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A Phase 1/2 Multicenter Study of BMS-986012 in Subjects With Relapsed/Refractory Small Cell Lung Cancer

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Clinical Protocol CA001030

A Phase 1/2 Multicenter Study of BMS-986012 in Subjects with Relapsed/Refractory Small Cell Lung Cancer

Revised Protocol Number: 03
Incorporates Amendment(s): 02, 03, and 04

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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 03	06-Jun-2016	Incorporates Amendment 04
Amendment 04	06-Jun-2016	Added new combination treatment arms of BMS-986012 in combination with nivolumab, including revision to study objectives; addition of eligibility criteria, revision of select eligibility criteria, and revision of concomitant therapies; revision of dose-limiting toxicity (DLT), dose modification, delay, re-initiation, and study therapy discontinuation criteria; update of overall risk/benefit assessment; addition of pharmacokinetic collection schedules and analyses; [redacted] and additions to the statistical analyses. Updates were made to distinguish the BMS-986012 monotherapy treatment arm and to align the BMS-986012 monotherapy safety information to Investigator Brochure v03. [redacted] Revised the definition of refractory and sensitive based on the response duration from first-line therapy from 3 months to 90 days. Administrative changes (including addition of collection of residual additional research samples and removal of pharmacogenetic samples), corrections, and minor clarifications of text were made.
Revised protocol 02	18-Dec-2015	Incorporates Amendment 03
Amendment 03	18-Dec-2015	Clarified the timing of the follow-up procedures, revised select eligibility criteria, updated the overall risk/benefit assessment to include preliminary clinical data, updated the drug product description, permitted utilization of on-going data to re-evaluate doses in expansion cohorts, adjusted the pharmacokinetic (PK) [redacted] sample collection schedule and added additional PK parameters. [redacted] Administrative changes, corrections and minor clarifications of text were made.
Revised protocol 01	17-Mar-2015	Incorporates Amendment 02
Amendment 02	17-Mar-2015	Included that a focused neurologic examination must be performed at each visit while subjects are on treatment and during clinical follow-up, revised several inclusion/exclusion criteria, treatment guidelines for infusion reactions including that premedication will now be required prior to administration of BMS-986012, and further clarified assessments conducted and collection of adverse events and serious adverse events during the Clinical and Survival Follow-up periods of the study. Clarified modified toxicity probability interval algorithm and used a less conservative lower limit for the DLT target rate. Administrative changes, corrections and minor clarifications of text were made.

Document	Date of Issue	Summary of Change
Amendment 01	10-Jun-2014	Pharmacogenetics Amendment
Original Protocol	10-Jun-2014	Not applicable

SYNOPSIS

Clinical Protocol CA001030

Protocol Title: A Phase 1/2 Multicenter Study of BMS-986012 in Subjects with Relapsed/Refractory Small Cell Lung Cancer

Investigational Product(s), Dose and Mode of Administration, Duration of Treatment with Investigational Product(s): Each subject will be administered an intravenous (IV) dose of BMS-986012 as monotherapy or in combination with nivolumab once every 21 days until meeting protocol-specified discontinuation criteria. With Amendment 02 prophylactic premedication with a H1 blocker will be routinely administered prior to each BMS-986012 infusion as described in Section 3.7.

Study Phase: 1/2

Research Hypothesis: There is no formal primary research hypothesis for this study to be statistically tested. It is anticipated that BMS-986012 as monotherapy and in combination with nivolumab will demonstrate adequate safety and tolerability at pharmacologically relevant doses, so as to permit further clinical development (at a recommended dose range).

Primary Objective: To determine the multidose safety, tolerability, dose-limiting toxicities (DLTs), and the maximum tolerated dose (MTD) of BMS-986012 administered as monotherapy and in combination with nivolumab in subjects with relapsed/refractory small cell lung cancer (SCLC).

Secondary Objectives:

- To characterize the pharmacokinetics (PK) of BMS-986012 as monotherapy and in combination with nivolumab.
- To investigate the preliminary anti-tumor activity of BMS-986012 as monotherapy and in combination with nivolumab as measured by objective response rate (ORR), duration of response, and progression-free survival (PFS).
- To characterize the immunogenicity of BMS-986012 as monotherapy and in combination with nivolumab as well as immunogenicity of nivolumab in combination with BMS-986012.
- To assess the effect of BMS-986012 as monotherapy and in combination with nivolumab on the QT interval.

Exploratory Objectives:

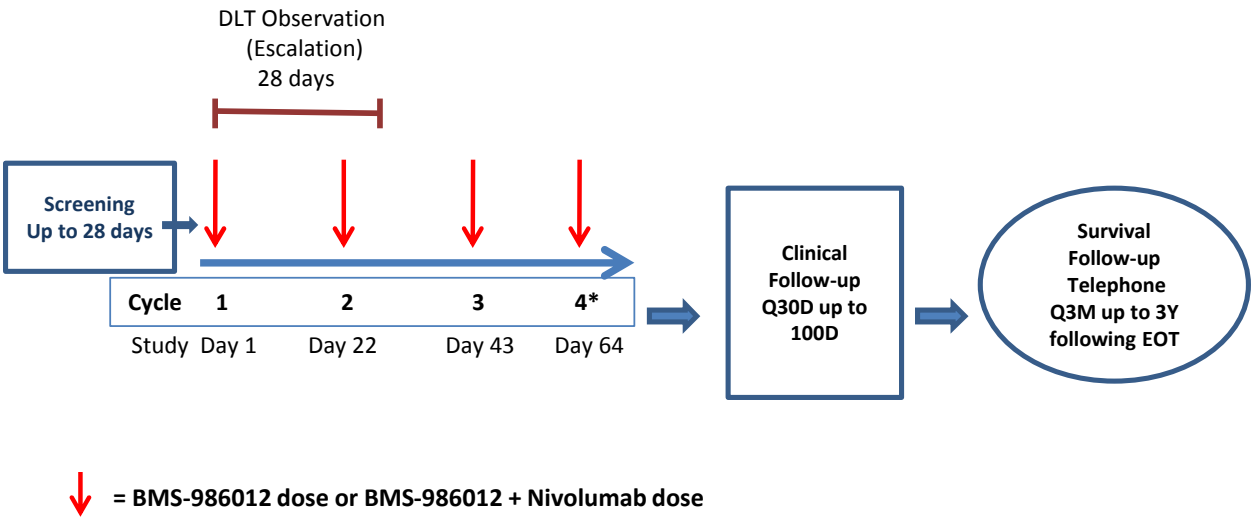
- To estimate the trough concentrations of nivolumab in combination with BMS-986012.
- To explore overall survival (OS).
- [redacted]

Study Design: This is an open-label, ascending multiple dose study of BMS-986012 administered once every 21 days (1 cycle) as a single agent and in combination with nivolumab and will be conducted in 4 parts. Dose escalation (BMS-986012 monotherapy [Part 1] and BMS-986012 and nivolumab combination therapy [Part 3]) is to

identify potential MTDs (or maximum administered doses [MAADs] if no MTDs are determined) for monotherapy or combination therapy, as applicable. In Parts 2 and 4 (dose expansion in BMS-986012 monotherapy and BMS-986012 and nivolumab combination therapy, respectively), additional subjects with SCLC will be enrolled at doses at or below the respective MTDs or MAADs to confirm safety and evaluate efficacy at these dose levels for BMS-986012 monotherapy and BMS-986012 and nivolumab combination therapy.

A study schematic is shown in Figure 1.

Figure 1: Study Design



Abbreviations: D = day; EOT = end of treatment; Q3M = every 3 months; Y = year.

*Subjects may receive additional cycles of treatment until protocol-specified discontinuation criteria are met. The DLT observation period pertains to Parts 1 and 3 (dose escalation) only.

Subjects will complete up to 4 periods in the study: Screening (up to 28 days), Treatment (until meeting protocol-specified discontinuation criteria), Clinical Follow-up (approximately 100 days), and Survival Follow-up (up to approximately 3 years following end of treatment). Screening and Treatment periods are calculated relative to the first dose of study drug. The Clinical Follow-up period begins 30 days (± 5 days) from the last dose of study drug, while the Survival Follow-up period occurs every 12 weeks (± 2 weeks) from the date of the 100-day Clinical Follow-up visit.

[redacted]

Each treatment cycle consists of an IV infusion of BMS-986012 monotherapy (Parts 1 and 2) or BMS-986012 and nivolumab combination therapy (Parts 3 and 4) once every 21 days. Tumor response will be assessed using Response Evaluation Criteria for Solid Tumors version 1.1 (RECIST v1.1). Subjects will be allowed to continue treatment until documentation of progressive disease (except as indicated in Section 4.5.4) or symptomatic deterioration, withdrawal of consent, unacceptable adverse events (AEs), and/or meeting other protocol-specified criteria for discontinuation.

Subjects who receive other anti-cancer therapies during the Clinical Follow-up period will remain in Clinical Follow-up for the 100-day period and all assessments will be collected. After completion of the Clinical Follow-up

period, all subjects will enter the Survival Follow-up period to collect data on survival status. The Clinical Follow-up period begins 30 days (± 5 days) from the last dose of study drug. The Survival Follow-up period occurs every 12 weeks (± 2 weeks) from the date of the 100-day Clinical Follow-up visit (see Section 3.1). Subjects with stable disease, partial response, or complete response at the last Clinical Follow-up visit should undergo tumor assessments every 3 to 4 months during the Survival Follow-up period until progression. Subjects will be permitted to receive other anti-cancer therapies, including investigational agents, during all follow-up periods. Subjects who have started new anti-cancer therapies or discontinued study due to progressive disease either during the Clinical Follow-up or Survival Follow-up periods will not undergo the computed tomography (CT)/magnetic resonance imaging (MRI) scans every 3 to 4 months. The end of the study will occur after the last treated subject has been followed for at least 6 months from his/her last treatment date.

Dose Escalation (Parts 1 and 3):

BMS-986012 Monotherapy Dose Escalation (Part 1):

Enrollment in dose escalation and MTD selection will adhere to a modified Toxicity Probability Interval (mTPI) design, using cohorts of 3 to 6 subjects within a dose level, and allowing flexible decision-making based on a minimum required cohort size. The design provides a simple algorithm for decisions on escalation, expanding at the same dose level, and de-escalation, depending on the number of observed toxicities after each dose cohort. The mTPI was selected over the rule based 3+3 design as the mTPI is more likely to select the true MTD and treat fewer subjects at suboptimal doses. The mTPI method utilizes a target toxicity (DLT) rate and equivalence interval (EI) to make decisions on escalation after each cohort and to estimate the MTD. For this study, the target DLT rate is 25% (EI [24%, 27%]). A total of approximately 30 evaluable subjects will be treated across the proposed dose levels as shown in Table -1. Doses intermediate to those specified may be evaluated if agreed upon by the Sponsor/Medical Monitor and investigators, provided the dose escalation increments are smaller than those specified. No intra-subject dose escalation of BMS-986012 is allowed at any dose level.

Dose escalation begins with Dose Level 1 and will be guided by the number of DLTs observed in 3 to 6 subjects treated initially per dose cohort and evaluable for safety for at least 28 days; additional subjects may be enrolled in cohorts of 3 to the same dose level if needed. If a decision to treat more subjects at a given dose level is specified by the mTPI algorithm when there are already at least 13 DLT evaluable subjects treated at the same dose level or a total of 30 DLT evaluable subjects treated at all dose levels, the dose escalation period will be stopped. To minimize risks to subjects from unanticipated acute toxicities, a waiting period of at least 5 days will occur between administrations of the first dose for the first, second, and third subjects to create an observation period prior to subsequent subject exposures. This waiting period is mandatory only in Cohort/Dose Level 1.

Decisions to escalate, add more subjects to the current dose level, de-escalate, or de-escalate and declare the current dose level as unacceptable (exceeding the MTD) will be based on the rate of DLTs in evaluable subjects within the 28-day DLT evaluation period (Figure 2). DLT evaluable subjects are defined as those receiving 2 doses of study drug in the first 28 days of dosing. At least 3 DLT evaluable subjects are required to enable a decision to escalate, add more subjects to the current dose level, or de-escalate.

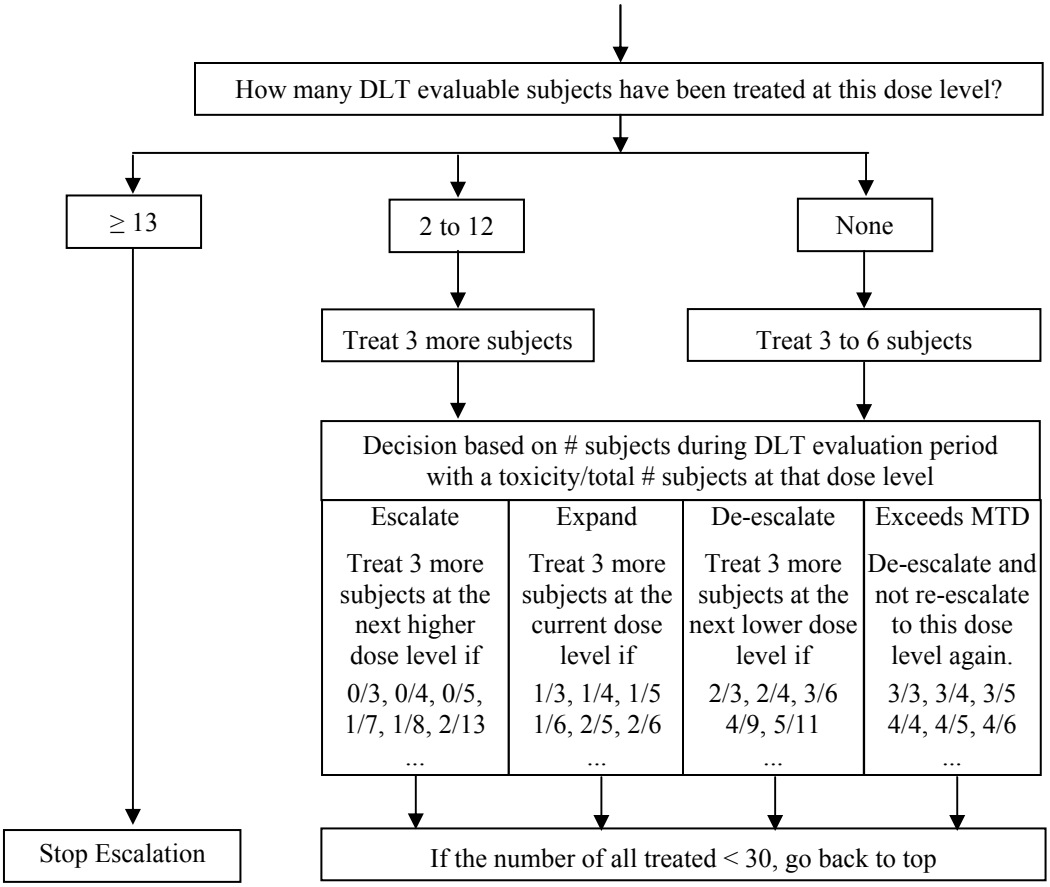
Figure 2 shows examples of scenarios guiding decision making that may be encountered during dose escalation with respect to the number of DLT evaluable subjects and the number of subjects with a DLT. All potential combinations of the number of DLTs and number of treated subjects evaluable for DLT are shown in Appendix 4. In addition to escalation or expansion decisions, dose re-escalation is permitted as per Figure 2 and Appendix 4 after a decision to de-escalate is made, except when a dose level has been identified as exceeding the MTD. Therefore, a dose level could be revisited multiple times under the mTPI design.

Table -1: Expected Dosages During BMS-986012 Monotherapy Dose Escalation [a]

Dose Level Number	BMS-986012 (mg IV Q3W)
-1	21
1	70
2	160
3	400
4	1000

[a] Interim doses may be explored.
Abbreviations: Q3W = every 3 weeks

Figure 2: BMS-986012 Monotherapy Dose Escalation Algorithm (Part 1)



At the end of the BMS-986012 monotherapy dose escalation period, the cumulative number of subjects who experience a DLT will be used to estimate the MTD using isotonic regression.

BMS-986012 and Nivolumab Combination Therapy Dose Escalation (Part 3)

A total of approximately 12 evaluable subjects will be treated across 2 dose levels. In combination therapy, nivolumab will be administered at 360 mg every 3 weeks (Q3W) in all combination dose levels, except as noted

below. BMS-986012 will be evaluated starting at 400 mg (Combination Dose Level 1). If safety and tolerability are established at 400 mg, Combination Dose Level 2 will be opened at 1000 mg. If toxicity is unacceptable at Combination Dose Level 1, additional combination dose level(s) may be evaluated using BMS-986012 dose of 160 mg and/or nivolumab dose of 240 mg Q3W. Selection of dose level for each study drug will be based on the nature and attribution of observed DLTs in previously evaluated dose levels. If toxicity is acceptable at Combination Dose Level 1 but unacceptable at Combination Dose Level 2, an intermediate dose level of BMS-986012 and/or nivolumab dose of 240 mg Q3W may be evaluated in additional cohort(s). The intermediate dose level of BMS-986012 will be selected based on combination therapy safety and available PK data.

Dose escalation with BMS-986012 and nivolumab combination therapy will follow similar guidelines as described above for Part 1. A mTPI design similar to that described for BMS-986012 monotherapy will guide dose escalation decisions. This design will use a target DLT rate of 29% (EI [28%, 31%]) for the combination setting and the mTPI Bayesian model and posterior inference to guide escalation decisions. The number of subjects in the initial cohort of each dose level will be 3 to 4. Decisions to escalate to the next dose level, expand (add more subjects to) the current dose level, or de-escalate will be guided by the number of DLTs observed, out of the total number of evaluable subjects at a current dose level, according to the design algorithm shown in Table 3.1.1.2-1. Enrollment of additional cohorts at the same dose level will proceed in sample sizes of 2 to 4 subjects. Subsequent dose levels will follow similar cohort enrollment size and decision rules.

To minimize risks to subjects from unanticipated acute toxicities, in all dose levels evaluated, at least 5 days must elapse between administration of the first dose for the first and second subjects to allow observation prior to subsequent exposures. In all Combination Dose levels, multiple subjects within a cohort will not be permitted to receive the initial dose of study drugs on the same day. Subjects must be clinically observed for at least 4 hours following the first 2 doses BMS-986012 and nivolumab combination therapy (ie, Cycles 1 and 2) and for at least 1 hour following doses beyond the first 2 doses of combination therapy (ie, Cycle 3 and beyond).

At the end of the BMS-986012 and nivolumab combination therapy dose escalation period, the cumulative number of subjects who experience a DLT at each dose level will be used to estimate the MTD of BMS-986012 in combination with nivolumab using isotonic regression. The MTD will be selected as the dose level with the smaller difference of estimated toxicity rate and the target DLT rate, among the dose levels explored.

Safety, including AEs occurring beyond the DLT observation period and available PK data, will also be considered in determining the recommended dose regimen of BMS-986012 and nivolumab to be administered in combination in Part 4. The dose regimen in Part 4 may be at or below the MTD of BMS-986012 and nivolumab combination therapy.

Dose-Limiting Toxicity

For the purpose of guiding dose escalation, DLTs will be determined based on the incidence, intensity, and duration of AEs occurring within 28 days of initiation of study drug (ie, the DLT evaluation period) for which no alternative cause can be identified. See Figure 2 and Appendix 4 for details of the mTPI dose escalation algorithm. The severity of AEs will be graded according to the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events version 4.03 (CTCAE v4.03). AEs occurring after the 28-day DLT evaluation period will be considered to represent DLTs 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.

Subjects must receive 2 doses of study drug during the 28-day DLT evaluation period to be considered evaluable for dose escalation decisions.

No intra-subject dose escalation is allowed. In the dose escalation period (Parts 1 and 3), subjects with insufficient data to establish safety during the DLT evaluation period at the current dose level may be replaced depending on the total number of DLT evaluable subjects at that dose level and the number of observed DLTs, and upon agreement of the Sponsor/Medical Monitor in collaboration with the investigators. DLTs are defined in detail in Section 3.1.3.

Dose Expansion (Parts 2 and 4)

BMS-986012 Monotherapy Dose Expansion (Part 2)

BMS-986012 monotherapy dose levels selected for the dose expansion period (Part 2) will not exceed the MTD or MAAD, but dose level selection may incorporate assessment of other data including toxicities and PK from Part 1. Part 2 will evaluate toxicity and preliminary efficacy of BMS-986012 as second-line treatment in subjects who have

relapsed following first-line chemotherapy as follows: (Table 2) Cohort A: ≤ 90 days response duration (refractory) at or below the MTD/MAAD, Cohort B: ≤ 90 days response duration (refractory) at a dose level below the MTD/MAAD, Cohort C: > 90 days response duration (sensitive) at or below the MTD/MAAD, and Cohort D: > 90 days response duration (sensitive) at a dose level below the MTD/MAAD. The response duration referenced above is relative to prior first-line therapy. Approximately 22 refractory and 28 sensitive subjects will be treated per cohort. As additional safety and PK data become available, the dose level of opened expansion cohorts may be re-evaluated, and an alternate dose level may be selected. Newly selected dose levels will not exceed the MTD/MAAD. Subjects currently dosing at the previously selected dose level will be permitted to continue at that dose level unless a protocol-specified dose modification (Section 4.5.1) is required. Enrollment will be guided by the Simon 2-stage design framework (see Table 3).

Anti-tumor activity will be assessed in approximately the first 9 or 10 evaluable subjects treated in each monotherapy cohort, with the option to stop enrolling in a cohort without an initial anti-tumor activity signal. The number of subjects needed for the Stage 1 review is guided by a Simon 2-Stage design, assuming a 25% desirable response rate (vs 10%) for refractory monotherapy cohort, and a 40% (vs 25%) for sensitive monotherapy cohort, with the following futility boundaries. After Stage 1, if none of the first 9 evaluable subjects in the refractory cohort, or if 2 or fewer subjects of the first 10 evaluable subjects in a sensitive cohort demonstrate clinical activity, enrollment in the cohort meeting criteria may not continue. As the expected time of response relative to dose initiation and the actual enrollment rate are unknown, it is expected that during the efficacy evaluation of subjects in Stage 1, more subjects may enroll and begin receiving treatment than the minimum needed for the Stage 1 assessment. Therefore, the above numbers are approximate and enrollment will continue during the evaluation of the interim data.

Evaluation of toxicity events in the cohort expansions will be performed throughout enrollment. If the aggregate rate of toxicities meeting DLT criteria exceeds 27% across all subjects treated in all monotherapy cohorts, the findings will be discussed and further enrollment may be interrupted. Depending on the nature and grade of toxicity and after assessing the risk/benefit ratio, additional subjects may be treated at, below, or intermediate to a dose level previously found to be safe following discussion by the Sponsor/Medical Monitor and investigators based on the available data. Selection of dose levels for these additional cohorts will be guided by accumulated safety and efficacy data; modeling may also be used to explore potential dose-response relationships.

Table 2: Dose Expansion Monotherapy Cohorts

Dose Expansion Cohorts		
Cohort	**Definition**	**Maximum* Approximate Number of Evaluable Subjects**
A	Refractory[a,b]	22
B	Refractory[a,c]	22
C	Sensitive[b,d]	28
D	Sensitive[c,d]	28

[a] ≤ 90-day response duration from first-line cancer therapy

[b] at or below MTD/MAAD

[c] at a dose level below MTD/MAAD

[d] > 90-day response duration from first-line cancer therapy

* Fewer subjects may be treated in a cohort with no evidence of tumor activity, as guided by a Simon 2-Stage design.

Following each treatment cycle, the decision to treat a subject with additional cycles of study therapy will be based on assessment of toxicity and tumor assessment. Subjects will generally be allowed to continue study therapy until the subject meets protocol-specified criteria for discontinuation of study therapy as outlined in Section 3.5.

BMS-986012 and Nivolumab Combination Therapy Dose Expansion (Part 4)

Part 4 will evaluate toxicity and preliminary efficacy of BMS-986012 and nivolumab combination therapy as second-line treatment in subjects who have relapsed following first-line chemotherapy. The dose levels of BMS-986012 and nivolumab selected for Part 4 will not exceed the MTD or MAAD of Part 3, but dose selection may incorporate assessment of toxicities, including those occurring beyond the DLT observation period, and available PK data from Part 3.

A total of approximately 30 evaluable subjects (refractory or sensitive to first-line chemotherapy) will be treated. Enrollment will be guided by the Simon 2-stage design framework.

Anti-tumor activity will be assessed in approximately the first 13 response-evaluable subjects, with the option to stop enrollment if no sufficient initial anti-tumor activity signal is observed. The number of subjects needed for the Stage 1 review is guided by a Simon 2-stage design, assuming a 40% desirable response rate (vs 20%), with the following futility boundaries. After Stage 1, if clinical activity is demonstrated in 2 or fewer of the first 13 evaluable subjects, enrollment may not continue. As the expected time of response relative to dose initiation and the actual recruitment rate are unknown, it is expected that during the efficacy evaluation of subjects in Stage 1, more subjects may have been enrolled and receiving treatment than the minimum needed for the Stage 1 assessment. Therefore, the above numbers are approximate and enrollment will continue during the evaluation of the interim data (see Table 3).

Evaluation of toxicity events in the cohort expansions will be performed throughout enrollment. If the aggregate rate of toxicities meeting DLT criteria exceeds 31% across all subjects treated in combination, the findings will be discussed and further enrollment may be interrupted. Enrollment may proceed at or below a dose level of BMS-986012 previously found to be safe. This may include an intermediate dose level. Selection of the dose level will depend on the nature and grade of toxicities and assessment of the risk/benefit ratio. A lower dose level of nivolumab (240 mg Q3W) may also be selected. Decisions will be made by the Sponsor/Medical Monitor, in collaboration with the investigators as indicated above in Part 2.

Duration of Study: The screening period will last up to 28 days. Subjects will receive BMS-986012 as monotherapy or in combination with nivolumab every 21 days until meeting protocol-specified criteria for discontinuation. The Clinical Follow-up period will be approximately 100 days following the last dose of study drug, including subjects discontinuing the study for disease progression unless subjects have withdrawn consent. After completing the Clinical Follow-up period, subjects will continue to be followed for overall survival up to 3 years from end of treatment. Subjects with stable disease, partial response, or complete response at end of treatment will also undergo tumor assessment every 3 to 4 months during the follow-up periods until progression. The end of the study will occur after the last treated subject has been followed for at least 6 months from his/her last treatment date.

Number of Subjects: During the BMS-986012 monotherapy dose escalation period (Part 1), up to approximately 30 evaluable subjects were expected to be treated. Although the exact number per dose level depends on the number of observed toxicities, approximately 3 to 9 subjects were expected to be evaluated in each dose level during dose escalation. In the BMS-986012 monotherapy dose expansion period (Part 2), approximately 100 evaluable subjects will be treated. During the dose escalation period with BMS-986012 and nivolumab combination therapy (Part 3), approximately 12 evaluable subjects are expected to be treated at 2 dose levels of BMS-986012 and nivolumab combination therapy. In the BMS-986102 and nivolumab combination therapy dose expansion period (Part 4), approximately 30 evaluable subjects will be treated. Approximately 230 subjects are estimated to be enrolled in this study, including subjects screened but not meeting eligibility criteria and subjects treated but requiring replacement. Additional subjects may be enrolled in escalation or expansion cohorts, if needed to maintain a sufficient number of subjects evaluable for safety or anti-tumor activity.

Study Population: Men and women at least 18 years of age or the local age of majority with histological or cytological confirmed pulmonary SCLC and Eastern Cooperative Oncology Group Performance Status 0 to 1 and meeting all other eligibility criteria may participate in the study. Subjects must not have central nervous system metastases, unless they are controlled and treated as outlined in the exclusion criteria. All SCLC subjects must have

relapsed after or be deemed refractory to first-line therapy. In Parts 1 and 3, subjects must have received at least 1 prior line of therapy. In Parts 2 and 4, subjects must have received only 1 prior line of therapy.

Women of childbearing potential must not be nursing or pregnant. All women must have a negative pregnancy test within 72 hours prior to dosing with study drug if enrolled in the BMS-986012 monotherapy (Parts 1 and 2) or 24 hours prior to dosing with study drug if enrolled in the BMS-986012 and nivolumab combination therapy (Parts 3 and 4).

Study Drug:

Study Drug for CA001030

Medication	Potency	Investigational Product (IP)/NonIP
BMS-986012 (Solution for Injection)	120 mg/vial (30 mg/mL)	IP
Nivolumab (Solution for Injection)	100 mg/vial (10 mg/mL)	IP

IP = investigational product.

Study Assessments:

Safety Outcome Measures: Adverse events will be assessed during treatment and until 100 days after the last treatment. Serious adverse events (SAEs) will be collected from the time a subject signs informed consent and for approximately 100 days after the last treatment. Adverse events will be coded using the most current version of Medical Dictionary for Regulatory Activities and reviewed for potential significance and importance. AEs will be evaluated according to the NCI CTCAE Version 4.03. Subjects should be followed until all AEs for which no clear alternative cause is identified other than to study treatment have recovered to baseline or are deemed irreversible by the investigator. Safety assessments will be based on medical review of AE reports and the results of vital sign measurements, physical examinations, and clinical laboratory tests. Serial electrocardiograms (ECGs) (reviewed by a central laboratory) will be collected from a minimum of 77 subjects across doses (including BMS-986012 monotherapy and BMS-986012 and nivolumab combination therapy) with most subjects at the MTD (MAAD) to measure QT, other ECG intervals, and heart rate to explore the potential effect of study drug on QTc.

Pharmacokinetic Measures: The following PK measures will be taken according to the times for each study Part, as detailed in Section 5.5: maximum observed concentration (Cmax), time of maximum observed concentration (Tmax), observed serum concentration at the end of a dosing interval (Ctau), area under the concentration-time curve from time zero to the time of the last quantifiable concentration (AUC[0-t]), area under the concentration-time curve over the dosing interval (AUC[TAU]), total body clearance (CLT), trough observed serum concentration (Ctrough), volume of distribution at steady state (Vss), average concentration over a dosing interval (Css-avg), accumulation index (AI) (for AUC[TAU], Cmax, and Ctau), and effective elimination half-life (T-HALFeff).

Efficacy Measures: Disease assessments using CT and/or MRI as appropriate, will be performed at baseline and every 6 weeks (every 2 cycles) until disease progression or as planned per protocol. Tumor responses will be determined by the investigator for subjects with adequate data as defined by RECIST v1.1. At the Sponsor's discretion, de-identified scans and measurements may be collected and reviewed by independent radiologists using RECIST v1.1 criteria at a later date, or at any time during the study.

Immunogenicity Measures: Serum samples to evaluate development of positive anti-drug antibody (ADA) response to BMS-986012 and nivolumab will be collected at specified time points.

[redacted]

[redacted]

Statistical Considerations:

Sample Size:

Dose Escalation (Parts 1 and 3)

A total of approximately 30 evaluable subjects are expected to be treated during BMS-986012 monotherapy dose escalation (Part 1) and approximately 12 evaluable subjects in BMS-986012 and nivolumab combination dose escalation, assuming 2 dose levels (Part 3). The exact number per dose level will depend on the number of observed DLTs and will be guided by the escalation design that selects as MTD the dose level with an estimated DLT rate closest to 25% target DLT rate in monotherapy (Part 1) and the dose level with DLT rate closest to 29% in combination therapy (Part 3). Between 2 and up to 13 DLT evaluable subjects may be enrolled to a given dose level in BMS-986012 monotherapy. Treating additional subjects beyond the 13 at the same dose level would be unlikely to alter the decision specified by the mTPI algorithm.

Dose Expansion (Parts 2 and 4)

The total sample size per each BMS-986012 monotherapy expansion cohort (approximately n = 22 for refractory and approximately n = 28 for sensitive) is planned to provide a reasonable false positive rate (FPR) and false negative rate (FNR), based on assumptions of true (target) and historic ORR for each tumor as seen below. In addition to the FPR and FNR, the lower limits of the confidence interval (CI) for ORR based on the Clopper-Pearson method are provided below by cohort.

For a refractory tumor dose expansion monotherapy cohort of 22 subjects and assuming a true ORR of 25%, there is an 84% chance of observing at least 4 responses, a 68% chance of observing at least 5 responses, and a 16% chance of observing 3 or fewer responses (FNR). If the true ORR is only 10% rather than 25%, then there is a 17% and 6% chance, respectively, that there will be at least 4 or at least 5 responses in 22 subjects (FPR). In addition, if 4 or 5 responses are observed, then the lower limit of the 80% CI for the ORR is 8.2% or 11.5%, respectively.

For a sensitive tumor dose expansion monotherapy cohort of 28 subjects and assuming a true ORR of 40%, there is an 85% chance of observing at least 9 responses, a 74% chance of observing at least 10 responses, and a 15% chance of observing 8 or fewer responses (FNR). If the true ORR for a tumor is only 25% rather than 40%, then there is a 25% and 14% chance, respectively, that there will be at least 9 or at least 10 responses in 28 subjects (FPR). In addition, if 8 or 9 responses are observed, then the lower limit of the 80% CI for the ORR is 17% or 20%, respectively.

In the combined sensitive and refractory monotherapy expansion cohort of 29 subjects and assuming a true ORR of 40%, there is an 88% chance of observing at least 9 responses, and a 12% chance of observing 8 or fewer responses (FNR). If the true ORR for a tumor is only 20% rather than 40%, then there is an 11% chance and a 5% chance that there will be at least 9 and at least 10 responses, respectively, in 29 subjects (FPR). In addition, if 10 or 11 responses are observed, then the lower limit of the 80% CI for the ORR is 23% or 26%, respectively.

The Simon 2-stage (optimal) design will be used for the expansion cohorts. In monotherapy cohorts after a minimum of 9 subjects per refractory cohort and 10 subjects per sensitive cohort are treated in Stage 1, there will be an initial evaluation of efficacy, independently in each cohort. Similarly, in the BMS-986012 and nivolumab combination therapy cohort (Part 4), after a minimum of 13 subjects are treated in the combination cohort in Stage 1, there will be an initial evaluation of efficacy in this cohort. This will inform potential early decisions and guide planning/operations or early termination after taking into consideration additional data, for example, duration of response and/or stable disease and safety. The operational characteristics of this Simon 2-stage design are provided in Table 3 although not used for hypothesis testing.

Table 3: Dose Expansion: Characteristics of the Simon 2-Stage Design in Monotherapy Refractory and Sensitive, and Combination Cohorts

Expansion Cohort	Historic ORR (%)	Target ORR (%)	Stage 1 /Total N	Stage 1 Responses Futility Boundary	Alpha/ Power (%)	Probability of Early Stopping (%)
Monotherapy Refractory	10	25	9/22	0	16/80	38.7
Monotherapy Sensitive	25	40	10/28	2	20/75	53
Combination[a]	20	40	13/29	2	10/86	50

[a] Refractory and Sensitive Subjects Combined

The number of subjects receiving treatment at the time of the Stage 1 efficacy evaluation is approximate and may exceed the specified minimum number of 9, 10, or 13 due to time needed for radiological tumor measurement, the unknown time to response, and the unknown true recruitment rate.

