Official Title of Study:

A Phase I/IIa Study of BMS-986148, a Mesothelin Directed Antibody Drug Conjugate, in Subjects With Select Advanced Solid Tumors

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CLINICAL PROTOCOL CA008002

A Phase I/IIa Study of BMS 986148, a Mesothelin Directed Antibody Drug Conjugate, in Subjects with Select Advanced Solid Tumors

Revised Protocol Number 04
Incorporates Amendments 01, 02, 03, 04, 05 & 06

[redacted]

24-hr Emergency Telephone Number
USA: [redacted]
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protocol may apply to partners to which BMS has transferred obligations, eg, a Contract Research Organization (CRO).

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

DOCUMENT HISTORY

Document	Date of Issue	Summary of Change
Revised Protocol 04	02-Nov-2016	Incorporates Amendment 06
Amendment 06	02-Nov-2016	Added additional echocardiogram to cycle 2 for Part 3 (nivolumab combination treatment arm). Clarification of dosing administration (line flush between doses of BMS986148 and nivolumab) in Part 3.
Revised Protocol 03	21-Jul-2016	Incorporates Amendment 03
Amendment 05	21-Jul-2016	Removed flat dosing option. Added BMS-986148 and nivolumab combination therapy arm (Part 3). [redacted] Corrected typographical and consistency errors.
Revised Protocol Number 02a - UK	19-May-2016	Incorporates Amendment 04
Amendment 04	19-May-2016	Incorporate changes [redacted] regarding use of contraceptives
Revised Protocol Number 02a - US	12-Apr-2016	Incorporates Amendment 03
Amendment 03	12-Apr-2016	Refined eligibility criteria [redacted]
Revised Protocol 02	02-Feb-2016	Incorporates Amendment 02
Amendment 02	02-Feb-2016	Added details for flat dosing, Added IHC scoring details for Part 2 of the study. Clarified eligibility criteria and corrected typographical errors.
Revised Protocol 01	31-Jul-2015	Incorporates Amendment 01
Amendment 01	31-Jul-2015	Incorporates [redacted] revisions regarding additional on-treatment echocardiograms, DLT definitions, and dose selection for Part 2. Enhanced the survival period duration of follow-up and alignment of the survival period with other early development protocols. Added additional detail to DLT criteria. Added exclusion criteria for troponin. Added additional guidance on the collection of triplicate ECGs. Modified text for clarity. Added windows for the collection on eye exams and laboratory collections. Added C1D15 vital signs and targeted PE to Q weekly dosing. Added wording to footnote in PK collection tables. Addresses typographical errors
Original Protocol	28-Nov-2014	Not applicable

SYNOPSIS

Clinical Protocol CA008002

Protocol Title: A Phase 1/2a Study of BMS 986148, a Mesothelin-Directed Antibody Drug Conjugate, in Subjects with Select Advanced Solid Tumors

Investigational Product(s), Dose and Mode of Administration, with Investigational Product(s): Each subject will be administered intravenous doses of BMS-986148 or BMS-986148 and nivolumab per the cohort assignment as indicated in the study design below (See Figure 1 and Figure 2 in the synopsis).

Study Phase: 1/2a

Research Hypothesis: There is no formal primary research hypothesis for this study to be statistically tested. The purpose of this study is to evaluate the safety profile, tolerability, preliminary efficacy, pharmacokinetics (PK), and pharmacodynamics (PD) of BMS-986148 administered alone and in combination with nivolumab in subjects with select advanced solid tumors.

Primary Objectives: To assess the safety and tolerability of BMS-986148 administered as monotherapy and in combination with nivolumab in subjects with select advanced solid tumors.

Secondary Objectives:

- To assess the preliminary anti-tumor activity of BMS-986148 as monotherapy and in combination with nivolumab as measured by objective response rate (ORR), response duration, and progression-free survival (PFS)
- To characterize the PK of the total antibody (unconjugated antibody + antibody conjugated to tubulysin or antibody conjugated to any tubulysin metabolites), active anti-drug conjugate (ADC, antibody conjugated to tubulysin), and unconjugated tubulysin when BMS-986148 is administered as monotherapy and in combination with nivolumab
- To characterize the PK of nivolumab when administered in combination with BMS-986148
- To assess the effect of BMS-986148 monotherapy dosage regimen and exposure (active ADC and unconjugated tubulysin) on the QT interval
- To characterize the immunogenicity of BMS-986148 as monotherapy and in combination with nivolumab
- To characterize the immunogenicity of nivolumab in combination with BMS-986148

[redacted]

[redacted]

Study Design: This is a Phase 1/2a, open-label study to characterize the safety and tolerability, as well as preliminary efficacy, PK, and PD of BMS-986148 administered alone and in combination with nivolumab in subjects with select advanced solid tumors (pancreatic, ovarian, non-small cell lung cancer [NSCLC], gastric, or mesothelioma). The study has 3 segments: Part 1 (Phase 1 study - dose escalation), Part 2 (Phase 2a - dose expansion), and Part 3 (BMS-986148 in combination with nivolumab; Part 3A - dose escalation and Part 3B - dose expansion) (see Figure 1). All subjects will complete up to 4 study periods: Screening (up to 28 days), Treatment (21 days/cycle for Q3W dosing and 28 days/cycle for QW dosing), Follow-up (60 days), and Survival Follow-up. After completing the Follow-up period, subjects will continue to be followed for [redacted] up to 2 years from first dose of study drug for subjects discontinuing study drug prior to 2 years. Subjects receiving study drug for more than 2 years, will be followed for 6 months from their last treatment date in the Survival Follow up Period (see Figure 2). With Amendment 3, a dose escalation phase will be conducted with BMS-986148 and nivolumab combination therapy (Part 3A). In the BMS-986148 and nivolumab combination therapy dose expansion phase (Part 3B), additional subjects with pancreatic, ovarian, NSCLC, gastric, or mesothelioma will be treated at or below the maximum tolerated dose (MTD) of the combination dose identified in Part 3A to confirm safety and evaluate anti-tumor activity.

Figure 1: **Sequence of Study Phases**

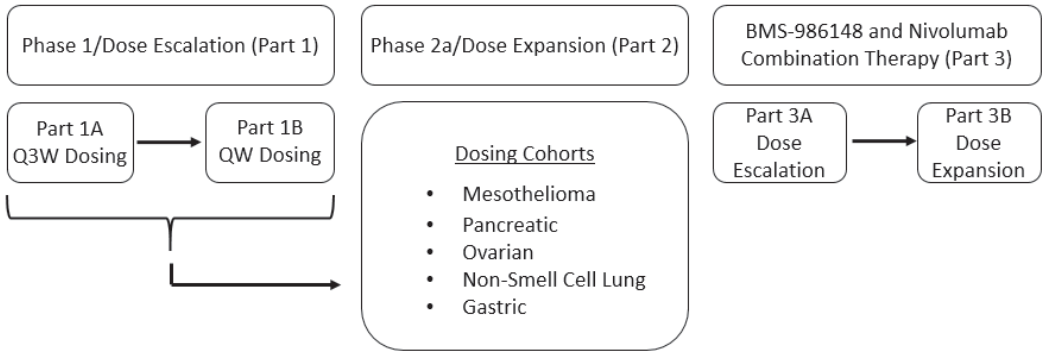
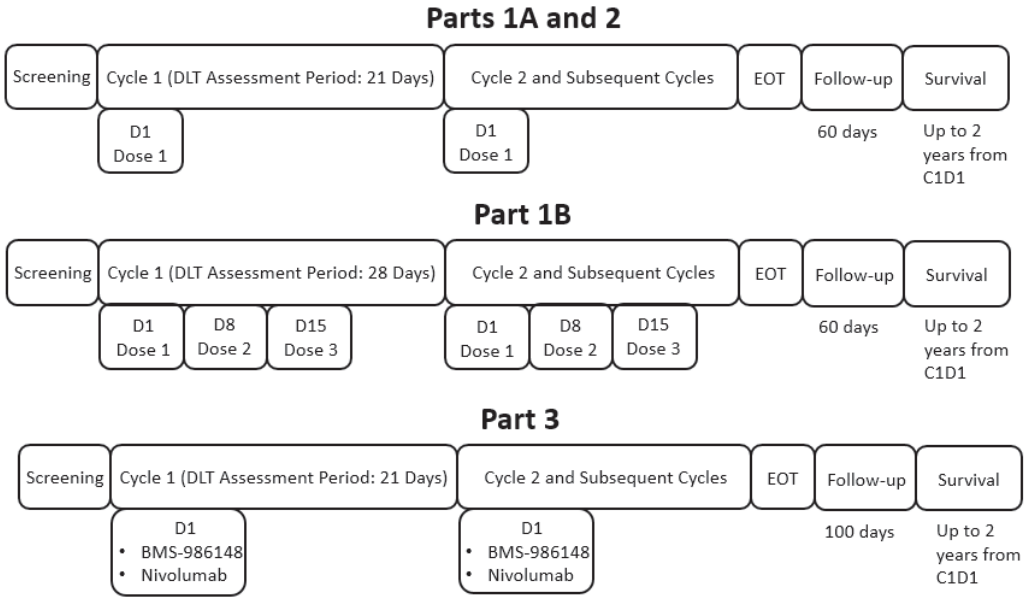


Figure 2: Dosing (Q3W and QW) and Study Periods



Note: Subjects treated for > 2 years will be followed for 6 months after EOT in the Survival Follow-Up. In the Survival Follow-up, subjects discontinuing study drug prior to 2 years will be followed for up to 2 years from first dose of study drug. Additionally, specifically in Part 3, treatment duration is 24 weeks to a maximum of 48 weeks.

C1D1: Cycle 1 Day 1 (first dose); D: day; DLT: dose-limiting toxicity; EOT: end of treatment; QW: every week; Q3W: every 3 weeks.

Part 1A: BMS-986148 Administered Every 3 Weeks

Approximately 30 subjects will be enrolled in ascending dose cohorts starting with a dose of 0.1 mg/kg. BMS-986148 will be administered Q3W in a 21-day cycle. The approach for selection of the next dose at each escalation step (including Fibonacci and modified Fibonacci methods) and the rules for escalation decision based on dose limiting toxicity (DLT) criteria guided by the modified Toxicity Probability Interval (mTPI) design are described in Section 3.1.1 of the protocol, with the dose escalation design described in Figure 3.1.1-1 of the protocol.

At the end of dose escalation, the MTD will be selected as the dose with the smaller difference of estimated toxicity and the target DLT rate (27%), among the doses used, with isotonic regression modeling of the accumulated DLT data based on the mTPI design.

Part 1B: BMS-986148 Administered Weekly for 3 Weeks and 1 Week Off

Approximately 24 subjects will be enrolled in ascending dose cohorts. Part 1B may begin after determining the MTD or a tolerated dose below the MTD in Part 1A. The starting dose for Part 1B will be chosen by modeling active ADC concentration-time data from Part 1A and selecting a fractionated dose that provides similar exposure to that of the MTD or a tolerated dose below the MTD. In the event that concentration-time data are not available for modeling, the starting dose will be 1/3rd of the MTD or a tolerated dose below the MTD from Part 1A. In Part 1B, BMS-986148 is administered every week for 3 weeks and 1 week off in a 28 day cycle. Similar to Part 1A, the approach for selection of the next dose at each escalation step (including Fibonacci and modified Fibonacci) and the rules for escalation decision based on DLT criteria guided by the mTPI design are described in Section 3.1.1 of the protocol, with the dose escalation design described in Figure 3.1.1-1 of the protocol.

Similar to the MTD determination in Part 1A, at the end of dose escalation, the MTD will be selected as the dose with the smaller difference of estimated toxicity and the target DLT rate (27%), among the doses used.

Once the safety (during DLT evaluation) of a dose level has been established (Part 1A and/or Part1B), additional subjects may be added at that dose to better characterize the PK, safety, and PD profile.

Part 2: Monotherapy Dose Expansion

The purpose of the cohort expansion will be to assess preliminary antitumor efficacy, expanded safety experience and PD effects of BMS-986148. Additional subjects will be treated after the completion of Part 1A and/or Part 1B, at the MTD, or at an alternative dose below MTD as agreed upon by the BMS Medical Monitor and investigators. Part 2 can begin before the completion of Part 1B as the Q3W dosing regimen is the intended regimen for Part 2. However, if the aggregate PK and safety data indicate similar safety but higher cumulative exposure with the weekly dose schedule, this schedule may also be evaluated in Part 2 in an additional cohort of 25 to 26 subjects, once the MTD or a tolerated dose below the MTD is identified in Part 1B. Treatment doses in the cohort expansion groups will not exceed the MTD.

Five expansion cohorts will be restricted to these tumor types 1) mesothelioma 2) pancreatic 3) ovarian 4) NSCLC, and 5) gastric cancer. Enrollment in cohort expansion will be determined by the mesothelin expression of an archived tumor sample (or fresh tumor sample if archived sample is not available). [redacted]

The enrollment in each expansion cohort will be guided by a Simon 2-Stage design framework exploring the efficacy in the following 2 populations: [redacted].

Safety monitoring of subjects enrolled in the Part 2 (Phase 2a) portion of the study will be the same as that conducted during the dose escalation portion. During Part 2, if in a given arm the combined incidence of study drug-related AEs that require dose modification exceeds 29% (of treated subjects), then further enrollment to that arm will be interrupted and the findings will be discussed between the BMS Medical Monitor and investigators. An agreement will be reached as to whether a lower dose or an alternate dose schedule of BMS-986148 should be examined or whether any additional treatment guidelines should be implemented prior to enrollment of additional subjects on study.

Part 3: BMS-986012 in Combination with Nivolumab

During the dose escalation phase with BMS-986148 and nivolumab combination therapy (Part 3A), approximately 12 evaluable subjects are expected to be treated at 2 doses of BMS-986148 (0.8 mg/kg Q3W and 1.2 mg/kg Q3W) and nivolumab (360mg, Q3W) combination therapy (21 day cycle). In the BMS-986148 and nivolumab combination therapy dose expansion phase (Part 3B), approximately 25 to 26 evaluable subjects will be treated in each tumor cohort.

Subsequent escalation to 1.2 mg/kg Q3W of BMS-986148 (or MTD determined from Part 1A) in combination with nivolumab 360 mg Q3W will be guided by the mTPI design described in Section 3.1.3 of the protocol. In the event that the first dose level of BMS-986148 is determined to exceed the MTD in combination with 360 mg Q3W of nivolumab, a lower BMS-986148 dose may be explored based on available safety, PK [redacted]. Nivolumab will be administered as 360 mg IV Q3W in all the dose cohorts. Dose escalation decisions are similar to Part 1A and described in Figure 3.1.1-1 of the protocol. A DLT target rate of 29% (EI = 28% to 31%) will be utilized for combination treatment to guide escalation decisions. Dose escalation decisions will be based on the total number of subjects in a dose level who were DLT evaluable and the number of DLTs, guided by the mTPI Bayesian model and posterior inference.

Similar to the MTD determination in monotherapy parts, at the end of dose escalation, the cumulative number of subjects who experience a DLT at each dose level will be used to estimate the MTD using isotonic regression as the dose with the smaller difference of estimated toxicity rate and the target DLT rate (29%), among the doses used.

Once the safety (during DLT evaluation) of a dose level has been determined, additional subjects may be added at that dose, to better characterize the PK, safety, and PD profile.

Part 3B: Dose Expansion

The purpose of the cohort expansion will be to assess preliminary anti-tumor efficacy, expanded safety experience, and PD effects of BMS-986148 in combination with nivolumab. Additional subjects will be treated after the completion of Part 3A, at the MTD, or at an alternative dose below the MTD as agreed upon by the BMS Medical Monitor and investigators. Five expansion cohorts will be restricted to these tumor types: 1) mesothelioma, 2) pancreatic, 3) ovarian, 4) NSCLC, and 5) gastric cancer. Enrollment in cohort expansion will be determined by the mesothelin expression of the archived tumor sample (or fresh tumor sample if archived sample is not available). [redacted]

The enrollment in each combination expansion cohort will also be guided by a Simon 2-Stage design framework (see Protocol Table 8.1-2), exploring efficacy in the [redacted].

Safety monitoring of subjects enrolled in the Part 3B portion of the study will be the same as that conducted during the dose escalation portion. During Part 3, if in a given arm the combined incidence of study drug-related AEs that require dose modification exceeds 31% (of treated subjects), then further enrollment to that arm will be interrupted, and the findings will be discussed between the BMS Medical Monitor and investigators. An agreement will be reached as to whether a lower dose or an alternate dose schedule of BMS-986148 in combination with nivolumab should be examined or whether any additional treatment guidelines should be implemented prior to enrollment of additional subjects on study.

***Administration of Additional Treatment Cycles (Part 3)**:*

In Part 3 of the study, all subjects will be treated for 24 weeks (up to 8 cycles) of BMS-986148 in combination with nivolumab unless criteria for study drug discontinuation are met earlier (see Protocol Section 3.5). All subjects completing approximately 24 weeks of study therapy with ongoing disease control (complete response [CR], partial response [PR], or stable disease [SD]) may be eligible for an additional 24 weeks of study therapy (see Protocol Section 3.1.7) at the originally assigned dose regimen in both escalation and cohort expansion beyond the initial 24 weeks, on a case-by-case basis, after careful evaluation and discussion with the BMS Medical Monitor to determine whether the benefit/risk ratio supports administration of further study therapy. Upon completion of 24 weeks of study therapy (or up to a maximum of 48 weeks if applicable), all subjects will enter the clinical/safety Follow-up period

Dose Limiting Toxicity: For the purpose of guiding dose escalation, DLTs are defined separately in Protocol Section 4.5.1 and will be determined based on the incidence, intensity, and duration of AEs for which no clear alternative cause is identified. The DLT evaluation period for dose escalation in Part 1A is 21 days. The DLT evaluation period for dose escalation in Part 1B is 28 days and subjects must receive 3 doses during this period (unless DLT has occurred) to be considered evaluable for dose escalation decisions. The DLT evaluation period for dose escalation in Part 3A is 21 days. Adverse events will be graded according to NCI CTCAE v4.03. For the purpose of subject management, any AE that meets DLT criteria, regardless of the cycle in which it occurs, will lead to dose interruption. Subjects who withdraw from the study during the DLT evaluation interval for reasons other than a DLT may be replaced at the same dose level. The incidence of DLT(s) during the first cycle of treatment (the DLT evaluation period) will be used in dose escalation decisions and to define the MTD. AEs occurring after the DLT period will be considered for the purposes of defining the MTD, upon agreement between the BMS Medical Monitor and investigators, if they are determined to have no clear alternative cause and are not related to disease progression. For Part 3A, every attempt must be made to assign relationship to BMS-986148, to nivolumab, or to both.
Once the safety (during DLT evaluation) of a dose level has been established (Parts 1A, 1B, and 3A), additional subjects may be added at that dose to better characterize the PK, safety, and PD profile.

Duration of Study: The total duration of the study is anticipated to be 5 years from the time of the first visit of the first subject to the required survival follow-up of the last subject enrolled. The end of the study will occur when the last subject has the last survival follow-up visit.

Number of Subjects: Approximately 179 to 204 subjects will be dosed in monotherapy (approximately 54 subjects in dose escalation [Part 1A and Part 1B] and approximately 125 to 150 subjects in dose expansion (Part 2]). Approximately 137 to 162 subjects will be dosed in combination therapy (approximately 12 subjects in dose escalation [Part 3A] and approximately 125 to 150 subjects in dose expansion [Part 3B]).

Study Population: The study population will include men and women who are at least age 18 who meet the study eligibility criteria. Subjects must have histological confirmation of one of the following advanced or metastatic tumor types to be eligible: pancreatic, ovarian, NSCLC, gastric, or mesothelioma. At least 1 site of measurable disease as defined by RECIST version 1.1 or Modified RECIST for malignant pleural mesothelioma (See Protocol Appendix 4) is mandatory. Additionally, in order to be eligible for enrollment to the study all subjects must have either archival tumor tissue (if slides are available, will require a minimum of 10 cut slides [for details of epitope stability, see lab manual]) identified and available, and consent to provide this archival tissue. Acquisition of adequate pre-treatment tumor tissue is mandatory for this study for all subjects. Subjects who do not have archival tissue available may consent to a pre-treatment fresh tumor biopsy to be eligible for this study if it can be performed at minimal acceptable clinical risk as judged by the investigator and if it is not in a target lesion or a lesion in an area treated with prior radiation therapy. For the dose escalation phase, subjects with advanced or metastatic solid tumors must have received standard regimen and either experienced tumor progression or were intolerant to a minimum of ONE standard treatment regimen. For the dose expansion phase, subjects with advanced or metastatic solid tumors with tumor mesothelin expression must have received and either progressed or been intolerant to standard treatment regimens.

Study Drug for CA008-002

Medication	Potency	IP/Non-IP
BMS-986148	50 mg/vial	IP
Nivolumab	100 mg/ vial (10 mg/mL)	IP

Study Assessments:

- Safety Outcome Measures: Adverse events will be assessed continuously during the study and for 60 days (or 100 days for combination therapy) after the last treatment. Adverse events will be coded using the most current version of MedDRA and reviewed for potential significance and importance. Adverse events will be evaluated according to the NCI CTCAE v4.03. Subjects should be followed until all AEs for which no clear alternative cause is identified other than BMS-986148 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.
- Efficacy Assessments: Tumor measurements with computed tomography (CT) and/or magnetic resonance imaging (MRI), as appropriate, will be conducted at screening, at the start of Cycle 3, and then every 2 cycles ± 1 week during the treatment phase. Tumor measurements should be conducted earlier, if clinically indicated. Subjects with SD, PR, or CR at the last clinical follow-up visit undergo tumor assessment via CT/MRI scans every 3 to 4 months during the survival follow-up phase until progression or death. Tumor measurements will be collected in all subjects until there is disease progression or until subjects discontinue from the study. Tumor response and progression will be evaluated in this study using RECIST version 1.1 or Modified RECIST for malignant pleural mesothelioma (See Protocol Appendix 4). Initial response assessment of PR or CR must be confirmed by a consecutive assessment no less than 4 weeks (28 days) later.
- Pharmacokinetic Measures: Serum samples will be collected from all subjects at specified timepoints to evaluate concentrations of the total antibody, [redacted] active ADC, and nivolumab. Plasma samples will be collected from all subjects at specified timepoints to evaluate concentrations of [redacted] unconjugated tubulysin. Pharmacokinetic parameters including Cmax, Tmax, AUC(0-t), AUC(TAU), Ctau, Ctrough, CLT, Vss, Vz, AI_AUC, AI_Cmax, AI_Ctau, Cavg, and T-HALF will be determined from serum and plasma concentration versus time data.
- Immunogenicity Measures: Serum samples will be collected from all subjects at specified time points to evaluate the development of anti-drug antibody (ADA) responses to BMS-986148 (i.e. active ADC and specificity to antibody and/or tubulysin domains) or nivolumab. Serum samples designated for PK [redacted] assessments may also be used for immunogenicity analysis.
- Biomarker Measures: [redacted]

[redacted] In addition, mesothelin protein expression will be assessed using IHC on FFPE tumor samples from Parts 2, and 3 of the study. [redacted] IHC data will be generated prospectively during the screening period in Parts 2 and 3B to select only those subjects with tumor mesothelin expression for inclusion for treatment.

Endpoints:

Primary Endpoints: Incidence of AEs at worst grade, serious AEs (SAEs) at worst grade, AEs leading to discontinuations, deaths, and frequency of laboratory test toxicity grade shifting from baseline. Safety will be evaluated from the time that the subject signs the informed consent, and for up to 60 days (or 100 days for combination therapy) after the last dose of study drug.

Pharmacokinetic: Select PK parameters including Cmax, Tmax, AUC(0-t), AUC(TAU), Ctau, Ctrough, CLT, Vss, Vz, AI_AUC, AI_Cmax, AI_Ctau, Cavg, and T-HALF will be assessed from serum and plasma concentration-time data collected during Cycle 1 and Cycle 4.

Efficacy: BOR, ORR, duration of response, PFS rate at select times [redacted].

Immunogenicity: Frequency of subject immunogenicity status.

Electrocardiography (ECG): Changes in QTcF (ΔQTcF) from baseline at selected times.

Analyses:

Efficacy Analyses: Efficacy results will be presented by tumor type, dose, and regimen for monotherapy and combination cohorts. Individual best overall response (BOR), duration of response and PFS will be listed using RECIST version 1.1 criteria or Modified RECIST for malignant pleural mesothelioma (Protocol Appendix 4). BOR outcomes will be tabulated by dose and dose regimen. The ORR and PFS rates (eg, at 24 weeks) and the confidence interval will be provided by dose and dose regimen for each tumor type if there is a large enough sample size. The duration of response and PFS will be estimated by Kaplan-Meier (K-M) methodology. PFS rates (eg, at 24 weeks) will be similarly estimated, based on K-M methodology. Individual changes in the tumor burden over time will be presented graphically by dose and dose regimen within a tumor type. [redacted] Sponsor can request scans for review at any time during or after the study.

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 physical examination 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 [redacted], ΔQTcF, ECG intervals QRS and PR, and changes in heart rate (ΔHR) will be tabulated by dose and study day. Frequency distributions of max QTcF values, max ΔQTcF, max QRS, max PR, and max HR in pre-specified categories will be tabulated by dose. Scatter plots of HR, ΔHR, QTc, and ΔQTcF versus time-matched active ADC and unconjugated tubulysin concentrations will be provided. A concentration-response effect of BMS-986148 on QTcF may be assessed by a linear mixed effects regression model for ΔQTcF on plasma and serum concentrations, stratified by study day, as well as pooled across days. Additional modeling of exposure-response may also be explored.

Pharmacokinetic Analyses: PK parameters for the total antibody, [redacted] active ADC, [redacted] and unconjugated tubulysin will be calculated using noncompartmental analysis and tabulated following monotherapy and combination treatments. Summary statistics will be tabulated for the PK parameters by dose, dose regimen, and study day for each select analyte. To describe the dependency on dose, scatter plots of Cmax and AUC (TAU) versus dose will be provided on indicated study days for each dose regimen. [redacted] To

assess the attainment of steady state geometric mean Cmin values will be plotted versus study day by dose and dose regimen. Summary statistics for nivolumab PK will also be tabulated.

Immunogenicity Analyses: All available immunogenicity data will be listed and flagged for subjects with at least 1 positive ADA. The frequency of subjects with at least 1 positive ADA assessment at baseline and the frequency of subjects who develop ADA after initiation of treatment (ADA positive) will be provided. Details and potentially additional endpoints (eg, incidence of persistent positive ADA) and analysis will be provided in the SAP. Associations of immunogenicity measures with PK and/or selected AE may be explored. The above analysis will be provided for BMS-986148 after monotherapy and combination treatments and for nivolumab.

Exploratory Biomarker Analyses: [redacted]

Association between efficacy measures [redacted] may be assessed by graphs and/or summary statistics for each select tumor type using data from Part 2. The same assessments will be made with respect to CA125 levels in the ovarian cancer and mesothelioma cohorts only and with respect to CA19-9 levels in the pancreatic cancer cohort only. [redacted]

For the combination treatment cohorts, changes in inflammatory cytokines and in markers related to peripheral blood immune cell subsets will be described similarly. Associations of other tumor-based baseline markers, and of mutations and other genetic anomalies with efficacy measures will be explored graphically and by summary statistics.

Interim Analysis:

Because of the exploratory nature of the early phase study, data emerging from each dose level or each part of the study will be examined prior to the formal locking of the study database for timely decisions about, such as but not limited to, dose selection, regimen selection, and early termination of the study. There will be no formal hypothesis testing, nor will multiplicity be adjusted.

Bayesian regression model may be utilized to inform dose selection starting for the third dose in Part 1A. A similar approach may be used in Part 1B.

TABLE OF CONTENTS

1 INTRODUCTION [redacted]

Patients with metastatic or refractory solid tumors have very poor prognosis.[1] Despite advances in multimodal therapy, increases in overall survival (OS) in this patient population have been limited. The unmet need resides in the lack of effective treatments to deliver long-term survival, hence the need to test compounds that have novel mechanisms of action in clinical studies to achieve better response rates.

Traditional cancer chemotherapy is often accompanied by systemic toxicity to the patient. Monoclonal antibodies against antigens on cancer cells offer an alternative tumor-selective treatment approach. However, most monoclonal antibodies are not sufficiently potent to be therapeutically active on their own. Antibody–drug conjugates (ADCs) use antibodies to deliver a potent cytotoxic compound selectively to tumor cells, thus improving the therapeutic index of chemotherapeutic agents. The recent approval of 2 ADCs, brentuximab vedotin[2] (BV) and trastuzumab emtansine (T-DM1),[3] for cancer treatment has spurred tremendous research interest in this field.

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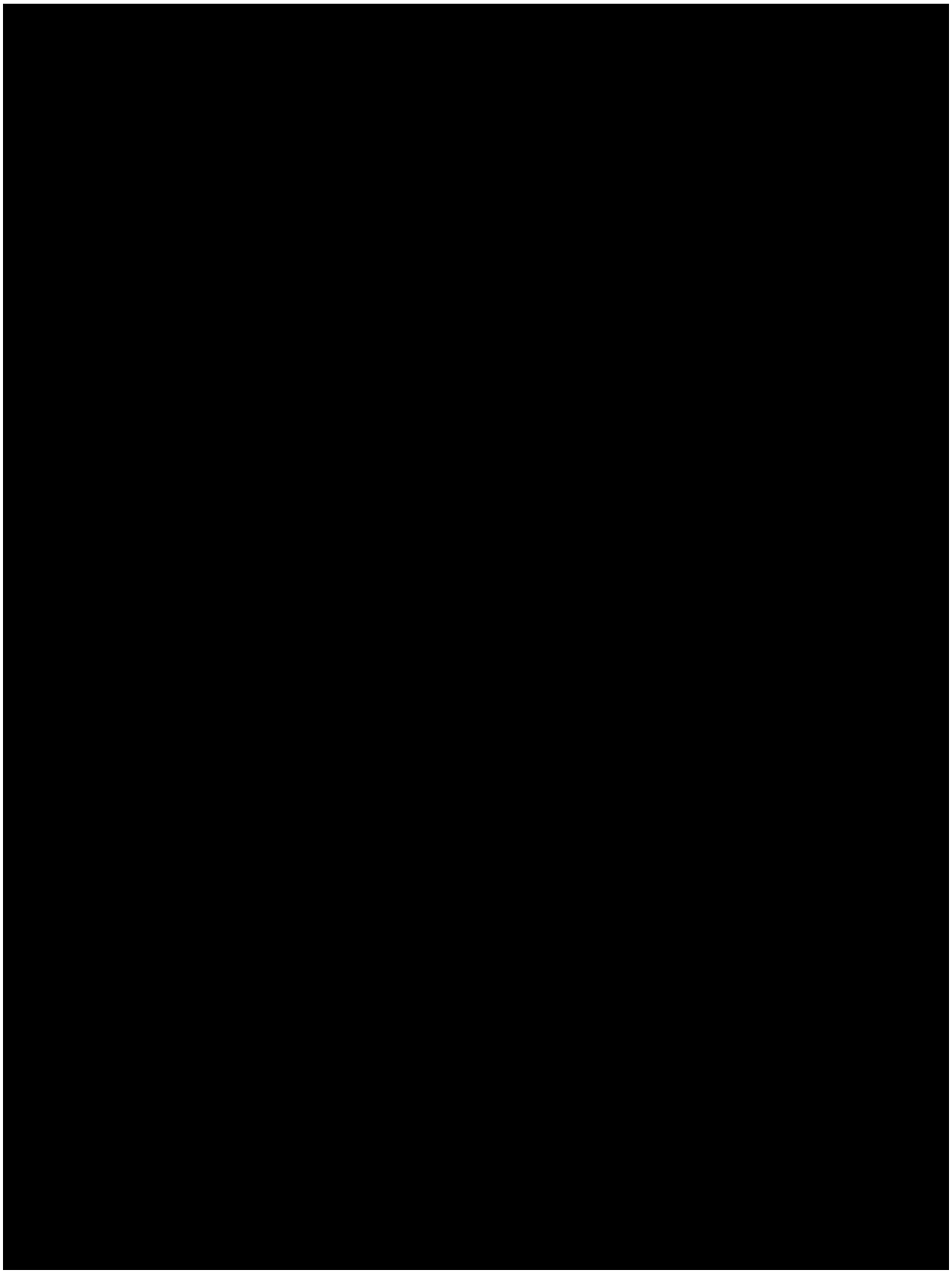

