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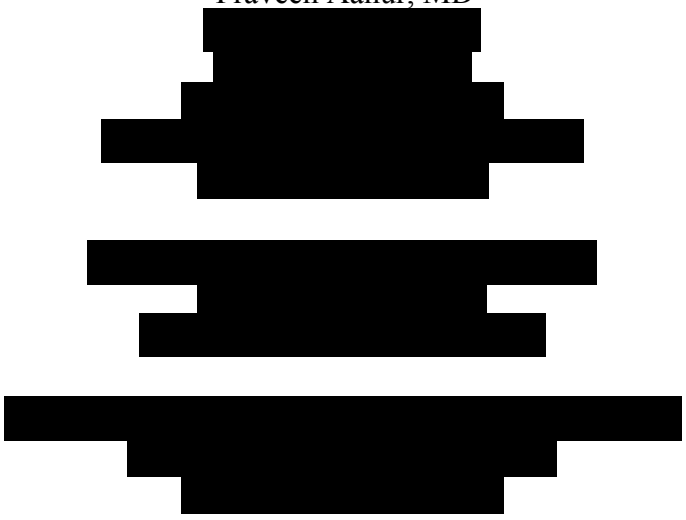
CLINICAL PROTOCOL CA015003

A Phase 1/2 Study of BMS-986183 in Subjects with Advanced Hepatocellular Carcinoma

Revised protocol Number: 03
Incorporates Amendment 03

Study Director / Medical Monitor
Praveen Aanur, MD



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

DOCUMENT HISTORY

Document	Date of Issue	Summary of Change
Revised Protocol 03	03-May-2017	Incorporates amendment 03
Amendment 03	03-May-2017	Clarifies and explains modified Fibonnaci sequence approach, removes hemolysis as hematologic DLT, defines immune modulated adverse events (IMAEs), adds criteria for dose modifications or delays for changes in total bilirubin, edits and clarifies some statistical language, clarifies some table and table footnote entries.
Revised Protocol 02	21-Mar-2017	Incorporates amendment 02

Document	Date of Issue	Summary of Change
Amendment 02	21-Mar-2017	Added dose escalation and expansion arms combining BMS-986183 and nivolumab, including revision of the study objectives, select eligibility criteria, concomitant therapies, follow-up visit schedule, and statistical analyses; updates to the overall risk/benefit assessment; and revision of dose-limiting toxicity, dose modification, dose delay, study drug re-initiation, and study therapy discontinuation criteria to align monotherapy and combination therapy. [redacted]. Clarified age criteria to include subjects 18 or age of majority. Changed hepatitis B titers to < 500 IU/mL. Added the option for treatment beyond disease progression for subjects treated with BMS-986183 and nivolumab combination therapy. Added option to receive combination therapy following disease progression in BMS-986183 dose expansion (Part 2). Updated the prior monotherapy analyses relevant to hepatocellular cancer and immune response, pharmacokinetic and anti-drug antibody samples, and mandatory and optional tumor biopsy requirements. Updated biomarker collection schedules for BMS-986183 dose escalation (Part 1) and BMS-986183 dose expansion (Part 2). Revised study design so that subjects with complete response that is confirmed at the next cycle will discontinue treatment and added that additional subjects may be added to BMS-986183 dose escalation (Part 1) to satisfy regional/local requirements (eg, in Chinese subjects where weight or genetic factors may play a role in safety, pharmacokinetics, and pharmacodynamics). Moved contraception information to an appendix, per BMS standards. Infusion reaction management text was moved to Section 3.7, Infusion Reactions. Clarified that there will be no individual dose escalations of BMS-986183, added information and a cross-reference regarding infusion reactions, and added cross-reference for dosing modifications. Added that intra-subject dose escalation is not allowed. Updated information for vital signs assessments and targeted physical examination. Clarified image collection and review and clarified that de-identified scans will be used. Added a section for immunogenicity analyses for all study parts. Changed additional research text so that prospective samples will not be collected and updated language for clarity. Changed the language describing when subjects will resume study therapy. Removed requirement for formalin-fixed, paraffin-embedded tumor samples. Clarified the use of triplicate and time-matched electrocardiograms. Updated Study Director/Central Medical Monitor address. Minor modifications, corrections, and other clarifications have been made throughout the protocol, including updates required to align with current BMS standards.
Revised Protocol 01	29-Jun-2016	Incorporates amendment 01
Amendment 01	29-Jun-2016	Changes include clarification of dose escalation decisions, clarification of hepatic DLT definition, insertion of additional ECHO/MUGA scans, clarification of additional research language, insertion of exclusion criteria for cytochrome P450 3A4 inhibitors, correction of typographical errors