Endpoints:

Primary endpoint:

Safety: The primary endpoint of this Phase 1/2 study is safety as measured by the rate of AEs, SAEs, AEs leading to discontinuations, deaths, and clinically significant laboratory abnormalities. Safety will be evaluated from the time a subject signs informed consent and for up to 100 days after the last dose of study drug.

Secondary endpoints:

Efficacy:

The ORR, duration of response, and PFS will be assessed based on RECIST v1.1 criteria. In addition, PFS rates at pre-specified time points (eg, 24, 36 weeks) will be assessed. Individual best overall response (BOR) will be a subject-level endpoint. The above will be determined based on tumor measurements occurring every 6 weeks during the Treatment period, and at approximately the 100-day Clinical Follow-up visit, according to institutional practice. Subjects not progressing at discontinuation of study treatment will undergo tumor assessments every 3 to 4 months or as per institutional practice until the date of the first objective documentation of tumor progression or death due to any cause. Overall survival and OS rate will be assessed as part of exploratory efficacy analysis.

Pharmacokinetics: Cmax, Tmax, Ctau, AUC(0-t), AUC(TAU), CLT, Ctrough, Vss, Css-avg, AI (for AUC[TAU], Cmax, and Ctau), and T-HALFeff.

Immunogenicity: Occurrence of specific ADA to BMS-986012 (as monotherapy and in combination with nivolumab) and to nivolumab (in combination with BMS-986012). Samples will be collected at multiple time points.

[redacted]

Safety Analyses

All recorded AEs will be listed and tabulated by system organ class, preferred term, and treatment. Vital signs and clinical laboratory test results will be listed and summarized by treatment. Any significant physical examination

findings and clinical laboratory results will be listed. ECG readings will be evaluated by the investigator and abnormalities, if present, will be listed.

For subjects with serial ECG measurements, changes in the QT interval Fridericia's correction formula (QTcF) (ΔQTcF), ECG intervals QRS, and PR, and in heart rate (ΔHR) will be tabulated by dose level and study day. Scatter plots of heart rate, ΔHR, QTcF, and ΔQTcF versus time-matched BMS-986012 concentrations will be provided. A concentration-response effect of BMS-986012 on QTcF may be assessed by a linear mixed effects regression model for ΔQTcF on serum BMS-986012 concentrations, stratified by study day, as well as pooled across days, for the BMS-986012 monotherapy and BMS-986012 and nivolumab combination therapy.

Efficacy Analyses

Individual BOR, duration of response and PFS will be listed using RECIST v1.1 criteria (Appendix 3). The ORR and PFS rate (eg, at 24 weeks) will be tabulated by study period (escalation, expansion) and dose for each BMS-981012 monotherapy dose expansion cohort (refractory or sensitive, Part 2), and the BMS-986012 and nivolumab combination therapy dose expansion cohort (Part 4). The CIs will be based on Clopper-Pearson method for ORR and using Greenwood formula for PFS rate. The duration of response and PFS will be estimated by Kaplan-Meier (K-M) methodology for each expansion cohort (Parts 2 and 4). Overall survival will also be assessed as part of exploratory efficacy analysis, by K-M plots and median OS as well as OS rates, at specified times (eg, at 6 or 12 months) and will be provided. Subjects from the same disease type in the expansion cohorts may be pooled, regardless of dose level, if deemed appropriate.

Pharmacokinetic Analyses

Descriptive statistics for BMS-986012 PK parameters will be tabulated by dose level and treatment (BMS-986012 monotherapy and BMS-986012 and nivolumab combination therapy). Geometric means and coefficients of variation, CV(%), will be presented for Cmax, AUC, Ctau, AI, CLT, Ctrough, Vss, and Css-avg. Medians and ranges will be presented for Tmax. PK trough concentrations for nivolumab will be tabulated.

Immunogenicity Analyses

All available immunogenicity data for BMS-986012 as monotherapy and in combination with nivolumab, as well as immunogenicity of nivolumab in combination with BMS-986012, will be listed, with flags for subjects with at least 1 positive ADA after initiation of treatment. The frequency of subjects with a positive ADA assessment at baseline, and frequency of subjects who develop ADA after initiation of treatment will be provided. Associations between immunogenicity measures and PK and/or select AEs may be explored.

[redacted]

Interim Analyses

Data emerging from this study may be needed for timely decisions about adjustments to procedures in subsequent parts of the study. Therefore, data may be reviewed prior to the final lock of the study database. Additional interim analyses may also be performed for administrative purposes or publications. Analyses may only consist of listings, summaries, and graphs of the available data. No formal inferences requiring any adjustment to statistical significance level will be performed. Efficacy analyses based on interim data may use response evaluable or all treated populations depending on the purpose of the analysis.

Other Analyses

Additional exposure response analysis may be performed to explore associations of BMS-986012 (or nivolumab) PK exposure with [redacted] selected safety measures, and/or efficacy measures.

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1 INTRODUCTION AND STUDY RATIONALE

1.1 Study Rationale

1.1.1 Lung Cancer

Lung cancer has been the most common cancer in the world for several decades, and in 2012 there were an estimated 1.8 million new cases, representing 12.9% of all new cancers. It is also the most common cause of death from cancer, with 1.59 million deaths (19.4% of the total).[1] From 2004 through 2010 in the United States (US), the overall 5-year survival for lung cancer was 16.8%.[2] In the US for 2014, the number of new cases of lung cancer was estimated to be 224,210 and the number of deaths from lung cancer was 159,260; accounting for 27% of all cancer deaths, more than any other cancer. Approximately 57% of patients have metastatic disease at diagnosis, and in these patients the prognosis is poor; with a 5-year survival less than 4%.[2]

These statistics include small cell lung cancer (SCLC), which has an even poorer prognosis. SCLC accounts for 12% to 16% of all lung cancers in the USA and Europe, and is distinguished by its rapid growth rate, early dissemination to regional lymph nodes and distant sites, and its sensitivity to chemotherapy and radiotherapy.[3] Patients with SCLC rarely survive more than a few months without treatment. However, SCLC is highly responsive to multiple chemotherapeutic drugs, and chemotherapy dramatically prolongs survival compared to best supportive care.[4] Management of SCLC depends on the stage of the disease at diagnosis.

The staging system most commonly used for SCLC is the Veterans Administration Lung Group system, defining limited and extensive stage disease. Sixty percent to 70% of patients have extensive disease at diagnosis.[5] Although American Joint Committee on Cancer TNM staging[6] correlates with prognosis in SCLC,[7,8,9,10,11,12,13,14,15,16,17,18,19] surgery is appropriate in less than 5% of patients. Most patients will receive chemotherapy with or without radiation. SCLC is a chemotherapy-sensitive disease, and 70% to 90% of newly-diagnosed patients will respond to first-line therapy chemotherapy. Regimens containing a platinum and etoposide are often chosen as first-line treatment in patients with good performance status. However, median survival is 9 to 11 months and long-term survival is rare. Fewer than 5% of patients with extensive disease live beyond 2 years, even with multi-agent, intensive treatment with multiple lines of therapy.

Few new agents with activity in SCLC have been identified, and none have been successful thus far in Phase 3 studies.

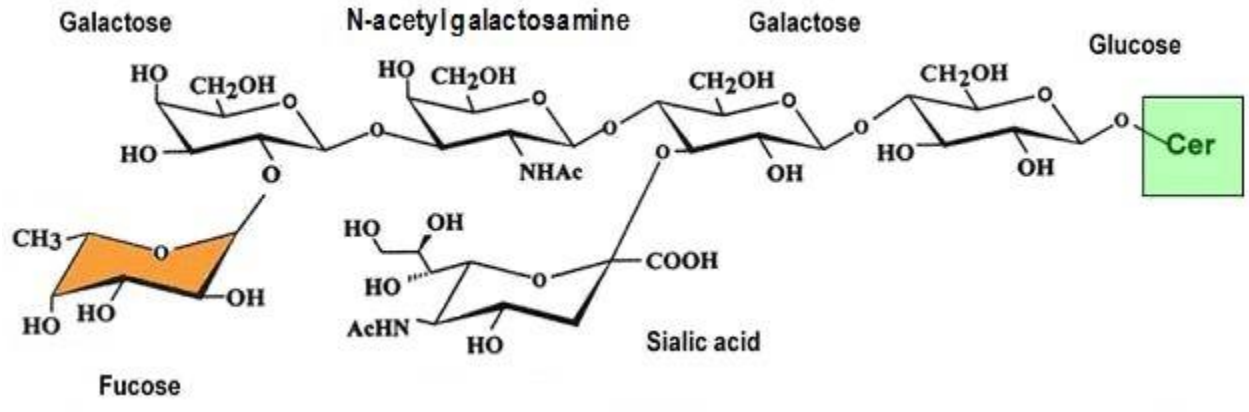
Fucosyl-GM1 (fuc-GM1) offers a cell surface target known to be expressed in 70% of SCLC tumors by immunohistochemistry (IHC).[20,21,22] BMS-986012 is being developed for the treatment of lung cancer and this first-in-human study will evaluate safety, tolerability, and preliminary efficacy as monotherapy and, with Amendment 04, in combination with nivolumab in the SCLC population.

1.1.2 Fucosyl-GM1

Carbohydrate antigens are the most abundantly expressed antigens on the surface of cancer cells.[23] Gangliosides are complex glycosphingolipids that contain sialic acid and that play a role in cell-cell and cell-extracellular matrix interactions. They have also been implicated in promoting cell proliferation, angiogenesis and immune tumor cell evasion. Antibodies to gangliosides have been shown to inhibit tumor growth and to induce apoptosis of antigen positive cells.[24]

Fucosylated-monosialotetrahexosylganglioside (fuc-GM1) (fucosyl-α1-2Galβ1-3GalNAcβ1-4(NeuAcα2-3)Galβ1-4Glcβ1-1Cer) is a sphingolipid monosialoganglioside composed of a ceramide lipid component which anchors the molecule in the cell membrane and a carbohydrate component which is exposed at the cell surface (Figure 1.1.2-1).

Figure 1.1.2-1: Structure of Fucosyl-GM1



1.1.3 Rationale for Fucosyl-GM1 as a Target Antigen

BMS-986012 is a first-in-class fully human immunoglobulin G (IgG) 1 monoclonal antibody (mAb) that specifically binds to the fuc-GM1 ganglioside. BMS-986012 is being developed for the treatment of SCLC, as IHC analysis of tumor samples with anti-fuc-GM1 mAb has demonstrated antigen expression in a high percentage of SCLC cases and little or no expression in normal tissues.[25,26,27,21,22] BMS-986012 exhibits high-affinity and dose-dependent saturable binding to fuc-GM1 and shows no detectable antigen-specific binding to closely related molecule monosialotetrahexosylganglioside. BMS-986012 was optimized to have enhanced effector functions by elimination of the fucosylation on the fragment crystallizable (Fc) domain. The absence of this fucosyl group in BMS-986012 (resulting from its expression in a cell line deficient in fucosyl transferase) confers higher affinity for Fc receptors resulting in enhanced antibody-dependent cellular cytotoxicity (ADCC).[28] Furthermore, the antibody was shown to mediate potent complement-dependent cytotoxicity (CDC) as well as antibody-dependent

cellular phagocytosis (ADCP). Please refer to the BMS-986012 Investigator Brochure (IB) for further details.[29]

Clinical experience with targeting fuc-GM1 comes from some early studies in SCLC patients who were vaccinated with keyhole limpet hemocyanin -conjugated fuc-GM1. These patients developed antibody titers to this antigen. In in vitro assays, these antibodies demonstrated specific binding to tumor cells and CDC directed against fuc-GM1 positive cell lines.[30,31] The investigators have initiated a further clinical trial to test a pentavalent vaccine containing GD2L, GD3L, Globo H, Fuc-GM1, and N-Propionylated Polysialic Acid.[32] Vaccine associated toxicities were mild and transient and 3 patients with limited-stage SCLC were relapse-free at 18, 24, and 30 months.[30,31]

Fuc-GM1 has been evaluated in mice bearing human SCLC tumors. Robust tumor-growth inhibition (TGI) was demonstrated in multiple xenograft models when mice were treated with BMS-986012 as a monotherapy. When BMS-986012 was administered in combination with cisplatin or etoposide, efficacy increased in 5 out of 6 xenograft models. These in vivo results demonstrate that BMS-986012, as a single agent, is a potent inhibitor of human SCLC tumor growth and can improve outcomes when combined with chemotherapy.[33,34,35,36,37,38,39,40,41,42]

1.1.4 Nivolumab Mechanism of Action

Cancer immunotherapy rests on the premise that tumors can be recognized as foreign rather than as self and can be effectively attacked by an activated immune system. An effective immune response in this setting is thought to rely on immune surveillance of tumor antigens expressed on cancer cells that ultimately results in an adaptive immune response and cancer cell death. Meanwhile, tumor progression may depend upon acquisition of traits that allow cancer cells to evade immunosurveillance and escape effective innate and adaptive immune responses.[43,44,45] Current immunotherapy efforts attempt to break the apparent tolerance of the immune system to tumor cells and antigens by either introducing cancer antigens by therapeutic vaccination or by modulating regulatory checkpoints of the immune system. T-cell stimulation is a complex process involving the integration of numerous positive, as well as negative, co-stimulatory signals in addition to antigen recognition by the T-cell receptor.[46] Collectively, these signals govern the balance between T-cell activation and tolerance.

Programmed cell death protein-1 (PD-1) is a member of the CD28 family of T-cell co-stimulatory receptors that also includes CD28, CTLA 4, ICOS, and BTLA.[47] PD-1 signaling has been shown to inhibit CD-28-mediated upregulation of interleukin (IL)-2, IL-10, IL-13, interferon (IFN)-γ, and Bcl-xL. PD-1 expression has also been noted to inhibit T-cell activation and expansion of previously activated cells. Evidence for a negative regulatory role of PD-1 comes from studies of PD-1 deficient mice, which develop a variety of autoimmune phenotypes.[48] These results suggest that PD-1 blockade has the potential to activate anti-self T-cell responses, but these responses are variable and dependent upon various host genetic factors. Thus, PD-1 deficiency or inhibition is not accompanied by a universal loss of tolerance to self-antigens.

In vitro, nivolumab (BMS-936558) binds to PD-1 with high affinity (EC50 0.39 to 2.62 nM) and inhibits the binding of PD-1 to its ligands programmed death-ligand (PD-L) 1 and PD-L2 (half maximal inhibitory concentration ± 1 nM). Nivolumab binds specifically to PD-1 and not to related members of the CD28 family such as CD28, ICOS, CTLA-4, and BTLA. Blockade of the PD-1 pathway by nivolumab results in a reproducible enhancement of both proliferation and IFN-γ release in the mixed lymphocyte reaction. Using a cytomegalovirus (CMV) re-stimulation assay with human peripheral blood mononuclear cells (PBMC), the effect of nivolumab on antigen specific recall response indicates that nivolumab augmented IFN-γ secretion from CMV specific memory T cells in a dose-dependent manner versus isotype-matched control. In vivo blockade of PD-1 by a murine analog of nivolumab enhances the anti-tumor immune response and result in tumor rejection in several immunocompetent mouse tumor models (MC38, SA1/N, and PAN02).[49]

1.1.5 Rationale for Immuno-oncology Therapeutic Approaches in SCLC

An analysis of PBMCs from SCLC patients has shown a higher number of T-effector cells in limited disease SCLC compared with extensive disease SCLC subjects and a higher T-effector to T-regulator ratio in long-term survivors of SCLC.[50] In a Phase 2 randomized study, phased ipilimumab (placebo + paclitaxel/carboplatin followed by ipilimumab + paclitaxel/carboplatin) showed improved progression-free survival (PFS) versus carboplatin and paclitaxel (5.7 months vs 4.6 months, hazard ratio = 0.72, P = 0.05.[51] Nivolumab at doses of 1, 3, and 10 mg/kg has been shown to be effective against non-small cell lung cancer (NSCLC) in a Phase 1 study (N = 122) with objective response rate (ORRs) of 6%, 27%, and 17% and PFS rates at 24 weeks of 25%, 44%, and 31%.[52,53]

In a Phase 1/2 study of nivolumab with or without ipilimumab for treatment of recurrent SCLC (CA209032), subjects who were platinum sensitive or refractory and had progressive disease (PD) were enrolled regardless of tumor PD-L1 status or number of prior chemotherapy regimens. This open-label study randomized subjects to nivolumab 3 mg/kg by intravenous (IV) infusion every 2 weeks (Q2W) or nivolumab + ipilimumab (1 + 1 mg/kg, 1 + 3 mg/kg, or 3 + 1 mg/kg) IV every 3 weeks (Q3W) for 4 cycles, followed by nivolumab 3 mg/kg Q2W. The primary objective was ORR. Other objectives were safety, PFS, overall survival (OS), and biomarker analysis. Seventy-five subjects were enrolled (nivolumab, n = 40; nivolumab + ipilimumab, n = 35); 59% of the enrolled subjects had at least 2 prior regimens. Drug-related adverse events (AEs) in ≥ 10% of subjects were fatigue (18%), diarrhea (13%), nausea (10%), and decreased appetite (10%) with nivolumab and fatigue (29%); diarrhea (17%); pruritus (14%); and nausea, endocrine disorders, and rash (11% each) with nivolumab + ipilimumab. Grade 3 or 4 drug-related AEs with nivolumab occurred in 7 (18%) subjects (all in n = 1 [3%]: stomatitis, fatigue, hyperglycemia, increased alanine aminotransferase (ALT), increased gamma-glutamyl transferase, encephalitis, and infusion-related reaction). Grade 3 or 4 drug-related AEs in ≥ 5% of subjects included diarrhea and rash (6% each in the nivolumab + ipilimumab arm). Drug-related pneumonitis occurred in 2 subjects (1 per arm). Limbic encephalitis was reported in 2 subjects in the nivolumab arm and 1 subject in the nivolumab + ipilimumab arm. The event resolved under steroid treatment in 2 subjects and continued despite immunosuppressive

treatment in 1 subject. Of 40 evaluable subjects treated with nivolumab, partial response (PR) was seen in 6 (15%; duration of ongoing responses 80 to 251+ days); stable disease (SD) in 9 (22.5%); and PD in 25 (62.5%). In conclusion, in this PD-L1 unselected, heavily pre-treated SCLC population including platinum-based first-line treatment, nivolumab treatment was well tolerated. The ORR was 15% for subjects with nivolumab with long lasting responses beyond 251 days, all ongoing at the time of the data cut off.

Considering the immune response seen in SCLC patients, and the results of checkpoint inhibitors nivolumab and ipilimumab in NSCLC patients, it is reasonable to expect that nivolumab monotherapy is likely to provide benefit in second-line treatment of SCLC.

1.1.6 Rationale for Combining BMS-986012 and Nivolumab

BMS-986012 in combination with nivolumab may provide clinical benefit to subjects with SCLC by combining the immune-based mechanisms of action (MOA) of both compounds. Although, syngeneic and genetically engineered mouse models (GEMM) are currently the best way to evaluate potential activity of immuno-oncology agents, there are few GEMMs in SCLC. Each of the SCLC GEMMs characterized to date has unique pathologic characteristics and it is unclear which, if any, best represents SCLC in general.[54] There have been no published studies to date of the utility of these models for determining the activity of immuno-oncology agents such as PD-1 inhibitors nor for the combination of immuno-oncology agents with other anti-cancer therapies. Additionally, fuc-GM1 tumor expression is currently unknown in these models. Therefore, no adequately characterized tumors in immune competent mice are available to determine pre-clinical efficacy. Internal evaluation to characterize 1 GEMM SCLC model (Rb, p53, and p130 knock-out) has begun and demonstrated no observed adverse effects such as weight loss or death when BMS-986012 and nivolumab were administered in combination, supporting the potential safety of this combination for clinical use.

Although pre-clinical efficacy has not been demonstrated due to a lack of adequately characterized models, potential areas of synergy include the following:

- Providing antigens to antigen-presenting cells (APCs) to induce T-cell activity: BMS-986012 has been shown in pre-clinical models to lead to cancer cell death, including by ADCP. Processing and presentation of antigens by APCs, such as macrophages, has been shown to increase T-cell responses in tumor models. Furthermore, suboptimal tumor antigen delivery and presentation have been postulated as another mechanism by which tumors can successfully evade immune system recognition. As nivolumab is known to increase T-cell activation, synergy is expected via this mechanism.
- Reducing tumor cell-derived immune inhibition: Tumors and tumor microenvironment are known to express a variety of factors that impede a robust immune response from eliminating the tumor. Soluble and membrane-bound factors have been shown to inhibit the cytolytic activity of tumor infiltrating T cells (eg, PD-L1 expression; transforming growth factor-beta). In addition, some tumor-derived factors are able to enhance immune system counter-regulatory systems (eg, increased T-regulatory cells). BMS-986012 monotherapy has demonstrated pre-clinical TGI and clinical activity including tumor reduction.[29] This anti-

tumor activity may lead to reduced immune inhibition and synergistic activity with the anti-PD-1 effects of nivolumab.

- Supporting immune-based MOA of BMS-986012: BMS-986012 demonstrated dose-dependent ADCC and ADCP.[29] Because BMS-986012 acts via multiple immune cell-based mechanisms, enhancement of the overall immune activation via the T-cell stimulatory effects of nivolumab may increase BMS-986012 anti-tumor activity.

1.1.7 Rationale for BMS-986012 Dose

1.1.7.1 Rationale for BMS-986012 Monotherapy Starting Dose

The BMS-986012 monotherapy starting dose of 70 mg was chosen using both pre-clinical toxicology and pharmacology studies. The flat dose of 70 mg BMS-986012, which approximates a 1 mg/kg dose, is 10-fold below the monkey no-observed-adverse-effect-level (NOAEL) and 150-fold below the highest non-severely toxic dose (HNSTD), but within the predicted pharmacologically active dose range. Due to the wide margin between the pharmacologically active dose range and the HNSTD, weight-based dosing to minimize variation in exposure is not needed, but the effect of body weight on exposure will be assessed in this study.

1.1.7.2 Estimate of BMS-986012 Monotherapy Human Pharmacologically Active Dose

Pharmacologically active doses were estimated by exploratory modeling and therapeutic translation of pre-clinical data. The therapeutic target response was set to 90% tumor volume regression in subjects with SCLC to approximate a near-complete response by Response Evaluation Criteria for Solid Tumors (RECIST) criteria. A potentially therapeutic dose regimen in subjects with SCLC ranges 0.6 to1 mg/kg BMS-986012 administered IV in 1 hour every 21 days; is predicted to achieve 90% tumor volume regression. The 21-day dose interval was selected to coincide with standard of care chemotherapy dose regimens (potential combination partners).

1.1.7.3 Estimate of BMS-986012 Monotherapy First-in-Human Dose

In a 1 month Good Laboratory Practices (GLP) study (DM13026), 5 male and 5 female cynomolgus monkeys (non-tumor bearing) per dose group received 10 and 150 mg/kg BMS-986012 IV over 3 minutes every week for 5 doses.[55] Serum BMS-986012 concentrations were measured at pre-determined times during the GLP study to estimate exposure. The HNSTD was 150 mg/kg BMS-986012 and the NOAEL was 10 mg/kg. Pharmacokinetic (PK) modeling of data from the 10 mg/kg dose group and allometric scaling methods with typical exponents were used to project linear clearance (4.3 mL/h), half-life (T-HALF) (21 days) and exposure in humans.

The NOAEL estimated in the GLP toxicology study in monkeys demonstrates safety in a non-tumor bearing species, however, studies of anti-tumor activity demonstrate pharmacologic activity at doses/exposures below the NOAEL. The starting dose in this study (subjects with SCLC) is predicted safe relative to the NOAEL and pharmacologically active.

The first human dose estimate and dose escalation scheme are intended to minimize the number of subjects exposed to subtherapeutic and toxic doses. Dose escalation increments are large enough (half log units) to rapidly achieve full therapeutic activity and possibly identify a maximally tolerated/feasible dose.

The first-in-human (FIH) dose is 70 mg (to approximate 1 mg/kg) BMS-986012 administered IV over 60 minutes every 21 days. This dose is predicted to result in human exposures 12 times below the NOAEL exposure in cynomolgus monkeys (Table 1.1.7.3-1). Subsequent doses to be studied by escalating in approximate half log units (2.5 fold increases) are 160, 400, and 1000 mg (2.3, 5.7, 14.3 mg/kg, respectively, in a 70 kg subject). Estimated PK exposure with corresponding safety margins (exposure multiple of NOAEL and HNSTD) are presented in Table 1.1.7.3-1.

Table 1.1.7.3-1: Projected Safety Margins for BMS-986012 Monotherapy

Dose Level number	BMS-986012 IV dose (mg)	Human Projected Cmax (μg/mL)	Human Projected AUC(0-tau) (μg•h/mL)	Safety Multiple AUC[a]	
				NOAEL	HNSTD
-1	21	13	3,687	44	596
1	70	47	13,398	12	164
2	160	110	31,983	5.1	69
3	400	278	82,126	2.0	27
4	1000	700	207,839	0.79	11

AUC = area under the concentration-time curve; Cmax = maximum observed concentration; QW = weekly.

[a] Safety multiples based on BMS-986012 monotherapy exposure following repeat IV QW dosing in cynomolgus monkeys at NOAEL (10 mg/kg) and HNSTD (150 mg/kg). Mean sex combined AUC(0-168h) from this study was normalized for 3 weeks of exposure in humans [AUC(0-504h)] by multiplying with a factor of 3 (to adjust for difference in dosing frequency), and margins are based on AUC(0-504h) of 163,800 μg•h/mL at 10 mg/kg (NOAEL) and 2,199,000 μg•h/mL at 150 mg/kg (HNSTD).

1.1.7.4 Rationale for BMS-986012 Dose in Combination with Nivolumab

There is no human experience combining BMS-986012 with nivolumab; therefore, rationale for the BMS-986012 dose is based on monotherapy clinical data. As of the last IB update (version 03, 23-May-2016, data cut-off date 05-Apr-2016),[29] 38 subjects with SCLC have been treated with BMS-986012 monotherapy IV at doses of 70, 160, 400 and 1000 mg Q3W during dose escalation and expansion in the current study. No DLTs occurred during dose escalation, establishing 1000 mg Q3W as the maximum administered dose (MAAD). In the ongoing dose expansion, 400- and 1000-mg doses are being administered IV Q3W to subjects with relapsed or refractory SCLC after 1 prior line of therapy. All data summarized below is preliminary and is subject to change.

AEs considered related to BMS-986012 and reported in > 10% of subjects were pruritus (76.3%), eye pruritus (23.7%), vulvovaginal pruritus (21.1% of all subjects; 38.1% of females),

generalized pruritus (21.1%), decreased appetite (15.8%), and rash (10.5%). These events were all mild to moderate in nature. There does not appear to be an association between the dose of BMS-986012 and the incidence or grade of AEs. Two serious adverse events (SAEs) considered related to BMS-986012 have been reported to date. One episode of Grade 3 fatigue lasting 7 days occurred in 1 subject at the 70-mg dose level. One episode of Grade 1 fever lasting 1 day but leading to hospitalization occurred in 1 subject at the 400-mg dose level. No Grade 4 or 5 events considered related to BMS-986012 have been reported. Seventeen deaths have occurred in treated subjects; out of these, 16 were considered related to disease progression and 1 was due to pneumonia. No deaths related to BMS-986012 have occurred.

As fuc-GM1 is expressed on peripheral nerve in humans, neuropathy is considered a potential on-target AE of BMS-986012. While peripheral neuropathy related to BMS-986012 has not been reported, there have been alterations in sensation including paresthesia and dysesthesia reported as related to BMS-986012. Two subjects experienced Grade 1 dysesthesia (400- and 1000-mg dose levels), and 3 subjects experienced Grade 1 paresthesia (1 subject in the 160-mg dose and 2 subjects in the 1000-mg dose levels). These changes did not appear related to dose, though subjects receiving 1000 mg of BMS-986012 did have longer duration of sensory changes.

No changes in chemistry laboratory values were reported to be related to BMS-986012. There were also no clinically significant changes in neutrophil, platelet, or red blood cell counts considered related to BMS-986012. Two- and 3-grade decreases in lymphocyte counts were observed in approximately 30% of subjects, but these changes were not reported as clinically significant AEs and therefore causality cannot be established; the clinical significance of these changes is unclear at this time. The change in lymphocyte counts does not appear to correlate with dose of BMS-986012. Details of the laboratory findings are provided in the IB.[29] Electrocardiogram (ECG) data, reported to date, do not suggest any clinically important trends.

Clinical benefit has been observed in 6 subjects across all dose levels in both dose escalation and dose expansion. One subject in the 70-mg dose level had a confirmed complete response (CR) that lasted for 53 weeks. One subject in the 400-mg dose level had a confirmed PR that lasted for 17 weeks. Four subjects had stable disease in the 160-, 400-, and 1000-mg dose levels, ranging in duration from 12 to 30 weeks, with 1 subject ongoing at 24 weeks.

Preliminary pharmacokinetic (PK) data are provided in Section 1.4.4.1.

In summary, the clinical data to date suggest there is no clear association between the dose of BMS-986012 and the incidence or grade of related-AEs. Furthermore, preliminary PK analysis shows a significant difference in exposure between the 400- and 1000-mg doses. Based on these data, combination dose escalation will proceed with 400 and 1000 mg (with a Dose Level -1 of 160 mg Q3W) of BMS-986012 for the BMS-986012 and nivolumab combination therapy.

1.1.8 Rationale for Nivolumab "Flat" Q3W Dose

Nivolumab monotherapy with body weight normalized dosing (mg/kg) has been extensively studied in the NSCLC patient population and other solid tumor indications. Nivolumab PK and exposures of subjects in these studies have been characterized by population pharmacokinetic

(PPK) analysis of data collected in these studies, together with PK data from several Phase 1, 2, and 3 clinical studies of nivolumab monotherapy in solid tumors. The PPK modeling of available data, as detailed below, supports the use of a flat dose of 360 mg to facilitate combination dosing with BMS-986012 on a Q3W schedule.

PPK analyses have shown that the PK of nivolumab is linear with proportional exposure over a dose range of 0.1 to 10 mg/kg, and no differences in PK across ethnicities and tumor types were observed. The PK of nivolumab were studied in subjects over a dose range of 0.1 to 10 mg/kg administered as a single dose or as multiple doses of nivolumab every 2 or 3 weeks. The geometric mean (coefficient of variation [CV]%) clearance (CL) was 9.5 mL/h (49.7%), geometric mean volume of distribution at steady state (Vss) was 8.0 L (30.4%), and geometric mean elimination T-HALF was 26.7 days (101%). Steady-state concentrations of nivolumab were reached by 12 weeks when administered at 3 mg/kg Q2W, and systemic accumulation was approximately 3-fold. The exposure to nivolumab increased dose proportionally over the dose range of 0.1 to 10 mg/kg administered Q2W. The clearance of nivolumab increased with increasing body weight. The PPK analysis suggested that the following factors had no clinically important effect on the CL of nivolumab: age (29 to 87 years), gender, race, baseline lactate dehydrogenase, PD-L1. A PPK analysis suggested no difference in CL of nivolumab based on age, gender, race, tumor type, baseline tumor size, and hepatic impairment. Although Eastern Cooperative Oncology Group (ECOG) status, baseline glomerular filtration rate, albumin, and body weight had an effect on nivolumab CL, the effect was not clinically meaningful.

As the PK of nivolumab is linear, the corresponding flat dose for a Q3W dosing regimen is nivolumab 360 mg. Using the PPK model developed, the exposures following administration of several dosing regimens of nivolumab administered as a flat dose were simulated, including 360 mg administered Q3W. The simulated steady-state average concentration following administration of nivolumab 360 mg Q3W is expected to be similar to those following administration of nivolumab 3 mg/kg Q2W to subjects weighing 80 kg, the approximate median weight of subjects used in the PPK analyses. The predicted steady-state peak concentrations following nivolumab 360 mg Q3W are predicted to be less than those following the administration of nivolumab 10 mg/kg Q2W providing sufficient safety margins. Currently, nivolumab is being studied as nivolumab 360 mg combined with platinum-doublet chemotherapy administered Q3W for the treatment of NSCLC in a Phase 3 study (Study CA209-227). Therefore, nivolumab 360 mg Q3W (with a Dose Level -1 of 240 mg Q3W) will be examined in the current study with BMS-986012.

1.1.9 Dose Escalation Design Rationale for BMS-986012 Monotherapy (Part 1) and BMS-986012 and Nivolumab Combination Therapy (Part 3)

Dose escalation will utilize a modified toxicity probability interval (mTPI) design.[56] Rationale for selection of a mTPI over a 3 + 3 design include the ability to enroll additional subjects to better accommodate dropouts, treatment of more subjects at the maximum tolerated dose (MTD) and a more accurate determination of MTD. The design provides a simple dose escalation algorithm (Figure 3.1.1.1-1 and Table 3.1.1.2-1) that increases the accuracy of MTD selection and treats fewer subjects at suboptimal doses.

In addition, the mTPI provides flexibility to allow for the up to 20% of subjects with SCLC who may not complete the dose-limiting toxicity (DLT) period for reasons other than DLT. Simulations of the operating characteristics of the mTPI escalation design relative to the traditional 3 + 3 design are presented in Appendix 1.

1.1.10 Effect of Drug on QT Interval for BMS-986012 Monotherapy and BMS-986012 and Nivolumab Combination Therapy

In this study, the effect of BMS-986012 monotherapy and the combination of BMS-986012 and nivolumab on the QT interval will be evaluated. Pre-clinical evaluations did not identify a signal indicating that BMS-986012 may increase the QT interval or affect cardiac conduction. Similar to other drugs in this class, the likelihood BMS-986012 directly or indirectly affects QTc intervals is low. Despite the low risk, such evaluation is required during the development of a therapeutic agent and the design of this study treating subjects across 4 BMS-986012 monotherapy doses is well suited for this type of evaluation. An intensive QT substudy indicated that nivolumab monotherapy at doses studies up to 10 mg/kg did not affect the QTc interval or other ECG findings.[57] During BMS-986012 monotherapy treatment in the current study, serial ECGs (reviewed by a central laboratory) will be collected with matching PK samples from all 30 subjects in dose escalation period (Part 1) and at least 20 subjects treated across the 2 BMS-986012 monotherapy doses in dose expansion period (Part 2 of the study). Serial ECGs (reviewed by a central laboratory) will also be collected with matched BMS-986012 PK samples for all 12 evaluable subjects in dose escalation period (Part 3) and at least 15 subjects treated in the BMS-986012 and nivolumab combination therapy dose expansion period (Part 4).