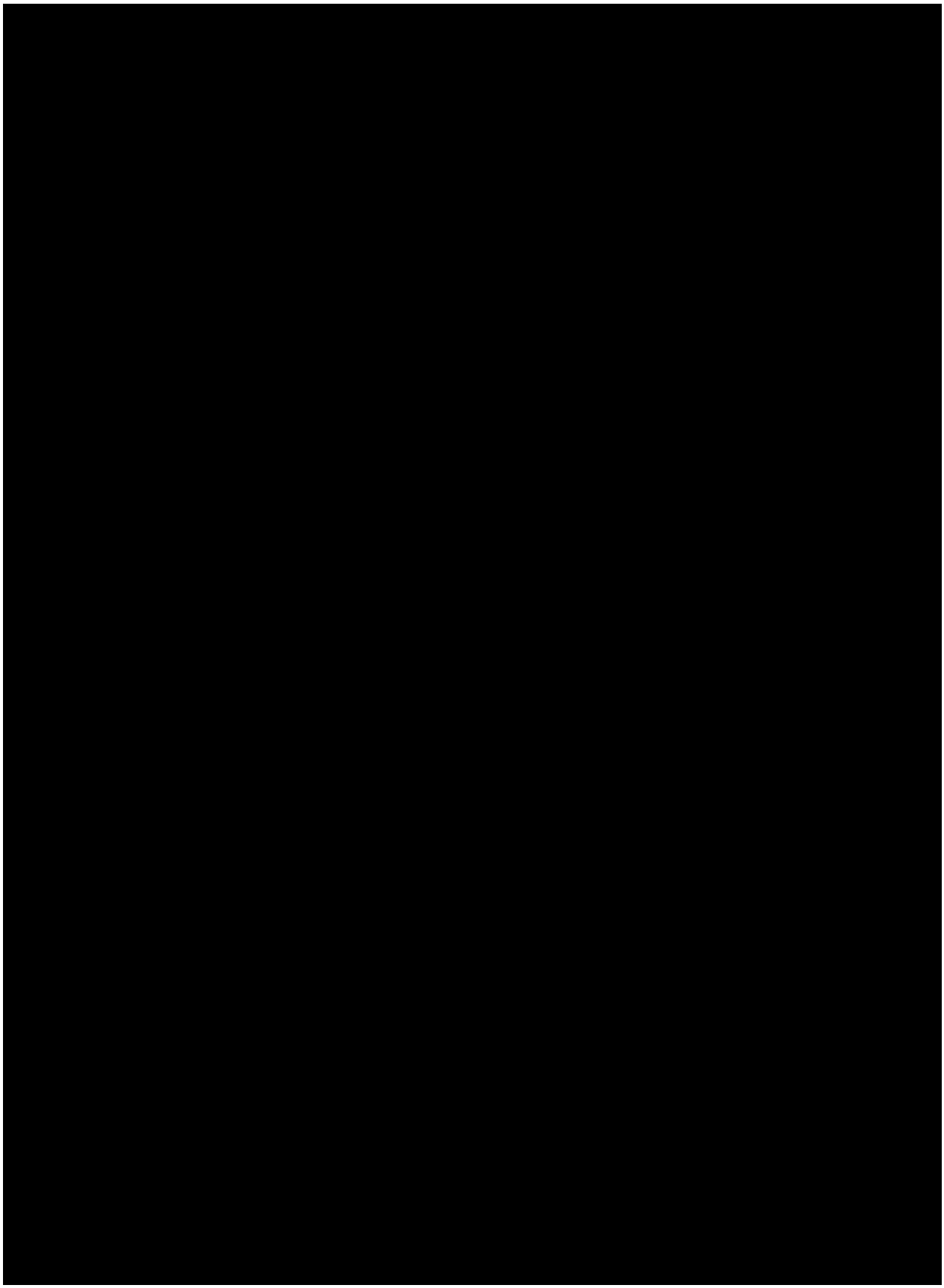

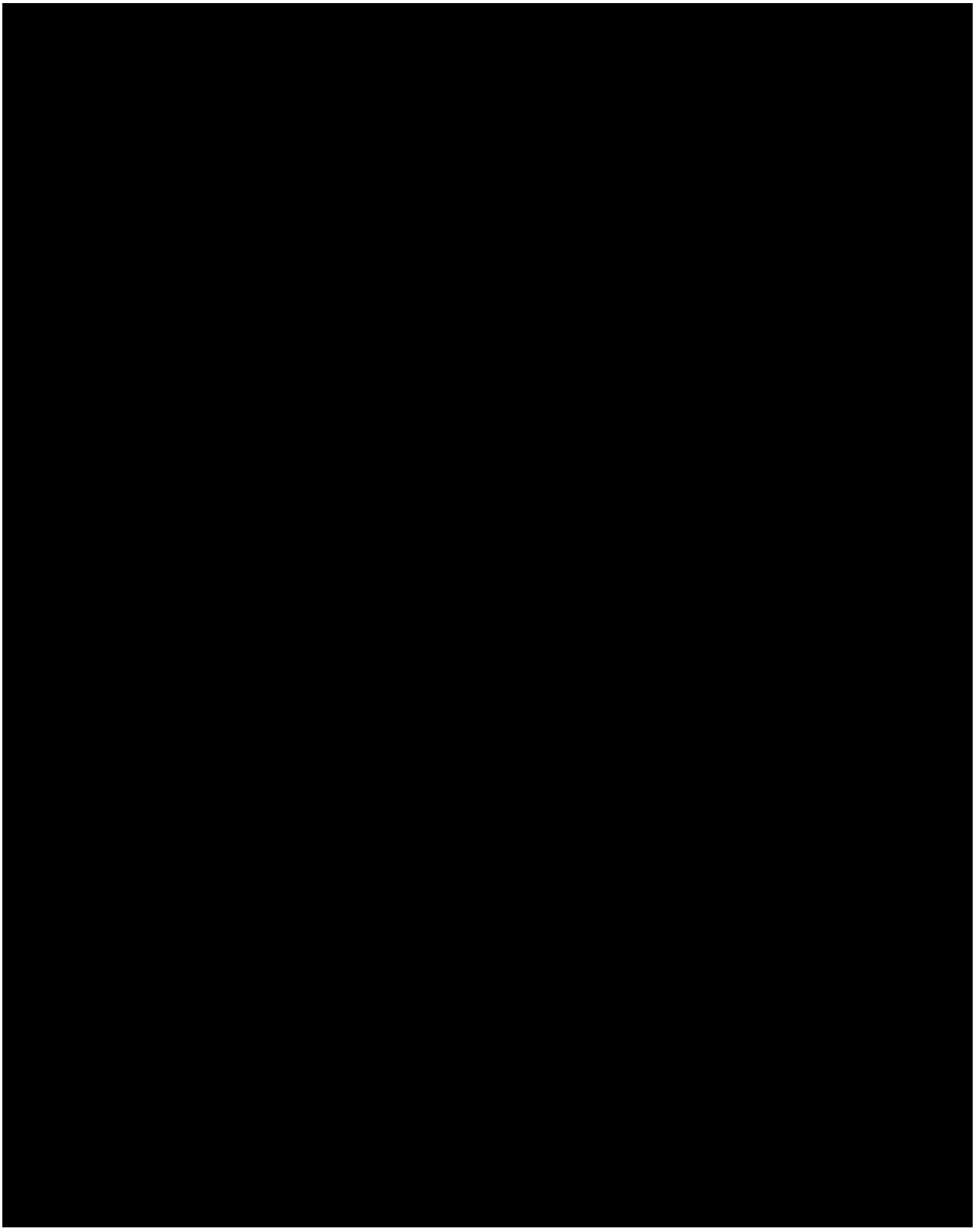

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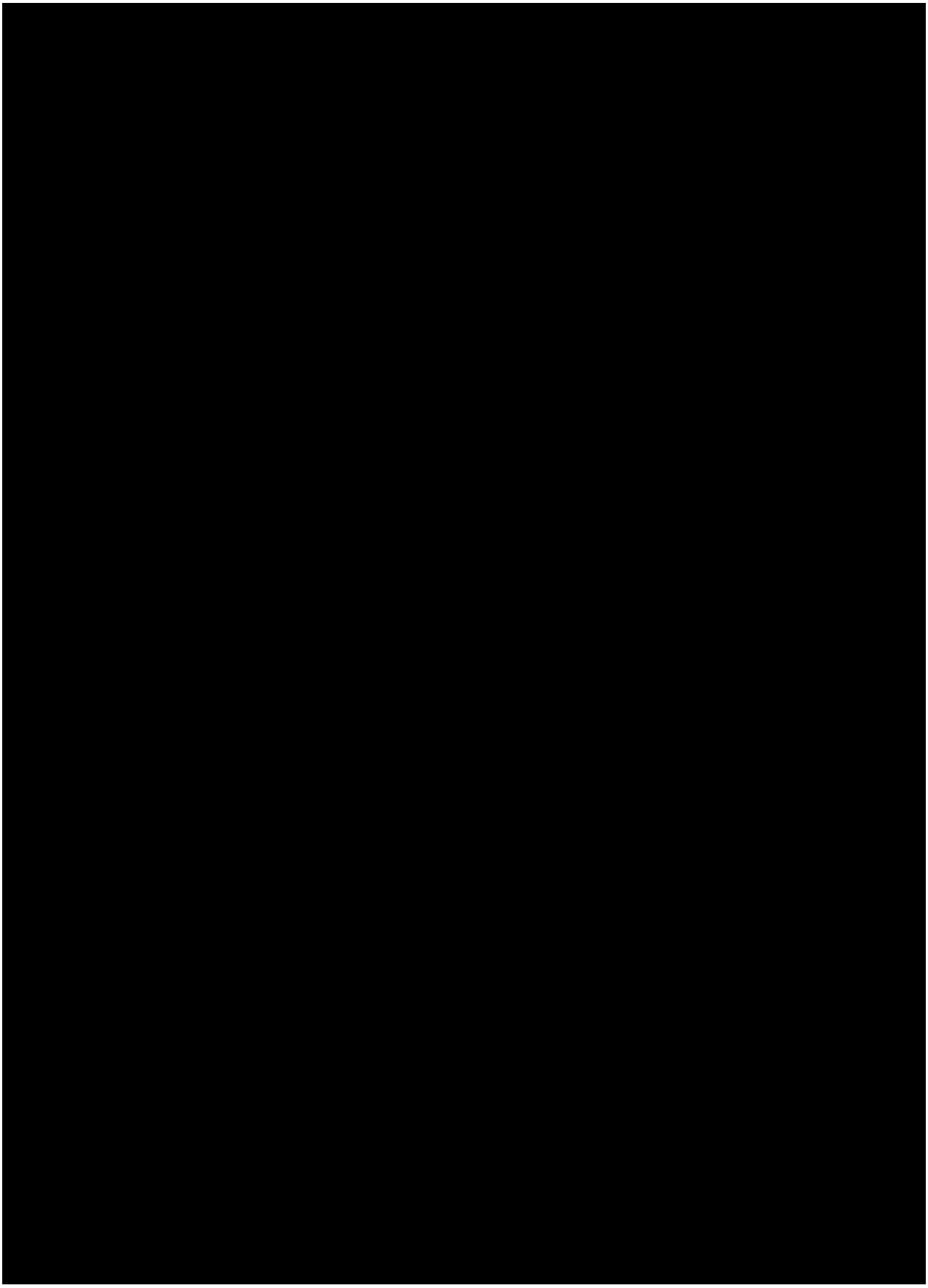
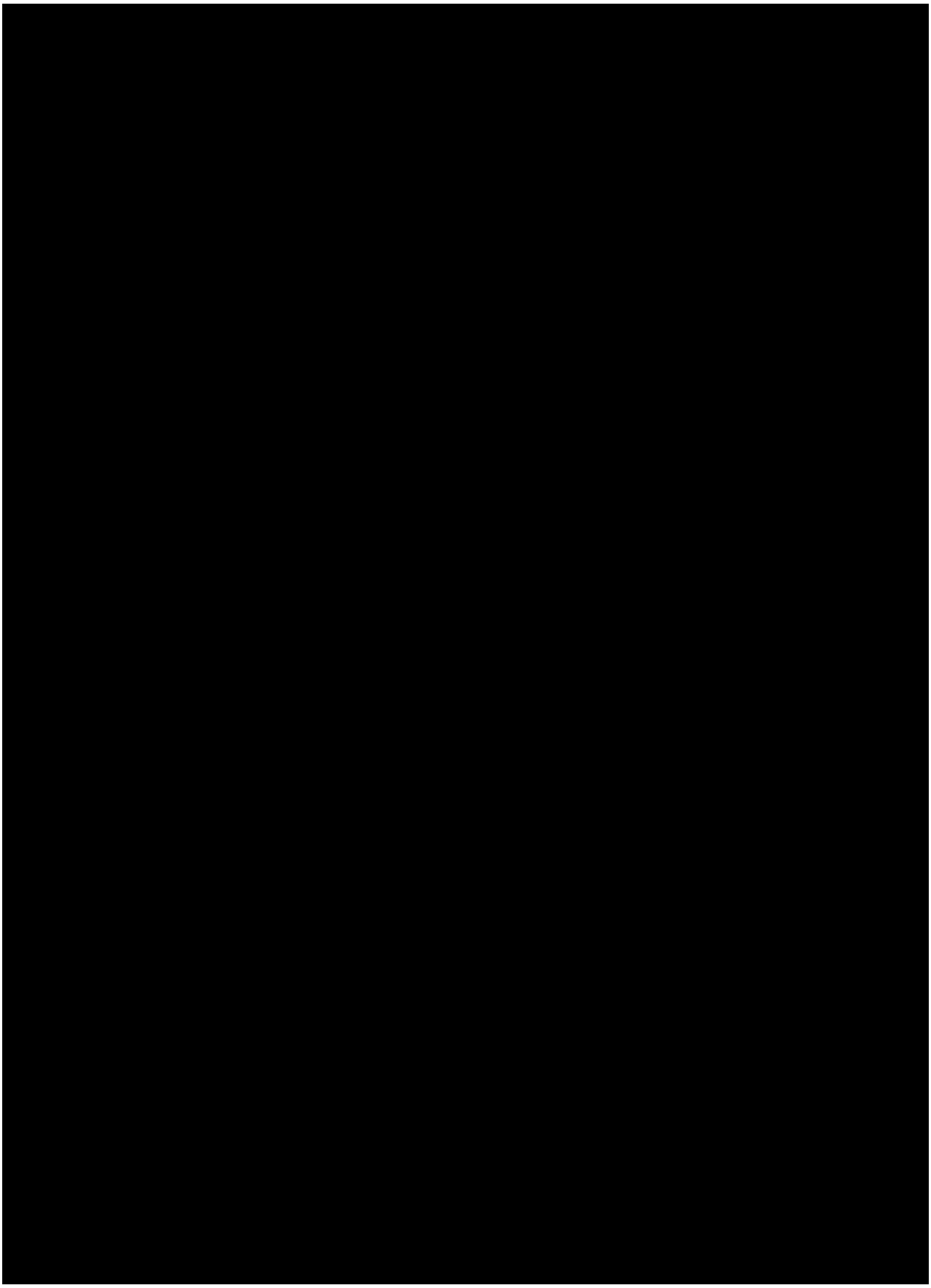
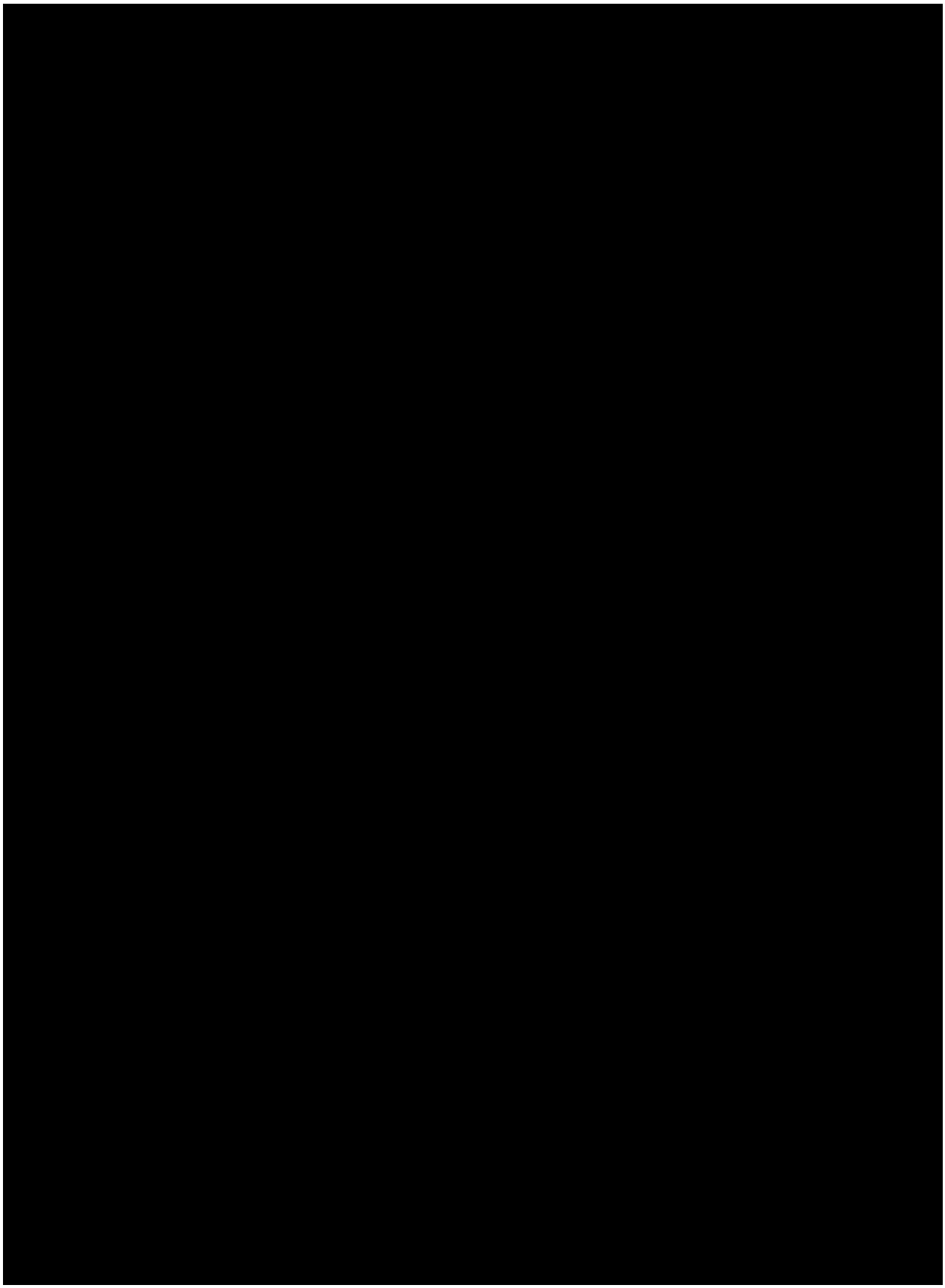
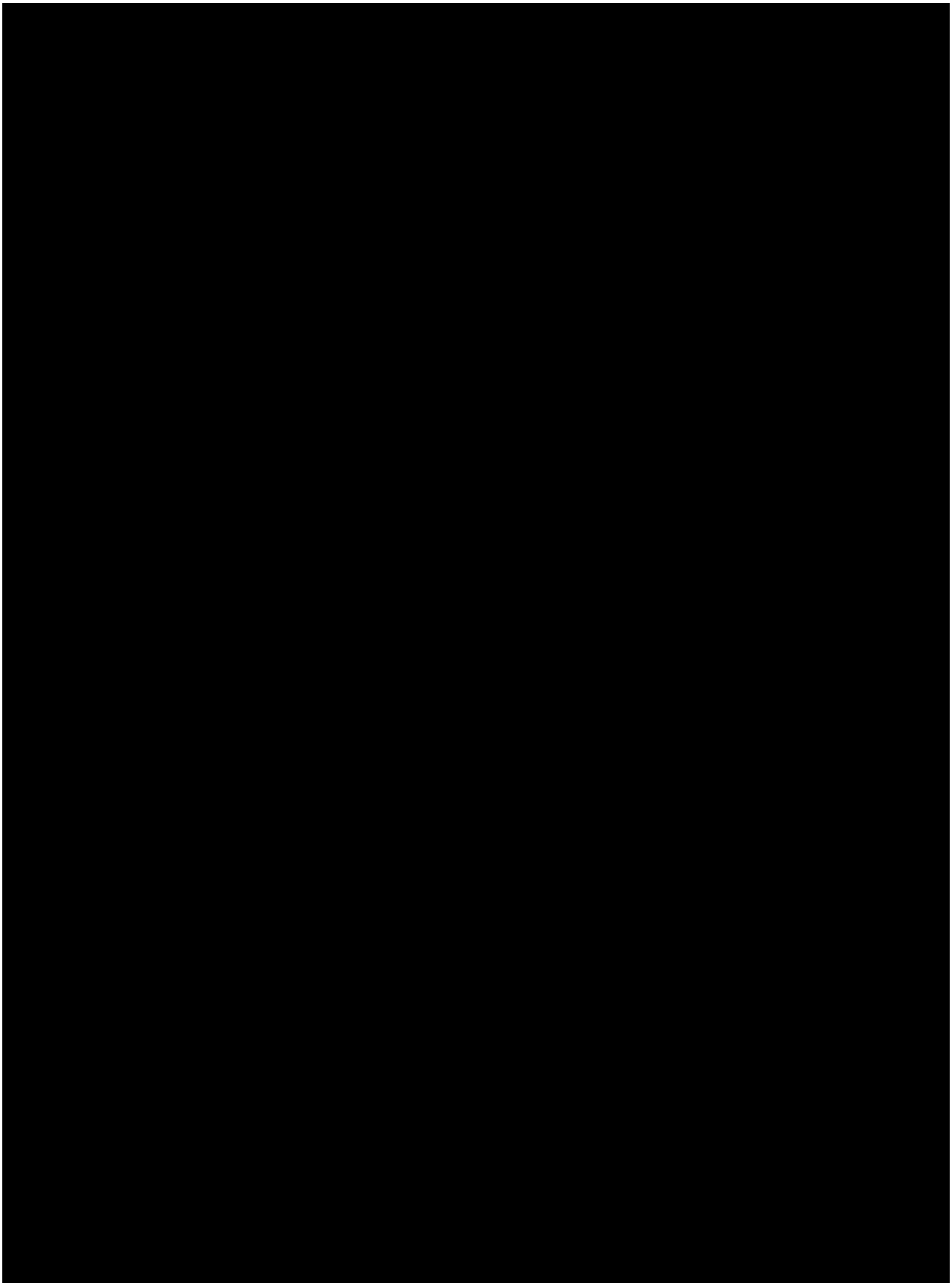
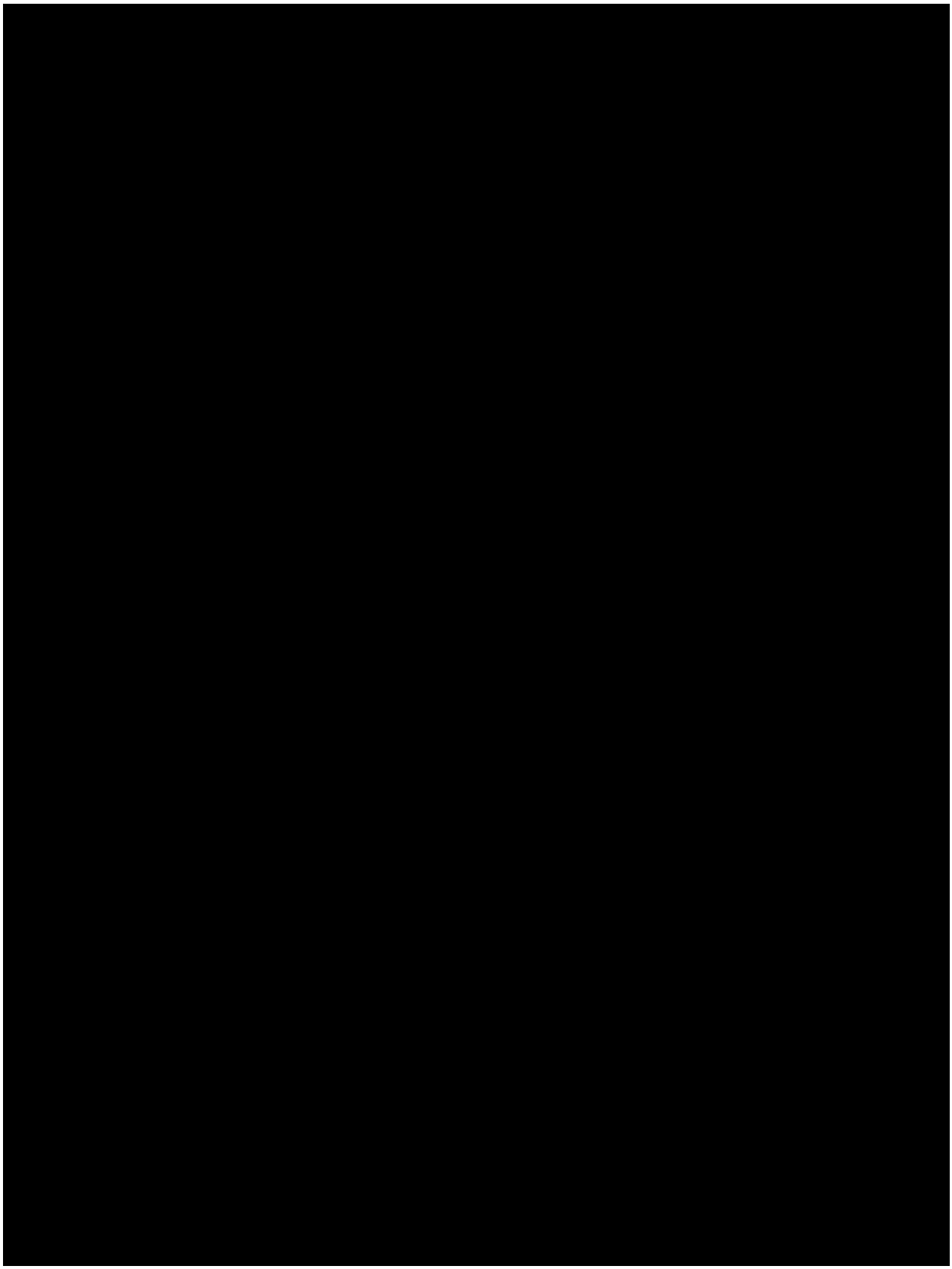










[redacted]

1.2 Research Hypothesis

There is no formal primary research hypothesis for this study to be statistically tested. The purpose of this study is to evaluate the safety profile, tolerability, preliminary efficacy, PK, and PD of BMS-986148 administered alone and in combination with nivolumab in subjects with select advanced solid tumors.

1.3 Objectives(s)

1.3.1 Primary Objectives

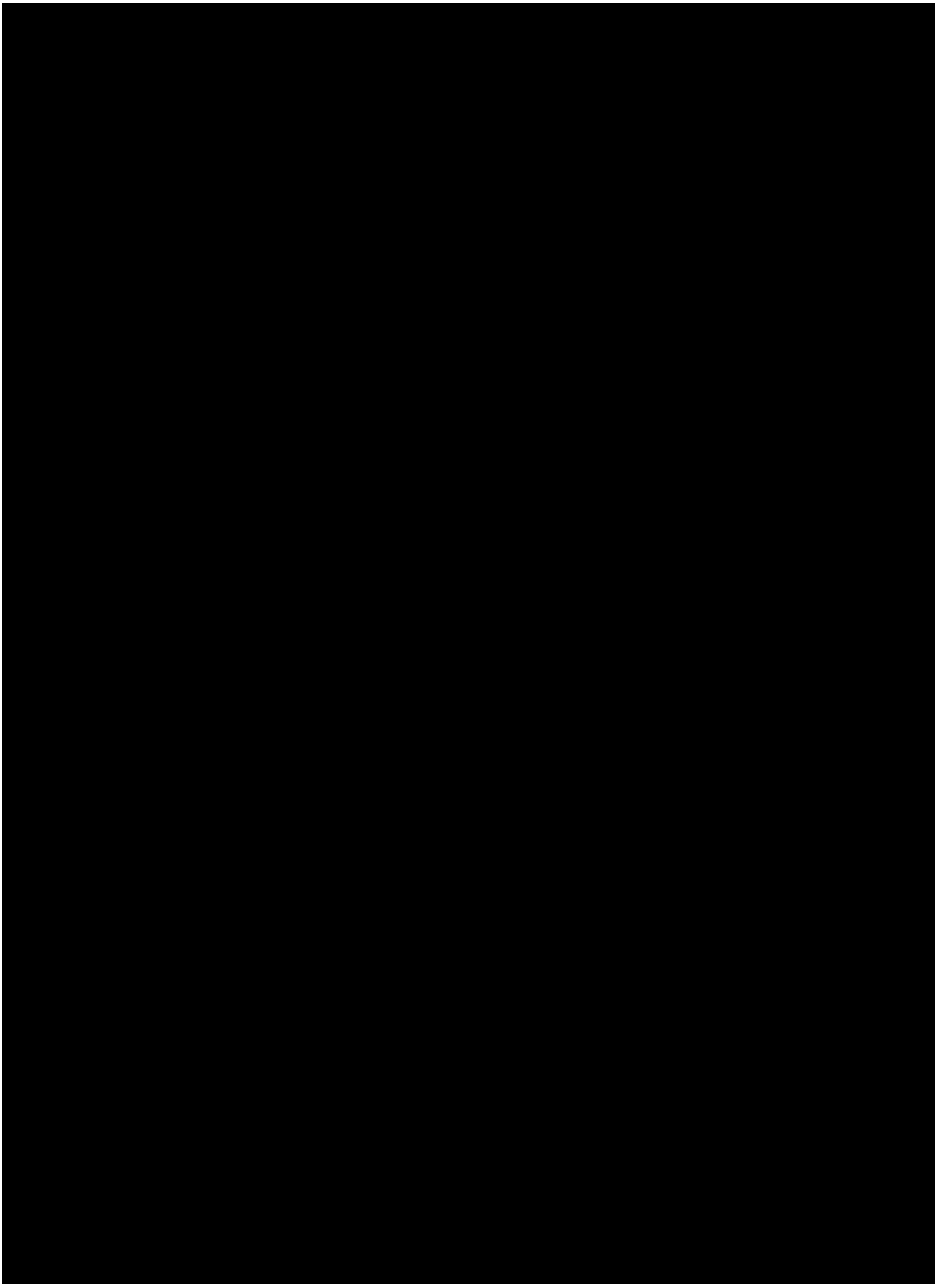
- To assess the safety and tolerability of BMS-986148 administered as monotherapy and in combination with nivolumab in subjects with select advanced solid tumors

1.3.2 Secondary Objectives

- To assess the preliminary anti-tumor activity of BMS-986148 as monotherapy and in combination with nivolumab as measured by objective response rate (ORR), response duration, and progression-free survival (PFS)
- To characterize the PK of the total antibody (unconjugated antibody + antibody conjugated to tubulysin or antibody conjugated to any tubulysin metabolites), active ADC (antibody conjugated to tubulysin), and unconjugated tubulysin when BMS-986148 is administered as monotherapy and in combination with nivolumab
- To characterize the PK of nivolumab when administered in combination with BMS-986148
- To assess the effect of BMS-986148 monotherapy dosage regimen and exposure (active ADC and unconjugated tubulysin) on the QT interval
- To characterize the immunogenicity of BMS-986148 as monotherapy and in combination with nivolumab
- To characterize the immunogenicity of nivolumab in combination with BMS-986148

[redacted]

[redacted]



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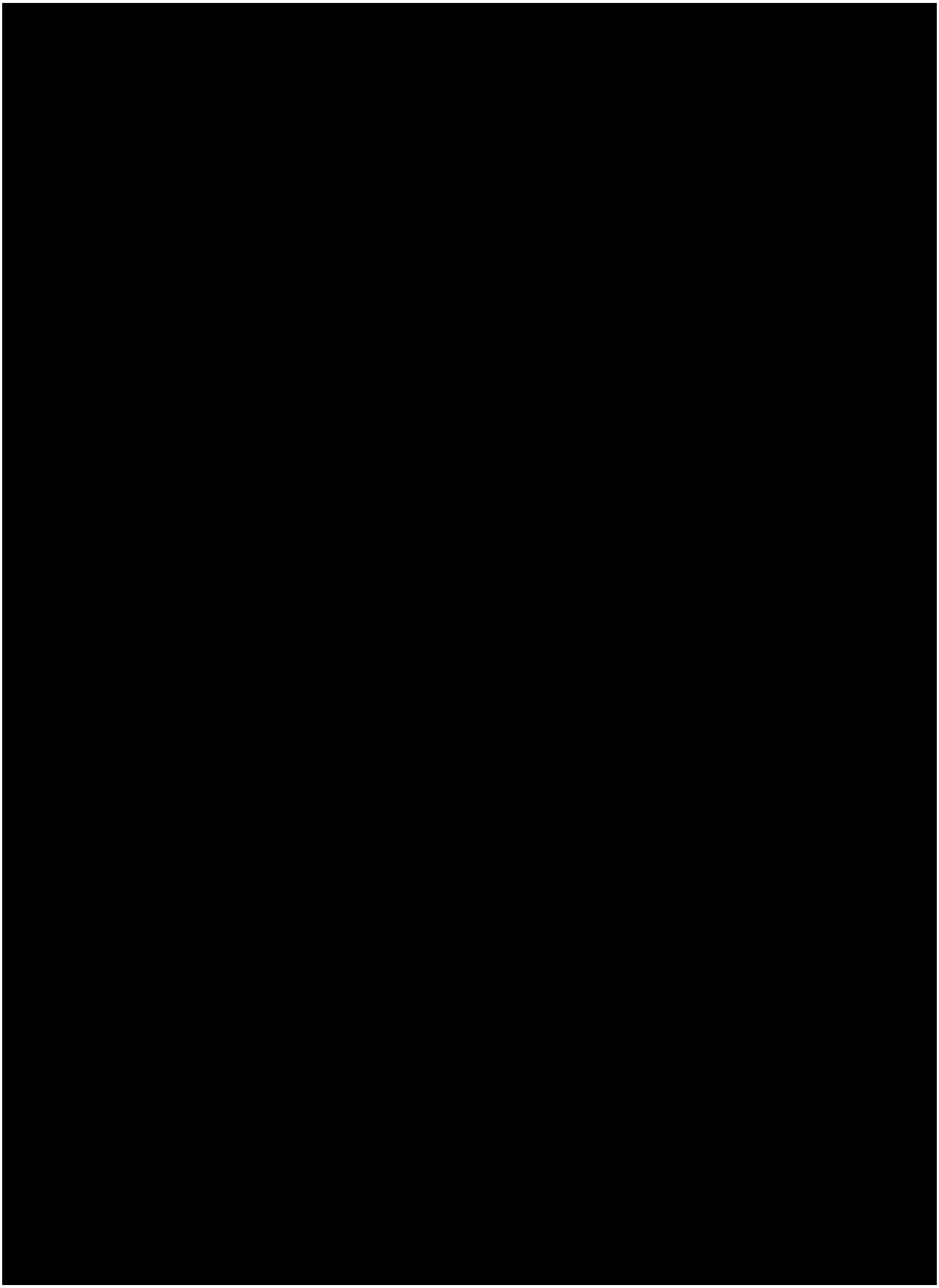
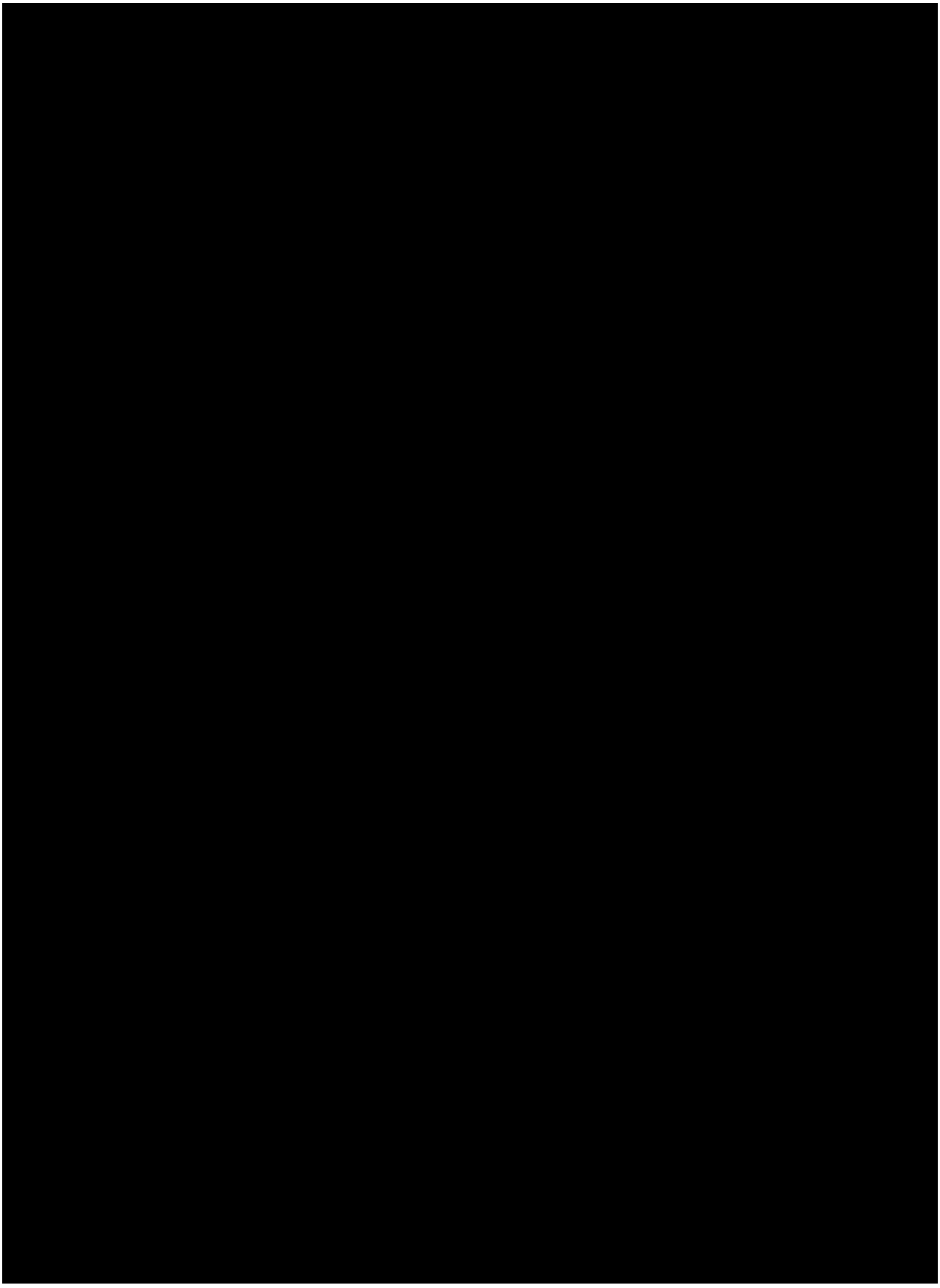
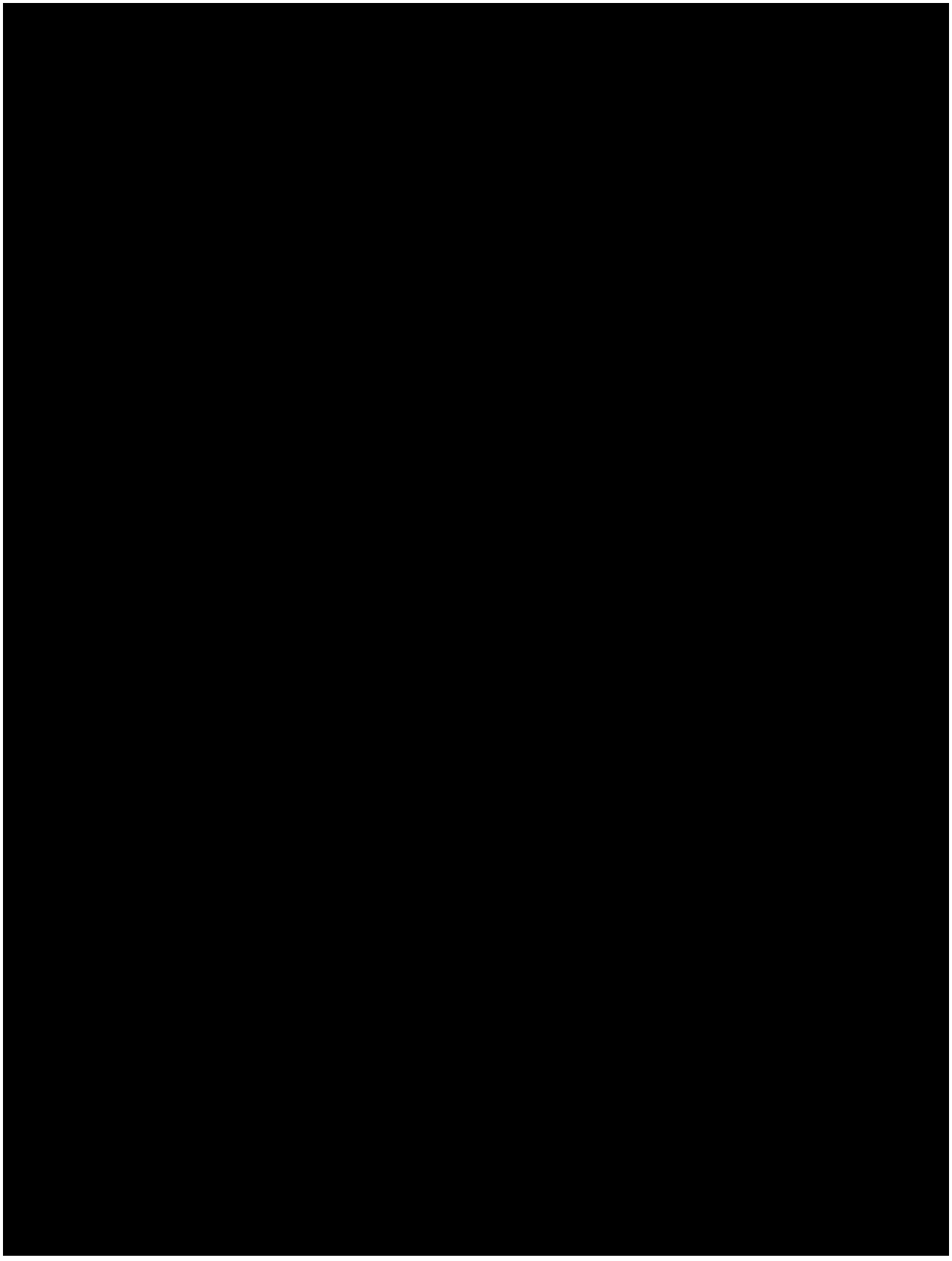






[redacted]

[redacted]

[redacted]

1.5 Overall Risk/Benefit Assessment

1.5.1 Risk/Benefit for BMS-986148 Monotherapy

There is no prior human experience with BMS-986148; therefore, clinical benefit has not been assessed in subjects with advanced cancer. Because of its high expression on multiple tumors, mesothelin has been suggested as an attractive target for antibody targeting. Several therapeutic agents that target cell surface mesothelin have been developed and some are being evaluated in preclinical and clinical studies. Three distinct molecules are in clinical development: an antibody fragment linked to an immunotoxin, a chimeric anti-mesothelin antibody, and an ADC linked to a cytotoxic payload DM-4.[47] Recombinant immunotoxin SS1P is composed of a variable anti mesothelin fragment (Fv) that was obtained from a phage library of mice immunized with recombinant mesothelin, which was then fused to *Pseudomonas* exotoxin A (PE38).[48,49] Two Phase 1 clinical trials of SS1P were completed at the National Cancer Institute (NCI).[50,51] Based on Phase 1 clinical data of SS1P and its anti-tumor activity, a clinical trial of SS1P in combination with chemotherapy is currently ongoing. However, there are limitations with the immunotoxins, including high immunogenicity which limits repeat dosing.

Additional clinical data comes from MORAb-009 (amatuximab), a chimeric antibody containing murine SS1 Fv and human IgGγ1 and κ constant region.[52] A Phase 1 clinical trial of MORAb-009 for mesothelioma, pancreatic cancer, and ovarian cancer patients was completed.[53] A total of 24 subjects were treated, including 13 mesothelioma, 7 pancreatic cancer, and 4 ovarian cancer patients. Eleven subjects had stable disease (SD). Of interest, treatment of patients with MORAb-009 led to a marked increase in the CA125 levels, which returned to baseline when treatment was terminated. Thus far, the safety profile has been favorable, with an MTD of 200 mg/m^2. Phase 2 studies of MORAb-009 in combination with pemetrexed and cisplatin in mesothelioma subjects[54] reported that the combination was well tolerated. Median OS was 14.8 months.[55]

BAY 94-9343 is a fully human anti-human mesothelin IgG1 antibody linked to a cytotoxic tubulin-binding maytansinoid payload, DM-4, and is in Phase 1 clinical trials for the treatment of patients with advanced solid tumors.[56] Based on poster and oral presentations at the 2013-American Association for Cancer Research meeting, the half-life was reported to be 6 days for the antibody and 3.5 days for the DM-4 payload. The MTD was determined to be 6.5 mg/kg, based on significant AEs at 7.5 mg/kg notable for ocular/corneal toxicity, amylase and lipase elevation, peripheral neuropathy, hyponatremia, and AST elevations. The trial continues to accrue subjects in the expansion phase of the study.[57]

The nonclinical toxicology studies in rats and monkeys primarily demonstrated the expected toxicity profile that results from microtubule inhibition via tubulysin and mesothelin antigen targeting. The primary antigen-dependent targets were the serosal surfaces of various thoracic and abdominal organs and the conjunctiva and cornea of the eye. Nonantigen dependent toxicities involved the GI, liver, and bone marrow. These toxicities were dose dependent. [redacted]

The nonclinical toxicity profile was used to determine the starting dose and develop appropriate exclusion criteria and safety monitoring for this study. In addition, frequent complete blood counts (CBCs) and chemistry (including liver function) tests will be performed to assess the potential nonantigen dependent myelosuppression and liver function effects of BMS-986148. Subjects will be evaluated frequently by physical examination (PE), and they will be assessed for the development of ocular symptoms and peripheral neuropathy (although not seen in toxicology studies, peripheral neuropathy is a known side effect of some microtubule inhibitors). Subjects with Grade 2 or higher ocular symptoms or peripheral neuropathy will be excluded from the study. Ophthalmological examination by an ophthalmologist or locally qualified personnel will include an 8-point exam (visual acuity, pupils, extraocular motility and alignment, tonometry, visual field, external examination, slit lamp examination, and fundoscopy) at baseline and focused exams with visual acuity, slit lamp, and as indicated will be conducted during the study. Safety assessments are outlined in Section 5.3. The dose escalation plan uses Grade 2 ocular symptoms, as well as other Grade 3 and 4 DLTs, to trigger a transition from 100% dose escalation increments to a dose escalation increment sequence of 67%, 50%, 40%, and

continuing at 33%, to reduce the risk of drug related AEs. No significant ocular toxicities have been observed in the 30 subjects dosed as of 01 July 2016.

In addition, subjects with a left ventricular ejection fraction (LVEF) below the lower limit of normal, New York Heart Association (NYHA) Class 2 or higher heart failure, and elevated Troponin I or T will be excluded from the study. Cardiac monitoring with echocardiogram, EKG, and Troponin T or I will be conducted during the study. Safety assessments are outlined in Section 5.3. As of 01 July 2016, no troponin elevations were noted in the 30 subjects dosed in the monotherapy escalation of Part 1A. One SAE of Grade 3 pericardial effusion related to study drug was observed after the second cycle of BMS-986148 at the high dose of 1.6 mg/kg Q3W in Part 1A. This dose has been determined to be above the MTD, and no additional subjects will be treated at this dose level.