Document	Date of Issue	Summary of Change
Original Protocol	03-May-2016	Not applicable

SYNOPSIS

Clinical Protocol CA015003

Protocol Title: A Phase 1/2 Study of BMS-986183 in Subjects with Advanced Hepatocellular Carcinoma

Investigational Product(s), Dose and Mode of Administration, Duration of Treatment with Investigational Product(s): Each subject will be administered a once-every-3-week intravenous (IV) dose of BMS-986183 monotherapy in BMS-986183 dose escalation (Part 1) or BMS-986183 dose expansion (Part 2), and a once-every-3-week IV dose of BMS-986183 and nivolumab (BMS-936558) in BMS-986183 and nivolumab dose escalation (Part 3) or BMS-986183 and nivolumab dose expansion (Part 4).

Study Phase: 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, pharmacokinetics (PK), and pharmacodynamics of BMS-986183 as monotherapy in BMS-986183 dose escalation (Part 1) and BMS-986183 dose expansion (Part 2) and in combination with nivolumab in BMS-986183 and nivolumab dose escalation (Part 3) and BMS-986183 and nivolumab dose expansion (Part 4) in subjects with hepatocellular carcinoma (HCC).

Objectives: The primary objective is to assess the safety and tolerability of BMS-986183 administered as monotherapy and in combination with nivolumab in subjects with HCC.

The secondary objectives are as follows:

- To assess the preliminary anti-tumor activity of BMS-986183 administered 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 antibody drug conjugate (ADC; antibody conjugated to tubulysin), and unconjugated tubulysin of BMS-986183 as monotherapy and in combination with nivolumab
- To assess the effect of dosage regimen and exposure (active ADC and unconjugated tubulysin) of BMS-986183 as monotherapy on the QT interval
- To characterize the immunogenicity of BMS-986183 as monotherapy and in combination with nivolumab

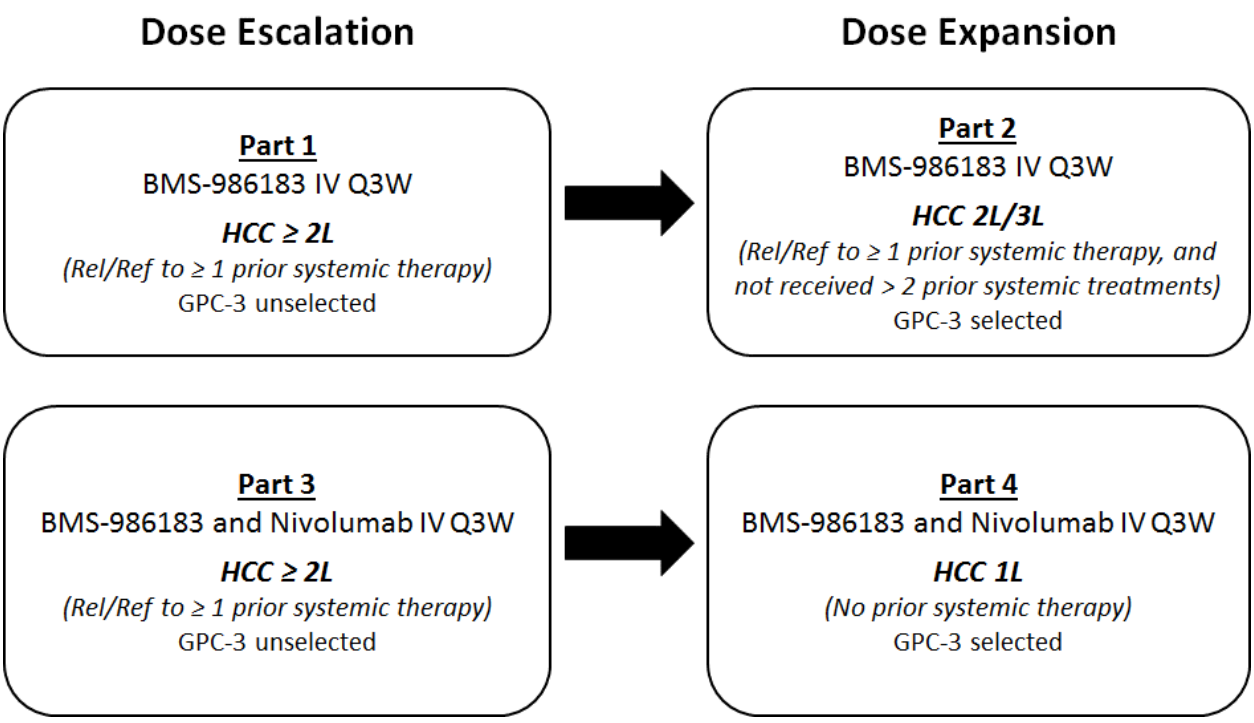
[redacted]

