a light meal approximately the same time each day.
Nivolumab Administration	80 mg		80 mg		480 mg			Nivolumab should be dispensed at Days 1 and 22 of Cycles 1 and 2 and Day 1 of Cycle 3 and beyond. After the first nivolumab infusion, subjects should be monitored per local/institutional guidelines. If no such guidelines exist, an observation period of 2 hours after the end of the nivolumab infusion is suggested.
Ipilimumab Administration	X		X					Ipilimumab should be dispensed on Days 1 and 22 of Cycles 1 and 2 only.
Pill Diary	X	**Pill diary must be completed with each administered daily dose of BMS-986205**					X	Review pill diary during each visit for compliance of daily administration of BMS-986205. Collect pill diary at the completion of each cycle and EOT.

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

[b] For subject who complete all scheduled cycles of therapy, the EOT visit will be the same as the last scheduled and completed on-treatment visit and the start of the Week 1 Clinical/Safety Follow-up visit.

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

Abbreviations: AE = adverse event; ALT = alanine aminotransferase; AST = aspartate aminotransferase; BMS EDC = Bristol-Myers Squibb Electronic Data Capture; BUN = blood urea nitrogen; CBC = complete blood count; CR = complete response; ECG = electrocardiogram; EOT = end of treatment; GGT = gamma-glutamyl transferase; hCG = human chorionic gonadotropin; IVRS = Interactive Voice Response System; IWG = International Working Group; LDH = lactate dehydrogenase; LFT = liver function test; PE = physical examination; Q2W = every 2 weeks; Q4W = every 4 weeks; RECIST = Response Evaluation Criteria In Solid Tumors; SAE = serious adverse event; TSH = thyroid-stimulating hormone; VS = vital signs; WOCBP = women of childbearing potential.

Table 5.1-13: Re-treatment Follow-up Procedural Outline (CA017003)

Procedure	Clinical/Safety Follow-up			Survival/Long-term Follow-up	Response Follow-up[c]	
	FU 1 30 days[a] (± 10 days)	FU 2 60 days (± 10 days)	FU 3 100 days (± 10 days)	All Subjects Begins After Completion of Clinical/Safety Follow-up Every 12 Weeks (± 2 weeks) until 2 Years After First Dose of Study Drug and a Minimum of 12 months After LAST Dose of Study Drug[b]	Begins After Completion of Safety Follow-up (± 2 weeks) Until End of Survival Follow-up	Notes
Safety Assessments						
Physical Examination	X	X	X			Symptom directed only.
Vital Signs	X	X	X		.	Includes body temperature, seated blood pressure, and heart rate. Blood pressure and heart rate should be measured after the subject has been seated quietly for at least 5 minutes
Laboratory Tests						
Chemistry (Excluding LFTs)	X	X	X			Includes assessments for sodium, potassium, chloride, total serum calcium, magnesium, bicarbonate/carbon dioxide, phosphorus, BUN, creatinine, glucose, total protein, albumin, amylase, lipase, and LDH,

Table 5.1-13: Re-treatment Follow-up Procedural Outline (CA017003)

Procedure	Clinical/Safety Follow-up			Survival/Long-term Follow-up	Response Follow-up[c]	
	FU 1 30 days[a] (± 10 days)	FU 2 60 days (± 10 days)	FU 3 100 days (± 10 days)	All Subjects Begins After Completion of Clinical/Safety Follow-up Every 12 Weeks (± 2 weeks) until 2 Years After First Dose of Study Drug and a Minimum of 12 months After LAST Dose of Study Drug[b]	Begins After Completion of Safety Follow-up (± 2 weeks) Until End of Survival Follow-up	Notes
						excluding AST, ALT, total bilirubin, direct bilirubin (only if total bilirubin is elevated), alkaline phosphatase, and GGT (only when alkaline phosphatase is increased to ≥ Grade 2).
Methemoglobin	X	X	X			Only to be if above ULN at last assessment; not required during follow-up.
CBC with Differential and Platelets	X	X	X			If methemoglobin is elevated, collect this assessment at same time point(s) as methemoglobin collection.
LFT Assessment	Collect at 30, 60, and 100 days following the last dose of study drug. For subjects with LFT abnormalities following the last dose of study drug, consider collecting weekly until normalized.					Includes AST, ALT, total bilirubin, direct bilirubin (only if total bilirubin is elevated), alkaline phosphatase,

Table 5.1-13: Re-treatment Follow-up Procedural Outline (CA017003)

Procedure	Clinical/Safety Follow-up			Survival/Long-term Follow-up	Response Follow-up[c]	
	FU 1 30 days[a] (± 10 days)	**FU 2 60 days (± 10 days)**	**FU 3 100 days (± 10 days)**	**All Subjects Begins After Completion of Clinical/Safety Follow-up Every 12 Weeks (± 2 weeks) until 2 Years After First Dose of Study Drug and a Minimum of 12 months After LAST Dose of Study Drug[b]**	**Begins After Completion of Safety Follow-up (± 2 weeks) Until End of Survival Follow-up**	**Notes**
						and GGT (only when alkaline phosphatase is ≥ Grade 2).
Thyroid Function Tests	X	X	X			To include TSH with reflex testing (free T3 and free T4).
Pregnancy Test	X	X	X			For WOCBP; serum or urine pregnancy test may be performed (clinic urine pregnancy test: minimum sensitivity 25 IU/L or equivalent units of hCG). If positive, perform confirmatory testing. If pregnancy is confirmed, immediately notify Sponsor per Section 6.4.
Adverse Event Reporting and Concomitant Medication Assessments						
Monitor for Nonserious Adverse Events	X	X	X			Nonserious AEs will be collected starting with the first dose of

Table 5.1-13: Re-treatment Follow-up Procedural Outline (CA017003)

Procedure	Clinical/Safety Follow-up			Survival/Long-term Follow-up	Response Follow-up[c]	
	FU 1 30 days[a] (± 10 days)	FU 2 60 days (± 10 days)	FU 3 100 days (± 10 days)	All Subjects Begins After Completion of Clinical/Safety Follow-up Every 12 Weeks (± 2 weeks) until 2 Years After First Dose of Study Drug and a Minimum of 12 months After LAST Dose of Study Drug[b]	Begins After Completion of Safety Follow-up (± 2 weeks) Until End of Survival Follow-up	Notes
						study drug and through 100 days after completion of study drugs (or 30 days if subject only received BMS-986205).
Monitor for Serious Adverse Events	X	X	X			All SAEs must be collected from the date of subject's written consent until 100 days after completion of study drugs (or 30 days if subject only received BMS-986205) or subject's participation in the study if the last scheduled visit occurs at a later time. eSAEs should be approved in the BMS EDC tool within 5 business days of entry.

Table 5.1-13: Re-treatment Follow-up Procedural Outline (CA017003)

Procedure	Clinical/Safety Follow-up			Survival/Long-term Follow-up	Response Follow-up[c]	
	FU 1 30 days[a] (± 10 days)	**FU 2 60 days (± 10 days)**	**FU 3 100 days (± 10 days)**	**All Subjects Begins After Completion of Clinical/Safety Follow-up Every 12 Weeks (± 2 weeks) until 2 Years After First Dose of Study Drug and a Minimum of 12 months After LAST Dose of Study Drug[b]**	**Begins After Completion of Safety Follow-up (± 2 weeks) Until End of Survival Follow-up**	**Notes**
Concomitant Medication Assessments	X	X	X			
Sample Collection						
Pharmacokinetic Assessments	See Section 5.5.4					
Immunogenicity (ADA) Assessments	See Section 5.5.4					
Efficacy Assessments						
Diagnostic Imaging			X		X	See Section 5.4
Assessment of Subject Survival Status				X		Subject status will be assessed by either a clinic visit or telephone contact.
New Subsequent Anti-cancer Therapies	X	X	X	X		Any new anti-cancer therapies (including surgery and radiotherapy) will be recorded.

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

[b] Follow up after first dose of combination therapy, not monotherapy lead-in.

[c] Only for SD, PR, and CR subjects at end of study.

Abbreviations: ADA = anti-drug antibody; AE = adverse event; ALT = alanine aminotransferase; AST = aspartate aminotransferase; BUN = blood urea nitrogen; CBC = complete blood count; CR = complete response; CRP = C-reactive protein; ECOG = Eastern Cooperative Oncology Group; FU = follow-up; GGT = gamma-glutamyl transferase; hCG = human chorionic gonadotropin; IWG = International Working Group; LDH = lactate dehydrogenase; LFT = liver function test; PR = partial response; RECIST = Response Evaluation Criteria In Solid Tumors; SAE = serious adverse event; SD = stable disease; TSH = thyroid-stimulating hormone; WOCBP = women of childbearing potential

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Table 5.1-14: On-treatment Procedure Outline QTc Substudy (Monotherapy BMS-986205)

Procedure		Cycle 0				Notes
	Day -1	Day 1	Day 2	Day 8	Day 14	
IVRS Assignment	X					Cycle 0 only. BMS-985205 IP assignment. Once subject eligibility has been confirmed, IVRS assignment can be performed within 3 days prior to first study drug administration. (Discuss with Sponsor if institutional policies and procedures require additional lead-time.)
Complete Physical Examination		X [b]				Predose
Symptom-directed PE			X	X	X	Predose
Vital Signs and Oxygen Saturations		X				Includes temperature, seated blood pressure, and heart rate. Blood pressure and heart rate should be measured after the subject has been seated quietly for at least 5 minutes.
12-lead ECG (Holter)	X				X	12-lead continuous ECG (Holter) monitoring will be started no later than 1 hour predose and continue until at least 6.5 hours postdose. From these recordings, after transmission to the central ECG laboratory, triplicate ECGs will be extracted during a 5-minute sampling period starting at the nominal times specified. Each 5-minute sampling period should be preceded by at least 10 minutes of rest in a supine position, which would be continued until the end of the 5-minute sampling period.

Table 5.1-14: On-treatment Procedure Outline QTc Substudy (Monotherapy BMS-986205)

Procedure		Cycle 0				Notes
	Day -1	Day 1	Day 2	Day 8	Day 14	
12-lead ECGs		X			X	For monitoring subject safety, at least 5 minutes after the end of triplicate ECG period at 4 hours post dose on Cycle 0 Days 1 and 14, the site's standard ECG machine will be connected using dual-snap electrodes without interrupting the Holter monitoring.
Laboratory Test[a] On-study laboratory tests (including pregnancy testing) to be done on site/local. Laboratory tests do not need to be repeated on Day 1 for Cycles 1 and onward, if completed within 72 hours. All laboratory testing will be done weekly for Cycle 1 only, unless otherwise specified.						
Chemistry (Excluding LFTs)		X[b]		X	X	Predose; includes assessments for sodium, potassium, chloride, total serum calcium, magnesium, bicarbonate/carbon dioxide, phosphorus, BUN, creatinine, glucose, total protein, albumin, amylase, lipase, and LDH.

Table 5.1-14: On-treatment Procedure Outline QTc Substudy (Monotherapy BMS-986205)

Procedure		Cycle 0				Notes
	Day -1	Day 1	Day 2	Day 8	Day 14	
Methemoglobin		X	X*	X	X	If elevated, draw reticulocyte count, LDH, and haptoglobin. Collect at predose and 2 and 4 hours postdose on Day 1; if elevated see Section 4.5.7. *Only collect predose on Day 2 if elevated either 2 or 4 hours postdose evaluation on Day 1. Please collect predose on Day 4 (±1 Day). Predose on Days 8 and 14. Additional collections as clinically indicated.
CBC with Differential and Platelets		X[b]	X	X	X	Collect predose. If methemoglobin is elevated, collect at 2 and 4 hours postdose on Day 1. Collect on Day 2 only if methemoglobin is elevated. Please collect predose on Day 4 (±1 Day).
LFT Assessments		X[b]		X	X	Includes AST, ALT, total bilirubin, direct bilirubin (only if total bilirubin is elevated), alkaline phosphatase, and GGT (only when alkaline phosphatase is increased to ≥ Grade 2).

Table 5.1-14: On-treatment Procedure Outline QTc Substudy (Monotherapy BMS-986205)

Procedure		Cycle 0				Notes
	Day -1	Day 1	Day 2	Day 8	Day 14	
Pregnancy Test (WOCBP)		X				Serum or urine pregnancy test must be performed (urine pregnancy test: minimum sensitivity 25 IU/L or equivalent units of hCG) within 24 hours prior to administration of study drug. If pregnancy test is positive, hold all study drugs and perform confirmatory testing. If pregnancy is confirmed, permanently discontinue all study drug and immediately notify Sponsor per Section 6.5.
Concomitant Medication Assessments		X	X	X	X	Review prior to dosing.
Monitor for Nonserious Adverse Events		X	X	X	X	Nonserious AEs will be collected starting with the first dose of study drug and 30 days after discontinuation of study drug.
Monitor for Serious Adverse Events		X	X	X	X	All SAEs must be collected from the date of subject's written consent until 30 days post discontinuation of study drug or subject's participation in the study if the last scheduled visit occurs at a later time. eSAEs should be approved in the BMS EDC tool within 5 business days of entry.
Pharmacokinetic (PK) Assessments					X	See Table 5.5.4.3-1 for details on PK collection

Table 5.1-14: On-treatment Procedure Outline QTc Substudy (Monotherapy BMS-986205)

Procedure		Cycle 0				Notes
	Day -1	Day 1	Day 2	Day 8	Day 14	
[redacted]						
Study Drug Administration		Details regarding preparation and administration are provided in the site training materials				
BMS-986205 Administration		X	**Continuous daily dosing during all cycles**			BMS-986205 administration must be performed daily. BMS-986205 must be administered with a light meal approximately the same time each day.
Pill Diary		X	**Pill diary must be completed with each administered daily dose of BMS-986205**			Review pill diary during each visit for compliance of daily administration of BMS-986205. Collect pill diary at the completion of each cycle.

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

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

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

Table 5.1-15: On-treatment Procedural Table for QTc Substudy (BMS-986205 + Nivolumab)

Procedure	Cycle 1				Cycles 2+			End of Treatment[a,b,c]	Notes
	Day 1	Day 8	Day 15	Day 22	Day 1	Day15 (±2 days)	Days 22 (+7 days)[d]		
IVRS Assignment									
IVRS Assignment	X				X				Once subject eligibility has been confirmed, IVRS assignment can be performed within 3 days prior to first study drug administration. (Discuss with Sponsor if institutional policies and procedures require additional lead-time.) For subjects receiving nivolumab 480 mg Q4W, nivolumab should be dispensed at Day 1 of each cycle.
Safety Assessments									
Complete Physical Examination	X				X				
Symptom-directed PE			X					X	

Table 5.1-15: On-treatment Procedural Table for QTc Substudy (BMS-986205 + Nivolumab)

Procedure	Cycle 1				Cycles 2+			End of Treatment[a,b,c]	Notes
	Day 1	Day 8	Day 15	Day 22	Day 1	Day15 (±2 days)	Days 22 (+7 days)[d]		
Vital Signs and Oxygen Saturations	X	X	X	X	X			X	Includes temperature, seated blood pressure, and heart rate. Blood pressure and heart rate should be measured after the subject has been seated quietly for at least 5 minutes. For nivolumab, VS should be obtained prior to the infusion and then every 30 minutes (± 10 minutes) until 1 hour following completion of the infusion, except on Cycle 1 Days 1 and 15 (for subjects receiving nivolumab 240 mg Q2W) and on Cycle 1 Day 1 (for subjects receiving nivolumab 480 mg Q4W) when VS will be obtained until 4 hours following completion of the infusion. If any vital sign is abnormal (based upon clinician assessment) at the final check, the subject must be observed further for a period of time, as clinically indicated.
12-lead ECG	X				X				12-lead ECGs should be recorded after the subject has been supine for at least 10 minutes. ECGs must be collected predose on Day 1 of each cycle.

Table 5.1-15: On-treatment Procedural Table for QTc Substudy (BMS-986205 + Nivolumab)

Procedure	Cycle 1				Cycles 2+			End of Treatment[a,b,c]	Notes
	Day 1	Day 8	Day 15	Day 22	Day 1	Day15 (±2 days)	Days 22 (+7 days)[d]		
Laboratory Tests	**On-study laboratory testing (including pregnancy testing) to be done on site/local. Laboratory tests do not need to be repeated on Day 1 for Cycles 1 and onward, if completed within the last 72 hours.** **All laboratory testing will be done weekly for Cycle 1 only, unless otherwise specified.**								
Chemistry (Excluding LFTs)	X	X	X	X	X			X	Predose; includes assessments for sodium, potassium, chloride, total serum calcium, magnesium, bicarbonate/carbon dioxide, phosphorus, BUN, creatinine, glucose, total protein, albumin, amylase, lipase, and LDH.
Methemoglobin	X	X	X	X	X			X	Collect predose Cycle 1 Days 1, 8, 15, 22, each subsequent Cycle Day 1 and EOT. If elevated, draw reticulocyte count, LDH, and haptoglobin. Additional collections to be drawn as clinically indicated.
CBC with Differential and Platelets	X	X	X	X	X			X	Predose.
LFT Assessments	X	X	X	X	X			X	Predose; includes AST, ALT, total bilirubin, direct bilirubin (only if total bilirubin is elevated), alkaline phosphatase, and GGT (only when alkaline phosphatase is increased to ≥ Grade 2).
Thyroid Function Tests	X				X			X	If collected at screening, do not repeat on Cycle 1 Day 1. Collect

Table 5.1-15: On-treatment Procedural Table for QTc Substudy (BMS-986205 + Nivolumab)

Procedure	Cycle 1				Cycles 2+			End of Treatment[a,b,c]	Notes
	Day 1	Day 8	Day 15	Day 22	Day 1	Day15 (±2 days)	Days 22 (+7 days)[d]		
									every 2 cycles, predose, beginning with Cycle 3 Day 1 and at the end of treatment. To include TSH with reflex testing (free T3 and free T4). Results should be examined by the investigator or appropriate designee within 48 hours of dose administration.
Pregnancy Test (WOCBP)	X				X			X	Serum or urine pregnancy test must be performed (urine pregnancy test: minimum sensitivity 25 IU/L or equivalent units of hCG) within 24 hours prior to administration of study drug. If pregnancy test is positive, hold all study drugs and perform confirmatory testing. If pregnancy is confirmed, permanently discontinue all study drug and immediately notify Sponsor per Section 6.5.
Adverse Event Reporting and Concomitant Medication Assessments									
Concomitant Medication Assessments	X	X	X	X	X	X	X	X	Review prior to dosing.
Monitor for Nonserious Adverse Events	X	X	X	X	X	X	X	X	Nonserious AEs will be collected starting with the first dose of study drug and through 100 days after completion of study drugs (or 30 days if subject only received BMS-

Table 5.1-15: On-treatment Procedural Table for QTc Substudy (BMS-986205 + Nivolumab)

Procedure	Cycle 1				Cycles 2+			End of Treatment[a,b,c]	Notes
	Day 1	Day 8	Day 15	Day 22	Day 1	Day15 (±2 days)	Days 22 (+7 days)[d]		
									986205).
Monitor for Serious Adverse Events	X	X	X	X	X	X	X	X	All SAEs must be collected from the date of subject's written consent until 100 days after completion of study drugs (or 30 days if subject only received BMS-986205) or subject's participation in the study if the last scheduled visit occurs at a later time. eSAEs should be approved in the BMS EDC tool within 5 business days of entry.
Sample Collection									
Pharmacokinetic Assessments	See Section 5.5.4								
Immunogenicity Assessments	See Section 5.5.4								
[redacted]									
Efficacy Assessments	See Section 5.4								

Table 5.1-15: On-treatment Procedural Table for QTc Substudy (BMS-986205 + Nivolumab)

Procedure	Cycle 1				Cycles 2+			End of Treatment[a,b,c]	Notes
	Day 1	Day 8	Day 15	Day 22	Day 1	Day15 (±2 days)	Days 22 (+7 days)[d]		
Study Drug Administration									Details regarding preparation and administration are provided in the site training materials.
BMS-986205 Administration	X	**Continuous daily dosing during all cycles**							BMS-986205 administration must be performed daily. BMS-986205 must be administered with a light meal approximately the same time each day.
Nivolumab Administration	X				X				After the first nivolumab infusion, subjects should be monitored per local/institutional guidelines. If no such guidelines exist, an observation period of 2 hours after the end of the nivolumab infusion is suggested.
Pill Diary	X	**Pill diary must be completed with each administered daily dose of BMS-986205**						X	Review pill diary during each visit for compliance of daily administration of BMS-986205. Collect pill diary at the completion of each cycle and EOT.

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

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

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

[d] Concomitant medication assessment and monitoring for nonserious AEs from Days 22 to 28 must be recorded on the next subject visit. for SAE, the guidance provided in Sectio 6.1 must be followed.