The frequent safety assessments will be utilized by the BMS Medical Monitor and investigators to determine whether dose modification, additional safety measures, or termination of the study is required at any time. Thorough evaluation of the above-described safety monitoring procedures and of AEs and SAEs will be reviewed on an ongoing basis by the BMS Medical Monitor and Global Pharmacovigilance and Epidemiology representatives to monitor for any safety signals or trends.

As BMS-986148 is an experimental agent, it is possible that unforeseen, unknown, or unanticipated reactions may occur. However, based on the clinical safety profile of BMS-986148 [redacted], and the 18.8-fold safety margin inherent in the planned starting dose of 0.1 mg/kg given Q3W followed by a cautious dose escalation scheme, the potential safety risks are expected to be minimized. Predicted human exposure at the starting dose of 0.1 mg/kg is consistent with exposures that demonstrated anti-tumor activity in mouse xenograft tumor models and may be beneficial to subjects enrolled in this clinical study.

A need exists for new therapies for subjects with advanced cancer that has progressed or not responded to other treatments. Once a pharmacologically-active dose range is reached, there may be potential benefits to study subjects. Furthermore, the substantial preclinical efficacy profile [redacted] and the evidence for mesothelin expression in many human cancers [redacted], indicates that the balance of benefit to risk is likely to be favorable for study subjects treated with BMS-986148 monotherapy.

1.5.2 Risk/Benefit for BMS-986148 and Nivolumab Combination Therapy

Nivolumab has demonstrated clinical activity in subjects with advanced NSCLC, renal cell carcinoma, melanoma, and lymphomas, as well as other tumors, including ovarian, gastric, and mesothelioma. The clinical activity of nivolumab monotherapy observed to date in these malignancies suggests the potential for improved clinical outcomes relative to other approved therapies.

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. There is no pattern in the incidence, severity, or causality of AEs with respect to nivolumab dose level. The most common AEs (as of 01 July

2016) 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 (Appendix 3).

There is potential for overlapping toxicity between clinical findings of BMS-986148 and nivolumab-related hepatoxicity, infusion-related reactions, and peripheral neuropathy.

Elevation of the liver transaminases were the DLTs noted in 4 of the 10 subjects treated with BMS-986148 at 1.6 mg/kg Q3W. This dose is above the MTD, and no additional subjects will be treated at this dose. At the selected starting dose of BMS-986148 of 0.8 mg/kg IV Q3W, no DLTs were observed in the 4 evaluable subjects. However, the incidence of nivolumab-related hepatitis is quite low (approximately 1%). Subjects in this study receiving BMS-986148 monotherapy or BMS-986148 and nivolumab combination therapy will be monitored closely for any LFT abnormalities via laboratory assessments and frequent assessment for the development of symptoms. Study drug will be discontinued for any significant LFT abnormalities.

Peripheral neuropathy related to BMS-986148 is infrequent. No events related to study drug are noted to date as of 01 July 2016. Details of these events are summarized in Section 1.5.1. For nivolumab monotherapy, the incidence of neuropathies was < 1%, and management guidelines have been established as detailed in the nivolumab IB. To minimize potential risks, criteria excluding subjects with peripheral neuropathy and dose modifications have been developed. In addition, subjects in this study receiving BMS-986148 monotherapy or BMS-986148 and nivolumab combination therapy will be monitored closely for any peripheral neuropathy via neurologic assessments and frequent assessment for the 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. For BMS-986148, no infusion reactions have been reported to date (as of 01 July 2016 data cut-off date). Subjects will be monitored during the first cycle of the combination therapy and will continue to be monitored during subsequent cycles. Detailed management guidelines for infusion reactions are provided (see Section 4.5).

Significant ocular toxicities as seen in the preclinical toxicology studies have not been noted in the study thus far. For nivolumab monotherapy, the incidence of uveitis was < 1%, and management guidelines have been established as detailed in the nivolumab IB. Subjects will continue to be monitored by opthalmologic examination for ocular symptoms, throughout the study treatment.

Subjects enrolling in Part 3 will have advanced solid tumor malignancies that has relapsed after standard of care chemotherapy or available therapies. The potential synergistic effects of nivolumab with BMS-986148 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 Bristol-Myers Squibb (BMS) immediately. A serious breach is a breach of the conditions and principles of GCP in connection with the study or the protocol, which is likely to affect, to a significant degree, the safety or physical or mental integrity of the subjects of the study or the scientific value of the study.

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

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

2.2 Institutional Review Board/Independent Ethics Committee

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

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

2.3 Informed Consent

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

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

BMS will provide the investigator with an appropriate (ie, Global or Local) sample informed consent form(s) 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 informed consent form and, in the US, the subjects' signed Health Insurance Portability and Accountability Act Authorization.

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

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

3 INVESTIGATIONAL PLAN

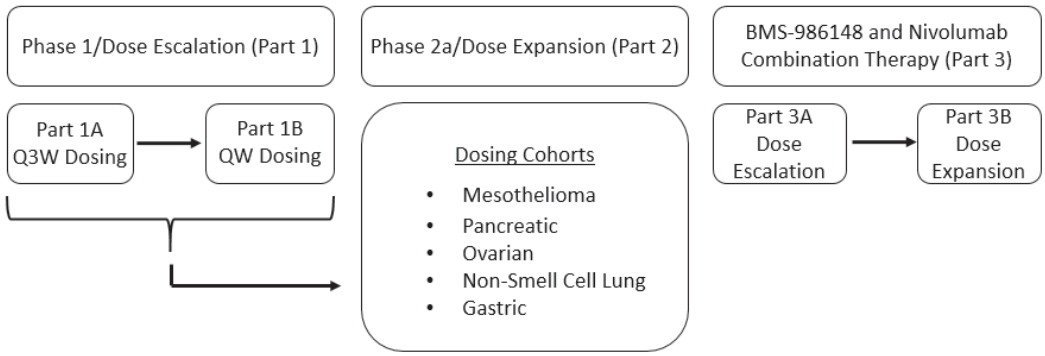
3.1 Study Design and Duration

This is a Phase 1/2a, open-label study to characterize the safety and tolerability, as well as preliminary efficacy, PK, and PD of BMS-986148 administered alone and in combination with nivolumab in subjects with select advanced solid tumors (pancreatic, ovarian, NSCLC, gastric, or mesothelioma). The study has 3 segments: Part 1 (Phase 1 study - dose escalation), Part 2 (Phase 2a - dose expansion), and Part 3 (BMS-986148 in combination with nivolumab; Part 3A - dose escalation and Part 3B - dose expansion) (see Figure 3.1-1). All subjects will complete up to 4 study periods: Screening (up to 28 days), Treatment (21 days/cycle Q3W or 28 days/cycle QW), Follow-up (60 or 100 days), and Survival Follow-up (see Figure 3.1-2). After completing the Follow-up period, subjects will continue to be followed for [redacted] up to 2 years from first dose

of study drug for subjects discontinuing study drug prior to 2 years. Subjects receiving study drug for more than 2 years will be followed in the Survival Follow-up period for 6 months from their last treatment date. With Amendment 3, a dose escalation phase will be conducted with BMS-986148 and nivolumab combination therapy (Part 3A). In the BMS-986148 and nivolumab combination therapy dose expansion phase (Part 3B), additional subjects with pancreatic, ovarian, NSCLC, gastric, or mesothelioma will be treated at or below the MTD of the combination dose identified in Part 3A to confirm safety and evaluate anti-tumor activity.

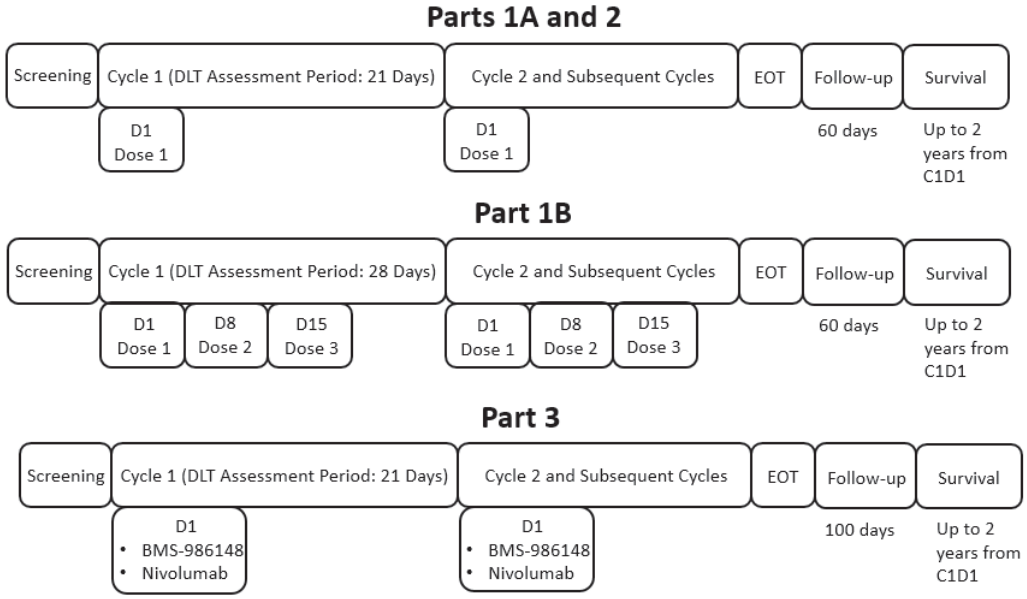
The duration of the study is anticipated to be approximately 5 years from the time of the first visit of the first subject to the required Survival Follow-up of the last subject enrolled. The end of the study will occur when the last subject has the last Survival Follow-up visit.

Figure 3.1-1: Sequence of Study Phases



QW: every week; Q3W: every 3 weeks.

Figure 3.1-2: Dosing (Q3W and QW) and Study Periods



Note: Subjects treated for > 2 years will be followed for 6 months after EOT in the Survival Follow-Up. Additionally, specifically in Part 3, treatment duration is 24 weeks to a maximum of 48 weeks.

C1D1: Cycle 1 Day 1 (first dose); D: day; DLT: dose-limiting toxicity; EOT: end of treatment; QW: every week; Q3W: every 3 weeks.

3.1.1 Dose Escalation (Part 1)

Part 1 is divided into 2 sections. In Part 1A, BMS-986148 will be administered with Q3W dosing (21 days/cycle), and in Part 1B, BMS-986148 will be administered with QW dosing for 3 weeks followed by 1 week off (28 days/cycle). Part 1B may be initiated once the MTD or a tolerated dose below the MTD for Part 1A is established.

Part 1A: BMS-986148 Administered Every 3 Weeks

Approximately 30 subjects will be enrolled in ascending dose cohorts starting with a dose of 0.1 mg/kg. BMS-986148 will be administered Q3W in a 21-day cycle. The approach for selection of the next dose at each escalation step and the rules for escalation decision based on DLT criteria guided by the mTPI design are described below, with more details in Section 4.5.1.

Part 1A: Selection of Doses

A modified Fibonacci dose escalation will be used.

The first cohort of subjects will receive a starting dose of 0.1 mg/kg. Dose escalation for each subsequent cohort of subjects will be guided by the incidence of BMS-986148-related AEs as graded by NCI Common Terminology Criteria for Adverse Events version 4.03 (NCI CTCAE v4.03) in the first 3 weeks of dosing (DLT evaluation period). Dose escalation will be in increments of 100% above the previous dose level until the first occurrence of any of the following: DLT, ≥ Grade 3 decrease in neutrophil count lasting > 72 hours, ≥ Grade 3 thrombocytopenia lasting > 72 hours, ≥ Grade 2 ocular toxicity, or 2 subjects with ≥ Grade 2 AEs in a single dose level cohort and considered related to BMS-986148 with the following exceptions: asymptomatic electrolyte abnormalities that can be managed with appropriate supplements and Grade 2 alopecia. In addition, Grade 2 fatigue that is less than 2 grades from baseline (ie, from Grade 1 to Grade 2) will not trigger a Fibonacci sequence. Once one or more of the above occur, a modified Fibonacci dose escalation will be employed for any subsequent dose escalations, with increments of 67%, 50%, 40%, and 33%. Any further dose escalations will be 33%.

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

Part 1A: Dose Escalation Decision Rules

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

(EI) to guide decisions on escalation after each cohort and to estimate the MTD. For this study the target DLT rate is 27%, and the EI is 25% to 29%.

Dose escalation will begin at a dose of 0.1 mg/kg dose (Dose Level 1) and will be guided by the cumulative number of subjects who are DLT evaluable and who experience a DLT. An initial cohort of 2 subjects will be enrolled to Dose Level 1 and subsequently dose level 2 (if no DLTs in Dose Level 1 and criteria above for transitioning from 100% increment to Fibonacci is not met) in Part 1A; otherwise, 3 to 4 patients will be treated. In the first cohort, a 5-day interval is required between Cycle 1, Day 1 dosing for the first 2 subjects (ie, 5 days between Cycle 1, Day 1 dosing for subjects 1 and 2). An initial cohort of 3 subjects will be enrolled to all other dose levels in Part 1A. A fourth subject may be enrolled in a dose escalation cohort following agreement between the investigator and the BMS 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. At any dose level, if the suggested decision by the mTPI design is to expand the same dose, 3 more subjects will be enrolled. If the suggested decision is to treat more subjects at a given dose level as 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, the dose escalation phase will be stopped.

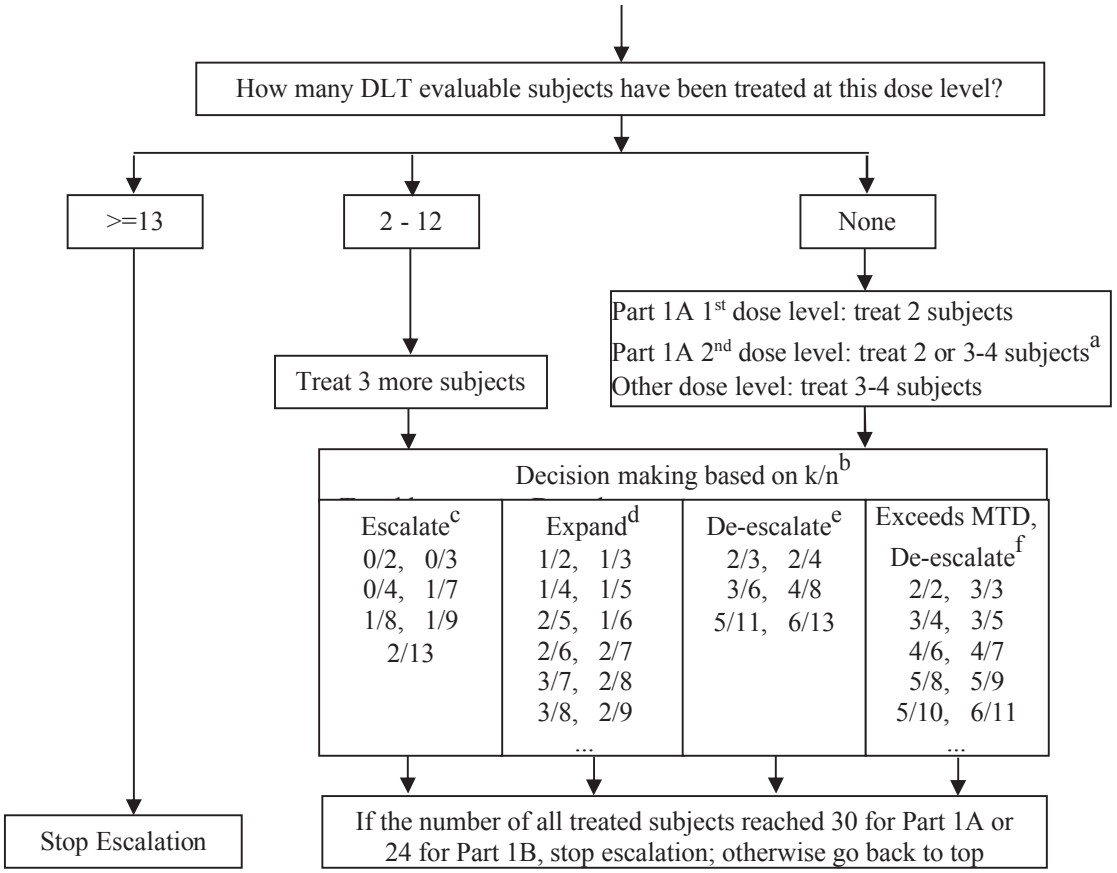
Decisions to escalate, add more subjects to the current dose, de-escalate, or de-escalate and declare the current dose as unacceptable (exceeding the MTD), will be based on the rate of DLTs in evaluable subjects within the 21-day DLT evaluation period for Part 1A guided by the mTPI model and posterior inference (Figure 3.1.1-1 and Appendix 1). At least 2 DLT-evaluable subjects treated at each of the lowest 2 dose levels and at least 3 DLT-evaluated subjects treated at each of the other dose levels are required to enable decision making. Subjects with insufficient data to establish safety during the DLT evaluation period at the dose tested (eg, omitted or reduced doses for reasons other than a DLT) may be replaced upon agreement of the BMS Medical Monitor and investigators.

In addition, if dose modifications for ocular toxicity occur in 2 or more subjects within the first 5 subjects treated on study, or if with greater patient numbers > 20% of subjects require a dose modification due to ocular toxicity, enrollment will be suspended at all dose levels equal to or greater than the lowest dose level with a dose modification due to ocular toxicity, in order to assess the safety data. Enrollment may continue at lower dose levels where no dose modifications have occurred due to ocular toxicity while this safety assessment is being conducted.

There will be no intrasubject dose escalation of BMS-986148.

Figure 3.1.1-1 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 1. In addition to escalation or expansion decisions, dose re-escalation is permitted as per Figure 3.1.1-1 and Appendix 1 after a decision to de-escalate is made, except when a dose has been identified as exceeding the MTD. Therefore, a dose level could be revisited multiple times under the mTPI design.

Figure 3.1.1-1: Dose Escalation Algorithm



[a] Treat 2 subjects initially if no DLTs in Dose Level 1 and criteria for transitioning from 100% increment to Fibonacci is not met; treat 3 to 4 subjects initially, otherwise.

[b] At the same dose, decision making based on other combinations of k/n are shown in Appendix 1.

[c] Treat the next cohort of subjects at the next higher dose.

[d] Treat 3 more subjects at the current dose.

[e] Treat 3 more subjects at the next lower dose.

[f] Unacceptable current dose. Do not re-escalate to this dose.

DLT: dose-limiting toxicity; k: cumulative number of subjects who experienced DLT; MTD: maximum tolerated dose; n: cumulative number of DLT evaluable subjects; QW: every week; Q3W: every 3 weeks.

Part 1A: Maximum Tolerated Dose Determination

At the end of dose escalation, the MTD will be selected as the dose with the smaller difference of estimated toxicity and the target DLT rate (27%), among the doses used, with isotonic regression modeling of the accumulated DLT data based on the mTPI design.

Part 1B: BMS-986148 Administered QW for 3 Weeks and 1 Week Off

Approximately 24 subjects will be enrolled in ascending dose cohorts. Part 1B may begin after determining the MTD or a tolerated dose below the MTD in Part 1A. The starting dose for Part 1B will be chosen by modeling active ADC concentration-time data from Part 1A and selecting a fractionated dose that provides similar exposure to that of the MTD or a tolerated dose below the MTD. In the event that concentration-time data are not available for modeling, the starting dose will be 1/3rd of the MTD or a tolerated dose below the MTD from Part 1A. In Part 1B, BMS-986148 is administered every week for 3 weeks and 1 week off in a 28 day cycle.

Part 1B: Selection of Doses

Similar to dose selection in Part 1A, a modified Fibonacci dose escalation will be used. Dose escalation for each subsequent cohort of subjects will be guided by the incidence of BMS-986148-related AEs as graded by NCI CTCAE v4.03 in the first 4 weeks of dosing (DLT evaluation period). Dose escalation will be in increments of 100% above the previous dose level until the first occurrence of any of the following: DLT, ≥ Grade 3 decrease in neutrophil count lasting > 72 hours, ≥ Grade 3 thrombocytopenia lasting for > 72 hours, ≥ Grade 2 ocular toxicity, or 2 subjects with ≥ Grade 2 AEs in a single dose level cohort and considered related to BMS-986148 with the following exceptions: asymptomatic electrolyte abnormalities that can be managed with appropriate supplements and Grade 2 alopecia. In addition, Grade 2 fatigue that is less than 2 grades from baseline (ie, from Grade1 to Grade 2) will not trigger a Fibonacci sequence. Once one or more of the above occur, a modified Fibonacci dose escalation will be employed for any subsequent dose escalations, with increments of 67%, 50%, 40%, and 33%. Any further dose escalations will be 33%.

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

Part 1B: Dose Escalation Decision Rules

The same mTPI design (Figure 3.1.1-1 and Appendix 1) as in Part 1A will be used to help guide escalation decisions except that all dose levels in Part 1B begin with an initial number of 3 to 4 subjects. A fourth subject may be enrolled in a dose escalation cohort following agreement between the investigator and the BMS 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. The DLT evaluation period will be 28 days. At least 3 DLT-evaluable subjects treated at each of the dose levels in Part 1B will be required to enable a decision to escalate, add more subjects to the current dose level, or de-escalate. Subjects must receive 3 doses in Part 1B during the DLT evaluation period (unless DLT has occurred) to be considered evaluable for dose escalation decisions. Subjects with insufficient data to establish safety during the DLT evaluation period at the dose tested (eg, omitted or reduced doses for reasons other than a DLT) may be replaced upon agreement of the BMS Medical Monitor and investigators.

Part 1B: Maximum Tolerated Dose Determination

Similar to the MTD determination in Part 1A, at the end of dose escalation, the MTD will be selected as the dose with the smallest difference of estimated toxicity and the target DLT rate (27%), among the doses used. See Section 4.5.1 for more information about DLTs.

Once the safety (during DLT evaluation) of a dose level has been established (Part 1A and/or Part 1B), additional subjects may be added at that dose to better characterize the PK, safety, and PD profile.

3.1.2 Dose Expansion (Part 2)

The purpose of the cohort expansion will be to assess preliminary antitumor efficacy, expanded safety experience, and PD effects of BMS-986148. Additional subjects will be treated after the completion of Part 1A and/ or Part 1B, at the MTD, or at an alternative dose below MTD as agreed upon by the BMS Medical Monitor and investigators. Part 2 can begin before the completion of Part 1B as the Q3W dosing regimen is the intended regimen for Part 2. However, if the aggregate PK and safety data indicate similar safety but higher cumulative exposure with the QW dose schedule, this schedule may also be evaluated in Part 2 in an additional cohort of 25 to 26 subjects, once the MTD or a tolerated dose below the MTD is identified in Part 1B. Treatment doses in the cohort expansion groups will not exceed the MTD.

Five expansion cohorts will be restricted to these tumor types 1) mesothelioma 2) pancreatic 3) ovarian 4) NSCLC, and 5) gastric cancer. Enrollment in cohort expansion will be determined by the mesothelin expression of the archived tumor sample (or fresh tumor sample if archived sample is not available). [redacted]

The enrollment in each expansion cohort will be guided by a Simon 2-Stage design framework (see Table 8.1-1) exploring efficacy in the following 2 populations: [redacted].

Anti-tumor activity will be assessed initially in approximately 12 to 15 evaluable subjects per tumor type (Stage 1) 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 as shown in Table 8.1-1 below for each tumor type with futility boundaries as follows: after Stage 1, if none of the first 15 evaluable subjects in the gastric or pancreatic cohorts, if ≤ 2 of the first 12 with mesothelioma, or ≤ 1 of the first 14 with NSCLC or ovarian cohort demonstrate clinical activity, enrollment in the cohort meeting criteria may be stopped for this population.

Evaluation of efficacy will occur independently in each tumor cohort. At the time of the Stage 1 efficacy assessment, [redacted] to allow an initial efficacy assessment in both the [redacted] populations. If there is a lack of signal for preliminary efficacy (number of responders not exceeding the boundary), and after evaluation of all available data, enrollment may be stopped in that population. Otherwise, additional subjects will be treated in Stage 2 for the population in which there was an initial signal. [redacted]

Of note, fresh tumor biopsy at screening and on treatment will be mandatory for 10 ovarian cancer subjects and 10 gastric cancer subjects enrolled in Part 2. Fresh tumor biopsy at screening and on treatment will be optional for subjects with other indications. [redacted]

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, additional subjects may have been enrolled and will be receiving treatment than the minimum needed for the Stage 1 assessment. Therefore, the above numbers are approximate, and enrollment may continue during the evaluation of the interim data.

Safety monitoring of subjects enrolled in the Part 2 (Phase 2a) portion of the study will be the same as that conducted during the dose escalation portion. During Part 2, if in a given arm the combined incidence of study drug-related AEs that require dose modification exceeds 29% (of treated subjects), then further enrollment to that arm will be interrupted, and the findings will be discussed between the BMS Medical Monitor and investigators. An agreement will be reached as to whether a lower dose or an alternate dose schedule of BMS-986148 should be examined or whether any additional treatment guidelines should be implemented prior to enrollment of additional subjects on study.

3.1.3 BMS-986148 in Combination with Nivolumab (Part 3)

During the dose escalation phase with BMS-986148 and nivolumab combination therapy (Part 3A), approximately 12 evaluable subjects are expected to be treated at 2 doses of BMS-986148 (0.8 mg/kg and 1.2 mg/kg Q3W) and nivolumab (360 mg Q3W) combination therapy. In the BMS-986148 and nivolumab combination therapy dose expansion phase (Part 3B), approximately 25 to 26 evaluable subjects will be treated at each tumor cohort.

3.1.3.1 Part 3A (Dose Escalation)

Selection of Dose Levels to be Evaluated

The starting dose of BMS-986148 to be combined with nivolumab at 360 mg Q3W in Part 3A will be 0.8 mg/kg administered IV Q3W.

Approximately 12 subjects will be enrolled in ascending dose cohorts starting with a dose of BMS-986148 (0.8 mg/kg IV Q3W, first dose level) with nivolumab 360 mg administered Q3W in a 21-day cycle. Subsequent escalation to 1.2 mg/kg Q3W of BMS-986148 (or MTD determined from Part 1A) in combination with nivolumab 360 mg Q3W will be guided by the mTPI design described below. In the event that the first dose level of BMS-986148 is determined to exceed the MTD in combination with 360 mg Q3W of nivolumab, a lower BMS-986148 dose tested in monotherapy escalation (such as 0.4 mg/kg and/or 0.2 mg/kg) may be explored based on available safety, PK[redacted]. Nivolumab will be administered as 360 mg IV Q3W in all dose cohorts.

Intermediate doses of BMS-986148 in combination with 360 mg Q3W of nivolumab may be evaluated if agreed upon by the BMS Medical Monitor and investigators. The next dose level will not exceed 100% of the dose increment.

Dose Escalation Decision Rules

A similar mTPI design as in Part 1A will be used to guide dose escalation decisions and to select the MTD. A DLT target rate of 29% (EI = 28% to 31%) will be utilized for combination treatment to guide escalation decisions. Dose escalation decisions will be based on the total number of subjects in a dose level who were DLT evaluable and the number of DLTs, guided by the mTPI Bayesian model and posterior inference.

The number of subjects at the initial cohort of all dose levels in Part 3A will be 3 to 4. A fourth subject may be enrolled in a dose escalation cohort following agreement between the investigator and the BMS 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. The DLT evaluation period will be 21 days. Enrollment of additional cohorts at the same dose level will proceed in sample sizes of up to 3 or 4 subjects. Subsequent dose levels will follow similar cohort enrollment size and decision rules. At least 3 DLT-evaluable subjects treated at each of the dose levels in Part 3A will be required to enable a decision to escalate, add more subjects to the current dose level, or de-escalate and declare the current dose as unacceptable (exceeding the MTD). Subjects with insufficient data to establish safety during the DLT evaluation period at the dose tested (eg, omitted or reduced doses for reasons other than a DLT) may be replaced upon agreement of the BMS Medical Monitor and investigators.

Table 3.1.3.1-1: Dose Escalation Decision Guide in Combination with Nivolumab

		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	E	S	S	S	S	E	E
	3	DU	DU	D	E	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

DLT: dose-limiting toxicity; E: escalate to next higher dose level; D: de-escalate to the next lower dose level; S: stay at the current dose level; DU: unacceptable dose level, not to be re-visited.

Part 3A: Maximum Tolerated Dose Determination

Similar to the MTD determination in monotherapy parts, at the end of dose escalation, the cumulative number of subjects who experience a DLT at each dose level will be used to estimate the MTD using isotonic regression as the dose with the smaller difference of estimated toxicity rate and the target DLT rate (29%), among the doses used. For DLT, see Section 4.5.1.

Once the safety (during DLT evaluation) of a dose level has been determined, additional subjects may be added at that dose, to better characterize the PK, safety, and PD profile.

3.1.3.2 Part 3B (Dose Expansion)

The purpose of the cohort expansion will be to assess preliminary anti-tumor efficacy, expanded safety experience, and PD effects of BMS-986148 in combination with nivolumab. Additional subjects will be treated after the completion of Part 3A, at the MTD or at an alternate dose below the MTD as agreed upon by the BMS Medical Monitor and investigators. Five expansion cohorts will be restricted to these tumor types: 1) mesothelioma, 2) pancreatic, 3) ovarian, 4) NSCLC, and 5) gastric cancer. Enrollment in cohort expansion will be determined by the mesothelin expression of the archived tumor sample (or fresh tumor sample if archived sample is not available). [redacted]

The enrollment in each combination expansion cohort will also be guided by a Simon 2-Stage design framework (see Table 8.1-2), exploring efficacy in the [redacted].

Anti-tumor activity will be assessed initially in approximately 11 to 14 evaluable subjects per tumor type treated in a combination 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 ORR as shown in Table 8.1-2 for each tumor type with futility boundaries as follows: after Stage 1, if 0 or 1 of the first 11 evaluable subjects in the gastric or pancreatic cohorts, 0 or 1 of the first 14 in the evaluable ovarian cohorts, ≤ 2 of the first 12 with mesothelioma cohort, or ≤1 in the first 10 in the NSCLC cohort show clinical activity, enrollment in the cohort meeting criteria may be stopped.

Evaluation of efficacy will occur independently in each tumor cohort. At the time of the Stage 1 efficacy assessment, subjects will be enrolled to include sufficient numbers in both the [redacted] populations to allow an initial (Stage 1) efficacy assessment. If there is a lack of signal for preliminary efficacy (number of responders not exceeding the boundary), and after evaluation of all available data, enrollment may be stopped in that population. Otherwise, additional subjects will be treated in Stage 2 for the population in which there was an initial signal. [redacted]

As described for the monotherapy expansion, the above numbers are approximate, and enrollment may continue during the evaluation of the interim data.

Of note, fresh tumor biopsy at screening and on treatment will be mandatory for 10 ovarian cancer subjects and for 10 gastric cancer subjects enrolled in Part 3B. Fresh tumor biopsy at screening and on-treatment will be optional for subjects with other indications. [redacted]

Safety monitoring of subjects enrolled in the Part 3B portion of the study will be the same as that conducted during the dose escalation portion. During Part 3, if in a given arm the combined incidence of study drug-related AEs that require dose modification exceeds 31% (of treated subjects), then further enrollment to that arm will be interrupted, and the findings will be discussed between the BMS Medical Monitor and investigators. An agreement will be reached as to whether a lower dose or an alternate dose schedule of BMS-986148 in combination with nivolumab should be examined or whether any additional treatment guidelines should be implemented prior to enrollment of additional subjects on study.

3.1.4 Administration of Additional Treatment Cycles (Part 3)

In Part 3 of this study, all subjects will be treated for 24 weeks (up to 8 cycles) of BMS-986148 in combination with nivolumab unless criteria for study drug discontinuation are met earlier (Section 3.5). All subjects completing approximately 24 weeks of study therapy with ongoing disease control (CR, PR, or SD) may be eligible for an additional 24 weeks of study therapy at the originally assigned dose regimen in both escalation and cohort expansion beyond the initial 24 weeks, on a case-by-case basis, after careful evaluation and discussion with the BMS Medical Monitor to determine whether the benefit/risk ratio supports administration of further study therapy. Upon completion of 24 weeks of study therapy (or up to a maximum of 48 weeks if applicable), all subjects will enter the clinical/safety Follow-up period.

Following every 2 treatment cycles (every 6 weeks [Q6W] for Part 3), the decision to treat a subject with additional cycles of study therapy will be based on radiological tumor assessments (initial evaluation performed at baseline and every 2 cycles or every 6 weeks). Treatment decisions related to subject management will be based exclusively on Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1 or Modified RECIST for malignant pleural mesothelioma (see Appendix 4).[58] Assessments of PR and CR must be confirmed at least 4 weeks following initial assessment. Subjects with an overall response of CR, PR, or SD will continue therapy until they develop CR confirmed, develop progressive disease, experience clinical deterioration, develop AEs requiring discontinuation of treatment, or withdraw consent. Individual subjects with confirmed CR will be given the option to continue BMS-986148 in combination with nivolumab on a case-by-case basis after specific consultation and agreement between the investigator and BMS Medical Monitor in settings where benefit/risk justify continuation of study therapy.

3.1.5 Treatment Beyond Progression

Treatment beyond progression in Part 3 of this study may be allowed in select subjects with initial RECIST version 1.1 or Modified RECIST for malignant pleural mesothelioma-defined progressive disease after discussion and agreement with the BMS Medical Monitor that the benefit/risk assessment favors continued administration of study therapy (eg, subjects are continuing to experience clinical benefit as assessed by the investigator, tolerating treatment, and meeting other criteria specified in Section 4.6).

3.1.6 Follow-Up

Subjects who develop toxicity requiring discontinuation of treatment will enter the Follow-up period. Subjects should be seen in follow up at least every 30 days, until the AE has resolved to baseline, stabilized, or been deemed irreversible. After completion of the Follow-up period, subjects will then enter the Survival Follow-up period. During this period, clinic visits or telephone contact every 3 months will be performed to assess survival status. The duration of this period is detailed in Section 3.1. Subjects in Survival Follow-up who have progression of disease will be eligible to receive anti-cancer therapy as appropriate.

3.1.7 Retreatment during Survival Follow-Up (Part 3)

Retreatment may be allowed in Part 3 of this study with disease progression during follow-up. Subjects completing approximately 24 weeks of study therapy (or up to a maximum of 48 weeks if applicable), who enter Survival Follow-up with ongoing disease control (CR, PR, or SD) for reasons other than drug-related toxicity, may be eligible for retreatment, upon subsequent confirmed disease progression within 12 months of the last dose of study drug, on a case-by-case basis, after careful evaluation and discussion with the BMS Medical Monitor to determine whether the benefit/risk ratio supports administration of further study therapy. Subjects meeting criteria for retreatment will be treated up to an additional approximately 24 weeks with the originally assigned dose regimen (eg, same dose and dose schedule administered during the first 24 weeks) or modified dose regimen, unless that dose and schedule were subsequently found to exceed the MTD, in which case the subject will be treated at the next lower or alternate dose and schedule (see Table 4.5.2-1). Subjects entering this phase will follow the schedule as outlined in Table 5.5.1-4. Samples for PK will be collected less frequently (Table 5.5.1-4). [redacted]

3.2 Post-Study Access to Therapy

At the end 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 subject MUST fulfill the required eligibility criteria prior to dosing on Day 1. No exceptions will be granted.

3.3.1 Inclusion Criteria

1) Signed Written Informed Consent

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

2) Target Population

a) Subjects must have histological confirmation of one of the following solid tumors for participation in the study:

i) Pancreatic cancer

ii) NSCLC (adenocarcinoma ONLY)

iii) Ovarian cancer (except mucinous carcinoma)

iv) Gastric cancer

v) Pleural or peritoneal mesothelioma (EXCLUDING sarcamatoid mesothelioma)

b) For dose escalation phase: Subjects with advanced or metastatic solid tumors must have received and either progressed or been intolerant to a minimum of ONE standard treatment regimen.

c) For the dose expansion phase: Subjects with advanced or metastatic solid tumors must have received and either progressed or been intolerant to standard treatment regimens. [redacted]

i) Pancreatic cancer

(a) Documented locally advanced, unresectable or metastatic pancreatic cancer who have failed (or are not candidates for) standard therapy.

ii) NSCLC

(a) Must have recurrent or progressive disease during or after platinum doublet-based chemotherapy for advanced or metastatic disease OR must have recurrent or progressive disease within 6 months after completing platinum-based chemotherapy for local disease.

(b) Subjects must have known epidermal growth factor receptor (EGFR), anaplastic lymphoma kinase (ALK) status, ROS1, and receptor tyrosine kinase mutational status.

(c) Subjects with an activating EGFR mutation must have received an EGFR tyrosine kinase inhibitor.

(d) Subjects with an ALK translocation must have received an ALK inhibitor.

(e) Subjects must have received prior immunotherapy, if available (such as, but not limited to, PD-1/PD-L1 inhibitors, applicable for Parts 1 and 2 monotherapy).

iii) Ovarian cancer

(a) Histologically or cytologically documented epithelial ovarian cancer, primary peritoneal carcinoma, or fallopian tube cancer.

(b) Completed at least 1 platinum-based therapy (PBT) regimen (carboplatin, cisplatin, or another organoplatinum compound).

(c) Evidence of platinum-resistant disease, relapse/progression within 6 months of the completion of PBT, or intolerant to PBT (inability to receive PBT due to hypersensitivity reactions to platinum).

(d) Documenetd germline BRCA mutation status, if known. If unknown, subjects must consent to allow submitted archived tumor tissue sample (block or unstained slides) to be tested.

iv) Gastric cancer

(a) Histologically confirmed, unresectable or metastatic gastric adenocarcinoma.

(b) Treatment with 1 to 2 prior chemotherapy regimens given in the metastatic setting for unresectable or metastatic gastric carcinoma.

(c) Documented HER2 mutation status, if known. If unkown, subjects must consent to allow submitted archived tumor tissue sample (block or unstained slides) to be tested.

v) Mesothelioma

(a) Subjects must have histologically confirmed pleural or peritoneal mesothelioma not amenable to potentially curative surgical resection.

(b) Subjects must have had at least 1 prior platinum-containing chemotherapy regimen.

d) All subjects must have at least 1 measurable lesion at baseline by computed tomography (CT) or magnetic resonance imaging (MRI) as per RECIST version 1.1 or Modified RECIST criteria for malignant pleural mesothelioma (see Appendix 4).[58]

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

e) All subjects must have archival tumor tissue (if slides are provided, will require minimum of 10 cut slides [details of epitope stability are provided in the lab manual]) identified and available [redacted]. All subjects must consent to provide tumor blocks or slides to the Sponsor, and the availability of the tissue must be confirmed prior to subjects receiving study medication. However, if an archived tumor specimen is unavailable or unsuitable [redacted], subjects may consent to a pre-treatment fresh tumor biopsy to be eligible for this study if it can be performed at minimal acceptable clinical risk as judged by the investigator and if it is not in a target lesion or a lesion in an area treated with prior radiation therapy. [redacted]

f) Fresh tumor biopsy at screening and on treatment will be mandatory for 10 ovarian cancer subjects and 10 gastric cancer subjects enrolled in Parts 2 and 3B of the study.

g) For indications other than ovarian and gastric cancer, subjects have the option to provide consent to obtain a fresh, pre-treatment biopsy in Parts 2 and 3B of the study. If consent is given to obtain this pre-treatment biopsy, then a fresh on-treatment biopsy will be mandatory.

h) Life expectancy of at least 3 months

i) ECOG performance status score 0 to 1 (See Appendix 5)

3) 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 randomized/has not been treated). If re-enrolled, the subject must be re-consented.

4) Previous Treatment

a) Prior anti-cancer treatments are permitted (ie, chemotherapy, radiotherapy, hormonal, or immunotherapy).

b) Toxicity (except for alopecia) related to prior anti-cancer therapy and/or surgery must either have resolved, returned to baseline or Grade 1, or been deemed irreversible.

c) At least 4 weeks for cytotoxic agents must have elapsed from last dose of prior anti-cancer therapy and the initiation of study therapy.

d) At least 4 weeks or 5 half-lives for noncytotoxic agents (whichever is shorter) must have elapsed from last dose of prior anti-cancer therapy and the initiation of study therapy. If 5 half-lives is shorter than 4 weeks, agreement with BMS Medical Monitor is mandatory.