1.2 Research Hypothesis

There is no formal primary research hypothesis for this study to be statistically tested. It is anticipated that BMS-986012 as monotherapy and in combination with nivolumab will demonstrate adequate safety and tolerability at pharmacologically relevant doses, so as to permit further clinical development (at a recommended dose range).

1.3 Objectives

1.3.1 Primary Objective

The primary objectives are to determine the multidose safety, tolerability, dose-limiting toxicities (DLTs), and the MTD of BMS-986012 administered as monotherapy and in combination with nivolumab in subjects with relapsed/refractory SCLC.

1.3.2 Secondary Objectives

- To characterize the PK of BMS-986012 as monotherapy and in combination with nivolumab.
- To investigate the preliminary anti-tumor activity of BMS-986012 as monotherapy and in combination with nivolumab, as measured by ORR, duration of response, and PFS.
- To characterize the immunogenicity of BMS-986012 as monotherapy and in combination with nivolumab, as well as immunogenicity of nivolumab in combination with BMS-986012.
- To assess the effect of BMS-986012 as monotherapy and in combination with nivolumab on the QT interval.

1.3.3 Exploratory Objectives

- To estimate the trough concentrations of nivolumab in combination with BMS-986012.
- To explore OS.

[redacted]

1.4 Product Development Background

Additional information for BMS-986012 is also available in the BMS-986012 IB.[29] Additional information for nivolumab is available in the nivolumab IB.[58]

1.4.1 Pharmacology

1.4.1.1 BMS-986012

BMS-986012 is a first in class fully human mAb which specifically binds to the ganglioside fuc-GM1. BMS-986012 exhibits high affinity, dose dependent and saturable binding to fuc-GM1[59] and shows no detectable antigen specific binding to a closely related molecule, GM1. Fuc-GM1 is a chemically defined antigen which is identical in all species; therefore BMS-986012 demonstrates high affinity binding to antigen in all species including mouse, cynomolgus monkeys, and humans.[60] IHC analysis of tumor samples with the use of a specific mouse mAb to fuc-GM1 has demonstrated antigen expression in a high percentage of SCLC cases (see Section 1.1.2 for more details).[20,21,22,26,60]

BMS-986012 is expressed in a fucosyl transferase deficient Chinese hamster ovary cell line resulting in the production of an antibody lacking fucose in its oligosaccharide chains. The absence of fucose from the oligosaccharide of IgG1 conveys increased antibody affinity for Fc receptor CD16 (FcγRIIIa).[28] This FcγR is expressed on natural killer cells and macrophages and is responsible for ADCC. BMS-986012 demonstrated a 40× increase in binding affinity for CD16 and a resulting 150× increase in ADCC activity, compared with parental fucosylated mAb. In vitro, the antibody was shown to mediate potent CDC as well as ADCP.[28] Robust in vivo TGI was demonstrated in 5 out of 7 tumor xenograft models treated with BMS-986012 as a

monotherapy and improved efficacy was observed in 6 out of 7 tumor models when BMS-986012 was administered with cisplatin or etoposide.[33,34,35,36,37,38,39]

1.4.1.2 Nivolumab

Single-dose PK of nivolumab were evaluated in subjects with multiple tumor types in Study CA209001, whereas multiple-dose PK was evaluated in subjects in Study CA209003. Single-dose PK of nivolumab was evaluated in 39 subjects with multiple tumor types in Study CA209001 in the dose range of 0.3 to 10 mg/kg. The median Tmax across single doses ranged from 1.6 to 3 hours with individual values ranging from 0.9 to 7 hours. Geometric mean maximum observed concentration (Cmax) and area under the concentration-time curve from time 0 to infinity (AUC[INF]) of nivolumab administered at dosages of 0.3, 1, 3, and 10 mg/kg demonstrated approximate dose proportionality. Geometric mean CL after a single IV dose ranged from 0.13 to 0.19 mL/h/kg, while mean volume of distribution during the terminal phase (Vz) varied between 83 to 113 mL/kg across doses. There was moderate variability in PK parameters among subjects, with CV of 20% to 32% in Cmax, 39% to 47% in AUC(INF), 17% to 43% in CL, and 23% to 40% in Vz. The mean terminal elimination T-HALF of nivolumab is 17 to 25 days, which is consistent with T-HALF of endogenous IgG4, indicating that the elimination mechanism of nivolumab may be similar to IgG4. Both elimination and distribution of nivolumab appear to be independent of dose in the dose range studied. Additional details are provided in the IB.[58]

In addition, a preliminary PPK model was developed by non-linear mixed effect modeling using data from 350 subjects from Studies CA209001, CA209002, and CA209003. CL of nivolumab is independent of dose in the dose range (0.1 to 10 mg/kg) and tumor types studied. The body weight normalized dosing produces approximately constant trough concentrations over a wide range of body weights, and hence is appropriate for future clinical trials of nivolumab.

1.4.2 Toxicity

1.4.2.1 BMS-986012

The structure of fuc-GM1 is homologous across all species, and BMS-986012 demonstrates high affinity binding in all species including mice, rats, cynomolgus monkeys, and humans. The non-clinical safety of BMS-986012 was evaluated in a series of in vitro tissue cross-reactivity studies and in vivo single- and repeat- dose IV toxicity studies. The BMS-986012 binding profile was similar in human and cynomolgus monkey tissues in the exploratory tissue cross reactivity study.[61] In a single-dose exploratory IV toxicity study in rats (0, 10, 40, or 150 mg/kg), BMS-986012 was clinically tolerated at 10 mg/kg.[61] The primary BMS-986012-related finding at all doses was dose-related hemolytic anemia and associated clinical toxicity resulting in humane euthanasia of all rats at $\geq$ 40 mg/kg by Day 8. This hemolytic anemia was considered to be pharmacologically mediated due to expression of fuc-GM1 on rat erythrocytes.[62] Fuc-GM1 is not expressed on erythrocytes in other species including humans.[63] Based on these findings, which are not considered to be relevant to humans, the rat was considered to be unacceptable for

toxicological assessment of BMS-986012. The mouse was selected as the rodent species for further toxicology evaluation of BMS-986012.

In a pivotal 1-month IV toxicity study in mice (0, 10 or 150 mg/kg, every week [QW], 5 doses), testicular toxicity characterized by decreased testes weights with a microscopic correlate of bilateral germ cell degeneration, retention of spermatids, and Sertoli cell vacuolation was observed at both doses.[64] The testicular toxicity observed in mice was considered pharmacologically mediated and species specific due to expression of fuc-GM1 in mouse testes.[65,66] Fuc-GM1 is not expressed in testes of other species, including humans; therefore, testicular toxicity in mice is considered not to be a concern in humans.[60] The high dose of 150 mg/kg was clinically tolerated, whereas the low dose of 10 mg/kg resulted in mortality following at least 2 weekly doses that was considered a consequence of an anti-drug antibody (ADA)-mediated hypersensitivity. After a 6-week recovery period, there was partial recovery of the BMS-986012-related testicular changes at 10 mg/kg and progression of testicular toxicity at 150 mg/kg. A NOAEL was not established in this pivotal study due to mortality at 10 mg/kg and testicular findings at 10 and 150 mg/kg. The cause of the moribundity/mortality at 10 mg/kg was not apparent from gross and microscopic examination of the tissues. However, considering that these deaths occurred shortly after repeated IV doses, the acute nature of the clinical signs, the presence of ADA in this group (in satellite animals; ADAs were not analyzed in the mice that were found dead or euthanized early), and the absence of BMS-986012-related clinical signs or mortality at the high dose of 150 mg/kg, these deaths at 10 mg/kg likely were a consequence of an ADA-mediated hypersensitivity reaction. A follow-up exploratory immunotoxicity study in mice was conducted to determine the potential contribution of ADA-mediated hypersensitivity as the cause of the moribundity and mortality at 10 mg/kg. In this study (0, 10, or 150 mg/kg, QW, up to 5 doses) in female mice, BMS-986012-related moribundity and mortality again occurred only at 10 mg/kg with a strong correlation with high ADA levels.[67] The occurrence of BMS-986012-related effects (moribundity and mortality) only at the low dose of 10 mg/kg, their onset after multiple injections, and the strong correlation with high ADA levels provide a weight of evidence of an ADA-mediated hypersensitivity reaction.[68] This conclusion is further supported by the lack of these findings in repeat dose studies (10 mg/kg, intraperitoneal, up to 14 doses) in severe combined immunodeficiency mice which cannot generate antibody responses.[40,41,42]

In an exploratory single-dose IV toxicity study in cynomolgus monkeys (0, 10, 40, or 150 mg/kg), BMS-986012 was clinically well tolerated at all doses with no adverse effects at any dose.[69] In the pivotal 1-month IV toxicity study in monkeys (0, 10 or 150 mg/kg, QW, 5 doses), BMS-986012 was clinically well tolerated at all doses.[55] Adverse findings were limited to the high dose of 150 mg/kg and included decreases in circulating neutrophils (0.02 to 0.54×) and platelets (0.32 to 0.50×) and increased spleen size/weight and minimal subacute splenic inflammation. Decreases in platelets and neutrophils were mostly seen in animals with high ADA levels and was likely due to Fc-mediated binding of BMS-986012/ADA immune complexes to these cells resulting in clearance predominantly in the spleen. After a 2-month

recovery period, all BMS-986012-related changes were partially to fully reversible. The low dose of 10 mg/kg (mean combined-sex AUC from 0 to 168 hours [AUC(0-168h)] 54,600 µg•h/mL) was considered a NOAEL. The high dose of 150 mg/kg (mean combined-sex AUC[0-168h] 733,000 µg•h/mL) was considered the HNSTD since it was clinically tolerated and all adverse histopathology findings were reversible.

No significant irritation or local tolerance issues were observed at the injection sites following repeated IV dose administration of BMS-986012 as a slow bolus injection at up to 150 mg/kg administered in the pivotal toxicity studies in mice and cynomolgus monkeys. There were no BMS-986012-related cardiovascular, respiratory, ophthalmologic, or neurological effects at ≤ 150 mg/kg in monkeys (mean Cmax ≤ 6,870 µg/mL). In a GLP-compliant tissue cross-reactivity study in normal human tissues,[70] there was binding of BMS-986012-fluorescein isothiocyanate (FITC) to neural elements (ganglion and satellite cells and axons) that was anticipated based on literature reports of fuc-GM1 expression in peripheral nerves and dorsal root ganglia.[71,72] Expression of fuc-GM1 in healthy tissue is very limited; however, expression has been associated with sensory nerves in monkeys and humans, making peripheral neuropathy a potential target liability of BMS-986012. Although fuc-GM1 is reported to be expressed in neural tissues of monkeys,[60] BMS-986012 (150 mg/kg, Q2W, IV) when given alone to monkeys for 90 days did not produce neurotoxicity or nerve conduction deficits and in combination with cisplatin (2.5 mg/kg, Q3W, IV) did not exacerbate cisplatin-induced neuropathy.[73] Additionally, there was no BMS-986012-FITC-specific staining in any of the adjacent-to-tumor lung samples from smokers or nonsmokers, suggesting that smoking did not induce the expression of fuc-GM1 in normal human lung tissue.[74] Overall, the non-clinical toxicology assessment of BMS-986012 has demonstrated an acceptable safety profile, supporting clinical use in subjects with cancer.

1.4.2.2 Nivolumab

Nivolumab, both as monotherapy and in combination with other drugs, can cause clinically relevant AEs, including liver toxicities, thyroiditis, pneumonitis, and diarrhea. However, these toxicities are typically manageable or reversible with the management algorithms provided in Appendix 2 and the nivolumab IB.[58]

Please refer to the nivolumab IB for further details on the toxicity profile of nivolumab.

1.4.3 Non-clinical Metabolism and Pharmacokinetics

1.4.3.1 BMS-986012

The PK of BMS-986012 were evaluated in mice (non-tumor-bearing mice and mice bearing human SCLC tumors), and cynomolgus monkeys.[75] For details, please see the IB.[29] Briefly, following intraperitoneal administration, BMS-986012 was well absorbed with an absolute bioavailability of 63% to > 100% in non-tumor-bearing mice and tumor-bearing mice. Following IV administration to human tumor-bearing mice, the total serum clearance (CLTs) and apparent elimination T-HALF values were 0.48 to 0.52 mL/h/kg and 130 to 153 hours, respectively. In non-tumor bearing mice, the CLTs and T-HALF values were 0.43 mL/h/kg and 189 hours,

respectively. In cynomolgus monkeys, following a single IV dose of 10 mg/kg of BMS-986012, the CLT was 0.12 to 0.21 mL/h/kg and T-HALF was 227 to 422 hours. The formation of ADAs was observed in several monkeys; the concomitant accelerated decline of drug concentrations, suggested that the ADA were drug-clearing. The Vss values of BMS-986012 (62 to 120 mL/kg) in mice and monkeys suggest that BMS-986012 has limited distribution outside of plasma and the Vss is not affected by expression levels of fuc-GM1 receptors or tumor type.

1.4.3.2 Nivolumab

In cynomolgus monkeys receiving 1 to 50 mg/kg IV single doses of nivolumab, the T-HALF estimates were long (124 to 148 hours after 1 mg/kg doses, 223 to 267 hours after 10 or 50 mg/kg doses), and serum clearance was low.[76,77,78] Systemic exposure to nivolumab increased in an approximately dose-proportional manner. Nivolumab was immunogenic in cynomolgus monkeys; generally, exposure to nivolumab in these anti-nivolumab-positive monkeys was lower than the mean exposures in animals in the same dose group with no detectable anti-nivolumab antibodies. The low volume of distribution in cynomolgus monkeys (0.046 L/kg to 0.071 L/kg) indicates that there is little extravascular distribution of nivolumab.

No mass balance or metabolism studies with nivolumab have been conducted in animals. The expected in vivo degradation of monoclonal antibodies is to small peptides and amino acids via biochemical pathways that are independent of drug metabolism enzymes.

Nivolumab is not expected to have any effect on cytochrome P450 or other drug metabolizing enzymes in terms of inhibition or induction, and is, therefore, not expected to induce these types of PK-based drug interactions.

1.4.4 Clinical Pharmacology and Safety

1.4.4.1 BMS-986012

The preliminary PK of BMS-986012 was evaluated in 30 subjects over a dose range of 70 to 1000 mg administered Q3W. The exposure of BMS-986012 appears to increase dose proportionally over the dose range of 70 to 1000 mg Q3W with moderate to high variability. BMS-986012 achieves peak concentrations approximately 2 hours after dosing and has possible a terminal T-HALF of approximately ≥ 10 days based on non-compartmental analysis (NCA). Preliminary analyses demonstrated that the mean Vss (standard deviation) after the first dose was 5.1 L (2.9 L), which is consistent across the doses tested. The small volume suggests that BMS-986012 is confined primarily to the extracellular fluid volume, which is consistent with the large molecular weight of a mAb. BMS-986012 is slowly eliminated with the estimated T-HALF ranging from 108 to 400 hours (4.5 to 16.6 days), which may be underestimated due to collection of plasma samples at 504 hours, which is approximately 2 half-lives. However, the preliminary estimate of T-HALF is consistent for a mAb.

Further details on the clinical pharmacology aspects of BMS-986012 can be found in the IB.[29]

1.4.4.2 Nivolumab

Nivolumab has been studied in over 8,600 subjects and is widely approved in multiple indications. Extensive details on the safety profile of nivolumab are available in the IB, and will not be repeated herein.[58]

Overall, the safety profile of nivolumab monotherapy as well as combination therapy with other drugs is manageable and generally consistent across completed and ongoing clinical trials with no MTD reached at any dose tested up to 10 mg/kg. Most AEs were low-grade (Grade 1 to 2) with relatively few related high-grade (Grade 3 to 4) AEs. There was no pattern in the incidence, severity, or causality of AEs with respect to nivolumab dose level.

A pattern of immune-related AEs has been defined, for which management algorithms have been developed; these are provided in Appendix 2. Most high-grade events were manageable with the use of corticosteroids or hormone replacement therapy (HRT) (endocrinopathies) as instructed in these algorithms. For additional material, see the nivolumab IB.[58]

Additional details on the safety profile and clinical pharmacology of nivolumab, including results from other clinical studies, are also available in the nivolumab IB.[58]

1.5 Overall Risk/Benefit Assessment

1.5.1 Risk/Benefit for BMS-986012 Monotherapy

This is the FIH study of BMS-986012 monotherapy and clinical benefit is currently being assessed in subjects with SCLC (see Section 1.1.7.4). BMS-986012 is a first-in-class antibody targeting a ganglioside antigen; therefore, no other compounds in development or approved for clinical use can inform the potential clinical risks and benefits of BMS-986012, although vaccines targeting ganglioside antigens in cancer patients have demonstrated preliminary evidence of clinical benefit as well as some preliminary evidence of increased neuropathy.

Clinical experience to date with BMS-986012 has shown evidence of preliminary clinical activity, with objective responses in 2 subjects, with duration of response greater than 1 year in 1 subject, and stable disease in 4 subjects.

To date, nearly all AEs considered related to BMS-986012 monotherapy have been mild to moderate in nature (Grade 1 or 2), with the exception of 1 subject with Grade 3 fatigue. While the majority of subjects have experienced pruritus, these events have been mild to moderate in nature and appeared to respond to medical management with antihistamines. Potential on-target adverse effects such as neutropenia, thrombocytopenia, and peripheral neuropathy, when occurring in a few subjects, have not been considered related to BMS-986012 monotherapy. Sensory changes related to BMS-986012 have been reported but have been mild to moderate in nature and have not progressed to neuropathy. Lymphopenia has also been observed, although its relation to BMS-986012 and clinical significance have not been established.

Because BMS-986012 is a mAb, infusion reactions are possible and will be monitored and managed. Guidelines for management of infusion reactions, should any occur, are provided in

Section 3.7. With Amendment 02, prophylactic premedication with a H1 blocker will be administered prior to administration of each BMS-986012 infusion as described in Section 3.7.

BMS-986012 is an experimental agent and clinical experience is limited at this time; therefore, it is possible that unforeseen, unknown, or unanticipated reactions may occur. Frequent 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. Data generated by the above-described safety monitoring procedures and assessment of adverse 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.

Subjects enrolling in Parts 1 and 2 will have SCLC that has relapsed after first line therapy. While approved therapies are available in this setting, clinical trials to identify more efficacious and/or less toxic alternatives are needed and recommended for patient care by treatment guidelines. The risks and benefits described above for BMS-986012 monotherapy support its continued development in this setting.

1.5.2 Risk/Benefit for BMS-986012 and Nivolumab Combination Therapy

Nivolumab has demonstrated clinical activity in subjects with advanced NSCLC, RCC, melanoma, and lymphomas, as well as other tumors including SCLC. The clinical activity of nivolumab monotherapy observed to date in SCLC suggests the potential for improved clinical outcomes relative to other approved therapies. In a Phase 1/2 trial in subjects with heavily pre-treated SCLC, nivolumab monotherapy showed an ORR of 15%.[79]

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 8,600 subjects treated to date at doses up to 10 mg/kg Q2W or Q3W. Based on the PPK model described in Section 1.1.8, the predicted steady-state peak concentrations following nivolumab 360 mg Q3W are predicted to be less than those following the administration of nivolumab 10 mg/kg Q2W, providing sufficient safety margins. There is no pattern in the incidence, severity, or causality of AEs with respect to nivolumab dose level. The most common AEs (as of 30-Jun-2015) 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.[58]

There is potential for overlapping toxicity between clinical findings of BMS-986012 and nivolumab involving neurotoxicity, infusion-related reactions, lymphocyte decreases, hypophysitis, and pruritus.

Peripheral neuropathy related to BMS-986012 has not been reported, and the sensory changes observed to date do not appear to be dose related (see Section 1.1.7.4). Furthermore, the acute onset and lack of worsening of sensory changes with repeated dosing of BMS-986012 differ

from the usual pattern of cumulative neurotoxicity observed with neuropathic agents such as cisplatin or taxanes. Details of these events are provided in the BMS-986012 IB.[29] For nivolumab monotherapy in subjects with SCLC, the incidence of neuropathies was < 1% and management guidelines have been established as detailed in the nivolumab IB.[58] To minimize potential risks, criteria excluding subjects with peripheral neuropathy or autoimmune neurologic diseases (including paraneoplastic syndrome) have been developed. In addition, subjects in Study CA001030 receiving BMS-986012 monotherapy or BMS-986012 and nivolumab combination therapy will be monitored closely for any neurologic changes via neurologic assessments and frequent assessment for the subjective development of neurologic symptoms. Study drug will be discontinued for any significant neurologic developments.

Infusion reactions, including high-grade hypersensitivity reactions, following administration of nivolumab are uncommon;[58] for BMS-986012, 2 Grade 2 infusion reactions have been reported to date (as of data cut-off date 05-Apr-2016).[29] Subjects will be monitored closely for extended periods during the first 2 cycles of the combination therapy and will continue to be monitored during subsequent cycles. Subjects also will receive prophylactic premedications, and detailed management guidelines for infusion reactions are provided in the protocol (see Section 3.7).

Lymphocyte decreases have also been observed following BMS-986012 and nivolumab given individually as monotherapies. Based on laboratory abnormalities reported for metastatic melanoma and NSCLC, > 40% of subjects treated with nivolumab had a lymphocyte decrease,[58] and approximately 30% of subjects to date have had lymphocyte declines during treatment with BMS-986012 monotherapy. The clinical significance of these observed declines in lymphocyte count is unclear, especially as there are multiple potential etiologies for changes in lymphocyte counts in cancer patients. Safety laboratory assessments will be performed frequently throughout the combination therapy.

Pruritus and skin rashes occurred in 37 of 38 subjects treated with BMS-986012 monotherapy. These were typically low grade, manageable with routine medical intervention, and do not appear related to dose.[29] Rash and pruritus were common AEs observed following treatment with nivolumab monotherapy. Most cases have been of low or moderate grade and generally manageable. More severe cases responded to systemic corticosteroids.[58] Subjects will be monitored closely for the development of rashes and pruritus during combination therapy, and dose modification guidelines were developed to help manage any of these AEs.

Hypophysitis is an uncommon event with nivolumab monotherapy, though the incidence is reported to be increased in subjects receiving combination therapy with ipilimumab.[58] Pre-clinical IHC studies with FITC-conjugated BMS-986012 demonstrated labeling of the adenohypophysis in the 4 species tested. However, there has been no evidence to date of endocrine-related events with BMS-986012 monotherapy. Furthermore, monoclonal antibodies have poor central nervous system (CNS) penetration across the blood-brain barrier, and, therefore, a synergistic effect between nivolumab and BMS-986012 in combination therapy is considered unlikely. However, thyroid testing will be utilized to indirectly monitor for

manifestation of hypophysitis and management of this immune-related AE is well established based on previous nivolumab trials.

Subjects enrolling in Parts 3 and 4 will have SCLC that has relapsed after first line therapy. While nivolumab is being evaluated as monotherapy in this setting in other studies, the potential synergistic effects of nivolumab with BMS-986012 and the risk/benefit ratio support evaluation of this combination.

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 European Union Directive 2001/20/EC and the United States 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.

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

Investigators must:

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

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

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

Subjects unable to give their written consent (eg, subjects with stroke 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

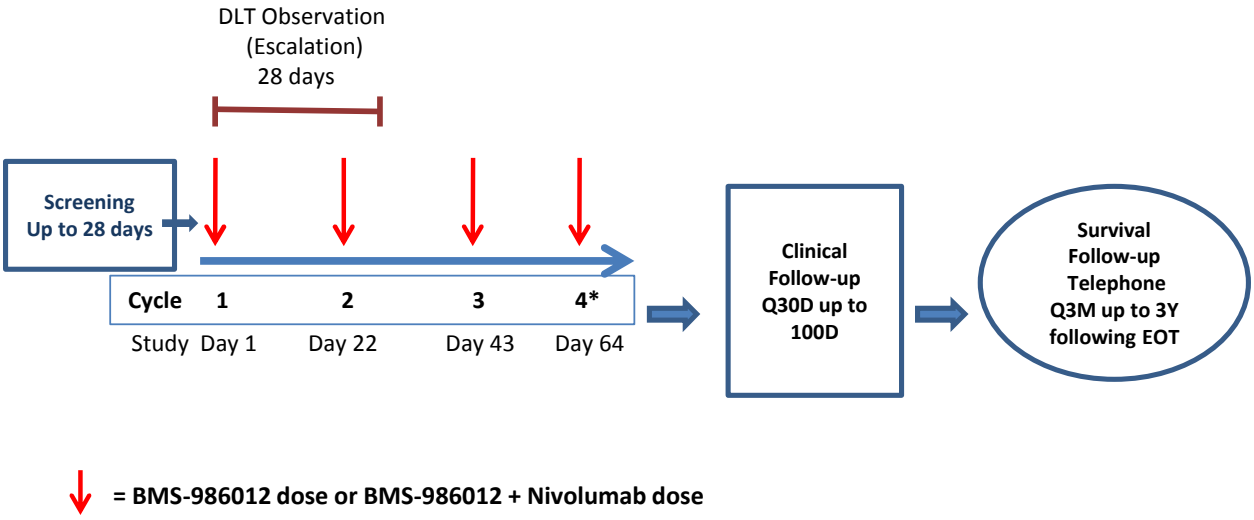
This is an open-label, ascending multiple dose study of BMS-986012 administered as a single agent and in combination with nivolumab to subjects with SCLC. The study will be conducted in 4 parts. A BMS-986012 monotherapy dose escalation period (Part 1) will be conducted to identify a potential MTD (or MAAD if no MTD is determined). In the BMS-986012 monotherapy dose expansion period (Part 2), additional subjects with SCLC will be treated at 2 dose levels of BMS-986012 monotherapy at or below the monotherapy MTD or MAAD to confirm safety and evaluate anti-tumor activity at these dose levels (see Section 3.1.1). With Amendment 04, a dose escalation period will be conducted with BMS-986012 and nivolumab combination therapy (Part 3). In the BMS-986012 and nivolumab combination therapy dose expansion period (Part 4), additional subjects with SCLC will be treated at or below the combination dose level identified in Part 3 to confirm safety and evaluate anti-tumor activity (see Section 3.1.1). In Parts 1 and 3, subjects must have received at least 1 prior line of therapy. In Parts 2 and 4, subjects must have received only 1 prior line of therapy.

Subjects will complete up to 4 periods in the study: Screening (within 28 days prior to administration of study medication), Treatment (until meeting protocol-specified discontinuation criteria), Clinical Follow-up (approximately 100 days, see Table 5.1-3), and Survival Follow-up (up to approximately 3 years following end of treatment [EOT], Table 5.1-3). Screening and Treatment periods are calculated relative to the first dose of study drug. The Clinical Follow-up period begins 30 days (± 5 days) from the last dose of study drug, while the Survival Follow-up period occurs every 12 weeks (± 2 weeks) from the date of the 100-day Clinical Follow-up visit. If a subject discontinues treatment due to AE(s), then the subject should be seen in follow-up at least every 30 days until the AE has resolved to baseline, stabilized, or been deemed irreversible. During Survival Follow-up, subject status will be assessed by either a clinic visit or telephone contact every 12 weeks (± 2 weeks) until the subject has been followed for approximately 3 years or until the last treated subject has been followed for at least 6 months from his/her last date of treatment. The nature and start dates of any new therapies during this period should be recorded. Only information related to subjects' survival and the start date of any subsequent therapies will be collected. Subjects will be permitted to receive other anti-cancer therapies, including investigational agents, during all follow-up periods. Subjects who receive other anti-cancer therapies during the Clinical Follow-up period will remain in Clinical Follow-up for the 100-day period and all assessments will be collected. After completion of the Clinical Follow-up period, all subjects will enter the Survival follow-up period to collect data on survival status. Subjects with SD, PR, or CR at the last Clinical Follow-up visit should undergo tumor

assessment via computed tomography (CT)/magnetic resonance imaging (MRI) scans every 3 to 4 months during the follow-up periods until progression (see Section 5.4.1 and Table 5.1-3). Subjects who have started new anti-cancer therapies or discontinued study due to PD either during the Clinical Follow-up or Survival Follow-up periods or discontinued the study due to PD will not undergo the CT/MRI scans every 3 to 4 months. The end of the study will occur after the last treated subject has been followed for at least 6 months from his/her last treatment date.

The study design schematic is presented in Figure 3.1-1.

Figure 3.1-1: Study Design



D = day; Q3M = every 3 months; Y = year.
*Subjects may receive additional cycles of treatment until protocol-specified discontinuation criteria are met. The DLT observation period pertains to Parts 1 and 3 (dose escalation) only.

Each treatment cycle consists of an IV infusion of BMS-986012 monotherapy (Parts 1 and 2) or BMS-986012 and nivolumab combination therapy (Parts 3 and 4) once every 21 days. BMS-986012 monotherapy or BMS-986012 and nivolumab combination therapy will be given on Day 1 of each treatment cycle. Tumor response will be assessed using RECIST v1.1 (Appendix 3) (see also Section 5.4.1). Following each treatment cycle, the decision to treat a subject with additional cycles of study therapy will be based on assessment of toxicity and tumor assessment. Subjects will be allowed to continue treatment until documentation of PD (except as indicated in Section 4.5.4) or symptomatic deterioration, withdrawal of consent, unacceptable AEs, and/or meeting other protocol-specified criteria for discontinuation as described in Section 3.5.

Safety, PK, [redacted] and efficacy assessments will occur as indicated in Table 5.1-1, Table 5.1-2, Table 5.1-3, Table 5.5.1-1, Table 5.5.1-2, Table 5.5.1-3:, and Table 5.5.1-4 and [redacted] Dose escalation and dose expansion are described in Sections 3.1.1 and 3.1.1, respectively.

Less than 300 mL of blood will be drawn from each subject during any 8-week period of the study.

Approximately 30 evaluable subjects were expected to be treated during the BMS-986012 monotherapy dose escalation period (Part 1). Although the exact number per cohort depends on the number of observed toxicities, approximately 3 to 9 subjects were expected to be evaluated in each dose escalation cohort. In the BMS-986012 monotherapy dose expansion period (Part 2), approximately 100 evaluable subjects will be treated. For the BMS-986012 and nivolumab combination therapy, approximately 12 evaluable subjects are expected to be treated at 2 dose

levels during the dose escalation period (Part 3), and approximately 30 evaluable subjects will be treated during dose expansion period (Part 4). Approximately 230 subjects are estimated to be enrolled in this study, including subjects screened but not meeting eligibility criteria and subjects treated but requiring replacement. Additional subjects may be enrolled in escalation or expansion cohorts, if needed to maintain a sufficient number of subjects evaluable for safety or anti-tumor activity.

3.1.1 Dose Escalation (Parts 1 and 3)

3.1.1.1 BMS-986012 Monotherapy Dose Escalation (Part 1)

The first cohort of subjects will receive 70 mg IV BMS-986012 every 21 days. Enrollment at each new dose level will consist of an initial cohort of 3 to 6 subjects. Subsequent cohorts of 3 subjects within a dose level will be enrolled as needed. A total of approximately 30 evaluable subjects will be treated across 4 proposed dose levels. Dose levels intermediate to those specified in Table 3.1.1.1-1 may be evaluated if agreed upon by the Sponsor/Medical Monitor and investigators, provided the dose escalation increments are smaller than those specified in Table 3.1.1.1-1. No intra-subject dose escalation of BMS-986012 is allowed at any dose level.

Table 3.1.1.1-1: Expected Dosages During BMS-986012 Monotherapy Dose Escalation (Part 1)

Dose Level	BMS-986012 (mg IV Q3W)[a]
-1	21
1	70
2	160
3	400
4	1000

[a] Interim dose levels may be explored.

Up to 6 subjects will initially be treated in Dose Level 1. To minimize risks to subjects from unanticipated acute toxicities, a waiting period of at least 5 days will occur between administrations of the first dose for the first, second, and third subjects to create an observation period prior to subsequent subject exposures. This waiting period is mandatory only in Cohort/Dose Level 1.

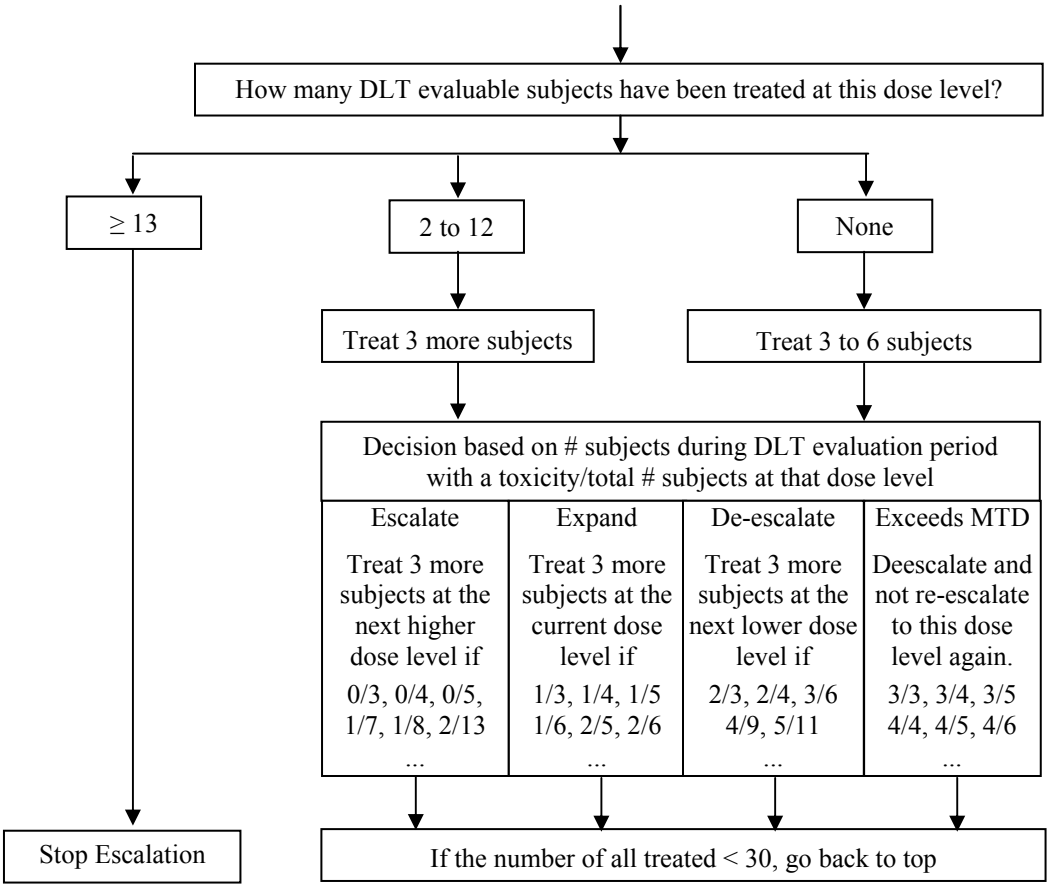
Dose escalation will be guided by the incidence of DLTs in the first 28 days of dosing (the DLT evaluation period) (see Section 3.1.3). Subjects must receive 2 doses of study drug during the DLT evaluation period (unless DLT has occurred) to be considered evaluable for dose escalation decisions. AEs occurring after the 28-day DLT evaluation period will be considered DLTs for the purposes of defining the MTD upon agreement between the Sponsor and the investigators if they are determined to have no clear alternative cause and not related to disease progression. Subjects with insufficient data to establish safety during the DLT evaluation period at the current

dose level (eg, omitted doses for reasons other than a DLT, use of systemic steroids for management of or prophylaxis of infusion reactions during the DLT evaluation period) may be replaced depending on the total number of DLT evaluable at that dose level and the number of observed DLTs (Figure 3.1.1.1-1), and upon agreement of the Sponsor/Medical Monitor, in collaboration with, the investigators. Due to the nature of the SCLC population and concern that subjects will progress rapidly due to disease, a DLT evaluation period of 28 days was selected.