Abbreviations: AE = adverse event; ALT = alanine aminotransferase; AST = aspartate aminotransferase; BMS EDC = Bristol-Myers Squibb Electronic Data Capture; BUN = blood urea nitrogen; CBC = complete blood count; CR = complete response; ECG = electrocardiogram; EOT = end of treatment; GGT = gamma-glutamyl transferase; hCG = human chorionic gonadotropin; IVRS = Interactive Voice Response System; IWG = International Working Group; LDH = lactate dehydrogenase; LFT = liver function test; PE = physical examination; Q2W = every 2 weeks; Q4W = every 4 weeks; RECIST = Response Evaluation Criteria In Solid Tumors; SAE = serious adverse event; TSH = thyroid-stimulating hormone; VS = vital signs; WOCBP = women of childbearing potential.

5.1.1 Retesting During Screening or Lead-in Period

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

Laboratory parameters and/or assessments that are included in Table 5.1-1 may be repeated in an effort to find all possible well-qualified subjects. Consultation with the medical monitor may be needed to identify whether repeat testing of any particular parameter is clinically relevant.

Retesting is limited to these specific laboratory parameters and/or assessments.

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 or basic cardiac life support) 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 supply study medications.

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. BMS/The Central Laboratory will provide labels and tubes for the collection of blood samples for PK/biomarker [redacted] analysis.

Additionally, the IVRS manual and pharmacy manual will also be provided.

5.3 Safety Assessments

AEs will be assessed continuously during the study and for 100 days after the last dose of study drug. AEs will be evaluated according to the NCI CTCAE v4.03 and should be followed per requirements in Sections 6.1.1 and 6.2.1. AEs will be coded using the most current version of Medical Dictionary for Regulatory Activities (MedDRA) and reviewed for potential significance and importance. Subjects should be followed until all treatment-related AEs have recovered to baseline or are deemed irreversible by the investigator.

Protocol-specified assessments are detailed in Section 5.1.

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

5.3.2 Laboratory Test Assessments

A local laboratory will perform the analyses and will provide reference ranges for these tests. Results of clinical laboratory tests performed up to Day -1 must be available prior to dosing. The following clinical laboratory tests will be performed:

Hematology

Hemoglobin
Hematocrit
Total leukocyte count, including differential
Platelet count
Methemoglobin
Reticulocyte counts and haptoglobin (at baseline and reflex when methemoglobin is elevated)
Ferritin (at Screening)
Glucose 6-Phosphate Dehydrogenase deficiency testing (at screening)

Serum Chemistry

Aspartate aminotransferase
Alanine aminotransferase
Total bilirubin
Direct bilirubin
Alkaline phosphatase
Lactate dehydrogenase
Creatinine
Blood urea nitrogen
Uric acid
Glucose (Fasting at screening only)
Amylase
Lipase
Gamma-glutamyl transferase only when alkaline phosphatase is ≥Grade 2
Total Protein
Albumin
Sodium
Potassium
Chloride
Calcium
Phosphorus
Magnesium
Creatinine clearance (CrCl)- screening only
Bicarbonate/carbon dioxide

Urinalysis (at screening)

Protein
Glucose
Blood
Leukocyte esterase
Specific gravity
pH
Other:
24 hour urine collection for testing of p-chloroaniline

Serology

Serum for hepatitis C antibody (if Hepatitis C antibody is positive reflex to hepatitis C RNA) or hepatitis C RNA, hepatitis B surface antigen, HPV status, HIV-1 and HIV-2 antibodies. (Testing for HIV-1 and HIV-2 must be performed at sites where mandated by local requirements)

Other Analyses

Pregnancy test (WOCBP only)
TSH with reflex to free T3 and free T4 as applicable.
FSH (if needed to document postmenopausal status as defined in Section 3.3.3)

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

5.3.2.1 Microsatellite Instability Testing

MSI-H (Microsatellite Instability High) in tumors refers to changes in 2 or more of the 5 National Cancer Institute-recommended panels of microsatellite markers in tumor tissue. The original (1997) Bethesda guidelines proposed a panel of five microsatellite markers for the uniform analysis of MSI in HNPCC. This panel, which is referred to as the Bethesda panel, included 2 mononucleotide (BAT-25 and BAT-26) and 3 dinucleotide (D5S346, D2S123, and D17S250) repeats[56]. Individual testing sites may utilize a slightly different panel of markers incorporating alternative mononucleotide or dinucleotide markers. Regardless of the panel of markers, samples with instability in 0 or 1 marker are designated as non-MSI-H (nMSI-H). Those with one unstable marker are designated as MSI-Low (MSI-L). Samples with no detectable alterations are MSI-stable (MSS). Samples with detectable alterations in two or more markers are considered MSI-High (MSI-H).

5.4 Efficacy Assessments

Assessment of tumor response will be reported by the investigator and recorded on the CRF for appropriate populations of subjects as defined by RECIST v1.1 (see Appendix 3) for subjects with solid tumors and IWG (see Appendix 4) for subjects with HL and NHL. Investigators will also report the number and size of new lesions that appear while on study.

For subjects with lymphoma with bone marrow involvement at screening, a bone marrow biopsy and aspirate will be required to confirm a CR.

Body Imaging

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

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

- **Parts 1, and Part 2:** end of Cycle 2 and then every 8 weeks throughout the treatment period.

- **Part 3:**
  - **Melanoma/ Ipi 1Q8**: At Week 12 (± 1 week) and then every 8 weeks (± 1 week) throughout the treatment period.
  - **NSCLC/ Ipi 1Q6**: At Week 6 (± 1 week) and then every 6 weeks (± 1 week) throughout the treatment period
  - **Bladder/ Ipi 3Q3**: At Week 6 (± 1 week) and then every 6 weeks (± 1 week) throughout the treatment period up to 24 weeks, after which they will occur every 12 weeks (± 1 week) throughout the treatment period.
  - **Mixed Tumor Type/ Ipi 1Q8**: At Week 8 (± 1 week) and then every 8 weeks (± 1 week) throughout the treatment period.

These efficacy assessment schedules were selected to allow for more direct comparisons of anti-tumor activity in this study to those of historical comparators for each tumor type.

For all study parts, assessments will be performed every 12 weeks for the first year after the EOT visit and then every 6 months thereafter, up to 2 years following the EOT visit. Efficacy assessments should continue until disease progression, the completion of follow-up, or until subjects withdraw from the study.

For subjects with HL and NHL, PET will be performed at baseline and in order to confirm a CR.

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

Brain Imaging

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

Bone Scan

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

Imaging Modalities

For all the solid tumor types subjects, the following imaging assessments should be performed at study-specified schedule: CT of the chest, CT or MRI of the abdomen, pelvis, and other known sites of disease, which is also summarized Table 5.4-1:

  - CT scans should be acquired with slice thickness of 5 mm or less with no intervening gap (continuous)
- Should a subject have a contraindication for CT IV contrast, a non-contrast CT of the chest and a contrast enhanced MRI of the abdomen and pelvis and other sites of disease may be

obtained. MRIs should be acquired with slice thickness of 5 mm or less with no gap (continuous).

- PET alone will not be considered for the disease assessment. Complementary CT and/or MRI or biopsy must be performed in such cases.
  Note: Use of CT component of a PET/CT scanner: Combined modality scanning, such as with FDG-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 FDG-PET/CT are of limited use in anatomically-based efficacy assessments, and it is, therefore, suggested that they should not be substituted for dedicated diagnostic contrast enhanced CT scans for anatomically-based RECIST (Appendix 7) measurements. However, if a site can document that the CT performed as part of a FDG-PET/CT is of identical diagnostic quality to a diagnostic CT (with IV and oral contrast), then the CT portion of the FDG-PET/CT can be used for RECIST 1.1 measurements. Note, however, that the FDG-PET portion of the CT introduces additional data which may bias an investigator if it is not routinely or serially performed.

For subjects with lymphomas, FDG PET-CT (or PET-MRI, or PET with CT/MRI) may be performed for tumor response assessment throughout the study. If CT performed as part of FDG PET-CT is of comparable quality to a diagnostic CT (+/- IV contrast), the adequate dose CT of the FDG PET-CT can be used for tumor measurements, otherwise additional diagnostic quality CT should be obtained, ideally with oral and intravenous contrast.

Table 5.4-1: Acceptable Imaging Assessment Methods for Different Anatomic Regions

Anatomic Region	Preferred Method	Alternative Methods
Chest, abdomen, and pelvis Note: Scan must cover lung apices to diaphragm, diaphragm through entire liver, and to below the pubic symphysis	CT with IV contrast	**For chest:** • CT without contrast can be used only if the subject has a clinical contraindication for iodine-based IV contrast (eg, hypersensitivity, renal insufficiency) **For abdomen and pelvis:** • MRI with gadolinium-based IV contrast is the first alternative method if the subject has a clinical contraindication for iodine-based IV contrast • CT without contrast can be used as the second alternative method only if the subject has a clinical contraindication for both contrast-enhanced CT and MRI.
Brain	MRI with IV contrast	• CT with IV contrast is the first alternative method if IV gadolinium is clinically contraindicated. • MRI without contrast can be used as a second alternative method if a subject has clinical contraindications for both contrast-enhanced CT and MRI
Bone	Bone scintigraphy	PET (18F-fluoride NaF or FDG) and 99m Technetium SPECT

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

5.4.1 Primary Efficacy Assessment

The primary efficacy assessments will include the ORR (eg, PR + CR rate), duration of response (DoR), and progression-free survival rate (PFSR) at time points (eg, 24 weeks) based on assessment of tumor response using RECIST v1.1 or IWG criteria for selected expansion cohorts in Part 2 and cohorts in Part 3.

5.4.2 Secondary Efficacy Assessments

The efficacy assessments will include the ORR (eg, PR + CR rate), DoR, and PFSR at time points (eg, 24 weeks) based on assessment of tumor response using RECIST v1.1 or IWG criteria for dose escalation (Part 1) and the clinical pharmacology substudy.

[redacted]

5.5 Pharmacokinetic Assessments

5.5.1 Pharmacokinetic Assessment following BMS-986205 Monotherapy

PK of BMS-986205 [redacted] will be derived from plasma concentration versus time and urinary excretion data. Individual subject PK parameter values will be derived by noncompartmental methods by a validated PK analysis program. Actual times will be used for the analyses.

The PK parameters to be assessed for BMS-986205 following multiple dose administration in Cycle 0 during the dose escalation phase and QTc substudy include but not limited to the following:

Cmax	Maximum observed plasma concentration
Tmax	Time of maximum observed plasma concentration
AUC(TAU)	Area under the concentration-time curve in 1 dosing interval
Ctrough	Trough observed plasma concentration at the end of the dosing interval
CLT/F	Apparent total body clearance
Vss/F	Apparent volume of distribution at steady-state
AI	Accumulation index, calculated based on ratio of AUC(TAU) and Cmax at steady state to after the first dose
%UR24	Percent urinary recovery over 24 hours

[redacted]

5.5.2 Pharmacokinetic Assessment following Combination Therapy of BMS-986205 and Nivolumab

Plasma samples for BMS-986205 will be collected for all subjects receiving combination treatment of BMS-986205 and nivolumab. Plasma concentration data will be tabulated using summary statistics. These data, together with data from the monotherapy, may also be pooled with other datasets for PPK analysis, which will be presented in a separate report.

Serum samples for nivolumab [redacted] immunogenicity assessments will be collected for all subjects receiving combination treatment of BMS-986205 and nivolumab. End-of-infusion and trough (Ctrough) concentrations will be tabulated using summary statistics. These data may also be pooled with other datasets for PPK analysis, which will be presented in a separate report.

5.5.3 Pharmacokinetic Assessment following Combination Therapy of BMS-986205, Nivolumab, and Ipilimumab

Serial plasma samples for BMS-986205 [redacted] will be collected for all subjects in the safety cohort receiving combination treatment of BMS-986205, nivolumab and ipilimumab. The PK parameters to be assessed for BMS-986205 [redacted] following multiple dose administration in combination with nivolumab and ipilimumab include but are not limited to:

Cmax	Maximum observed plasma concentration
Tmax	Time of maximum observed plasma concentration
AUC(TAU)	Area under the concentration-time curve in 1 dosing interval
Ctrough	Trough observed plasma concentration at the end of the dosing interval
CLT/F	Apparent total body clearance
Vss/F	Apparent volume of distribution at steady-state
AI	Accumulation index, calculated based on ratio of AUC(TAU) and Cmax at steady state to after the first dose

[redacted]

Plasma samples for BMS-986205 and serum samples for [redacted] nivolumab and ipilimumab immunogenicity assessments will be collected for all subjects in the expansion cohort receiving the combination treatment. Plasma concentration data for BMS-986205 [redacted] will be tabulated using summary statistics. These data may also be pooled with other datasets for PPK analysis, which will be presented in a separate report.

5.5.4 Pharmacokinetics: Collection and Processing

5.5.4.1 BMS-986205 Monotherapy and in Combination with Nivolumab (Parts 1 and 2)

Detailed sampling schedules to be followed for the assessment of PK and immunogenicity for all analytes in Parts 1 and 2 of the study are provided in this section. All time points are relative to the start of BMS-986205 dosing. Predose samples should be taken within 30 minutes before the start of BMS-986205 administration. [redacted] Further details of sample collection,

processing, and shipment will be provided in the laboratory procedures manual. On-treatment PK samples are intended to be drawn relative to actual dosing days; if a dose occurs on a different day within the cycle due to delays or minor schedule adjustments, PK samples should be adjusted accordingly.

Table 5.5.4.1-1: Pharmacokinetic, ADA/Immunogenicity for BMS986205 [redacted] (Dose Escalation Part 1 and Dose Expansion Part 2)

Study Day of Sample Collection	Event	Time (Relative To BMS-986205 Dose) Hour: Min	BMS-986205 [redacted] Plasma Sample	BMS-986205 Biotransformation Sample	BMS-986205 [redacted] Urine Sample	[redacted]	Nivolumab ADA Sample	[redacted]
Cycle 0 [a]								
C0D1	Predose	0	X	X	X			
		1	X		X 0-8 h			
		2	X					
		3	X					
		4	X					
		6	X					
		8	X					
C0D2	Predose	0	X		X 8-24 h			
C0D8	Predose	0	X					
C0D14	Predose	0	X	X				
		1	X	X				
		2	X	X				
		3	X					
		4	X	X				
		6	X	X				
		8	X	X				
CD015	Predose[b]		X	X				

Table 5.5.4.1-1: Pharmacokinetic, ADA/Immunogenicity for BMS986205 [redacted] (Dose Escalation Part 1 and Dose Expansion Part 2)

Study Day of Sample Collection	Event	Time (Relative To BMS-986205 Dose) Hour: Min	BMS-986205 [redacted] Plasma Sample	BMS-986205 Biotransformation Sample	BMS-986205 [redacted] Urine Sample	[redacted]	Nivolumab ADA Sample	[redacted]
Cycle 1								
C1D1	Predose	0[c]	X	X			X	
	EOI[d]	1.0	X					
		2.5-4	X					
C1D15	Predose[e]	0	X					
Cycle 3								
C3D1	Predose	0	X				X	
	EOI	1.0	X					
		2.5-4	X					
Cycle 5								
Every 4 Cycles from C5D1 [f]	Predose	0	X				X	
	EOI	1.0	X					
EOT and FU								
EOT			X				X	
FU [g]			X				X	

[a] Dose escalation only.

[b] This sample should be taken 24 hours after the previous BMS-986205 dose on Cycle 0 Day 14 if Cycle 1 Day 1 does not occur on the next day of Cycle 0 Day 14.

[c] This sample should be taken 24 hours after the previous BMS-986205 dose on Cycle 0 Day 14 if Cycle 1 Day 1 does not occur on the next day of Cycle 0 Day 14.

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

[e] If biopsy does not occur on C1D15, than an additional predose PK sample should be collected on the day of biopsy.

[f] For subjects who will not receive additional treatment beyond Cycle 12, follow the EOT and FU schedules

[g] First 2 follow-up visits.

Abbreviations: ADA = anti-drug antibody; ECG = electrocardiogram; EOI = end of infusion; EOT = end of treatment; FU = follow-up; PK = pharmacokinetic.

Table 5.5.4.1-2: Pharmacokinetic and ADA Sampling Schedule for BMS-986205 [redacted] for Re-treatment

Study Day of Sample Collection	Event	Time (Relative to BMS-986205 Dose) Hour: Min	BMS-986205 [redacted] Plasma Sample	[redacted]	Nivolumab ADA Sample
1	Predose	0	X		X
113[a]	Predose	0	X		X
EOT and FU					
EOT			X		X
FU[b]			X		X

[a] Day 113 of retreatment = C5D1 of retreatment.

[b] First 2 follow-up visits (up to 100 days from end of treatment visit)

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

5.5.4.2 BMS-986205 in Combination with Both Nivolumab and Ipilimumab (Part 3)

Detailed sampling schedules to be followed for the assessment of PK and immunogenicity for all analytes in Part 3 of the study are provided below. All time points are relative to the start of BMS-986205 dosing. Predose samples should be taken within 30 minutes before the start of BMS-986205 administration. [redacted] Further details of sample collection, processing, and shipment will be provided in the laboratory procedures manual. On-treatment PK samples are intended to be drawn relative to actual dosing days; if a dose occurs on a different day within the cycle due to delays or minor schedule adjustments, PK samples should be adjusted accordingly.

Table 5.5.4.2-1: Pharmacokinetic, ADA/Immunogenicity Assessments for Melanoma and Mixed Tumor Type Cohorts in Part 3

Study Day of Sample Collections (1 Cycle = 8 Weeks)	Event	Time (Relative to BMS-986205 Dose) Hour: Min	BMS-986205 [redacted] Plasma Sample	[redacted]	Nivolumab ADA Sample	[redacted]	Ipilimumab ADA Sample
C1D1	Predose	0	X		X		X
	Nivo EOI	1	X				
	Ipi EOI	2	X				
		3[a]	X				
		4[a]	X				
		6[a]	X				
		8[a]	X				
C1D2	Predose[b]	0[a]	X				
C1D15	Predose[c]	0	X				
		1[a]	X				
		2[a]	X				
		3 [a]	X				
		4[a]	X				
		6[a]	X				
		8[a]	X				
C1D16 [a]	Predose[d]	0	X				

Table 5.5.4.2-1: Pharmacokinetic, ADA/Immunogenicity Assessments for Melanoma and Mixed Tumor Type Cohorts in Part 3

Study Day of Sample Collections (1 Cycle = 8 Weeks)	Event	Time (Relative to BMS-986205 Dose) Hour: Min	BMS-986205 [redacted] Plasma Sample	[redacted]	Nivolumab ADA Sample	[redacted]	Ipilimumab ADA Sample
C2D1	Predose	0	X		X		X
	Nivo EOI	1	X				
	Ipi EOI	2	X				
Every 2 Cycles starting C4D1[e]	Predose	0	X		X		X
EOT			X		X		X
FU[f]			X		X		X

[a] Safety cohort only

[b] This sample should be taken 24 hours after the previous BMS-986205 dose on Cycle 1 Day 1

[c] If biopsy does not occur on C1D15, collect an additional Predose PK sample on the day of the biopsy.

[d] This sample should be taken 24 hours after the previous BMS-986205 dose on Cycle 1 Day 15.

[e] For subjects who will not receive additional treatment beyond Cycle 6, follow the EOT and FU schedules at the end of Cycle 6

[f] First 2 follow-up visits.

Abbreviations: ADA= anti-drug antibody; C=cycle; D= day; Ipi=ipilimumab; EOI = end of infusion; EOT = end of treatment; FU = follow-up; Nivo=nivolumab; PK = pharmacokinetic

Table 5.5.4.2-2: Pharmacokinetic, ADA/Immunogenicity Assessments for NSCLC Cohorts in Part 3

Study Day of Sample Collections (1 Cycle = 6 Weeks)	Event	Time (Relative to BMS-986205 Dose) Hour: Min	BMS-986205 [redacted] Plasma Sample	[redacted]	Nivolumab ADA Sample	[redacted]	Ipilimumab ADA Sample
C1D1	Predose	0	X		X		X
	Nivo EOI	1	X				
	Ipi EOI	2	X				
		3[a]	X				
		4[a]	X				
		6[a]	X				
		8[a]	X				
C1D2	Predose[b]	0[a]	X				
C1D15	Predose[c]	0	X				
		1[a]	X				
		2[a]	X				
		3[a]	X				
		4[a]	X				
		6[a]	X				
		8[a]	X				
C1D16[a]	Predose[d]	0	X				
C2D1	Predose	0	X		X		X
	Nivo EOI	1	X				
	Ipi EOI	2	X				
Every 3 Cycles starting C5D1[e]	Predose	0	X		X		X
EOT			X		X		X
FU[f]			X		X		X

[a] Safety cohort only

[b] This sample should be taken 24 hours after the previous BMS-986205 dose on Cycle 1 Day 1.

[c] If biopsy does not occur on C1D15, collect an additional Predose PK sample on the day of the biopsy.

[d] This sample should be taken 24 hours after the previous BMS-986205 dose on Cycle 1 Day 16.

[e] For subjects who will not receive additional treatment beyond Cycle 8, follow the EOT and FU schedules at the end of Cycle 8.