5) Age and Reproductive Status

a) Males and females, 18 years of age or greater 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) within 24 hours prior to the start of study drug.

c) Women must not be breastfeeding. WOCBP must agree to follow instructions for method(s) of contraception for the duration of treatment with BMS-986148 monotherapy plus 5 half-lives of the total antibody (approximately 60 days) plus 30 days (duration of ovulatory cycle) for a total of 90 days post-treatment completion (Part 1 and Part 2).

WOCBP must agree to follow instructions for method(s) of contraception for the duration of treatment with BMS-986148 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 (Part 3).

d) Males who are sexually active with WOCBP must agree to follow instructions for method(s) of contraception for the duration of treatment with BMS-986148 monotherapy plus 5 half-lives of the total antibody (approximately 60 days) plus 90 days (duration of sperm turnover) for a total of 150 days post-treatment completion (Part 1 and Part 2). If treated with BMS-986148 and nivolumab combination, 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 (Part 3).

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

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

At a minimum, subjects must agree to use 1 highly effective method listed below:

Highly Effective Methods of Contraception

Highly effective methods of contraception have a failure rate of < 1% when used consistently and correctly. WOCBP and female partners of male subjects, who are WOCBP, are expected to use 1 of the highly effective methods of contraception listed below for at least 4 weeks before dosing. Male subjects must inform their female partners who are WOCBP of the contraceptive requirements of the protocol and are expected to adhere to using contraception with their partner. Contraception methods are as follows:

- Progestogen only hormonal contraception associated with inhibition of ovulation
- Hormonal methods of contraception, including oral contraceptive pills containing combined estrogen + progesterone, vaginal ring, injectables, implants, and intrauterine devices (IUDs) such as Mirena®
- Nonhormonal IUDs, such as ParaGard®
- Bilateral tubal occlusion
- Vasectomized partner with documented azoospermia 90 days after procedure
  - Vasectomized partner is a highly effective birth control method provided that partner is the sole sexual partner of the WOCBP trial participant and that the vasectomized partner has received medical assessment of the surgical success.
- Intrauterine hormone-releasing system

- Complete abstinence
  - Complete abstinence is defined as the complete avoidance of heterosexual intercourse (refer to Glossary of Terms).
  - Complete abstinence is an acceptable form of contraception for all study drugs and must be used throughout the duration of the study treatment (plus 5 half-lives of the study drug plus 30 days for females, or plus 90 days for males).
  - It is not necessary to use any other method of contraception when complete abstinence is elected.
  - Female subjects who choose complete abstinence must continue to have pregnancy tests, as specified in Section 6.4.
  - Acceptable alternate methods of highly effective contraception must be discussed in the event that the subject chooses to forego complete abstinence.
  - The reliability of sexual abstinence needs to be evaluated in relation to the duration of the clinical trial and the preferred and usual lifestyle of the subject.

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

Unacceptable Methods of Contraception

- Periodic abstinence (calendar, symptothermal, postovulation methods)
- Withdrawal (coitus interruptus)
- Spermicide only
- Lactation amenorrhea method

3.3.2 Exclusion Criteria

1) Target Disease Exceptions

a) Subjects with known or suspected brain metastases or brain as the only site of disease

b) However, subjects with controlled brain metastases (no radiographic progression at least 4 weeks following radiation and/or surgical treatment, no new or progressive neurological signs or symptoms, and off glucocorticoids for at least 4 weeks) will be allowed

2) Medical History and Concurrent Diseases

a) A serious, uncontrolled medical disorder which would impair the ability of the subject to receive protocol therapy

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

c) Any major surgery within 4 weeks of study drug administration.

d) Subjects with concomitant second malignancies (except adequately treated nonmelanomatous 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

e) Uncontrolled or significant cardiovascular disease including:

i) Congestive heart failure NYHA Class 2 or greater within 3 months (Appendix 6)

ii) LVEF < the institutional lower limit of normal as determined by MUGA or echocardiogram

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

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

v) Troponin (T or I) > the institutional upper limit of normal (ULN)

vi) History of myocarditis of any etiology

f) NCI CTCAE v4.03 Grade 2 or higher peripheral neuropathy (sensory or motor)

g) Grade 2 of higher eye disorders (inclusive of all NCI CTCAE v4.03 criteria). Mild eye symptoms such as blurry vision, either age-related or due to ocular or systemic disorder (eg, diabetes, dry eyes, cataracts, uncorrected refraction abnormality) may be allowed at the discretion of the ophthalmologist if deemed as not constituting a predisposition to drug-induced corneal deposits and blurry vision.

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

i) **For Part 3 only :** Active, known, or suspected autoimmune disease

- Participants with well-controlled asthma and/or mild allergic rhinitis (seasonal allergies) are eligible
- Participants with the following disease conditions are also eligible:
  - Vitiligo
  - Type 1 diabetes mellitus
  - Residual hypothyroidism due to autoimmune condition only requiring hormone replacement
  - Euthyroid participants with a history of Grave's disease (participants suspected autoimmune thyroid disorders must be negative for thyroglobulin and thyroid peroxidase antibodies and thyroid stimulating immunoglobulin prior to first dose of study drug)

j) Psoriasis not requiring systemic treatment or conditions not expected to recur in the absence of an external trigger are permitted to enroll.

3) Physical and Laboratory Test Findings

a) Inadequate bone marrow function defined as:

i) Absolute neutrophil count < 1,500 cells/mm3

ii) Platelet count < 100,000 cells/mm3

iii) Hemoglobin < 9.0 g/dL

b) Subjects with a stable chronic transfusion requirement (eg, due to cumulative toxicity from previous therapy) of no more than once per month will be allowed if the trough hemoglobin is ≥ 8.0 g/dL.

c) Inadequate hepatic function defined as:

i) TB > 1.5 times the institutional ULN (except known Gilbert's syndrome)

ii) ALT or AST > 3 times the institutional ULN

d) Inadequate renal function defined as:

i) Blood creatinine > 1.5 times the institutional ULN or creatinine clearance (CrCl) < 40 mL/min (measured using the Cockcroft-Gault formula below):

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

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

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

ii) QTcF ≥ 450 msec for males, ≥ 470 msec for females, except right bundle branch block

f) Past or active hepatitis B or C infection (Does not include positive serologies resulting from passive transfer of antibodies, eg, intravenous immunoglobulin). Hepatitis B surface antigen and hepatitis C antibody (if hepatitis C antibody is positive reflex to hepatitis C ribonucleic acid [RNA]) or hepatitis C RNA will be done at screening for Part 3. Subjects with the following will be excluded:

1. Positive test for hepatitis B surface antigen
2. Positive test for qualitative hepatitis C viral load by polymerase chain reaction (PCR)

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

– Additional testing or substitute testing per institutional guidelines to rule out infection is permitted.

g) Subjects with known or suspected human immunodeficiency virus (HIV). No HIV testing is required during screening unless required locally.

4) Allergies and Adverse Drug Reaction

a) History of allergy to mesothelin-directed antibodies, tubulysin, monoclonal antibodies, or related compounds.

5) Prohibited Treatments or Therapies

a) Prior exposure to BMS-986148 or other mesothelin-directed monoclonal antibodies or ADCs

b) Exposure to any investigational drug within 4 weeks for cytotoxic agents

c) For noncytotoxic agents, investigational drug exposure within 4 weeks or 5 half-lives (whichever is shorter) is prohibited. If 5 half-lives is shorter than 4 weeks, agreement with BMS Medical Monitor is mandatory.

d) Subjects with prior exposure to therapy with any agent specifically targeting checkpoint pathway inhibition (such as anti-PD-1, anti-PD-L1, anti-PD-L2, anti-LAG-3, and anti-CTLA-4 antibody) are permitted after a washout period of any time greater than 4 weeks from the last treatment.

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

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

g) Exposure to any investigational drug concurrent with study drug administration.

h) Use of medications causing Torsades de Pointes within 1 week or 5 half-lives (whichever is longer) (see Appendix 7).

6) Other Exclusion Criteria

a) Prisoners or subjects who are involuntarily incarcerated

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

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

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

3.3.3 Women of Childbearing Potential

WOCBP is defined as any female who has experienced menarche, 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 > 40 mIU/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 periods below are suggested guidelines and the investigators should use their judgement in checking serum FSH levels. If the serum FSH level is > 40 mIU/ml at any time during the washout period, the woman can be considered postmenopausal.

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

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

3.4 Concomitant Treatments

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

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

3.4.1 Prohibited and/or Restricted Treatments

Prohibited and/or restricted medications taken prior to study drug administration in the study are described in Section 3.3.2. Medications taken within 4 weeks prior to study drug administration and until AEs and SAEs are collected in the Follow-up Period (until Day 60 post-treatment for Parts 1 and 2 and Day 100 for Part 3) must be recorded on the CRF; however, anti-cancer treatments will be collected during the Follow-up period. Medications for the treatment of SAEs will also be collected.

Concomitant medications are collected within 4 weeks prior to and during retreatment.

Specific medications that may not be administered concomitantly with BMS-986148 include the following:

- Concurrent chemotherapy, immunotherapy regimens, or radiation therapy, standard or investigational
- Any investigational drug other than BMS-986148 or nivolumab
- Medications causing Torsades de Pointes (See Appendix 7)
- The following medications are prohibited during the study unless utilized to treat a drug-related AE (**this criteria applies only to the BMS-986148 and nivolumab combination therapy in Part 3**):
  - Immunosuppressive agents
  - Immunosuppressive doses of systemic corticosteroids (except as stated below)
    - Subjects with a condition requiring systemic treatment with either corticosteroids (> 10 mg daily prednisone equivalent) or other immunosuppressive medications within 14 days of the first dose of study drug are excluded. Inhaled or topical steroids and adrenal replacement steroid doses > 10 mg daily prednisone equivalent are permitted in the absence of active autoimmune disease.

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

3.4.2 Guidelines for the Management of Infusion Reactions

In case of hypersensitivity reactions, the investigator should institute treatment measures deemed medically appropriate in accordance with current medical practice and treatment guidelines. Prophylactic premedication will not be routinely given before the first dose of Cycle 1. Prophylactic medication to prevent future infusion reactions may be considered after discussion and agreement between investigator(s) and the BMS Medical Monitor. Infusion reactions should be graded according to NCI CTCAE v4.03 guidelines and recorded in the CRF. Treatment recommendations are provided and may be modified based on local treatment standards and guidelines, as appropriate: In the case of infusion reactions during nivolumab administration, subsequent infusion times for individual subjects may be extended at the discretion of the investigator.

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

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

For Grade 2 symptoms (moderate reaction; requires therapy or infusion interruption but responds promptly to symptomatic treatment [eg, antihistamines, nonsteroidal anti-inflammatory drugs, narcotics, corticosteroids, 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 diphenhydramine 50 mg IV (or equivalent) and/or acetaminophen/paracetamol 325 to 1000 mg; remain at bedside and monitor subject until resolution of symptoms. Corticosteroid therapy and/or bronchodilator may also be administered as appropriate.
- 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 drug will be administered at that visit.
- The amount of study drug infused must be recorded on the CRF.
- The following prophylactic premedications are recommended for future infusions: diphenhydramine 50 mg (or equivalent), acetaminophen/paracetamol 325 to 1000 mg, and/or corticosteroids (up to 25 mg of hydrocortisone or equivalent) 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 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 1:1,000 solution for subcutaneous administration, 0.3 mg of a 1:1,000 solution for intramuscular administration, or 0.1 to 0.25 mg of a 1:10,000 solution slowly for IV administration, and/or 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.
- The amount of study drug infused must be recorded on the CRF.
- For Grade 3 infusion reactions that resolve within 6 hours, the following prophylactic premedications are recommended for future infusions: diphenhydramine 50 mg (or equivalent), acetaminophen/paracetamol 325 to 1000 mg, and/or corticosteroids (up to 25 mg of hydrocortisone or equivalent) should be administered at least 30 minutes before additional BMS-986148 administrations. Remain at bedside and monitor subject until recovery from symptoms.
- For a Grade 3 infusion reaction that does not resolve in 6 hours and Grade 4 infusion reactions, study drug will be permanently discontinued.
- Investigators should follow their institutional guidelines for the treatment of anaphylaxis.
- Remain at bedside and monitor subject until recovery from symptoms.
- In the case of late-occurring hypersensitivity symptoms (eg, appearance of a localized or generalized pruritus within 1 week after treatment), symptomatic treatment may be given (eg, oral antihistamine or corticosteroids).

3.5 Discontinuation of Subjects following any Treatment with Study Drug

Subjects MUST discontinue investigational product (and noninvestigational product at the discretion of the investigator) for any of the following reasons:

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

- Confirmed CR as defined by RECIST version 1.1 or Modified RECIST for malignant pleural mesothelioma (see Appendix 4)[58] unless subject meets criteria to continue treatment with nivolumab
- Documented disease progression as defined by RECIST version 1.1 or Modified RECIST criteria for malignant pleural mesothelioma (see Appendix 4) unless subject meets criteria for treatment beyond progression (Section 4.5) (for subjects in Part 3)
- AE(s) requiring discontinuation as outlined in the Dose Modification section (See Section 4.5.2)

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

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

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

3.6 Post-Study Drug Follow Up

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

BMS may request that survival data be collected on all treated subjects outside of the protocol-defined window (Table 5.1-2 through Table 5.1-8). 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 a third-party representative to assist in the follow-up portion of the study has been included in the subject's informed consent, then the investigator may use a Sponsor-retained third-party representative to assist site staff with obtaining subject's contact information or other public vital status data necessary to complete the follow-up portion of the study. The site staff and representative will consult publicly available sources, such as public health registries and databases, in order to obtain updated contact information. If after all attempts, the subject remains lost to follow-up, then the last known alive date as determined by the investigator should be reported and documented in the subject's medical records.

4 STUDY DRUG

Study treatment includes both investigational medicinal product (IMP)/investigational product (IP) and noninvestigational medicinal product (NIMP)/non-IP and can consist of the following:

- All products being tested in a clinical trial.
- Study required premedication, and other drugs administered as part of the study that are critical to claims of efficacy (eg, background therapy, rescue medications)
- Diagnostic agents (such as glucose for glucose challenge) given as part of the protocol requirements must also be included in the dosing data collection.

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

Table 4-1: Study Drugs for CA008002

Product Description Class and Dosage Form	Potency	IP/NIMP	Blinded or Open Label	Packaging/Appearance	Storage Conditions (per Label)
BMS-986148-01 for Injection	50 mg/vial	IP	Open	10 cc vial/White to off white, whole or fragmented cake in a vial Lyophilized	Protect from light Store at 2°C to 8°C
Nivolumab	100 mg/ vial (10 mg/mL)	IP	Open	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 - 46°F) Protect from light. Protect from freezing.

IP: investigational product; NIMP: non-investigational medicinal product.

4.1 Investigational Product

Study treatment is defined as any investigational treatment(s), marketed product(s), placebo or medical device intended to be administered to a study participant according to the study randomization or treatment allocation. An investigational product, also known as an IMP 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 investigational product should be stored in a secure area according to local regulations. It is the responsibility of the investigator to ensure that investigational product is only dispensed to study subjects. The investigational product must be dispensed only from official study sites by authorized personnel according to local regulations.

4.2 Noninvestigational Product

Other medications used as support or escape medication for preventative, diagnostic, or therapeutic reasons, as components of the standard of care for a given diagnosis, may be considered noninvestigational products. Not applicable for this study.

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.

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).

BMS-986148 Preparation

BMS-986148 is supplied as a sterile, nonpyrogenic, single use, preservative-free lyophilized cake with a strength of 50 mg/vial that must be reconstituted and diluted prior to dosing the subject as an IV injection formulation. A sufficient excess of BMS-986148 is incorporated into each vial to account for withdrawal losses.

Solutions for infusion are prepared by injecting a specific volume of BMS-986148 drug product and normal saline into an empty 50-cc IV infusion bag (supplied by the site) to yield appropriate solutions for infusion.

BMS-986148-01 for injection is to be administered as an IV infusion, following reconstitution with sterile water for injection, and further dilution with normal saline (0.9% w/v sodium chloride) to concentrations appropriate for the dosing cohort.

Instructions for the drug product preparation, administration, and storage are provided in the pharmacy manual.

BMS-986148 Administration

The administration of the entire bag contents (or the amount needed if the total dose is less than 50 mg) should be infused within approximately 60 minutes through an IV infusion set (sterile, nonpyrogenic, low protein binding, polyethersulfone 0.2-µm in-line filter) (supplied by the site). Care must be taken to ensure the sterility of the prepared solution, as the drug product does not contain antimicrobial preservatives or bacteriostatic agents. Equilibration to room temperature is recommended for the drug product, infusion fluid, and their combination prior to administration.

Reconstituted (with sterile water for injection) and diluted solutions (in normal saline) of BMS-986148-01 for injection are stable for up to 24 hours, at either refrigerated conditions, 2°C to 8°C (36°F to 46°F), and light protected or 4 hours at room temperature conditions, 15°C to 25°C (59°F to 77°F), under ambient light. The constituted vial and diluted bag should not be shaken. Infusion of BMS-986148-01 injection must be completed within 24 hours of dilution. The start of drug infusion equals 0 hour.

For subjects receiving nivolumab in combination with BMS-986148, subjects should receive nivolumab at a dose of 360 mg as a 30-minute infusion on Day 1 of each 21-day treatment cycle until disease progression, unacceptable toxicity, withdrawal of consent, or the study ends, whichever occurs first.

For combination treatment in Part 3, BMS-986148 will be administered as an infusion up to 60 minutes. The infusion line containing BMS 986148 should be flushed with an appropriate amount of diluent to ensure that the entire dose is administered and that the infusion line is cleared of any remaining BMS-986148. The nivolumab dose would then be infused not less than 30 minutes from the completion of the BMS-986148 infusion, which would then be infused over a period of 30 minutes.

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

Refer to the IB for additional details about BMS-986148.

Nivolumab Preparation

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 acute infusion reaction is noted, subjects should be managed according to Section 4.5. 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, or discontinued depending on how well the subject tolerates the treatment. Dosing visits are not skipped, only delayed.

Nivolumab is administered as an IV infusion over 30 minutes. At the end of 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-986148 on the same day.

For details regarding drug storage, preparation, administration, and use time, refer to the nivolumab IB and/or Pharmacy Manual.

4.4 Method of Assigning Subject Identification

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

Until an IWRS/IVRS 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 phase (Parts 1A, 1B, and 3A), if a subject discontinues treatment with BMS-986148 during the DLT 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 BMS Medical Monitor and investigators.

IWRS/IVRS 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 dose level as listed in sequential order during dose escalation (see Section 3.1.1). Subjects in the expansion cohorts will be enrolled at or below the

MTD as agreed upon by the BMS Medical Monitor and investigators (see Section 3.1.2). See Section 3.1.3 for combination therapy guidelines.

4.5.1 Dose Limiting Toxicities

For the purpose of guiding dose escalation, DLTs will be defined based on incidence, intensity, and duration of AEs for which no clear alternative cause is identified. The DLT evaluation period for dose escalation in Part 1A is 21 days. The DLT evaluation period for dose escalation in Part 1B is 28 days and subjects must receive 3 doses during this period (unless DLT has occurred) to be considered evaluable for dose escalation decisions. The DLT evaluation period for dose escalation in Part 3A is 21 days. AEs will be graded according to the NCI CTCAE v4.03. For the purpose of subject management, any AE that meets DLT criteria, regardless of the cycle in which it occurs, will lead to dose interruption. Subjects who withdraw from the study during the DLT evaluation interval for reasons other than a DLT may be replaced at the same dose level. The incidence of DLT(s) during the first cycle of treatment (the DLT evaluation period) will be used in dose escalation decisions and to define the MTD. AEs occurring after the DLT period will be considered for the purposes of defining the MTD, upon agreement between the BMS Medical Monitor and investigators, if they are determined to have no clear alternative cause and are not related to disease progression.

For Part 3A, every attempt must be made to assign relationship to BMS-986148, to nivolumab, or to both.

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

Nonhematologic DLT

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

- ≥ Grade 2 uveitis or eye pain or reduction in visual acuity (defined as 20/40 or worse and at least 2-line reduction from baseline visual acuity and accompanied by symptoms limiting age appropriate instrumental activities of daily living [ADL] or diagnostic observations) that requires systemic treatment
- ≥ Grade 2 uveitis or eye pain or reduction in visual acuity (defined as 20/40 or worse and at least 2-line reduction from baseline visual acuity and accompanied by symptoms limiting age appropriate instrumental ADL or diagnostic observations) that does not respond to topical therapy and that does not improve to Grade 1 within 2 weeks of initiation of topical therapy

- ≥ Grade 3 infusion-related reactions that recur despite appropriate medical management as in Section 3.4.1
- ≥ Grade 3 nonhematologic toxicity, with the following exceptions.

  The following Grade 3 or greater nonhematologic events will NOT be considered DLTs:

  - ≥ Grade 3 electrolyte abnormalities that are not complicated by associated clinical AEs, are not clinically significant, last less than 72 hours, and either resolve spontaneously or respond to conventional medical intervention.
  - Grade 3 elevations in serum transaminases (AST, ALT) or alkaline phosphatase that last ≤ 5 days and are not associated with clinical symptoms, and bilirubin is not greater than 2× the ULN in the absence of cholestasis.
  - Grade 3 nausea, vomiting, or diarrhea that lasts less than 48 hours and either resolves spontaneously or responds to conventional medical intervention.
  - ≥ Grade 3 elevations of amylase or lipase that are not associated with clinical or radiographic evidence of pancreatitis.
  - Isolated Grade 3 fever that is not associated with hemodynamic compromise (ie, hypotension, clinical or laboratory evidence of impaired end-organ perfusion).
  - Grade 3 endocrinopathy that is well controlled by hormone replacement.
  - Grade 3 tumor flare (defined as pain, irritation, or rash that localizes to sites of known or suspected tumor)
  - Grade 3 fatigue that lasts for less than 7 days.
  - Grade 3 infusion reaction that returns to Grade 1 in less than 6 hours.

Hematologic DLT

- Grade 4 neutropenia > 5 days in duration
- Grade 4 febrile neutropenia of any duration
- Grade 3 febrile neutropenia
- Grade 4 thrombocytopenia or Grade 3 thrombocytopenia associated with clinically significant bleeding
- ≥ Grade 3 hemolysis
- Grade 4 anemia

4.5.2 Guidelines for Dose Modifications

Subjects will be monitored continuously for AEs while on study therapy. Subjects will be instructed to notify their physician immediately for any and all AEs. For the purposes of subject management, drug-related AEs occurring at any time that meet the DLT definition will lead to dose interruption, dose modifications, and/or permanent discontinuation of study drug as defined in Table 4.5.2-1 and in this section. The criteria presented in this section and Table 4.5.2-1 for dose modifications and delays are meant as general guidelines.

- Subjects will continue to receive therapy as long as they have not had disease progression, meet discontinution criteria, or drug-related AE requiring dose modification as described below.
- Dose modification, interruption, or delay may occur in the setting of lower grade AE and/or be more conservative than indicated in Table 4.5.2-1 based on the clinical judgment of the investigator and in consultation with the BMS Medical Monitor.
- Dose reductions in this study are applicable to the administration of BMS-986148 and should be to the previous lower dose level. There are no dose reductions for nivolumab (applicable for Part 3).
- If several AEs of varying grade or severity occur simultaneously, the dose modification applied should be the greatest reduction of BMS-986148 applicable.
- Assessment of causality (chronology, confounding factors such as disease, concomitant medications, diagnostic tests, and previous experience with the agent) must be determined and documented by the investigator prior to dose modification.
- If the same ≥ Grade 3 nonhematologic AE recurs despite a dose reduction, a second dose reduction versus discontinuation of the subject from further protocol therapy will be discussed and agreed upon by the BMS Medical Monitor and investigators.
- No more than 2 dose reductions of BMS-986148 will be allowed per subject. If a third dose reduction is required, the subject must discontinue study drug. Dose re-escalation after a dose reduction may occur in limited circumstances (such as a change in attribution of an AE) after discussion and agreement of the BMS Medical Monitor and investigators.
- Skipped BMS-986148 doses in Part 1B will not be administered within the same cycle.
- For an AE requiring dose modification, study drugs should be interrupted to allow recovery from the AE. Re-initiation of study drug cannot occur until AE decreases to ≤ Grade 1 or baseline assessment (See exception for Part 3 below in Section 4.5.4). In case of delayed recovery to ≤ Grade 1 or baseline (except for alopecia) from treatment-related AEs that results in a delay of treatment for > 30 days, the subject will not receive additional protocol-related therapy (applies to BMS-986148 monotherapy in Parts 1 and 2) and will still continue in follow-up periods unless discussed and agreed upon by the BMS Medical Monitor and investigators that it is in the best interest of the subject to receive additional therapy with BMS-986148 (for example, if the subject has demonstrated a response to therapy). For dose delay in Part 3, see below.
- For additional dose modifications pertinent to nivolumab (Part 3), see Sections 4.5.3 through 4.5.5 below.
- During the DLT evaluation period, if a subject is dose reduced and experiences a DLT at the lower dose, this DLT will be attributed to the highest dose level administered.

Table 4.5.2-1: Dose Modifications

Dose Modification Criteria for Drug-Related Adverse Events	BMS-986148 (Parts 1, 2, and 3) (Modification at Next Dose)
Grade 4 neutropenia lasting > 5 days	Decrease 1 level.
Grade 3 febrile neutropenia lasting > 48 hours	Decrease 1 level.
Grade 4 febrile neutropenia	Discontinue.
Grade 4 thrombocytopenia or ≥ Grade 3 thrombocytopenia with clinically significant bleeding	Decrease 1 level.
QTcF > 500 msec confirmed by at least 1 repeat ECG and at least 60 msec above baseline	Interrupt if needed to optimize electrolyte management; if persists after electrolyte optimization (including dose modification of BMS-986148, if necessary), discontinue.
Grade 1 Troponin I or T confirmed when repeated in 72 hours	Discontinue.
Grade 3 Troponin I or T	Discontinue.
AST or ALT > 5 times the institutional ULN that last ≥ 5 days or is symptomatic	Decrease 1 level.
≥ Grade 3 infusion-related reaction	See Section 3.4.1.
≥ Grade 3 peripheral neuropathy	Discontinue.
≥ Grade 2 uveitis or eye pain or reduction in visual acuity[a] that improve to Grade 1 within 2 weeks of initiation of topical therapy	Interrupt dosing until improvement to Grade 1 or baseline and decrease 1 level.
≥ Grade 2 uveitis or eye pain or reduction in visual acuity[a] that does not respond to topical therapy and that does not improve to Grade 1 within 2 weeks of initiation of topical therapy	Discontinue. After improvement to Grade 1 or baseline, additional therapy with BMS-986148 (decrease 1 level) may be considered after discussion and agreement by the BMS Medical Monitor and investigators that it is in the best interest of the subject (for example, if the subject has demonstrated a response to therapy).
≥ Grade 3 eye symptoms	Discontinue.

Table 4.5.2-1: Dose Modifications

Dose Modification Criteria for Drug-Related Adverse Events	BMS-986148 (Parts 1, 2, and 3) (Modification at Next Dose)
Any other drug-related ≥ Grade 3 nonhematologic AE (except in subjects not receiving maximum medical management or electrolyte abnormalities that may be managed with supplements) that does not meet permanent discontinuation criteria (Section 3.5).	Decrease 1 level.

[a] Reduction in visual acuity is defined as 20/40 or worse and at least 2-line reduction from baseline visual acuity and accompanied by symptoms limiting age appropriate instrumental ADL or diagnostic observations.

ADL: activities of daily living; AE: adverse event; ALT: alanine transaminase; AST: aspartate transaminase; ECG: electrocardiogram; PI: principal investigator; QTcF: QT interval corrected by Fridericia's formula; ULN: upper limit of normal.

4.5.3 Dose Delay Criteria (Applicable for Part 3)

Subjects who experience a DLT must have both study drugs held. Every attempt must be made to assign relationship to BMS-986148, to nivolumab, or to both. If the toxicity is attributed to BMS-986148 (eg, early onset liver function tests [LFT] abnormalities or AEs similar to profile determined from monotherapy cohorts) will lead to dose modification of BMS-986148 according to Table 4.5.2-1 and nivolumab can be resumed. Similarly if the toxicitiy is attributed to nivolumab (eg, pneumonitis), dosing of nivolumab can be delayed or discontinued per the guidelines below and BMS-986148 can be resumed. Such modifications should be discussed and agreed upon by the BMS Medical Monitor and investigators. In addition, all Grade 2 hepatic, pulmonary, renal, gastrointestinal, and neurological AEs seen with nivolumab should be evaluated and managed per the toxicity management algorithms (Appendix 3). Subjects not meeting guidelines for permanent discontinuation will be permitted to resume therapy based on the criteria specified in Table 4.5.2-1. Subjects eligible to resume study therapy will resume study therapy at the treatment visit following their last received study drug dose.

The end-of-cycle tumor assessments (ie, CT/MRI, positron emission tomography, etc) will continue on an every-6-week schedule relative to the subject's first dose regardless of any treatment delay incurred.

Study drug administration should be delayed for the following:

- Any Grade ≥ 2 nonskin, drug-related AE, with the following exception:
  - Grade 2 drug-related fatigue does not require a treatment delay.
- Grade 2 drug-related creatinine, AST, ALT, or TB abnormalities
- Any Grade 3 skin, drug-related AE
- Any Grade 3 drug-related laboratory abnormality (excluding AST, ALT, or TB), with the following exceptions for lymphopenia and asymptomatic amylase or lipase:
  - Grade 3 lymphopenia does not require dose delay.
  - Any Grade ≥ 3 drug-related amylase or lipase abnormality that is not associated with symptoms or clinical manifestations of pancreatitis does not require dose delay.
- Any AE, laboratory abnormality, or intercurrent illness that, in the judgment of the investigator, warrants delaying the dose of study medication.

Subjects who require delay of study drugs should be re-evaluated QW or more frequently if clinically indicated and resume nivolumab dosing when retreatment criteria are met.

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

4.5.4 Criteria to Resume Treatment for Part 3

Subjects may resume treatment with study drugs when the drug-related AE(s) resolves to Grade ≤ 1 or baseline value, with the following exceptions:

- Subjects may resume treatment in the presence of Grade 2 fatigue.

- Subjects who have not experienced a Grade 3 drug-related skin AE may resume treatment in the presence of Grade 2 skin toxicity.
- For subjects with Grade 2 creatinine, AST, ALT, or TB 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 TB values meeting discontinuation parameters (Section 3.5) 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.

4.5.5 Study Drug Discontinuation (Part 3)

In certain circumstances of nivolumab-related AE's requiring discontinuation that do not overlap with known BMS-986148 toxicities, eg, pneumonitis, BMS-986148 can be resumed after discussion with the Sponsor/Medical Monitor if is in the best interest of the subject to receive additional therapy with BMS-986148 (for example, if the subject has demonstrated a response to therapy):

- Any drug-related AE occurring at any time that meets DLT criteria as outlined in Section 4.5.1 will require discontinuation of nivolumab and/or dose modification of BMS-986148 (Table 4.5.2-1), with the exception of the following:
  - Grade 3 diarrhea, nausea, vomiting, or abdominal pain that returns to Grade 1 or baseline within 3 days with medical intervention
  - Grade 3 pruritus or rash that returns to Grade 1 or baseline within 7 days, or baseline with medical intervention;
  - Isolated Grade 3 or 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 neutropenia < 5 days in duration
  - Grade 4 lymphopenia or leukopenia
  - Grade 3 or 4 increase in amylase or lipase that is not associated with clinical or radiographic evidence of pancreatitis
  - Grade 3 or 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

- ♦ Dosing delays to allow for prolonged steroid tapers to manage drug-related AEs are allowed. Prior to reinitiating treatment in a subject with a dosing delay lasting > 6 weeks from the previous dose, the BMS Medical Monitor must be consulted. Tumor assessments should continue as per protocol even if dosing is delayed. Periodic study visits to assess safety and laboratory studies should also continue Q6W for Parts 1A, 2, and 3 and every 8 weeks [Q8W] for Part 1B or more frequently if clinically indicated during such dosing delays.
- ♦ Dosing delays lasting > 6 weeks from the previous dose that occur for nondrug-related reasons may be allowed if approved by the BMS Medical Monitor. Prior to reinitiating treatment in a subject with a dosing delay lasting > 6 weeks, the BMS Medical Monitor must be consulted. Tumor assessments should continue as per protocol even if dosing is delayed. Periodic study visits to assess safety and laboratory studies should also continue Q6W or more frequently if clinically indicated during such dosing delays.

- Any AE, laboratory abnormality, or intercurrent illness, which, in the judgment of the investigator, presents a substantial clinical risk to the subject with continued nivolumab dosing.

4.6 Treatment beyond Disease Progression

Accumulating evidence indicates a minority of subjects treated with immunotherapy may derive clinical benefit despite initial evidence of progressive disease.

Subjects treated with study drugs will be permitted to continue treatment beyond initial RECIST version 1.1-defined progressive disease, 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, central nervous system 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 progressive disease. 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 subject continues to achieve clinical benefit by continuing treatment with the study drugs, the subject should remain on the trial and continue to receive monitoring according to the Time and Events Schedule (see Section 5.1).

4.6.1 Discontinuation Due to Further Progression (Confirmed Progression)

For the subjects who continue 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 progressive disease. 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 progressive disease. Study 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 least15 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.

For statistical analyses that include the investigator-assessed progression date, subjects who continue treatment beyond initial investigator-assessed, RECIST version 1.1-defined progressive disease will be considered to have investigator-assessed progressive disease at the time of the initial progression event.

4.7 Management Algorithms for Immuno-oncology Agents

Immuno-oncology (I-O) agents are associated with AEs that can differ in severity and duration than 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 and Appendix 3 of this protocol.

4.8 Blinding/Unblinding

Not applicable.

4.9 Treatment Compliance

Study drug will be administered in the clinical facility by qualified 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 BMS-986148 administration in subjects' medical records and CRF. Drug supplies will be inventoried and accounted for throughout the study. The Drug Accountability Log should 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.

4.10 Destruction of Study Drug

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

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

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

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

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

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

4.11 Return of Study Drug

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

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

5 STUDY ASSESSMENTS AND PROCEDURES

5.1 Flow Chart/Time and Events Schedule

Study assessments and procedures are presented in Table 5.1-2 through Table 5.1-8. The study assessments and procedures tables corresponding to each part of the study are outlined in Table 5.1-1. In limited instances, scheduled events can occur outside of the indicated timeframes, but BMS should be notified.

Table 5.1-1: List of Study Parts and Corresponding Study Assessments and Procedures Tables

Part of Study	Table
1A	Table 5.1-2, Screening and Cycle 1 Table 5.1-3, Cycle 2 to Off Study Visit
1B	Table 5.1-4, Screening and Cycle 1 Table 5.1-5, Cycle 2 to Off Study Visit
2	Table 5.1-2 and Table 5.1-4, Screening and Cycle 1 for Q3W and QW dosing, respectively Table 5.1-3 and Table 5.1-5, Cycle 2 to Off Study Visit for Q3W and QW dosing, respectively
3A	Table 5.1-6, Screening and Cycle 1 Combination Therapy Table 5.1-7, Cycle 2 to Off Study Visit Combination Therapy Table 5.1-8, Part 3 Retreatment (Part 3 subjects only)
3B	Table 5.1-6, Screening and Cycle 1 Combination Therapy Table 5.1-7, Cycle 2 to Off Study Visit Combination Therapy Table 5.1-8, Part 3 Retreatment (Part 3 subjects only)

Table 5.1-2: Screening and Cycle 1, Parts 1A and 2 (Q3W BMS-986148 Monotherapy Dosing / 21 Day Cycle) Procedural Outline (CA008002)

Procedure[a]	Pre-Screening	Screening Visit D-28 to D-1	C1D1	C1D2	C1D4[b]	C1D8	C1D15	Notes
Eligibility Assessments								
Informed Consent		X						A subject is considered enrolled only when a protocol specific informed consent is signed. In Part 2, if allowed by institutional practices, sites are encouraged to use a pre-screening consent for the mesothelin-expressing tumor analysis. Other screening procedures should not be done before the mesothelin-expressing tumor analysis is available for the determination of subject eligibility.
Inclusion/Exclusion Criteria		X						
ECOG		X	X					
Medical History		X						Also include any toxicities or allergy related to previous treatments. Smoking history for all subjects.
[redacted]								
Prior Treatments		X						Including prior cancer treatment regimens and medications administered within 4 weeks of dosing.
Safety Assessments								
PE		X	X					If the screening PE is performed within 24 hours prior to dosing on Day 1, then a single exam may count as both the screening and pre-dose evaluation. A neurological exam must be included at the screening or pre-dose at the C1D1 visit.

Table 5.1-2: Screening and Cycle 1, Parts 1A and 2 (Q3W BMS-986148 Monotherapy Dosing / 21 Day Cycle) Procedural Outline (CA008002)

Procedure[a]	Pre-Screening	Screening Visit D-28 to D-1	C1D1	C1D2	C1D4[b]	C1D8	C1D15	Notes
Targeted PE						X	X	To include signs and symptoms of peripheral neuropathy and ocular toxicity. Any grade ocular toxicity requires ophthalmologist consultation and discussion with medical monitor as appropriate.
Ophthalmological Examination[c]		X						Performed by ophthalmologist or locally qualified personnel. Any abnormality must be discussed with the medical monitor prior to dosing.
Physical Measurements		X	X					Height (screening only), weight.
Vital Signs[d]		X	X			X	X	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	X	X		X		ECGs should be recorded after the subject has been supine for at least 5 minutes. Triplicate ECGs should be taken within 5 minutes of the previous measurement. For ALL subjects in Part 1 and up to 20 subjects in Part 2: time matched for PK; triplicate evaluations at C1D1 pre-dose and EOI, C1D2 (24 hours post dose), and C1D8 (168 hours post dose) AND at C4D1 pre-dose and EOI, C4D2 (24 hours post dose), and C4D8 (168 hours post dose). QTcF assessment > 450 msec must be confirmed on repeat ECG.
MUGA/Echocardiogram		X						MUGA or echocardiogram done at screening to document LVEF. Echocardiogram done at the start of Cycle 3, then evey 3 cycles thereafter, and as clinically indicated for the evaluation of pericardial

Table 5.1-2: Screening and Cycle 1, Parts 1A and 2 (Q3W BMS-986148 Monotherapy Dosing / 21 Day Cycle) Procedural Outline (CA008002)

Procedure[a]	Pre-Screening	Screening Visit D-28 to D-1	C1D1	C1D2	C1D4[b]	C1D8	C1D15	Notes
								effusion.
Laboratory Tests		X	X	X	X	X	X	If the screening laboratory tests are performed within 24 hours prior to dosing on Day 1, then a single exam may count as both the screening and pre-dose evaluation. See Section 5.3.1 Urine - screening only, unless clinically indicated. C1D4 and C4D4: CBC only.
Troponin T or I		X	X			X	X	During Part 1 only. The same evaluation must be collected throughout the study.
Pregnancy Test		X	X					
PK and Immunogenicity Assessments (See Section 5.5)								
Biomarker Assessments [redacted]								
[redacted]								
Tumor Sample (or Archival) Part 2: Required for Eligibility	X Part 2 only	X (Part 1A and if not pre-screened in Part 2)						In Part 2, subjects must have tumor mesothelin expression (refer to Section 5.6 for additional details on specific cut-off selection criteria). No other protocol-specific eligibility procedures/assessment should be conducted until the tumor mesothelin expression is confirmed. Tumor material from archived samples will be used for the IHC analyses. If archived tumor material is

Table 5.1-2: Screening and Cycle 1, Parts 1A and 2 (Q3W BMS-986148 Monotherapy Dosing / 21 Day Cycle) Procedural Outline (CA008002)

Procedure[a]	Pre-Screening	Screening Visit D-28 to D-1	C1D1	C1D2	C1D4[b]	C1D8	C1D15	Notes
								unavailable or unsuitable for evaluation, then tumor material from a fresh biopsy must be provided for these analyses. If archived tumor material is to be used, then a tumor paraffin block or unstained slides from a tumor tissue block must be provided. [redacted] Every effort should be made to provide 20 slides (minimum of 10 slides) for mesothelin IHC testing. Individual sample availability should be discussed with the Sponsor if at least 10 slides are not available for any subject.
Mandatory Fresh Tumor Biopsy Part 2 Only		X						For 10 ovarian cancer subjects and 10 gastric cancer subjects who consent to provide pre- and on-treatment biopsies (C2D1 ±3 days).
Optional Fresh Tumor Biopsy Part 2 Only								For subjects with indications other than ovarian cancer and gastric cancer who consent to provide pre- and on-treatment biopsies (C2D1 ±3 days).
Tumor Assessment		X						Baseline must be within approximately 30 days of C1D1.
Tumor Markers (CA125 and CA19-9)			X					At the time of tumor assessments: serum CA125 for ovarian cancer **and** mesothelioma subjects only, serum CA19-9 for pancreatic cancer subjects only. Baseline sample collection pre-dose on C1D1.
Concomitant Treatments			X	X	X	X	X	

Table 5.1-2: Screening and Cycle 1, Parts 1A and 2 (Q3W BMS-986148 Monotherapy Dosing / 21 Day Cycle) Procedural Outline (CA008002)

Procedure[a]	Pre-Screening	Screening Visit D-28 to D-1	C1D1	C1D2	C1D4[b]	C1D8	C1D15	Notes
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 Non-SAEs			X	X	X	X	X	Non-SAEs will be collected starting with the first dose of study medication and through 60 days after discontinuation of dosing.
Monitor for SAEs		X	X	X	X	X	X	All SAEs must be collected from the date of subject's written consent until 60 days from the last dose of study drug or subject's participation in the study if the last scheduled visit occurs at a later time.
Clinical Drug Supplies								
Dose Level Assignment		X						At the completion of screening procedures and eligibility determination.
BMS-986148 Administration			X					Those supplied by BMS.