Part 1 of the study uses the mTPI model based design[56] for escalation decisions and to select the MTD, based on 3 to 6 subjects in the initial cohort and continuing enrollment in cohorts of 3. If a decision to treat more subjects at a given dose level is specified by the mTPI algorithm when there are already at least 13 DLT evaluable subjects treated at the same dose level or a total of 30 evaluable subjects treated at all dose levels, the dose escalation period will be stopped. Decisions to escalate to the next dose level, expand (add more subjects to the current dose level), or de-escalate will be guided by the number of DLTs observed, out of the total n evaluable at a current dose level, according to the design algorithm (Figure 3.1.1.1-1, Appendix 4). The mTPI method requires a pre-specified 'target' DLT rate (and equivalence interval, EI) for escalation decisions and to estimate the MTD, guided by Bayesian model and posterior inference. For this study, the target DLT rate selected as clinically relevant in monotherapy is 25% (EI=[24%, 27%).

Figure 3.1.1.1-1 depicts scenarios of potential actions based on the number of observed DLTs and the number of DLT evaluable subjects treated at any one dose level.

Figure 3.1.1.1-1: BMS-986012 Monotherapy Dose Escalation Algorithm (Part 1)



All potential combinations of numbers of DLTs and number of treated subjects evaluable for DLT may be found in Appendix 4.

Subjects will be enrolled and treated in cohorts of at least 3 subjects. Dose escalation decisions are based on a total number of subjects in a dose level receiving 2 doses of study drug within the DLT evaluation period (these subjects are referred to as "DLT evaluable"), and the number of DLTs observed. At least 3 DLT evaluable subjects are required in the first cohort of each dose to enable a decision about the next cohort on whether to escalate, expand (add more subjects to) the current dose level, or de-escalate. However if > 3 subjects in a cohort are treated it may be necessary to wait for those subjects to complete the DLT evaluation period. The number of DLT evaluable subjects may not always be a multiple of 3 (Table 3.1.1.1-1), as decisions to escalate may be made based on a minimum of required subjects such as if 1 DLT is observed out of 4 subjects. If 2 out of 6 evaluable drop out replacement of the 2 subjects is not needed.

An example of one possible dose escalation scenario follows:

- If no DLTs occur in a total of 6 DLT evaluable subjects treated at Dose Level 1, escalation to the next higher Dose Level 2 is permitted.
- If 2 DLTs are then observed in 3 DLT evaluable subjects in Dose Level 2, de-escalation will occur and a new cohort of 3 subjects will be treated in Dose Level 1, bringing the total number of subjects treated at Dose Level 1 to 9.

- If 1 DLT is observed in 9 subjects treated at Dose Level 1, re-escalation to Dose Level 2 is permitted (Appendix 4), and 3 additional subjects will be treated at Dose Level 2, bringing the cumulative number of subjects treated at Dose Level 2 to 6.
- If all 6 subjects complete the DLT evaluation period without the occurrence of additional DLTs, Dose Level 2 is expanded by a new cohort of 3 subjects (since 2 DLTs had occurred in the first 3 subjects treated at Dose Level 2).

Dose re-escalation may occur according to Figure 3.1.1.1-1 except when a dose level has been identified as exceeding the MTD (eg, if 3 of 5 or 4 of 6 subjects experience a DLT).

No intra-subject dose escalation of BMS-986012 monotherapy is allowed.

All actions related to decisions on treating a new cohort of subjects at or below any dose level previously established as safe may be made following discussion by the Sponsor/Medical Monitor in collaboration with the investigators based on the available safety data. In addition, investigators and Sponsor may stop the dose escalation part after observing sufficient data to show the MTD is likely to be reached and examining other safety information.

At the end of BMS-986012 monotherapy dose escalation period, the cumulative number of subjects who experience a DLT will be used to estimate the MTD using isotonic regression. The MTD is selected as the dose level with the smaller difference of estimated toxicity and the target DLT rate, among the dose levels used.

3.1.1.2 BMS-986012 and Nivolumab Combination Therapy Dose Escalation (Part 3)

Dose escalation with BMS-986012 and nivolumab combination therapy will follow the same guidelines as described in Section 3.1.1.1. An mTPI design similar to that described for BMS-986012 monotherapy (see Section 3.1.1.1) will guide dose escalation decisions. A total of approximately 12 evaluable subjects will be treated across 2 dose levels. Additional subjects may be treated if additional dose levels are required as described in "Selection of Dose Levels" below.

To minimize risks to subjects from unanticipated acute toxicities, in all dose levels evaluated, 5 days must elapse between administration of the first dose for the first and second subjects to allow observation prior to subsequent exposures.

In all Combination Dose levels, multiple subjects within a cohort will not be permitted to receive the initial dose of study drugs on the same day. Subjects must be clinically observed for at least 4 hours following the first 2 doses of BMS-986012 and nivolumab combination therapy (ie, Cycles 1 and 2) and for at least 1 hour following doses beyond the first 2 doses of combination therapy (ie, Cycle 3 and beyond).

Selection of Dose Levels to be Evaluated

In combination therapy, nivolumab will be administered at 360 mg Q3W in all combination dose levels, except as noted below. BMS-986012 will be evaluated starting at 400 mg (Combination Dose Level 1). If safety and tolerability are established at 400 mg, Combination Dose Level 2 will be opened at 1000 mg. If toxicity is unacceptable at Combination Dose Level 1, additional

combination dose level(s) may be evaluated using BMS-986012 dose of 160 mg and/or nivolumab dose of 240 mg Q3W. Selection of dose level for each study drug will be based on the nature and attribution of observed DLTs in previously evaluated dose levels. If toxicity is acceptable at Combination Dose Level 1 but unacceptable at Combination Dose Level 2, an intermediate dose level of BMS-986012 and/or nivolumab dose of 240 mg Q3W may be evaluated in additional cohort(s). The intermediate dose level of BMS-986012 will be selected based on combination therapy safety and available PK data.

No intra-subject dose escalation of BMS-986012 or nivolumab is allowed at any dose level.

Dose Escalation Decision Guide

As in Part 1, an mTPI design (Table 3.1.1.2-1) will be used to guide dose escalation decisions and to select the MTD. A DLT target rate of 29% (EI=[28%, 31%]) will be used for combination therapy. Toxicity assessments will be based on a 28-day DLT evaluation period. See Section 3.1.3 for further details of DLT evaluation. Dose escalation decisions will be based on a total number of subjects in a dose level receiving 2 doses of both BMS-986012 and nivolumab within the DLT evaluation period and who are followed for 28 days (these subjects are referred to as “DLT evaluable”), and the number of DLTs observed at that dose level.

The number of subjects in the initial cohort of each dose level will be 3 to 4. Decisions to escalate to the next dose level, expand (add more subjects to) the current dose level, or de-escalate will be guided by the number of DLTs observed, out of the total number of evaluable subjects at a current dose level, according to the design algorithm shown in Table 3.1.1.2-1. Enrollment of additional cohorts at the same dose level will proceed in sample sizes of 2 to 4 subjects. Subsequent dose levels will follow the same cohort enrollment size and decision rules. Subjects with insufficient data to establish safety during the DLT evaluation period at a dose level (eg, withdrawal from the study or study treatment discontinuation prior to completion of DLT evaluation period) may be replaced

When more than 3 subjects are enrolled in a cohort, the fourth subject may be enrolled following agreement between the investigator and the Sponsor/Medical Monitor if able to start the first day of dosing within approximately 1 week of the third subject in the same dose escalation cohort. When 3 or 4 subjects are enrolled in a cohort, at least 3 DLT evaluable subjects in that cohort will be required to enable a decision to escalate, add more subjects to the current dose level, or de-escalate.

Table 3.1.1.2-1: Dose Escalation Decision Guide by mTPI for Dose Combination

		Number of DLT Evaluable Subjects at a Dose Level									
		3	4	5	6	7	8	9	10	11	12
N of DLT at a Dose Level	0	E	E	E	E	E	E	E	E	E	E
	1	S	S	S	E	E	E	E	E	E	E
	2	D	S	S	S	S	S	S	S	E	E
	3	DU	DU	D	S	S	S	S	S	S	S
	4		DU	DU	DU	D	D	S	S	S	S
	5			DU	DU	DU	DU	DU	D	S	S
	6				DU	DU	DU	DU	DU	DU	D
	7					DU	DU	DU	DU	DU	DU
	8						DU	DU	DU	DU	DU
	9							DU	DU	DU	DU
	10								DU	DU	DU
	11									DU	DU
	12										DU

mTPI with target DLT rate of 29% (EI=[28%, 31%])

D: De-escalate to the next lower dose level, E: Escalate to next higher dose level, S: Stay at the current dose level. U: Unacceptable dose level, not to be re-visited.

Dose Selection for Part 4:

At the end of the BMS-986012 and nivolumab combination therapy dose escalation period, the cumulative number of subjects who experience a DLT at each dose level will be used to estimate the MTD of BMS-986012 in combination with nivolumab using isotonic regression. The MTD will be selected as the dose level with the smaller difference of estimated toxicity rate and the target DLT rate, among the dose levels explored.

Safety, including AEs occurring beyond the DLT observation period and available PK data, will also be considered in determining the recommended dose regimen of BMS-986012 and nivolumab to be administered in combination in Part 4. The dose regimen in Part 4 may be at or below the MTD of BMS-986012 and nivolumab combination therapy.

3.1.2 Dose Expansion (Parts 2 and 4)

3.1.2.1 BMS-986012 Monotherapy Dose Expansion (Part 2)

BMS-986012 monotherapy dose levels selected for the dose expansion period (Part 2) will not exceed the MTD or MAAD, but dose selection may incorporate assessment of other data including toxicities and PK from Part 1. Part 2 will evaluate toxicity and preliminary efficacy of BMS-986012 as second-line treatment in subjects who have relapsed following first-line chemotherapy as follows: Cohort A: ≤ 90-day response duration (refractory) at or below the

MTD/MAAD, Cohort B: ≤ 90-day response duration (refractory) at a dose level below the MTD/MAAD, Cohort C: > 90-day response duration (sensitive) at or below the MTD/MAAD, and Cohort D: > 90-day response duration (sensitive) at a dose level below the MTD/MAAD. The response duration referenced above is relative to the prior first-line therapy. Approximately 22 refractory and 28 sensitive subjects will be treated per cohort. As additional safety and PK data become available, the dose level of opened expansion cohorts may be re-evaluated, and an alternate dose level may be selected. Newly selected dose levels will not exceed the MTD/MAAD. Subjects currently dosing at the previously selected dose level will be permitted to continue at that dose level unless a protocol-specified dose modification (Section 4.5.1) is required. Enrollment will be guided by the Simon 2-stage design framework (see Table 8.1.2-1).

Anti-tumor activity will be assessed in approximately the first 9 or 10 evaluable subjects treated in each monotherapy cohort, with the option to stop enrolling in a cohort without an initial anti-tumor activity signal. The number of subjects needed for the Stage 1 review is guided by a Simon 2-stage design, assuming a 25% desirable response rate (vs 10%) for refractory monotherapy cohort, and a 40% (vs 25%) for sensitive monotherapy cohort, with the following futility boundaries. After Stage 1, if none of the first 9 evaluable subjects in the refractory cohort or if 2 or fewer subjects of the first 10 evaluable subjects in a sensitive cohort demonstrate clinical activity, enrollment in the cohort meeting criteria may not continue. As the expected time of response relative to dose initiation and the actual recruitment rate are unknown, it is expected that during the efficacy evaluation of subjects in Stage 1, more subjects may have been enrolled and receiving treatment than the minimum needed for the Stage 1 assessment. Therefore, the above numbers are approximate and enrollment will continue during the evaluation of the interim data.

Evaluation of toxicity events in the cohort expansions will be performed throughout enrollment. If the aggregate rate of toxicities meeting DLT criteria exceeds 27% across all subjects treated in all monotherapy cohorts, the findings will be discussed and further enrollment may be interrupted. Depending on the nature and grade of toxicity and after assessing the risk/benefit ratio, additional subjects may be treated at, below, or intermediate to a dose level previously found to be safe following discussion by the Sponsor/Medical Monitor and investigators, based on the available data. Selection of dose levels for these additional cohorts will be guided by accumulated safety, available PK, and efficacy data; modeling may also be used to explore potential dose-response relationships.

3.1.2.2 BMS-986012 and Nivolumab Combination Therapy Dose Expansion (Part 4)

Part 4 will evaluate toxicity and preliminary efficacy of BMS-986012 and nivolumab combination therapy as second-line treatment in subjects who have relapsed following first-line chemotherapy. The dose levels of BMS-986012 and nivolumab selected for Part 4 will not exceed the MTD or MAAD of Part 3, but dose selection may incorporate assessment of toxicities including those occurring beyond the DLT observation period and available PK data from Part 3.

A total of approximately 30 evaluable subjects (refractory or sensitive to first line chemotherapy) will be treated. Enrollment will be guided by the Simon 2-stage design framework (see Table 8.1.2-1).

Anti-tumor activity will be assessed in approximately the first 13 response evaluable subjects, with the option to stop enrollment if no sufficient initial anti-tumor activity signal is observed. The number of subjects needed for the Stage 1 review is guided by a Simon 2-Stage design, assuming a 40% desirable response rate (vs 20%), with the following futility boundaries. After Stage 1, if clinical activity is demonstrated in 2 or fewer of the first 13 evaluable subjects, enrollment may not continue. As the expected time of response relative to dose initiation and the actual recruitment rate are unknown, it is expected that during the efficacy evaluation of subjects in Stage 1, more subjects may have been enrolled and receiving treatment than the minimum needed for the Stage 1 assessment. Therefore, the above numbers are approximate and enrollment will continue during the evaluation of the interim data.

Evaluation of toxicity events in the cohort expansions will be performed throughout enrollment. If the aggregate rate of toxicities meeting DLT criteria exceeds 31% across all subjects treated in combination, the findings will be discussed and further enrollment may be interrupted. Enrollment may proceed at or below a dose level of BMS-986012 previously found to be safe. This may include an intermediate dose level. Selection of the dose level will depend on the nature and grade of toxicities and assessment of the risk/benefit ratio. A lower dose level of nivolumab (240 mg Q3W) may also be selected. Decisions will be made by the Sponsor/Medical Monitor in collaboration with the investigators as indicated in Part 2.

3.1.3 Dose-Limiting Toxicities

For the purpose of guiding decisions regarding dose escalation, dose-limiting toxicity (DLT) will be determined based on the incidence, intensity, and duration of AEs occurring within 28 days of initiation of study drug (ie, the DLT evaluation period) for which no alternative cause can be identified. The severity of AEs will be graded according to National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) v4.03. AEs occurring after the 28-day DLT evaluation period will be considered to represent DLTs 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 not related to disease progression.

See Sections 4.5.1 and 4.5.3 for dose modifications including dose delays and permanent discontinuation criteria, respectively.

In the event that study treatment cannot be administered at a scheduled visit during the DLT evaluation period, it must be administered as soon as possible thereafter. If the delay is between 1 and 7 days, the procedures at the original scheduled visit should be performed and subjects will be considered evaluable for DLT determination. If the delay is more than 7 days, the dose will be considered missed and will not be replaced. For the purpose of making decisions on dose escalation from a safety perspective, subjects must have received both of the scheduled study treatment doses (for BMS-986012 monotherapy or BMS-986012 and nivolumab combination

therapy, as applicable) within the DLT evaluation period. Nonevaluable subjects may be replaced at the same dose level.

Hepatic, non-hematologic, and hematologic DLTs are defined separately as outlined below.

3.1.3.1 Hepatic DLT

Any of the following events for which no clear alternative cause is identified other than study treatment will be considered a hepatic DLT:

- Grade ≥ 3 ALT or aspartate aminotransferase (AST) (> 5 × upper limit of normal [ULN]), regardless of duration, or
- Grade ≥ 3 total bilirubin (> 3 × ULN), or
- Combination of AST or ALT and direct bilirubin meeting criteria for potential drug-induced liver injury (DILI; see Section 6.6):
  - Aminotransferase (ALT or AST) elevation > 3 × ULN if liver chemistries are normal at baseline; if liver chemistries are abnormal at baseline, then > 2 × baseline values or any value > 8 × ULN should be used as cutoffs,

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

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

3.1.3.2 Hematologic DLT

Any of the following events for which no clear alternative cause is identified other than the study treatment will be considered a hematologic DLT:

- Grade 4 febrile neutropenia of any duration
- Grade 4 neutropenia that lasts > 7 days
- Grade 4 thrombocytopenia or platelet cell decreased
- Grade 4 anemia
- Grade 3 thrombocytopenia (or platelet cell decreased) that lasts > 7 days and/or associated with clinically significant bleeding
- Grade 3 febrile neutropenia that lasts > 48 hours
- Grade 3 hemolysis
- Grade 4 lymphopenia > 7 days

3.1.3.3 Non-hepatic, Non-hematologic DLT

Any of the following events for which no clear alternative cause is identified other than to study treatment will be considered a non-hematologic DLT:

- Grade ≥ 3 non-hepatic, non-hematologic toxicity with the exceptions noted below

The following Grade 3 non-hepatic, non-hematologic events **will not** be considered DLTs:

- Grade 3 electrolyte abnormality that lasts ≤ 72 hours, is not clinically complicated, and resolves spontaneously or responds to conventional medical intervention
- Grade 3/4 increase in amylase or lipase not associated with clinical or radiographic evidence of pancreatitis
- Grade 3 abdominal pain, nausea, diarrhea, or vomiting that lasts ≤ 48 hours, and resolves to Grade ≤ 1 either spontaneously or with conventional medical intervention
- Grade 3 fever that lasts ≤ 72 hours, and is not associated with hemodynamic compromise (including hypotension, or clinical or laboratory evidence of end organ perfusion impairment)
- Grade 3 endocrinopathy adequately controlled with physiologic hormone replacement
- Grade 3 tumor flare (defined as pain, irritation, or rash that localizes to sites of known or suspected tumor)
- Grade 3 fatigue
- Grade 3 pruritus or rash lasting ≤ 7 days.

Additional non-hepatic, non-hematologic DLT criteria applicable to BMS-986012 and nivolumab combination therapy only:

- Grade ≥ 2 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

3.2 Post-study Access to Therapy

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

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

2. Target Population

a) Men and women at least 18 years of age or local age of majority

   i) with histological or cytological confirmed pulmonary SCLC.

   ii) without symptomatic CNS metastases (see exclusion criteria for details).

   iii) ECOG performance status 0 to 1

b) Subjects with limited or extensive pulmonary SCLC who

   i) have received at least 1 prior line of therapy (dose escalation, Parts 1 and 3), or

   ii) have relapsed after or are refractory to first-line therapy and have not yet received 2 or more lines of anti-cancer treatment (dose expansion, Parts 2 and 4).

   Note: With Amendment 04, subjects who have received maintenance immunotherapy following platinum-based, first-line treatment are excluded. Subjects who have received other maintenance therapies, such as tyrosine kinase inhibitor or other chemotherapies, are permitted to enroll after discussion with the Sponsor/Medical Monitor or designee.

c) At least 4 weeks must have elapsed from the last exposure of anti-cancer therapy (such as cytotoxic chemotherapy, targeted therapy, or mAb) or any investigational drug and the initiation of study drug administration.

d) Subjects must have at least 1 measurable lesion per RECIST v1.1 (Appendix 3) that is not amenable to resection.

e) Adequate organ function as defined by the following:

   i) Absolute neutrophil count $\geq 1500/mm^3$

   ii) Platelet count $\geq 100{,}000/mm^3$

   iii) Hemoglobin ≥ 9 g/dL; Subjects with a stable chronic transfusion requirement (eg, due to cumulative toxicity from previous therapy) will be allowed if the trough hemoglobin is > 8.0 g/dL

   iv) Adequate hepatic function as defined by:

      (1) Total bilirubin level $\leq 1.5 \times$ ULN

      (2) AST and ALT levels $< 3 \times$ ULN

   v) Adequate renal function defined as serum creatinine $\leq 1.5 \times$ institutional ULN or calculated creatinine clearance (CrCl) ≥ 40 mL/min (using the Cockcroft-Gault formula).

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

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

72 × serum creatinine in mg/dL

vi) White blood cells ≥ 2000/mm$^{3.}$

f) Ability to comply with visit schedule, treatment schedule, sample collection for laboratory tests, and treatment and follow-up.

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

[redacted]

3. Age and Reproductive Status

a) Males and Females ≥ 18 years of age or local age of majority.

b) Women of childbearing potential (WOCBP) must have a negative serum or urine pregnancy test (minimum sensitivity 25 IU/L or equivalent units of human chorionic gonadotrophin [HCG]) during screening within 72 hours prior to the start of study drug if enrolled in the BMS-986012 monotherapy (Parts 1 and 2) or 24 hours prior to the start of study drug if enrolled in the BMS-986012 and nivolumab combination therapy (Parts 3 and 4).

c) Women must not be breastfeeding. WOCBP must agree to follow instructions for method(s) of contraception (see Appendix 5) for the duration of treatment with BMS-986012 monotherapy plus 5 half-lives of study drug (105 days) plus 30 days (duration of ovulatory cycle) for a total of 135 days post-treatment completion (Parts 1 and 2). WOCBP must agree to follow instructions for method(s) of contraception (see Appendix 5) for the duration of treatment with BMS-986012 and nivolumab combination therapy for 23 weeks (30 days plus the time required for nivolumab to undergo 5 half-lives) after the last dose of study drug (Parts 3 and 4).

d) Males who are sexually active with WOCBP must agree to follow instructions for method(s) of contraception (see Appendix 5) for the duration of treatment with BMS-986012 monotherapy (s) plus 5 half-lives of the study drug (105 days) plus 90 days (duration of sperm turnover) for a total of 195 days post-treatment completion (Parts 1 and 2). If treated with BMS-986012 and nivolumab combination therapy, males who are sexually active with WOCBP must continue contraception for 31 weeks (90 days plus the time required for nivolumab to undergo 5 half-lives) after the last dose of study drug (Parts 3 and 4).

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

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

At a minimum, subjects must agree to the use of 2 methods of contraception, with 1 method being highly effective and the other being either highly effective or less effective as listed in Appendix 5.

3.3.2 Exclusion Criteria

1) Target Disease Exceptions

a) Subjects with known or suspected brain metastasis, or brain as the only site of disease are excluded with the following exception:

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

b) Non-pulmonary small cell cancer

c) Prior treatment with an anti-PD-1, anti-PD-L1, anti-PD-L2, anti-CD137, anti-CTLA-4 antibody, or any other antibody or drug specifically targeting T-cell co-stimulation or checkpoint pathways. This criteria applies only to the BMS-986012 and nivolumab combination therapy (Parts 3 and 4).

2) Medical History and Concurrent Diseases

a) Any significant acute or chronic medical illness which would interfere with study treatment or follow-up.

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

i) Uncontrolled hypertension which is defined as systolic blood pressure > 150 mmHg or diastolic blood pressure > 90 mmHg despite optimal medical management

ii) Active coronary artery disease, including unstable or newly diagnosed angina, within 3 months of study enrollment

iii) Myocardial infarction in the past 6 months

iv) History (family or subject) of congenital long QT syndrome

v) History of clinically significant arrhythmias (such as ventricular tachycardia, ventricular fibrillation, or Torsade de pointes)

vi) Subjects classified as 3 or 4 by New York Heart Association Functional Classification, defined as: Class 3: Subjects with marked limitation of physical activity, comfortable at rest, but less than ordinary activity causes symptoms. Class 4: Subjects are unable to carry on any physical activity without symptoms and symptoms are present even at rest.

vii) With Amendment 04, subjects with a history or current diagnosis of myocarditis. This criterion applies only to BMS-986012 and nivolumab combination therapy (Parts 3 and 4).

c) Evidence of uncontrolled, active infection, requiring systemic antibacterial, antiviral or antifungal therapy ≤ 7 days prior to administration of study medication.

d) At least 14 days must have elapsed since prior surgery except for the placement of venous access device or bronchoscopy.

e) Grade 2 or higher peripheral neuropathy by NCI CTCAE v4.03.

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

g) Not applicable per Protocol Amendment 02. Donation of blood to a blood bank or in a clinical study (except a screening visit) within 4 weeks of study drug administration (within 2 weeks for plasma only).

h) Inability to be venipunctured and/or tolerate venous access.

i) Human immunodeficiency virus (HIV)-related disease or known positivity for HIV or known acquired immunodeficiency syndrome. No HIV testing is required during screening but must be performed at sites where mandated locally.

j) Past or active hepatitis B or C infection. (Does not include positive serologies resulting from passive transfer of antibodies, eg, intravenous immunoglobulin). With Amendment 04, testing at screening is required and subjects are excluded if any positive test for hepatitis B virus (HBV) or hepatitis C virus (HCV) indicating acute or chronic infection, and/or detectable virus.

   Note: With Amendment 04, subjects with a positive test for HCV antibody but no detection of HCV RNA, indicating no current infection, are eligible.

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

l) History of severe hypersensitivity reaction to other monoclonal antibodies.

m) With Amendment 04, documented carcinomatous meningitis.

n) With Amendment 04, subjects with an active, known or suspected autoimmune disease. Subjects with type I diabetes mellitus, hypothyroidism requiring only hormone replacement, skin disorders (such as vitiligo, psoriasis, or alopecia) not requiring systemic treatment, or conditions not expected to recur in the absence of an external trigger are permitted to enroll. This criterion applies only to the BMS-986012 and nivolumab combination therapy (Parts 3and 4).

o) With Amendment 04, subjects with autoimmune neurologic disorders, including paraneoplastic syndrome involving the central nervous system, peripheral sensory nerves, or peripheral motor nerves/neuromuscular junction, are excluded.

p) With Amendment 04, subjects with a condition requiring systemic treatment with either corticosteroids (> 10 mg daily prednisone equivalent) or other immunosuppressive medications within 14 days of starting study treatment. Inhaled or topical steroids and adrenal replacement steroid doses > 10 mg daily prednisone equivalent are permitted in the absence of active autoimmune disease.

3) Physical and Laboratory Test Findings

a) QT interval corrected for heart rate using Fridericia's formula (QTcF) ≥480 ms on 12-lead ECG prior to study drug administration, confirmed by repeat assessment.

4) Allergies and Adverse Drug Reaction

a) History of allergy to BMS-986012 or related compounds, including fuc-GM1 vaccine or history of allergy or hypersensitivity to nivolumab (if enrolled in BMS-986012 and nivolumab combination therapy) or any other study drug component.

b) History of any significant drug allergy (such as anaphylaxis or hepatotoxicity).

5) Other Exclusion Criteria

a) Prisoners or subjects who are involuntarily incarcerated. (Note: under certain specific circumstances a person who has been imprisoned may be included or permitted to continue as a subject. Strict conditions apply and Bristol-Myers Squibb (BMS) approval is required.)

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

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

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

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

3.4 Concomitant Treatments

3.4.1 Prohibited and/or Restricted Treatments

Prohibited and/or restricted medications taken prior to study drug administration in the study are described below. Medications taken within 4 weeks prior to study drug administration and up to 100 days during clinical follow-up must be recorded on the case report form (CRF).

1) Prior exposure to BMS-986012 or fuc-GM-1 vaccine or similar vaccine targeting ganglioside antigens
2) Exposure to any anti-cancer therapy (such as chemotherapy, targeted therapy, or mAb) or any investigational drug within 4 weeks of or concurrent with study drug administration.
3) Use of any herbal preparations within 1 week prior to or any time during study drug administration except those medications cleared by the BMS Medical Monitor.
4) Additional criteria that apply only to the BMS-986012 and nivolumab combination therapy (Parts 3 and 4) include the following:
    a. Immunosuppressive agents
    b. Immunosuppressive doses of systemic corticosteroids (except as stated in Section 3.4.2 or management of infusion reactions)

Any concomitant therapies must be recorded on the CRF.

3.4.2 Other Restrictions and Precautions and Permitted Therapies

1) Granulocyte-macrophage colony-stimulating factor/granulocyte-colony stimulating factor (G-CSF) will be permitted. However, the use of growth factors is allowed per their respective label indications to treat chemotherapy induced neutropenia (eg, febrile neutropenia). They must not be used for the treatment of cancer or for primary prophylaxis only while on study.
2) Subjects may receive Best Supportive Care on-study, which may include, but is not limited to: analgesics (including opiates), bone directed radiotherapy, bisphosphonates, denosumab, antibiotics, treatment for metabolic disorders, and nutritional support.
3) Subjects are permitted the use of topical, ocular, intra-articular, intranasal, and inhalational corticosteroids or other immunosuppressive agents (with minimal systemic absorption). Adrenal replacement steroid doses > 10 mg daily prednisone are permitted. A brief (less than 3 weeks) course of corticosteroids for infusion reactions and/or for prophylaxis (eg, contrast dye allergy) or for treatment of non-autoimmune conditions (eg, delayed-type hypersensitivity reaction caused by a contact allergen) is permitted.

3.5 Discontinuation of Subjects from Treatment

Subjects MUST discontinue investigational product (IP) for any of the following reasons:

- Withdrawal of informed consent (subject's decision to withdraw for any reason)
- Any clinical AE, laboratory abnormality or intercurrent illness which, in the opinion of the investigator, indicates that continued participation in the study is not in the best interest of the subject

- Disease progression unless subject meets criteria for treatment beyond progression as detailed in Section 4.5.4
- Clinical deterioration
- Pregnancy
- 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
- Protocol-defined reasons for discontinuation (Section 4.5.3)

All subjects who discontinue IP should comply with protocol specified follow-up procedures as outlined in Section 3.6. 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).

In the case of pregnancy, the investigator must immediately notify the Sponsor or designee of this event. In most cases, the study drug will be permanently discontinued in an appropriate manner (eg, dose tapering if necessary for subject safety). Please contact the Sponsor or designee within 24 hours of awareness of the pregnancy. If the investigator determines a possible favorable benefit/risk ratio that warrants continuation of study drug, a discussion between the investigator and the Sponsor or designee must occur.

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

3.6 Post-study Drug Follow-up

In this study, safety and survival are important endpoints of the study. Post-study follow-up is of critical importance and is essential to preserving subject safety and the integrity of the study. Subjects who discontinue study drug must continue to be followed for collection of safety, survival outcome and other data as described in Table 5.1-3 and Sections 5.3 and 5.4.1.

BMS may request that survival data be collected on all treated subjects outside of the protocol-defined window (see Table 5.1-3). At the time of this request, each subject will be contacted to determine their survival status unless the subject has withdrawn consent for all contacts or is lost to follow-up.

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 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, 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.

3.7 Infusion Reactions

With Amendment 02, prophylactic premedication will be routinely administered prior to each BMS-986012 infusion. All subjects initiating BMS-986012 treatment will be premedicated prior to the infusion of BMS-986012 with a H1 blocker (such as diphenhydramine 25 to 50 mg oral or IV). Subjects may continue taking H1 blockers and/or topical treatments to relieve symptoms as needed at the discretion of the treating physician. Subjects should be provided with a H1 blocker for at least 24 hours following the BMS-986012 infusion. Additional premedications (eg, H2 blockers) are also permitted, although the benefit of the H2 blocker has not been established. All premedications and subsequent doses of H1 blockers must be recorded on the appropriate CRF pages.

If 1 or more subjects experience a Grade $\geq$ 3 infusion reaction other than pruritus/itching of the skin and eyes, dry skin, rashes including folliculitis, and periorbital erythema, the infusion time for BMS-986012 will be increased from 60 to 90 minutes for all future infusions in ongoing and newly enrolled subjects. If a Grade $\geq$ 3 infusion reaction other than pruritus/itching of the skin and eyes, dry skin, rashes including folliculitis, and periorbital erythema occurs in a subject receiving BMS-986012 over 90 minutes, the infusion time for BMS-986012 will be increased to 120 minutes for all future infusions in ongoing and newly enrolled subjects (refer also to Section 5.5.1 for additional ADA sample collection). Additional prophylactic medication to prevent future infusion reactions may be considered after discussion and agreement between

investigator(s) and Sponsor/Medical Monitor. In the case of infusion reactions during nivolumab administration, subsequent infusion times for individual subjects may be extended at the discretion of the investigator.

Infusion reactions should be graded according to CTCAE (Version 4.03) guidelines. Treatment recommendations are provided 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.
- Administer additional H1 blocker such as diphenhydramine 25 to 50 mg oral or IV (or equivalent) and/or acetaminophen and/or non-steroidal anti-inflammatory drugs (NSAIDS) every 4 to 6 hours as needed.

For Grade 2 symptoms (moderate reaction; requires therapy or infusion interruption but responds promptly to symptomatic treatment [eg, antihistamines, NSAIDS, narcotics, corticosteroids, IV fluids]; prophylactic medications indicated for < 24 hours):

- Stop the study drug infusion, begin an IV infusion of normal saline, and treat the subject with additional H1 blocker such as diphenhydramine 50 mg IV (or equivalent) and/or acetaminophen; and/or NSAIDS; remain at bedside and monitor subject until resolution of symptoms. Corticosteroid therapy may also be administered as appropriate. H1 blocker should be given every 4 to 6 hours as needed. If infusion is interrupted, then restart the infusion at 50% of the original infusion rate when symptoms resolve; if no further complications ensue after 30 minutes, the rate may be increased to 100% of the original infusion rate. Monitor subject closely.
- If symptoms recur, then no further study drugs will be administered at that visit.
- The amount of study drug infused must be recorded on the CRF.
- Additional H1 blocker such as diphenhydramine 50 mg (or equivalent), acetaminophen, and/or corticosteroids and/or NSAIDS should be administered at least 30 minutes before additional study drug administrations. Remain at bedside and monitor subject until recovery from symptoms.

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

- Immediately discontinue infusion of all study drugs.
- Begin an IV infusion of normal saline and treat the subject as follows: Recommend bronchodilators, epinephrine 0.2 to 1 mg of a 1:1000 solution for subcutaneous administration, 0.3 mg of a 1:1000 solution for intramuscular administration, or 0.1 to 0.25 mg of a 1:10000 solution slowly for IV administration, and/or additional H1 blocker such as diphenhydramine 50 mg IV (or equivalent) with methylprednisolone 100 mg IV (or equivalent), as needed.