[f] First 2 follow-up visits

Abbreviations: ADA= anti-drug antibody; C=cycle; D= day; Ipi=ipilimumab; EOI = end of infusion; EOT = end of treatment; FU = follow-up; Nivo=nivolumab; PK = pharmacokinetic

Table 5.5.4.2-3: Pharmacokinetic, ADA/Immunogenicity Assessments for Bladder Cohorts in Part 3

Study Day of Sample Collections (1 Cycle = 6 Weeks for C1 and C2, 4 Weeks for C3+)	Event	Time (Relative to BMS-986205 Dose) Hour: Min	BMS-986205 [redacted] Plasma Sample	[redacted]	Nivolumab ADA Sample	[redacted]	Ipilimumab ADA Sample
C1D1	Predose	0	X		X		X
	Nivo EOI	1	X				
	Ipi EOI	2	X				
		3[a]	X				
		4[a]	X				
		6[a]	X				
		8[a]	X				
C1D2	Predose[b]	0[a]	X				
C1D15[c]	Predose	0	X				
		1[a]	X				
		2[a]	X				
		3[a]	X				
		4[a]	X				
		6[a]	X				

Table 5.5.4.2-3: Pharmacokinetic, ADA/Immunogenicity Assessments for Bladder Cohorts in Part 3

Study Day of Sample Collections (1 Cycle = 6 Weeks for C1 and C2, 4 Weeks for C3+)	Event	Time (Relative to BMS-986205 Dose) Hour: Min	BMS-986205 [redacted] Plasma Sample	[redacted]	Nivolumab ADA Sample	[redacted]	Ipilimumab ADA Sample
		8[a]	X				
C1D16[a]	Predose[d]	0	X				
C2D1	Predose	0	X		X		X
	Nivo EOI	1	X				
	Ipi EOI	2	X				
C3D1	Predose	0	X		X		X
	Nivo EOI	1	X				
Every 4 Cycles starting C7D1[e]	Predose	0	X		X		
EOT			X		X		X
FU[f]			X		X		X

[a] Safety cohort only

[b] This sample should be taken 24 hours after the previous BMS-986205 dose on Cycle 1 Day 1

[c] If biopsy does not occur on C1D15, collect an additional Predose PK sample on the day of the biopsy.

[d] This sample should be taken 24 hours after the previous BMS-986205 dose on Cycle 1 Day 15

[e] For subjects who will not receive additional treatment beyond Cycle 11, follow the EOT and FU schedules at the end of Cycle 11

[f] First 2 follow-up visits

Abbreviations: ADA= anti-drug antibody; C=cycle; D= day; Ipi=ipilimumab; EOI = end of infusion; EOT = end of treatment; FU = follow-up; Nivo=nivolumab; PK = pharmacokinetic

Table 5.5.4.2-4: Pharmacokinetic and ADA Assessments During Re-Treatment in Part 3

Study Day of Sample Collection	Event	Time (Relative to BMS-986205 Dose) Hour: Min	**BMS-986205** [redacted] Plasma Sample	[redacted]	Nivolumab ADA Sample	[redacted]	Nivolumab ADA Sample
1	Predose	0	**X**		x		x
113[a]	Predose	0	**X**		x		x
EOT and FU							
EOT[b]			**X**		x		x
FU			**X**		x		x

[a] Day 113 of retreatment = C5D1 of retreatment.

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

[b] First 2 follow-up visits

5.5.4.3 Pharmacologic Substudy

Table 5.5.4.3-1 lists the ECG and PK sampling schedules to be followed for the QTc substudy. Twelve-lead continuous ECG (Holter) will be used in the QTc substudy. Each ECG time point will be collected in triplicates. ECGs should be performed after the subject has been resting supine for at least 10 minutes and should be completed prior to any PK/PD sample blood collections when assessments occur at the same time points. All serial ECGs will be transmitted to a central laboratory for measurement of intervals and classification of ECG abnormalities. Following Cycle 0, subjects in the QTc SubStudy will follow the sampling schedule as outlined in Table 5.5.4.1-1 for subsequent treatment cycles.

Table 5.5.4.3-1: Serial ECG and Pharmacokinetic Collection Schedule for QTc Substudy (Baseline and Cycle 0)

Study Day of Sample Collection	**Event**	**Time (Relative to BMS-986205 Dose) Hour: Min**	**ECG Collection[a]**	**BMS-986205** [redacted] **Plasma Sample**
-1 (ECG baseline)[b]	(Predose)[c]	-0:45	X	
		1:45	X	
		2:45	X	
		3:45	X	
		5:45	X	
C0D14	Predose	-0:45	X	

Table 5.5.4.3-1: Serial ECG and Pharmacokinetic Collection Schedule for QTc Substudy (Baseline and Cycle 0)

Study Day of Sample Collection	Event	Time (Relative to BMS-986205 Dose) Hour: Min	ECG Collection[a]	BMS-986205 [redacted] Plasma Sample
	Predose	0		X
		1		X
		1:45	X	
		2		X
		2:45	X	
		3		X
		3:45	X	
		4		X
		5:45	X	
		6		X
		8		X
C0D15	Predose[d]	0		X

[a] See Table 5.1-15 for detailed instructions on ECG collections.

[b] Allowed up to 5 days prior to the start of cycle 0

[c] No drug is given on the Day-1 visit; Event and Times listed for this visit are intended to approximate the same time as on the treatment day (C0D14)

[d] This sample should be taken 24 hours after the previous BMS-986205 dose on Cycle 0 Day 14 if Cycle 1 Day 1 does not occur on the next day of Cycle 0 Day 14.

5.5.5 *Pharmacokinetic Sample Analyses*

The plasma and urine samples of BMS-986205 [redacted] will be analyzed by validated liquid chromatography-mass spectrometry (LC-MS) assays, and serum samples of [redacted] anti-nivolumab antibody will be analyzed by validated immunoassays. [redacted]

5.5.6 *Labeling and Shipping of Biological Samples*

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

5.6 Biomarker Assessments

Blood and tumor samples will be collected at the times indicated in Table 5.6-1 for the measurement of biomarkers relevant to dose selection [redacted]. Further details of blood and tumor collection and processing will be provided to the site in the procedure manual.

Table 5.6-1: BMS-986205 Plus Nivolumab Dose Escalation Part 1 Biomarker Sampling Schedule

Study Day[a]	Time (Event) Hour	Time (Relative to Dosing) Hour: Min	PD Serum Sample for Kynurenine Metabolite	[redacted]	PD Tumor Biopsy	[redacted]
Screening D-28 to Day -1	0 (predose)					
C0D1	0 (predose)	00:00	X		X[b]	
C0D1	6	6:00	X			
C0D2	0 (predose)	00:00	X			
C0D8	0 (predose)	00:00	X			
C1D1	0 (predose)	00:00	X			
C1D15	0 (predose)	00:00	X		X[b,c]	
C2D1	0 (predose)	00:00	X			
C3D1	0 (predose)	00:00	X			

[redacted]

b Pre- and on-treatment biopsies are mandatory for subjects in Part 1. Additional subjects may be added to dose levels 1 and 2 for pre and on-treatment biopsies if initial PK/PD analyses suggests these dose levels are biologically active.

c C1D15 biopsy specimens may be obtained within a collection window of C1D15 through C1D28 for all subjects. PD serum [redacted] C1D15 samples should be collected on day of biopsy if possible.

Abbreviations: C = cycle; D = day; [redacted] PD = pharmacodynamics.

Table 5.6-2: Dose Expansion Part 2 Biomarker Sampling Schedule

Study Day	Time (Event) Hour	Time (Relative to Dosing) Hour: Min	PD Serum Sample for Kynurenine Metabolite	[redacted]	PD Tumor Biopsy	[redacted]
Screening D-28 to Day -1	0 (predose)				X[b]	
C1D1	0 (predose)	00:00	X			
C1D8[c]	0 (predose)	00:00	X			
C1D15	0 (predose)	00:00	X		X[b]	
C2D1	0 (predose)	00:00	X			
C3D1	0 (predose)	00:00	X			
Unscheduled/EOT/at progression[d]			X[e]		X[e]	

[redacted]

[b] Pre-treatment biopsies are required for participants that do not have sufficient archival tissue. On-treatment biopsies will be mandatory for all subjects. Additional subjects may be added to dose levels 1 and 2 for mandatory pre and on-treatment biopsies if initial PK/PD analyses suggests these dose levels are biologically active.

[c] C1D8 visit is not required during retreatment.

[d] Unscheduled visit included to allow for biopsy and biomarker collection at beginning of re-treatment or at progression.

[e] Tumor biopsy is optional at the unscheduled visit. If tumor biopsy is collected, PD serum [redacted] samples should be collected on the same day.

Abbreviations: C = cycle; D = day; [redacted] EOT = end of treatment; PD = pharmacodynamics

Table 5.6-3: Part 3 Biomarker Sampling Schedule: Melanoma, NSCLC, and Bladder

Study Day	Time (Event) Hour	Time (Relative to Dosing) Hour: Min	PD Serum Sample for Kynurenine Metabolite	[redacted]	PD Tumor Biopsy	[redacted]
Screening D-28 to Day-1	0 (predose)				X[a]	
C1D1	0 (predose)	00:00	X			
C1D8	0 (predose)	00:00	X			
C1D15	0 (predose)	00:00	X		X[a]	
C2D1	0 (predose)	00:00	X			
C3D1	0 (predose)	00:00	X			
Unscheduled/EOT/ at progression[b]			X[c]		X[c]	

[a] Pre- and on-treatment biopsies will be mandatory for Part 3; C1D15 biopsy may be obtained between C1D15 and C1D28.

[b] Unscheduled visit included to allow for biopsy and biomarker collection at beginning of re-treatment or at progression.

[c] Tumor biopsy is optional at the unscheduled visit. If tumor biopsy is collected, PD serum [redacted] samples should be collected on the same day.

Abbreviations: C = cycle; D = day; [redacted] EOT = end of treatment; PD = pharmacodynamics.

5.7 [redacted] Biomarker Assessments

5.7.1 Peripheral Blood Markers

[redacted]

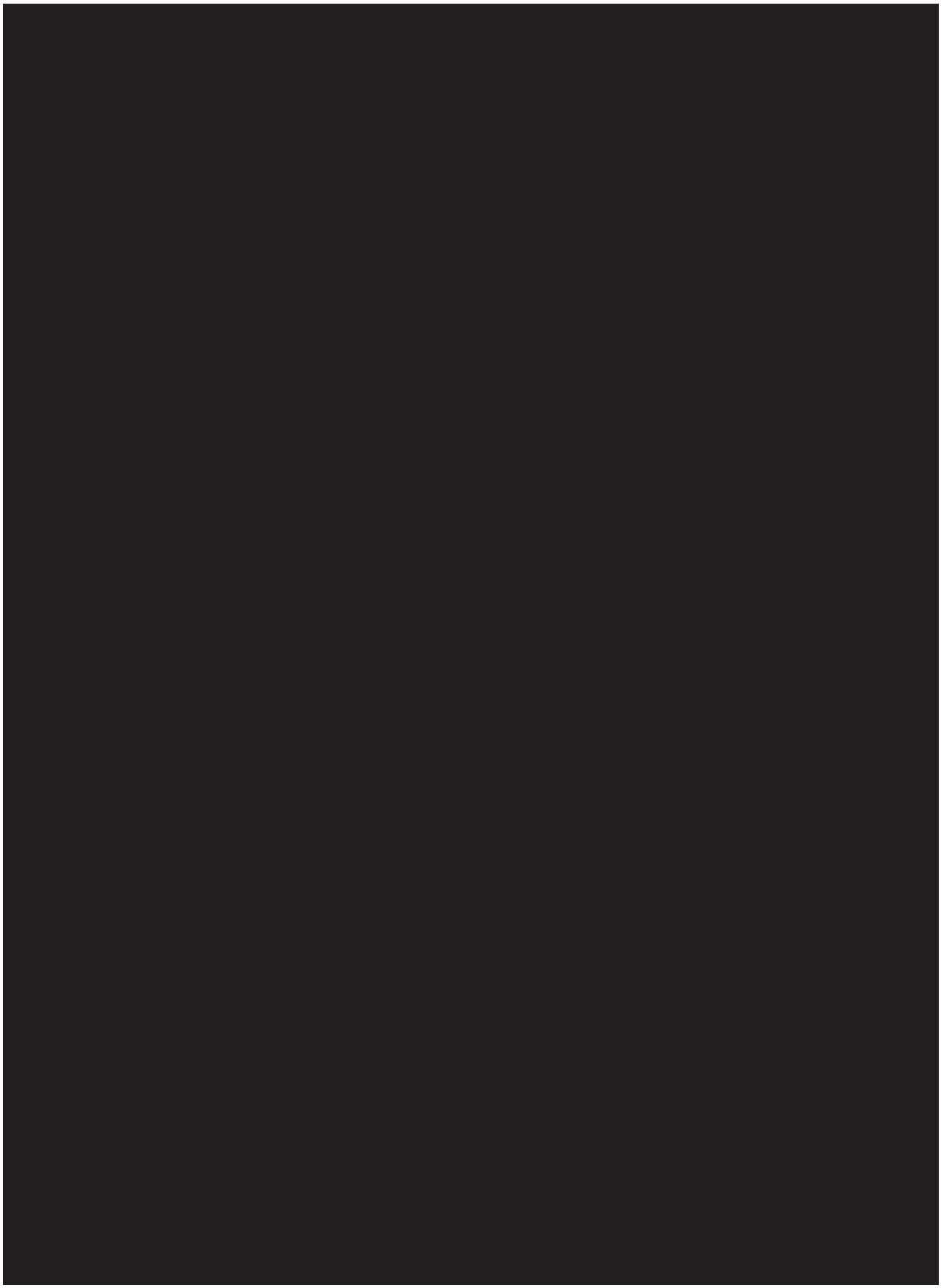
5.7.1.2 Serum [redacted] for Kynurenine and Related Metabolites

Serum [redacted] will be collected from all subjects at time points as indicated in Table 5.6-1, Table 5.6-2, and Table 5.6-3.

[redacted]

Levels of kynurenine, tryptophan, and related metabolites in serum will be determined by LC-MS analysis. Serum levels will be measured on serum frozen after collection from subjects. [redacted]

[redacted]



5.7.2 Tissue Markers from Fresh Tumor Biopsies

[redacted] With Amendment 14, all subjects in Parts 1 and 3 (as well as subjects in other parts without archival tissue meeting the requirements above) will be required to undergo mandatory pre-treatment biopsies. All subjects will be required to undergo an on-treatment biopsy at acceptable clinical risk as judged by the investigator. Please notify the BMS Medical Monitor if biopsy on-treatment may pose unacceptable clinical risk, or if tumor at the time of on-treatment biopsy is not accessible for sampling.

An optional specimen (not mandatory) at the time of disease progression or during another clinically meaningful event (eg, response or AE) may be collected.

Where possible, biopsied lesions should be distinct from index lesions being evaluated for radiological response. Biopsies may be excisional, incisional, or core needle. Excisional biopsies are strongly encouraged where feasible. Biopsies from previously irradiated lesions are only suitable if they subsequently progressed. Baseline samples may be obtained at any time following other screening procedures and prior to first dose of study drug (administered on Cycle 0 Day 1 in Part 1 or Cycle 1 Day 1 in Parts 2 and 3). In limited circumstances, recent fresh samples (frozen and FFPE) obtained prior to start of screening that meet biomarker requirements of the study as determined by the Study Director or Medical Monitor may be substituted for fresh biopsies, after permission from the Study Director or Medical Monitor is obtained. Cycle 1 Day 15 specimens may be obtained within a collection window of Cycle 1 Day 15 through Cycle 1 Day 28.

As described previously, complete instructions on the collection, processing, handling, and shipment of all biomarker specimens will be provided in a separate procedure manual. Please refer to this manual for information pertaining to the collection and processing of tissue via biopsy or core needle. Collection procedures at baseline and on-treatment (and at progression) should be completed on a single, appropriately accessible lesion, when applicable. In the case that the lesion sampled at baseline is no longer accessible or within acceptable clinical risk to re-biopsy during study (at Cycle 1 Day 15 or at progression), tissue from alternative lesion(s) may be obtained. This should be documented. Immediate confirmation for presence of viable tumor cells from collected tissue samples is strongly recommended. If adequate tissue is not obtained following initial passages of the needle, repeat passages may be required.

Subjects whose baseline or on-treatment biopsy yields inadequate tissue quantity or quality (lack of tumor) will be allowed to continue in the study [redacted]

[redacted] If tissue obtained from a large proportion of subjects is deemed inadequate for testing (eg, possesses low tumor cell content), additional subjects may be enrolled in an attempt to obtain tissue specimens better-suited for testing.

5.7.2.1 Tumor Kynurenine and Related Metabolites

Tumor levels of kynurenine, tryptophan, and related metabolites will be measured in fresh frozen tumor biopsies collected at baseline and on treatment. Kynurenine, tryptophan, and related metabolites will be assessed by LC-MS methods. On-treatment reduction in tumor kynurenine level is the predicted effect of IDO1 inhibition.

[redacted]

[redacted]

5.7.3 Tissue Markers from Archived Tumor Samples

Submission of baseline tumor tissue sample is mandatory from all patients. Tumor tissue samples at baseline should be either archival tumor FFPE, FFPE slides and/or fresh biopsy in FFPE block - specified with cohort. One FFPE block of < 1 year old or 20 slides (fewer slides may be acceptable with the approval of the medical monitor, but generally 15 will be required) of less than 4 months old will be requested from patients with no mandatory fresh biopsy requirement at baseline; archival samples from subjects in Parts 1 and 3 are not subject to these time limitations as these subjects will also undergo fresh pretreatment biopsies. These specimens will be submitted for central PD-L1 immunohistochemistry (IHC) in melanoma and NSCLC patients. The pre-treatment tumor samples must be a core biopsy, punch biopsy, excisional biopsy, or surgical specimen. Fine needle aspirates or other cytology specimens are insufficient for enrollment. Tumor samples obtained from bone lesion are not acceptable.

Molecular characterization of archival specimens will be similar to the characterizations described above (IHC [redacted]) but are likely to focus on the expression of PD-L1 [redacted] as candidate markers associated with response to combination therapy. [redacted]

Note that HPV status, a known prognostic factor for cervical cancer and SCCHN, will be monitored via CRF. When HPV status is unknown for cervical or SCCHN (oropharyngeal primary location) cancer subjects, HPV status (and type) may be assessed/confirmed retrospectively using archival and/or fresh specimens. Analyses may include p16 IHC and/or HPV detection methods such as, but not limited to, in situ hybridization and PCR-based techniques.

5.8 Outcomes Research Assessments

Not applicable.

[redacted]

[redacted]

6 ADVERSE EVENTS

An ***AE*** is defined as any new untoward medical occurrence or worsening of a pre-existing 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 AEs. The causal relationship can be 1 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.

AEs can be spontaneously reported or elicited during open-ended questioning, examination, or evaluation of a subject. (In order to prevent reporting bias, subjects should not be questioned regarding the specific occurrence of 1 or more AEs.)

6.1 Serious Adverse Events

An ***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 1 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 DILI is also considered an important medical event (see Section 6.7 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 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 drug (eg, death is an endpoint; if death occurred due to anaphylaxis, anaphylaxis must be reported) should be reported as an 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 colorectaloscopy)
- 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 IB represent the Reference Safety Information to determine expectedness of SAEs 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 100 days of discontinuation of dosing and for 30 days post discontinuation of study drug for subjects not receiving combination

therapy. If applicable, SAEs must be collected that relate to any later protocol-specified procedure (eg, a follow-up skin biopsy).

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

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

SAE Email Address: Refer to Contact Information list.

SAE Facsimile Number: Refer to Contact Information list.

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

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

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

If an ongoing SAE changes in its intensity or relationship to study drug or if new information becomes available, the SAE report must be updated and submitted within 24 hours to BMS (or designee) using the same procedure used for transmitting the initial SAE report.

All SAEs must be followed to resolution or stabilization.

6.2 Nonserious Adverse Events

A ***nonserious AE*** is an AE not classified as SAE.

6.2.1 Nonserious Adverse Event Collection and Reporting

The collection of nonserious AE information should begin at initiation of study drug. Nonserious AE information should also be collected from the start of a placebo lead-in period or other observational period intended to establish a baseline status for the 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 Adverse Events of Special Interest

Adverse events of special interest (AEOSI) have been defined for this protocol which require expedited reporting by the investigator of these adverse events to BMS. These are:

- Hemophagocytic lymphohistiocytosis (HLH; also known as histiocytosis haematophagic)
- Drug reaction with eosinophilia and systemic symptoms (DRESS) syndrome

These AEOSI, whether related or not related to study drug, must be reported to BMS or designee within 24 hours of awareness of the event. These AEOSI are medically important events and are therefore considered SAEs. The reporting system for SAEs should be used (see Section 6.1.1).