[a] In the event multiple procedures are required at a single time point, the following is a list of procedures from highest priority to low: 1) ECG, 2) PK sampling, and 3) clinical labs.

[b] C1D4 visit: ± 1 day.

[c] Ophthalmological examination: 8-point exam (visual acuity, pupils, extraocular motility and alignment, tonometry, visual field, external examination, slit lamp examination and fundoscopy) conducted at baseline and focused exams with visual acuity, slit lamp, and as indicated will be conducted at the end of Cycle 1 (pre-dose Cycle 2), every other cycle, EOT, and as clinically indicated during the study.

[d] During Cycle 1: vital signs will be obtained before the BMS-986148 infusion and then every 15 minutes (± 5 minutes) until 60 minutes after completion of the infusion. After Cycle 1, vital signs may be obtained pre-dose, every 30 minutes (± 10 minutes) until 30 minutes following completion of the 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).

[redacted] C: cycle; CBC: complete blood cell (count); CRF: case report form; D: day; [redacted] ECG: electrocardiogram; ECOG: Eastern Cooperative Oncology Group; EOI: end of infusion; EOT: end of treatment; IHC: immunohistochemistry; LVEF: left ventricular ejection fraction; MUGA: multigated acquisition; PE: physical examination; PK: pharmacokinetics; Q3W: every 3 weeks; QTcF: QT interval corrected by Fridericia's formula; SAE: serious adverse event.

Table 5.1-3: Cycle 2 to Off Study Visit, Parts 1A and 2 (Q3W Dosing BMS-986148 Monotherapy Dosing / 21 Day Cycle) Procedural Outline (CA008002)

Procedure[a]	C2 and C3			C4					C5 and Beyond	EOT	Follow-up (30 and 60 Days After Last Dose)	Survival Follow-up[b]	Notes
	D1	D8	D15	D1	D2	D4[c]	D8	D15	D1		(±5 days)	(±2 weeks)	
Safety Assessments													
Targeted PE	X	X	X	X					X	X	X		To include signs and symptoms of peripheral neuropathy and ocular toxicity. Any ocular toxicity requires ophthalmologist consultation and discussion with medical monitor as appropriate.
Ophthalmological Examination[d]	Start of Cycle 2, every 2 cycles thereafter and as clinically indicated									X			Performed by ophthalmologist or locally qualified personnel. Any abnormality must be discussed with the medical monitor prior to dosing. Ophthalmological exams can be done up to 72 hours prior to dosing.
Physical Measurements	X			X					X	X	X		Weight only.
Vital Signs[e]	X	X	X	X					X	X	X		See note in screening procedures.
ECGs	X			X	X		X		X	X	X		See note in screening procedures.

Table 5.1-3: Cycle 2 to Off Study Visit, Parts 1A and 2 (Q3W Dosing BMS-986148 Monotherapy Dosing / 21 Day Cycle) Procedural Outline (CA008002)

Procedure[a]	C2 and C3			C4					C5 and Beyond	EOT	Follow-up (30 and 60 Days After Last Dose)	Survival Follow-up[b]	Notes
	D1	D8	D15	D1	D2	D4[c]	D8	D15	D1		(±5 days)	(±2 weeks)	
Echocardiogram	Start of Cycle 3, then every 3 cycles thereafter, and as clinically indicated.									X			On treatment echocardiogram exams may be done up to 72 hours prior to dosing.
Laboratory Tests	X	X	X	X		X			X	X	X		See note in screening procedures and Section 5.3.1. Lab tests can be performed up to 24 hours prior to dosing. C4D4 (CBC only) collection to be time matched with PK collection pre-dose.
Mandatory Fresh Tumor Biopsy Part 2 Only	X												C2D1 (±3 days). For 10 ovarian cancer subjects and 10 gastric cancer subjects who provided pre-treatment biopsies.
Optional FreshTumor Biopsy Part 2 Only	X												C2D1 (±3 days). For subjects with indications other than ovarian cancer and gastric cancer who provide pre-treatment biopsies.
Pregnancy Test	X			X					X	X	X		

Table 5.1-3: Cycle 2 to Off Study Visit, Parts 1A and 2 (Q3W Dosing BMS-986148 Monotherapy Dosing / 21 Day Cycle) Procedural Outline (CA008002)

Procedure[a]	C2 and C3			C4					C5 and Beyond	EOT	Follow-up (30 and 60 Days After Last Dose)	Survival Follow-up[b]	Notes
	D1	D8	D15	D1	D2	D4[c]	D8	D15	D1		(±5 days)	(±2 weeks)	
Concomitant Treatments	X	X	X	X	X	X	X	X	X	X	X[f]		
Adverse Event Reporting													
Monitor for Non-SAEs	X	X	X	X	X	X	X	X	X	X	X		See note in screening procedures.
Monitor for SAEs	X	X	X	X	X	X	X	X	X	X	X		See note in screening procedures.
PK and Immunogenicity Assessments (See Section 5.5)													
[redacted]													
Efficacy Assessments													
Tumor Assessment	At the start of Cycle 3 and then every 2 cycles thereafter (±1 week).									X	X[g]	X[h]	See Section 5.4.1.
Tumor Markers (CA125 and CA19-9)	At the start of Cycle 3 and then every 2 cycles thereafter (±1 week).									X	X	X	See note in screening procedures. Baseline sample collection pre-dose on C1D1.
Clinical Drug Supplies													
BMS-986148 Administration	X			X					X				Those supplied by BMS.
Other													
Survival Follow-up												X[i]	

[a] In the event multiple procedures are required at a single time point, the following is a list of procedures from highest priority to low: 1) ECG, 2) PK sampling, and 3) clinical labs.

[b] In the Survival Follow-up, subjects discontinuing study drug prior to 2 years will be followed for up to 2 years from first dose of study drug. Subjects treated for > 2 years will be followed for 6 months after EOT.

[c] C4D4: ± 1 day.

[d] Ophthalmological examination: 8-point exam (visual acuity, pupils, extraocular motility and alignment, tonometry, visual field, external examination, slit lamp examination and fundoscopy) conducted at baseline and focused exams with visual acuity, slit lamp, and as indicated will be conducted at the end of Cycle 1 (pre-dose Cycle 2), every other cycle, EOT and as clinically indicated during the study.

[e] Vital signs will be obtained before the BMS-986148 infusion and then every 30 minutes (± 10 minutes) until 30 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).

[f] Only anti-cancer treatments.

[g] Only at the 60-day follow-up visit, unless discontinued for disease progression.

[h] Subjects with SD, PR, or CR at the last clinical follow-up visit should undergo tumor assessment via CT/MRI scans at least every 3 to 4 months during the Survival Follow-up (Section 8.3.2.2) phase until progression.

[i] Subject status will be assessed by either a clinic visit or telephone contact every 12 weeks (± 2 weeks) until the last treated subject has been followed for 2 years from his/her first 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 at these telephone contacts. Subjects will be permitted to receive other anti-cancer therapies, including investigational agents, during this follow-up period once the 60-day follow-up visit is completed.

C: cycle; CBC: complete blood cell (count); CR: complete response; CT: computed tomography; D: day; ECG: electrocardiogram; EOT: end of treatment; MRI: magnetic resonance imaging; PE: physical examination; PK: pharmacokinetics; PR: partial response; Q3W: every 3 weeks; SAE: serious adverse event; SD: stable disease.

Table 5.1-4: Screening and Cycle 1, Part 1B (Weekly Dosing BMS-986148 Monotherapy Dosing / 28 Day Cycle) Procedural Outline (CA008002)

Procedure[a]	Pre-Screening	Screening Visit D-28 to D-1	C1D1	C1D2	C1D4[b]	C1D8	C1D15	C1D22	Notes
Eligibility Assessments									
Informed Consent		X							A subject is considered enrolled only when a protocol specific informed consent is signed. In Part 2, if allowed by institutional practices, sites are encouraged to use a pre-screening consent for the mesothelin-expressing tumor analysis. Other screening procedures should not be done before the mesothelin-expressing tumor analysis is available for the determination of subject eligibility.
Inclusion/Exclusion Criteria		X							
ECOG		X	X						
Medical History		X							Also include any toxicities or allergy related to previous treatments. Smoking history for all subjects.
[redacted]									
Prior Treatments		X							Including prior cancer treatment regimens and medications administered within 4 weeks of dosing.

Table 5.1-4: Screening and Cycle 1, Part 1B (Weekly Dosing BMS-986148 Monotherapy Dosing / 28 Day Cycle) Procedural Outline (CA008002)

Procedure[a]	Pre-Screening	Screening Visit D-28 to D-1	C1D1	C1D2	C1D4[b]	C1D8	C1D15	C1D22	Notes
Safety Assessments									
PE		X	X						If the screening PE is performed within 24 hours prior to dosing on Day 1, then a single exam may count as both the screening and pre-dose evaluation. A neurological exam must be included at screening or pre-dose at the C1D1 visit.
Targeted PE						X	X	X	To include signs and symptoms of peripheral neuropathy and ocular toxicity. Any grade ocular toxicity requires ophthalmologist consultation and discussion with medical monitor as appropriate.
Ophthalmological Examination[c]		X							Performed by ophthalmologist or locally qualified personnel. Any abnormality must be discussed with the medical monitor prior to dosing.
Physical Measurements		X	X						Height (screening only), weight.
Vital Signs[d]		X	X			X	X	X	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.

Table 5.1-4: Screening and Cycle 1, Part 1B (Weekly Dosing BMS-986148 Monotherapy Dosing / 28 Day Cycle) Procedural Outline (CA008002)

Procedure[a]	Pre-Screening	Screening Visit D-28 to D-1	C1D1	C1D2	C1D4[b]	C1D8	C1D15	C1D22	Notes
ECGs		X	X	X		X	X		ECGs should be recorded after the subject has been supine for at least 5 minutes. Triplicate ECGs should be taken within 5 minutes of the previous measurement. For ALL subjects in Part 1 and up to 20 subjects in Part 2: time matched for PK; triplicate evaluations at C1D1 pre-dose and EOI, C1D2 (24 hours post dose), and C1D8 (168 hours post dose) AND at C4D1 pre-dose and EOI, C4D2 (24 hours post dose), and C4D8 (168 hours post dose). QTcF assessment > 450msec must be confirmed on repeat ECG.
MUGA/Echocardiogram		X							MUGA or echocardiogram done at screening to document LVEF. Echocardiogram done at the start of Cycle 3, then evey 3 cycles thereafter, and as clinically indicated for the evaluation of pericardial effusion.
Laboratory Tests		X	X	X	X	X	X	X	If the screening laboratory is performed within 24 hours prior to dosing on Day 1, then a single exam may count as both the screening and pre-dose evaluation. See Section 5.3.1, Urine - screening only, unless clinically indicated. C1D4 and C4D4: CBC only.

Table 5.1-4: Screening and Cycle 1, Part 1B (Weekly Dosing BMS-986148 Monotherapy Dosing / 28 Day Cycle) Procedural Outline (CA008002)

Procedure[a]	Pre-Screening	Screening Visit D-28 to D-1	C1D1	C1D2	C1D4[b]	C1D8	C1D15	C1D22	Notes
Troponin I or T		X	X			X	X	X	For Part 1 only. The same evaluation must be collected throughout the study.
Pregnancy Test		X	X			X	X		
PK and Immunogenicity Assessments (See Section 5.5)									
Biomarker Assessments [redacted]									
[redacted]									
Tumor Sample (or Archival) Part 2: Required for Eligibility	X								For Part 2, subjects must have tumor mesothelin expression [redacted] No other protocol-specific eligibility procedures/assessment should be conducted until the tumor mesothelin expression is confirmed. Tumor material from archived samples will be used for the IHC analyses. If archived tumor material is unavailable or unsuitable for evaluation, then tumor material from a fresh biopsy must be provided for these analyses. If archived tumor material is to be used, then a tumor paraffin block or unstained slides from a tumor tissue

Table 5.1-4: Screening and Cycle 1, Part 1B (Weekly Dosing BMS-986148 Monotherapy Dosing / 28 Day Cycle) Procedural Outline (CA008002)

Procedure[a]	Pre-Screening	Screening Visit D-28 to D-1	C1D1	C1D2	C1D4[b]	C1D8	C1D15	C1D22	Notes
									block must be provided. [redacted] Every effort should be made to provide 20 slides (minimum of 10 slides) for mesothelin IHC testing.
Tumor Assessment		X							Baseline must be within approximately 30 days of C1D1.
Tumor Markers (CA125 and CA19-9)			X						At the time of tumor assessments: serum CA125 for ovarian cancer **and** mesothelioma subjects only, serum CA19-9 for pancreatic cancer subjects only. Baseline sample collection pre-dose on C1D1.
Concomitant Treatments			X	X	X	X	X	X	
Adverse Event Reporting									
Clinical Complaints		X							Clinical complaints related to the disease under study must be collected within 14 days of the first dose of study drug.
Monitor for Non-SAEs			X	X	X	X	X	X	Non-SAEs will be collected starting with the first dose of study medication and through 60 days after discontinuation of dosing.
Monitor for SAEs		X	X	X	X	X	X	X	All SAEs must be collected from the date of subject's written consent until

Table 5.1-4: Screening and Cycle 1, Part 1B (Weekly Dosing BMS-986148 Monotherapy Dosing / 28 Day Cycle) Procedural Outline (CA008002)

Procedure[a]	Pre-Screening	Screening Visit D-28 to D-1	C1D1	C1D2	C1D4[b]	C1D8	C1D15	C1D22	Notes
									60 days from the last dose of study drug or subject's participation in the study if the last scheduled visit occurs at a later time.
Clinical Drug Supplies									
Dose Level Assignment		X							At the completion of screening procedures and eligibility determination.
BMS-986148 Administration			X			X	X		Those supplied by BMS.

[a] In the event multiple procedures are required at a single time point, the following is a list of procedures from highest priority to low: 1) ECG, 2) PK sampling, and 3) clinical labs.

[b] C1D4: ± 1 day.

[c] Ophthalmological examination: 8-point exam (visual acuity, pupils, extraocular motility and alignment, tonometry, visual field, external examination, slit lamp examination and fundoscopy) conducted at baseline and focused exams with visual acuity, slit lamp, and as indicated will be conducted at the end of Cycle 1 (pre-dose Cycle 2), every other cycle, EOT and as clinically indicated during the study.

[d] Cycle 1, Day 1: vital signs will be obtained before the BMS-986148 infusion and then every 15 minutes (± 5 minutes) until 60 minutes after completion of the infusion. During subsequent treatment visits, vital signs may be obtained every 30 minutes (± 10 minutes) until 30 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).

[redacted] C: cycle; CBC: complete blood cell (count); CRF: case report form; D: day; [redacted] ECG: electrocardiogram; ECOG: Eastern Cooperative Oncology Group; EOI: end of infusion; EOT: end of treatment; IHC: immunohistochemistry; LVEF: left ventricular ejection fraction; MUGA: multigated acquisition; PE: physical examination; PK: pharmacokinetics; QTcF: QT interval corrected by Fridericia's formula; SAE: serious adverse event.

Table 5.1-5: Cycle 2 to Off Study Visit, Part 1B (Weekly Dosing BMS-986148 Monotherapy Dosing / 28 Day Cycle) Procedural Outline (CA008002)

Procedure[a]	C2 and C3				C4					C5 and Beyond			EOT	Follow-up (30 and 60 Days After Last Dose)	Survival Follow-up[b]	Notes
	D1	D8	D15	D22	D1	D2	D4[c]	D8	D15	D1	D8	D15		(±5 days)	(±2 weeks)	
Safety Assessments																
Targeted PE	X	X	X	X	X					X			X	X		To include signs and symptoms of peripheral neuropathy and ocular toxicity. Any grade ocular toxicity requires ophthalmologist consultation and discussion with medical monitor as appropriate.
Ophthalmological Examination[d]	Start of Cycle 2, every 2 cycles thereafter, and as clinically indicated.												X			Performed by ophthalmologist or locally qualified personnel. Any abnormality must be discussed with the medical monitor prior to dosing. Ophthalmological exams can be done up to 72 hours prior to dosing.
Physical	X				X					X			X	X		Weight only.

Table 5.1-5: Cycle 2 to Off Study Visit, Part 1B (Weekly Dosing BMS-986148 Monotherapy Dosing / 28 Day Cycle) Procedural Outline (CA008002)

Procedure[a]	C2 and C3				C4					C5 and Beyond			EOT	Follow-up (30 and 60 Days After Last Dose)	Survival Follow-up[b]	Notes
	D1	D8	D15	D22	D1	D2	D4[c]	D8	D15	D1	D8	D15		(±5 days)	(±2 weeks)	
Measurements																
Vital Signs[e]	X	X	X	X	X			X	X	X			X	X		See note in screening procedures.
ECGs	X				X	X		X	X	X			X	X		See note in screening procedures.
Echocardiogram	Start of Cycle 3, then every 3 cycles thereafter, and as clinically indicated.												X			On treatment echocardiogram exams may be done up to 72 hours prior to dosing.
Laboratory Tests	X	X	X	X	X		X	X	X	X			X	X		See note in screening procedures and Section 5.3.1. Lab tests can be performed up to 24 hours prior to dosing. C4D4 (CBC only) collection to be time matched with PK collection pre-dose.

Table 5.1-5: Cycle 2 to Off Study Visit, Part 1B (Weekly Dosing BMS-986148 Monotherapy Dosing / 28 Day Cycle) Procedural Outline (CA008002)

Procedure[a]	C2 and C3				C4					C5 and Beyond			EOT	Follow-up (30 and 60 Days After Last Dose)	Survival Follow-up[b]	Notes
	D1	D8	D15	D22	D1	D2	D4[c]	D8	D15	D1	D8	D15		(±5 days)	(±2 weeks)	
Tumor Biopsy (Fresh) Part 2 Only	X															C2D1 (±3 days). For 10 ovarian cancer subjects and 10 gastric cancer subjects who provided pre-treatment biopsies.
Pregnancy Test	X	X	X		X			X	X	X	X	X	X	X		
Concomitant Treatments	X	X	X	X	X	X	X	X	X	X	X	X	X	X[f]		
Adverse Event Reporting																
Monitor for Non-SAEs	X	X	X	X	X	X	X	X	X	X	X	X	X	X		See note in screening procedures.
Monitor for SAEs	X	X	X	X	X	X	X	X	X	X	X	X	X	X		See note in screening procedures.
PK and Immunogenicity Assessments (See Section 5.5)																
[redacted]																
Efficacy Assessments																
Tumor Assessment	At the start of Cycle 3 and then every 2 cycles thereafter (±1 week).												X	X[g]	X[h]	See Sections 5.3.1 and 5.4.1.
Tumor Markers (CA125 and	At the start of Cycle 3 and then every 2 cycles thereafter (±1 week).												X	X	X	See note in screening procedures. Baseline

Table 5.1-5: Cycle 2 to Off Study Visit, Part 1B (Weekly Dosing BMS-986148 Monotherapy Dosing / 28 Day Cycle) Procedural Outline (CA008002)

Procedure[a]	C2 and C3				C4					C5 and Beyond			EOT	Follow-up (30 and 60 Days After Last Dose)	Survival Follow-up[b]	Notes
	D1	D8	D15	D22	D1	D2	D4[c]	D8	D15	D1	D8	D15		(±5 days)	(±2 weeks)	
CA19-9)																sample collection pre-dose on C1D1.
Clinical Drug Supplies																
BMS-986148 Administration	X	X	X		X			X	X	X	X	X				Those supplied by BMS.
Other																
Survival Follow-up															X[i]	

[a] In the event multiple procedures are required at a single time point, the following is a list of procedures from highest priority to low: 1) ECG, 2) PK sampling, and 3) clinical labs.

[b] In the Survival Follow-up, subjects discontinuing study drug prior to 2 years will be followed for up to 2 years from first dose of study drug. Subjects treated for > 2 years will be followed for 6 months after EOT.

[c] C4D4: ± 1 day.

[d] Ophthalmological examination: 8-point exam (visual acuity, pupils, extraocular motility and alignment, tonometry, visual field, external examination, slit lamp examination and fundoscopy) conducted at baseline and focused exams with visual acuity, slit lamp, and as indicated will be conducted at the end of Cycle 1 (pre-dose Cycle 2), every other cycle, EOT and as clinically indicated during the study.

[e] Vital signs will be obtained before the BMS-986148 infusion and then every 30 minutes (± 10 minutes) until 30 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).

[f] Only anti-cancer treatments.

[g] Only at the 60-day follow-up visit, unless discontinued for disease progression.

[h] 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 Survival Follow-up (Section 8.3.2.2) phase until progression.

[i] Subject status will be assessed by either a clinic visit or telephone contact every 12 weeks (± 2 weeks) until the last treated subject has been followed for 2 years from his/her first 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 at these telephone contacts. Subjects will be permitted to receive other anti-cancer therapies, including investigational agents, during this follow-up period once the 60-day follow-up visit is completed.

C: cycle; CBC: complete blood cell (count); CR: complete response; CT: computed tomography; D: day; ECG: electrocardiogram; EOT: end of treatment; MRI: magnetic resonance imaging; PE: physical examination; PK: pharmacokinetics; PR: partial response; SAE: serious adverse event; SD: stable disease.

Table 5.1-6: Screening and Cycle 1 (Part 3: Nivolumab Combination Arm / 21 Day Cycle) Procedural Outline (CA008002)

Procedure[a]	Pre-Screening	Screening Visit D-28 to D-1	C1D1	C1D2	C1D4[b]	C1D8	C1D15	Notes
Eligibility Assessments								
Informed Consent		X						A subject is considered enrolled only when a protocol specific informed consent is signed. In Part 3B, if allowed by institutional practices, sites are encouraged to use a pre-screening consent for the mesothelin-expressing tumor analysis. Other screening procedures should not be done before the mesothelin-expressing tumor analysis is available for the determination of subject eligibility.
Inclusion/Exclusion Criteria		X						
ECOG		X	X					
Medical History		X						Also include any toxicities or allergy related to previous treatments. Smoking history for all subjects.
[redacted]								
Prior Treatments		X						Including prior cancer treatment regimens and medications administered within 4 weeks of dosing.
Safety Assessments								
PE		X	X					If the screening PE is performed within 24 hours prior to dosing on Day 1 then a single exam may count as both the screening and pre-dose evaluation.

Table 5.1-6: Screening and Cycle 1 (Part 3: Nivolumab Combination Arm / 21 Day Cycle) Procedural Outline (CA008002)

Procedure[a]	Pre-Screening	Screening Visit D-28 to D-1	C1D1	C1D2	C1D4[b]	C1D8	C1D15	Notes
								A neurological exam must be included at the screening or pre-dose at the C1D1 visit.
Targeted PE						X	X	To include signs and symptoms of peripheral neuropathy and ocular toxicity. Any grade ocular toxicity requires ophthalmologist consultation and discussion with medical monitor as appropriate.
Ophthalmological Examination[c]		X						Performed by ophthalmologist or locally qualified personnel. Any abnormality must be discussed with the medical monitor prior to dosing.
Physical Measurements		X	X					Height (screening only), weight.
Vital Signs[d]		X	X			X	X	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.
Oxygen Saturation		X						Pulse oximetry collected at rest and as clinically indicated on study.
ECGs		X	X	X		X		ECGs should be recorded after the subject has been supine for at least 5 minutes.
MUGA/Echocardiogram		X						MUGA or echocardiogram done at screening to document LVEF.
Laboratory Tests		X	X	X	X	X	X	If the screening laboratory tests are performed within 24 hours prior to dosing on Day 1 then a single exam may count as both the screening and pre-dose evaluation.

Table 5.1-6: Screening and Cycle 1 (Part 3: Nivolumab Combination Arm / 21 Day Cycle) Procedural Outline (CA008002)

Procedure[a]	Pre-Screening	Screening Visit D-28 to D-1	C1D1	C1D2	C1D4[b]	C1D8	C1D15	Notes
								Hep B surface antigen and Hep C antibody (if Hep C antibody is positive reflex to Hep C RNA) or Hep C RNA will be done at screening. Note: Testing for HIV-1 and HIV-2 must be performed at sites where mandated by local requirements. See Section 5.3.1 Urine - screening only, unless clinically indicated. C1D4: CBC only.
Thyroid Function		X						TSH with reflexive fT3 and fT4.
Troponin T or I		X	X			X	X	During Part 3A only. The same evaluation must be collected throughout the study.
Pregnancy Test		X	X					
PK and Immunogenicity Assessments (See Section 5.5)								
Biomarker Assessments [redacted]								
[redacted]								
Tumor Sample (or Archival) Part 3B: Required for Eligibility	X Part 3B only	X (Part 3A and if not pre-screened in						For Part 3B, subjects must have tumor mesothelin expression [redacted]. No other protocol-specific eligibility procedures/assessment should be conducted

Table 5.1-6: Screening and Cycle 1 (Part 3: Nivolumab Combination Arm / 21 Day Cycle) Procedural Outline (CA008002)

Procedure[a]	Pre-Screening	Screening Visit D-28 to D-1	C1D1	C1D2	C1D4[b]	C1D8	C1D15	Notes
		Part 3B)						until the tumor mesothelin expression is confirmed. Tumor material from archived samples will be used for the IHC analyses. If archived tumor material is unavailable or unsuitable for evaluation, then tumor material from a fresh biopsy must be provided for these analyses. If archived tumor material is to be used, then a tumor paraffin block or unstained slides from a tumor tissue block must be provided. [redacted] Every effort should be made to provide 20 slides (minimum of 10 slides) for mesothelin IHC testing.
Mandatory Fresh Tumor Biopsy Part 3B Only		X						For 10 ovarian cancer subjects and 10 gastric cancer subjects who consent to provide pre- and on-treatment biopsies (C2D1 ±3 days).
Optional Fresh Tumor Biopsy Part 3B Only								For subjects with indications other than ovarian and gastric cancer who consent to provide pre- and on-treatment biopsies (C2D1±3 days).
Tumor Assessment		X						Baseline must be within approximately 30 days of C1D1.

Table 5.1-6: Screening and Cycle 1 (Part 3: Nivolumab Combination Arm / 21 Day Cycle) Procedural Outline (CA008002)

Procedure[a]	Pre-Screening	Screening Visit D-28 to D-1	C1D1	C1D2	C1D4[b]	C1D8	C1D15	Notes
Tumor Markers (CA125 and CA19-9)			X					At the time of tumor assessments: serum CA125 for ovarian cancer **and** mesothelioma subjects only, serum CA19-9 for pancreatic cancer subjects only. Baseline sample collection pre-dose on C1D1.
Concomitant Treatments			X	X	X	X	X	
Adverse Event Reporting								
Clinical Complaints		X						Clinical complaints related to the disease under study must be collected within 14 days of the first dose of study drug.
Monitor for Non-SAEs			X	X	X	X	X	Non-SAEs 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	X	X	X	All SAEs must be collected from the date of subject's written consent until 100 days from the last dose of study drug or subject's participation in the study if the last scheduled visit occurs at a later time.
Clinical Drug Supplies								
Dose Level Assignment		X						At the completion of screening procedures and eligibility determination.
BMS-986148 Administration			X					Supplied by BMS.
Nivolumab Administration			X					Supplied by BMS. For Parts 3A and 3B only. See Section 4 for administration details. Observation in a clinical setting is required

Table 5.1-6: Screening and Cycle 1 (Part 3: Nivolumab Combination Arm / 21 Day Cycle) Procedural Outline (CA008002)

Procedure[a]	Pre-Screening	Screening Visit D-28 to D-1	C1D1	C1D2	C1D4[b]	C1D8	C1D15	Notes
								for 4 hours after dose administration for Cycles 1 and 2 and 1 hour after dose administration in subsequent cycles.

[a] In the event multiple procedures are required at a single time point, the following is a list of procedures from highest priority to low: 1) ECG, 2) PK sampling, and 3) clinical labs.

[b] C1D4 visit: ± 1 day.

[c] Ophthalmological examination: 8-point exam (visual acuity, pupils, extraocular motility and alignment, tonometry, visual field, external examination, slit lamp examination and fundoscopy) conducted at baseline and focused exams with visual acuity, slit lamp, and as indicated will be conducted at the end of Cycle 1 (pre-dose Cycle 2), every other cycle, EOT and as clinically indicated during the study.

[d] During Cycle 1: vital signs will be obtained before the BMS-986148 infusion and then every 15 minutes (± 5 minutes) until 60 minutes after completion of the infusion. After Cycle 1 vital signs may be obtained pre-dose, every 30 minutes (± 10 minutes) until 30 minutes following completion of the 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).

[redacted] C: cycle; CBC: complete blood cell (count); CRF: case report form; D: day; [redacted] ECG: electrocardiogram; ECOG: Eastern Cooperative Oncology Group; EOT: end of treatment; fT3: free triiodothyronine; fT4: free thyroxine; Hep: hepatitis; HIV: human immunodeficiency virus; IHC: immunohistochemistry; LVEF: left ventricular ejection fraction; MUGA: multigated acquisition; PE: physical examination; PK: pharmacokinetics; RNA ribonucleic acid; SAE: serious adverse event; TSH: thyroid-stimulating hormone.

Table 5.1-7: Cycle 2 to Off Study Visit (Part 3: Nivolumab Combination Arm / 21 Day Cycle) Procedural Outline (CA008002)

Procedure[a]	C2 and C3			C4					C5 and Beyond	EOT	Follow-up (30, 60, and 100 Days after Last Dose)	Survival Follow-up[b]	Notes
	D1	D 8	D1 5	D1	D2	D4[c]	D8	D15	D1		(±5 days)	(±2 weeks)	
Safety Assessments													
Targeted PE	X	X	X	X					X	X	X		To include signs and symptoms of peripheral neuropathy and ocular toxicity. Any ocular toxicity requires ophthalmologist consultation and discussion with medical monitor as appropriate. If a subject shows pulmonary-related signs (hypoxia, fever) or symptoms (eg, dyspnea, cough, and 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 nivolumab IB.

Table 5.1-7: Cycle 2 to Off Study Visit (Part 3: Nivolumab Combination Arm / 21 Day Cycle) Procedural Outline (CA008002)

Procedure[a]	C2 and C3			C4					C5 and Beyond	EOT	Follow-up (30, 60, and 100 Days after Last Dose)	Survival Follow-up[b]	Notes
	D1	D 8	D1 5	D1	D2	D4[c]	D8	D15	D1		(±5 days)	(±2 weeks)	
Ophthalmological Examination[d]	Start of Cycle 2, every 2 cycles thereafter and as clinically indicated									X			Performed by ophthalmologist or locally qualified personnel. Any abnormality must be discussed with the medical monitor prior to dosing. Ophthalmological exams can be done up to 72 hours prior to dosing.
Physical Measurements	X			X					X	X	X		Weight only.
Vital Signs[e]	X	X	X	X					X	X	X		See note in screening procedures.
ECGs	X			X	X		X		X	X	X		See note in screening procedures.
Echocardiogram	X			See notes						X			Echocardiogram done at the start of Cycle 2 and Cycle 3, then every 3 cycles thereafter, and as clinically indicated for the evaluation of pericardial effusion. On treatment echocardiogram exams may be done up to 72 hours prior to dosing.
Laboratory Tests	X	X	X	X		X			X	X	X		See note in screening procedures and Section 5.3.1.

Table 5.1-7: Cycle 2 to Off Study Visit (Part 3: Nivolumab Combination Arm / 21 Day Cycle) Procedural Outline (CA008002)

Procedure[a]	C2 and C3			C4					C5 and Beyond	EOT	Follow-up (30, 60, and 100 Days after Last Dose)	Survival Follow-up[b]	Notes
	D1	D8	D15	D1	D2	D4[c]	D8	D15	D1		(±5 days)	(±2 weeks)	
													Lab tests can be performed up to 24 hours prior to dosing. C4D4 (CBC only) collection to be time matched with PK collection pre-dose.
Tumor Biopsy (Fresh) (Mandatory) - Part 3B Only	X												C2D1 (±3 days). For 10 ovarian cancer subjects and 10 gastric cancer subjects who provided pre-treatment biopsies.
Tumor Biopsy (Fresh) (Optional) - Part 3B Only	X												C2D1 (±3 days). For subjects with indications other than ovarian cancer and gastric cancer.
Thyroid Function	X								Odd cycles				TSH with reflexive fT3 and fT4 to be done every 6 weeks.
Pregnancy Test	X			X					X	X	X		
Concomitant Treatments	X	X	X	X	X	X	X	X	X	X	X[f]		
Adverse Event Reporting													
Monitor for Non-SAEs	X	X	X	X	X	X	X	X	X	X	X		Collected continuously during the treatment period and for a minimum of 100 days following discontinuation of

Table 5.1-7: Cycle 2 to Off Study Visit (Part 3: Nivolumab Combination Arm / 21 Day Cycle) Procedural Outline (CA008002)

Procedure[a]	C2 and C3			C4					C5 and Beyond	EOT	Follow-up (30, 60, and 100 Days after Last Dose)	Survival Follow-up[b]	Notes
	D1	D 8	D1 5	D1	D2	D4[c]	D8	D15	D1		(±5 days)	(±2 weeks)	
													study treatment. Every AE must be assessed by the investigator with regard to whether it is considered immune-mediated. For events which are potentially immune-mediated, additional information will be collected on the subject's case report form.
Monitor for SAEs	X	X	X	X	X	X	X	X	X	X	X		See note in screening procedures.
PK and Immunogenicity Assessments (See Section 5.5)													
[redacted]													
Efficacy Assessments													
Tumor Assessment	At the start of Cycle 3 and then every 2 cycles thereafter (±1 week).									X	X[g]	X[h]	See Section 5.4.1.
Tumor Markers (CA125 and CA19-9)	At the start of Cycle 3 and then every 2 cycles thereafter (±1 week).									X	X	X	See note in screening procedures. Baseline sample collection pre-dose on C1D1.
Clinical Drug Supplies													
BMS-986148 Administration	X			X					X				Supplied by BMS.

Table 5.1-7: Cycle 2 to Off Study Visit (Part 3: Nivolumab Combination Arm / 21 Day Cycle) Procedural Outline (CA008002)

Procedure[a]	C2 and C3			C4					C5 and Beyond	EOT	Follow-up (30, 60, and 100 Days after Last Dose)	Survival Follow-up[b]	Notes
	D1	D 8	D1 5	D1	D2	D4[c]	D8	D15	D1		(±5 days)	(±2 weeks)	
Nivolumab Administration	X			X					X				Supplied by BMS. For Parts 3A and 3B 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.
Other													
Survival Follow-up												X[i]	

[a] In the event multiple procedures are required at a single time point, the following is a list of procedures from highest priority to low: 1) ECG, 2) PK sampling, and 3) clinical labs.

[b] In the Survival Follow-up, subjects discontinuing study drug prior to 2 years will be followed for up to 2 years from first dose of study drug. Subjects treated for > 2 years will be followed for 6 months after EOT.

[c] C4D4: ± 1 day.

[d] Ophthalmological examination: 8-point exam (visual acuity, pupils, extraocular motility and alignment, tonometry, visual field, external examination, slit lamp examination and fundoscopy) conducted at baseline and focused exams with visual acuity, slit lamp, and as indicated will be conducted at the end of Cycle 1 (pre-dose Cycle 2), every other cycle, EOT and as clinically indicated during the study.

[e] Vital signs will be obtained before the BMS-986148 infusion and then every 30 minutes (± 10 minutes) until 30 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).

[f] Only anti-cancer treatments.

[g] Only at the 60- and 100-day follow-up visits, unless discontinued for disease progression.

[h] Subjects with SD, PR, or CR at the last clinical follow-up visit should undergo tumor assessment via CT/MRI scans at least every 3 to 4 months during the Survival Follow-up (Section 8.3.2.2) phase until progression.

[i] Subject status will be assessed by either a clinic visit or telephone contact every 12 weeks (± 2 weeks) until the last treated subject has been followed for 2 years from his/her first 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 at these telephone contacts. Subjects will be permitted to receive other anti-cancer therapies, including investigational agents, during this follow-up period once the 100-day follow-up visit is completed.

AE: adverse event; C: cycle; CBC: complete blood cell (count); CR: complete response; CT: computed tomography; D: day; ECG: electrocardiogram; EOT: end of treatment; fT3: free triiodothyronine; fT4: free thyroxine; IB: Investigator's Brochure; MRI: magnetic resonance imaging; PE: physical examination; PK: pharmacokinetics; PR: partial response; SAE: serious adverse event; SD: stable disease; TSH: thyroid-stimulating hormone.