- Subject should be monitored until the investigator is comfortable that the symptoms will not recur. All study drugs 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.
- Obtain additional ADA blood sample as noted in Table 5.5.1-1.

In the case of late-occurring drug-related 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 STUDY DRUG

All protocol-specified IPs and nonIPs are considered study drug.

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

The start and stop time of the all study therapy infusions and any interruptions or infusion rate reductions should be documented.

Table 4-1: Product Description and Dosage Form

Product Description Class and Dosage Form	Potency	IP/NonIP	Blinded or Open Label	Packaging/Appearance	Storage Conditions (per label)
BMS-986012 Solution for Injection	120 mg/vial (30 mg/mL)	IP	Open Label	Primary Packaging: 5 mL (5 cc) glass vial Secondary Packaging: Outer carton Appearance: Vial containing 4 mL clear to slightly opalescent, colorless to pale yellow liquid. May contain few white or translucent particles.	2°C to 8°C (36°F to 46°F). Protect from Light. Protect from Freezing.
Nivolumab Solution for Injection	100 mg/vial (10 mg/mL)	IP	Open Label	Primary Packaging: 10 mL (10 cc) glass vial Secondary Packaging: Outer carton Appearance: Vial containing 10 mL clear to opalescent, colorless to pale yellow liquid, light (few) particulates may be present.	2°C to 8°C (36°F to 46°F). Protect from Light. Protect from Freezing.

IP = investigational medicinal product.

4.1 Investigational Product

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

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

In this protocol, IPs are: BMS-986012 and nivolumab.

4.1.1 BMS-986012

There will be no individual subject dose escalations of BMS-986012 allowed. Subjects should be carefully monitored for infusion reactions during BMS-986012 administration. If an infusion reaction is noted, subjects should be managed according to the guidance provided in Section 3.7.

Doses of BMS-986012 may be interrupted, delayed, skipped, or discontinued as described in Sections 3.7 and 4.5.

BMS-986012 is to be administered as an IV infusion. The administration of the entire bag contents should be completed within approximately 60 minutes. At the end of the infusion, an IV line flush should be performed by adding 30 mL normal saline into the infusion bag and then finishing the infusion at a rate of 1 to 2 mL per minute. For details regarding drug storage, preparation, administration, and use time, refer to the BMS-986012 IB[29] and/or Pharmacy Manual.

4.1.2 Nivolumab

There will be no individual subject dose escalations or reductions of nivolumab allowed. Subjects should be carefully monitored for infusion reactions during nivolumab administration. If an infusion reaction is noted, subjects should be managed according to the guidance provided in Section 3.7. Subjects must be monitored in the clinic for at least 4 hours following the first 2 doses of nivolumab and at least 1 hour following subsequent doses.

Doses of nivolumab may be interrupted, delayed, skipped, or discontinued as described in Sections 3.7 and 4.5.

Nivolumab injection is to be administered as an IV infusion over 30 minutes. At the end of the infusion, the IV line should be flushed with an appropriate amount (15 to 20 mL) of diluent to ensure that the total dose is administered. Separate infusion bags and filters should be used when administering nivolumab and BMS-986012 on the same day. For details regarding drug storage, preparation, administration, and use time, refer to the nivolumab IB[58] and/or Pharmacy Manual.

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 as nonIPs.

In this protocol there are no nonIPs.

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 should be 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 that includes all processes required to ensure drug is accurately administered. This includes documentation of drug storage, administration and, as applicable, storage temperatures, reconstitution, and use of required processes (eg, required diluents, administration sets).

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

This is an open-label study. All enrolled subjects, including those not dosed, will be assigned sequential subject numbers starting with 00001, eg, 00001, 00002, 00003.... 00010. Following implementation of interactive voice/web-based response system (IVRS/IWRS), subject numbers beginning 00101 will be assigned sequentially. Those enrolled subjects meeting inclusion and exclusion criteria will be eligible to be dosed. The distinct patient identification number will ultimately be comprised of the site number and subject number, eg, 0002 00001.

Until an IVRS/IWRS system is implemented, once informed consent has been obtained, the investigator (or designee) will register the subject by transmitting a copy of the completed enrollment worksheet (registration form) to the Sponsor. The following information is required for registration:

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

Treatment groups and/or dose levels will be provided to the site study team after the subject has registered and eligibility for the study confirmed. Site personnel/investigator will receive a

receipt confirming treatment assignment. A copy of this documentation should remain in the subject's chart.

In the dose escalation period (Parts 1 and 3), if a subject discontinues treatment with BMS-986012 monotherapy or in combination with nivolumab, or discontinues nivolumab in combination with BMS-986012 during the DLT evaluation period for reasons other than DLT, the subject may be replaced if necessary for safety assessments. Replacement subjects will receive the same treatment but will be assigned a new subject number.

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

In the BMS-986012 monotherapy dose expansion period (Part 2) of the study, subjects will be assigned to one of the treatment arms based on whether they are considered sensitive or refractory to prior treatment and then alternately assigned to a dose level as outlined in Section 3.1.2.

Based on the rate of subject enrollment and addition of clinical sites, the Sponsor may elect to implement an IVRS/IWRS to assign subject numbers and dose level as well as manage drug supply. If IVRS/IWRS is implemented, instructions will be provided to the clinical site in a separate instruction manual.

4.5 Selection and Timing of Dose for Each Subject

Each subject will be assigned to a specific BMS-986012 dose level as listed in sequential order during dose escalation (Parts 1 and 3, see Section 3.1.1). Subjects in the expansion cohorts (Parts 2 and 4) will be enrolled at BMS-986012 dose levels at or below the MTD or MAAD as agreed upon by the investigator and the Sponsor (Section 3.1.2).

Subjects in the dose expansion cohorts will be enrolled at dose levels at or below the MTD or MAAD of BMS-986012 monotherapy or BMS-986012 and nivolumab combination therapy, respectively.

For subjects receiving either BMS-968012 monotherapy or BMS-986012 and nivolumab combination therapy, BMS-986012 will be administered as an IV infusion of approximately 60-minute duration every 21 days. The expected dosages to be used for each monotherapy dose level are shown in Table 3.1.1.1-1. Dose levels intermediate to the estimated dose levels may be evaluated if agreed upon by the Sponsor/Medical Monitor and investigators, as long as the dose escalation increments are smaller than those specified in the protocol.

For subjects receiving nivolumab in combination with BMS-986012, subjects should receive nivolumab as a 30-minute infusion on Day 1 of each 21-day treatment cycle until PD (except as indicated in Section 4.5.4) or symptomatic deterioration, withdrawal of consent, unacceptable AEs, and/or meeting other protocol-specified discontinuation criteria (see Section 3.5), whichever occurs first.

For BMS-986012 and nivolumab combination therapy, BMS-986012 will be administered over a 60-minute infusion followed by a 30-minute flush, and then nivolumab will be administered over

30 minutes followed by an IV line flush with an appropriate amount of diluent (15 to 20 mL) to ensure that the total dose is administered. Subjects must be clinically observed for at least 4 hours following the first 2 doses of BMS-986012 and nivolumab combination therapy (ie, Cycles 1 and 2) and at least 1 hour following doses beyond the first 2 doses of combination therapy (ie, Cycle 3 and beyond).

4.5.1 Guidelines for Dose Modification

4.5.1.1 Intra-subject Dose Escalation

Intra-subject dose escalation of BMS-986012 monotherapy or BMS-986012 and nivolumab combination therapy is not permitted.

4.5.1.2 Management Algorithms for Immuno-oncology Agents: BMS-986012 and Nivolumab Combination Therapy Only

Immuno-oncology (I-O) agents are associated with AEs that can differ in severity and duration from AEs caused by other therapeutic classes. Nivolumab is considered an I-O agent in this protocol. Early recognition and management of AEs associated with I-O agents may mitigate severe toxicity. Management algorithms have been developed to assist investigators in assessing and managing the following groups of AEs:

- Gastrointestinal
- Renal
- Pulmonary
- Hepatic
- Endocrinopathy
- Skin
- Neurological

The above algorithms are found in the nivolumab IB[58] and Appendix 2 of this protocol. In addition to the guidance provided in these algorithms, it is recommended that consultation with a nephrologist be obtained for subjects with Grade 2 or 3 renal immuno-oncology-related AEs. Also, the use of infliximab for immuno-oncology-related AEs has the most data for treatment of colitis/diarrhea, while use in other AEs has not been well established. Infusion reaction management is provided in Section 3.7.

4.5.1.3 Dose Reductions

For subjects responding to treatment (ie, SD, PR, or CR demonstrated on imaging evaluations), intra-subject dose reduction of BMS-986012 may be permitted on a case by case basis (for reasons such as, but not limited to toxicity), after discussion and agreement between the Sponsor/Medical Monitor and the treating investigator. Once reduced, the dose level administered will not be re-escalated. Dose reductions of nivolumab for individual subjects are not permitted.

4.5.1.4 Dose Delay Criteria

Subjects who experience the following must have all study therapy interrupted:

- Select AEs and laboratory abnormalities for which no clear alternative cause is identified other than study treatment:
  - Grade ≥ 2 abnormality in AST, ALT, or total bilirubin (see also Section 6.6, Potential Drug Induced Liver Injury).
  - Grade ≥ 2 abnormality in amylase or lipase only if associated with radiographic and/or clinical evidence of pancreatitis
  - Grade ≥ 2 creatinine
  - Grade ≥ 2 neurological AE
  - Any Grade 3 skin, drug-related AE, including pruritus
  - Immune-related AEs as indicated in Section 4.5.1.2 and Appendix 2
  - Other Grade 2 events, including laboratory abnormalities, require discussion with the Sponsor/Medical Monitor to assess eligibility for continued study treatment prior to continued study treatment
- AE, laboratory abnormality, or concurrent illness that, in the judgment of the investigator, warrants delaying the dose of study drug.

Note: Subjects who require delay of any study drug should be re-evaluated weekly (or more frequently if clinically indicated) and resume dosing when retreatment criteria are met. During BMS-986012 and nivolumab combination therapy, if there is toxicity requiring a dose delay and the toxicity is considered related to 1 study drug while clinical benefit has been observed, treatment must be discontinued for the study drug to which the toxicity is attributed but may continue for the other study treatment only after discussion and agreement with the BMS Medical Monitor.

Dose delays > 7 days will be considered missed and will not be replaced. Subjects who meet criteria listed in Section 3.5 and Section 4.5.3 are required to permanently discontinue all study drug(s), which include dose delays lasting > 6 weeks (with exceptions as noted). All other subjects will be permitted to resume therapy with study drug(s) following resolution of the AE as described in Sections 4.5.1.3 and 4.5.2.

4.5.2 Criteria to Resume Treatment After Dose Delay

All Grade 2 toxicities for which no clear alternative cause is identified other than study treatment should be discussed with the BMS Medical Monitor prior to subsequent dosing.

Subjects will be permitted to resume therapy at the same dose level(s) following resolution of the AE to Grade ≤ 1 or to baseline within 6 weeks after last dose, with the following exceptions:

- Subjects may resume treatment in the presence of Grade 2 fatigue and anorexia.
- For subjects with Grade 2 AST, ALT, or total bilirubin elevations, dosing may resume when laboratory values return to baseline and management with corticosteroids, if needed, is complete.
  - Subjects with combined Grade 2 AST/ALT and total bilirubin values meeting discontinuation parameters (see Section 4.5.3 and Section 3.1.3.1) should have treatment permanently discontinued.

- Drug-related pulmonary toxicity, diarrhea or colitis must have resolved to baseline before treatment is resumed. Subjects with persistent Grade 1 pneumonitis after completion of a steroid taper over at least 1 month may be eligible for retreatment if discussed with and approved by BMS Medical Monitor.
- Subjects with drug-related endocrinopathies adequately controlled with only physiologic hormone replacement may resume treatment after consultation with the BMS Medical Monitor.
- For delays due to laboratory value changes, subsequent dosing may continue if subjects continue to meet laboratory criteria as listed in Section 3.3.1, subsection 2.e). The investigator will determine if subsequent dosing is appropriate for subjects who have laboratory or clinical abnormalities that do not meet DLT (Section 3.1.3) or discontinuation criteria (Section 4.5.3).

If the toxicity resolves to Grade ≤ 1 or baseline (except as otherwise noted in the exceptions above) > 6 weeks after last dose, but the subject does not otherwise meet the criteria for permanent discontinuation (see Sections 3.5 and 4.5.3), and the investigator believes that the subject is deriving clinical benefit, then the subject may be eligible to resume the study drug(s) following the approval of the BMS Medical Monitor. Subjects who meet criteria for permanent discontinuation should receive no further study therapy.

4.5.3 Guidelines for Permanent Discontinuation

Subjects meeting any of the following criteria will be required to permanently discontinue study treatment.

- Progression of disease, except as described in Section 4.5.4.
- Clinical deterioration as assessed by the investigator
- Grade 3 infusion reaction
- Any toxicity that meets DLT criteria as defined in Section 3.1.3; however, an exception may be made for the following upon consultation between the investigator and BMS Medical Monitor:
  - Isolated Grade 4 electrolyte imbalances/abnormalities that are not associated with clinical sequelae and are corrected with supplementation/appropriate management within 72 hours of their onset
  - Grade 4 drug-related endocrinopathy AEs, such as adrenal insufficiency, adrenocorticotropic hormone deficiency, 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.
  - For immune-related events, as indicated in Section 4.5.1.2 and Appendix 2.
  - Grade 3 neurologic toxicity except if resolving to baseline in ≤ 14 days
  - In most cases of Grade 3 AST or ALT elevation, study drug(s) will be permanently discontinued. If the investigator determines a possible favorable benefit/risk ratio that

warrants continuation of study drug(s), a discussion between the investigator and the BMS Medical Monitor/designee must occur.

- Any dosing interruption lasting > 6 weeks after last dose with the following exceptions:
  - Dosing interruptions to allow for prolonged steroid tapers to manage AEs for which no clear alternative cause is identified other than to study treatment are allowed.
  - Prior to re-initiating treatment in a subject with a dosing interruption lasting > 6 weeks after last dose and with no more than 3 missed doses, the BMS Medical Monitor must be consulted. Periodic study visits to assess safety and laboratory studies should also continue every 6 weeks or more frequently if clinically indicated during such dosing delays. Tumor assessments should continue as per protocol even if dosing is interrupted.
  - Dosing interruptions > 6 weeks after last dose that occur for non-drug related events may be allowed if approved by the BMS Medical Monitor. Prior to re-initiating treatment in a subject with a dosing interruption lasting > 6 weeks after last dose and with no more than 3 missed doses, the BMS Medical Monitor must be consulted. Periodic study visits to assess safety and laboratory studies should also continue every 6 weeks or more frequently if clinically indicated during such dosing delays. Tumor assessments should continue as per protocol even if dosing is interrupted. Subjects must otherwise meet the criteria for continued treatment at the time re-initiation of study therapy is considered.

If the investigator determines a possible favorable benefit/risk ratio that warrants continuation of study drug(s), a discussion between the investigator and the BMS Medical Monitor/designee must occur including during BMS-986012 and nivolumab combination therapy. If there is toxicity requiring discontinuation and the toxicity is considered related to 1 study drug while clinical benefit has been observed, treatment with the study drug to which the toxicity is attributed must be discontinued, but may be resumed for the other study drug, but only after discussion and agreement with the BMS Medical Monitor (or designee).

The consideration to re-initiate study therapy 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 study Sponsor.

4.5.4 Treatment Beyond Disease Progression in BMS-986012 and Nivolumab Combination Therapy

Accumulating evidence indicates a minority of subjects treated with immunotherapy may derive clinical benefit despite initial evidence of PD.[49]

Subjects treated with BMS-986012 and nivolumab combination therapy may be permitted to continue nivolumab monotherapy beyond initial RECIST v1.1-defined PD, as assessed by the investigator, as long as they meet the following criteria:

- Investigator-assessed clinical benefit
- 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 additional nivolumab treatment. All other elements of the main consent including description of reasonably foreseeable risks or discomforts, or other alternative treatment options will still apply.

A radiographic assessment/scan should be performed within 6 weeks of initial investigator-assessed progression to determine whether there has been a decrease in the tumor size or continued PD. The assessment of clinical benefit should be balanced by clinical judgment as to whether the subject is clinically deteriorating and unlikely to receive any benefit from continued treatment with nivolumab.

If the investigator feels that the nivolumab subject continues to achieve clinical benefit by continuing treatment, the subject should remain on the trial and continue to receive monitoring according to the Table 5.1-2.

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

New lesions are considered measureable at the time of initial progression if the longest diameter is at least 10 mm (except for pathological lymph nodes which must have a short axis of at least 15 mm). Any new lesion considered nonmeasureable at the time of initial progression may become measureable and therefore included in the tumor burden if the longest diameter increases to at least 10 mm (except for pathological lymph nodes, which must have a short axis of at least 15 mm). In situations where the relative increase in total tumor burden by 10% is solely due to inclusion of new lesions which become measurable, these new lesions must demonstrate an absolute increase of at least 5 mm. The criteria for progression during treatment beyond progression are for subject management purpose only. Statistical analysis of efficacy will be based on RECIST v1.1.

4.6 Blinding/Unblinding

Not applicable.

4.7 Treatment Compliance

Study drug will be administered in the clinical facility by trained medical personnel. The investigator and the study personnel will ensure that each subject receives the calculated dose of the study drug. Treatment compliance will be monitored by drug accountability, as well as recording study treatment administration in subjects' medical records and CRF.

Drug supplies will be inventoried and accounted for throughout the study. The Drug Accountability Log will be reviewed by the study monitor during site visits and at the completion of the study. Any discrepancy should be brought to the attention of the Sponsor.

4.8 Destruction of Study Drug

For this study, study drug, 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).

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

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

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

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

Please refer to Section 9.2.2 for additional guidance on IP records and documentation.

It is, however, the investigator's or designee'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. The return of full or partially used IP supplied by BMS or its vendors will be arranged by the responsible Study Monitor.

Please refer to Section 9.2.2 for guidance on IP records and documentation.

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

5 STUDY ASSESSMENTS AND PROCEDURES

5.1 Flow Chart/Time and Events Schedule

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

Table 5.1-1: CA001030 Screening Procedural Outline

Procedure	Screening Visit	Notes
Eligibility Assessments		
Informed Consent	X	A subject is considered enrolled only when a protocol specific informed consent is signed.
Inclusion/Exclusion Criteria	X	All inclusion/exclusion criteria must be met for subjects to participate in the study.
Medical History	X	May include more detailed history of risk factors for potential events such as neurological toxicity, infusion or hypersensitivity reactions, smoking history, and. alcohol use.
Safety Assessments		
PE	X	If the screening PE is performed within 72 hours of dosing on Cycle 1 Day 1 then a single exam may count as both the screening and pre-dose evaluation. Physical exams must include a baseline neurological assessment at screening and/or predose at Cycle 1, Day 1.
ECOG Performance Status	X	See Appendix 6
Physical Measurements	X	Includes height and weight.
Vital Signs	X	Includes body temperature, 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.
ECGs	X	12-lead ECG. QTcF assessments ≥ 480 ms must be confirmed on repeat ECG. ECGs should be recorded after the subject has been supine for at least 5 minutes.
Laboratory Tests	X	Includes blood and urine samples. See Section 5.3.1
Oxygen Saturation	X	Required for BMS-986012 and nivolumab combination therapy only. Pulse oximetry at rest (also monitor amount of supplemental oxygen if applicable).
Thyroid Panel including TSH, free T3, and free T4	X	Required for BMS-986012 and nivolumab combination therapy only. See Section 5.3.1.
Urinalysis	X	
Serology for HBV and HCV testing (HBVsAg and HCVAb or HCV RNA)	X	Required for all subjects upon approval of Amendment 04. See Section 5.3.1.
Serum or Urine Pregnancy Test	X	For WOCBP only. WOCBP must have a negative test within 72 hours prior to the start of study drug if enrolled in the BMS-986012 monotherapy or 24 hours prior to the start of

Table 5.1-1: CA001030 Screening Procedural Outline

Procedure	Screening Visit	Notes
		study drug if enrolled in combination therapy and evaluated prior to study drug administration. Sensitivity of test must be at least 25 IU/L or equivalent units of HCG.
FSH	X	If needed to document post-menopausal status as defined in Section 3.3.3.
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
Efficacy Assessments		
Tumor Assessments	X	See Section 5.4.1
Brain Imaging	X	See Section 5.4.1
Adverse Event Reporting		
Clinical Complaints	X	Clinical complaints related to the disease under study must be collected within 14 days of the first dose of study drug.
Monitor for SAEs	X	All SAEs must be collected from the date of subject's written consent until 100 days post discontinuation of dosing or subject's participation in the study if the last scheduled visit occurs at a later time.

Abbreviations: HBVsAg = HBV surface antigen; HCVAb = HCV antibody; PE = physical examination; T3 = triiodothyronine; T4 = thyroxine; TSH = thyroid stimulating hormone.

Table 5.1-2: CA001030 On Treatment Procedural Outline

Procedure	Treatment Period							
Study Cycle (N=21 days)	**1 and 2**				**3[a]**	**Cycle 4 & Subsequent Cycles (Day 1)[b]**	**EOT**	
Study Cycle Day	**1**	**2**	**8**	**15**	**1**	**1**	**1**	**Notes**
Safety Assessments								
PE	X		X	X	X	X	X	Full PE Cycle 1 Day 1. Targeted PE only thereafter. All physical exams must include a neurological assessment. If there are any new or worsening clinically significant changes since the last examination, report changes on the appropriate non-serious or serious adverse event CRF page.
Performance Status (ECOG)	X (Cycle 1 only)						X	See Appendix 6
Physical Measurements	X				X	X	X	Weight only.

Table 5.1-2: CA001030 On Treatment Procedural Outline

Procedure	Treatment Period							
Study Cycle (N=21 days)	1 and 2				3[a]	Cycle 4 & Subsequent Cycles (Day 1)[b]	EOT	
Study Cycle Day	1	2	8	15	1	1	1	Notes
Vital Signs[c]	X		X	X	X	X	X	Includes body temperature, 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. On Cycle 1 Day 1, vital signs will be obtained before the BMS-986012 infusion and then every 15 minutes (± 5 minutes) until 60 minutes after completion of the BMS-986012 infusion. Vital signs on subsequent treatment visits will be collected predose and every 30 minutes (± 10 minutes) until 60 minutes following completion of the infusion. When slowing or re-starting an infusion due to an infusion reaction, vital signs should be monitored every 15 minutes (± 5 minutes) or as directed by the investigator until the infusion is completed and/or the subject is stabilized.
Oxygen Saturation	X				X	X	X	Required for BMS-986012 and nivolumab combination therapy only. Pulse oximetry at rest (also monitor amount of supplemental oxygen, if applicable) prior to dosing and at any time a subject has new or worsening respiratory symptoms.
12-lead ECGs	X Refer to Table 5.5.1-1, Table 5.5.1-2,				X	X	X	See Table 5.5.1-1 Table 5.5.1-2 Table 5.5.1-3: and Table 5.5.1-4). Triplicate

Table 5.1-2: CA001030 On Treatment Procedural Outline

Procedure	Treatment Period							
Study Cycle (N=21 days)	1 and 2				3[a]	Cycle 4 & Subsequent Cycles (Day 1)[b]	EOT	
Study Cycle Day	1	2	8	15	1	1	1	Notes
	Table 5.5.1-3:, and Table 5.5.1-4)							12-lead ECGs will be collected prior to the first BMS-986012 dose during Cycle 1, Day 1. Single 12-Lead ECGs will be collected thereafter.
Chemistry/ Hematology	X		X	X	X	X	X	Pre-dose testing to be performed within 72 hours of dosing. See Section 5.3.1, section on "Hematology" and "Serum Chemistry" for specific tests to be included.
Urinalysis	X		X	X	X	X	X	
Thyroid Function Testing	X				X	X	X	Required for BMS-986012 and nivolumab combination therapy only. Includes TSH (reflex to free T3 and free T4 if abnormal result). To be performed every other cycle after Cycle 3 (ie, Cycle 5, 7, etc)
Brain Imaging								As clinically indicated
Bone Scan								As clinically indicated
Pregnancy Test	X				X	X	X	For WOCBP only. Sensitivity of test must be at least 25 IU/L or equivalent units of HCG. WOCBP must have a negative test within 72 hours prior to the start of study drug if enrolled in the BMS-986012 monotherapy or 24 hours prior to the start of study drug if enrolled in combination therapy and evaluated prior to study drug administration.

Table 5.1-2: CA001030 On Treatment Procedural Outline

Procedure	Treatment Period							
Study Cycle (N=21 days)	1 and 2				3[a]	Cycle 4 & Subsequent Cycles (Day 1)[b]	EOT	
Study Cycle Day	1	2	8	15	1	1	1	Notes
Adverse Event Reporting								
Monitor for Non-Serious Adverse Events	X	X	X	X	X	X	X	Non-serious AEs will be collected starting with the first dose of study medication and through 100 days after discontinuation of dosing.
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 dosing or subject's participation in the study if the last scheduled visit occurs at a later time.
Sample Collection								
PK Assessments	See Table 5.5.1-1, Table 5.5.1-2, Table 5.5.1-3:, and Table 5.5.1-4 for time points							
Immunogenicity (ADA) Assessments	See Table 5.5.1-1, Table 5.5.1-2, Table 5.5.1-3:, and Table 5.5.1-4 for time points. Samples will also be taken every 4th cycle after Cycle 7 (Cycle 7, 11, 15, 19, etc). Additional samples for immunogenicity assessments, referred to as "ADA Event Driven" samples may be justified in cases of Grade 3/4 infusion or hypersensitivity reactions (see Section 3.7 and Section 5.5.1).							
[redacted]	[redacted]							
Efficacy Assessments								
Tumor Assessments	Every 6 weeks (± 5 days of targeted tumor assessment date)						X	MRI/CT with contrast.
Clinical Drug Supplies								
BMS-986012 administration	X				X	X		See Section 4 for administration details. Prophylactic pre-infusion medications should be given prior to any BMS-986012

Table 5.1-2: CA001030 On Treatment Procedural Outline

Procedure	Treatment Period							
Study Cycle (N=21 days)	1 and 2				3[a]	Cycle 4 & Subsequent Cycles (Day 1)[b]	EOT	
Study Cycle Day	1	2	8	15	1	1	1	Notes
								infusions (See Section 3.7).
Nivolumab administration	X				X	X		For Parts 3 and 4 only. See Section 4 for administration details. Observation in a clinical setting is required for 4 hours after dose administration for Cycles 1 and 2 and 1 hour after dose administration in subsequent cycles.

[a] See details of PK, ADA and ECG sampling in Section 5.5.1

[b] Including treatment beyond progression with nivolumab monotherapy.

[c] Vital signs should be checked at the indicated time points, however documentation of vital signs on the CRF is only necessary if this data is clinically significant, in which case an adverse event should also be documented.

In the event of multiple procedures are required at a single time point, please perform in the following order:

1) Safety (ECG)
2) Safety (clinical labs)
3) Pharmacokinetic Sampling

Table 5.1-3: CA001030 Toxicity/Clinical Follow-up and Survival Follow-up Period Procedural Outline

Procedure	Clinical Follow-up			Survival Follow-up	
	1 30 days (+/- 5 days)	2 60 days (+/- 5 days)	3 100 days (+/- 5 days)	Every 12 weeks (+/- 2 weeks)	Notes
Safety Assessments					Subjects will be permitted to receive other anti-cancer therapies, including investigational agents, during all follow-up periods including clinical and survival follow-up. All assessments will be collected during clinical follow-up regardless of whether a subject has initiated a new anti-cancer therapy. See Section 5.3.
PE	X	X	X		All PEs must include a neurological assessment.
Vital Signs	X	X	X		Includes body temperature, 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.
Thyroid Function Testing	X	X	X		Required for BMS-986012 and nivolumab combination therapy only. Includes TSH (reflex to free T3 and free T4 if abnormal result).
Pregnancy Test	X	X	X		For WOCBP only. Sensitivity of test must be at least 25 IU/L or equivalent units of HCG.
Adverse Event Reporting					
Monitor for non-SAEs	X	X	X		Non-serious AEs will be collected starting with the first dose of study medication and through 100 days after discontinuation of dosing.
Monitor for SAEs	X	X	X		All SAEs must be collected starting at the time a subject signs informed consent and through 100 days after discontinuation of dosing.

Table 5.1-3: CA001030 Toxicity/Clinical Follow-up and Survival Follow-up Period Procedural Outline

Procedure	Clinical Follow-up			Survival Follow-up	
	1 **30 days** **(+/- 5 days)**	**2** **60 days** **(+/- 5 days)**	**3** **100 days** **(+/- 5 days)**	**Every 12 weeks** **(+/- 2 weeks)**	**Notes**
Sample Collection					
PK Assessments	See Table 5.5.1-1, Table 5.5.1-2, Table 5.5.1-3, and Table 5.5.1-4 for time points				
Immunogenicity Assessments	See Table 5.5.1-1, Table 5.5.1-2, Table 5.5.1-3, and Table 5.5.1-4 for time points.				

Table 5.1-3: CA001030 Toxicity/Clinical Follow-up and Survival Follow-up Period Procedural Outline

Procedure	Clinical Follow-up			Survival Follow-up	
	1 **30 days** **(+/- 5 days)**	**2** **60 days** **(+/- 5 days)**	**3** **100 days** **(+/- 5 days)**	**Every 12 weeks** **(+/- 2 weeks)**	**Notes**
Efficacy Assessments					
Tumor Measurements			X (see Notes)	X (see Notes)	See Section 5.4.1. During the clinical follow-up period, for subjects who have not discontinued study treatment for progressive disease, tumor measurements will be collected as close as possible to the 100-day follow-up visit (ie, CT/MRI scans conducted per the subject's routine standard of care visit for this assessment at approximately 100 days can be used). Tumor measurements should be conducted earlier, if clinically indicated. Except for subjects who start new anti-cancer therapies, subjects with stable disease, PR or CR at the last clinical follow-up visit should undergo tumor assessment via CT/MRI scans every 3 to 4 months during the survival follow-up period until progression. The Clinical Follow-up period begins 30 days (± 5 days) from the last dose of study drug while the Survival Follow-up period occurs every 12 weeks (± 2 weeks) from the date of the 100-day Clinical Follow-up visit.

Table 5.1-3: CA001030 Toxicity/Clinical Follow-up and Survival Follow-up Period Procedural Outline

Procedure	Clinical Follow-up			Survival Follow-up	
	1 **30 days** **(+/- 5 days)**	**2** **60 days** **(+/- 5 days)**	**3** **100 days** **(+/- 5 days)**	**Every 12 weeks** **(+/- 2 weeks)**	**Notes**
Survival Status					
Assess Subject Survival Status				X (see Notes)	Subject status will be assessed by either a clinic visit or telephone contact every 12 weeks (± 2 weeks) until the subject has been followed for approximately 3 years or until the last treated subject has been followed for 6 months from his/her last date of treatment. The nature and start dates of any new therapies during this period should be recorded. Only information related to subjects' survival and the start date of any subsequent therapies will be collected. Except for subjects who start new anti-cancer therapies, subjects with stable disease, PR or CR at the last clinical follow-up visit should undergo tumor assessment via CT/MRI scans every 3 to 4 months during the survival follow-up period until progression.

Abbreviations: PE = physical examination; T3 = triiodothyronine; T4 = thyroxine; TSH = thyroid stimulating hormone.

5.1.1 Retesting During Screening Period

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

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.

5.2 Study Materials

The site will provide all required materials for the tests performed locally (ie, relevant clinical laboratory tests). The site will have available a well-calibrated scale for recording body weight, a 12-lead ECG machine, and a sphygmomanometer and thermometer for vital signs assessments, an X-ray machine for chest X-rays, an oximeter for oxygen saturation, a CT, and MRI. Normal saline bags and infusion sets with 0.2- to 1.2-µm polyethersulfone (PES, Supor®) in-line filter will be provided by the site for the infusion of BMS-986012. Normal saline bags and infusion sets with 0.2- to 1.2-µm pore size and low-protein binding in-line filter will be provided by the site for the infusion of nivolumab. A current and fully-stocked advanced cardiac life support cart will be immediately available on the premises and all medications to manage acute infusion reactions should be available. The site will have 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, serum and plasma samples. The site will provide all materials required for accurate source documentation of study activities.

BMS will provide a BMS-approved protocol and any amendments or administrative letters (if required), IBs, and Pharmacy Manual. Case report forms (electronic or hard copy) will be provided by BMS. The Central Laboratory will provide labels and tubes for the collection of blood samples for PK, ADA, [redacted] Until an IVRS/IWRS system is implemented, enrollment registration worksheets will be provided to the study sites. Sites will fax/e-mail enrollment worksheets to BMS at the time of informed consent. Once an IVRS/IWRS system is implemented, instructions will be provided to the sites. NCI CTCAE criteria will be provided to study sites prior to site initiation.

5.3 Safety Assessments

Subjects will be considered evaluable for safety if they have received any dose of study drug. Any occurrence of an SAE from the time of enrollment until 100 days post-discontinuation of study drug dosing will be documented. Any occurrence of non-serious AEs will be collected from first dose of study drug until 100 days post-discontinuation of dosing.

AEs will be coded using the most current version of MedDRA and reviewed for potential significance and importance. AEs will be evaluated according to the NCI CTCAE Version 4.03. Subjects should be followed until all AEs for which no clear alternative cause is identified other than to study treatment have recovered to baseline or are deemed irreversible by the investigator. Safety assessments will be based on medical review of AE reports and the results of vital sign

measurements, physical examinations (PE) and clinical laboratory tests. The incidence of AEs will be tabulated and reviewed for potential significance and clinical importance.

The schedule of required visits, tests, procedures and assessments are described in Table 5.1-1, Table 5.1-2, and Table 5.1-3. In limited instances, scheduled events (including events other than safety assessments) can occur outside of the indicated timeframes but the Sponsor should first be notified.

If a subject has a delay in study drug administration for any reason, then assessments and laboratory tests (with the exception of any tests needed to ensure subject safety) should be correspondingly delayed with the exception of tumor assessments (continue scans every 6 weeks ± 5 days regardless of dosing delays).

At baseline, a medical history will be obtained to capture relevant underlying conditions. Baseline signs and symptoms are those that are assessed within 2 weeks prior to subject enrollment. The baseline PE should include weight, height, heart rate, blood pressure, temperature and ECOG status and should be performed within 28 days of treatment assignment (see Table 5.1-1 and Table 5.1-2).

Body weight should be assessed at each on-study visit. ECOG performance status will be assessed at baseline and EOT. On Cycle 1 Day 1, vital signs will be obtained before the BMS-986012 infusion and then every 15 minutes (± 5 minutes) until 60 minutes after completion of the monotherapy or combination therapy infusion(s) as applicable. During subsequent treatment visits, vital signs may be obtained every 30 minutes (± 10 minutes) until 60 minutes following completion of the last infusion. If any vital sign is abnormal at the final check, the subject must be observed further for a period of time, as clinically indicated. The start and stop time of the study drug infusion should be documented (start of drug infusion = 0 hour). Any new or worsening clinically significant changes must be reported on the appropriate non-serious or SAE page.