Both HLH and DRESS syndrome may both pose diagnostic challenges due to varying clinical manifestations and signs and symptoms that may overlap with other clinical events. To assist investigators in identifying constellations of clinical symptoms that may be consistent with one of these diagnoses, standardized scoring criteria are provided in Appendix 12. Formal evaluation and documentation of diagnostic scores based on these systems is not required; investigators should use their best clinical judgement as informed by these provided criteria to determine if a subject has experienced one of these AEOSI.

6.4 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 possible, the clinical rather than laboratory term would be used by the reporting investigator (eg, anemia versus low hemoglobin value).

6.5 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 + 30 days after nivolumab administration (for a total of 23 weeks post-treatment

completion), the investigator must immediately notify the BMS Medical Monitor/designee of this event and complete and forward a Pregnancy Surveillance Form to the BMS designee within 24 hours of awareness of the event and in accordance with SAE reporting procedures described in Section 6.1.1.

In most cases, the study drug will be permanently discontinued in an appropriate manner (eg, dose tapering if necessary for subject safety).

If the investigator determines a possible favorable benefit/risk ratio that warrants continuation of study treatment, or re-initiation of study treatment, a discussion between the investigator and the BMS Medical Monitor/designee must occur. If, for whatever reason, the pregnancy has ended, confirmed by negative serum pregnancy test, treatment may be resumed (at least 3 weeks and not greater than 6 weeks after the pregnancy has ended), following approvals of subject /sponsor /IRB/EC, as applicable.

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 subject should be reported to BMS. Information on this pregnancy will be collected on the Pregnancy Surveillance Form.

6.6 Overdose

An overdose is defined as the accidental or intentional administration of any dose of a product that is considered both excessive and medically important. Overdoses meeting the regulatory definition of SAE must be reported as an SAE (see Section 6.1.1 for reporting details).

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

1) Contact the Medical Monitor/designee immediately
2) Closely monitor the subject for AEs/SAEs and laboratory abnormalities
3) Document the quantity of the excess dose as well as the duration of the overdosing in the CRF.

Decisions regarding dose interruptions or modifications will be made by the investigator in consultation with the Medical Monitor/designee based on the clinical evaluation of the subject.

6.7 Potential Drug-induced Liver Injury

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

Potential DILI is defined as:

1) Aminotransaminases (ALT or AST) elevation > 3 times ULN

   AND

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

   AND

3) No other immediately apparent possible causes of aminotransaminases 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 or biliary obstruction caused by tumor.

6.8 Other Safety Considerations

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

7 DATA MONITORING COMMITTEE AND OTHER EXTERNAL COMMITTEES

Not applicable.

8 STATISTICAL CONSIDERATIONS

8.1 Sample Size Determination

8.1.1 Dose Escalation (Part 1)

As a Phase 1 dose escalation trial, the sample size at each dose in these arms depends on observed toxicity and posterior inference. For BMS-986205 in combination with nivolumab (with BMS-986205 lead-in), approximately 30 subjects are expected to be treated during the dose escalation phase. Initially, approximately 3 subjects will be treated at the starting dose levels of BMS-986205 in combination with nivolumab. Due to the potential for early discontinuation, an additional subject(s) may be enrolled to ensure approximately 3 evaluable subjects at each dose level.

During the dose escalation phase, once a dose level has been decided, a set of approximately 3 subjects will be treated at that specified dose level. Cohort-tolerability assessment and subsequent dose recommendation will occur when 2 evaluable subjects within a set have completed a 6-week DLT evaluation period (2 weeks of monotherapy lead-in plus 4 weeks of combination treatment). If the potential DLT occurring in any third evaluable subject regarding the specific dose level does not influence the dose recommendation by BLRM (-Copula), the BLRM (-Copula)-recommended next dose level may proceed without waiting for the third subject to complete the corresponding DLT observation period, after discussion and agreement between sponsor and investigators. Continuous re-assessment of dose recommendation by BLRM in the lead-in phase and BLRM-Copula in the combination phase will be carried out at each dose level.

Additional increments of approximately 3 evaluable subjects will be treated in recommended dose levels per BLRM-copula model during the dose escalation phase. At least 6 DLT-evaluable subjects will be treated in the selected dose cohort(s) chosen for expansion. Due to the BMS-986205 lead-in period, more than 3 subjects per cohort may be treated per BMS-986205 dose level considering potential DLTs happened within lead-in period.

Up to 12 additional subjects may be treated at any dose level below the estimated MTD/MAD for further evaluation of safety and pharmacodynamic/PK parameters as required.

8.1.2 Dose Expansion (Part 2)

Dose expansions of BMS-986205 administered in combination with nivolumab in 8 disease-restricted populations, and subjects in 1 mixed cohort of additional signal-seeking tumor types will be included. The following 7 tumor-specific cohorts will be classified into 3 categories according to different sample size modeling settings: SCCHN and bladder cancer in a group; cervical cancer, DLBCL, melanoma with prior anti-PD-(L)1 therapy, NSCLC with prior anti-PD-(L)1 therapy, and pancreatic cancer in a different group; and melanoma with prior anti-PD-(L)1 and anti-CTLA-4 therapy in another group. The two last groups will be analyzed using a Simon 2-stage design.

A Simon 2-stage (optimal) design will be used as a guide for many of the tumor-specific cohorts (see below for exceptions). The 2-stage design with a reasonable FPR and FNR, based on assumptions of true (target) and historic ORR for each indication, will provide guidance for the total sample size for these cohorts. The sample size and operational characteristics of using a 2-stage design are provided in Table 8.1.2-1, although not used for hypothesis testing. For example, guided by, initially, a minimum of 10 subjects for the SCCHN tumor type will be treated in Stage 1 for an initial evaluation of efficacy. Assuming the true response rate is 50% when treated with BMS-986205 in combination with nivolumab, if there are 2 or fewer responses in 10 treated subjects, the cohort would likely not be considered as efficacious. The probability of early stopping for futility is approximately 53% in this case if in fact the treatment is inefficacious. The totality of efficacy data and response profile will be considered while making the decision to terminate. Enrollment will be continued during initial efficacy evaluation (ie, with the indicated number of subjects at Stage 1) to ensure that additional subjects are enrolled to account for unexpected trial impact, such as response non-evaluable subjects due to early drop-out, design parameter change (eg, historical rate update), and so on.

For an expansion cohort of approximately 35 subjects in the cervical, melanoma: prior anti-PD-(L)1, pancreatic, NSCLC: prior anti-PD-(L)1, and DLBCL cohorts, and an assumed true response rate of 30%, there is a 94% chance of observing at least 7 responses (in other words, the FNR is 6%). If the true response rate is only 10% rather than 30%, then there is a 6% chance that there will be at least 7 responses in 35 subjects (in other words, FPR is 6%). Also if 7 responses are observed (eg, 20% observed response rate), the lower bound of the 80% confidence interval (CI) for the ORR is 11% (higher than historical ORR of 10%). The CI is calculated using the Clopper-Pearson method.

For an expansion cohort of approximately 27 subjects in the bladder and SCCHN tumors and assumed true response rate of 50%, there is a 88% chance of observing at least 11 responses (in other words, the FNR is 12%). If the true response rate is only 25% rather than 50%, then there is a 5% chance that there will be at least 11 responses in 27 subjects (in other words, FPR is 5%). If 11 responses are observed (eg, 40% observed response rate), the lower limit of the 80% CI for the ORR is 28% (higher than historical ORR of 25%). The CI is calculated using the Clopper Pearson method.

For an expansion cohort of approximately 37 subjects with melanoma with prior anti-PD-(L)1 and anti-CTLA-4 therapy, and an assumed true response rate of 20%, there is a 85% chance of observing at least 5 responses (in other words, the FNR is 15%). If the true response rate is only 5% rather than 20%, then there is a 14% chance that there will be at least 5 responses in 37 subjects (in other words, FPR is 14%). Also, if 5 responses are observed (eg, 14% observed response rate), the lower bound of the 80% CI for the ORR is 7% (higher than historical ORR of 5%). The CI is calculated using the Clopper-Pearson method.

The Simon 2-stage design will not be used for the mixed cohort of additional signal-seeking tumor types in Part 2. Approximately 35 to 40 subjects will be enrolled to allow for the exploration of early efficacy signals seen during the dose escalation portion of the trial as well as potential signals arising from ongoing trials of other IDO1 inhibitors in combination with anti-PD-(L)1. A 2-stage design will also not be utilized for the RCC and I-O naïve melanoma and NSCLC cohorts, as nivolumab is already an established standard of care in these settings. Approximately 40 subjects will be enrolled in each of these cohorts to allow for the exploration of early efficacy signals of BMS-986205 in combination with nivolumab.

Approximately 16 melanoma I-O naïve BRAF mutant subjects' post-BRAF inhibitor therapy will be randomized into 2 cohorts and will either be treated with nivolumab or nivolumab in combination with BMS-986205, but will not be used for formal statistical comparison.

Table 8.1.2-1: Dose Expansion: Example of Simon 2-stage Design Characteristics

Expansion Cohort	Historic ORR (%)	Target ORR (%)	Stage 1 /Total N	Stage 1 Responses Futility Boundary	Alpha/ Power (%)	Probability of Early Stopping (%)
Cervical, Melanoma: Prior anti-PD-(L)1, Pancreatic NSCLC: Prior anti-PD-(L)1, and DLBCL	10	30	12/35	1	10/90	66
Bladder and SCCHN	25	50	10/27	2	10/90	53
Melanoma: Prior anti-PD-(L)1 and anti-CTLA-4	5	20	12/37	0	10/90	54

*Note: For the melanoma, prior anti-PD-(L)1, and prior anti-PD-(L)-1/anti-CTLA-4 cohorts, the analysis will be focused on approximately 35 subjects who are BRAF (wild-type) WT.

Abbreviations: CTLA-4 = cytotoxic T lymphocyte-associated antigen 4; DLBCL = diffuse large B cell lymphoma; I-O = immuno-oncology; NSCLC = non-small cell lung cancer; PD-1 = programmed cell death; PD-L1 = programmed death receptor-ligand 1; PD-(L)1 = either PD-1 or PD-L1; ORR = objective response rate; SCCHN = squamous cell carcinoma of the head and neck..

8.1.3 Combination with Both Nivolumab and Ipilimumab (Part 3)

The combination of BMS-986205 with nivolumab and ipilimumab in Part 3 will be evaluated in 2 parts, the safety evaluation phase and the cohort expansion phase of the combination in melanoma, NSCLC, and bladder cancer as well as a mixed tumor type cohort.

All safety cohorts will begin with an assessment of safety and tolerability of the triplet combination regimen in a limited number of subjects, including a sentinel subject. As described in Section 3.1.1.2, the NSCLC and melanoma regimen cohorts will begin enrollment first, followed by the bladder regimen cohort once safety and tolerability has been established in either NSCLC or melanoma. Initially, approximately 3 subjects will be treated at the selected dose combination of BMS-986205 with nivolumab and ipilimumab. Due to the potential for early discontinuation, an additional subject(s) may be enrolled to ensure approximately 3 DLT evaluable subjects. Initial safety assessment to allow enrollment in the bladder safety cohort will occur when at least 2 evaluable subjects in either the NSCLC or melanoma safety cohorts have completed a 6-week DLT evaluation period (see Section 4.5.1 for criteria for DLTs). In the melanoma and NSCLC safety evaluation cohorts, if the potential DLT occurring in any third evaluable subject regarding the specific dose combination does not influence the recommendation by BLRM (-Copula) to open enrollment in the bladder safety cohort, then the bladder safety cohort may proceed with enrollment without waiting for the third subject to complete the corresponding DLT observation period. After the initial subjects in each treatment regimen are evaluated, additional increments of approximately 3 to 6 subjects will be treated in the same safety cohort as per BLRM-copula model recommendation that the dose combination is safe. At least 6 DLT-evaluable subjects will be treated and assessed in the selected dosing regimen safety cohort before starting enrollment in the expansion cohort for that tumor type/regimen. Up to 12 DLT-evaluable subjects in total may be treated in the safety evaluation cohort for each tumor type at the dose selected for expansion cohorts for evaluation of safety and pharmacodynamic/PK parameters as required. BLRM (-copula) will be used to monitor the safety of the triplet dose combination on an ongoing basis. If, at any time, the aggregate rate of treatment related toxicities meeting DLT criteria within an individual treatment tumor type/regimen exceeds 33% across all subjects treated in the safety evaluation and dose expansion cohorts, the findings will be discussed and further enrollment may be interrupted. At that time, depending on the nature and grade of the toxicities and after assessing the risk/benefit ratio, a new dose(s) of BMS 986205 for subjects within that dosing regimen may be initiated at a previously tested lower dose level or at a dose level intermediate to previously tested lower dose levels.

Once the initial safety and tolerability has been established independently for each regimen based on safety cohort evaluations, enrollment will begin of subjects into expansion cohorts for further evaluation of safety and tolerability, as well as preliminary evaluation of anti-tumor

efficacy. In the expansion cohorts, BMS 986205 will be administered at a dose determined to be tolerable in combination with each nivolumab and ipilimumab regimen. Each BMS-986205 and nivolumab/ipilimumab combination regimen will be evaluated in tumor-specific cohorts based on the tumor type evaluated in the safety cohorts. The Ipi 1Q8 regimen will also be evaluated in a mixed tumor-type cohorts which may incorporate tumor types evaluated in Part 2 Dose Escalation. This 40 subject cohort is used to obtain preliminary safety, PK, and PD data for the triplet combination in other tumor types.

As all subjects in the melanoma, NSCLC, and bladder disease-specific cohorts will be receiving agents (nivolumab and ipilimumab) with known efficacy, a single-stage design will be utilized for each of these tumor types. Approximately 40 subjects will be enrolled in each of the following cohorts: melanoma PD-L1 positive, melanoma PD-L1 negative, NSCLC PD-L1 positive, NSCLC PD-L1 negative and bladder, mixed tumor type to allow for the exploration of early efficacy signals of BMS-986205 in combination with both nivolumab and ipilimumab in relevant subpopulations. In each NSCLC expansion cohort, approximately 10 subjects will be IO-treatment naive, 25 will be treatment-naive, and 5 IO-therapy experienced. In the melanoma cohorts, approximately 35 will be treatment-naïve in the advanced setting and 5 will be IO-therapy experienced in each cohort. In the bladder expansion cohort in Part 3, at least 30 subjects will be IO-therapy naive.

The anti-tumor activity of the expansion cohorts will be continuously monitored in all subjects who are evaluable for response using the measurements described in Section 8.3.1. In the NSCLC cohort, 16 of 25 responses for the treatment naïve subjects would result in 80% CIs for an ORR that is strictly higher than the historical rate of 45.3%.[60] In the melanoma cohort, 22 of 35 responses for the treatment naïve subjects would result in 80% CIs for ORRs that are strictly higher than the historical rates of 580.0%.[28] In the bladder cohort, 16 of 30 responses would result in 80% CI for ORR that is strictly higher than the historical rate of 38.5%.[61] The CIs are calculated using the Clopper-Pearson method.

8.2 Populations for Analyses

1) All Enrolled Subjects: All subjects who have signed an ICF and are registered into the IVRS.
2) All Treated Subjects: All subjects who received at least 1 dose of study drug.
3) The PK dataset includes all available concentration-time data from the subjects who received any BMS-986205 or nivolumab or ipilimumab.
4) The Immunogenicity dataset consists of all available immunogenicity data from the subjects who receive nivolumab or ipilimumab and have a baseline and at least 1 post-treatment immunogenicity measurement.
5) The Biomarker dataset includes all available biomarker data from the subjects who receive any study drug.

Analyses of safety, extent of exposure, biomarkers, PK, efficacy, and pharmacodynamics will be based on all treated subjects.

8.3 Endpoints

8.3.1 Primary Endpoint(s)

- The primary objective of this study is to establish safety, tolerability, and the MTD/MAD/alternate dose. The assessment of safety will be based on the incidence of AEs, SAEs, AEs leading to discontinuation, and deaths. In addition, clinical laboratory test abnormalities will be examined. AEs and laboratory values will be graded according to the NCI CTCAE v4.03.
- The co-primary objective, anti-tumor activity of BMS-986205 in combination with nivolumab in Part 2 (dose expansion) and BMS-986205 in combination with both nivolumab and ipilimumab in Part 3, will be measured by ORR, DoR, and PFSR based on RECIST v1.1 for solid tumors or IWG for blood tumor. For Parts 1 and 2, disease assessment with CT and/or MRI as appropriate will be performed at baseline, end of Cycle 2, and every 8 weeks. For Part 3, in the melanoma cohorts, the first tumor assessment will occur at Week 12 (± 1 week); subsequent imaging will be every 8 weeks thereafter during the treatment period; for NSCLC, imaging assessments will occur every 6 weeks during the treatment period; for bladder, imaging assessments will occur every 6 weeks during the treatment period up to 24 weeks, and then occur every 12 weeks thereafter during the treatment period. For all study parts, assessments continue every 12 weeks for the first year after the EOT visit, and then every 6 months thereafter, up to 2 years following the EOT visit until disease progression per RECIST v1.1 or IWG, or until confirmed disease progression for subjects treated beyond progression (defined as an additional 10% or greater increase in tumor burden volume from time of initial progression including all target lesions and new measurable lesions), at the completion of follow-up, or until subjects withdraw from the study.
- Best overall response (BOR) is defined as the best response designation over the study as a whole, recorded between the dates of first dose until the last tumor assessment prior to subsequent therapy. CR or PR determinations included in the BOR assessment must be confirmed by a second scan performed no less than 4 weeks after the criteria for response are first met. For those subjects who have surgical resection, only presurgical tumor assessments will be considered in the determination of BOR.
- ORR is defined as the proportion of all treated subjects whose BOR is either a CR or PR.
- DoR, computed for all treated subjects with a BOR of CR or PR, is defined as the time between the date of first response and the date of disease progression or death, whichever occurs first.
- PFSR at 24 weeks, 1 year, and 2 years: The proportion of treated subjects remaining progression free and surviving at 24 weeks, 1 year, and 2 years if sufficient data are available. The proportion will be calculated by the Kaplan-Meier estimate, which takes into account censored data.

8.3.2 Secondary Endpoint(s)

8.3.2.1 Pharmacokinetics

For the first secondary objective (PK), selected BMS-986205 parameters, such as Cmax, Tmax, AUC(TAU), Ctrough, CLT/F, CLR/F, Vss/F, AI, %UR24, [redacted] from concentration-time

data during BMS-986205 monotherapy and concentrations at end of infusion and Ctrough during combination treatment. Concentrations at end of infusion and Ctrough for nivolumab and ipilimumab (where applicable) will be assessed during combination treatment (see Section 5.5).

8.3.2.2 Pharmacodynamics

The second secondary objective of pharmacodynamics, assessed by change from baseline for serum kynurenine and percent change from baseline, will be summarized.

8.3.2.3 Efficacy

The BOR, ORR, DoR, and PFS rates at pre-specified time points based on RECIST v1.1 and IWG will be the secondary efficacy endpoints for dose escalation and clinical pharmacology substudies.

8.3.2.4 Immunogenicity

The third secondary objective of immunogenicity will be assessed by the frequency of positive anti-drug antibody (ADA) to nivolumab or ipilimumab.

8.4 Analyses

8.4.1 Demographics and Baseline Characteristics

Frequency distributions of gender and race will be tabulated. Summary statistics for age, body weight, height, and body mass index will be tabulated.

8.4.2 Efficacy Analyses

Listing of tumor measurements will be provided by subject and study day in each arm and dose level. Individual subject's BOR will be listed based on RECIST v1.1 for solid tumors and IWG for blood tumor.

To describe the anti-tumor activity of BMS-986205 in combination with nivolumab and in combination with both nivolumab and ipilimumab, ORR will be calculated. ORR and corresponding 2-sided exact 95% CI by the Clopper and Pearson method will be provided by treatment, and/or dose level and tumor type (if appropriate). Median DoR and corresponding

2-sided 95% CI may be reported by treatment, and/or dose level and tumor type (if appropriate). DoR will be analyzed using the Kaplan-Meier method.

In addition, PFSR, the probability of a subject remaining progression free or surviving to 24 weeks, will be estimated by the Kaplan-Meier methodology, by treatment, tumor type and dose level. The corresponding 90% CI will be derived based on the Greenwood formula.

[redacted]

8.4.3 Safety Analyses

All recorded AEs will be listed and tabulated by system organ class, preferred term, treatment arm, and dose level and coded according to the most current version of MedDRA. 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.

8.4.4 Pharmacokinetic Analyses

All individual PK parameters will be listed for each analytic including any exclusions and reasons for exclusion from summaries. Summary statistics will be tabulated for each PK parameter by treatment. Geometric means and coefficients of variation will be presented for Cmax, AUC(TAU), Ctrough, CLT/F, and CLR/F, after multiple-dose PK. Medians and ranges will be presented for Tmax. Means and standard deviations will be presented for all other PK parameters.

BMS-986205 dose dependency will be assessed in dose escalation lead-in. To describe the dependency on dose of BMS-986205, scatter plots of Cmax and AUC(TAU) versus dose may be provided for each day measured. [redacted]

Urinary recovery data of BMS-986205 will be listed if available. Cumulative amount and cumulative percent recovered per interval will be summarized. Plots of individual cumulative percent of dose recovered in urine versus end of interval time will be provided. Mean plots of cumulative percent of dose recovered in urine versus end of interval time will also be provided.