Table 5.1-8: Retreatment Day 0 and Cycle 1 Onwards (Part 3 Retreatment): Nivolumab Combination Arm / 21 Day Cycle) Procedural Outline (CA008002)

Procedure[a]	Day 0	C1 and Beyond D1	EOT	Follow-up (30, 60, and 100 Days after Last Dose) (±5 days)	Survival Follow-up[b] (±2 weeks)	Notes
Eligibility Assessments						
ECOG	X	X				
Medical History	X					Interim history (medical, AE or SAE) that occurred during the Survival Follow-up period that was not previously reported.
[redacted]						
Prior Treatments	X					Medications administered within 4 weeks of dosing.
Safety Assessments						
PE	X	X				If the screening PE is performed within 24 hours prior to dosing on Day 1 then a single exam may count as both the screening and pre-dose evaluation. A neurological exam must be included at the screening or pre-dose at the C1D1 visit.
Targeted PE			X	X	X	To include signs and symptoms of peripheral neuropathy and ocular toxicity. Any grade ocular toxicity requires ophthalmologist consultation and discussion with medical monitor as appropriate.
Ophthalmological Examination[c]	X		X			Performed by ophthalmologist or locally qualified personnel. Any abnormality must be discussed with the medical monitor prior to dosing. Performed on Day 0, start of Cycle 2, every 2

Table 5.1-8: Retreatment Day 0 and Cycle 1 Onwards (Part 3 Retreatment): Nivolumab Combination Arm / 21 Day Cycle) Procedural Outline (CA008002)

Procedure[a]	Day 0	C1 and Beyond D1	EOT	Follow-up (30, 60, and 100 Days after Last Dose) (±5 days)	Survival Follow-up[b] (±2 weeks)	Notes
						cycles thereafter and as clinically indicated.
Physical Measurements	X	X	X	X		Height (screening only), weight.
Vital Signs[d]	X	X	X	X		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.
Oxygen Saturation	X					Pulse oximetry collected at rest at Day 0 and as clinically indicated on study.
ECGs	X	X	X	X		ECGs should be recorded after the subject has been supine for at least 5 minutes.
MUGA/Echocardiogram	X	See notes	X			MUGA or echocardiogram done at Day 0 to document LVEF. Echocardiogram done at the start of Cycle 2 and Cycle 3, then every 3 cycles thereafter, and as clinically indicated for the evaluation of pericardial effusion
Laboratory Tests	X	X	X	X		If the Day 0 laboratory tests are performed within 24 hours prior to dosing on Day 1 then a single exam may count as both the screening and pre-dose evaluation. Repeat the following if >6 months since last treatment: Hep B surface antigen and Hep C antibody (if Hep C antibody is positive reflex to Hep C RNA) or Hep C RNA will be done at screening. Note: Testing for HIV-1 and HIV-2 must be performed at sites where mandated by local

Table 5.1-8: Retreatment Day 0 and Cycle 1 Onwards (Part 3 Retreatment): Nivolumab Combination Arm / 21 Day Cycle) Procedural Outline (CA008002)

Procedure[a]	Day 0	C1 and Beyond D1	EOT	Follow-up (30, 60, and 100 Days after Last Dose) (±5 days)	Survival Follow-up[b] (±2 weeks)	Notes
						requirements See Section 5.3.1 Urine - Day 0 only, unless clinically indicated.
Thyroid Function	X	X				TSH with reflexive fT3 and fT4 to be done every 6 weeks.
Pregnancy Test	X	X	X	X		
PK and Immunogenicity Assessments (See Table 5.5.1-4)						
[redacted]						
Tumor Assessment	X		X	X[e]	X[f]	Baseline must be within approximately 30 days of C1D1. Then at the start of Cycle 3 and then every 6 weeks thereafter (±1 week). See Section 5.4.1.
Tumor Markers (CA125 and CA19-9)	X		X	X	X	At the time of tumor assessments: serum CA125 for ovarian cancer and mesothelioma subjects only, serum CA19-9 for pancreatic cancer subjects only. Baseline sample collection pre-dose on C1D1.
Concomitant Treatments	X	X	X	X[g]		
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 Non-SAEs		X	X	X		Non-SAEs will be collected starting with the

Table 5.1-8: Retreatment Day 0 and Cycle 1 Onwards (Part 3 Retreatment): Nivolumab Combination Arm / 21 Day Cycle) Procedural Outline (CA008002)

Procedure[a]	Day 0	C1 and Beyond D1	EOT	Follow-up (30, 60, and 100 Days after Last Dose) (±5 days)	Survival Follow-up[b] (±2 weeks)	Notes
						first dose of study medication and through 100 days after discontinuation of dosing.
Monitor for SAEs	X	X	X	X		All SAEs must be collected from the date of subject's written consent until 100 days from the last dose of study drug
Clinical Drug Supplies						
Dose Level Assignment	X					At the completion of Day 0 procedures and eligibility assessements (see above) cofirmed.
BMS-986148 Administration		X				Supplied by BMS.
Nivolumab Administration		X				Supplied by BMS. 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.
Other						
Survival Follow-up					X[h]	

[a] In the event multiple procedures are required at a single time point, the following is a list of procedures from highest priority to low: 1) ECG, 2) PK sampling, and 3) clinical labs.

[b] In the Survival Follow-up, subjects discontinuing study drug prior to 2 years will be followed for up to 2 years from first dose of study drug. Subjects treated for > 2 years will be followed for 6 months after EOT.

[c] Ophthalmological examination: 8-point exam (visual acuity, pupils, extraocular motility and alignment, tonometry, visual field, external examination, slit lamp examination, and fundoscopy) conducted at baseline and focused exams with visual acuity, slit lamp, and as indicated will be conducted at the end of Cycle 1 (pre-dose Cycle 2), every other cycle, EOT, and as clinically indicated during the study.

[d] Vital signs will be obtained before the BMS-986148 infusion and then every 30 minutes (± 10 minutes) until 30 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).

[e] Only at the 60- and 100-day follow-up visits, unless discontinued for disease progression.

[f] Subjects with SD, PR, or CR at the last clinical follow-up visit should undergo tumor assessment via CT/MRI scans at least every 3 to 4 months during the Survival Follow-up (Section 8.3.2.2) phase until progression.

[g] Only anti-cancer treatments.

[h] Subject status will be assessed by either a clinic visit or telephone contact every 12 weeks (± 2 weeks) until the last treated subject has been followed for 2 years from his/her first 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 at these telephone contacts. Subjects will be permitted to receive other anti-cancer therapies, including investigational agents, during this follow-up period once the 100-day follow-up visit is completed.

AE: adverse event; C: cycle; CR: complete response; CRF: case report form; CT: computed tomography; D: day; ECG: electrocardiogram; ECOG: Eastern Cooperative Oncology Group; EOT: end of treatment; fT3: free triiodothyronine; fT4: free thyroxine; Hep: hepatitis; HIV: human immunodeficiency virus; LVEF: left ventricular ejection fraction; MRI: magnetic resonance imaging; MUGA: multigated acquisition; PE: physical examination; PK: pharmacokinetics; PR: partial response; RNA ribonucleic acid; SAE: serious adverse event; SD: stable disease; TSH: thyroid-stimulating hormone.

5.1.1 Retesting During Screening

Retesting of laboratory parameters and/or other assessments within any single Screening 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 (the central laboratory will provide the machine for protocol required collections), and a calibrated sphygmomanometer and thermometer for vital signs assessments. A current and fully-stocked advanced cardiac life support or basic cardiac life support cart will be immediately available on the premises 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. The site will provide all materials required for accurate source documentation of study activities and for housing the subjects during the study.

ECG (12-lead) machine should be provided by the central vendor.

BMS will provide a BMS-approved protocol, any amendments or administrative letters (if required), and IB. CRFs (electronic or hard copy) will be provided by BMS. BMS/the central laboratory will provide labels and tubes for the collection of blood samples for PK, [redacted] analysis.

5.3 Safety Assessments

All subjects who receive at least 1 dose of study drug will be evaluated for safety parameters. Additionally, any occurrence of an SAE from the time of consent until 60 days (or 100 days for combination therapy) post discontinuation of study drug dosing will be documented. Any occurrence of nonserious AEs will be collected from first dose of study drug until 60 days (or 100 days for combination therapy) post discontinuation of dosing.

AEs will be coded using the most current version of Medical Dictionary for Regulatory Activities and reviewed for potential significance and importance. Adverse events will be evaluated according to the NCI CTCAE v4.03. Subjects should be followed until all AEs for which no clear alternative cause is identified other than BMS-986148 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, PEs, 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 5.1-2 through Table 5.1-8. In limited instances, scheduled events (including events other than safety assessments) can occur outside of the indicated timeframes but the Sponsor should be notified.

Only data for the procedures and assessments specified in this protocol (see Table 5.1-2 through Table 5.1-8) should be submitted to BMS. Additional procedures and assessments may be performed as part of standard of care; however, data for these assessments should remain in the subject's medical record and should not be provided to BMS unless specifically requested by the Sponsor.

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 (ie, continue scans Q6W for Parts 1A, 2, and 3 and Q8W for Part 1B ± 1 week 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. Any new or worsening clinically significant changes must be reported on the appropriate nonserious or serious AE page.

Additional measures, including nonstudy required laboratory tests, should be performed as clinically indicated.

Sites should collect these screening samples between -28 to -1 days from enrollment to ensure that results required for eligibility purposes are verified prior to registration (tumor scans are allowed approximately 30 days prior to dosing). Pregnancy testing must be performed within 24 hours prior to the initial administration of investigational product at baseline and then prior to administration of either study medication during study therapy and at the follow-up visit. CBC plus differential and serum chemistry panel should be drawn within 24 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. Grade 3 decreases in neutrophil and thrombocytopenia must be repeated within 72 hours. 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 Follow-up period via on site/local labs until all study drug toxicities for which no clear alternative cause is identified other than BMS-986148 or nivolumab resolve to baseline, stabilize, or are deemed irreversible.

Ophthalmological examination by an ophthalmologist or locally qualified personnel will include an 8-point exam (visual acuity, pupils, extraocular motility and alignment, tonometry, visual field, external examination, slit lamp examination, and fundoscopy) at baseline and focused exams with visual acuity, slit lamp, and as indicated will be conducted at the end of cycle 1 (pre-dose cycle 2), at EOT, and as clinically indicated during the study. Any abnormality must be discussed with the medical monitor prior to dosing. For symptoms of ocular toxicity that occur at any time during the treatment with study drug, dose interruption of study drug is recommended and prompt consultation and management with an ophthalmologist is recommended until the symptoms resolves. After recovery, dose reduction or discontinuation should be considered, depending on the severity of the eye symptoms and at the discretion of the consulting ophthalmologist and discussion with the medical monitor (see Section 3.1.1).

Cardiac monitoring with echocardiogram at baseline, start of Cycle 3, then every 3 cycles, and EOT will be conducted during the Part 1 and 2 (Monotherapy treatrment) . For subject in Part 3 combination treatment, an additional echocardiogram at the start of cycle 2 will be done. MUGA scan can be used for the assessment of LVEF at baseline. Echocardiograms done during treatment for the monitoring of pericardial effusion may be obtained more frequently if indicated. Troponin T or I will be monitored QW during the first cycle. Grade 1 elevation requires dose interruption of study drug and repeat assessment within 72 hours; BMS-986148 should be discontinued if Grade 1 Troponin T or I is confirmed when repeated assessment occurs. If persistent elevation, dose discontinuation should be considered at the discretion of the consulting cardiologist and discussion with the medical monitor. Grade 3 elevation of Troponin I or T requires discontinuation of study drug and prompt consultation and management with a cardiologist is recommended until it resolves.

5.3.1 Laboratory Test Assessments

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

Results of clinical laboratory tests performed on Day 1 must be available prior to dosing.

The following clinical laboratory tests will be performed:

Hematology

Hemoglobin	Hematocrit
Total leukocyte count, including differential	Platelet count

Serum Chemistry

AST	Total Protein
ALT	Albumin
TB	Sodium
Direct bilirubin (only if TB is elevated)	Potassium
Alkaline phosphatase	Chloride
Lactate dehydrogenase	Calcium
Creatinine	Phosphorus
Blood urea nitrogen or Urea	Magnesium
Uric acid	
Glucose	Creatine kinase with reflex measurement of isoenzymes if elevated
Part 3 only:	Troponin I or T at screening and Part 1 and Part 3A cycle 1 only.
Thyroid panel (including thyroid-stimulating hormone, free T3, and free T4)	
Amylase and Lipase (at screening only and as clinically indicated)	

Serology

Serum for hepatitis C antibody (if hepatitis C antibody is positive reflex to hepatitis C RNA) or

hepatitis C RNA, Hepatitis B surface antigen, HIV-1, HIV-2 antibody (testing for HIV-1 and HIV-2 must be performed at sites where mandated by local requirements).

Screening only:
FSH (Section 3.3.3)
Urinalysis

Protein	Leukocyte esterase
Glucose	Specific gravity
Blood	pH

Microscopic examination of the sediment if blood, protein or leukocytes esterase are positive on the dipstick

Other Analyses

At the time of tumor assessments:

- CA125 for subjects with ovarian carcinoma and mesothelioma
- CA19-9 for subjects with pancreatic carcinoma

Pregnancy test (WOCBP only: screening, pre-dose [each dose of BMS-986148], EOT, and follow-up).

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

5.4 Efficacy Assessments

Data for the tumor assessments specified in this protocol (see Table 5.1-2 through Table 5.1-8) should be submitted to BMS. Additional assessments may be performed as part of standard of care; however, data for these assessments should remain in the subject's medical record and should not be provided to BMS unless specifically requested by the Sponsor. Sponsor can request scans for review at any time during or after the study.

5.4.1 Primary Efficacy Assessment

Tumor measurements with CT and/ or MRI, as appropriate, will be conducted at screening, at the start of Cycle 3, and then every 2 cycles (± 1 week) during the treatment phase. Tumor measurements should be conducted earlier, if clinically indicated. Subjects with SD, PR, or CR at the last clinical follow-up visit undergo tumor assessment via CT/MRI scans every 3 to 4 months during the Survival Follow-up (Sections 8.3.2.2 and 8.5) phase until progression or death. Tumor measurements will be collected in all subjects until progression or the subject's

discontinuation from the study as per Table 5.1-2 to Table 5.1-8. Tumor response and progression will be evaluated in this study using RECIST version 1.1 criteria or Modified RECIST for malignant pleural mesothelioma (Appendix 4).[58] 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 version 1.1 criteria or Modified RECIST for malignant pleural mesothelioma at a later date or at any time during the study.

[redacted]

5.4.3 Imaging Assessment for the Study

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

Computed Tomography/Magnetic Resonance Imaging

Contrast-enhanced CT scans acquired on dedicated CT equipment is preferred for this study. CT with contrast of the chest, abdomen, and pelvis are to be performed for tumor assessments as indicated in Table 5.1-2 through Table 5.1-8. CT scans should be acquired with 5 mm slices with no intervening gap (contiguous).

Should a subject have a contraindication for CT IV contrast, a noncontrast CT of the chest and a contrast enhanced MRI of the abdomen and pelvis may be obtained. MRIs should be acquired with slice thickness of ≤ 5 mm with no gap (contiguous).

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

It is the local imaging facility's responsibility to determine, based on subject attributes (eg, allergy history, diabetic history, and renal status), the appropriate imaging modality and contrast regimen for each subject. Imaging contraindications and contrast risks should be considered in this assessment. Subjects with renal insufficiency should be assessed as to whether or not they should receive contrast and if so, what type and dose of contrast is appropriate. Specific to MRI, subjects with severe renal insufficiency (ie, estimated glomerular filtration rate < 30 mL/min/1.73m^2) are at increased risk of nephrogenic systemic fibrosis. MRI contrast should not be given to this subject population. In addition, subjects are excluded from MRI if they have tattoos, metallic implants, pacemakers, etc.

The ultimate decision to perform MRI in an individual subject in this study rests with the site radiologist, the investigator, and the standard set by the local Ethics Committee.

5.5 Pharmacokinetic and Immunogenicity Assessments

Serum samples for total antibody, active ADC, [redacted] and nivolumab PK assessments as well as plasma samples for [redacted] unconjugated tubulysin PK assessments will be collected in all subjects. Serum samples for antibody-drug antibody (ADA) assessments will also be collected in all subjects. The PK parameters to be assessed include:

Cmax	Maximum observed serum or plasma concentration
Tmax	Time of maximum observed serum or plasma concentration
AUC(0-t)	Area under the concentration-time curve from time 0 to the time of the last quantifiable concentration
AUC(TAU)	Area under the concentration-time curve in 1 dosing interval
Ctau	Concentration in a dosing interval
Ctrough	Trough observed serum or plasma concentration (this includes pre-dose concentrations and Ctau concentrations)
CLT	Total body clearance calculated as Dose divided by AUC(TAU)
Vss	Volume of distribution at steady state
Vz	Apparent volume of distribution at steady state
AI_AUC	AUC accumulation index; ratio of AUC(TAU) at steady-state to AUC(TAU) after the first dose
AI_Cmax	Cmax accumulation index; ratio of Cmax at steady-state to Cmax after the first dose
AI_Ctau	Ctau accumulation index; ratio of Ctau at steady-state to Ctau after the first dose
Cavg	Average concentration over a dosing interval calculated by dividing AUC(TAU) by tau
T-HALF	Terminal serum or plasma half-life

Individual subject PK parameter values will be derived by noncompartmental methods using a validated PK analysis program. Actual times will be used for the analyses.

5.5.1 Pharmacokinetics and Immunogenicity: Collection and Processing

Table 5.5.1-1 and Table 5.5.1-2 list the sampling schedules to be followed for the assessment of PK and ADA for the every 3 week (Q3W) and the QW for 3 weeks followed by 1 week off dosing regimens, respectively. Table 5.5.1-3 lists the sampling schedules to be followed for the assessment of PK and ADA for the Q3W dosing regimen in combination with nivolumab. Table 5.5.1-4 lists the sampling schedules to be followed for the assessment of PK and ADA for the Q3W dosing regimen during retreatment with BMS-986148 in combination with nivolumab. All time points are relative to the start of study drug administration. Pre-dose samples should be taken within 30 minutes before the start of dose administration. If the end of the infusion is delayed to beyond the nominal infusion duration, the collection of this sample should also be delayed accordingly. On-treatment PK samples are intended to be drawn relative to actual dosing days, if a dose occurs on a different day within the cycle due to delays or minor schedule adjustments, PK samples should be adjusted accordingly. Samples for ADA are to be collected prior to the administration of study drug. Further details of sample collection, processing, and shipment will be provided in the laboratory procedures manual. Serum samples designated for

PK [redacted] assessments may also be used for immunogenicity analysis, if required (eg, insufficient volume for complete immunogenicity assessment or to follow up on a suspected immunogenicity-related AE).

Table 5.5.1-1: PK and ADA Sampling Schedule for BMS-986148 Monotherapy Q3W Dosing Regimen

Study Day of Sample Collection	Event	Time (Relative To Start of Infusion) Hour: Min	PK Sample (Serum and Plasma)	ADA Sample (Serum)
Cycle 1				
1	Predose	00:00	X	X
1	EOI[a]	01:00	X	
1		04:00	X	
2		24:00	X	
4[redacted]		72:00	X	
8		168:00	X	
15		336:00	X	X
Cycle 2				
1	Predose	00:00	X	
1	EOI	01:00	X	
Cycle 3				
1	Predose	00:00	X	X
1	EOI	01:00	X	
Cycle 4				
1	Predose	00:00	X	X
1	EOI	01:00	X	
1		04:00	X	
2		24:00	X	
4[redacted]		72:00	X	
8		168:00	X	
15		336:00	X	
Every 2 Cycles Starting at Cycle 5 (PK Only)				
1	Predose	00:00	X	
Every 5 Cycles Starting at Cycle 9 (PK and ADA)				
1	Predose	00:00	X	X
EOT			X	X

Table 5.5.1-1: PK and ADA Sampling Schedule for BMS-986148 Monotherapy Q3W Dosing Regimen

Study Day of Sample Collection	Event	Time (Relative To Start of Infusion) Hour: Min	PK Sample (Serum and Plasma)	ADA Sample (Serum)
30-Day Follow-Up			X	
60-Day Follow-Up			X	X
Event Driven[c]			X	X

[a] EOI = Sample must be collected immediately following the end of the infusion. End of Infusion Serum will be collected for measuring total antibody, [redacted] and active ADC concentrations. Plasma will be collected for measuring [redacted] unconjugated tubulysin concentrations.

[redacted]

[c] In the event that labs are drawn and the subject is not dosed.

ADA: anti-drug antibody; ADC: antibody-drug conjugate; EOI: end of infusion; EOT: end of treatment; min: minimum; PK: pharmacokinetics; Q3W: every 3 weeks.

Table 5.5.1-2: PK and ADA Sampling Schedule for BMS-986148 Monotherapy QW Dosing Regimen

Study Day of Sample Collection	Event	Time (Relative To Start of Infusion) Hour: Min	PK Sample (Serum and Plasma)	ADA Sample (Serum)
Cycle 1				
1	Predose	00:00	X	X
1	EOI[a]	01:00	X	
1		04:00	X	
2		24:00	X	
4[redacted]		72:00	X	
8	Predose	00:00	X	
8	EOI	01:00	X	
15	Predose	00:00	X	X
15	EOI	01:00	X	
22		168:00	X	
Cycle 3				
1	Predose	00:00	X	X
Cycle 4				

Table 5.5.1-2: PK and ADA Sampling Schedule for BMS-986148 Monotherapy QW Dosing Regimen

Study Day of Sample Collection	Event	Time (Relative To Start of Infusion) Hour: Min	PK Sample (Serum and Plasma)	ADA Sample (Serum)
1	Predose	00:00	X	X
1	EOI	01:00	X	
1		04:00	X	
2		24:00	X	
4[redacted]		72:00	X	
8	Predose	00:00	X	
8	EOI	01:00	X	
15	Predose	00:00	X	
15	EOI	01:00	X	
22		168:00	X	
Every 2 Cycles Starting at Cycle 5 (PK Only)				
1	Predose	00:00	X	
Every 4 Cycles Starting at Cycle 8 (PK and ADA)				
1	Predose	00:00	X	X
EOT			X	X
30-Day Follow-Up			X	
60-Day Follow-Up			X	X
Event Driven[c]			X	X

[a] EOI = Sample must be collected immediately following the end of the infusion. End of Infusion Serum will be collected for measuring total antibody, [redacted] and active ADC concentrations. Plasma will be collected for measuring [redacted] unconjugated tubulysin concentrations.

[redacted]

[c] In the event that labs are drawn and the subject is not dosed.

ADA: anti-drug antibody; ADC: antibody-drug conjugate; EOI: end of infusion; EOT: end of treatment; min: minimum; PK: pharmacokinetics; QW: every week.

Table 5.5.1-3: PK and Anti-Drug Antibody Sampling Schedule for BMS-986148 Q3W Dosing Regimen in Combination with Nivolumab

Study Day of Sample Collection	Event	Time (Relative to Start of Infusion) Hour:Min	BMS-986148 PK Sample (Serum and Plasma)	Nivolumab PK Sample (Serum)	BMS-986148 and Nivolumab ADA Samples (Serum)
Cycle 1					
1	Predose	00:00	X	X	X
1	EOI[a]	00:30		X	
1	EOI[a]	01:00	X		
1		04:00	X		
2[b]		24:00	X	X	
4[redacted]		72:00	X	X	
8		168:00	X	X	
15		336:00	X	X	X
Cycle 2					
1	Predose	00:00	X	X	
1	EOI	00:30		X	
1	EOI	01:00	X		
Cycle 3					
1	Predose	00:00	X	X	X
1	EOI	00:30		X	
1	EOI	01:00	X		
Cycle 4					
1	Predose	00:00	X	X	X
1	EOI	00:30		X	
1	EOI	01:00	X		
1		04:00	X		
2[b]		24:00	X	X	
4[redacted]		72:00	X	X	
8		168:00	X	X	
15		336:00	X	X	
Every 2 Cycles Starting at Cycle 5 (PK Only)					
1	Predose	00:00	X	X	

Table 5.5.1-3: PK and Anti-Drug Antibody Sampling Schedule for BMS-986148 Q3W Dosing Regimen in Combination with Nivolumab

Study Day of Sample Collection	Event	Time (Relative to Start of Infusion) Hour:Min	BMS-986148 PK Sample (Serum and Plasma)	Nivolumab PK Sample (Serum)	BMS-986148 and Nivolumab ADA Samples (Serum)
Every 5 Cycles Starting at Cycle 9 (PK and ADA)					
1	Predose	00:00	X	X	X
EOT			X	X	X
30-Day Follow-Up			X	X	X
60-Day Follow-Up			X	X	X
100-Day Follow-Up			X	X	X
Event Driven[d]			X	X	X

[a] EOI = Sample must be collected immediately following the end of the infusion. End of Infusion Serum will be collected for measuring total antibody, [redacted] and active ADC concentrations. Plasma will be collected for measuring [redacted] unconjugated tubulysin concentrations.

[b] ± 2 hours.

[redacted]

[d] In the event that labs are drawn and the subject is not dosed.

ADA: anti-drug antibody; ADC: antibody-drug conjugate; EOI: end of infusion; EOT: end of treatment; min: minimum; PK: pharmacokinetics; Q3W: every 3 weeks.

Table 5.5.1-4: PK and Anti-Drug Antibody Sampling Schedule for BMS-986148 Q3W Dosing Regimen in Combination with Nivolumab During Retreatment

Study Day of Sample Collection	Event	Time (Relative to Start of Infusion) Hour:Min	BMS-986148 PK Sample (Serum and Plasma)	Nivolumab PK Sample (Serum)	BMS-986148 and Nivolumab ADA Samples (Serum)
Cycle 1					
1	Predose	00:00	X	X	X
Cycle 3					
1	Predose	00:00	X	X	X
Cycle 4					
1	Predose	00:00	X	X	X

Table 5.5.1-4: PK and Anti-Drug Antibody Sampling Schedule for BMS-986148 Q3W Dosing Regimen in Combination with Nivolumab During Retreatment

Study Day of Sample Collection	Event	Time (Relative to Start of Infusion) Hour:Min	BMS-986148 PK Sample (Serum and Plasma)	Nivolumab PK Sample (Serum)	BMS-986148 and Nivolumab ADA Samples (Serum)
Every 5 Cycles Starting at Cycle 9					
1	Predose	00:00	X	X	X
EOT			X	X	X
30-Day Follow-Up			X	X	X
60-Day Follow-Up			X	X	X
100-Day Follow-Up			X	X	X
Event Driven[a]			X	X	X

[a] In the event that labs are drawn and the subject is not dosed.

ADA: anti-drug antibody; ADC: antibody-drug conjugate; EOI: end of infusion; EOT: end of treatment; min: minimum; PK: pharmacokinetics; Q3W: every 3 weeks.

5.5.2 Pharmacokinetic Sample Analyses

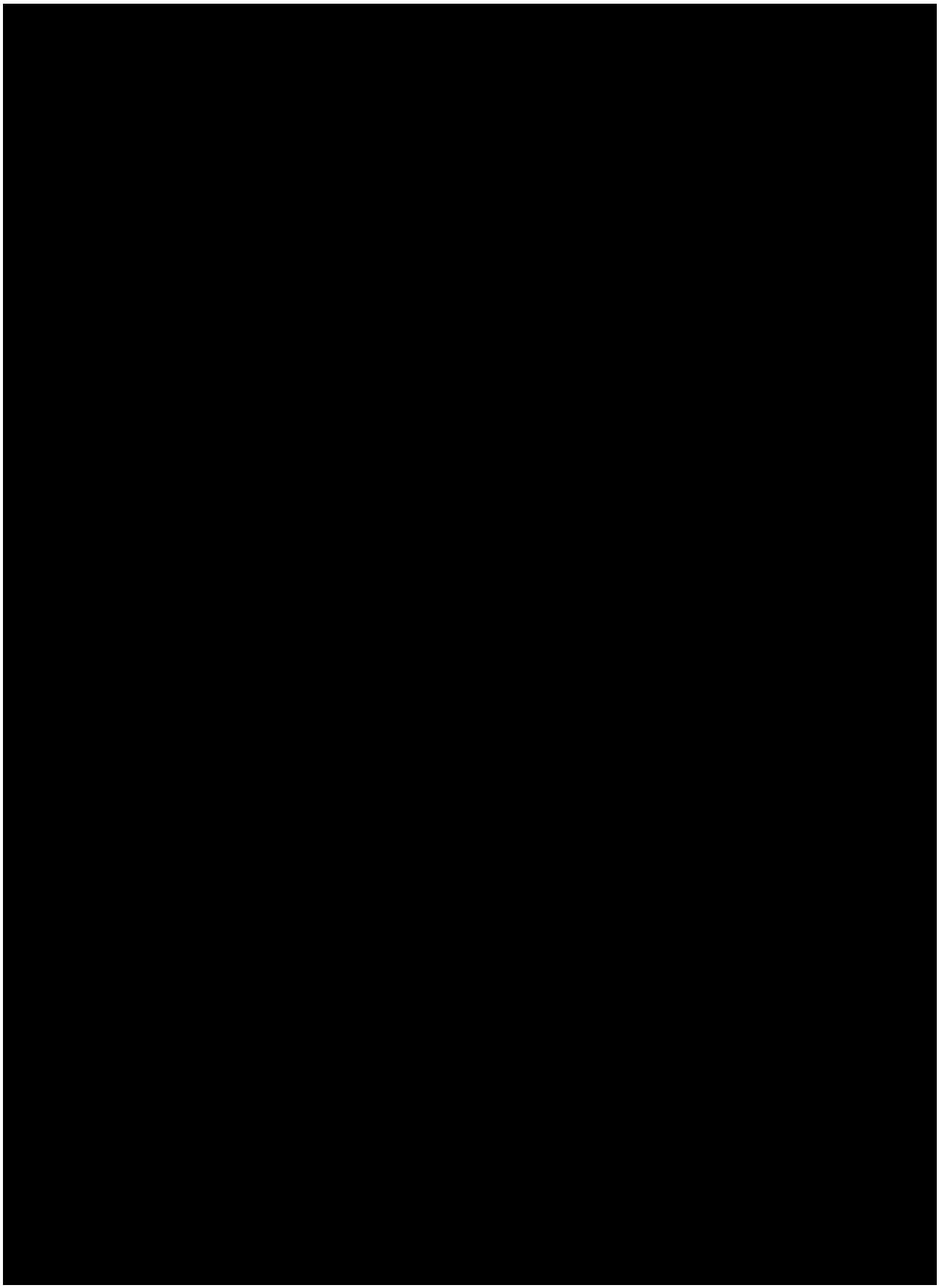
Serum samples for total antibody, [redacted] active ADC, and nivolumab concentrations and plasma samples for unconjugated tubulysin concentrations will be analyzed using a series of validated assays. [redacted]

5.5.3 Antibody-Drug Antibody Sample Analyses

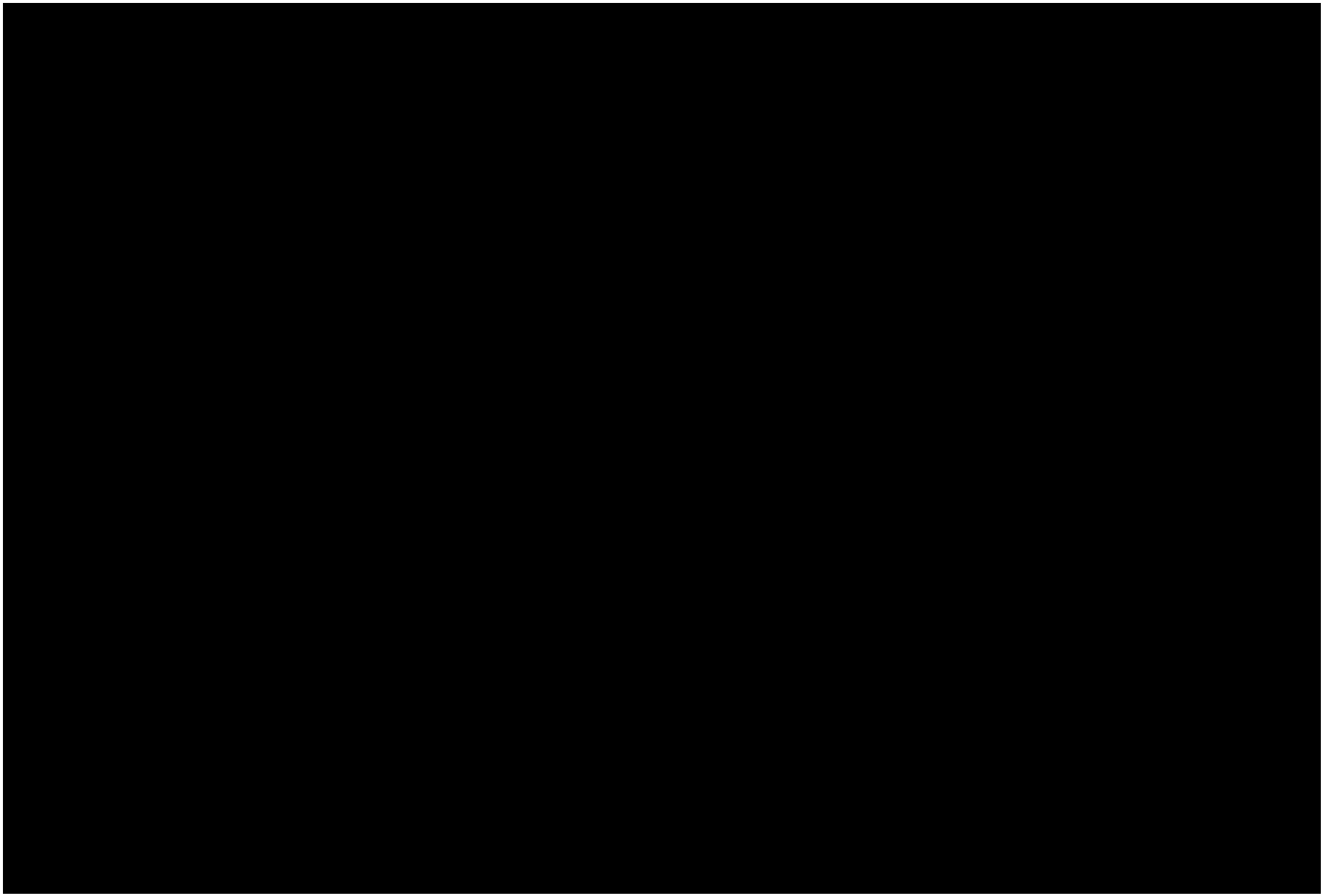
ADA assessment utilizes a tiered approach to testing for ADA through detection, confirmation, and titer and domain specificity characterization as is applicable. All assay tiers are fully validated ligand binding assays.

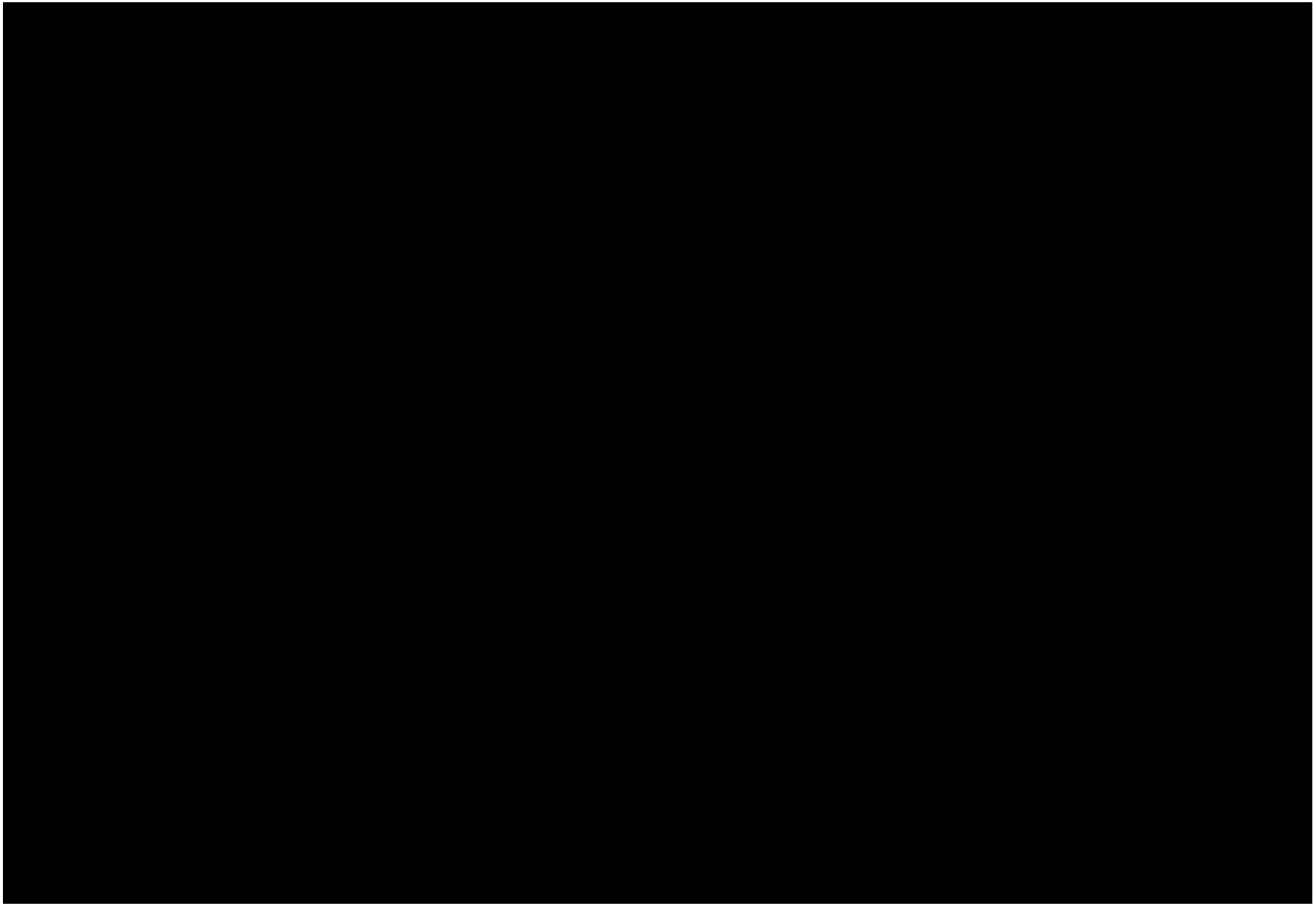
5.5.4 Labeling and Shipping of Biological Samples

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



[redacted]





[redacted]

5.8 Outcomes Research Assessments

Not applicable.

[redacted]

5.10 Results of Central Assessments

Not applicable

[redacted]

[redacted]

6 ADVERSE EVENTS

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

The causal relationship to study drug is determined by a physician and should be used to assess all AEs. The causal relationship can be 1 of the following:

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

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

Adverse events can be spontaneously reported or elicited during open-ended questioning, examination, or evaluation of a subject. (In order to prevent reporting bias, subjects should not be questioned regarding the specific occurrence of 1 or more AEs.)

6.1 Serious Adverse Events

An ***SAE*** is any untoward medical occurrence that at any dose:

- Results in death
- Is life-threatening (defined as an event in which the subject was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe)
- Requires inpatient hospitalization or causes prolongation of existing hospitalization (see **NOTE** below)
- Results in persistent or significant disability/incapacity

- Is a congenital anomaly/birth defect
- Is an important medical event (defined as a medical event(s) that may not be immediately life-threatening or result in death or hospitalization but, based upon appropriate medical and scientific judgment, may jeopardize the subject or may require intervention [eg, medical, surgical] to prevent 1 of the other serious outcomes listed in the definition above). Examples of such events include, but are not limited to, intensive treatment in an emergency room or at home for allergic bronchospasm; blood dyscrasias, or convulsions that do not result in hospitalization. p-DILI is also considered an important medical event. (See Section 6.6 for the definition of p-DILI.)

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

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

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

NOTE:

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

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

6.1.1 Serious Adverse Event Collection and Reporting

Sections 5.6.1 and 5.6.2 in the IB represent the Reference Safety Information to determine expectedness of serious AEs 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 60 days (or 100 days for combination

therapy) of discontinuation of dosing. 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 electronic case report form (eCRF). The paper SAE/pregnancy surveillance forms are only intended as a back-up option when the eCRF system is not functioning. In this case, the paper forms are to be transmitted via email or confirmed facsimile (fax) transmission to:

SAE Email Address: Refer to Contact Information list.

SAE Facsimile Number: Refer to Contact Information list.

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

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

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

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

All SAEs should be followed to resolution or stabilization.

6.2 Nonserious Adverse Events

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

6.2.1 Nonserious Adverse Event Collection and Reporting

The collection of non-SAE information should begin at initiation of study drug. Non-SAE 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-SAEs 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-SAEs that cause interruption or discontinuation of study drug and for those present at the end of study treatment as appropriate. All identified non-SAEs must be recorded and described on the non-SAE page of the CRF (paper or electronic).

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

6.3 Laboratory Test Result Abnormalities

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

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

It is expected that wherever possible, the clinical rather than laboratory term would be used by the reporting investigator (eg, anemia versus low hemoglobin value).

6.4 Pregnancy

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

In most cases, the study drug will be permanently discontinued in an appropriate manner (eg, dose tapering if necessary for subject safety).

In the rare event that the benefit of continuing study drug is thought to outweigh the risk, after consultation with BMS, the pregnant subject may continue study drug after a thorough discussion of benefits and risk with the subject.