Additional measures including non-study required laboratory tests should be performed as clinically indicated or where required by institutional or local regulations.

Clinical laboratories will be assessed (see Table 5.1-1, Table 5.1-2, and Table 5.1-3). Sites should collect these samples between -28 to -1 days from enrollment to insure that results required for eligibility purposes are verified prior to registration. Pregnancy testing must be performed within 72 hours prior to the initial administration of IP at baseline, at subsequent cycles during study therapy, and at the 3 clinical follow-up visits if enrolled in the BMS-986012 monotherapy or 24 hours prior to the initial administration of IP at baseline, subsequent cycles during study therapy, and at the 3 clinical follow-up visits if enrolled in BMS-986012 and nivolumab combination therapy. Complete blood count plus differential and serum chemistry panel should be drawn within 72 hours prior to each subsequent scheduled cycle. On-study laboratory tests will be performed on site/locally. Laboratory tests may be obtained more frequently if indicated. Additional laboratory tests should be performed as per standard of care.

Laboratory toxicities (eg, suspected drug induced liver enzyme elevations) will be monitored during the Clinical Follow-up period via on site/local labs until all study drug toxicities for which no clear alternative cause is identified other than to study treatment resolve, return to baseline, or are deemed irreversible.

For the BMS-986012 and nivolumab combination therapy (Parts 3 and 4), if a subject shows pulmonary-related signs (hypoxia or fever) or symptoms (eg, dyspnea, cough, or fever) consistent with possible pulmonary AEs, the subject should be immediately evaluated to rule out pulmonary toxicity, according to the suspected pulmonary toxicity management algorithm in the current nivolumab IB.[58]

5.3.1 Laboratory Test Assessments

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

Results of clinical laboratory tests performed predose must be available prior to dosing.

The following clinical laboratory tests will be performed:

Hematology

Hemoglobin and hematocrit
Total white blood cell count, including differential
Platelet count

Serum Chemistry

Aspartate aminotransferase (AST)
Alanine aminotransferase (ALT)
Total bilirubin (with reflex to direct bilirubin or conjugated bilirubin)
Alkaline phosphatase
Lactate dehydrogenase (LDH)
Blood Urea Nitrogen or Urea
Uric acid
Glucose
Amylase*
Lipase*
Thyroid stimulating hormones*
Free triiodothyronine*
Free thyroxine*
Total Protein
Albumin
Sodium
Potassium
Carbon dioxide or Bicarbonate
Chloride
Calcium
Phosphorus
Magnesium
Creatinine or CrCl, using the Cockcroft-Gault formula:
Female CrCl = ([140 - age in years] × weight in kg × 0.85) / (72 × serum creatinine in mg/dL)

Male CrCl = ([140 - age in years]) × weight in kg × 1.00) / (72 × serum creatinine in mg/dL)

** BMS-986012 and nivolumab combination therapy only (Parts 3 and 4)*

Serology for HBV and HCV testing (HBV surface antigen and HCV antibody or HCV RNA) at screening

Urinalysis

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

Other Analyses

Pregnancy test (WOCBP only).
FSH

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 determined by 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 Laboratory Test Result Abnormalities).

5.4 Efficacy Assessments

5.4.1 Primary Efficacy Assessment

Tumor measurements will be conducted at screening and every 6 weeks during the Treatment period. During the Clinical Follow-up period, tumor measurements will be collected as close as possible to the 100-day follow-up visit (ie, CT/MRI scans conducted per the subject's routine standard of care visit for this assessment at approximately 100 days can be used). Tumor measurements should be conducted earlier, if clinically indicated. Tumor measurements during follow-up only apply to subjects who discontinue study therapy for reasons other than PD. Subjects with SD, PR, or CR at the last clinical follow-up visit should undergo tumor assessment via CT/MRI scans every 3 to 4 months during the follow-up periods (Section 8.3.2.2 and Section 8.4.3) until progression or death. Tumor measurements will be collected in all subjects until progression or the subject's discontinuation from the study as per Section 5.1. Tumor response and progression will be evaluated in this study using RECIST v1.1 (Appendix 3) for endpoint analysis. Subjects may continue nivolumab monotherapy and, for the purpose of subject management (eg, decision to treat beyond progression), will also be assessed as indicated in Section 4.5.4. Statistical analysis of efficacy will be based on RECIST v1.1 criterion. Initial response assessment of PR or CR must be confirmed by a consecutive assessment no less than 4 weeks (28 days) later. At the Sponsor's discretion, de-identified scans and measurements may be

collected and reviewed by independent radiologists using RECIST v1.1 criteria at a later date, or at any time during the study.

The tumor assessment performed during screening will be used as a baseline for efficacy assessments. CT/MRI imaging of the chest and abdomen is required at Screening and at each TA, regardless of the location of known metastases. The same imaging modality must be used for all TAs, unless contraindicated.

Brain scans are required at Screening to document potential asymptomatic CNS metastases. If CNS lesions are documented at baseline, brain scans should be performed at each TA. In addition, brain scans are to be repeated as clinically indicated. Contrast enhanced CTs are preferred, MRIs are a second choice.

Imaging-based evaluation is preferred to clinical examination. Helical (spiral) CT scans of the chest and abdomen are preferred. If not available, conventional (non-helical, non-spiral CT) should be used; however, a measurable lesion must not have the longest diameter smaller than 20 mm by conventional CT or MRI (10 mm on spiral CT). IV contrast should be used for all CT scans; if IV contrast is contraindicated, CT without contrast may be used, or MRI should be used at the Screening exam and at all TA time points. Subjects who develop contrast allergy after study enrollment must be followed by CT without contrast or MRI for subsequent tumor measurements.

Sections should be contiguous, similarly sized and consistent from visit-to-visit. Section thickness must be based on institutional standards (eg, from 5 to 8 mm, 10 mm cuts are not recommended). Chest x-rays and ultrasound are not acceptable methods to measure disease. Response and progression of disease must be documented by CT or MRI similar to the methods used at Screening.

Bone scans may be utilized at the investigator's discretion and per institutional guidelines. In case of new lesions such as pleural effusion, cytology must be performed to identify and confirm malignancy. Skin and soft tissue lesions will be captured as non-measurable lesions through PE only.

Any subject who develops an objective tumor response (CR or PR) is required to undergo confirmatory scans no less than 4 weeks since the prior scan in order to verify the reliability of the radiologic finding.

5.4.2 Secondary Efficacy Assessments

Not applicable.

5.5 Pharmacokinetic Assessments

Monoclonal antibodies exhibit complex PK as a result of linear and non-linear disposition processes operating simultaneously. At low (below saturation of the target) concentrations the non-linear process dominates elimination (non-linear clearance > linear clearance), by the capacity limited process known as target (expressed on tumor) mediated disposition. At high

concentrations the capacity limited process becomes saturated and the linear process dominates elimination (linear clearance > non-linear clearance). The transitions from non-linear to linear dominated clearance and back complicates the PK data analysis and interpretation, in addition to the effect of the expected down regulation of the target resulting from anti-tumor activity by BMS-986012. The planned PK data analysis by NCA methods is limited to computing parameters where the assumption of linearity is not critical.

The PK of BMS-986012 will be derived from serum concentration versus time data. A detailed schedule of PK evaluation during the BMS-986012 monotherapy dose escalation period (Part 1) and the BMS-986012 monotherapy dose expansion period (Part 2) is provided in Table 5.5.1-1 and Table 5.5.1-2, respectively.

The PK of BMS-986012 in combination with nivolumab will be derived from serum. A detailed schedule of PK evaluation during BMS-986012 and nivolumab combination therapy dose escalation period (Part 3) and BMS-986012 and nivolumab combination therapy dose expansion period (Part 4) is provided in Table 5.5.1-3: and Table 5.5.1-4, respectively.

The BMS-986012 PK parameters to be assessed following dose administration at Cycle 1 and Cycle 3 (Parts 1, 2, 3, and 4) include the following, if data permits:

Cmax	Maximum observed serum concentration
Tmax	Time of maximum observed serum concentration
Ctau	Observed serum concentration at the end of a dosing interval
AUC(0-t)	Area under the serum concentration-time curve from time zero to time of last quantifiable concentration
AUC(TAU)	Area under the serum concentration-time curve in one dosing interval

If data permits, the following single dose BMS-986012 PK parameters may also be assessed (Part 1 and 3):

CLT	Total body clearance
Ctrough	Trough observed serum concentration (this includes pre-dose concentrations and Ctau concentrations).
Vss	Volume of distribution at steady state

The BMS-986012 PK parameters to be assessed following multiple dose administration (Parts 1, 2, 3, and 4) include but are not limited to the following:

Cmax	Maximum observed serum concentration
Tmax	Time of maximum observed serum concentration
AUC(0-t)	Area under the serum concentration-time curve from time zero to time of last quantifiable concentration
AUC(TAU)	Area under the serum concentration-time curve in one dosing interval
Css-avg	Average concentration over a dosing interval (AUC[TAU]/tau)

AI	Accumulation Index. Ratio of an exposure measure at steady state (eg, following Cycle 3 Day 1 dose) to that after the first dose (exposure measure includes AUC[TAU], Cmax, and Ctau)
T-HALFeff	Effective elimination T-HALF that explains the degree of accumulation observed for a specific exposure measure (exposure measure includes AUC[TAU], Cmax)

Individual subject PK parameter values will be derived by non-compartmental methods by a validated PK analysis program. Actual time of PK draw must be documented and should be used for the analyses. Additional PK parameters may be computed as appropriate. The PK data from this study may be pooled with other studies to enhance the PK characterization of BMS-986012 and/or nivolumab (Parts 3 and 4) and will be part of a separate report.

5.5.1 Pharmacokinetics and Anti-drug Antibody (Immunogenicity): Collection and Processing

Table 5.5.1-1 and Table 5.5.1-3: list the sampling schedule to be followed for the assessment of PK during dose escalation in BMS-986012 monotherapy (Part 1) and BMS-986012 and nivolumab combination therapy (Part 3), respectively. Table 5.5.1-2 lists the sampling schedule to be followed for the assessment of PK during dose expansion for BMS-986012 monotherapy upon approval of Amendment 3. Table 5.5.1-4 lists the sampling schedule to be followed for the assessment of PK during dose expansion for BMS-986012 and nivolumab combination therapy. Further details of blood collection and processing of serum will be provided to the site in the procedure manual.

Additional samples for immunogenicity assessments, referred to as "ADA Event Driven" samples may be justified in cases of Grade 3/4 infusion or hypersensitivity reactions (see Section 3.7). The immunogenicity (and corresponding drug exposure) data from these samples will be reported as part of a subject's overall immunogenicity assessment. Uniquely identified specimen collection kits and instructions for collection of "ADA Event Driven" samples will be provided by the central laboratory vendor.

Table 5.5.1-1: PK, ADA, and ECG Assessment Schedule for BMS-986012 Monotherapy - Dose Escalation, EOT, and Clinical Follow-up (Part 1)

Cycle	Study Day	Time (Event) Hour	Time (Relative to Start of BMS-986012 Infusion)[a] Hour:Min	Blood Sample (PK)	Blood Sample (ADA)	ECG[b]
1	1	0 (predose)	00:00	X	X	triplicate[c]
1	1	end of infusion	01:00	X		
1	1		02:00	X		X
1	1		04:00	X		
1	1		08:00	X		X
1	2		24:00 (+24:00)	X		X
1	4		72:00 (+24:00)	X		
1	8		168:00 (±48:00)	X		
1	15		336:00 (±48:00)	X		X
2	1	0 (predose)	00:00	X	X	X
2	1	end of infusion	01:00	X		
2	1		08:00	X		
3	1	0 (predose)	00:00	X	X	X
3	1	end of infusion	01:00	X		
3	1		02:00	X		X
3	1		04:00	X		
3	1		08:00	X		X
3	2		24:00 (+24:00)	X		X
3	4		72:00 (+24:00)	X		
3	8		168:00 (±48:00)	X		
3	15		336:00 (±48:00)	X		
4	1	0 (predose)	00:00	X		X
7 (then every 4th cycle, ie, Cycle 11, 15, 19, etc)	1	0 (predose)	00:00	X	X	X
EOT	EOT	0	00:00	X	X	X

Table 5.5.1-1: PK, ADA, and ECG Assessment Schedule for BMS-986012 Monotherapy - Dose Escalation, EOT, and Clinical Follow-up (Part 1)

Cycle	Study Day	Time (Event) Hour	Time (Relative to Start of BMS-986012 Infusion)[a] Hour:Min	Blood Sample (PK)	Blood Sample (ADA)	ECG[b]
Follow-up (60 days)	FU2	0	00:00	X	X	
Follow-up (100 days)	FU3	0	00:00	X	X	
ADA Event Driven[d]		0	00:00	X	X	

[a] If infusion times are extended due to Infusion Reactions (refer to Section 3.7) PK [redacted] samples are taken relative to the start of the BMS-986012 infusion.

[b] ECGs should be completed predose on Day 1 of each treatment cycle.

[c] Collected in triplicate within 24 hours prior to dose on Cycle 1 Day 1 only. Single 12-Lead ECGs will be collected thereafter.

[d] Samples for immunogenicity assessments, referred to as "ADA Event Driven" samples may be justified in cases of Grade 3/4 infusion or hypersensitivity reactions (see Section 3.7). Samples should be taken as close to the beginning of the Event as possible and the time the sample(s) were taken must be documented.

Abbreviations: FU = follow-up.

Table 5.5.1-2: PK, ADA, and ECG Assessment Schedule for BMS-986012 Monotherapy - Dose Expansion, EOT, and Clinical Follow-up (upon Approval of Amendment 03) (Part 2)

Cycle	Study Day	Time (Event) Hour	Time (Relative to Start of BMS-986012 Infusion)[a] Hour:Min	Blood Sample (PK)	Blood Sample (ADA)	ECG[b]
1	1	0 (predose)	00:00	X	X	triplicate[c]
1	1	end of infusion	01:00	X		
1	1		04:00 (+2:00)	X		X
1	2		24:00 (+24:00)	X		X
1	8		168:00 (±48:00)	X		
1	15		336:00 (±48:00)	X		X
2	1	0 (predose)	00:00	X	X	X
2	1	end of infusion	01:00	X		
3	1	0 (predose)	00:00	X	X	X
3	1	end of infusion	01:00	X		
3	1		04:00 (+2:00)	X		X
4	1	0 (predose)	00:00	X		X
7 (then every 4th cycle, ie C11, C15, C19, etc)	1	0 (predose)	00:00	X	X	X
EOT	EOT	0	00:00	X	X	X
Follow-up (60 days)	FU2	0	00:00	X	X	
Follow-up (100 days)	FU3	0	00:00	X	X	
ADA Event Driven[d]		0	00:00	X	X	

[a] If infusion times are extended due to Infusion Reactions (refer to Section 3.7) PK [redacted] samples are taken relative to the start of the BMS-986012 infusion.

[b] ECGs should be completed predose on Day 1 of each treatment cycle.

[c] Collected in triplicate within 24 hours prior to dose on Cycle 1 Day 1 only. Single 12-Lead ECGs will be collected thereafter.

[d] Samples for immunogenicity assessments, referred to as "ADA Event Driven" samples may be justified in cases of Grade 3/4 infusion or hypersensitivity reactions (see Section 3.7). Samples should be taken as close to the beginning of the Event as possible and the time the sample(s) were taken must be documented.

Abbreviations: FU = follow-up.

Table 5.5.1-3: PK, ADA, and ECG Assessment Schedule for BMS-986012 and Nivolumab Combination Therapy - Dose Escalation, EOT and Clinical Follow-up (Part 3)

Cycle	Study Day	Time (Event) Hour	Time (Relative to Start of BMS-986012 Infusion)[a] Hour:Min	Blood Sample (PK) for BMS-986012	Blood Sample (PK) for nivolumab	Blood Sample (ADA) for BMS-986012 and nivolumab	ECG[b]
1	1	0 (predose)	00:00	X	X	X	triplicate[c]
1	1	end of infusion	01:00	X			X
1	1		04:00 (+2:00)	X			
1	2		24:00 (+24:00)	X			X
1	8		168:00 (±48:00)	X	-	-	-
1	15		336:00 (±48:00)	X			X
2	1	0 (predose)	00:00	X	X	X	X
2	1	end of infusion	01:00	X			
3	1	0 (predose)	00:00	X	X	X	X
3	1	end of infusion	01:00	X			X
4	1	0 (predose)	00:00	X	X	X	X
7 (then every 4th cycle, ie, C11, C15, C19, etc)	1	0 (predose)	00:00	X	X	X	X
EOT	EOT	0	00:00	X	X	X	X
Follow-up (60 day)	FU2	0	00:00	X	X	X	
Follow-up (100d)	FU3	0	00:00	X	X	X	
ADA Event Driven[d]		0	00:00	X	X	X	

[a] If infusion times are extended due to Infusion Reactions (refer to Section 3.7) PK [redacted] samples are taken relative to the start of the BMS-986012 infusion. BMS-986012 is infused first followed by nivolumab. All times are relative to the start of the BMS-986012 infusion.

[b] ECGs should be completed predose on Day 1 of each treatment cycle.

[c] Collected in triplicate within 24 hours prior to dose on Cycle 1 Day 1 only. Single 12-Lead ECGs will be collected thereafter.

[d] Samples for immunogenicity assessments, referred to as "ADA Event Driven" samples may be justified in cases of Grade 3/4 infusion or hypersensitivity reactions (see Section 3.7). Samples should be taken as close to the beginning of the Event as possible and the time the sample(s) were taken must be documented.

Abbreviations: FU = follow-up.

Table 5.5.1-4: PK, ADA, and ECG Assessment Schedule for BMS-986012 and Nivolumab Combination Therapy - Dose Expansion, EOT, and Clinical Follow-up (Part 4)

Cycle	Study Day	Time (Event) Hour	Time (Relative to Start of BMS-986012 Infusion)[a] Hour:Min	Blood Sample (PK) for BMS-986012	Blood Sample (PK) for nivolumab	Blood Sample (ADA) for BMS-986012 & nivolumab	ECG[b]
1	1	0 (predose)	00:00	X	X	X	triplicate[c]
1	1	end of infusion	01:00	X			X
1	1		04:00 (+2:00)	X			
1	2		24:00 (+24:00)	X			X
1	8		168:00 (±48:00)	X			
1	15		336:00 (±48:00)	X			X
2	1	0 (predose)	00:00	X	X	X	X
2	1	end of infusion	01:00	X			
3	1	0 (predose)	00:00	X	X	X	X
3	1	end of infusion	01:00	X			X
4	1	0 (predose)	00:00	X	X		X
7 (then every 4th cycle, ie, C11, C15, C19, etc)	1	0 (predose)	00:00	X	X	X	X
EOT	EOT	0	00:00	X	X	X	X
Follow-up (60 days)	FU2	0	00:00	X	X	X	
Follow-up (100 days)	FU3	0	00:00	X	X	X	
ADA Event Driven[d]		0	00:00	X	X	X	

[a] If infusion times are extended due to Infusion Reactions (refer to Section 3.7) PK [redacted] samples are taken relative to the start of the BMS-986012 infusion. BMS-986012 is infused first followed by nivolumab. All times are relative to the start of the BMS-986012 infusion.

[b] ECGs should be completed predose on Day 1 of each treatment cycle.

[c] Collected in triplicate within 24 hours prior to dose on Cycle 1 Day 1 only. Single 12-Lead ECGs will be collected thereafter.

[d] Samples for immunogenicity assessments, referred to as "ADA Event Driven" samples may be justified in cases of Grade 3/4 infusion or hypersensitivity reactions (see Section 3.7). Samples should be taken as close to the beginning of the Event as possible and the time the sample(s) were taken must be documented.

Abbreviations: FU = follow-up.

5.5.2 Pharmacokinetic Sample Analyses

Validated immunoassays will be used to measure concentrations of BMS-986012 and nivolumab in serum.

5.5.3 Immunogenicity Sample Analysis

Validated immunoassays will be used to assay samples for the presence of, and measure titers of anti-BMS-986012 and nivolumab antibodies in serum. Samples will be collected from all subjects as indicated in Table 5.1-2, Table 5.1-3 and Table 5.5.1-1, Table 5.5.1-2, Table 5.5.1-3:, and Table 5.5.1-4.

5.5.4 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.

[redacted]

[redacted]

[redacted]

5.8 Outcomes Research Assessments

Not applicable.

5.9 Other Assessments

Not applicable.

5.10 Results of Central Assessments

Not applicable.

5.11 Additional Research Collection

With Amendment 04, this protocol will include residual sample storage for additional research. This collection for additional research is intended to expand the translational R&D capability at BMS, and will support as yet undefined research aims that will advance our understanding of disease and options for treatment. It may also be used to support health authority requests for analysis, and advancement of pharmacodiagnostic development to better target drugs to the right patients. This may also include genetic/genomic exploration aimed at exploring disease pathways, progression, and response to treatment. All requests for access to samples or data for additional research will be vetted through a diverse committee of the study sponsor's senior leaders in Research and Development to ensure the research supports appropriate and well-defined scientific research activities.

Residual samples for future research will also be retained by the BMS Biorepository [redacted] at a BMS-approved third party storage management facility for additional research purposes. Additional research samples will be retained for 15 years or the maximum allowed by applicable law. No additional sampling is required for residual collections.

Additional research collections and retention are mandatory for all subjects, except where prohibited by local laws or regulations. Further details of sample collection and processing will be provided to the site in the laboratory manual.

6 ADVERSE EVENTS

An ***Adverse Event (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 one of the following:

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

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

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 one or more AEs.)

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

6.1 Serious Adverse Events

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

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

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

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

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

NOTE:

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

- a visit to the emergency room or other hospital department < 24 hours, that does not result in admission (unless considered an important medical or life-threatening event)
- elective surgery, planned prior to signing consent
- admissions as per protocol for a planned medical/surgical procedure
- routine health assessment requiring admission for baseline/trending of health status (eg, routine colonoscopy)
- medical/surgical admission other than to remedy ill health and planned prior to entry into the study. Appropriate documentation is required in these cases

- admission encountered for another life circumstance that carries no bearing on health status and requires no medical/surgical intervention (eg, lack of housing, economic inadequacy, caregiver respite, family circumstances, administrative reason).
- Admission for administration of anti-cancer 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 IBs 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. For subjects assigned to treatment and never treated with study drug, SAEs should be collected for 30 days from the date of treatment assignment. If applicable, SAEs must be collected that relate to any later protocol-specified procedure (eg, a follow-up skin biopsy).

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

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

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

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

SAE Email Address: Refer to Contact Information list.

SAE Facsimile Number: Refer to Contact Information list.

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

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

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

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

All SAEs should be followed to resolution or stabilization.

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

6.2 Non-serious Adverse Events

A ***non-serious AE*** is an AE not classified as serious.

6.2.1 Non-serious Adverse Event Collection and Reporting

The collection of non-serious AE information should begin at initiation of study drug. Non-serious 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.

Non-serious 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 non-serious AEs that cause interruption or discontinuation of study drug and for those present at the end of study treatment as appropriate. All identified non-serious AEs must be recorded and described on the non-serious 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.

For subjects receiving study treatment, all non-serious AEs (not only those deemed to be treatment-related) should be collected continuously during the treatment period and for a minimum of 100 days following discontinuation of study treatment.

Every AE must be assessed by the investigator with regard to whether it is considered immune mediated. For events that are potentially immune mediated, additional information will be collected on the subject's case report form.

6.3 Laboratory Test Result Abnormalities

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

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

6.4 Pregnancy

If, following initiation of the IP, it is subsequently discovered that a study subject is pregnant or may have been pregnant at the time of study exposure, including during at least 5 half-lives after product administration (105 days from the last dose of BMS-986012 monotherapy or 23 weeks from the last dose of nivolumab in BMS-986012 and nivolumab combination therapy), the investigator must immediately notify the BMS Medical Monitor/designee of this event and complete and forward a Pregnancy Surveillance Form to BMS Designee within 24 hours and in accordance with SAE reporting procedures described in Section 6.1.1.

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

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

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

6.5 Overdose

An overdose is defined as the accidental or intentional administration of any dose of a product that is considered both excessive and medically important. All occurrences of overdose must be reported as an SAE (see Section 6.1.1 for reporting details.).

6.6 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. Aminotransferase (ALT or AST) elevation > 3 × ULN if liver chemistries are normal at baseline; if liver chemistries are abnormal at baseline, then > 2 × baseline values or any value > 8 × ULN should be used as cutoffs,

   AND

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

   AND

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

6.7 Other Safety Considerations

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

7 DATA MONITORING COMMITTEE AND OTHER EXTERNAL COMMITTEES

Not applicable

8 STATISTICAL CONSIDERATIONS

8.1 Sample Size Determination

8.1.1 Dose Escalation (Parts 1 and 3) Sample Size

A total of approximately 30 evaluable subjects are expected to be treated during BMS-986012 monotherapy dose escalation (Part 1), and approximately 12 evaluable subjects in BMS-986012 and nivolumab combination dose escalation, assuming 2 dose levels (Part 3). The exact number per dose level will depend on the number of observed DLTs and will be guided by the escalation design algorithm that selects as MTD the dose level with an estimated DLT rate closest to 25% target DLT rate in monotherapy (Part 1) and the dose level with DLT rate closest to 29% in combination therapy (Part 3). Between 2 and up to 13 DLT evaluable subjects may be enrolled to a given dose level in BMS-986012 monotherapy. Treating additional subjects beyond the 13 at the same dose level would be unlikely to alter the decision specified by the mTPI algorithm.

8.1.2 Dose Expansion (Parts 2 and 4) Sample Size

The total sample size per each BMS-986012 monotherapy expansion cohort (approximately n = 22 for refractory and approximately n=28 for sensitive) is planned to provide a reasonable false positive rate (FPR) and false negative rate (FNR), based on assumptions of true (target) and historic ORR for each tumor[80] as seen below. In addition to the FPR and FNR, the lower limits of the confidence interval (CI) for ORR based on the Clopper-Pearson method are provided below by cohort.

For a refractory tumor dose expansion monotherapy cohort of 22 subjects and assuming a true ORR of 25%, there is an 84% chance of observing at least 4 responses, a 68% chance of observing at least 5 responses, and a 16% chance of observing 3 or fewer responses (FNR). If the true ORR is only 10% rather than 25%, then there is a 17% and 6% chance, respectively, that there will be at least 4 or at least 5 responses in 22 subjects (FPR). In addition, if 4 or 5 responses are observed, then the lower limit of the 80% CI for the ORR is 8.2% or 11.5%, respectively.

For a sensitive tumor dose expansion monotherapy cohort of 28 subjects and assuming a true ORR of 40%, there is a 85% chance of observing at least 9 responses, a 74% chance of observing at least 10 responses, and a 15% chance of observing 8 or fewer responses (FNR). If the true ORR for a tumor is only 25% rather than 40%, then there is a 25% and 14% chance, respectively, that there will be at least 9 or at least 10 responses in 28 subjects (FPR). In addition,

if 8 or 9 responses are observed, then the lower limit of the 80% CI for the ORR is 17% or 20%, respectively.

In the combined sensitive and refractory expansion monotherapy cohort of 29 subjects and assuming a true ORR of 40% there is an 88% chance of observing at least 9 responses, and a 12% chance of observing 8 or fewer responses (FNR). If the true ORR for a tumor is only 20% rather than 40%, then there is an 11% chance and a 5% chance that there will be at least 9 and at least 10 responses, respectively, in 29 subjects (FPR). In addition, if 10 or 11 responses are observed then the lower limit of the 80% CI for the ORR is 23% or 26%, respectively.

The Simon 2-stage (optimal) design, will be used for the expansion cohorts. In monotherapy cohorts after a minimum of 9 subjects per refractory cohort and 10 subjects per sensitive cohort are treated in Stage 1, there will be an initial evaluation of efficacy, independently in each cohort. Similarly, in the BMS-986012 and nivolumab combination therapy cohort (Part 4), after a minimum of 13 subjects are treated in Stage 1 there will be an initial evaluation of efficacy in this cohort. This will inform potential early decisions and guide planning/operations or early termination after taking into consideration additional data, for example, duration of response and/or stable disease and safety. The operational characteristics of this Simon 2-stage design are provided in Table 8.1.2-1 below, although not used for hypothesis testing.

Table 8.1.2-1: Dose Expansion: Characteristics of the Simon 2-stage Design in Monotherapy Refractory and Sensitive, and Combination Cohorts

Expansion Cohort	Historic ORR (%)	Target ORR (%)	Stage 1 /Total N	Stage 1 Responses Futility Boundary	Alpha/ Power (%)	Probability of Early Stopping (%)
Monotherapy Refractory	10	25	9/22	0	16/80	38.7
Monotherapy Sensitive	25	40	10/28	2	20/75	53
Combination[a]	20	40	13/29	2	10/86	50

[a] Refractory and Sensitive Subjects Combined

The number of subjects receiving treatment at the time of the Stage 1 efficacy evaluation for each expansion cohort is approximate and may exceed the specified minimum number of 9, 10, or 13 due to time needed for radiologic tumor evaluation, the unknown time to response, and the unknown true recruitment rate.

8.2 Populations for Analyses

- All Enrolled Subjects: All subjects who sign an informed consent form.
- All Treated Subjects: All subjects who receive at least 1 dose of study medication.

- PK Subjects: All subjects who receive at least 1 dose of BMS-986012 (and nivolumab in the combination therapy) and have available serum concentration data for the corresponding analyte.
- [redacted]
- Immunogenicity (ADA) Population: all treated subjects who had at least 1 post-treatment immunogenicity assessment
- The ECG evaluable population will consist of all treated subjects who had a baseline ECG and at least 1 on-study ECG.
- Response Evaluable Population: all treated subjects who had baseline tumor measurement and at least 1 other tumor measurement after treatment, clinical progression, or death prior to the first on-treatment tumor assessment.

8.3 Endpoints

8.3.1 Primary Endpoint(s)

The primary endpoint of this Phase 1/2 study is safety as measured by the incidence of AEs, SAEs, AEs leading to discontinuations, and deaths. In addition, clinical laboratory test abnormalities will be examined. Safety will be evaluated from the time that the subject signs the informed consent, and for up to 100 days after the last dose of study drug.

8.3.2 Secondary Endpoint(s)

8.3.2.1 Pharmacokinetics

The PK of BMS-986012 as monotherapy and in combination with nivolumab will be characterized using the following endpoints:

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

8.3.2.2 Efficacy

Efficacy based on RECIST v1.1 (Appendix 3) will be assessed using the following secondary endpoints:

- Best overall response (BOR): defined as the best response designation over the study as a whole, recorded between the dates of first dose of study medication and 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 pre-surgical tumor assessments will be considered in the determination of BOR.
- ORR: defined as the total number of subjects whose BOR is either a CR or PR divided by the total number of subjects in the population of interest.
- Duration of Response: defined as the time between the date of first response and the subsequent date of objectively documented disease progression or death, whichever occurs first. For those subjects who remain alive and have not progressed or received subsequent therapy, duration of response will be censored on the date of last tumor assessment
- PFS: defined as the time from the first dose of study medication to the date of the first objective documentation of tumor progression or death due to any cause. Subjects who did not progress nor die will be censored on the date of their last tumor assessment. Subjects who did not have any on-study tumor assessments will be censored on the date of the first dose of study medication.
- Progression Free Survival Rate (PFSR) at week 't': defined as the proportion of subjects who remain progression free and surviving at 't' weeks (t=12, 24, 36, etc). The proportion will be calculated by the product-limit method (Kaplan-Meier estimate) which takes into account censored data.
- The following exploratory efficacy endpoints will be used for the OS objective.
- OS: defined as the time between the date of first dose of study medication and the date of death. For subjects without documentation of death, OS will be censored on the last date the subject was known to be alive.
- Overall Survival Rate at month 't': defined as the proportion of subjects surviving at 't' months (eg, t=6, 12, 24 months). The proportion will be calculated by the product-limit method (Kaplan-Meier estimate).

8.3.2.3 Anti-drug Antibodies

The immunogenicity of BMS-986012 (as monotherapy and in combination with nivolumab) and nivolumab (in combination with BMS-986012) will be measured by assessment of the presence or absence of specific ADA to BMS-986012 or nivolumab. The incidence of positive ADA will be calculated. Details on this and potentially additional endpoints (eg, incidence of persistent positive ADA), and analysis will be provided in the Statistical Analysis Plan (SAP).

[redacted]

[redacted]

8.4 Statistical Analyses

8.4.1 Demographics and Baseline Characteristics

Frequency distributions of gender and race and ECOG performance status will be tabulated. Summary statistics for age, body weight, and height will be tabulated. Prior cancer therapy will be listed and tabulated.

8.4.2 Safety Analyses

All recorded AEs will be listed and tabulated by system organ class, preferred term, and treatment. Clinical laboratory test results will be listed and summarized by treatment. Any significant PE findings and clinical laboratory results will be listed. Vital sign measurements will be listed. ECG readings (reviewed by a central laboratory) will be evaluated by the investigator and abnormalities, if present, will be listed.

For subjects with serial ECG measurements, changes in the QTcF (ΔQTcF), ECG intervals QRS, and PR, and in heart rate (ΔHR) will be tabulated by dose level and study day. Frequency distributions of maximum QTcF values, maximum ΔQTc, maximum QRS, maximum PR and of maximum heart rate in pre-specified categories will be tabulated by dose. Scatter plots of heart rate, ΔHR, QTc, and ΔQTcF versus time-matched BMS-986012 concentrations will be provided. A concentration-response effect of BMS-986012 on QTcF may be assessed by a linear mixed effects regression model for ΔQTcF on serum BMS-986012 concentrations, stratified by study day, as well as pooled across days, for the BMS-986012 monotherapy and BMS-986012 and nivolumab combination therapy.

8.4.3 Efficacy Analyses

Individual BOR, duration of response and PFS will be listed using RECIST v1.1 criteria (Appendix 3). The ORR and PFS rate (eg, at 24 weeks) will be tabulated by study period (escalation, expansion) and dose and for each BMS-986012 monotherapy dose expansion cohort (refractory or sensitive, Part 2), and the BMS-986012 and nivolumab combination therapy dose expansion cohort (Part 4). The CIs will be based on Clopper-Pearson method for ORR and using Greenwood formula for PFSR. The duration of response and PFS will be estimated by Kaplan-Meier methodology, for each expansion cohort (Parts 2 and 4). Individual changes in the tumor burden over time will be presented graphically by dose level within each cohort. Overall survival will also be assessed as part of exploratory efficacy analysis, by Kaplan-Meier plots and median OS as well as OS rates, at specified times (eg, at 6 or 12 months) and will be provided.