8.4.5 Biomarker Analyses

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

[redacted]

8.4.7 Outcomes Research Analyses

Not applicable.

8.4.8 Other Analyses

Not applicable.

8.4.9 Immunogenicity Analyses

A listing of all available immunogenicity data will be provided by treatment, dose, and immunogenicity status. The frequency of subjects with a baseline and/or at least 1 positive ADA assessment of nivolumab and/or ipilimumab will be summarized.

8.4.10 ECG Analyses

Summary statistics will be presented for each ECG parameter (heart rate, QTcF, PR, and QRS) and the corresponding changes from baseline by dose and time points. Scatter plots of change from baseline values in each ECG parameter versus the nearest corresponding plasma drug concentrations will be presented. The plot of ΔQTcF versus drug concentrations will include the estimated linear regression taken from the results of fitting a random intercept and slope model (mixed model). The frequency of subjects' maximum recorded postdose QTcF, PR, QRS, and ΔQTcF will be tabulated by treatment and summarized.

[redacted] Additional ECG data and time matched concentrations may be pooled from other studies to perform an integrated analysis. The results of the analysis will be reported separately.

8.5 Interim Analyses

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

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

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

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

In addition, the study may be evaluated by 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, 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

BMS 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 procedures, 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, and 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 the investigational product. 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
- retained samples for BA/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 EDC 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. 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 EDC 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 EDC 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:

- External principal investigator designated at protocol development
- National coordinating investigator
- Study steering committee chair or their designee
- Subject recruitment (eg, among the top quartile of enrollers)
- Involvement in trial design
- Regional representation (eg, among top quartile of enrollers from a specified region or country)
- Other criteria (as determined by the study team)

For this single site protocol, the principal investigator for the site will sign the clinical study report.

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 is defined as complete avoidance of heterosexual intercourse and 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, postovulation methods) or withdrawal, which are not acceptable methods of contraception. Women must continue to have pregnancy tests. Acceptable alternate methods of highly or less effective contraceptive methods must be discussed in the event that the subject chooses to forego complete abstinence.
[redacted]	

11 LIST OF ABBREVIATIONS

Term	Definition
ADA	anti-drug antibody
ADME	absorption, distribution, metabolism, and excretion
AE	adverse event
AI	accumulation index
AJCC	American Joint Committee on Cancer
ALK	anaplastic lymphoma kinase
ALT	alanine aminotransferase
APC	antigen-presenting cell
AST	aspartate aminotransferase
AUC	area under the concentration-time curve
AUC(INF)	area under the concentration-time curve from time zero extrapolated to infinite time
AUC(0-24h)	area under the concentration-time curve from time zero to 24 hours postdose
AUC(0-T)	area under the concentration-time curve from time zero to the time of the last quantifiable concentration
AUC(TAU)	area under the concentration-time curve in 1 dosing interval
AUEC	area under the effect curve
BCRP	breast cancer resistance protein
BDC	bile duct-cannulated
BLRM	Bayesian Logistic Regression Method
BMS	Bristol-Myers Squibb
BMS EDC	Bristol-Myers Squibb Electronic Data Capture
BOR	best overall response
BSEP	bile salt export pump
BUN	blood urea nitrogen
C24	observed plasma concentration at 24 hours
Cavgss	average steady-state concentrations
CBC	complete blood count
CI	confidence interval

Term	Definition
CrCl	creatinine clearance
CLR/F	apparent renal clearance
CLT/F (or CLT)	apparent total body clearance
Cmax	maximum observed plasma concentration
Cmin1	trough concentration after the first dose
Cmaxss	steady-state peak concentration
Cminss	trough steady-state concentration
CNS	central nervous system
CR	complete response
CRC	colorectal cancer
CRF	case report form
CRP	C-reactive protein
CT	computed tomography
CTA	clinical trial agreement
CTLA-4	cytotoxic T lymphocyte-associated antigen 4
Ctrough	trough observed plasma concentration at the end of the dosing interval
%CV	coefficient of variation
[redacted]	[redacted]
CYP	cytochrome P450
DL-1	dose level-1
DDI	drug-drug interaction
DILI	drug-induced liver injury
DLBCL	diffuse large B-cell lymphoma
DLT	dose limiting toxicity
DoR	duration of response
[redacted]	[redacted]
EC50	half maximal effective concentration
ECG	electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	electronic case report form

Term	Definition
EDC	electronic data capture
EGFR	epidermal growth factor receptor
[redacted]	[redacted]
EMH	extramedullary hematopoiesis
EOI	end of infusion
EOT	end of treatment
EU	European Union
FDA	Food and Drug Administration
FNR	false negative rate
FPR	false positive rate
FSH	follicle stimulating hormone
FU	follow-up
GCP	Good Clinical Practice
GGT	gamma-glutamyl transferase
GM	geometric mean
hCG	human chorionic gonadotropin
HDPE	high-density polyethylene
HEK293	human embryonic kidney 293
HED	human equivalent dose
hERG	human ether-à-go-go-related gene
HIV	human immunodeficiency virus
HL	Hodgkin's lymphoma
HNSTD	highest non-severely toxic dose
HPV	human papillomavirus
hWB	human whole blood
IC50	half maximal inhibitory concentration
ICF	informed consent form
IDO1	indoleamine 2,3-dioxygenase 1
HRT	hormone replacement therapy
IB	Investigator's Brochure

Term	Definition
ICH	International Conference on Harmonisation
IEC	Independent Ethics Committee
IFNγ	interferon-gamma
IgG4	immunoglobulin G4
IHC	Immunohistochemistry
IMP	investigational medicinal products
I-O	immuno-oncology
IP	investigational product
IRB	Institutional Review Board
IUD	intrauterine devices
IV	intravenous
IVRS	Interactive Voice Response System
IWG	International Working Group
K_I	inhibitor concentration corresponding to the half-maximal rate of inactivation
K_d	dissociation constant
LC-MS	liquid chromatography-mass spectrometry
LDH	lactate dehydrogenase
LFT	liver function test
MAD	maximum administered dose
MATE1	multidrug and toxin extrusion 1
MCV	mean corpuscular volume
MCHC	mean corpuscular hemoglobin concentration
MedDRA	Medical Dictionary for Regulatory Activities
[redacted]	[redacted]
MLR	mixed lymphocyte reaction
MM	Medical Monitor
[redacted]	[redacted]
[redacted]	[redacted]

Term	Definition
[redacted]	[redacted]
[redacted]	[redacted]
MRI	magnetic resonance imaging
mRNA	messenger ribonucleic acid
MSI	Microsatellite Instability
MSI-H	Microsatellite Instability High
MTD	maximum tolerated dose
NA	not applicable
NAFLD	nonalcoholic fatty liver disease
NCI CTCAE	National Cancer Institute Common Terminology Criteria for Adverse Events
NHL	non-Hodgkin's lymphoma
[redacted]	[redacted]
NOAEL	no-observed adverse effect level
NSCLC	non-small cell lung cancer
OATP	organic anion transporting polypeptide
OCT1	organic cation transporting polypeptide
ORR	objective response rate
[redacted]	[redacted]
Pc	permeability coefficient
PCR	polymerase chain reaction
PD	progressive disease
PD-1	programmed cell death-1
PD-L1	programmed death receptor-ligand 1
PD-(L)1	either PD-1 or PD-L1
PE	physical examination
PET	positron emission tomography
PFSR	progression-free survival rate
P-gp	P-glycoprotein
PI	principal investigator

Term	Definition
PID	subject identification number
PK	pharmacokinetic(s)
PPK	population pharmacokinetics
PR	partial response
PT	prothrombin time
PTT	partial thromboplastin time
Q2W	every 2 weeks
Q4W	every 4 weeks
QD	quaque die, once daily
QTcF	QT interval corrected for heart rate using Fridericia's formula
RBC	red blood cell
RECIST	Response Evaluation Criteria In Solid Tumors
RCC	renal cell carcinoma
RNA	ribonucleic acid
[redacted]	[redacted]
SAE	serious adverse event
SD	stable disease
SCCHN	squamous cell carcinoma of the head and neck
[redacted]	[redacted]
STD10	severe toxicity to 10%
TCGA	The Cancer Genome Atlas
T-HALF	apparent terminal phase half-life
Tmax	time of maximum observed plasma concentration
Treg	regulatory T cells
TSH	thyroid-stimulating hormone
ULN	upper limit of normal
%UR24	Percent urinary recovery over 24 hours
US	United States
Vss/F (or Vss)	apparent volume of distribution at steady state

Term	Definition
Vz/F (or Vz)	volume of distribution of terminal phase (if IV and if multi-exponential decline)
WBC	white blood cell
WOCBP	women of childbearing potential

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APPENDIX 1 STATISTICAL METHODOLOGY

Statistical Details for Bayesian Logistic Regression Model (BLRM and BLRM-Copula) and Priors for Dose Escalation and Safety Monitoring

1 MODEL SETUP FOR BMS-986205 LEAD-IN (MONOTHERAPY)

1.1 Monotherapy Methodology Description

An adaptive 2-parameter Bayesian Logistic Regression Model (BLRM) guided by the escalation with overdose control (EWOC) principle[1,2,3] will be used to guide the dose escalation of BMS-986205 alone in the lead-in phase for dose recommendation during dose escalation.

The BLRM will be fitted on the dose limiting toxicity (DLT) data for BMS-986205 within the 2 weeks lead-in throughout the dose escalation to model the dose-toxicity relationship of BMS-986205 in the lead-in phase.

The dose-toxicity relationships for BMS-986205 alone follow a logistic model as follows:

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

Note that the α_1 and β_1 parameters are assumed positive, and d_1^* is the reference dose for BMS-986205 (please refer to the meaning of α_1 and β_1 in Section 1.2.1 for detailed implementation).

1.2 Prior Specification for BMS-986205 Monotherapy

The Bayesian approach requires the specification of prior distributions for model parameters, which include parameters (α_1, β_1) for BMS-986205. The prior distributions for BMS-986205 single agent activity were derived using a weakly informative prior based on published indoleamine 2,3-dioxygenase (IDO) clinical trial data[4] as well as discussion with the Bristol-Myers Squibb (BMS) clinical team.

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

1.2.1 Prior Derivation for BMS-986205 Parameters ($log\ (\alpha_1), log\ (\beta_1)$)

A weakly informative prior will be used for parameters (α_1, β_1) for BMS-986205 to reflect the potential of different toxicity of BMS-986205 from historical IDO data and to allow for considerable prior uncertainty.

Further details are provided below.

Weakly Informative Prior

The median DLT rate at the reference dose (BMS-986205 at 800 mg QD) was assumed to be 30%, ie, mean ($\log(\alpha_1)$) = -0.847.

A doubling in dose was assumed to double the odds of DLT, ie, mean($\log(\beta_1)$) = 0.

The standard deviation of $\log(\alpha_1)$ was set to 0.722 using the following steps:

- Toxicity probability range was set to be [5%, 80%], then the toxicity interval would be logit(0.8)-logit(0.05) = 4.33.
- To cover 99.7% of the variance, the toxicity interval will cover 6*sd($\log(\alpha_1)$).

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

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

Table 1: Prior Distribution for Model Parameters for BMS-986205

Parameter	Means	Standard Deviations	Correlation
$\log(\alpha_1)$, $\log(\beta_1)$	(-0.847, 0)	(0.722, 1)	0

2 MODEL SETUP FOR BMS-986205 AND NIVOLUMAB COMBINATION

2.1 Methodology Description for Combination therapy

Toxicity profiles of both BMS-986205 monotherapy and nivolumab monotherapy will be incorporated to develop the combination model framework. A copula-type model will be utilized to cover all general combination cases, including additive and synergistic effects. The combination of 2 treatments will be explored using a Bayesian hierarchical model by utilizing the toxicity profiles of single agents as prior marginal profiles for the combination. The following copula-type model[5] will be used.

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

Where p_i is the pre-specified best guess toxicity probability for agent A, q_j is the pre-specified best guess toxicity probability for agent B, and m and n characterize the individual drug effect and γ characterizes drug-drug interactive effect.

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

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

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

Since only a fixed nivolumab dose (240 mg) will be used in BMS-986205 and nivolumab combination, this surface will be simplified into a 2-dimensional dose-toxicity curve. Posteriors for the corresponding 5 parameters (2 logistic regression parameters $[\alpha_1, \beta_1]$ for BMS-986205 and 2 logistic regression parameters for Nivolumab $[\alpha_2, \beta_2]$ as well as 1 interaction parameter for the copula-type model [γ, which will be discussed in detail in the following session]) will be fit into the in-house developed model, which implements the above described theoretical setup.

2.2 Priors Specification for Combination Studies

2.2.1 Prior for BMS-986205

Posterior information on ($\log(\alpha_1)$ and $\log(\beta_1)$) from the lead-in part of the study will be used as marginal BMS-986205 prior for combination with nivolumab. This prior information is not pre-specified and will be continuously updated when additional toxicity (DLT) information from the lead-in is available. In the simulation (see Section 2.4), the prior of BMS-986205 as described in Section 1.2.1(Table 1) is used for illustration purposes, as no real-time DLT data are available at this time.

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

Similar to BMS-986205 monotherapy in the lead-in phase, the logistic model for nivolumab is as follows:

$$logit(q_j) = log(\alpha_2) + \beta_2 log(^{d_{2j}}/_{d_2^*}) \text{ , where } \alpha_2,\ \beta_2\ > 0.$$

Note that the α_2 and β_2 parameters are assumed positive, and d_2^* is the reference dose for nivolumab.

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

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

First, a prior distribution for nivolumab was developed:

- The median DLT rate at the reference dose (3 mg/kg every 2 weeks) was assumed to be 10%, ie, mean ($\log(\alpha_2)$) = logit(1/10) = log(1/9) = -2.197.
- A doubling in dose was assumed to double odds of DLT, ie, mean($\log(\beta_2)$) = 0.
- The standard deviation of $\log(\alpha_2)$ was set to 2, and the standard deviation of $\log(\beta_2)$ to 1, which allows for considerable prior uncertainty for the dose-toxicity profile.
- The correlation between $\log(\alpha_2)$,and $\log(\beta_2)$ is assumed to be 0 (assuming independence of $\log(\alpha_2)$ and $\log(\beta_2)$).

- In addition, heterogeneity between the historical study and current study was incorporated using a meta-analytic predictive approach, by defining between-trial standard deviations τ_1 and τ_2 for $\log(\alpha_2)$ and $\log(\beta_2)$, respectively. The between-trial variability is assumed to be moderate. Therefore, τ_1 and τ_2 were set to follow a log-normal distribution with mean log(0.25) and log(0.125), respectively, with a common standard deviation log(2)/1.96.

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

Table 2: Data from Single Agent Nivolumab Study CA209003

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

Abbreviation: DLT = dose limiting toxicity.

Table 3: Prior Distribution for Model Parameters for Nivolumab

Parameter	Means	Standard Deviations	Correlation
$\log(\alpha_2)$, $\log(\beta_2)$	(-3.269, -0.152)	(1.186, 0.771)	-0.369

Note: Nivolumab prior information was based on mg/kg dosing instead of flat dosing. If real pharmacokinetic (PK) data from this study show difference from mg/kg assumption, the nivolumab prior will be revisited and modified accordingly.

2.2.3 Prior for Interaction Parameters for Joint Toxicity of BMS-986205 and Nivolumab Combination

A gamma prior distribution for the interaction parameter γ is derived to reflect the current uncertainty about the toxicity profile of the combination of BMS-986205 and nivolumab. Although no PK drug-drug interaction is expected, the possibility of significant positive interaction between BMS-986205 and nivolumab cannot be totally excluded. The interaction parameter γ was chosen accordingly but with a degree of uncertainty in order to allow for the possibility that the interaction may be positive or negative. Therefore, the following assumptions are made for the interaction parameter:

- γ follows a gamma distribution and with a mean centered at 1.1, which means the combination of 2 agents only has a little bit of synergistic effect.

- The 97.5 percentile of γ is log(3), ie, 3-fold increase in odds of DLT due to interaction over independence at the combination starting dose.

This assumes, a priori, that there is a small synergistic interaction but also allows for the potential of significant synergism of the toxic profiles. It also does not completely ignore the possibility of antagonism since we consider 40% prior probability that γ is less than 1.

2.3 Parameters for Dose Recommendation Decision for the Lead-in Phase and Combination Phase

Dose recommendation for BMS-986205 alone and in combination with nivoluamb will be based on inference from Bayesian posterior, and the probability that the true DLT rate for each dose lies in one of the following categories:

- [0,16%) under-dosing
- [16%,35%) targeted toxicity
- [35%,100%] excessive toxicity

Following the principle of EWOC, after gaining information of each cohort of subjects, the candidate doses are the ones fulfilling the overdose criterion that there is less than 35% chance of excessive toxicity. Only the candidate doses will be considered for the next dose decision by Investigators and BMS study personnel based on a synthesis of all relevant data available from all dose levels evaluated in the ongoing study.

Any information on the dose-DLT relationship generated by publicly available IDO clinical trial data as well as nivolumab prior data from Study CA209003 will be incorporated into the prior distribution before the first dose-escalation decision is made within this study in order to reflect all relevant information at that time.

The final recommended maximum tolerated dose (MTD)/maximum administered dose (MAD)/alternate dose of BMS-986205 in combination with nivolumab for cohort expansion will be based on the recommendation from the BLRM-copula model and a synthesis of all the data available on all dosed subjects, including clinical and laboratory safety assessments and PK and pharmacodynamic and efficacy data from all treated patients at each dose level up to the MTD/MAD. For further details of the BLRM-copula model and results under a variety of scenarios, refer to the simulation results in Section 2.4.

2.4 Operating Characteristics

The BLRM and BLRM-copula models should make reasonable decisions during a study based on the observed toxicities particularly in early cohorts. After completion of a given cohort, the decision to dose escalate and actual dose chosen for the subsequent cohort will depend on the recommendation of the BLRM (-copula) EWOC principle and medical review of all relevant data available up to date. Operating characteristics of BMS-986205 in combination with nivolumab using BLRM-copula models are shown in this section with simulation results. The

provisional dose levels for BMS-986205 are 25, 50, 100, 200, 400, 600, and 800 mg. Nivolumab is fixed at a 240-mg flat dose.

In order to show how the design performs, 4 hypothetical scenarios were investigated (please refer to Table 3 for more details):

- Scenario 1: General dose-DLT relationship with the assumption that the increased dose will have increased DLT rates, with the highest dose reaching the target toxicity rate (**Additive**)
- Scenario 2: All higher toxicity rates 50% higher than the additive scenario 1 along with increased dose levels, with the highest dose toxicity level above 33% (**Synergistic**)
- Scenario 3: All dose levels with toxicities 25% lower than the additive scenario 1 (**Cancel effect**)
- Scenario 4: All dose levels with toxicities 50% lower than the additive scenario 1 (**Strong Cancel effect**)

Table 4: Toxicity Rates for Each Scenario Across All 7 Pre-specified Dose Levels

Scenario/Dose Level	25 mg BMS-986205 + 240 mg Nivolumab	50 mg BMS-986205 + 240 mg Nivolumab	100 mg BMS-986205 + 240 mg Nivolumab	200 mg BMS-986205 + 240 mg Nivolumab	400 mg BMS-986205 + 240 mg Nivolumab	600 mg BMS-986205 + 240 mg Nivolumab	800 mg BMS-986205 + 240 mg Nivolumab
Scenario 1 Additive	0.05	0.06	0.09	0.13	0.21[a]	0.27[a]	0.33[a]
Scenario 2 Synergistic	0.08	0.09	0.14	0.2[a]	0.32[a]	0.41	0.5
Scenario 3 Cancel effect	0.04	0.05	0.07	0.1	0.15	0.2[a]	0.25[a]
Scenario 4 Strong Cancel effect	0.02	0.03	0.04	0.06	0.09	0.13	0.15

[a] Doses with true toxicity rate within the target toxicity interval [16%, 35%).

Simulation Parameters

One thousand trial simulations were used for each scenario. The number of subjects to be treated in each patient cohort in a specific dose level and the stopping rules used to declare MTD were defined as:

I. Fixed cohort size: 3
II. Probability of overdosing: <35%
III. Maximum number of subjects treated: 30
IV. Probability of target toxicity: >50%
V. Minimum number of subjects treated at a given dose level in order to declare MTD: 6

All simulations were run using in house-developed code via R and Openbugs, and EAST 6.3.1® software.