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

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

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

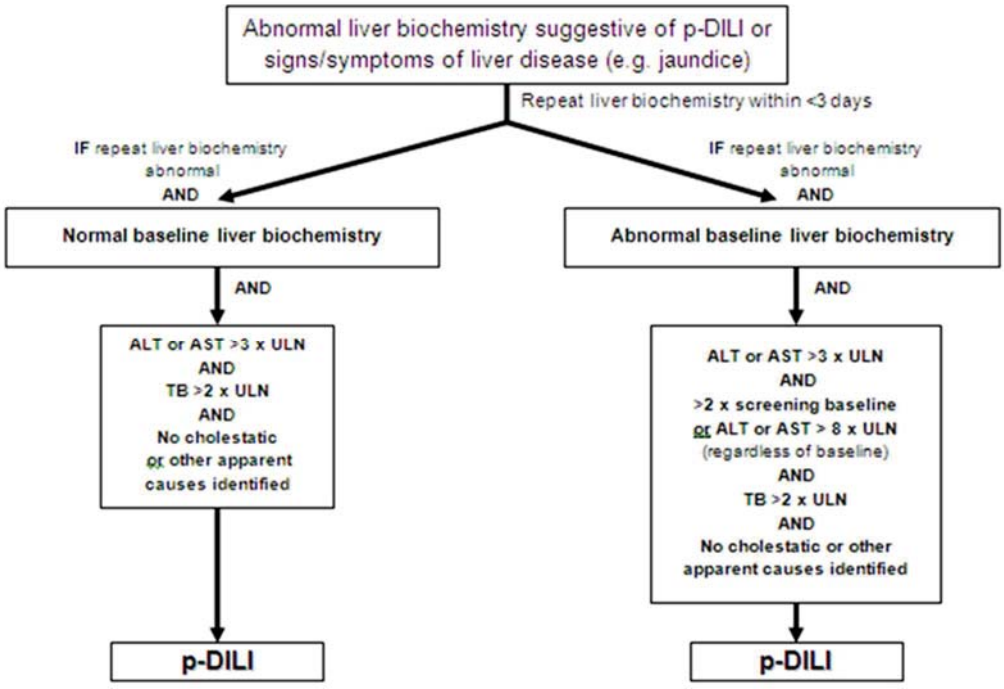
6.5 Overdose

All occurrences of overdose must be reported as SAEs (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 p-DILI event. All occurrences of p-DILIs, meeting the defined criteria, must be reported as SAEs (see Section 6.1.1 for reporting details). The criteria for identifying p-DILI events depend on whether the subject's baseline liver biochemistry is normal or abnormal (see Figure 6.6-1).

Figure 6.6-1: Algorithm for p-DILI Identification and Mandatory SAE Reporting in Subjects with (i) Normal Baseline Liver Biochemistry and (ii) Abnormal Baseline Liver Biochemistry



ALT: alanine transaminase; AST: aspartate transaminase; SAE: serious adverse event; p-DILI: potential drug-induced liver injury; TB: total bilirubin; ULN: upper limit of normal.

The key responsibilities for investigators during p-DILI assessment include: (i) Early detection, medical evaluation (including the exclusion of other potential causes), and rapid laboratory confirmation of liver-related abnormalities, and (ii) BMS notification of p-DILI cases via SAE forms. Following the gathering and assessment of relevant clinical information BMS is responsible for: (iii) Timely evaluation and triaging of p-DILI cases, (iv) Expedited reporting of p-DILI cases, and (v) Expanded review of p-DILI cases including a detailed assessment of all available clinical information, investigations, and biochemical data.

Investigators are expected to monitor ongoing routine and ad hoc hepatic laboratory test results to rapidly determine whether a subject meets p-DILI criteria. They are expected to promptly notify BMS of all p-DILI cases. p-DILI cases may be identified by abnormal liver biochemistry values, whether or not they are accompanied by liver-related signs and/or symptoms. In both cases, expedited confirmation with repeat laboratory testing should occur within 3 business days using a Hepatic Laboratory Panel (ALT, AST, TB, and alkaline phosphatase). Any subject with an abnormal Hepatic Laboratory Panel that meets p-DILI criteria (see Figure 6.6-1) is a candidate for study drug discontinuation. Any confirmed p-DILI events must be reported (along with a description of the clinical findings) to BMS as an SAE within 24 hours of confirmation.

An extensive clinical history, examination, and appropriate investigations should be obtained to exclude cholestatic and other apparent causes that may explain the observed abnormalities in liver function and/or hepatic signs and symptoms. Other apparent causes include, nonexhaustively and by way of example only: infectious diseases (such as active hepatitis A, B, and C), congenital diseases (such as Gilbert's syndrome), neoplastic diseases (such as hepatocellular carcinoma), automimmune diseases (such as primary biliary cirrhosis), and the use of concomitant hepatotoxic medications (such as antibiotics, the oral contraceptive pill, and herbal medicines). All investigations to exclude potential causes of liver function abnormalities or hepatic signs and/or symptoms should be guided by relevant factors such as the subject's age, gender, clinical history, and signs and symptoms.

6.7 Other Safety Considerations

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

7 DATA MONITORING COMMITTEE AND OTHER EXTERNAL COMMITTEES

Not applicable

8 STATISTICAL CONSIDERATIONS

8.1 Sample Size Determination

Dose Escalation: In the monotherapy dose escalation part of the study, ie, both Parts 1A and 1B, a total of approximately 30 and 24 evaluable subjects are expected to be treated, respectively. The exact sample size per dose level cannot be precisely determined but depends on the observed DLT and will be guided by the mTPI design, with a target DLT rate of 27% (25% to 29%), based on Bayesian modeling and posterior inference. Between 2 and up to 13 DLT evaluable subjects may be enrolled to a given monotherapy cohort in Part 1A. Treating additional subjects beyond the 13 would be unlikely to alter the decision specified by the mTPI algorithm. In the combination dose escalation part (Part 3A), a total of approximately 12 evaluable subjects are expected to be treated across 2 dose levels, with the sample size per dose level guided by a mTPI design with target DLT rate of 29% (28% to 31%).

Cohort Expansion: During this part of the study, approximately up to 25 to 26 subjects in the population of interest [redacted] are expected to be treated in each tumor cohort at the MTD or alternate dose below the MTD (as determined from dose escalation), or other agreed dose level. This number per cohort is based on achieving a reasonable precision of the ORR and adequate control on the false negative rate (FNR) and false positive rate (FPR) (assuming a historic and target response rate as shown for monotherapy cohorts below):

In a cohort of 25 marker positive subjects, if 5 or 6 responses are observed (eg, for gastric or pancreatic cohorts), then the ORR 90% confidence intervals (CIs) are (8.2%, 37.5%) and (11%, 42%), respectively. If 7 responses are observed (eg, NSCLC and ovarian cohorts), then the 90% CI is (14%, 46.2%), and if 8 or 9 responses are observed (eg, mesothelioma cohort), then the 90% CIs for ORR are: (17%, 50.4%) and (20%, 54.4%), respectively. These calculations are based on the Clopper-Pearson method for exact CIs.

In addition, 25 subjects per cohort provide the following FNR and FPR under assumptions of expected true ORR. If the true ORR is 40% (eg, mesothelioma), then with 25 subjects in a cohort there is 97% and 93% chance of observing at least 6 or 7 responses, respectively, and there is 7% chance of observing 6 or fewer responses (FNR). If the true ORR for this tumor is only 20% (rather than 40%), then there is 22% and 11% chance respectively of observing at least 7 and at least 8 responses among 25 subjects (FPR).

Similarly if the true ORR is 20% (eg, gastric and pancreatic cohorts), then there is 97% and 90% probability of observing at least 2 or 3 responses respectively, among 25 subjects and 10% of observing 2 or fewer responses (FNR). If the true ORR for these tumors is 10% (rather than 20%) then there is 24% and 10% chance, respectively, of observing at least 4 and at least 5 responses (FPR).

If the true ORR is 30% (eg, NSCLC and ovarian cohorts), then there is 91% and 81% probability of observing at least 5 or 6 responses, respectively, in 25 subjects and 9% of observing 5 or fewer responses (FNR). If the true ORR for these tumors is 15% (rather than 30%) then there is 16% and 7% chance, respectively, of observing at least 6 and at least 7 responses (FPR).

The Simon 2-Stage design will be used in the monotherapy and nivolumab combination expansion cohorts, with a minimum of subjects treated initially as per the Stage 1 n of Table 8.1-1 and Table 8.1-2 below. Efficacy will be explored in both the [redacted] populations; there will be no adjustment for multiple comparisons. In each of monotherapy or combination cohorts after a minimum number of subjects (n for Stage 1) are treated, there will be an initial evaluation of efficacy independently in each cohort. If there is a lack of signal in either population, then treatment in that cohort may be stopped in that population; if there is an initial efficacy signal, subjects will continue to be treated in Stage 2 for the population in which there was a signal. [redacted]

The above results 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 SD and safety. The operational characteristics of these Simon 2-Stage designs are provided in the following tables.

Table 8.1-1: Monotherapy Operating Characteristics for 2-Stage Simon Design

Tumor Type	Historic ORR (%)	Target ORR (%)	Stage 1/ Total n	Stage 1[a] Futility Boundary	Alpha / Power	Early Stopping Probability
Gastric	10	20	15 / 25	0	0.24 / 0.76	0.21
Mesothelioma	20	40	12 / 25	2	0.10 / 0.80	0.45
NSCLC Adeno	15	30	14 / 26	1	0.18 / 0.82	0.36
Ovarian	15	30	14 / 26	1	0.18 / 0.82	0.36
Pancreatic	10	20	15 / 25	0	0.24 / 0.76	0.21

[a] Number of responses indicating the cut-off for lack of efficacy signal.
n: number of subjects; NSCLC: non-small cell lung carcinoma; ORR: objective response rate.

Similarly the operating characteristics of the 2-stage Design in the expansion cohort are shown in Table 8.1-2 below:

Table 8.1-2: Nivolumab Combination Operating Characteristics for 2-Stage Simon Design

Tumor Type	Historic ORR (%)	Target ORR (%)	Stage 1/ Total n	Stage 1[a] Futility Boundary	Alpha / Power	Early Stopping Probability
Gastric	10	30	11 / 25	1	0.10 / 0.84	0.70
Mesothelioma	20	40	12 / 25	2	0.10 / 0.80	0.45
NSCLC Adeno	15	40	10 / 22	1	0.10 / 0.90	0.54
Ovarian	15	30	14 / 26	1	0.18 / 0.82	0.36
Pancreatic	10	30	11 / 25	1	0.10 / 0.84	0.70

[a] Number of responses indicating the cut-off for lack of efficacy signal.
n: number of subjects; NSCLC: non-small cell lung carcinoma; ORR: objective response 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-986148 and have available serum and plasma concentration data.

[redacted]

- Immunogenicity (ADA) Population: all treated subjects who had baseline and at least 1 post-treatment immunogenicity assessment
- ECG Evaluable Population: 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)

Incidence of AEs at worst grade, SAEs at worst grade, AEs leading to discontinuations, deaths, and frequency of laboratory test toxicity grade shifting from baseline. Safety will be evaluated from the time that the subject signs the informed consent, and for up to 60 days (or 100 days for combination therapy) after the last dose of study drug.

8.3.2 Secondary Endpoint(s)

8.3.2.1 Pharmacokinetics

The PK of total antibody, active ADC, unconjugated tubulysin, and nivolumab will be characterized using the following endpoints (previously defined in Section 5.5):

- Cmax
- Tmax
- Ctau
- Ctrough
- AUC(0-t)
- AUC(TAU)
- T-HALF
- CLT
- Vss
- Vz
- AI_AUC
- AI_Cmax
- AI_Ctau
- Cavg

[redacted]

8.3.2.2 Efficacy

Efficacy based on RECIST version 1.1 or Modified RECIST for malignant pleural mesothelioma (Appendix 4)[58] 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 until the last tumor assessment prior to subsequent therapy. CR or PR determinations included in the BOR assessment must be confirmed by a second scan performed no less than 4 weeks after the criteria for response are first met. For those subjects who have surgical resection, only 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 died will be censored on the date of their last tumor assessment. Subjects who did not have any on-study tumor assessments will be censored on the date of the first dose of study medication.
- PFS rate at week 't': defined as the proportion of subjects who remain progression free and surviving at 't' weeks (eg, t=12, 24, and 36 weeks, and following the corresponding planned tumor scan visit). The proportion will be calculated by the product-limit method (Kaplan-Meier estimate) which takes into account censored data.

[redacted]

8.3.2.3 QTc

Changes in QTcF (ΔQTcF) from baseline, at selected times.

8.3.2.4 Immunogenicity (Anti-Drug Antibodies)

The endpoints of immunogenicity of BMS-986148 (after monotherapy and after combination with nivolumab) include frequency of different subject immunogenicity status, for example, subject positive ADA, persistent positive ADA, and others. The above endpoints will also be generated for nivolumab. Definitions of all the immunogenicity endpoints will be provided in the Statistical Analysis Plan.

8.4 Analyses

8.4.1 Demographics and Baseline Characteristics

Frequency distributions of gender and race will be tabulated. Summary statistics for age, body weight, height, and body mass index will be tabulated. Prior therapy will be tabulated.

8.4.2 Efficacy Analyses

Efficacy results will be presented by tumor type, dose and regimen for monotherapy and combination cohorts. Individual BOR, duration of response and PFS will be listed using RECIST version 1.1 criteria or Modified RECIST for malignant pleural mesothelioma (Appendix 4). BOR outcomes will be tabulated by dose and dose regimen. The ORR and PFS rates (eg, at 24 weeks) and the CI will be provided by dose and dose regimen for each tumor type if there is a large enough sample size. The duration of response and PFS will be estimated by Kaplan-Meier (K-M) methodology, PFS rates (eg, at 24 weeks) will be similarly estimated, based on K-M methodology. Individual changes in the tumor burden over time will be presented graphically by dose and dose regimen within a tumor type. [redacted] Sponsor can request scans for review at any time during or after the study. Sponsor can request scans for review at any time during or after the study.

8.4.3 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 and time-matched PK related to [redacted] changes in the QTcF (ΔQTcF), ECG intervals QRS and PR, and in heart rate (ΔHR) will be tabulated by dose and study day. Frequency distributions of max QTcF values, max ΔQTcF, max QRS, max PR, and max HR in pre-specified categories will be tabulated by dose. Scatter plots of HR, ΔHR, QTc, and ΔQTcF versus time-matched active ADC and unconjugated tubulysin concentrations will be provided. A concentration-response effect of BMS-986148 on QTcF may be assessed by a linear mixed effects regression model for ΔQTcF on plasma and serum concentrations, stratified by study day, as well as pooled across days. Additional modeling of exposure-response may also be explored.

8.4.4 Pharmacokinetic Analyses

PK parameters for the total antibody, [redacted] active ADC, [redacted] and unconjugated tubulysin will be calculated using noncompartmental analysis and tabulated following monotherapy and combination treatments.

[redacted]

To describe the dependency on dose, scatter plots of Cmax and AUC (TAU) versus dose will be provided on indicated study days for each dose regimen. [redacted] To assess the attainment of steady state geometric mean minimum serum concentration values will be plotted versus study day by dose and dose regimen.

Summary statistics for nivolumab PK will also be tabulated.

Associations between PK and select safety measures may be explored.

Population PK and exposure-response analyses may be conducted, which would be presented in a separate report.

8.4.5 Immunogenicity Analysis

All available immunogenicity data will be listed and flagged for subjects with at least 1 positive ADA. The frequency of subjects with at least 1 positive ADA assessment at baseline and the frequency of subjects who develop ADA after initiation of treatment (ADA positive) will be provided. Details and potentially additional endpoints (eg, incidence of persistent positive ADA) and analysis will be provided in the SAP. Associations of immunogenicity measures with PK and/or selected AE may be explored. The above analysis will be provided for BMS-986148 after monotherapy and combination treatments and for nivolumab.

[redacted]

[redacted]

8.4.8 Outcomes Research Analyses

Not applicable.

8.4.9 Other Analyses

The effect of treatment on changes in CA125 levels in the ovarian cancer and mesothelioma cohorts only and changes in CA19-9 levels in the pancreatic cancer cohort only will also be explored by summary statistics and plots over time. [redacted]

8.5 Interim Analyses

Because the exploratory nature of the early phase study, data emerging from each dose level or each part of the study will be examined prior to the formal locking of the study database for timely decisions about, such as but not limited to, dose selection, regimen selection and early termination of the study. There will be no formal hypothesis testing, nor will multiplicity be adjusted.

Bayesian regression model may be utilized to inform dose selection starting for the third dose in Part 1A. A similar approach may be used in Part 1B.

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, and 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: AE reporting, study details and procedure, electronic CRFs, study documentation, informed consent, and enrollment of WOCBP.

9.2 Records

9.2.1 Records Retention

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

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

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

9.2.2 Study Drug Records

It is the responsibility of the investigator to ensure that a current disposition record of study drug (inventoried and dispensed) is maintained at the study site to include investigational product. Records or logs must comply with applicable regulations and guidelines and should include:

- amount received and placed in storage area
- amount currently in storage area
- label identification number or batch number
- amount dispensed to and returned by each subject, including unique subject identifiers
- amount transferred to another area/site for dispensing or storage
- nonstudy disposition (eg, lost, wasted)
- amount destroyed at study site, if applicable
- amount returned to BMS
- retain samples for bioavailability/bioequivalence, if applicable
- dates and initials of person responsible for Investigational Product dispensing/accountability, as per the Delegation of Authority Form.

BMS will provide forms to facilitate inventory control if the investigational site does not have an established system that meets these requirements.

9.2.3 Case Report Forms

An investigator is required to prepare and maintain adequate and accurate case histories designed to record all observations and other data pertinent to the investigation on each individual treated or entered as a control in the investigation. Data that are derived from source documents and reported on the CRF must be consistent with the source documents or the discrepancies must be explained. Additional clinical information may be collected and analyzed in an effort to enhance understanding of product safety. CRFs may be requested for AEs and/or laboratory abnormalities that are reported or identified during the course of the study.

For sites using the BMS EDC tool, electronic CRFs will be prepared for all data collection fields except for fields specific to SAEs and pregnancy, which will be reported on the paper or electronic SAE form and Pregnancy Surveillance form, respectively. Spaces may be left blank only in those circumstances permitted by study-specific CRF completion guidelines provided by BMS.

The confidentiality of records that could identify subjects must be protected, respecting the privacy and confidentiality rules in accordance with the applicable regulatory requirement(s).

The investigator will maintain a signature sheet to document signatures and initials of all persons authorized to make entries and/or corrections on CRFs.

The completed CRF, including any paper or electronic SAE/pregnancy CRFs, must be promptly reviewed, signed, and dated by the investigator or qualified physician who is a subinvestigator and who is delegated this task on the Delegation of Authority Form .For electronic CRFs, review and approval/signature is completed electronically through the BMS EDC tool. The investigator must retain a copy of the CRFs including records of the changes and corrections.

Each individual electronically signing electronic CRFs must meet BMS training requirements and must only access the BMS EDC tool using the unique user account provided by BMS. User accounts are not to be shared or reassigned to other individuals.

9.3 Clinical Study Report and Publications

A signatory investigator must be selected to sign the clinical study report.

For this protocol, the signatory investigator will be selected as appropriate based on the following criteria:

- 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 patient. This does not mean periodic abstinence (eg, calendar, ovulation, symptothermal, profession of abstinence for entry into a clinical trial, postovulation 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.
Additional 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
ADA	antibody-drug antibody
ADC	antibody-drug conjugate
ADL	activities of daily living
[redacted]	[redacted]
AE	adverse event
AI_AUC	AUC Accumulation Index; ratio of AUC(TAU) at steady state to AUC(TAU) after the first dose
AI_Cmax	Cmax Accumulation Index; ratio of Cmax at steady state to Cmax after the first dose
AI_Ctau	Ctau Accumulation Index; ratio of Ctau at steady state to Ctau after the first dose
ALK	anaplastic lymphoma kinase
ALT	alanine aminotransferase
AST	aspartate aminotransferase
AUC	area under the curve
AUC(0-t)	area under the concentration-time curve from time 0 to the time of the last quantifiable concentration
AUC(TAU)	area under the concentration-time curve in 1 dosing interval
[redacted]	[redacted]
BMS	Bristol-Myers Squibb
BOR	best overall response
BV	brentuximab vedotin
Cavg	average concentration
[redacted]	[redacted]
CBC	complete blood count
CI	confidence interval
[redacted]	[redacted]
CL	clearance
CLT	total body clearance
Cmax	maximum observed plasma concentration

Term	Definition
[redacted]	[redacted]
CR	complete response
CRCl	creatinine clearance
CRF	case report form, paper or electronic
CT	computed tomography
Ctau	Concentration in a dosing interval (eg, concentration at 24 hours, concentration at 12 hours, etc.)
CTCAE	Common Terminology Criteria for Adverse Events
CTLA-4	cytotoxic T-lymphocyte associated antigen 4
Ctrough	trough observed plasma concentration
CV	cardiovascular
DLT	dose-limiting toxicity
[redacted]	[redacted]
ECG	electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	electronic case report form
EDC	electronic data capture
EI	equivalence interval
EGFR	epidermal growth factor receptor
EOT	end of treatment
FFPE	formalin-fixed, paraffin-embedded
FNR	false negative rate
FPR	false positive rate
FSH	follicle stimulating hormone
GCP	Good Clinical Practice
[redacted]	[redacted]
GI	gastrointestinal tract
[redacted]	[redacted]
[redacted]	[redacted]
HER2	human epidermal growth factor receptor 2

Term	Definition
HIV	human immunodeficiency virus
[redacted]	
HR	heart rate
HRT	hormone replacement therapy
I-O	immuno-oncology
IB	Investigator's Brochure
ICH	International Conference on Harmonisation
IEC	Independent Ethics Committee
[redacted]	
IHC	immunohistochemistry
[redacted]	
IMP	investigational medicinal product
IP	investigational product
IRB	Institutional Review Board
IUD	intrauterine device
IV	intravenous
IVIG	intravenous immunoglobulin
IVRS	interactive voice response system
k	cumulative number of subjects who experienced DLT
Kd	dissociation constant
[redacted]	
LVEF	left ventricular ejection fraction
[redacted]	
MRI	magnetic resonance imaging
[redacted]	
MTD	maximum tolerated dose
mTPI	modified toxicity probability interval
MUGA	multigated acquisition

Term	Definition
n	cumulative number of DLT evaluable subjects
NCI	National Cancer Institute
NIMP	noninvestigational medicinal product
NSCLC	non-small cell lung cancer
NYHA	New York Heart Association
ORR	objective response rate
OS	overall survival
[redacted]	
PBT	platinum-based therapy
p-DILI	potential drug-induced liver injury
PD	pharmacodynamics
PD-1	programmed cell death protein 1
PD-L1	programmed death protein ligand 1
PE	physical examination
PI	prediction interval
PFS	progression-free survival
PK	pharmacokinetics
[redacted]	
PR	partial response
QW	once a week/weekly
Q2W	every 2 weeks
Q3W	every 3 weeks
Q6W	every 6 weeks
Q8W	every 8 weeks
RECIST	Response Evaluation Criteria in Solid Tumors
RNA	ribonucleic acid
SAE	serious adverse event
[redacted]	
SD	stable disease

Term	Definition
[redacted]	
TB	total bilirubin
T-DM1	trastuzumab emtansine
T-HALF	terminal half-life
Tmax	time of maximum observed concentration
ULN	upper limit of normal
USP	U.S. Pharmacopeia
Vss/F (or Vss)	apparent volume of distribution at steady state
Vz	volume of distribution of terminal phase (if IV and if multi-exponential decline)
WOCBP	women of childbearing potential

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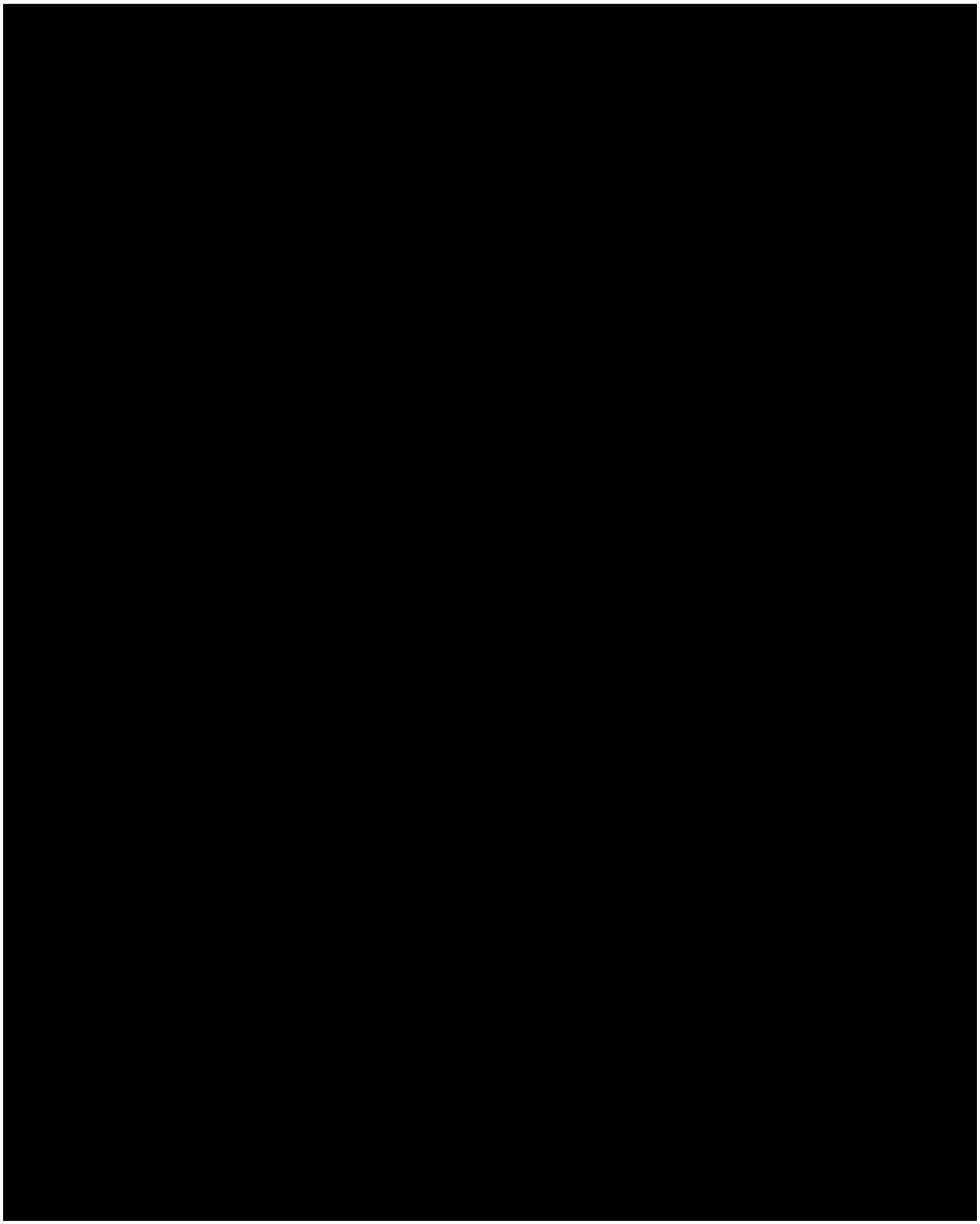

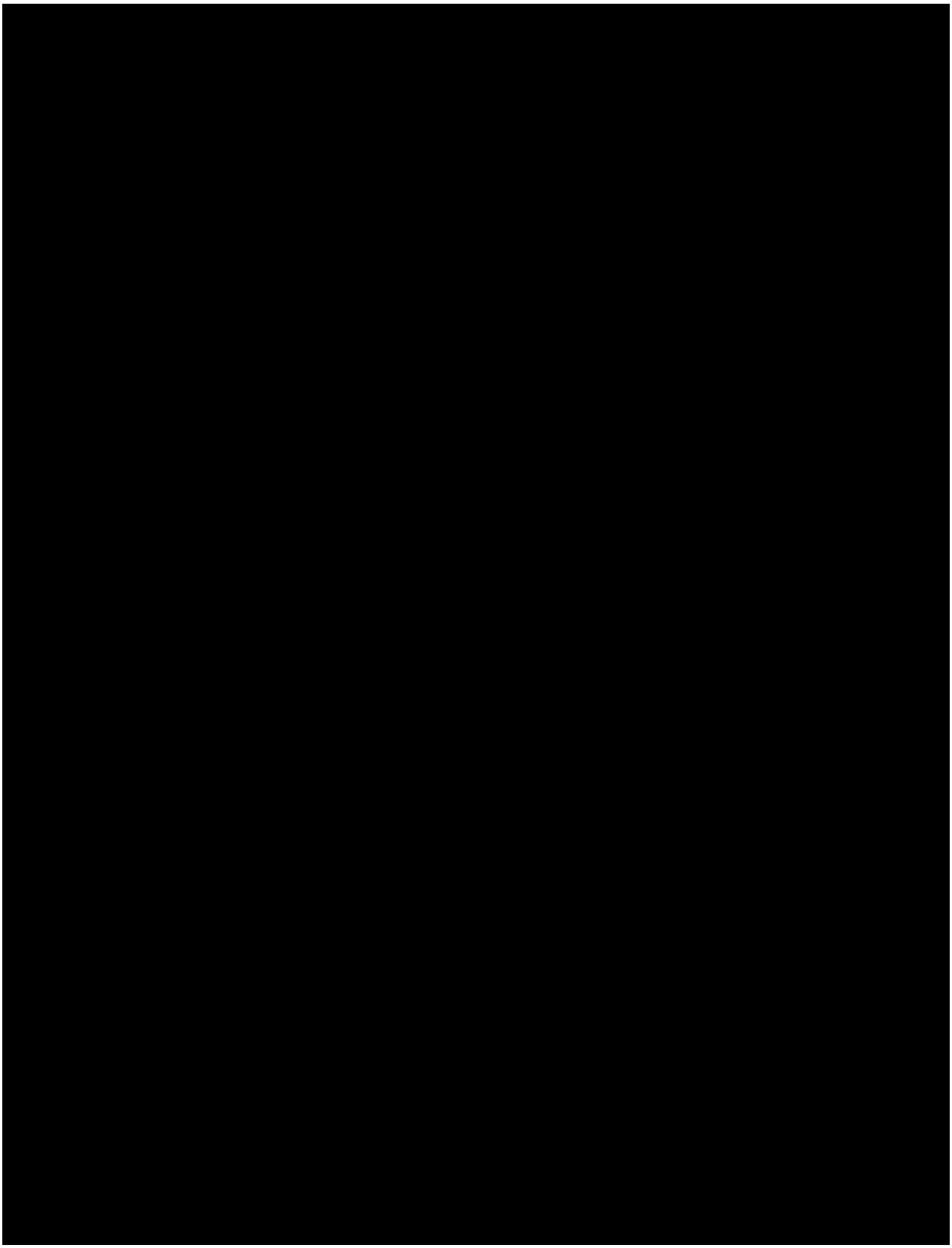

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APPENDIX 1 DOSE ESCALATION DESIGN ALGORITHM BASED ON MODIFIED TOXICITY PROBABILITY INTERVAL (MTPI) METHOD FOR MONOTHERAPY

Table 1:[a] mTPI Design[b] Decision Rule with up to 15 Subjects at a Dose

Number of subjects with DLT	Number of patients treated at current dose														
	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15
0	E	E	E	E	E	E	E	E	E	E	E	E	E	E	E
1	D	S	S	S	S	S	E	E	E	E	E	E	E	E	E
2		DU	D	D	S	S	S	S	S	S	S	S	E	E	E
3			DU	DU	DU	D	S	S	S	S	S	S	S	S	S
4				DU	DU	DU	DU	D	S	S	S	S	S	S	S
5					DU	DU	DU	DU	DU	DU	D	S	S	S	S
6						DU	DU	DU	DU	DU	DU	DU	D	S	S
7							DU	DU	DU	DU	DU	DU	DU	DU	DU
8								DU	DU	DU	DU	DU	DU	DU	DU
9									DU	DU	DU	DU	DU	DU	DU
10										DU	DU	DU	DU	DU	DU
11											DU	DU	DU	DU	DU
12												DU	DU	DU	DU
13													DU	DU	DU
14														DU	DU
15															DU

[a] **E** = Escalate to next higher dose, S = Stay at the current dose, **D** = De-escalate to the next lower dose, **U** = The current dose is unacceptably toxic

[b] Target DLT at MTD = 27% (+/-2%), flexible cohort size

APPENDIX 2 SIMULATIONS OF MTPI VS 3 + 3 DOSE ESCALATION DESIGNS

1 SIMULATIONS FOR MONOTHERAPY DOSE ESCALATION, WITH 6 DOSE LEVELS

Simulations of mTPI and 3+3 designs, as shown below, demonstrate that the mTPI design has a greater chance of selecting the correct MTD than the 3+3 design, and treating fewer subjects at sub-optimal doses.

The mTPI uses a set of decision rules guided by simple Bayesian models and requires a clinically relevant pre-determined target DLT rate and an equivalence interval (EI), within which any dose is considered close to the true maximum tolerated dose (MTD). For this study, the selected target toxicity (DLT) rate is 27% and EI [25%, 29%].

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

- E: escalating to the higher dose if interval (0, 25%) has the largest unit probability mass,
- S: staying at the same dose if interval [25, 29%] has the largest unit probability mass,
- D: de-escalating to the lower dose if interval (29, 100%) has the largest unit probability mass.

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

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

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

Settings of simulation:

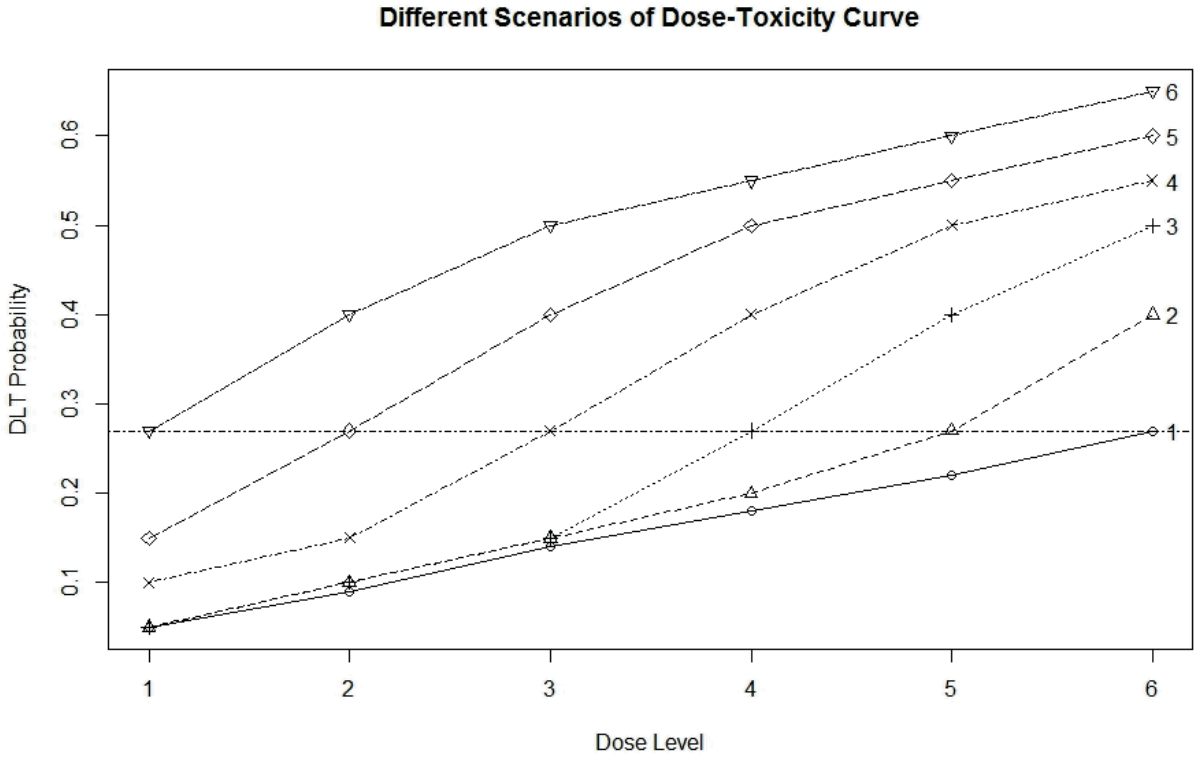
- 6 dose-toxicity scenarios, each of which with a number of 6 (expected) dose levels
- 1000 trials per scenario
- Target toxicity (Pt) for mTPI design: 27% with Equivalence Interval (EI) = [25, 29%]
- mTPI: an initial cohort size of 2 followed by (multiple) cohort size of 3 for the lowest 2 dose levels, and an initial cohort size of 3 followed by (multiple) cohort size of 3 for the rest of the 4 dose levels.
- Stopping rule for mTPI: When there are already 13 DLT evaluable subjects treated at a dose level, and mTPI still make 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

Six (6) scenarios of dose-toxicity (DLT) curves are selected to cover various possibilities and presented in the following figure with scenario ID shown at the end of line. The target toxicity rate of 0.27 is also superposed in the figure as a horizontal dashed line. The exact numeric values of DLT probability are available in each of the simulation results.

Figure 1-1: Dose-Toxicity Probability Scenarios for Monotherapy



Simulation Results

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

- MTD Selected: Frequency of each dose level being selected as MTD.
- Subjects Allocated: Number of subjected being allocated to each dose level.
- DLT rate: The average number of subjects who have DLT across all dose levels.
- Average Sample Size: The average number of subjects across all dose levels.
- Early Stop Prob: For mTPI only. It is frequency that mTPI stopping rule was triggered during the trials.

Scenario 1		Dose Level							Average DLT Rate	Average Sample Size
		-1	1	2	3	4	5	**6**		
True DLT rate			0.05	0.09	0.14	0.18	0.22	**0.27**		
MTD Selected (%)	3+3	3.6	7.8	15.8	19.3	18.2	14.1	**21.3**	15.5	
	mTPI	0.1	2.4	5.0	19.7	24.4	23.7	**24.7**	16.2	
Subjects Allocated (n)	3+3		3.6	4.0	4.0	3.4	2.7	**1.5**		19.1
	mTPI		2.9	3.8	6.6	5.8	4.2	**3.0**		26.2

Note:

The true MTD is dose level 6, the highest dose level. This represents the case that all the tested doses can be considered to be tolerated. In this case, mTPI has a better chance of picking the highest dose level.

Scenario 2		Dose Level							Average DLT Rate	Average Sample Size
		-1	1	2	3	4	**5**	6		
True DLT rate			0.05	0.10	0.15	0.20	**0.27**	0.40		
MTD Selected (%)	3+3	2.8	9.6	16.8	19.7	23.9	**18.4**	8.8	16.8	
	mTPI	0.2	2.0	8.2	20.6	30.3	**28.0**	10.8	18.4	
Subjects Allocated (n)	3+3		3.7	4.1	4.0	3.6	**2.7**	1.2		19.2
	mTPI		2.9	4.1	6.6	6.3	**4.3**	1.6		25.8

Note:

The true MTD is dose level 5, the second highest dose level. This presents the case when there is an over-toxic dose in the selected doses. mTPI picks the correct MTD by nearly 10 points (0.10) more than 3+3 does. Selection of dose level 6, the over toxicity dose, is slightly higher for mTPI.

Scenario 3		Dose Level							Average DLT Rate	Average Sample Size
		-1	1	2	3	**4**	5	6		
True DLT rate			0.05	0.10	0.15	**0.27**	0.40	0.50		
MTD Selected (%)	3+3	3.4	10.0	17.3	33.9	**25.4**	7.5	2.5	18.6	
	mTPI	0.4	3.5	6.6	29.9	**42.0**	15.2	2.4	20.6	
Subjects Allocated (n)	3+3		3.7	4.1	4.3	**3.7**	1.9	0.5		18.2
	mTPI		3.0	4.0	7.5	**7.3**	2.7	0.5		25.1

Note:

The true MTD is dose level 4, and as such, there are three sub-optimal dose levels and two over toxicity dose levels. mTPI chooses the correct MTD with 42% rate, more than 16 points over 3+3. Selection of over toxicity dose levels is more frequently by mTPI, however, at 17.6% chance versus 10.0% of 3 + 3.

Scenario 4		Dose Level							Average DLT Rate	Average Sample Size
		-1	1	2	3	4	**5**	6		
True DLT rate			0.10	0.15	**0.27**	0.40	0.50	0.55		
MTD Selected (%)	3+3	8.3	19.3	35.5	**26.7**	8.4	1.7	0.1	22.8	
	mTPI	1.8	7.3	22.4	**48.3**	17.0	2.7	0.5	24.6	
Subjects Allocated (n)	3+3		4.1	4.5	**3.9**	2.0	0.6	0.1		15.1
	mTPI		3.7.1	5.9	**8.9**	3.8	0.7	0.1		23.1

Note:

The true MTD is dose level 3. Under this case, there are two sub-optimal doses and three over toxicity dose levels. mTPI picks the correct MTD by nearly 22 points (0.22) more than 3+3 does. Selection of over toxicity dose levels by mTPI is more frequently relative to 3+3 by 10 points (0.10).