8.4.4 Pharmacokinetic Analyses

Descriptive statistics for BMS-986012 PK parameters will be–tabulated by dose level and treatment (BMS-986012 monotherapy and BMS-986012 and nivolumab combination therapy). Geometric means and coefficients of variation, CV (%), will be presented for Cmax, AUC, Ctau, AI, CLT, Ctrough, Vss, T-HALFeff, and Css-avg. Medians and ranges will be presented for Tmax. PK trough concentrations for nivolumab will be tabulated.

8.4.5 Immunogenicity Analyses

All available immunogenicity data for BMS-986012 as monotherapy and in combination with nivolumab, as well as immunogenicity of nivolumab in combination with BMS-986012, will be listed, with flags for subjects with at least 1 positive ADA after initiation of treatment. The frequency of subjects with a positive ADA assessment at baseline and frequency of subjects who develop ADA after initiation of treatment (ADA positive) will be provided. Details on this and potentially additional endpoints (eg, incidence of persistent positive ADA) and analysis will be provided in the SAP. Associations between immunogenicity measures and PK and/or select AEs may be explored.

[redacted]

8.4.7 Outcomes Research Analyses

Not applicable.

8.4.8 Other Analyses

Additional exposure response analysis may be performed to explore associations of BMS-986012 (or nivolumab) PK exposure with [redacted] selected safety measures, and/or efficacy measures.

8.5 Interim Analyses

Data emerging from this study may be needed for timely decisions about adjustments to procedures in subsequent parts of the study. Therefore, data may be reviewed prior to the final

lock of the study database. Additional interim analyses may also be performed for administrative purposes or publications. Analyses will only consist of listings, summaries, and graphs of the available data. No formal inferences requiring any adjustment to statistical significance level will be performed. Efficacy analyses based on interim data may use response evaluable or all treated populations depending on the purpose of the analysis.

9 STUDY MANAGEMENT

9.1 Compliance

9.1.1 Compliance with the Protocol and Protocol Revisions

The study shall be conducted as described in this approved protocol. All revisions to the protocol must be discussed with, and be prepared by, BMS. The investigator should not implement any deviation or change to the protocol without prior review and documented approval/favorable opinion from the IRB/IEC of an amendment, except where necessary to eliminate an immediate hazard(s) to study subjects.

If a deviation or change to a protocol is implemented to eliminate an immediate hazard(s) prior to obtaining IRB/IEC approval/favorable opinion, as soon as possible the deviation or change will be submitted to:

- IRB/IEC for review and approval/favorable opinion
- BMS
- Regulatory Authority(ies), if required by local regulations

Documentation of approval signed by the chairperson or designee of the IRB(s)/IEC(s) must be sent to BMS.

If an amendment substantially alters the study design or increases the potential risk to the subject: (1) the consent form must be revised and submitted to the IRB(s)/IEC(s) for review and approval/favorable opinion; (2) the revised form must be used to obtain consent from subjects currently enrolled in the study if they are affected by the amendment; and (3) the new form must be used to obtain consent from new subjects prior to enrollment.

If the revision is done via an administrative letter, investigators must inform their IRB(s)/IEC(s).

9.1.2 Monitoring

Representatives of BMS must be allowed to visit all study site locations periodically to assess the data quality and study integrity. On site they will review study records and directly compare them with source documents, discuss the conduct of the study with the investigator, and verify that the facilities remain acceptable.

In addition, the study may be evaluated by BMS internal auditors and government inspectors who must be allowed access to CRFs, source documents, other study files, and study facilities. BMS audit reports will be kept confidential.

The investigator must notify BMS promptly of any inspections scheduled by regulatory authorities, and promptly forward copies of inspection reports to BMS.

9.1.2.1 Source Documentation

The investigator is responsible for ensuring that the source data are accurate, legible, contemporaneous, original and attributable, whether the data are hand-written on paper or entered electronically. If source data are created (first entered), modified, maintained, archived, retrieved, or transmitted electronically via computerized systems (and/or any other kind of electronic devices) as part of regulated clinical trial activities, such systems must be compliant with all applicable laws and regulations governing use of electronic records and/or electronic signatures. Such systems may include, but are not limited to, electronic medical/health records, 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 procedure, electronic CRFs, study documentation, informed consent, and enrollment of WOCBP.

9.2 Records

9.2.1 Records Retention

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

BMS will notify the investigator when the study records are no longer needed.

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

9.2.2 Study Drug Records

It is the responsibility of the investigator to ensure that a current disposition record of IP (inventoried and dispensed) is maintained at each study site where study drug is inventoried and dispensed. 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
- non-study disposition (eg, lost, wasted)
- amount destroyed at study site, if applicable
- amount returned to BMS
- any temperature excursions of study drug
- retain samples for bioavailability/bioequivalence, if applicable
- dates and initials of person responsible for Investigational Product dispensing/accountability, as per the Delegation of Authority Form.

Records for IP and nonIP (whether supplied by BMS, its vendors, or the site) must substantiate IP/non-IP integrity and traceability from receipt, preparation, administration, and through destruction or return. Records must be made available for review at the request of BMS/designee or a Health Authority.

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 electronic SAE form and Pregnancy Surveillance form, respectively. If the electronic SAE form is not available, a paper SAE form can be used. Spaces may be left blank only in those circumstances permitted by study-specific CRF completion guidelines provided by 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 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:

- Subject recruitment (eg, among the top quartile of enrollers)
- Involvement in trial design
- Other criteria (as determined by the study team)

The data collected during this study are confidential and proprietary to BMS. Any publications or abstracts arising from this study require approval by BMS prior to publication or presentation and must adhere to BMS's publication requirements as set forth in the approved clinical trial agreement (CTA). All draft publications, including abstracts or detailed summaries of any proposed presentations, must be submitted to BMS at the earliest practicable time for review, but at any event not less than 30 days before submission or presentation unless otherwise set forth in the CTA. BMS shall have the right to delete any confidential or proprietary information contained in any proposed presentation or abstract and may delay publication for up to 60 days for purposes of filing a patent application.

10 GLOSSARY OF TERMS

Term	Definition
Complete Abstinence	If 1 form of contraception is required, Complete Abstinence is defined as complete avoidance of heterosexual intercourse and is an acceptable form of contraception for all study drugs. Female subjects must continue to have pregnancy tests. Acceptable alternate methods of highly effective contraception must be discussed in the event that the subject chooses to forego complete abstinence. If 2 forms of contraception is required, Complete abstinence is defined as complete avoidance of heterosexual intercourse and is an acceptable form of contraception for all study drugs. Subjects who choose complete abstinence are not required to use a second method of contraception, but female subjects must continue to have pregnancy tests. Acceptable alternate methods of highly effective contraception must be discussed in the event that the subject chooses to forego complete abstinence. **Expanded definition** Complete abstinence as defined as complete avoidance of heterosexual intercourse is an acceptable form of contraception for all study drugs. This also means that abstinence is the preferred and usual lifestyle of the subject. This does not mean periodic abstinence (eg, calendar, ovulation, symptothermal, profession of abstinence for entry into a clinical trial, post-ovulation methods) and withdrawal, which are not acceptable methods of contraception. Subjects who choose complete abstinence are not required to use a second method of contraception, but female subjects must continue to have pregnancy tests. Acceptable alternate methods of highly effective contraception must be discussed in the event that the subject chooses to forego complete abstinence.
Medical Research	Those scientific activities which cannot be reasonably anticipated at the time of trial design, for which we would like to collect and/or retain samples from study participants. Examples of Medical Research include, but are not limited to, new assay development and validation, companion diagnostic development, new hypotheses in the interaction of drug and the human body, and exploration of emerging science in the understanding of disease.

11 LIST OF ABBREVIATIONS

Term	Definition
ΔHR	change in heart rate
ΔQTcF	change in QTcF
AE	adverse event
ADA	anti-drug antibody
ADCC	antibody-dependent cellular cytotoxicity
ADCP	antibody-dependent cellular phagocytosis
AI	Accumulation Index. Ratio of an exposure measure at steady state (eg, following Cycle 3 Day 1 dose) to that after the first dose (exposure measure includes AUC(TAU), Cmax and Ctau)
ALT	alanine aminotransferase
APC	antigen-presenting cell
AST	aspartate aminotransferase
AT	Aminotransaminases
AUC	area under the concentration-time curve
AUC(INF)	area under the concentration-time curve from time 0 to infinity
AUC(TAU)	area under the concentration-time curve over the dosing interval
AUC(0-n)	area under the concentration-time curve from time 0 to n hours
AUC(0-t)	area under the concentration-time curve from time zero to the time of the last quantifiable concentration
BMS	Bristol-Myers Squibb
C	cycle
CDC	complement-dependent cytotoxicity
CFR	Code of Federal Regulations
CI	confidence interval
CL	clearance
CLT	total body clearance
Cmax	maximum observed concentration
CMV	cytomegalovirus
CNS	central nervous system
CR	complete response

Term	Definition
CrCl	creatinine clearance
CRF	Case Report Form, paper or electronic
Css-avg	Average concentration over a dosing interval (AUC[TAU]/tau)
CT	computed tomography
CTA	clinical trial agreement
Ctau	Observed serum concentration at the end of a dosing interval
CTC	circulating tumor cell
Ctrough	Trough observed serum concentration (this includes pre-dose concentrations and Ctau concentrations).
CV	coefficient of variation
D	day
DILI	drug-induced liver injury
DLT	dose-limiting toxicity
ECG	electrocardiogram
ECOG	Eastern Cooperative Oncology Group
EDC	electronic data capture
EI	equivalence interval (of the mTPI design)
ELISA	enzyme-linked immunosorbent assay
EOT	end of treatment
Fc	fragment crystallizable (region)
FcγR	Fc gamma receptor
FDA	Food and Drug Administration
FIH	first in human
FITC	fluorescein isothiocyanate
FSH	follicle-stimulating hormone
FU	follow-up
Fuc-GM1	fucosylated monosialotetrahexosylganglioside
GCP	Good Clinical Practice
GEMM	genetically engineered mouse model
GLP	Good Laboratory Practices
HBV	hepatitis B virus

Term	Definition
HBVsAg	HBV surface antigen
HCG	human chorionic gonadotrophin
HCV	hepatitis C virus
HCVAb	HCV antibody
HIV	human immunodeficiency virus
HNSTD	highest non-severely toxic dose
HRT	hormone replacement therapy
IB	Investigator Brochure
ICH	International Conference on Harmonisation
IEC	Independent Ethics Committee
IFN	interferon
IgG	immunoglobulin G
IL	interleukin
IMP	investigational medicinal product
I-O	immuno-oncology
IP	investigational product
IRB	Institutional Review Board
IV	intravenous
IVRS/IWRS	interactive voice/web-based response system
MAAD	maximum administered dose
mAb	monoclonal antibody
MOA	mechanism of action
MRI	magnetic resonance imaging
MTD	maximum tolerated dose
mTPI	modified toxicity probability interval
NCA	non-compartment analysis
NK	natural killer
NOAEL	no-observed-adverse-effect level
NSAID	non-steroidal anti-inflammatory drug
NSCLC	non-small cell lung cancer

Term	Definition
ORR	objective response rate
OS	overall survival
PBMC	peripheral blood mononuclear cell
PD	progressive disease
PD-1	Programmed cell death protein 1
PD-L	Programmed death-ligand
PE	physical examination
PFS	progression-free survival
PFSR	progression-free survival rate
PK	pharmacokinetic(s)
PPK	population pharmacokinetics
PR	partial response
Q2W	every 2 weeks
Q3W	every 3 weeks
QTcF	QT interval corrected for heart rate using Fridericia's formula
QW	every week
RECIST	Response Evaluation Criteria for Solid Tumors
SAE	serious adverse event
SAP	Statistical Analysis Plan
SCLC	small cell lung cancer
SD	stable disease
T3	triiodothyronine
T4	thyroxine
TBNK	T, B, and NK flow assay
TGI	tumor-growth inhibition
T-HALF	half-life
T-HALFeff	Effective elimination half-life that explains the degree of accumulation observed for a specific exposure measure (exposure measure includes AUC(TAU), Cmax)
Tmax	time of maximum observed concentration
TSH	thyroid stimulating hormone

Term	Definition
ULN	upper limit of normal
US/USA	United States (of America)
USP	United States Pharmacopeia
Vss	volume of distribution at steady state
Vz	volume of distribution during the terminal phase
WOCBP	women of childbearing potential

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APPENDIX 1 SIMULATION TO EXAMINE MTPI VS 3 + 3 DESIGN FOR DOSE ESCALATION

1 SIMULATION RESULTS FOR MONOTHERAPY DOSE ESCALATION, WITH 4 DOSE LEVELS

Simulations of modified toxicity probability interval (mTPI) and 3 + 3 designs, as shown below, demonstrate that the mTPI design has a greater chance of selecting the correct maximum tolerated dose (MTD) and treating fewer subjects at suboptimal doses than the 3 + 3 design. In addition, it allows flexibility in making decisions by requiring a minimum cohort size and therefore can handle a dropout rate of 20% without always requiring replacement.

The mTPI uses a set of decision rules guided by simple Bayesian models and requires a clinically relevant predetermined target dose-limiting toxicity (DLT) rate and an equivalence interval (EI), within which any dose is considered close to the true MTD. For this study, in monotherapy setting the selected target toxicity (DLT) rate is 25% (EI [24%, 27%]).

The mTPI design makes decisions using the same 2 observed numbers as the traditional 3 + 3 design, the number of DLT evaluable subjects and the number of subjects with DLT. Based on these 2 numbers, unit probability mass is calculated within each of 3 regions as stated above, and the decision is based on which region has the largest unit probability mass:

- E: escalating to the higher dose if interval [0, 24%] has the largest unit probability mass,
- S: staying at the same dose if interval [24, 27%] has the largest unit probability mass,
- D: de-escalating to the lower dose if interval [27, 100%] has the largest unit probability mass.

At the end of the trial, MTD will be picked by isotonic regression estimation method to be the dose with the estimated toxicity rate closest to the target toxicity rate among all the tried doses.

Due to an expected 20% drop-out rate, mTPI design is conducted in a flexible way such that if there are at least 3 DLT evaluable subjects in the initial cohort of 3 to 6 subjects for each dose, the subjects who dropped out would not be replaced and the decision will be based on the available (≥ 3) DLT evaluable subjects. At least 3 subjects are enrolled initially, which is considered a safe approach because of BMS-986012's tolerability at high doses. After the initial 3 to 6 subjects, subjects in cohorts of sample sizes of 3 subjects will be enrolled to the same dose when requested by mTPI decision rules. Once again, subjects who were added and dropped out are not to be replaced either unless all the added subjects dropped out.

Simulations were performed to examine the performance of mTPI and a 3 + 3 design for this study. Escalation decisions based on the mTPI are shown in Appendix 4. Decisions based on the 3 + 3 design are shown below:

- E: no subject with DLT out of 3 DLT evaluable subjects initially, or at most 1 subject with DLT out of 6 DLT evaluable subjects after adding 3 more subjects.
- S: 1 subject with DLT out of 3 DLT evaluable subjects initially.
- D: at least 2 subjects with DLT out of 3 DLT evaluable subjects initially, or at least 2 subjects with DLT out of 6 DLT evaluable subjects after adding 3 more subjects.

In the simulation with mTPI, a 20% drop-out rate is used. Dropout is not simulated in the 3 + 3 design, since replacement subject is always needed to reach a decision.

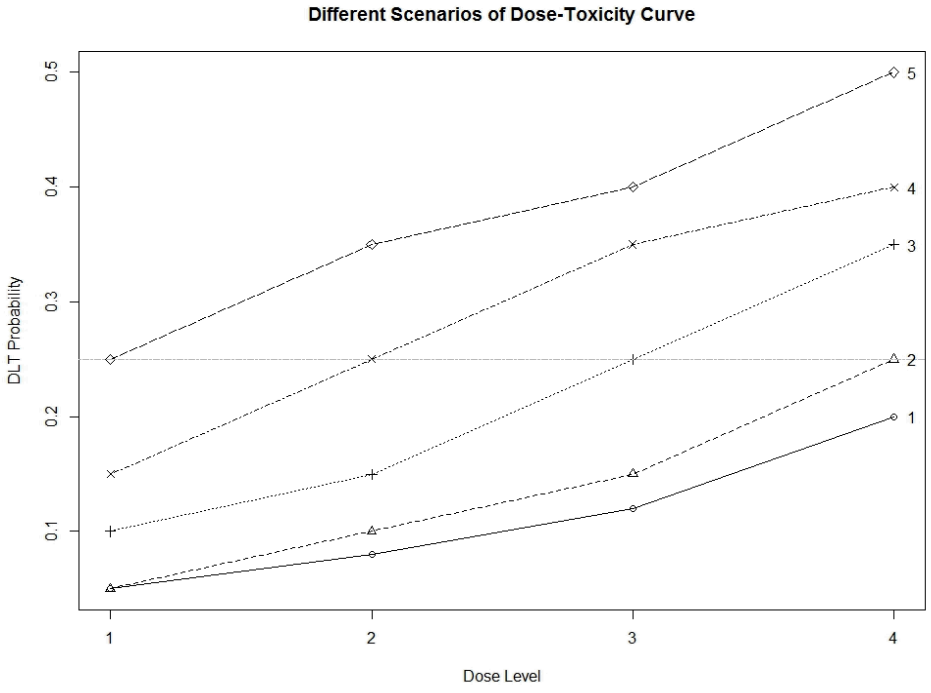
Settings of simulation:

- 5 dose-toxicity scenarios
- 1,000 trials per scenario
- Target toxicity (Pt) for mTPI design: 25% with (EI [24, 27%])
- mTPI: an initial cohort size of 6 followed by (multiple) cohort size of 3
- Stopping rule for mTPI: When there are already 13 DLT evaluable subjects treated at a dose level, and mTPI still makes the decision to treat more subjects at the same dose level, dose escalation can be stopped.
- Maximum number of DLT evaluable subjects for the study is 30
- A nominal dose level of -1 is added to account for the case when de-escalation decision is made for dose level 1. However, no subjects will be assigned to dose level -1, and simulation will stop.

Dose-Toxicity Curve Scenarios

Five scenarios of dose-toxicity (DLT) curves are selected to cover various possibilities, including that the MTD could be any or none of the tested dose levels. The 5 dose-toxicity curves are presented in Figure 1-1 with scenario identification shown at the end of the line. Numeric values are available in each of the simulation results.

Figure 1-1: Dose-Toxicity Probability Scenarios



Simulation Results

Simulation results are summarized from all the simulated trials per scenario and include the following statistics:

- MTD selected: frequency of each dose level being selected as MTD.
- Sample size: number of subjects being allocated to each dose level.
- Average DLT rate: the average percentage of subjects who have DLT across all dose levels among all of the subjects.
- Average sample size: the average number of subjects across all dose levels.

Scenario 1		**Dose Level**					**Average DLT Rate**	**Average Sample Size**
		-1	1	2	3	4		
True DLT rate			0.05	0.08	0.12	0.2		
3 + 3	MTD Selected (%)	2.3%	5.9%	11.9%	24.2%	55.7%	10.9%	
	Sample Size (n)		3.5	3.9	4.1	3.4		14.85
mTPI	MTD Selected (%)	0.9%	1.4%	7.8%	31.3%	58.6%	11.4%	
	Sample Size (n)		5.9	6.3	6.5	4.7		23.4
Note: The true MTD is higher than dose level 4, the highest dose level. This represents the case that all the tested doses are well tolerated and have a lower toxicity rate than the target value (25%). In this case, mTPI has a slightly better chance of picking the highest dose level than 3 + 3. Both have similar average toxicity rate.								

Scenario 2		**Dose Level**					**Average DLT Rate**	**Average Sample Size**
		-1	1	2	3	4		
True DLT rate			0.05	0.1	0.15	0.25		
3 + 3	MTD Selected (%)	2.1%	8.5%	19.1%	28.5%	41.8%	13.1%	
	Sample Size (n)		3.6	4.2	4.3	3.0		15.0
mTPI	MTD Selected (%)	0.5%	2.6%	12.2%	37.7%	47.0%	13.1%	
	Sample Size (n)		5.8	6.9	6.7	3.9		23.3
Note: The true MTD is dose level 4. Similar performances are observed as in scenario 1. mTPI picks the correct MTD about 5% more than 3 + 3 does.								

Scenario 3		Dose Level					Average DLT Rate	Average Sample Size
		-1	1	2	3	4		
True DLT rate			0.10	0.15	0.25	0.35		
3 + 3	MTD Selected (%)	11.0%	16.7%	29.6%	24.4%	18.3%	20.4%	
	Sample Size (n)		4.2	4.2	3.7	2.0		14.2
mTPI	MTD Selected (%)	2.7%	8.8%	33.2%	40.6%	14.7%	18.4%	
	Sample Size (n)		6.9	8.0	5.5	1.5		28.8

Note:
The true MTD is dose level 3. This presents the case when there is an over-toxic dose in the selected doses. mTPI picks the correct MTD about 16% more frequently than 3 + 3, and furthermore, it picks the correct MTD slightly less often the toxic dose (level 4).

Scenario 4		Dose Level					Average DLT Rate	Average Sample Size
		-1	1	2	3	4		
True DLT rate			0.15	0.25	0.35	0.40		
3 + 3	MTD Selected (%)	22.2%	32.7%	26.7%	11.6%	6.8%	28.0%	
	Sample Size (n)		4.8	4.0	2.3	0.9		12.0
mTPI	MTD Selected (%)	8.1%	29.6%	42.3%	16.9%	3.1%	24.8%	
	Sample Size (n)		8.5	7.6	2.8	0.4		19.3

Note:
The true MTD is dose level 2. This presents the case when there are 2 over-toxic doses. mTPI picks the correct MTD about 15% more frequently than 3 + 3 and picks over-toxic doses (level 3 & 4) at similar frequency as 3 + 3.

Scenario 5		Dose Level					Average DLT Rate	Average Sample Size
		-1	1	2	3	4		
True DLT rate			0.25	0.35	0.40	0.50		
3 + 3	MTD Selected (%)	44.8%	35.1%	14.8%	3.5%	1.8%	36.6%	
	Sample Size (n)		5.1	3.0	1.1	0.3		9.4
mTPI	MTD Selected (%)	23.9%	48.8%	20.6%	5.6%	0.1%	33.2%	
	Sample Size (n)		9.9	4.5	1.0	0.1		15.6

Note:
The true MTD is dose level 1. This presents the case when only the first dose is considered to be tolerable. mTPI picks the correct MTD about 13% more frequently than 3 + 3; however, it picks the toxic doses more often. Overall, mTPI picks over-toxic doses (levels 2, 3, and 4) 26.3% of the time, while 3 + 3 picks them 20.1% of the time. 3 + 3's average toxicity is slightly higher, similar with both designs.

2 SIMULATION RESULTS FOR COMBINATION THERAPY DOSE ESCALATION, WITH 2 DOSE LEVELS

Similar to the monotherapy setting, simulations for the BMS-986012 and nivolumab combination therapy show that the mTPI design has a greater chance of selecting the correct MTD than the 3 + 3 design and treats fewer subjects at suboptimal doses than the 3 + 3 design.

The mTPI design described above was set up with a target toxicity (DLT) rate of 29% (EI [28%, 31%]) because somewhat higher toxicity is expected and acceptable in the combination setting.

The mTPI design makes decisions using the number of DLT evaluable subjects and the number of subjects with DLT. Based on these 2 numbers, the unit probability mass calculated in each region is defined by the EI for the combination setting, with the decision based on the region that has the largest unit probability mass, similar to what is described above for the monotherapy setting.

In the simulation with mTPI, 1 out of 4 subjects may drop out with a probability of 0.5. Dropout is not simulated in the 3 + 3 design, since replacement subject is always needed to reach a decision.

Settings of Simulation:

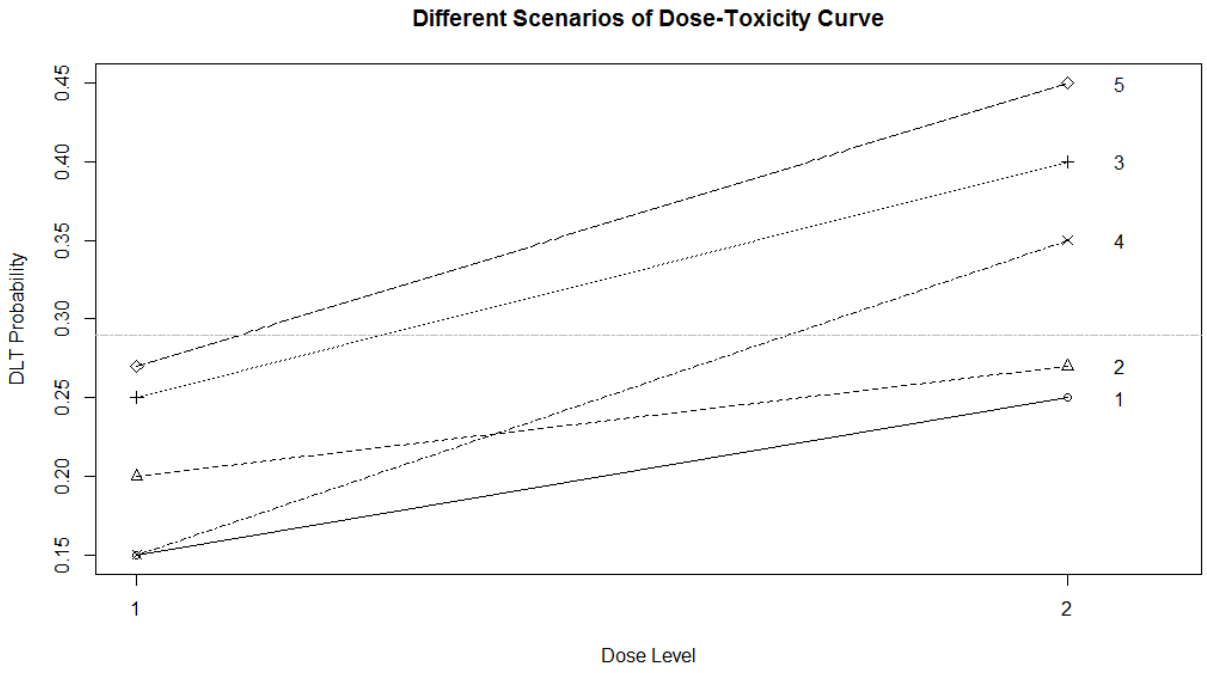
- 5 dose-toxicity scenarios, each of which with a number of 2 (expected) dose levels
- 1,000 trials per scenario
- Target toxicity (Pt) for mTPI design: 29% (EI [28, 31%])
- mTPI: an initial cohort size of 4 followed by (multiple) cohort size of 4
- Stopping rule for mTPI: When there are already 9 DLT evaluable subjects treated at a dose level and mTPI still makes the decision to treat more subjects at the same dose level, dose escalation can be stopped.

- Maximum number of DLT evaluable subjects for the study is 12.
- A nominal dose level of -1 is added to account for the case when de-escalation decision is made for dose level 1. However, no subjects will be assigned to dose level -1, and simulation will stop.

Dose-Toxicity Curve Scenarios

Five scenarios of dose-toxicity (DLT) curves are selected to cover various possibilities and presented in Figure 2-1 with scenario identification shown at the end of the line. The target toxicity rate of 0.29 is also superposed in the figure as a horizontal dashed line. The exact numeric values of DLT probability are available in each of the simulation results.

Figure 2-1: Dose-Toxicity Probability Scenarios



Simulation Results

Simulation results are summarized from all the simulated trials per scenario and include the same statistics as for the monotherapy simulations: MTD selected, sample size, average DLT rate, and average sample size, as defined previously.

Scenario 1		Dose Level			Average DLT Rate	Average Sample Size
		-1	1	**2**		
True DLT rate			0.15	0.25		
3 + 3	MTD Selected (%)	19.7	31.3	49.0	19.8	
	Sample Size (n)		4.7	3.4		8.1
mTPI	MTD Selected (%)	3.7	30.3	66.0	22.0	
	Sample Size (n)		5.0	4.5		9.5
Note: The true MTD is higher than dose level 2. This represents a case when both doses are well tolerated (DLT rate < 29%). In this case, mTPI has a 17% better chance of picking the correct MTD than 3 + 3 and is 16% less likely to pick a lower than tested dose. Both have similar average DLT rate.						

Scenario 2		Dose Level			Average DLT Rate	Average Sample Size
		-1	1	**2**		
True DLT rate			0.20	0.27		
3 + 3	MTD Selected (%)	33.3	26.7	40.0	25.4	
	Sample Size (n)		4.7	2.9		7.6
mTPI	MTD Selected (%)	9.1	38.0	52.9	26.5	
	Sample Size (n)		5.3	3.7		9.0
Note: The true MTD is dose level 2. The performance is similar as in scenario 1; mTPI picks the correct MTD 12.9% more often than 3 + 3 does and picks the lower than tested dose 24.2% less often than the 3 + 3.						

Scenario 3		Dose Level			Average DLT Rate	Average Sample Size
		-1	**1**	2		
True DLT rate			0.25	0.40		
3 + 3	MTD Selected (%)	45.5	37.4	17.1	35.1	
	Sample Size (n)		5.1	2.5		7.6
mTPI	MTD Selected (%)	14.6	51.7	33.7	34.0	
	Sample Size (n)		5.7	2.7		8.4

Note:

The true MTD is dose level 1. This represents the case when 1 dose is over-toxic; mTPI picks the correct MTD 14.3% more frequently than 3 + 3 and picks lower than tested dose 30.9% time less often than 3 + 3; mTPI also picks the highest (more toxic) dose 16.6% more often than the 3 + 3.

Scenario 4		Dose Level			Average DLT Rate	Average Sample Size
		-1	**1**	2		
True DLT rate			0.15	0.35		
3 + 3	MTD Selected (%)	21.2	47.3	31.5	23.9	
	Sample Size (n)		5.1	3.5		8.6
mTPI	MTD Selected (%)	4.3	40.4	55.3	25.7	
	Sample Size (n)		5.3	4.2		9.5

Note:

The true MTD is dose level 1, and Dose Level 2 exceeds MTD. mTPI has a slightly lower chance (6.9%) of picking the correct MTD than 3 + 3, a higher chance (23.8%) of picking a higher dose, and a lower chance (16.9%) of picking the dose below the lowest tested.

Scenario 5		Dose Level			Average DLT Rate	Average Sample Size
		-1	**1**	2		
True DLT rate			0.27	0.45		
3 + 3	MTD Selected (%)	49.7	37.3	13.0	37.4	
	Sample Size (n)		5.1	2.4		7.5
mTPI	MTD Selected (%)	15.8	54.4	29.8	35.4	
	Sample Size (n)		5.7	2.6		8.3

Note:

The true MTD is dose level 1. mTPI picks the correct MTD about 17.1% more frequently than 3 + 3; it also picks the highest dose 16.8% more frequently than 3 + 3 and picks a dose below the lower tested dose 33.9% less often than 3 + 3.

APPENDIX 2 MANAGEMENT ALGORITHMS

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 (I-O) 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.

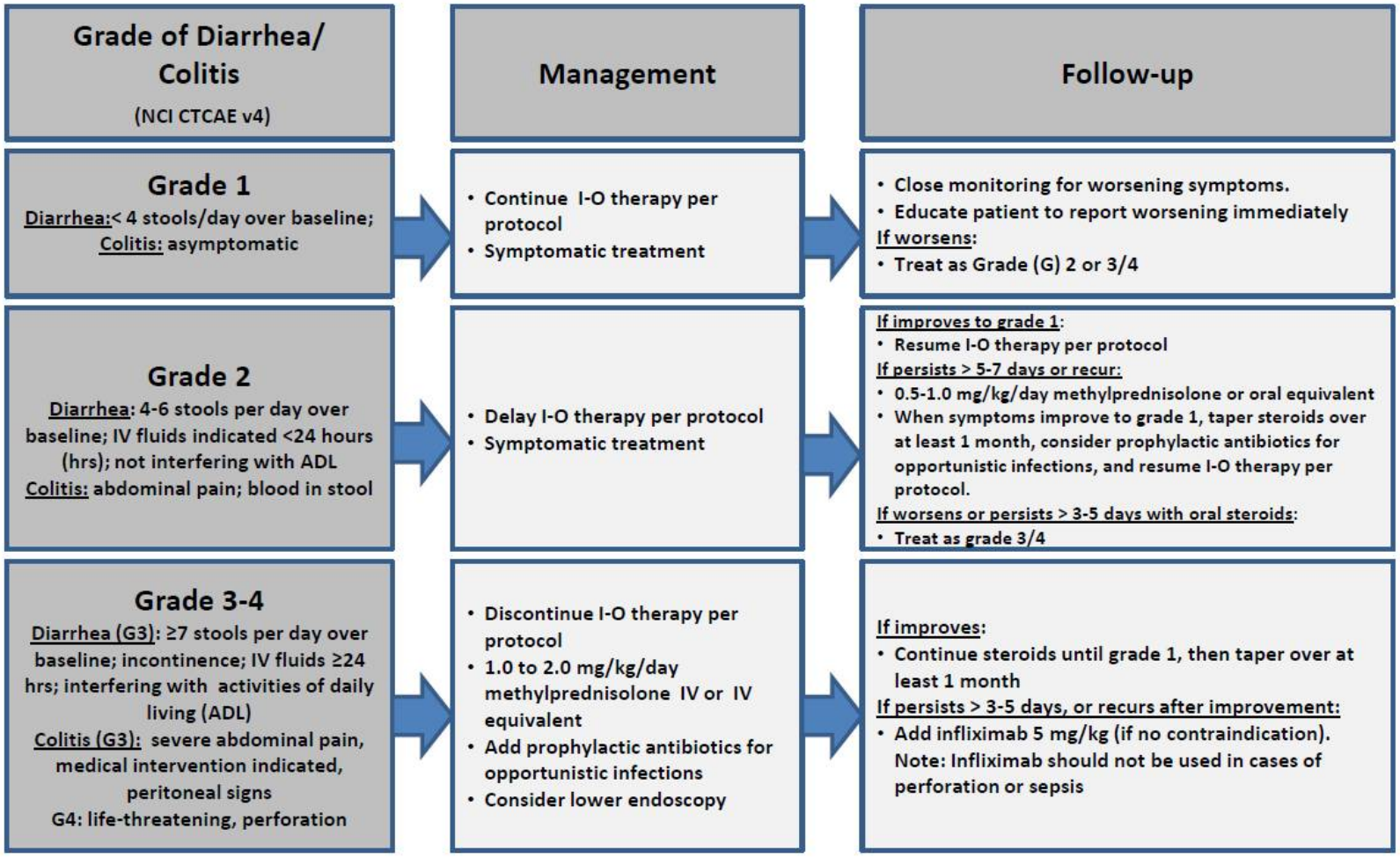
Corticosteroids are a primary therapy for I-O drug-related adverse events. The oral equivalent of the recommended intravenous (IV) doses may be considered for ambulatory patients with low-grade toxicity. The lower bioavailability of oral corticosteroids should be taken into account when switching to the equivalent dose of oral corticosteroids.