Simulation Results

Operating characteristics from the simulations were reviewed to assess the relative performance under each true scenario. The metrics reviewed are:

1. Percentage of trials with MTD being selected at dose levels with the pre-specified toxicities fall within the range of [16%, 35%) (**Correct MTD)**
2. Percentage of trials with MTD being selected at dose levels with the pre-specified toxicities fall within the range of [35%, 100%] (**MTD Too High**)
3. Percentage of trials with MTD being selected at dose levels with the pre-specified toxicities fall with the range of [0%, 16%) (**MTD Too Low**)
4. Percentage of trials with MTD being selected at the dose level with the pre-specified toxicity most closest to 33% and ≤ 33% (**MTD Point**)
5. The 25% quantile of 1000 trials' fitted MTDs derived by solving the logistic regression formula using posterior medians of parameters, as well as 33% as target DLT rate (**Fitted MTD**)
6. Percentage of trials stopped before declaring MTD due to the reason that MTD is below the lowest dose level (simulation parameter II) (**EWOC Stop**)
7. Percentage of trials stopped due to reaching the probability cutoff of posterior percentage fall in the target toxicity range (simulation parameter IV) and a minimum sample size of N = 6 at the declared MTD (simulation parameter V) (**Target Range Stop**)
8. Percentage of trials stopped due to reaching the maximum assigned sample size of N = 30 (simulation parameter III) (**MaxN Stop**)
9. Average sample size for each scenario (**Average Sample Size**)

Below summarizes the simulated operating characteristics of the model for the 4 different scenarios studied. One thing to note is that the following simulation results are only for illustrative purposes. This might not fully represent real trial conduction scenarios due to software/current programming code limitations as well as not considering the clinical team's decision overwriting BLRM-copula recommendation based on the totality of data.

Table 5: Simulation Results for Operating Characteristics

	MTD Range			Point Estimate		Good Stopping		Bad Stopping	Average Sample Size
	Correct MTD (%)	MTD Too High (%)	MTD Too Low (%)	MTD Point (%)	Fitted MTD (True MTD) (mg)	EWOC Stop (%)	Target Range Stop (%)	MaxN Stop (%)	
Scenario 1: Additive	90.7	0	8.7	24.2	771.1 (800)	0.6	99.3	0.1	12.7
Scenario 2: Synergistic	83.2	12	3.4	46.1	640.4 (400, 600)[a]	1.4	98.5	0	13.6
Scenario 3: Cancel effect	88.3	0	11.6	37.4	850.4 (>800)	0.1	99.8	0.1	12.2
Scenario 4: Strong Cancel effect	NA[b]	0	99.9	62.6	1030.9 (>>800)	0.1	99.9	0	11.7

[a] Means the true MTD falls into the range between 400 and 600 mg.

[b] NA because pre-specified toxicity are all below [16%, 35%) target toxicity range.

Abbreviations: EWOC = escalation with overdose control; MTD = maximum tolerated dose; NA = not applicable.

Overall, from the scenarios illustrated above, it can be shown that the model performs very well under the hypothetical scenarios investigated. The model allows for high MTD identification accuracy (using the MTD range), a small average sample size (less than half of the proposed sample size), a high probability of good stopping with great confidence (> 98%), and a low probability of bad stopping (~ 0%) when all of the subjects have been used.

In this simulation, different angles have been investigated regarding the performance of the model in terms of identifying the true MTDs under different scenarios. For scenario 1, the MTD point estimate is the lowest (24.2%) across all 4 scenarios. This means the dose level (800 mg) corresponding to the toxicity rate of 0.33 has only been identified 24.2% times as the MTD among all 1000 simulations. When it comes to the "correct MTD" (considering the MTD range), which is the accumulated percentages, scenario 1 is the highest among all 4 scenarios (90.7%). This can possibly be attributed to the simulation set-up on pre-specified toxicity rates. The toxicity levels are relatively similar to each other among the last 3 higher dose levels in scenario 1, where 400 mg is associated with a toxicity rate of 0.21, 600 mg with a toxicity rate of 0.27, and 800 mg with a toxicity rate of 0.33, all falling within the target interval of [16%,35%). This could also be explained by the model fitted MTD (771.1 mg), which is slightly lower than the true MTD of 800 mg. To improve the model's performance under such scenario, dose levels with similar toxicity rates might be combined or dose levels might be assigned with more distinguishable toxicity rates

For "MTD too high" cases, scenarios 1, 3, and 4 show no possibility of overdosing. On the other hand, scenario 2 shows a rate of 12% of overdosing. This is matching with the model fitted MTD at 640.4 mg, which falls out of the range of the hypothetical true MTD (between 400 and 600 mg). The slightly higher estimated MTD might be ascribed to the deviation of the prior distribution from the true underlying dose-DLT relationship. There is only 30% of the DLT rate assumed as current prior at the reference dose level of 800 mg, which is much lower than the true toxicity rate (50%) at this dose level. As in all parametric models, the prior distribution plays an important role in the performance of the BLRM-copula model under each scenario.

For "MTD too low" cases, scenarios 1, 2, and 3 show very low percentages of under-dosing (all < 12%), which is consistent with the hypothetical Pr (DLT). This also benefits from the properly defined overdose control probability of (Pr(overdose) < 35%). In scenario 4, a very strong cancel effect has been investigated with the highest toxicity level set as 0.15. In this case, the "fitted MTD" of 1030.9 mg could provide more guidance for the clinical team during trial conduction.

Different reasons for stopping have been investigated to obtain a deeper understanding of the operating characteristics of the BLRM-copula model. The performance of a "Good Stopping/Target Range Stop" (a stop due to high confidence about the recommended MTD fall in the pre-specified target toxicity interval) is good across all 4 scenarios (all high above 98%). Another indicator of a "Good Stopping" is the EWOC Stop; the overdosing control is low (< 2%) across all 4 scenarios. Low values are good because all of the toxicities among the 4 scenarios that correspond to the starting dose are low (ranging from 0.02 to 0.08). Therefore, the chance of stopping early and declaring the MTD lower than the pre-specified lowest dose level should rarely happen. This is consistent with our hypothetical scenarios. Additionally, "Bad

Stopping" due to reaching the maximum pre-assigned sample size (max N = 30) is around 0 for all 4 scenarios, which is ideal for early phase trials.

The average sample size from all 1000 simulations for each scenario is below or equal to 14, which is less than the pre-specified maximum sample size (N = 30). To control the possible heterogeneity between the prior distribution and the underlying true dose-DLT relationship, more information from the current study is warranted. Increasing the "total maximum number of subjects" for the trial or adding a stopping rule for the "maximum number of subjects enrolled for a next to-be dose level," or adding a restriction for "dose skipping," might be implemented during the conduction of the trial to gain more information from the trial. Also, intermediate dose levels and/or flexible cohort sizes might be investigated in the real study.

3 MODEL SETUP FOR BMS-986205, NIVOLUMAB AND IPILIMUMAB COMBINATION

3.1 Methodology Description for Triplet Combination therapy

Toxicity profiles of BMS-986205 monotherapy, nivolumab and ipilimumab monotherapy will be incorporated to develop the triplet combination model framework. A copula-type model will be utilized to cover all general combination cases, including additive and synergistic effects. The combination of 3 treatments will be explored using a Bayesian hierarchical model by utilizing the toxicity profiles of single agents as prior marginal profiles for the combination. The following copula-type model[6] will be used.

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

Where p_i is the pre-specified best guess toxicity probability for agent A, q_j is the pre-specified best guess toxicity probability for agent B and r_k is the pre-specified best guess toxicity probability for agent C. Here m , n and t characterize the individual drug effect and γ characterizes drug-drug interactive effect.

The joint toxicity framework models toxicity rates of both agents as well as their interaction effects in a multi-parameter hierarchical model, where each of the monotherapy dose-toxicity relationship will be characterized by a 2-parameter BLRM model (see Section 1.1). There are 4 additional parameters for the copula-type model, 1 for each agent as well as 1 for the interaction term. A dose-toxicity surface will be characterized for different dose combinations of these 3 agents.

As there is currently no historical data/prior knowledge to indicate how much information to be borrowed for each of the single agents, parameters *m*, *n* and *t* are both set to be 1, meaning borrowing 100% of the information from all 3 agents. The above formula is then simplified into a 7-parameter model as follows:

$$p_{ijk} = 1 - exp(-\left[\{-log(1-p_i)\}^{1/\gamma} + \{-log(1-q_j)\}^{1/\gamma} + \{-log(1-r_k)\}^{1/\gamma}\right]^{\gamma}$$

Since only a fixed nivolumab and ipilimumab dose will be used in BMS-986205, nivolumab and ipilimumab combination, in each safety cohort, this surface will be simplified into a 2-

dimensional dose-toxicity curve. Posteriors for the corresponding 7 parameters (2 logistic regression parameters $[\alpha_1, \beta_1]$ for BMS-986205, 2 logistic regression parameters for Nivolumab $[\alpha_2, \beta_2]$ and 2 logistic regression parameters for Ipilimumab $[\alpha_3, \beta_3]$ as well as 1 interaction parameter for the copula-type model[γ, which will be discussed in detail in the following session]) will be fit into the in-house developed model, which implements the above described theoretical setup.

3.2 Priors Specification for Combination Studies

3.2.1 Prior for BMS-986205

Posterior information on ($\log(\alpha_1)$, $\log(\beta_1)$) from the BMS 986205 lead-in and BMS 986205 and nivolumab combination part of the study will be used as marginal BMS-986205 prior for combination of BMS 986205 with nivolumab and ipilimumab. This prior information is not pre-specified and will be continuously updated when additional toxicity (DLT) information from the study is available.

3.2.2 Prior for Nivolumab

Posterior information on ($\log(\alpha_2)$, $\log(\beta_2)$) from the BMS 986205 and nivolumab combination part of the study will be used as marginal nivolumab prior for combination of BMS 986205 with nivolumab and ipilimumab. This prior information is not pre-specified and will be continuously updated when additional toxicity (DLT) information from the study is available.

3.2.3 Prior Derivation for Ipilimumab Parameters (log(α_3),log(β_3))

Similar to nivolumab monotherapy in the two drug combination part, the logistic model for ipilimumab is as follows:

$$logit(r_k) = log(\alpha_3) + \beta_3 log(^{d_{3k}}/_{d_3^*}) \text{ , where } a_3,\ \beta_3\ > 0.$$

Note that the α_3 and β_3 parameters are assumed positive, and d_3^* is the reference dose for ipilimumab.

The toxicity profile of ipilimumab has been studied in several studies. A bivariate normal prior for the ipilimumab model parameters ($\log(\alpha_3)$, $\log(\beta_3)$) was obtained by extracting a posterior of ipilimumab using safety data from multiple studies, which is used later as the meta-analytical-predictive (MAP) prior for ipilimumab. Since DLT information from ipilimumab studies was not available, incidence of treatment-related Grade 3-4 AEs from various Phase 2/3 ipilimumab studies at BMS in subjects with previously treated or untreated advanced melanoma was used in lieu of DLT rate in order to derive the prior for the BLRM parameters, ($\log(\alpha_3)$,$\log(\beta_3)$): a Phase 3 study of ipilimumab administered at 3 mg/kg vs 10 mg/kg (CA184169, N=360 per arm), a Phase 2 study of multiple doses of ipilimumab monotherapy (CA184022, N=71 per arm), a Phase 3 study in HLA-A*0201positive subjects (MDX010-20, ipilimumab 3 mg/kg monotherapy arm with N=131), and data from other various Phase 2 studies (N=111 for pooled 3 mg/kg; N=325 for pooled 10 mg/kg).

The following steps describe how this MAP component is obtained.

First, a prior distribution for ipilimumab was developed:

- The median toxicity rate at the ipilimumab reference dose (10 mg/kg Q3W) was assumed to be 30%, i.e., mean ($\log(\alpha_3)$) = logit(0.30)= -0.847.
- A doubling in dose was assumed to double the odds of DLT, i.e. mean ($\log(\beta_3)$) = 0.
- The standard deviation of $\log(\alpha_3)$ was set to 2, and the standard deviation of $\log(\beta_3)$ was set to 1, which allows for considerable prior uncertainty for the dose-toxicity profile.
- The correlation between $\log(\alpha_3)$ and $\log(\beta_3)$ was assumed to be 0 (assuming independence of $\log(\alpha_3)$ and $\log(\beta_3)$).
- In addition, heterogeneity between the historical study and the current study was incorporated using a meta-analytic predictive approach, by defining between-trial standard deviations τ_1 and τ_2 for $\log(\alpha_3)$ and $\log(\beta_3)$, respectively. The between-trial variability is assumed to be moderate. Therefore, τ_1 and τ_2 were set to follow a log-normal distribution with mean log(0.25) and log(0.125) respectively with a common standard deviation log(2)/1.96.

With this prior, the clinical trial data below were used to generate the posterior for ipilimumab, which is then used as the MAP prior for this study.

Table 6: Data from Phase 2/3 ipilimumab studies

Dose of Ipilimumab (mg/kg)	Toxicity (percentage [number of subjects/total subjects]) [a]
0.3	10% (7/72)
3	18% (119/675)
10	32% (242/760)

[a] % of subjects with treatment-related Grade 3-4 AEs

Table 7: MAP prior distribution for model parameters of Ipilimumab

Parameter	Means	Standard deviations	Correlation
($\log(\alpha_3)$, $\log(\beta_3)$)	(-0.797, -0.588)	(0.405, 0.255)	0.072

Note: Ipilimumab prior information stated here is based on different dosing schedules than the ones being used in Part 3 combination. If real safety and pharmacokinetic (PK) data from this study show difference, the prior will be revisited and modified accordingly.

3.2.4 Updated Marginal Posterior for BMS-986205, Nivolumab and Ipilimumab from Ongoing Studies

As multiple nivolumab and ipilimumab combinations studies in different indications with similar dosing schedule to Part 3 triplet combinations are ongoing, the final nivolumab and/or

ipilimumab marginal prior used in triplet combination may be further updated to incorporate recent safety information if available during the study.

3.2.5 Prior for Interaction Parameters for Joint Toxicity of BMS-986205, Nivolumab and Ipilimumab Combination

A gamma prior distribution for the interaction parameter γ is derived to reflect the current uncertainty about the toxicity profile of the combination of BMS-986205, nivolumab and ipilimumab. Although no PK drug-drug interaction is expected, the possibility of significant positive interaction between BMS-986205, nivolumab and ipilimumab cannot be totally excluded. The interaction parameter γ was chosen accordingly but with a degree of uncertainty in order to allow for the possibility that the interaction may be positive or negative. Therefore, the following assumptions are made for the interaction parameter:

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

This assumes, a priori, that there is a small synergistic interaction but also allows for the potential of significant synergism of the toxic profiles. It also does not completely ignore the possibility of antagonism since we consider 40% prior probability that γ is less than 1.

As specified in Section3.2.1, 3.2.2 and 3.2.4, recent safety information from other parts of the current study as well as multiple ongoing nivolumab and ipilimumab combinations studies may be used to update the prior distributions for the marginal of the individual drugs. Similarly, the interaction parameter may also be updated based on current safety data on an ongoing basis.

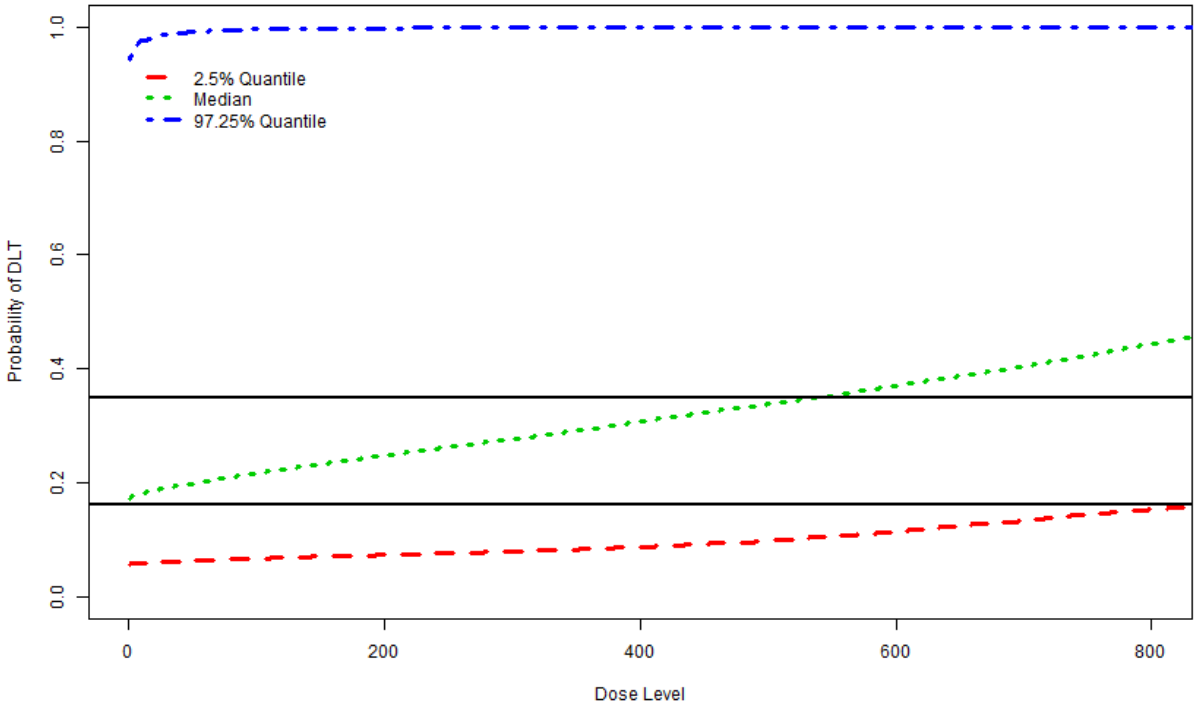
3.3 Safety Monitoring Examples with BLRM (-Copula) for BMS-986205, Nivolumab and Ipilimumab Combination

In order to provide a comprehensive view of the dynamics of the models, although no study data from triplet combination are available at this point, prior information is used to illustrate hypothetical scenarios. For the simplicity of illustration purposes, a static cohort size of 3 subjects is applied for the initial safety cohort. BLRM -Copula models are also designed to fit various different cohort sizes, adaptively, and will be used for safety monitoring on a continued basis.

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

- Dose-DLT profile for the entire dose range of BMS-986205. The doses ranging between 0 mg and 800 mg (Figure 1).
- Stacking histograms displaying predictive probabilities on DLT rates classified into 3 different categories (Underdosing, Target dosing and Overdosing) (Figure 2).

Figure 1: Dose-DLT profile after incorporating prior information

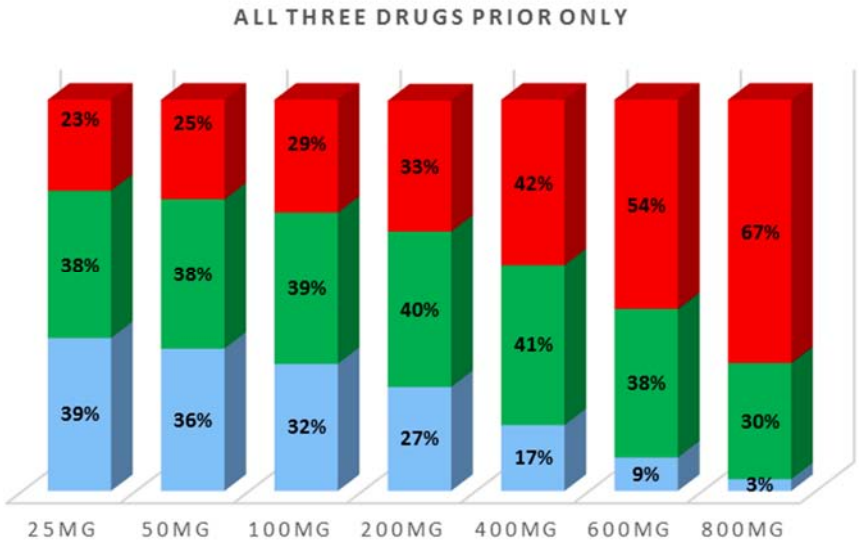


Interpretation and usage of Figure 1:

Figure 1 is a snapshot of the dose-DLT profile with prior information only. The dose-DLT profile is captured with a continuous dose spectrum ranging from 0 mg to 800 mg. For each dose within the range, there is a corresponding distribution of the predicted DLT rates calculated from the samples of the model parameters. This figure will be updated each time new DLT information becomes available. In Figure 1, there are 3 different quantiles (2.5%, 50%, and 97.5%) plotted to characterize the current trend of the toxicity profile (as shown by the 50% quantile), as well as the variation of the dose-DLT profile (as shown by the 2.5% percentile and the 97.5% percentile), according to the accumulation of DLT data from all previous and current dose levels. The toxicity boundaries (0.16 and 0.35) are illustrated in two dotted horizontal lines to benchmark the way in which the dose-DLT profile is trending. From this plot, based on only the prior information for the individual drugs, for BMS-986205 doses 25mg, 50mg, 100mg, 200mg and 400mg, the median dose-DLT curve lies between the pre-specified toxicity interval limits of 16% and 35%.

If the proposed triplet combination is found to have safety concerns, and is considered intolerable, lower dose levels can also be identified using different boundary cutoffs from this plot. For example, using the 50% percentile curve (green line), which represents the median DLT distribution for each dose level, a potential lower dose level corresponding to a pre-specified DLT rate could be determined and used as a new dose.