Scenario 5		Dose Level							Average DLT Rate	Average Sample Size
		-1	1	**2**	3	4	**5**	6		
True DLT rate			0.15	**0.27**	0.40	0.50	0.55	0.60		
MTD Selected (%)	3+3	19.3	39.8	**30.3**	8.6	1.8	0.2	0.0	28.9	
	mTPI	3.6	26.8	**44.2**	21.7	3.3	0.4	0.0	28.7	
Subjects Allocated (n)	3+3		4.9	**4.2**	2.2	0.6	0.1	0.0		12.1
	mTPI		6.2	**7.9**	5.3	0.9	0.1	0.0		20.4

Note:

The true MTD is dose level 2, the second lowest dose level. This presents the case when there is one sub-optimal dose level and four over-toxic dose levels. mTPI picks the correct MTD about 44% while 3+3 picks about 30% of times. For selection of over toxicity dose levels, mTPI picks more often, about 15 points (0.15) more than 3+3.

Scenario 6		Dose Level							Average DLT Rate	Average Sample Size
		-1	**1**	2	3	4	**5**	6		
True DLT rate			**0.27**	0.40	0.50	0.55	0.60	0.65		
MTD Selected (%)	3+3	48.1	**37.9**	11.9	1.9	0.2	0.0	0.0	38.8	
	mTPI	24.8	**46.8**	24.0	4.2	0.2	0.0	0.0	40.9	
Subjects Allocated (n)	3+3		**5.2**	2.8	0.8	0.1	0.0	0.0		9.0
	mTPI		**8.8**	5.2	1.7	0.1	0.0	0.0		15.8

Note:

The true MTD is dose level 1, the lowest dose, which represents an unlikely case when only the lowest dose level is considered to be tolerated. mTPI selects the correct MTD 46.8% while 3+3 does similarly, 37.9%. mTPI picks dose level -1 at a much lower rate, but chooses high dose levels more frequently.

2 SIMULATIONS FOR NIVOLUMAB COMBINATION DOSE ESCALATION, WITH 2 DOSE LEVELS

Similarly to the monotherapy setting simulations for the BMS-986148 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, similarly as described above for the monotherapy.

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.

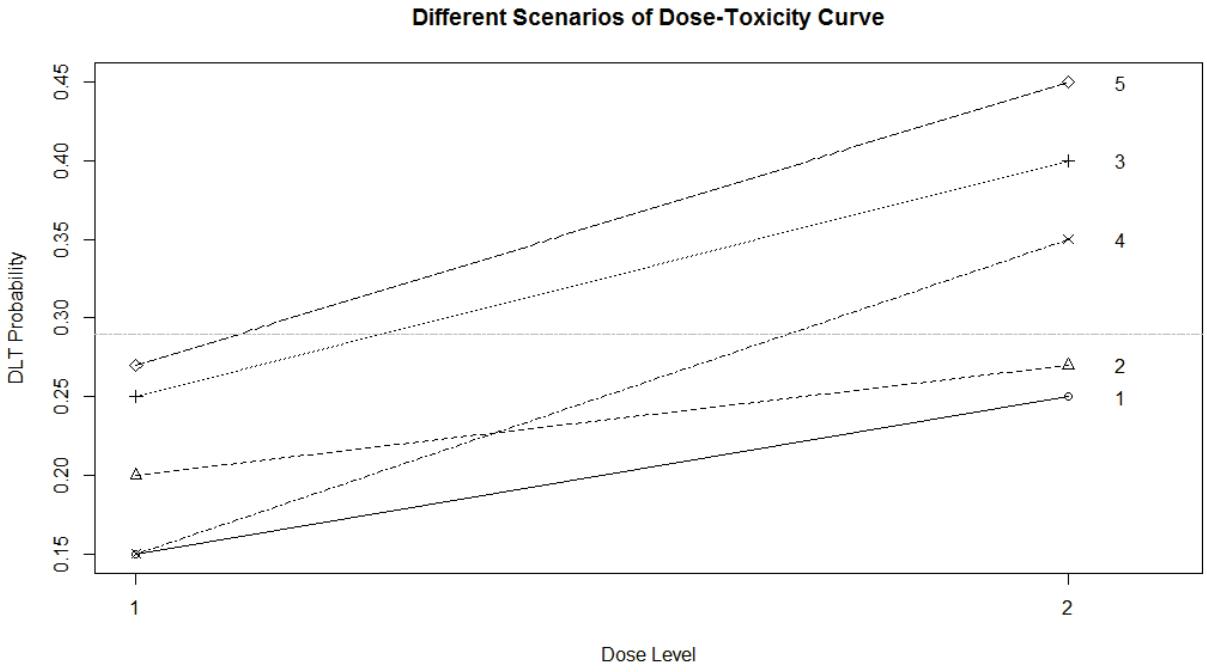
Settings of Simulation:

- 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 for Combination Therapy



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, subjects allocated, 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**		
MTD Selected (%)	3 + 3	19.7	31.3	**49.0**	19.8	
	mTPI	3.7	30.3	**66.0**	22.0	
Sample size (n)	3 + 3		4.7	**3.4**		8.1
	mTPI		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**		
MTD Selected (%)	3 + 3	33.3	26.7	**40.0**	25.4	
	mTPI	9.1	38.0	**52.9**	26.5	
Subjects Allocated (n)	3 + 3		4.7	**2.9**		7.6
	mTPI		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		
MTD Selected (%)	3 + 3	45.5	**37.4**	17.1	35.1	
	mTPI	14.6	**51.7**	33.7	34.0	
Subjects Allocated (n)	3 + 3		**5.1**	2.5		7.6
	mTPI		**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		
MTD Selected (%)	3 + 3	21.2	**47.3**	31.5	23.9	
	mTPI	4.3	**40.4**	55.3	25.7	
Subjects Allocated (n)	3 + 3		**5.1**	3.5		8.6
	mTPI		**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		
MTD Selected (%)	3 + 3	49.7	**37.3**	13.0	37.4	
	mTPI	15.8	**54.4**	29.8	35.4	
Subjects Allocated (n)	3 + 3		**5.1**	2.4		7.5
	mTPI		**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 3 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 agents and regimens.

A general principle is that differential diagnoses should be diligently evaluated according to standard medical practice. Non-inflammatory etiologies should be considered and appropriately treated.

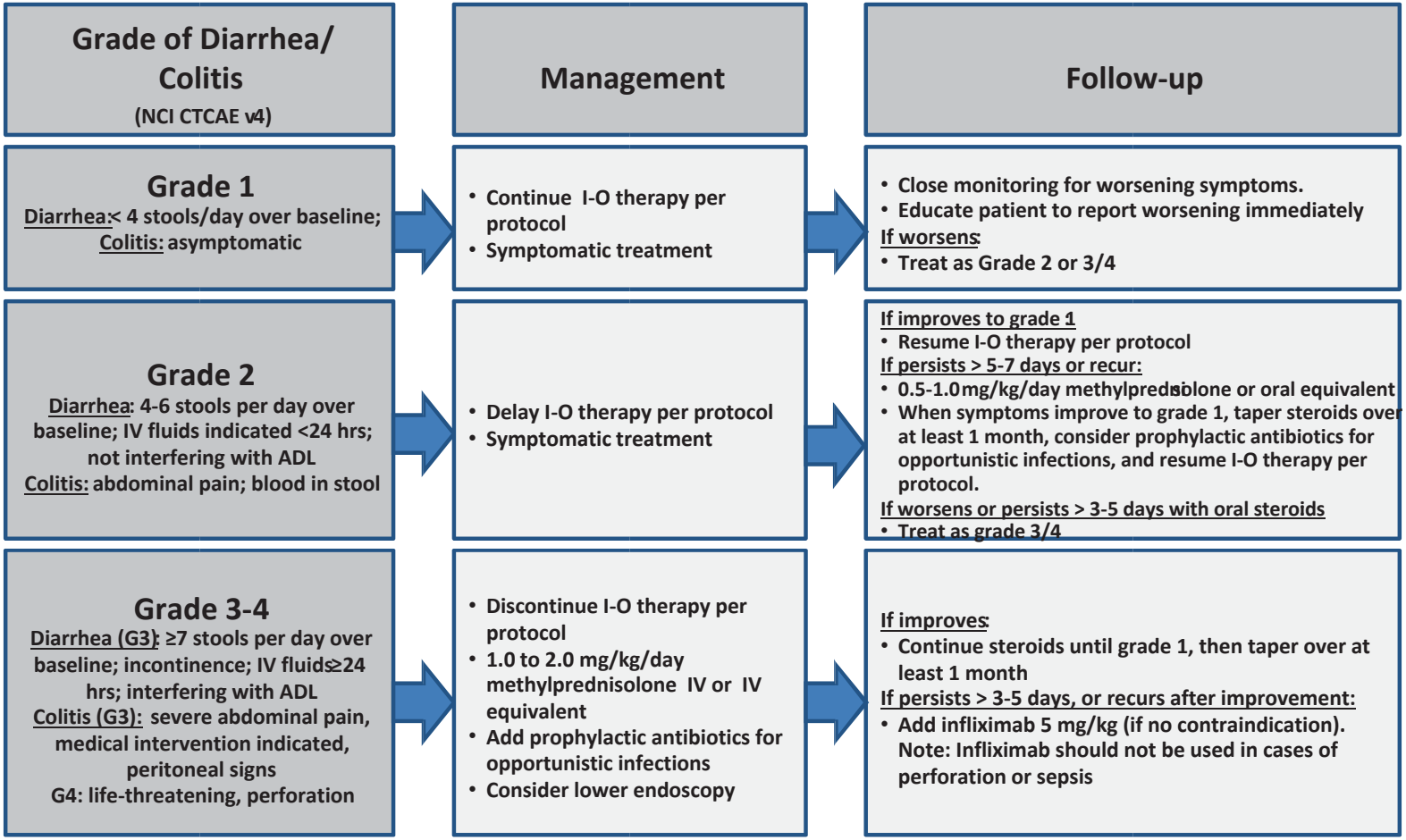
Corticosteroids are a primary therapy for immuno-oncology drug-related adverse events. The oral equivalent of the recommended IV doses may be considered for ambulatory patients with low-grade toxicity. The lower bioavailability of oral corticosteroids should be taken into account when switching to the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

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

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

GI ADVERSE EVENT MANAGEMENT ALGORITHM

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

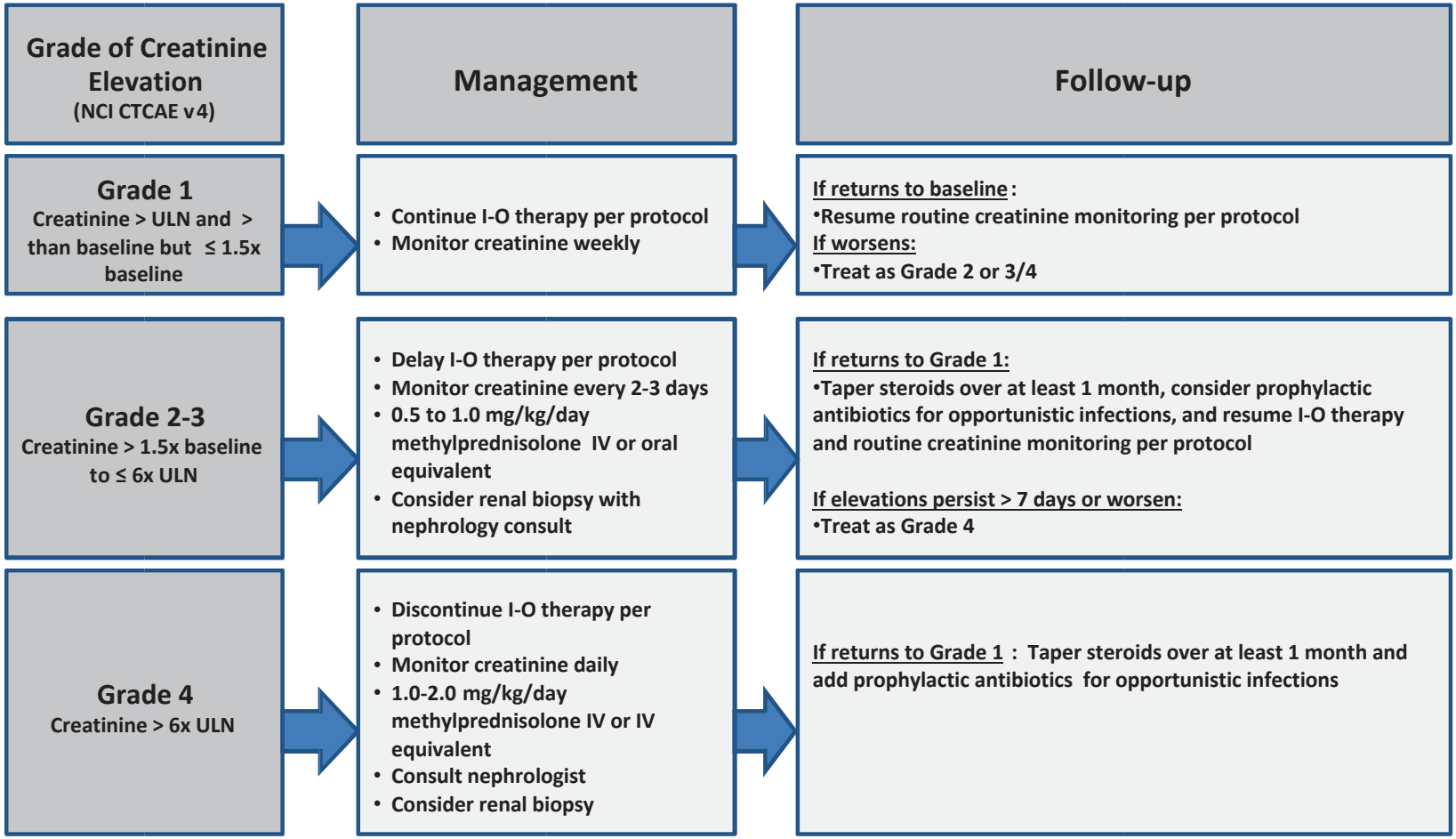


Patients on IV steroids may be switched to an equivalent dose of oral corticosteroids (e.g. prednisone) at start of tapering or earlier, once sustained clinical improvement is observed. Lower bioavailability of oral corticosteroids should be taken into account when switching to the equivalent dose of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

Updated 05-Jul-2016

RENAL ADVERSE EVENT MANAGEMENT ALGORITHM

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

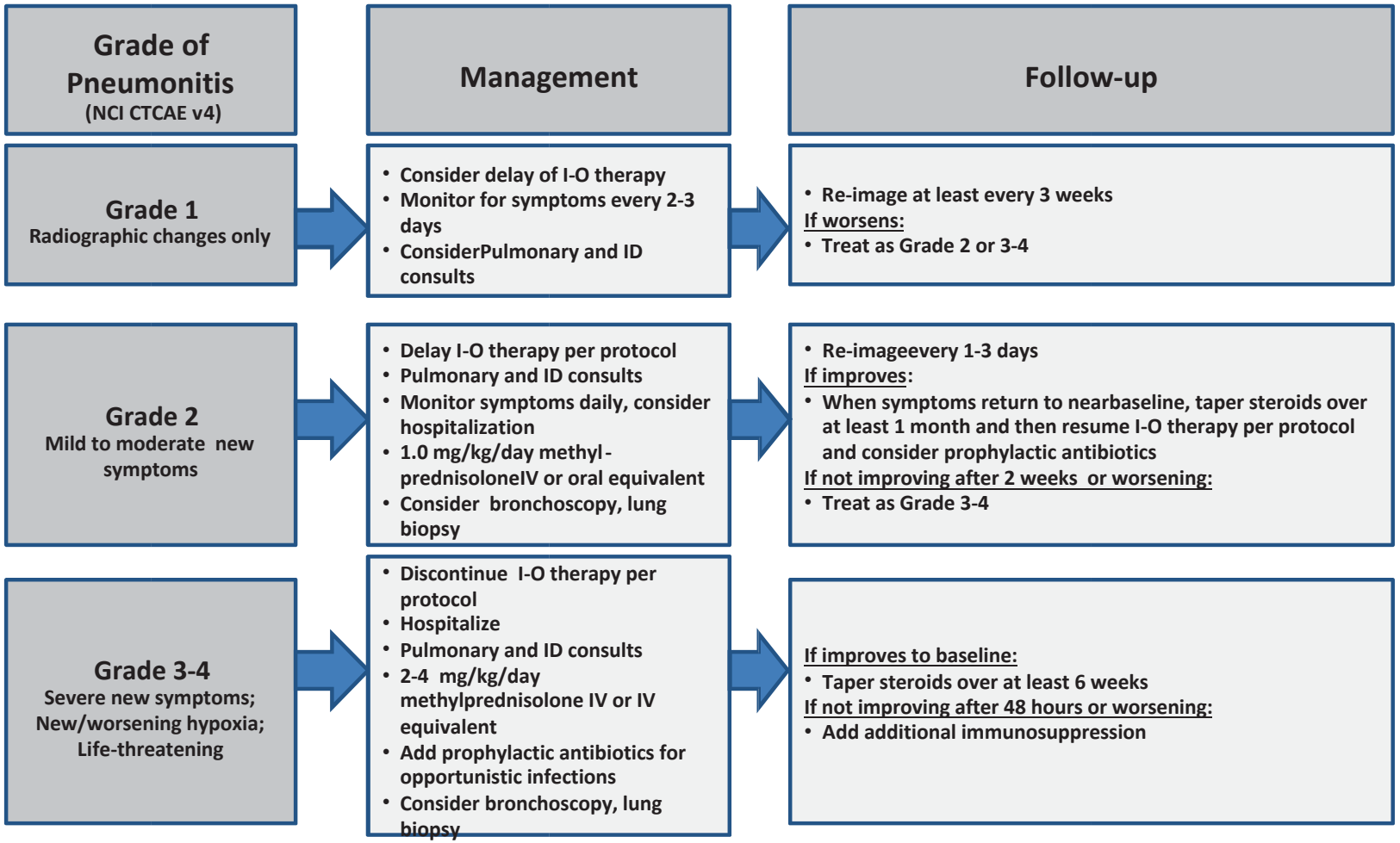


Patients on IV steroids may be switched to an equivalent dose of oral corticosteroids (e.g. prednisone) at start of tapering or earlier, once sustained clinical improvement is observed. Lower bioavailability of oral corticosteroids should be taken into account when switching to the equivalent dose of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

Updated 05-Jul-2016

PULMONARY ADVERSE EVENT MANAGEMENT ALGORITHM

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

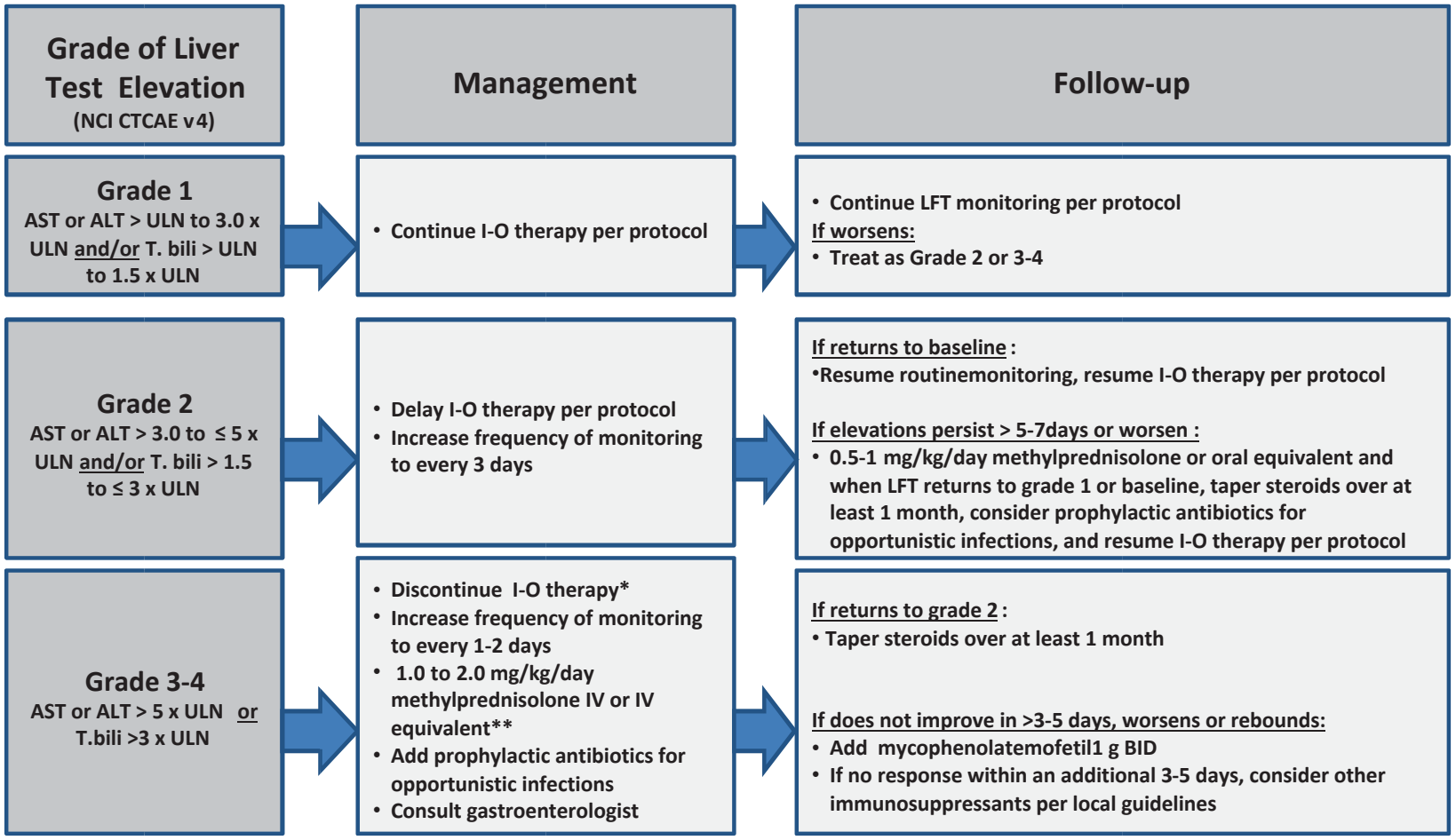


Patients on IV steroids may be switched to an equivalent dose of oral corticosteroids (e.g. prednisone) at start of tapering or earlier, once sustained clinical improvement is observed. Lower bioavailability of oral corticosteroids should be taken into account when switching to the equivalent dose of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

Updated 05-Jul-2016

HEPATIC ADVERSE EVENT MANAGEMENT ALGORITHM

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



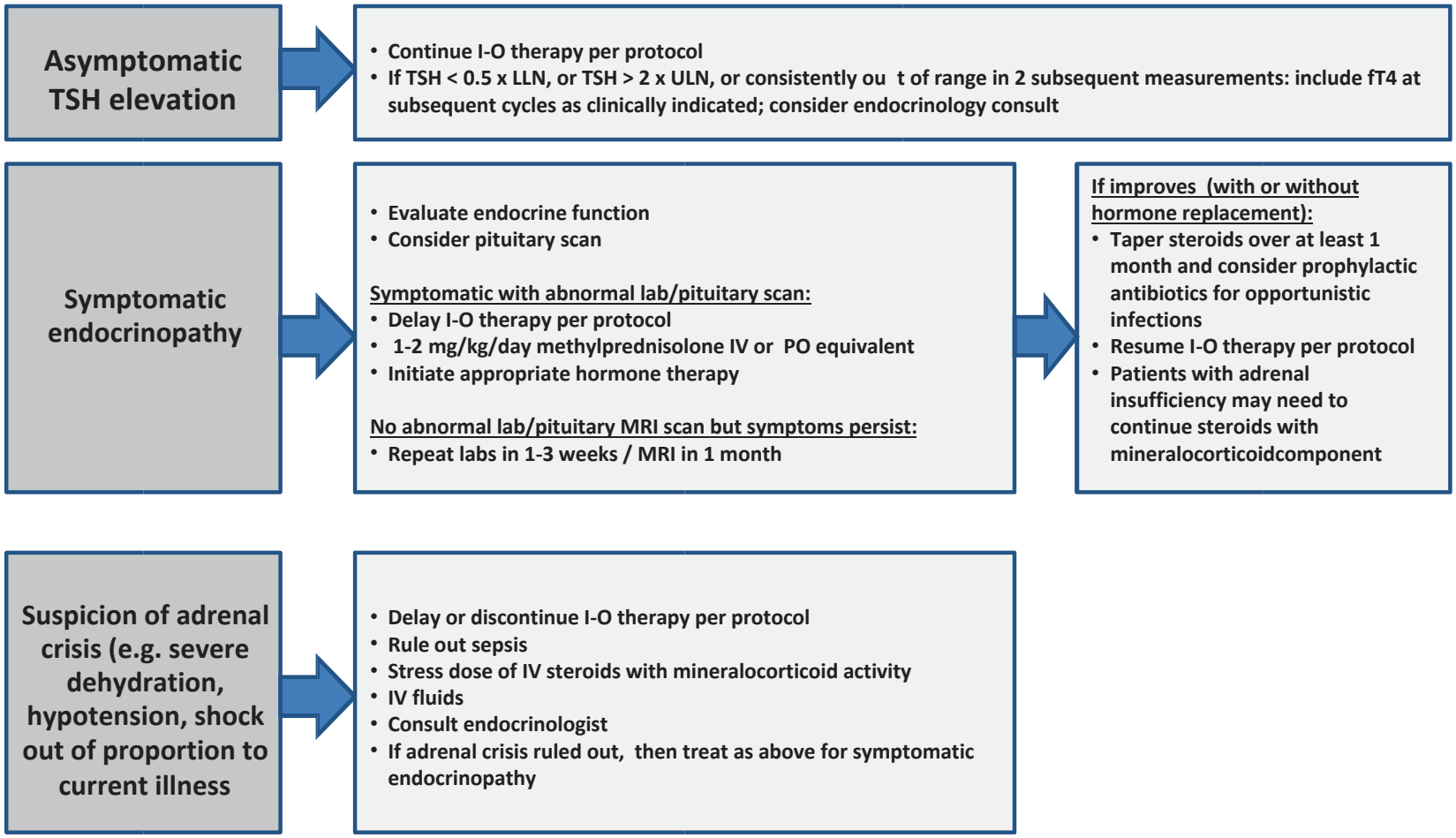
Patients on IV steroids may be switched to an equivalent dose of oral corticosteroids (e.g. prednisone) at start of tapering or earlier, once sustained clinical improvement is observed. Lower bioavailability of oral corticosteroids should be taken into account when switching to the equivalent dose of oral corticosteroids. *I-O therapy may be delayed rather than discontinued if AST/ALT ≤ 8 x ULN or T.bili ≤ 5 x ULN.

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

Updated 05-Jul-2016

ENDOCRINOPATHY MANAGEMENT ALGORITHM

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

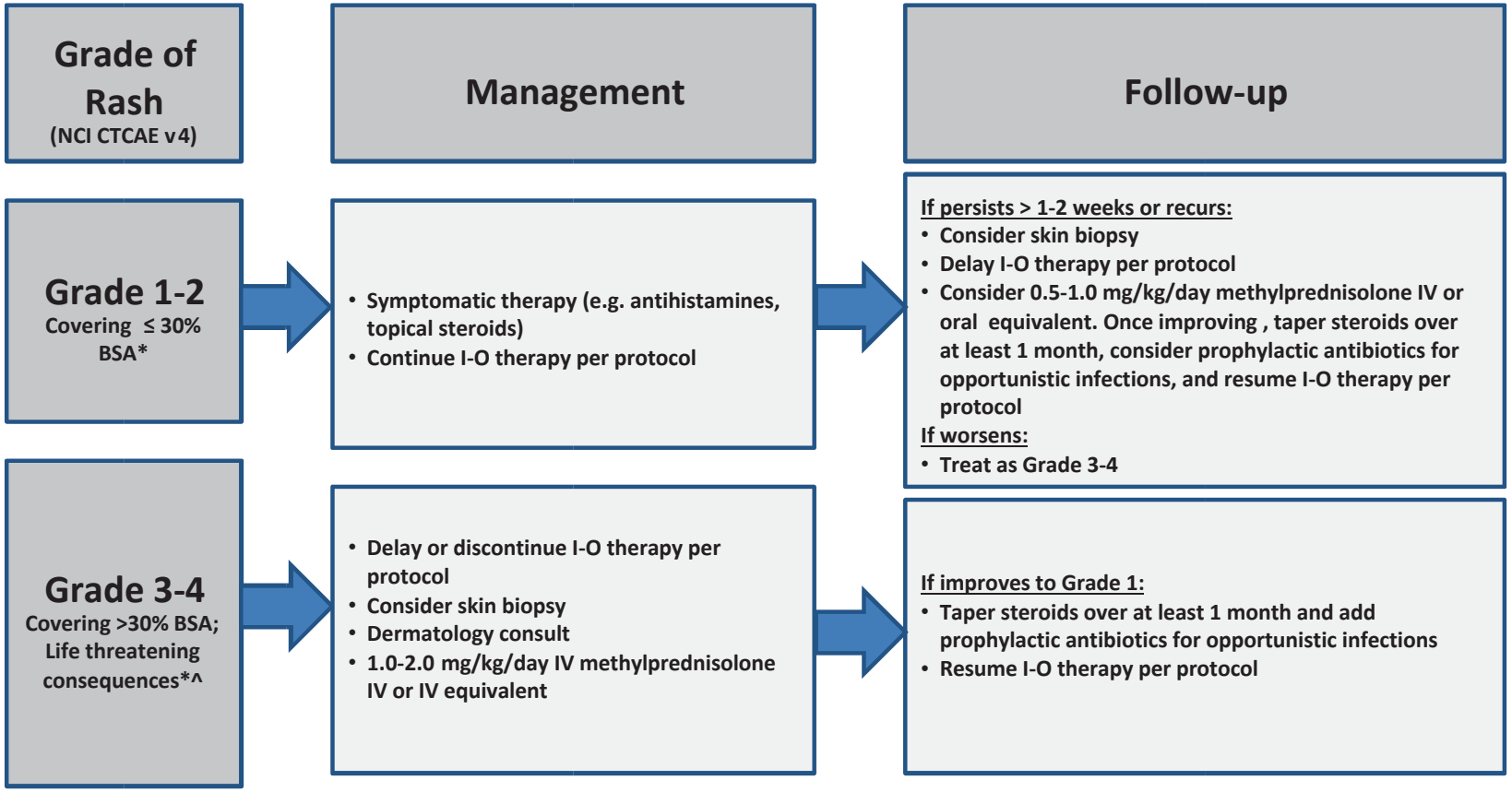


Patients on IV steroids may be switched to an equivalent dose of oral corticosteroids (e.g. prednisone) at start of tapering or earlier, once sustained clinical improvement is observed. Lower bioavailability of oral corticosteroids should be taken into account when switching to the equivalent dose of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

Updated 05-Jul-2016

SKIN ADVERSE EVENT MANAGEMENT ALGORITHM

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



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

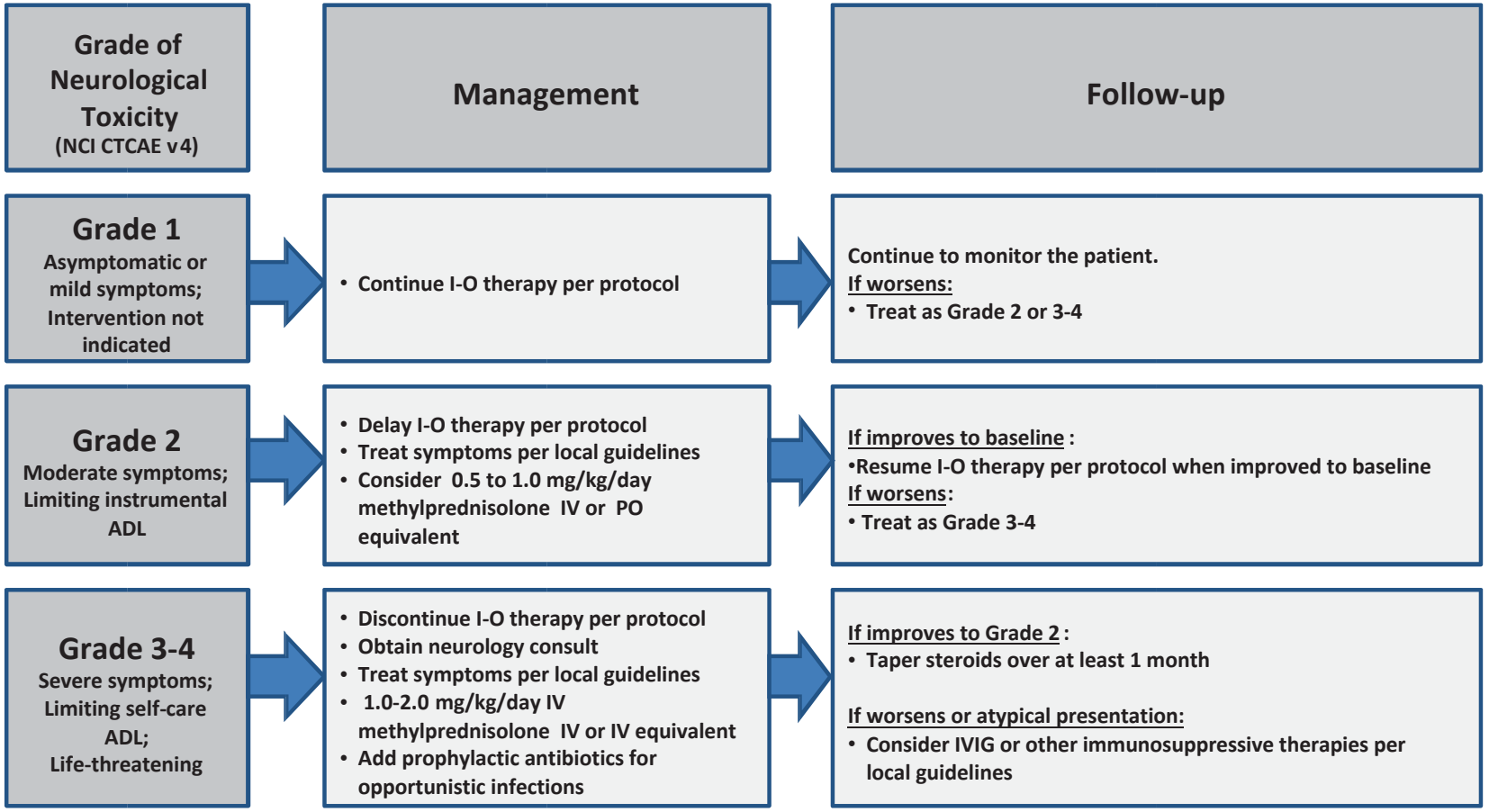
*Refer to NCI CTCAE v4 for term-specific grading criteria.

^If SJS/TEN is suspected, withhold I-O therapy and refer patient for specialized care for assessment and treatment. If SJS or TEN is diagnosed, permanently discontinue I-O therapy.

Updated 05-Jul-2016

NEUROLOGICAL ADVERSE EVENT MANAGEMENT ALGORITHM

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



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

Updated 05-Jul-2016

APPENDIX 4 RECIST V1.1 & MODIFIED RECIST CRITERIA FOR ASSESSMENT OF RESPONSE IN MALIGNANT PLEURAL MESOTHELIOMA

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 lesions*** and will be recorded and measured at baseline.

Target lesions should be selected on the basis of their **size** (lesions with the longest diameter), be representative of all involved organs, and should lend themselves to ***reproducible repeated measurements*.**

A ***sum of the diameters*** (longest for non-nodal lesions, short axis for nodal lesions) for all target lesions will be calculated and reported as the ***baseline sum diameters*.** If lymph nodes are to be included in the sum, then as noted below, only the ***short*** axis is added into the sum. The baseline sum diameters will be used as reference to further characterize any objective tumor regression in the measurable dimension of the disease.

2.1.1 Lymph nodes

Lymph nodes merit special mention since they are normal anatomical structures 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 non-pathological and should not be recorded or followed.

2.2 Non-target lesions

All other lesions (or sites of disease) including pathological lymph nodes should be identified as *non-target lesions* and should also be recorded at baseline. Measurements are not required and these lesions should be followed as **'present', 'absent', or in rare cases 'unequivocal progression'.** In addition, it is possible to record multiple non-target lesions involving the same organ as a single item on the case record form (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 non-pathological and should not be recorded or followed.

3.1.1.2 Target lesions that become 'too small to measure'

All lesions (nodal and non-nodal) recorded at baseline should have their actual measurements recorded at each subsequent evaluation, even when very small (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 non-pathological 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 non-measurable) a useful test that can be applied when assessing subjects for unequivocal progression is to consider if the increase in overall disease burden based on the change in non-measurable disease is comparable in magnitude to the increase that would be required to declare PD for measurable disease: 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
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.

Modified RECIST criteria for assessment of response in malignant pleural mesothelioma

The current standard for medical image-based tumor response assessment for patients with malignant pleural mesothelioma is the modified Response Evaluation Criteria In Solid Tumors (RECIST) measurement technique with changes classified according to the standard RECIST response classification criteria. While the modified RECIST measurement technique was developed specifically for the unique morphology and growth patterns of mesothelioma and is as follows.[1] Uni-dimensional measurements of tumor thickness perpendicular to the chest wall or mediastinum should be performed, measured in **2 sites** at **3 different levels** on CT scan. Transverse cuts used for measurement must be at least 1 cm apart, and related to anatomical landmarks in the thorax, preferably above the level of division of the main bronchi. At reassessment, pleural thickness must be measured at the same position and level. Nodal, subcutaneous, and other bi-dimensionally measurable lesions are measured uni-dimensionally as per the RECIST criteria. Uni-dimensional measurements are added to produce the total tumor measurement. The sum of 6 pleural thickness measurements = one univariate diameter[2]

CR was defined as the disappearance of all target lesions with no evidence of tumor elsewhere, and PR was defined as at least a 30% reduction in the total tumor measurement. A confirmed response required a repeat observation on two occasions 4 weeks apart. Progressive disease (PD) was defined as an increase of at least 20% in the total tumor measurement over the nadir measurement, or the appearance of one or more new lesions. Patients with stable disease (SD) were those who fulfilled the criteria for neither PR nor PD.

[1] Byrne MJ, Nowak AK. Modified RECIST criteria for assessment of response in malignant pleural mesothelioma. Ann Oncol. 2004 Feb;15(2):257-60. PubMed PMID: 14760119.

[2]Tsao AS, Garland L, Redman M, Kernstine K, Gandara D, Marom EM. A practical guide of the Southwest Oncology Group to measure malignant pleural mesothelioma tumors by RECIST and modified RECIST criteria. J Thorac Oncol. 2011 Mar;6(3):598-601. doi: 10.1097/JTO.0b013e318208c83d. PubMed PMID: 21270668; PubMed Central PMCID: PMC3643692.

APPENDIX 5 ECOG PERFORMANCE STATUS

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

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

APPENDIX 6 NYHA CLASSIFICATION

NYHA Classification

Class I	Subjects with no limitation of physical activity; ordinary physical activity does not cause undue fatigue, palpitation, or dyspnea (shortness of breath).
Class II	Subjects with slight limitation of physical activity; they are comfortable at rest, but ordinary physical activity results in fatigue, palpitation, or dyspnea.
Class III	Subjects with marked limitation of physical activity; they are comfortable at rest, but less than ordinary activity causes fatigue, palpitation, or dyspnea.
Class IV	Subjects who are unable to carry out any physical activity without discomfort; they have symptoms of cardiac insufficiency at rest; if any physical activity is undertaken, discomfort is increased.

APPENDIX 7 DRUGS WITH RISK OF TORSADES DE POINTES

Refer to:

http://www.azcert.org/medical-pros/drug-lists/drug-lists.cfm

https://crediblemeds.org/index.php/drugsearch

https://crediblemeds.org/oncosupport/

Subjects are prohibited from taking medications listed in Category 1: Drugs with Risk of Torsades de Pointes. Caution is warranted when administering BMS-986148 to subjects taking drugs associated with prolongation of QTc listed in Category 2: Drugs with Possible Risk of Torsades de Pointes.

Although ondansetron is listed in Category 1, because the effect on QTc has been shown to occur at the highest drug concentrations, IV doses of ondansetron not greater than 16 mg are permitted, as are any oral doses.

Additional information on ondansetron is available at:

http://www.fda.gov/Safety/MedWatch/SafetyInformation/SafetyAlertsforHumanMedicalProducts/ucm310219.htm

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