Consultation with a medical or surgical specialist, especially prior to an invasive diagnostic or therapeutic procedure, is recommended.

The frequency and severity of the related adverse events covered by these algorithms will depend on the I-O agent or regimen being used.

Figure 1: Gastrointestinal Adverse Event Management Algorithm

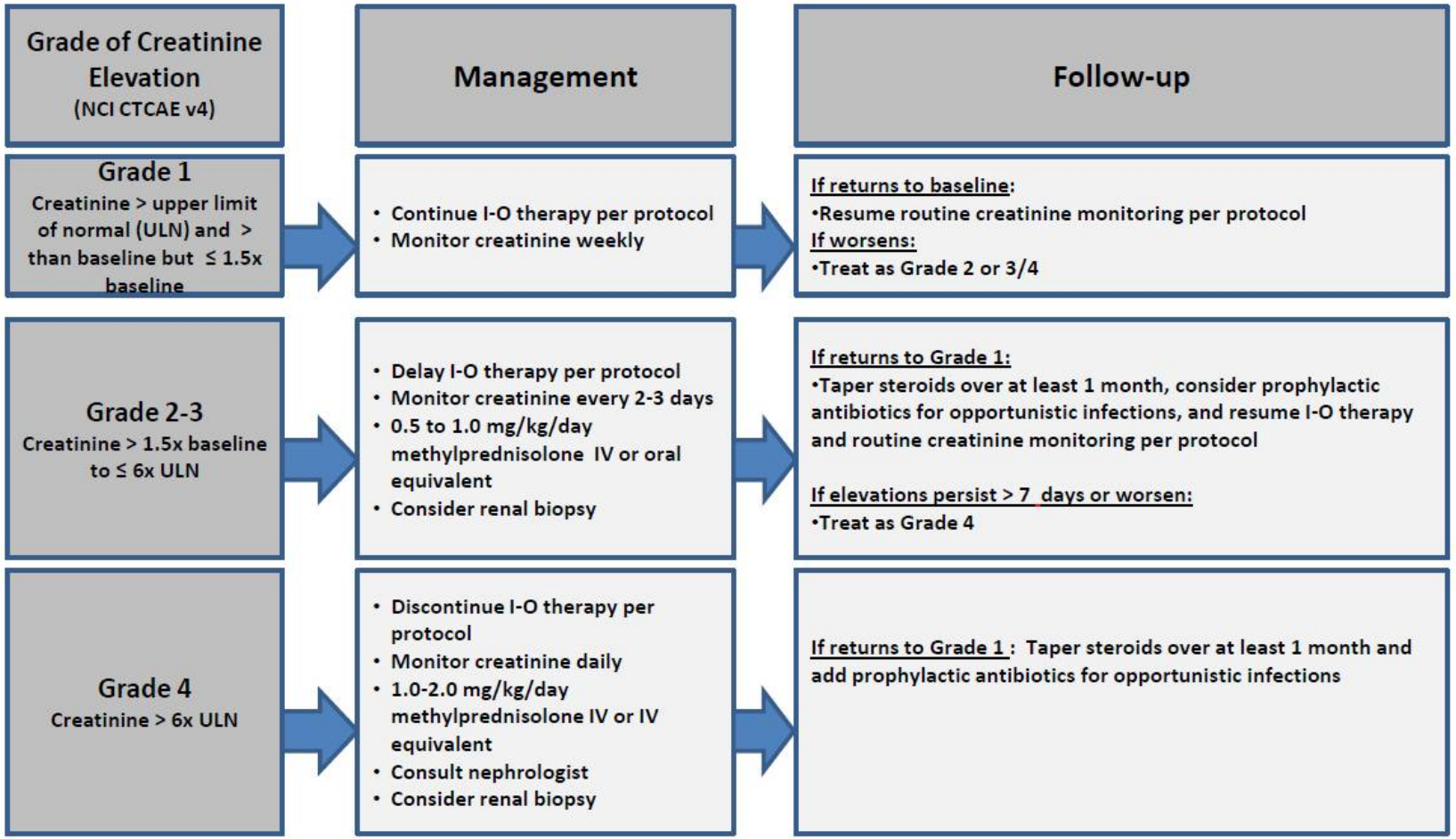
Rule out non-inflammatory causes. If non-inflammatory cause is identified, treat accordingly and continue I-O therapy. Opiates/narcotics may mask symptoms of perforation. Infliximab should not be used in cases of perforation or sepsis.



Patients on IV steroids may be switched to an equivalent dose of oral corticosteroids (eg, 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.

Figure 2: Renal Adverse Event Management Algorithm

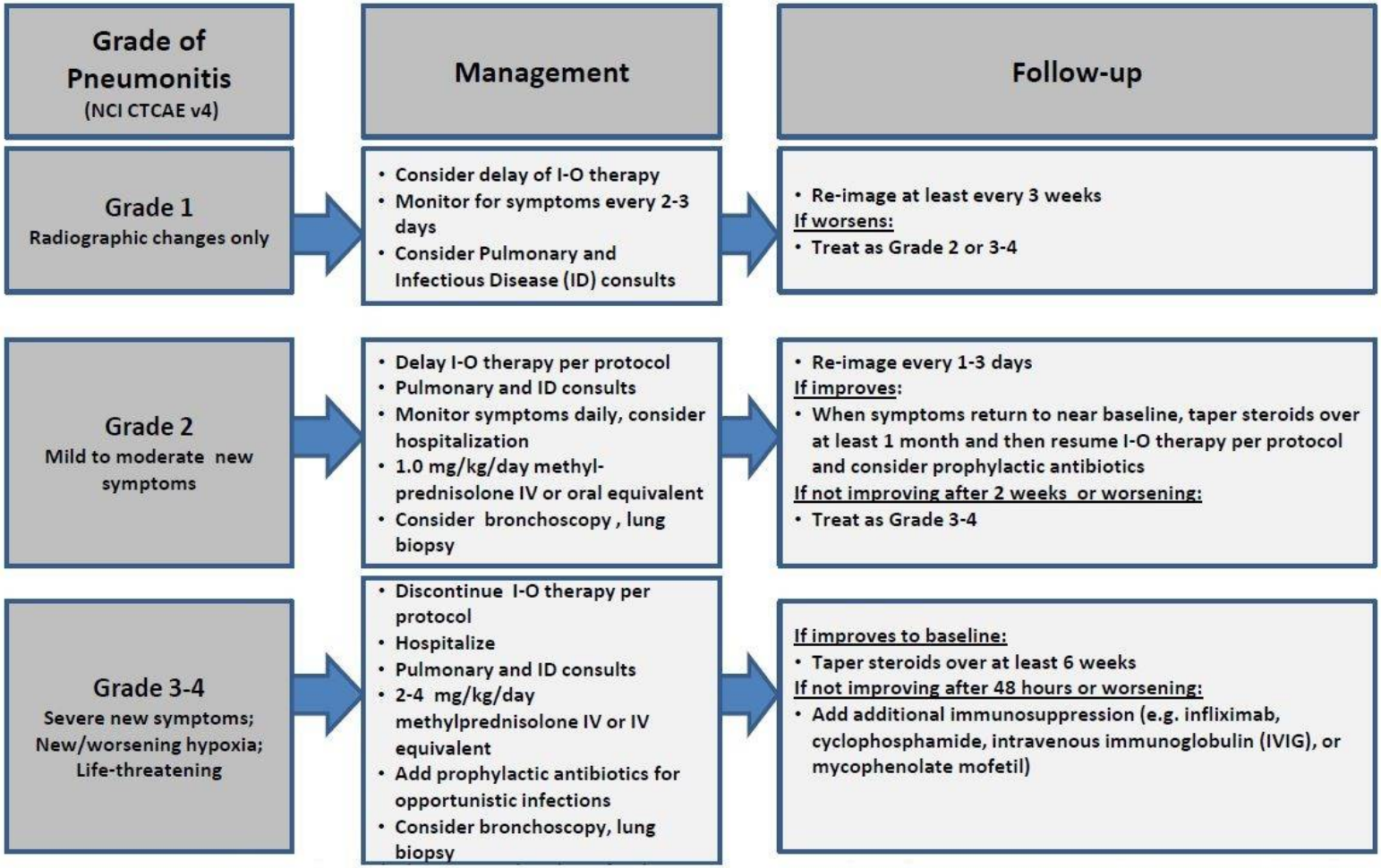
Rule out non-inflammatory causes. If non-inflammatory cause, treat accordingly and continue I-O therapy.



Patients on IV steroids may be switched to an equivalent dose of oral corticosteroids (eg, 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.

Figure 3: Pulmonary Adverse Event Management Algorithm

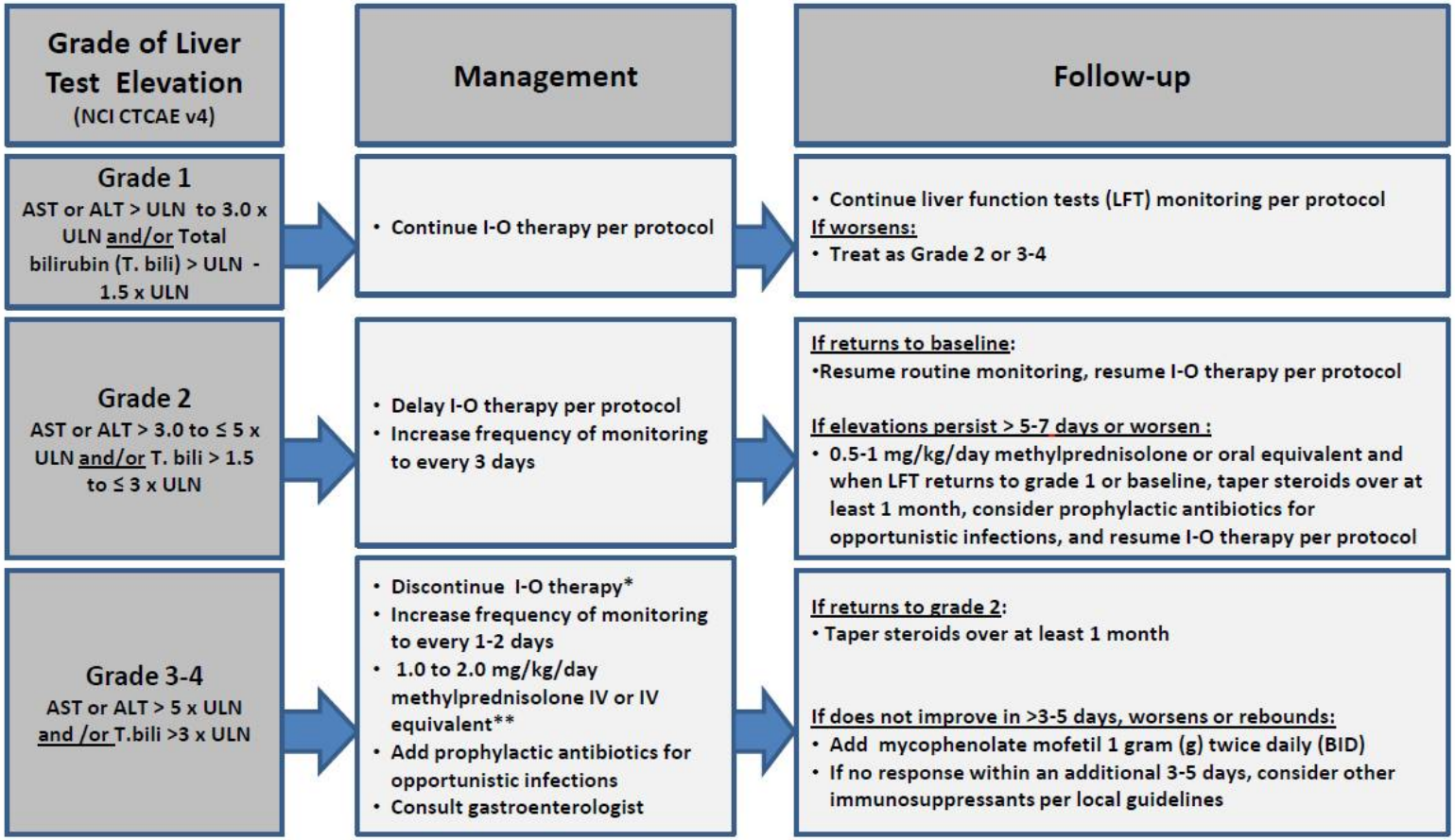
Rule out non-inflammatory causes. If non-inflammatory cause, treat accordingly and continue I-O therapy. Evaluate with imaging and pulmonary consultation.



Patients on IV steroids may be switched to an equivalent dose of oral corticosteroids (eg, 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.

Figure 4: 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.



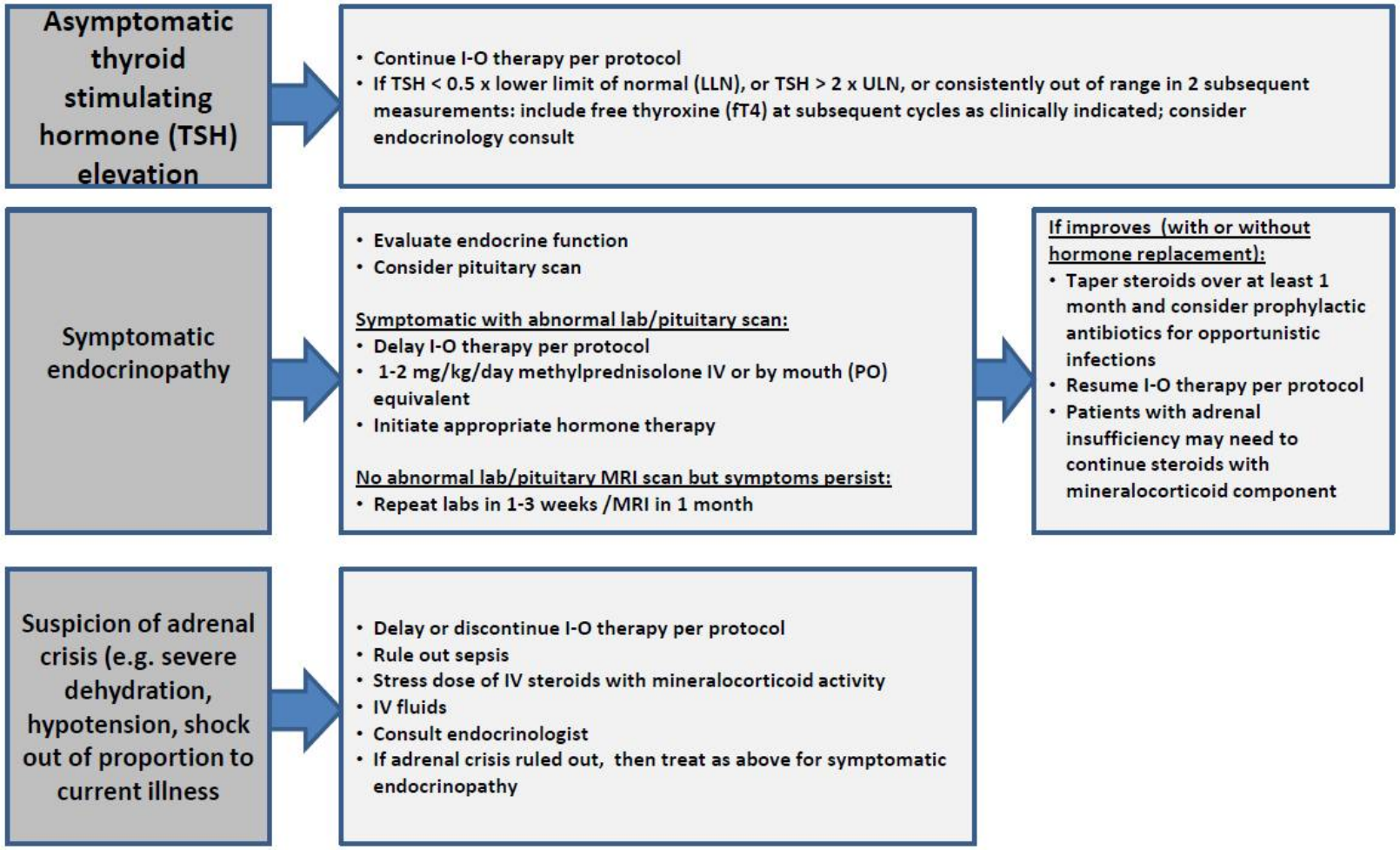
Patients on IV steroids may be switched to an equivalent dose of oral corticosteroids (eg, prednisone) at start of tapering or earlier, once sustained clinical improvement is observed. Lower bioavailability of oral corticosteroids should be taken into account when switching to the equivalent dose of oral corticosteroids.

***I-O therapy may be delayed rather than discontinued if AST/ALT ≤ 8 × ULN and total bilirubin ≤ 5 × ULN.**

**The recommended starting dose for Grade 4 hepatitis is 2 mg/kg/day methylprednisolone IV.

Figure 5: Endocrinopathy Management Algorithm

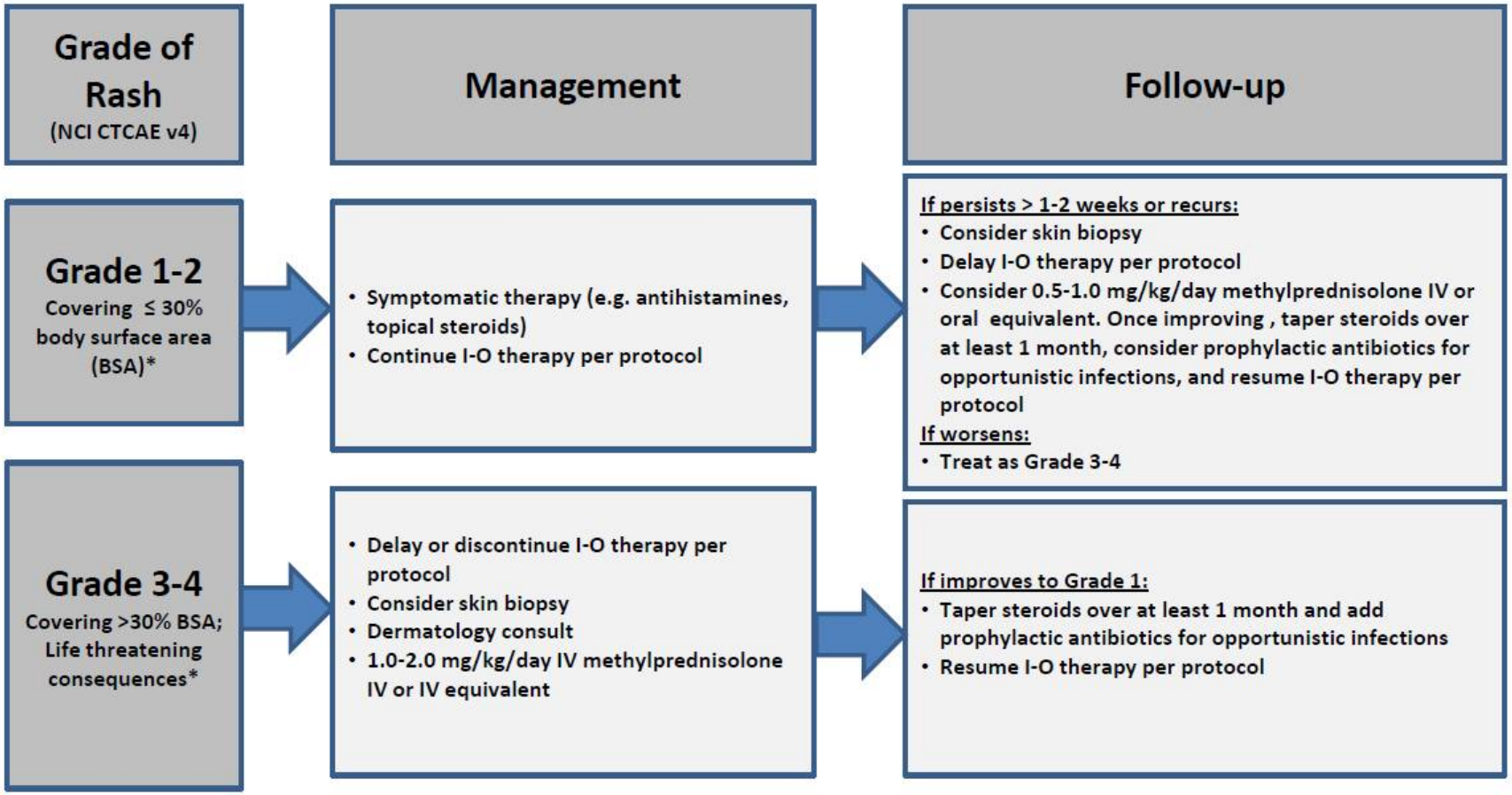
Rule out non-inflammatory causes. If non-inflammatory cause, treat accordingly and continue I-O therapy. Consider visual field testing, endocrinology consultation, and imaging.



Patients on IV steroids may be switched to an equivalent dose of oral corticosteroids (eg, 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.

Figure 6: Skin Adverse Event Management Algorithm

Rule out non-inflammatory causes. If non-inflammatory cause, treat accordingly and continue I-O therapy.

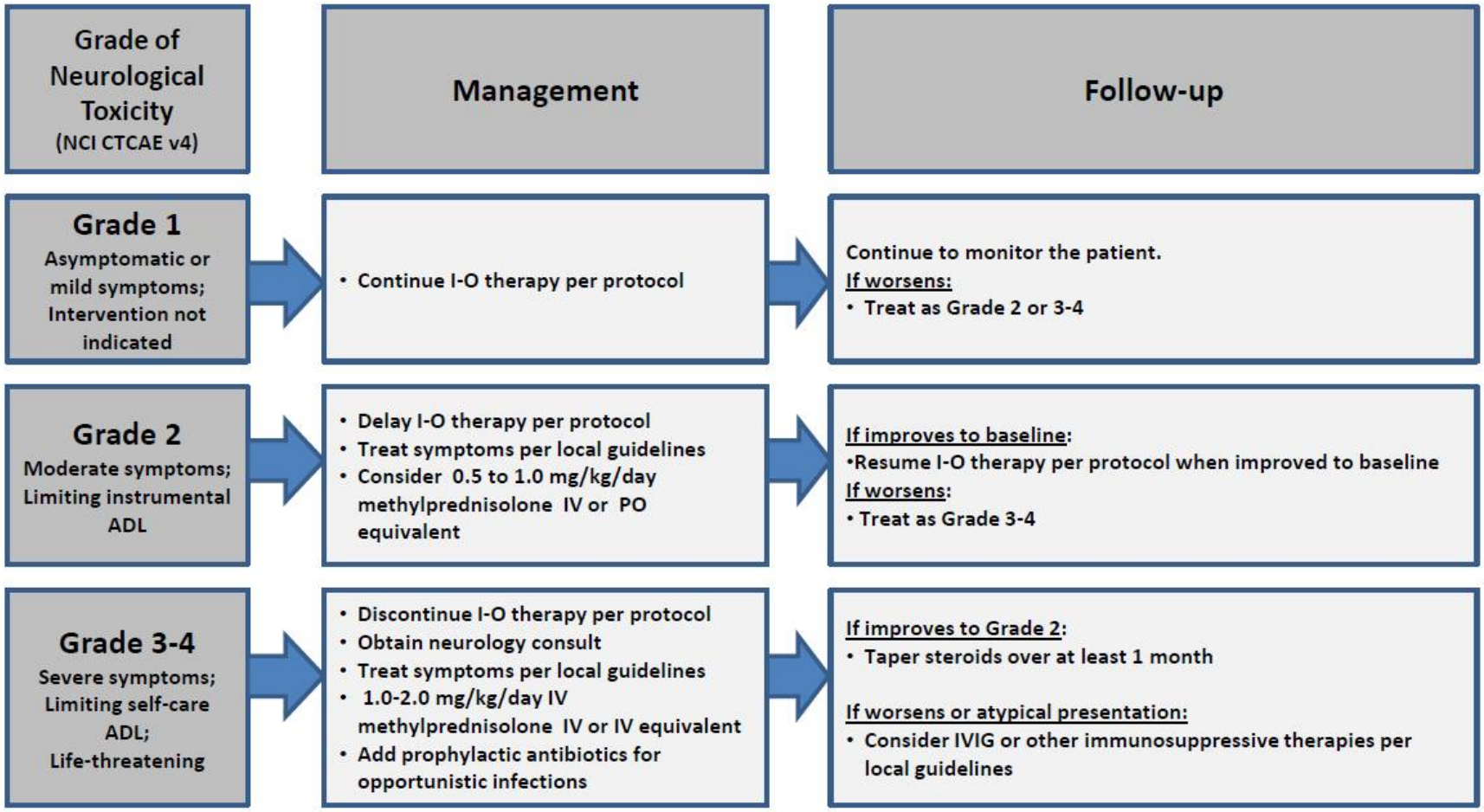


Patients on IV steroids may be switched to an equivalent dose of oral corticosteroids (eg, prednisone) at start of tapering or earlier, once sustained clinical improvement is observed. Lower bioavailability of oral corticosteroids should be taken into account when switching to the equivalent dose of oral corticosteroids.

*Refer to NCI CTCAE v4 for term-specific grading criteria.

Figure 7: Neurological Adverse Event Management Algorithm

Rule out non-inflammatory causes. If non-inflammatory cause, treat accordingly and continue I-O therapy.



Patients on IV steroids may be switched to an equivalent dose of oral corticosteroids (eg, prednisone) at start of tapering or earlier, once sustained clinical improvement is observed. Lower bioavailability of oral corticosteroids should be taken into account when switching to the equivalent dose of oral corticosteroids.

APPENDIX 3 RECIST V1.1

1 ASSESSMENT OF OVERALL TUMOR BURDEN AND MEASURABLE DISEASE

Subjects must have measureable disease to be eligible for this study.

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 one measurable tumor lesion. When 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 measurable or non-measurable as follows:

1.1 Measurable Lesions

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

- 10 mm by CT/MRI scan - (CT/MRI scan slice thickness no greater than 5 mm)
- 10 mm caliper measurement by clinical exam (lesions which 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: leptomeningeal disease, ascites, pleural or pericardial effusion, inflammatory breast disease, lymphangitic involvement of skin or lung, abdominal masses/abdominal organomegaly identified by physical exam that in not measurable by reproducible imaging techniques.

1.3 Special Considerations Regarding Lesion Measurability

1.3.1 Bone Lesions

- Bone scan, 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. Measurable lesions may be in an irradiated field as long as there is documented progression and the lesion(s) can be reproducibly measured.

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 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 one measurable lesion is present at baseline all lesions up to **a maximum of five lesions total (and a maximum of two lesions per organ) representative of all involved organs should be identified as *target lesion**s*** 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 which may be visible by imaging even if not involved by tumor. Pathological nodes which are defined as measurable and may be identified as target lesions must meet the criterion of a **short axis of ≥ 15 mm by CT scan**. Only the *short* axis of these nodes will contribute to the baseline sum. Nodes that have a short axis < 10 mm are considered nonpathological 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 (e.g. '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 one or more new lesions is also considered progression).

Stable Disease (SD): Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as reference the smallest sum diameters while on study.

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 which may be visible by imaging even if not involved by tumor. Pathological nodes which are defined as measurable and may be identified as target lesions must meet the criterion of a **short axis of ≥ 15 mm by CT scan**. Only the *short* axis of these nodes will contribute to the baseline sum. Nodes that have a short axis <10 mm are considered nonpathological 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 (e.g. 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 to then:

- 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.

Complete Response (CR): Disappearance of all non-target lesions. All lymph nodes must be nonpathological in size (< 10 mm short axis).

Non-CR/Non-PD: Persistence of one or more non-target lesion(s).

Progressive Disease (PD): *Unequivocal progression* of existing non-target lesions. (*Note:* the appearance of one or more new lesions is also considered progression).

3.2.1 Special Notes on 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 presence of SD or PR in target disease, the overall tumor burden has increased sufficiently to merit discontinuation of therapy.
- A modest 'increase' in the size of one or more non-target lesions is usually not sufficient to 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 one 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 nonmeasurable) 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: i.e. an increase in tumor burden representing an additional 73% increase in 'volume' (which is equivalent to a 20% increase diameter in a

measurable lesion). Examples include an increase in 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 will not be used to assess objective tumor responses.

3.3 New Lesions

The appearance of new malignant lesions denotes disease progression. The finding of a new lesion should be unequivocal: i.e. 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 partial or complete response. For example, necrosis of a liver lesion may be reported on a CT scan report as a 'new' cystic lesion, which it is not.

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 which 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.*

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 1 provides a summary of the overall response status calculation at each time point.

Table 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

Table 1. Time Point Response: Subjects With Target (+/– Non-target) Disease

Target lesions	Non-target lesions	New lesions	Overall response
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 within 4 weeks to ensure 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 is known. It is the best response recorded from the start of the study treatment until the end of treatment 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. Complete or partial responses 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 2. When SD is believed to be 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 2. 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 or progressive disease is objectively documented (taking as reference for progressive disease the smallest measurements recorded on study).

The duration of overall complete response 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

Stable disease 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).

Eisenhauer et al. New response evaluation criteria in solid tumours: revised RECIST guideline (version 1.1). European Journal of Cancer. 2009. Vol 45, p 228-247.

APPENDIX 4 DOSE ESCALATION DESIGN ALGORITHM BASED ON MODIFIED TOXICITY PROBABILITY INTERVAL (MTPI) METHOD FOR MONOTHERAPY

	Number of patients treated at current dose																														
	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26	27	28	29	30
0	E	E	E	E	E	E	E	E	E	E	E	E	E	E	E	E	E	E	E	E	E	E	E	E	E	E	E	E	E	E
1	D	S	S	S	S	S	E	E	E	E	E	E	E	E	E	E	E	E	E	E	E	E	E	E	E	E	E	E	E	E
2		DU	D	D	S	S	S	S	S	S	S	S	E	E	E	E	E	E	E	E	E	E	E	E	E	E	E	E	E	E
3			DU	DU	DU	D	S	S	S	S	S	S	S	S	S	S	S	S	E	E	E	E	E	E	E	E	E	E	E	E
4				DU	DU	DU	DU	DU	D	S	S	S	S	S	S	S	S	S	S	S	S	S	S	S	S	E	E	E	E	E
5					DU	DU	DU	DU	DU	DU	D	S	S	S	S	S	S	S	S	S	S	S	S	S	S	S	S	S	S	S	E
6						DU	DU	DU	DU	DU	DU	DU	DU	D	S	S	S	S	S	S	S	S	S	S	S	S	S	S	S	S	S
7							DU	DU	DU	DU	DU	DU	DU	DU	DU	DU	D	S	S	S	S	S	S	S	S	S	S	S	S	S	S
8								DU	DU	DU	DU	DU	DU	DU	DU	DU	DU	DU	S	S	S	S	S	S	S	S	S	S	S	S	S
9									DU	DU	DU	DU	DU	DU	DU	DU	DU	DU	DU	DU	DU	S	S	S	S	S	S	S	S	S	S
10										DU	DU	DU	DU	DU	DU	DU	DU	DU	DU	DU	DU	DU	DU	DU	S	S	S	S	S	S	S
11											DU	DU	DU	DU	DU	DU	DU	DU	DU	DU	DU	DU	DU	DU	DU	DU	DU	DU	S	S	S
12													DU	DU	DU	DU	DU	DU	DU	DU	DU	DU	DU	DU	DU	DU	DU	DU	DU	DU	DU

E = Escalate to next higher dose,

S = Stay at the current dose,

D = De-escalate to the next lower dose,

U = The current dose is unacceptably toxic

Target DLT at MTD = 25% (-1%/+2%), flexible cohort size

Flexible design allows enrolling initially 6 subjects in each new dose cohort, with an additional number if needed, at the same dose, based on design suggestion for the observed number of DLT, and the number of dropouts in the first 6. For example, an initial cohort of n = 6, allows escalation decision with n = 4 in the case of 0 DLTs and 2 dropouts, and escalation decision with an additional enrollment of 4 in case there is 1 DLT and 2 dropouts, to ensure 7 evaluable subjects.

APPENDIX 5 GUIDANCE ON CONTRACEPTION

ACCEPTABLE METHODS FOR PROTOCOLS WHERE EMBRYO-FETAL DEVELOPMENT STUDIES OF ANY STUDY DRUG DEMONSTRATES A TERATOGENIC PROFILE OR IN THE ABSENCE OF SUFFICIENT DATA TO EXCLUDE TERATOGENICITY

AT A MINIMUM SUBJECTS MUST AGREE TO THE USE OF TWO METHODS OF CONTRACEPTION, WITH ONE METHOD BEING HIGHLY EFFECTIVE AND THE OTHER METHOD BEING HIGHLY EFFECTIVE OR LESS. LOCAL LAWS AND REGULATIONS MAY REQUIRE USE OF ALTERNATIVE AND/OR ADDITIONAL CONTRACEPTION METHODS.

HIGHLY EFFECTIVE METHODS OF CONTRACEPTION

- Male condoms with spermicide
- Hormonal methods of contraception including combined oral contraceptive pills, vaginal ring, injectables, implants and intrauterine devices (IUDs) such as Mirena® by WOCBP subject or male subject's WOCBP partner. Female partners of male subjects participating in the study may use hormone based contraceptives as one of the acceptable methods of contraception since they will not be receiving study drug
- Non-hormonal IUDs, such as ParaGard®
- Tubal ligation
- Vasectomy.
- Complete Abstinence*

*Complete abstinence is defined as complete avoidance of heterosexual intercourse and is an acceptable form of contraception for all study drugs. Subjects who choose complete abstinence are not required to use a second method of contraception, but female subjects must continue to have pregnancy tests. Acceptable alternate methods of highly effective contraception must be discussed in the event that the subject chooses to forego complete abstinence.

LESS EFFECTIVE METHODS OF CONTRACEPTION

- Diaphragm with spermicide
- Cervical cap with spermicide
- Vaginal sponge
- Male Condom without spermicide
- Progestin only pills by WOCBP subject or male subject's WOCBP partner
- Female Condom*

  * A male and female condom must not be used together

APPENDIX 6 ECOG PERFORMANCE STATUS

ECOG PERFORMANCE STATUS[1]

Grade	ECOG
0	Fully active, able to carry on all pre-disease performance without restriction.
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light house work, office work.
2	Ambulatory and capable of all self-care but unable to carry out any work activities. Up and about more than 50% of waking hours.
3	Capable of only limited self-care, confined to bed or chair more than 50% of waking hours.
4	Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair.
5	Dead

[1] Oken MM, Creech RH, Tormey DC, Horton J, Davis TE, McFadden ET, and Carbone PP. Toxicity and Response Criteria of the Eastern Cooperative Oncology Group. Am J Clin Oncol 1982;5:649-655.