Figure 2: **Stacking histogram after incorporating prior information to classify predicted DLT rates into 3 categories (Underdosing, Target Dosing and Overdosing)**



Interpretation and usage of Figure 2:
Figure 2 is a snapshot of stacking histogram with all prior information available. This figure will also be updated each time new DLT information becomes available.

When evaluating the dose levels based on prior information or current safety data, the model will first exclude doses that are intolerable from consideration (with overdosing probabilities > 35%, the rate that has been specified for BMS-986205 combination). All of the remaining doses will be considered "tolerable", however the model will also identify the dose that maximizes the probability of being within the target toxicity range (DLT rate of 16% up to 35%).

As illustrated in Figure 2, based on the prior information, the distribution of predicted DLT rates will be characterized into possibilities falling into 3 different categories. First, dose levels of 400, 600mg and 800 mg are considered unsafe according to the higher-than-cutoff (0.35) overdosing probabilities. Among the remainder of tolerable dose levels (25 mg, 50 mg, 100 and 200 mg), using the BLRM-Copula model the dose level that maximizes the probability of being within the target dosing interval can also be identified. Here dose level 200 mg is associated with the highest target dosing probability of 40% compared with other dose levels.

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

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APPENDIX 2 ECOG PERFORMANCE STATUS

ECOG PERFORMANCE STATUS[a]	
0	Fully active, able to carry on all pre-disease performance without restriction
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, eg, light house work, office work
2	Ambulatory and capable of all selfcare but unable to carry out any work activities. Up and about more than 50% of waking hours
3	Capable of only limited selfcare, confined to bed or chair more than 50% of waking hours
4	Completely disabled. Cannot carry on any selfcare. Totally confined to bed or chair
5	Dead

[a] 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 3 RECIST 1.1

1 ASSESSMENT OF OVERALL TUMOR BURDEN AND MEASURABLE DISEASE

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

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

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

1.1 Measurable Lesions

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

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

1.2 Non-measurable Lesions

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

1.3 Special Considerations Regarding Lesion Measurability

1.3.1 Bone Lesions

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

1.3.2 Cystic Lesions

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

1.3.3 Lesions with Prior Local Treatment

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

1.4 Specifications by Methods of Measurements

1.4.1 Measurement of Lesions

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

1.4.2 Method of Assessment

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

1.4.2.1 CT/MRI Scan

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

1.4.2.2 Chest X-ray

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

1.4.2.3 Clinical Lesions

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

1.4.2.4 Ultrasound

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

1.4.2.5 Endoscopy, Laparoscopy

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

1.4.2.6 Tumor markers

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

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

2.1 Target Lesions

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

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

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

2.1.1 Lymph Nodes

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

2.2 Non-target Lesions

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

3 TUMOR RESPONSE EVALUATION

3.1 Evaluation of Target Lesions

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

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

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

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

3.1.1 Special Notes on the Assessment of Target Lesions

3.1.1.1 Lymph Nodes

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

3.1.1.2 Target Lesions That Become 'Too Small to Measure'

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

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

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

3.1.1.3 Target Lesions That Split or Coalesce on Treatment

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

3.2 Evaluation of Non-target Lesions

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

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

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

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

3.2.1 Special Notes on the Assessment of Non-target Lesions

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

3.2.1.1 When the Subject Also Has Measurable Disease

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

3.2.1.2 When the Subject Has Only Non-measurable Disease

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

3.2.1.3 Tumor Markers

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

3.3 New Lesions

The appearance of new malignant lesions denotes disease progression. The finding of a new lesion should be unequivocal, ie, not attributable to differences in scanning technique, change in

imaging modality, or findings thought to represent something other than tumor (for example, some 'new' bone lesions may be simply healing or flare of pre-existing lesions). This is particularly important when the subject's baseline lesions show PR or CR. For example, necrosis of a liver lesion may be reported on a CT scan report as a 'new' cystic lesion, which it is not.

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

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

3.3.1 FDG-PET Evaluation

While [^{18}F] fluorodeoxyglucose (FDG)-PET response assessments need additional study, it is sometimes reasonable to incorporate the use of the qualitative assessment of FDG-PET scanning to complement CT scanning in the assessment of progression (particularly possible 'new' disease). New lesions on the basis of FDG-PET imaging can be identified according to the following algorithm:

- Negative FDG-PET at baseline with a positive FDG-PET at follow-up is a sign of PD based on a new lesion.
- 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 positive 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.

4 RESPONSE CRITERIA

4.1 Time Point Response

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

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

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

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

CR = complete response, PR = partial response, SD = stable disease, PD = progressive disease, NE = not evaluable.

4.1.1 Missing assessments and not evaluable designation

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

4.1.2 Confirmation Scans

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

4.2 Best Overall Response: All Time Points

The best overall response is determined once all the data for the subject are known. It is the best response recorded from the start of the study treatment until objectively documented progression per RECIST Criteria or subsequent cancer therapy, whichever happens first taking into account any requirement for confirmation. The subject's best overall response assignment will depend on the findings of both target and non-target disease and will also take into consideration the appearance of new lesions.

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

In this circumstance, the best overall response can be interpreted as specified in Table 4.2-1. When SD is believed to be the best response, it must meet the protocol-specified minimum time from baseline. Measurements must have met the SD criteria at least once after study entry at a minimum interval (in general not less than 6–8 weeks) that is defined in the study protocol.

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

Overall Response	Overall Response	BEST Overall Response
First Time Point	**Subsequent Time Point**	
CR	CR	CR
CR	PR	SD, PD or PR[a]
CR	SD	SD provided minimum criteria for SD duration met, otherwise, PD
CR	PD	SD provided minimum criteria for SD duration met, otherwise, PD
CR	NE	SD provided minimum criteria for SD duration met, otherwise NE
PR	CR	PR
PR	PR	PR
PR	SD	SD
PR	PD	SD provided minimum criteria for SD duration met, otherwise, PD
PR	NE	SD provided minimum criteria for SD duration met, otherwise NE
NE	NE	NE

CR = complete response, PR = partial response, SD = stable disease, PD = progressive disease, NE = not evaluable.

[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 subject had PR, not CR at the first time point. Under these circumstances, the original CR should be changed to PR and the best response is PR.

4.3 Duration of Response

4.3.1 Duration of Overall Response

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

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

4.3.2 Duration of Stable Disease

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

CR (Complete Remission)

The designation of CR requires the following:

1. Complete disappearance of all detectable clinical evidence of disease and disease-related symptoms, if present before therapy.
   a) Typically FDG-avid lymphoma: in patients with no pretreatment PET scan or when the PET scan was positive before therapy, a post-treatment residual mass of any size is permitted as long as it is PET negative.
   b) Variably FDG-avid lymphomas/FDG avidity unknown: in patients without a pretreatment PET scan, or if a pretreatment PET scan was negative, all lymph nodes and nodal masses must have regressed on CT scan to normal size (≤ 1.5 cm in their greatest transverse diameter for nodes > 1.5 cm before therapy). Previously involved nodes that were 1.1 to 1.5 cm in their long axis and > 1.0 cm in their short axis before treatment must have decreased to ≤ 1.0 cm in their short axis after treatment.
2. The spleen and/or liver, if considered enlarged before therapy on the basis of a physical examination or CT scan, should not be palpable on physical examination and should be considered normal size by imaging studies, and nodules related to lymphoma should disappear. However, determination of splenic involvement is not always reliable because a spleen considered normal in size may still contain lymphoma, whereas an enlarged spleen may reflect variations in anatomy, blood volume, the use of hematopoietic growth factors, or causes other than lymphoma.
3. If the bone marrow was involved by lymphoma before treatment, the infiltrate must have cleared on repeat bone marrow biopsy. The biopsy sample on which this determination is made must be adequate (with a goal of > 20 mm unilateral core). If the sample is indeterminate by morphology, it should be negative by immunohistochemistry. A sample that is negative by immunohistochemistry but demonstrates a small population of clonal lymphocytes by flow cytometry will be considered a CR until data become available demonstrating a clear difference in patient outcome.

PR (Partial Remission)

The designation of PR requires all of the following:

1. At least a 50% decrease in the sum of the product of the diameters (SPD) of up to 6 of the largest dominant nodes or nodal masses. These nodes or masses should be selected according to all of the following: they should be clearly measurable in at least 2 perpendicular dimensions; if possible, they should be from disparate regions of the body; and they should include mediastinal and retroperitoneal areas of disease whenever these sites are involved.
2. No increase should be observed in the size of other nodes, liver, or spleen.

3. Splenic and hepatic nodules must regress by ≥ 50% in their SPD or, for single nodules, in the greatest transverse diameter.
4. With the exception of splenic and hepatic nodules, involvement of other organs is usually assessable, and no measurable disease should be present.
5. Bone marrow assessment is irrelevant for the determination of a PR if the sample was positive before treatment. However, if positive, the cell type should be specified (eg, large-cell lymphoma or small neoplastic B cells). Patients who achieve a CR by the above criteria but have persistent morphologic bone marrow involvement will be considered partial responders. When the bone marrow was involved before therapy and a clinical CR was achieved but with no bone marrow assessment after treatment, patients should be considered partial responders.
6. No new sites of disease should be observed.
7. FDG:
   a) Typically FDG-avid lymphoma: for patients with no pretreatment PET scan or if the PET scan was positive before therapy, the post-treatment PET should be positive in at least 1 previously involved site.
   b) Variably FDG-avid lymphomas/FDG-avidity unknown: for patients without a pretreatment PET scan, or if a pretreatment PET scan was negative, CT criteria should be used. In patients with follicular lymphoma or mantle-cell lymphoma, a PET scan is only indicated with 1 or at most 2 residual masses that have regressed by > 50% on CT; those with more than 2 residual lesions are unlikely to be PET negative and should be considered partial responders.

SD (Stable Disease)

SD is defined as the following:

1. A patient is considered to have SD when he or she fails to attain the criteria needed for a CR or PR but does not fulfill those for PD (see Relapsed Disease [after CR]/PD [after PR, SD]).
2. Typically FDG-avid lymphomas: the PET should be positive at prior sites of disease with no new areas of involvement on the post-treatment CT or PET scan.
3. Variably FDG-avid lymphomas/FDG-avidity unknown: for patients without a pretreatment PET scan or if the pretreatment PET was negative, there must be no change in the size of the previous lesions on the post-treatment CT scan.

PD: Relapsed Disease (after CR)/PD (after PR, SD)

Lymph nodes should be considered abnormal if the long axis is > 1.5 cm regardless of the short axis. If a lymph node has a long axis of 1.1 to 1.5 cm, it should only be considered abnormal if its short axis is > 1.0. Lymph nodes ≤ 1.0 x ≤ 1.0 cm will not be considered abnormal for relapse or PD.

1. Appearance of any new lesion > 1.5 cm in any axis during or at the end of therapy, even if other lesions are decreasing in size. Increased FDG uptake in a previously unaffected site should only be considered relapsed or PD after confirmation with other modalities. In

patients with no prior history of pulmonary lymphoma, new lung nodules identified by CT are mostly benign. Thus, a therapeutic decision should not be made solely on the basis of the PET without histologic confirmation.

2. At least a 50% increase from nadir in the SPD of any previously involved nodes, or in a single involved node, or the size of other lesions (eg, splenic or hepatic nodules). To be considered PD, a lymph node with a diameter of the short axis of < 1.0 cm must increase by ≥ 50% and to a size of 1.5 × 1.5 cm or > 1.5 cm in the long axis.
3. At least a 50% increase in the longest diameter of any single previously identified node > 1 cm in its short axis.
4. Lesions should be PET positive if observed in a typical FDG-avid lymphoma or the lesion was PET positive before therapy unless the lesion is too small to be detected with current PET systems (< 1.5 cm in its long axis by CT).

Measurable extranodal disease should be assessed in a manner similar to that for nodal disease. For these recommendations, the spleen is considered nodal disease. Disease that is only assessable (eg, pleural effusions, bone lesions) will be recorded as present or absent only, unless, while an abnormality is still noted by imaging studies or physical examination, it is found to be histologically negative.

In clinical trials where PET is unavailable to the vast majority of participants, or where PET is not deemed necessary or appropriate for use (eg, a trial in patients with MALT lymphoma), response should be assessed as above, but only using CT scans. However, residual masses should not be assigned CRu status but should be considered PRs.

APPENDIX 4 INTERNATIONAL WORKSHOP GROUP RESPONSE CRITERIA FOR NHL (2014)[1]

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: LDi > 1.5 cm and Increase by ≥ 50% from PPD nadir and An increase in LDi or SDi from nadir 0.5 cm for lesions ≤ 2 cm 1.0 cm for lesions > 2 cm 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 New or recurrent splenomegaly
Nonmeasured lesions	None	New or clear progression of preexisting nonmeasured lesions

(continued on following page)

Response and Site	PET-CT–Based Response	CT-Based Response
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 A new node > 1.5 cm in any axis 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 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.

Reference:

[1] Cheson BD, et al: Recommendations for initial evaluation, staging, and response assessment of Hodgkin and non-Hodgkin lymphoma: the Lugano classification. J Clin Oncol. 2014; 32:3059-68.

APPENDIX 5 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 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.

Updated: 05-Jul-2016

GI Adverse Event Management Algorithm

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

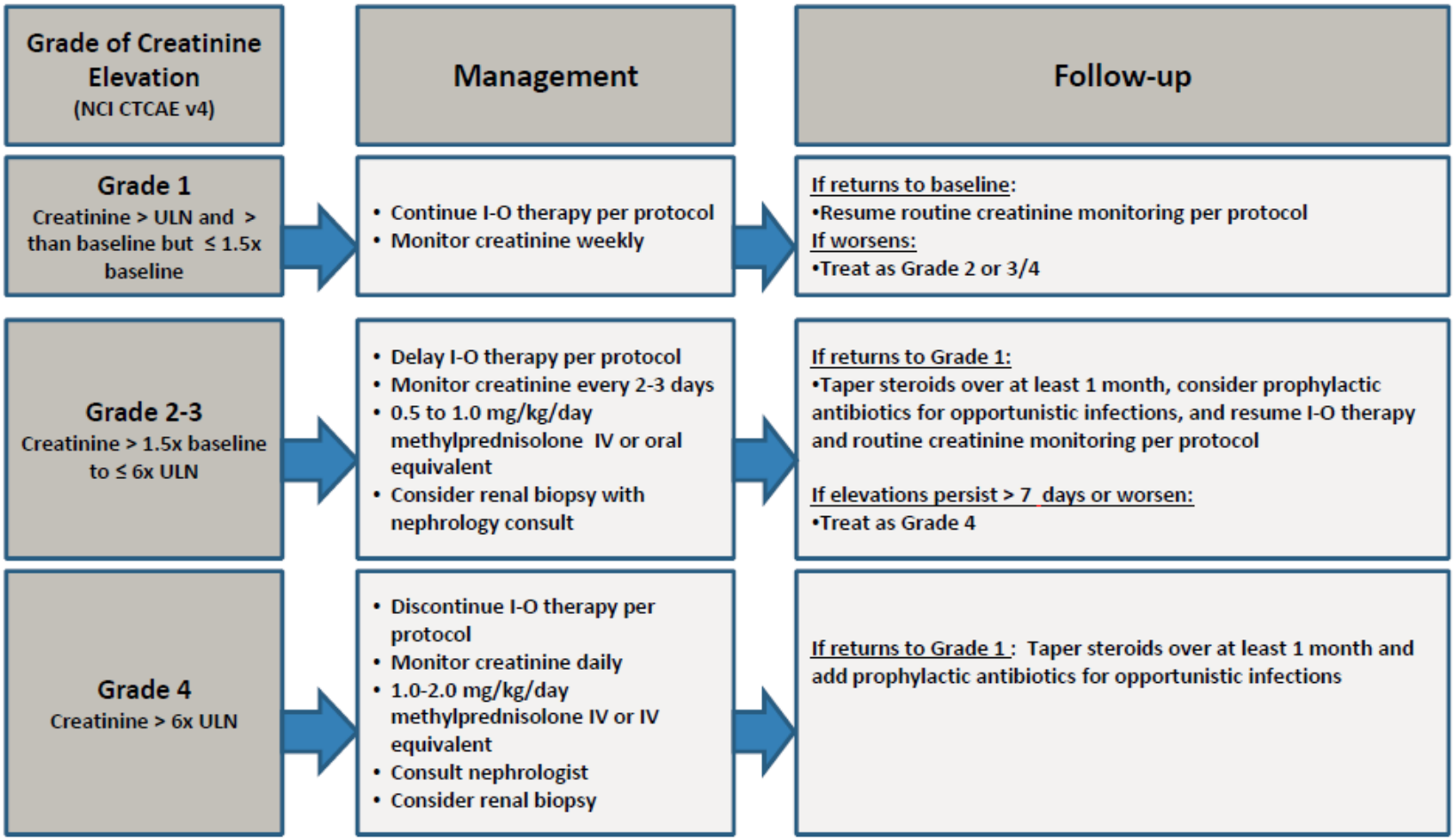
Grade of Diarrhea/ Colitis (NCI CTCAE v4)	Management	Follow-up
Grade 1 Diarrhea:< 4 stools/day over baseline; Colitis: asymptomatic	• Continue I-O therapy per protocol • Symptomatic treatment	• Close monitoring for worsening symptoms. • Educate patient to report worsening immediately If worsens: • Treat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

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

Updated 05-Jul-2016

Renal Adverse Event Management Algorithm

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



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

Updated 05-Jul-2016

Pulmonary Adverse Event Management Algorithm

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

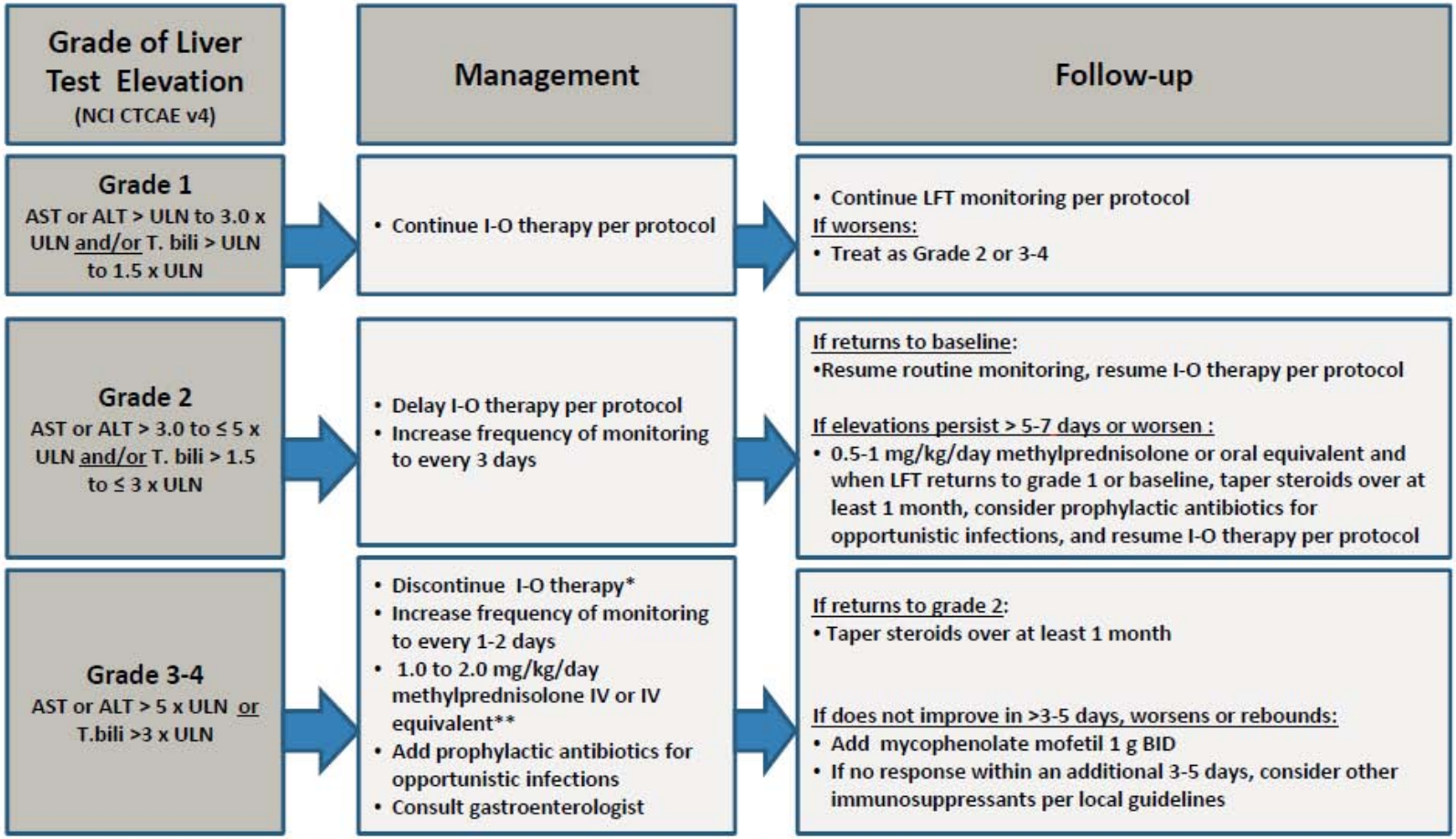
Grade of Pneumonitis (NCI CTCAE v4)	Management	Follow-up
Grade 1 Radiographic changes only	• Consider delay of I-O therapy • Monitor for symptoms every 2-3 days • Consider Pulmonary and ID consults	• Re-image at least every 3 weeks If worsens: • Treat as Grade 2 or 3-4
Grade 2 Mild to moderate new symptoms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

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

Updated 05-Jul-2016

Hepatic Adverse Event Management Algorithm

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



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

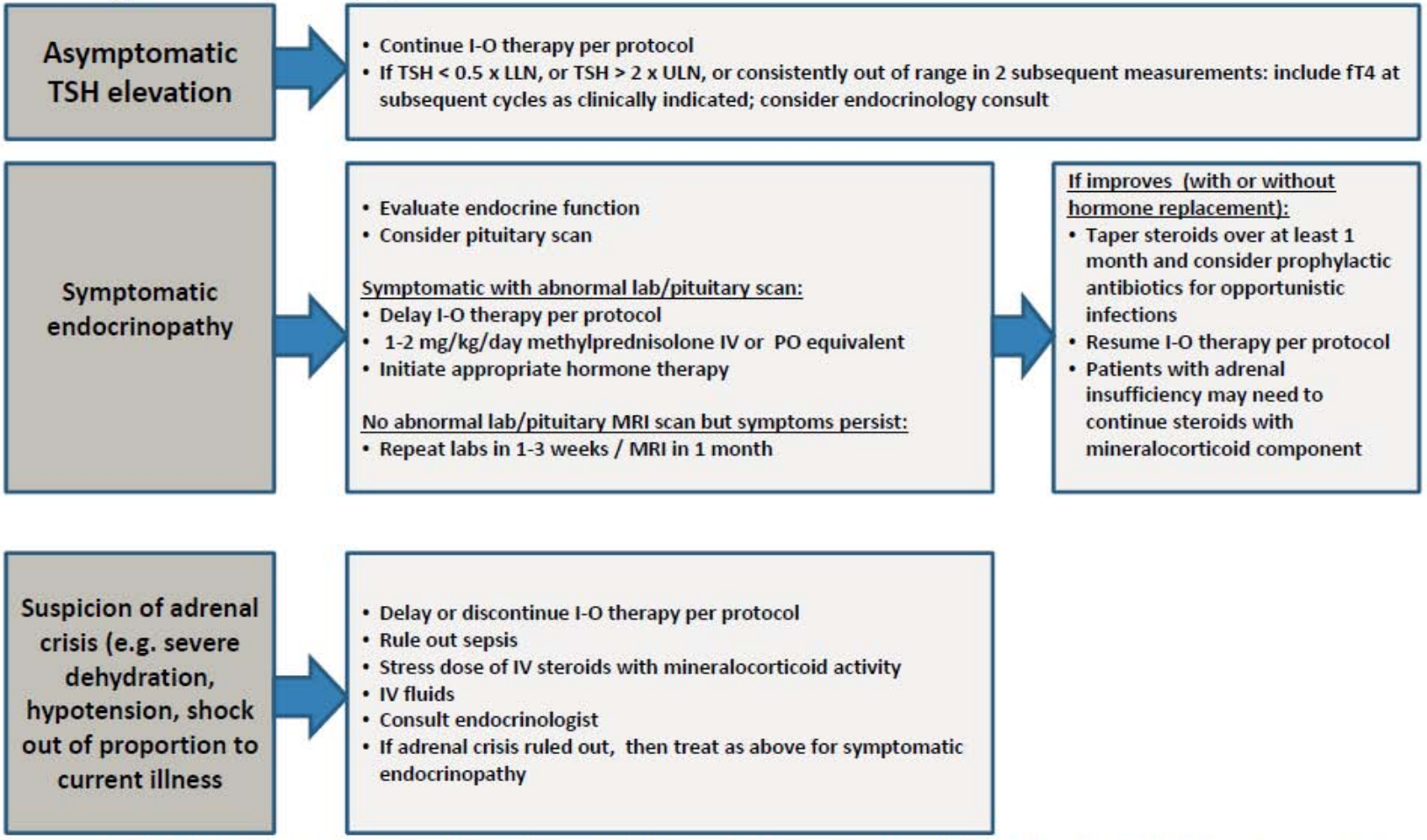
***I-O therapy may be delayed rather than discontinued if AST/ALT ≤ 8 x ULN or T.bili ≤ 5 x ULN.**

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

Updated 05-Jul-2016

Endocrinopathy Management Algorithm

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

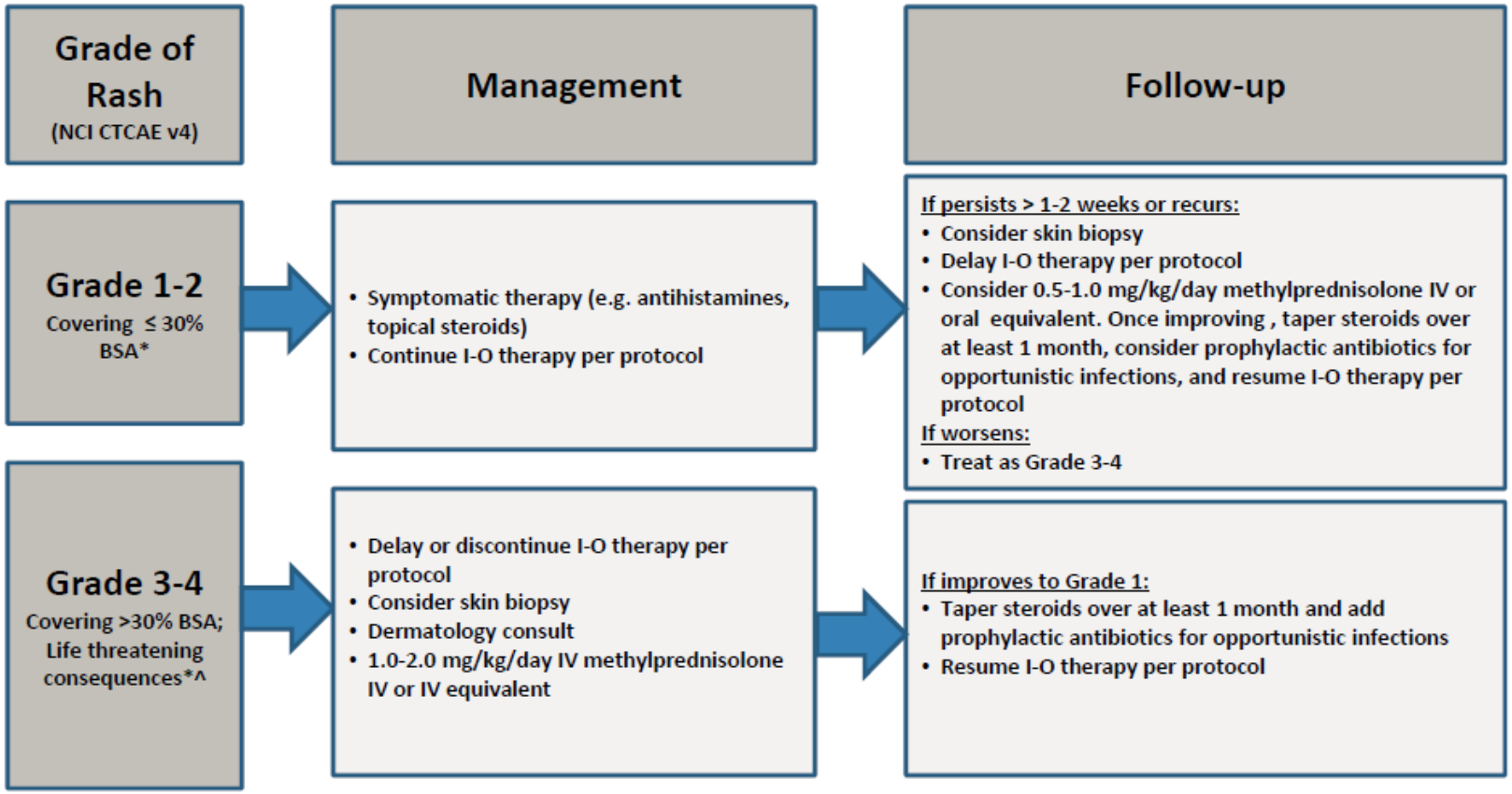


Patients on IV steroids may be switched to an equivalent dose of oral corticosteroids (e.g. prednisone) at start of tapering or earlier, once sustained clinical improvement is observed. Lower bioavailability of oral corticosteroids should be taken into account when switching to the equivalent dose of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

Updated 05-Jul-2016

Skin Adverse Event Management Algorithm

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



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

Updated 05-Jul-2016

Neurological Adverse Event Management Algorithm

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

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

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

Updated 05-Jul-2016

APPENDIX 6 REVISED INTERNATIONAL PROGNOSTIC INDEX (IPI) SCALE*

Composite score was determined by assigning 1 point for each of the following factors:

- Age > 60 years
- ECOG PS > 2
- Elevated Serum LDH
- More than 1 extranodal site
- Stage III/IV disease (Ann Arbor staging)

*Sehn LH, Berry B, Chhanabhai M, et al. The revised International Prognostic Index (R-IPI) is a better predictor of outcome than the standard IPI for patients with diffuse large B-cell lymphoma treated with R-CHOP. Blood 2007 109: 1857-1861

APPENDIX 7 CYP3A4, CYP1A2 AND CYP2B6 GUIDANCE

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

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

Table 1: Classification of In Vivo Inhibitors of CYP Enzymes

CYP Enzymes	Strong Inhibitors[a] ≥ 5-fold Increase in AUC or > 80% Decrease in CL	Moderate Inhibitors[b] ≥ 2 but < 5-fold Increase in AUC or 50-80% Decrease in CL	Weak Inhibitors[c] ≥ 1.25 but < 2-fold Increase in AUC or 20-50% Decrease in CL
CYP3A	Boceprevir, clarithromycin, conivaptan, grapefruit juice,[d] indinavir, itraconazole, ketoconazole, lopinavir/ritonavir, mibefradil,[e] nefazodone, nelfinavir, posaconazole, ritonavir, saquinavir, telaprevir, telithromycin, voriconazole	Amprenavir, aprepitant, atazanavir, ciprofloxacin, darunavir/ritonavir, diltiazem, erythromycin, fluconazole, fosamprenavir, grapefruit juice,[d] imatinib, verapamil	Alprazolam, amiodarone, amlodipine, atorvastatin, bicalutamide, cilostazol, cimetidine, cyclosporine, fluoxetine, fluvoxamine, ginkgo,[f] goldenseal,[f] isoniazid, nilotinib, oral contraceptives, ranitidine, ranolazine, tipranavir/ritonavir, zileuton
CYP1A2	ciprofloxacin, enoxacin, fluvoxamine[g], zafirlukast	methoxsalen, mexiletine, oral contraceptives	acyclovir, allopurinol, cimetidine, peginterferon alpha-2a, piperine, 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 1.25-fold.

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

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

[f] Herbal product.

[g] Strong inhibitor of CYP1A2 and CYP2C19, and moderate inhibitor of CYP2D6 and CYP3A

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, phenytoin, rifampin, St. John's wort[b]	Bosentan, efavirenz, etravirine, modafinil, nafcillin	Amprenavir, aprepitant, armodafinil, echinacea,[c] pioglitazone, prednisone, rufinamide
CYP1A2		Phenytoin[d], rifampin[e], ritonavir[f], smoking, teriflunomide	

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.

[d] Strong inducer of CYP3A and moderate inducer of CYP1A2, CYP2C19.

[e] Strong inducer of CYP2C19, CYP3A, and moderate inducer of CYP1A2, CYP2B6, CYP2C8, CYP2C9.

[f] Strong inducer of CYP2C19 and moderate inducer of CYP1A2, CYP2B6, CYP2C9.

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

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

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

Please note that this is not an exhaustive list.

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

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

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

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

APPENDIX 8 MEDICATIONS ASSOCIATED WITH QT PROLOGATION

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

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

APPENDIX 9 P-GP AND BCRP GUIDANCE

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

http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/DrugInteractionsLabeling/ucm080499.htm

Table 1: Examples of In Vivo Substrates for Selected Transporters

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

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

APPENDIX 10 AGENTS KNOWN TO CAUSE METHEMOGLOBINEMIA

- Acetanilid
- p-Amino salicylic acid
- Aniline, aniline dyes
- Benzene derivatives
- Clofazimine
- Chlorates
- Chloroquine
- Dapsone
- Local anesthetic agents
  - Benzocaine
  - Lidocaine
  - Prilocaine
- Menadione
- Metoclopramide
- Methylene blue*
- Naphthoquinone
- Naphthalene
- Nitrites
  - Amyl nitrite
  - Farryl nitrite
  - Sodium nitrite
  - Nitroglycerin
  - Nitric oxide
- Nitrobenzene
- Paraquat
- Phenacetin
- Phenazopyridine
- Primaquine
- Rasburicase
- Resorcinol
- Sulfonamides

While methylene blue is a recognized treatment for methemoglobinemia, it is an agent with oxidant potential (and may worsen the clinical situation) since in individuals with glucose-6-phosphate dehydrogenase deficiency, it induces acute hemolysis that can further decrease oxygen delivery to the tissues. Paradoxically, in high doses, methylene blue can also increase methemoglobinemia.

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.

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.*****

Note: Hormone-based contraceptives are <u>not</u> considered highly effective methods of contraception for WOCBP participants recieving BMS-986205.

Highly Effective Contraceptive Methods That Are User Dependent *Failure rate of <1% per year when used consistently and correctly.*[a]
• **Not for WOCBP participants recieving BMS-986205:** Combined (estrogen- and progestogen-containing) hormonal contraception associated with inhibition of ovulation[b] – oral – intravaginal – transdermal

• **Not for WOCBP participants recieving BMS-986205:** Progestogen-only hormonal contraception associated with inhibition of ovulation[b] – oral – injectable
Highly Effective Methods That Are User Independent
• **Not for WOCBP participants recieving BMS-986205:** Implantable progestogen-only hormonal contraception associated with inhibition of ovulation [b] • Intrauterine device (IUD)[c] • Bilateral tubal occlusion
• **Not for participants receiving BMS-986205:** Vasectomized partner A vasectomized partner is a highly effective contraception method for provided that the partner is the sole male sexual partner of the WOCBP and the absence of sperm has been confirmed. If not, an additional highly effective method of contraception should be used.
• Sexual abstinence *Sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the study drug. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the study and the preferred and usual lifestyle of the participant.* • It is not necessary to use any other method of contraception when complete abstinence is elected. • WOCBP participants who choose complete abstinence must continue to have pregnancy tests, as specified in Section 2. • Acceptable alternate methods of highly effective contraception must be discussed in the event that the WOCBP participants chooses to forego complete abstinence
NOTES: [a] Typical use failure rates may differ from those when used consistently and correctly. Use should be consistent with local regulations regarding the use of contraceptive methods for participants participating in clinical studies. [b] Hormonal contraception may be susceptible to interaction with the study drug, which may reduce the efficacy of the contraceptive method. Hormonal contraception is permissible only when there is sufficient evidence that the IMP and other study medications will not alter hormonal exposures such that contraception would be ineffective or result in increased exposures that could be potentially hazardous. In this case, alternative methods of contraception should be utilized. [c] Intrauterine devices and intrauterine hormone releasing systems are acceptable methods of contraception in the absence of definitive drug interaction studies when hormone exposures from intrauterine devices do not alter contraception effectiveness. The absence of such interactions is not known for BMS-986205 when administered with nivolumab. Therefore, for participants of child-bearing potential who receive these 2 medications, intrauterine hormone releasing systems are not acceptable methods of contraception.

Unacceptable Methods of Contraception*
• Male or female condom with or without spermicide. Male and female condoms cannot be used simultaneously

- Diaphragm with spermicide
- Cervical cap with spermicide
- Vaginal Sponge with spermicide
- Progestogen-only oral hormonal contraception, where inhibition of ovulation is not the primary mechanism of action
- Periodic abstinence (calendar, symptothermal, post-ovulation methods)
- Withdrawal (coitus interruptus).
- Spermicide only
- Lactation amenorrhea method (LAM)

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

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

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

- Inform any and all partner(s) of their participation in a clinical drug study and the need to comply with contraception instructions as directed by the investigator.
- Male participants are required to use a synthetic or latex male condom for any sexual activity with WOCBP for the study duration and until 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 sexual activity or use a synthetic or latex male condom during each episode of sexual activity for the duration of study treatment, and until 7 months after the end of study treatment.
- Refrain from donating sperm for the duration of the study treatment and until 7 months after the end of study treatment.

COLLECTION OF PREGNANCY INFORMATION

Guidance for collection of Pregnancy Information and outcome of pregnancy on the Pregnancy Surveillance Form is provided in Section 6.5 and the Appendix for Adverse Events and Serious Adverse Events Definitions and procedures for Evaluating, Follow-up and Reporting.

APPENDIX 12 DIAGNOSTIC CRITERIA FOR HLH AND DRESS SYNDROME

Table 1. Diagnostic criteria for HLH used in the HLH-2004 trial*

The diagnosis of HLH† may be established:
A. Molecular diagnosis consistent with HLH: pathologic mutations of *PRF1*, *UNC13D*, *Munc18-2*, *Rab27a*, *STX11*, *SH2D1A*, or *BIRC4*
or
B. Five of the 8 criteria listed below are fulfilled:
1. Fever ≥ 38.5°C
2. Splenomegaly
3. Cytopenias (affecting at least 2 of 3 lineages in the peripheral blood)
Hemoglobin < 9 g/dL (in infants < 4 weeks: hemoglobin < 10 g/dL)
Platelets < 100×10^3/mL
Neutrophils < 1×10^3/mL
4. Hypertriglyceridemia (fasting, > 265 mg/dL) and/or hypofibrinogenemia (< 150 mg/dL)
5. Hemophagocytosis in bone marrow, spleen, lymph nodes, or liver
6. Low or absent NK-cell activity
7. Ferritin > 500 ng/mL‡
8. Elevated sCD25 (α-chain of sIL-2 receptor)§

*Adapted from Henter et al.

†In addition, in the case of familial HLH, no evidence of malignancy should be apparent.

‡Although the HLH-2004 protocol uses ferritin > 500 ng/mL, we generally view ferritin > 3000 ng/mL as concerning for HLH and ferritin > 10 000 as highly suspicious.

§Elevations above age-adjusted, laboratory-specific normal levels (defined as > 2 SD from the mean) appear more meaningful than the original designation of > 2400 U/mL because of variations between laboratories.

Jordan et al. How I treat hemophagocytic lymphohistiocytosis. Blood. 2011;118(15):4041. Epub 2011 Aug 9

Jordan et al. How I treat hemophagocytic lymphohistiocytosis. Blood. 2011;118(15):4041. Epub 2011 Aug 9.

Table 2 Scoring system for classifying HSS/DRESS cases as definite, probable, possible or no case

Score	−1	0	1	2	Min.	Max.
Fever ≥ 38·5 °C	No/U	Yes			−1	0
Enlarged lymph nodes		No/U	Yes		0	1
Eosinophilia		No/U			0	2
Eosinophils			$0{\cdot}7–1{\cdot}499 \times 10^9\ L^{-1}$	$\geq 1{\cdot}5 \times 10^9\ L^{-1}$		
Eosinophils, if leucocytes $< 4{\cdot}0 \times 10^9\ L^{-1}$			10–19·9%	≥ 20%		
Atypical lymphocytes		No/U	Yes		0	1
Skin involvement					−2	2
Skin rash extent (% body surface area)		No/U	> 50%			
Skin rash suggesting DRESS	No	U	Yes			
Biopsy suggesting DRESS	No	Yes/U				
Organ involvement[a]					0	2
Liver		No/U	Yes			
Kidney		No/U	Yes			
Lung		No/U	Yes			
Muscle/heart		No/U	Yes			
Pancreas		No/U	Yes			
Other organ		No/U	Yes			
Resolution ≥ 15 days	No/U	Yes			−1	0
Evaluation of other potential causes						
Antinuclear antibody						
Blood culture						
Serology for HAV/HBV/HCV						
Chlamydia/mycoplasma						
If none positive and ≥ 3 of above negative			Yes		0	1
Total score					−4	9

U, unknown/unclassifiable; HAV, hepatitis A virus; HBV, hepatitis B virus; HCV, hepatitis C virus. [a]After exclusion of other explanations: 1, one organ; 2, two or more organs. Final score < 2, no case; final score 2–3, possible case; final score 4–5, probable case; final score > 5, definite case.

Kardaun et al., Variability in the clinical pattern of cutaneous side-effects of drugs with systemic symptoms: does a DRESS SHBr J Dermatol. 2007 Mar;156(3):609-11.