Study Design: This is a Phase 1/2, open-label study to characterize the safety and tolerability of BMS-986183 administered as a single agent and in combination with nivolumab to subjects with HCC. The study has 4 parts: Part 1 (Phase 1 - BMS-986183 dose escalation), Part 2 (Phase 2 - BMS-986183 dose expansion), Part 3 (Phase 1 - BMS-986183 and nivolumab dose escalation), and Part 4 (Phase 2 - BMS-986183 and nivolumab dose expansion). BMS-986183 dose escalation (Part 1) and BMS-986183 and nivolumab dose escalation (Part 3) will include subjects with HCC who have received and either progressed or been refractory or intolerant to at least 1 standard prior systemic treatment regimen. BMS-986183 dose expansion (Part 2) will include only subjects with HCC who have progressed or been refractory to at least 1 standard prior systemic treatment regimen (and not received more than 2 prior systemic treatments) AND with a plasma membrane or cytoplasmic H score $\geq$ 50 for GPC-3 expression in the tumor tissue. The dose chosen for BMS-986183 dose expansion (Part 2) will be based on results (safety, PK, and all available data) from BMS-986183 dose escalation (Part 1). BMS-986183 and nivolumab dose expansion (Part 4) will include subjects who have received no prior systemic therapy for HCC AND with a plasma membrane or cytoplasmic H score $\geq$ 50 for GPC-3 expression in the tumor tissue. The dose chosen for BMS-986183 and nivolumab dose expansion (Part 4) will be based on results (safety, PK, and all available data) from BMS-986183 and nivolumab dose escalation (Part 3).

All subjects will complete up to 4 study periods: screening (up to 28 days), treatment (for approximately 1 year or 17 cycles, with 21 days/cycle), safety follow-up (for a total of 60 days after the last dose of study drug for BMS-986183 dose escalation [Part 1]) and BMS-986183 dose expansion [Part 2] and for a total of 100 days after the last dose of study drug for BMS-986183 and nivolumab dose escalation [Part 3] and BMS-986183 and nivolumab dose expansion [Part 4]), with simultaneous response and survival follow-up periods. All subjects will continue to be followed up to 6 months from last dose of study drug. Subjects in BMS-986183 and nivolumab dose escalation (Part 3) and BMS-986183 and nivolumab dose expansion (Part 4) may also be eligible for retreatment with their originally assigned dose regimen with disease progression during follow-up. In BMS-986183 dose expansion (Part 2) only, subjects who have disease progression on BMS-986183 monotherapy will be able to receive combination treatment (their current BMS-986183 dose + flat dose of nivolumab, provided that this combination dose has been tested and found to be safe from BMS-986183 and nivolumab dose escalation [Part 3]) and after careful evaluation and discussion with the BMS Medical Monitor.

A total of approximately 151 subjects will be treated in the entire study, with approximately up to 30 subjects in BMS-986183 dose escalation (Part 1) and approximately 50 subjects in BMS-986183 dose expansion (Part 2), approximately 21 subjects in BMS-986183 and nivolumab dose escalation (Part 3), and approximately 50 subjects in BMS-986183 and nivolumab dose expansion (Part 4). The approximate duration of the study is 4 years. The end of the study will occur when the last subject has the last survival follow-up visit.

See the figure below for a schematic of the study design.



1L = first-line; 2L = second-line; IV = intravenous; Q3W = every 3 weeks; Ref = refractory; Rel = relapse.

Study Population: Subjects must have advanced HCC not amenable for management with curative intent by surgery or local therapeutic measures and must have histological confirmation of HCC, Child-Pugh Score of 6 points or less, and Eastern Cooperative Oncology Group Performance Status of 0 to 1. BMS-986183 dose escalation (Part 1) and BMS-986183 and nivolumab dose escalation (Part 3) (**dose escalation period**) will include subjects with HCC who have received and either progressed or been refractory or intolerant to at least 1 standard prior systemic treatment regimen. BMS-986183 dose expansion (Part 2) (**dose expansion period**) will include only subjects with HCC who have progressed or been refractory to at least 1 standard prior systemic treatment regimen (and not received more than 2 prior systemic treatments) AND with a plasma membrane or cytoplasmic H score of ≥ 50 for GPC-3 expression in the tumor tissue. BMS-986183 and nivolumab dose expansion (Part 4) (**dose expansion period**) will include subjects who have received no prior systemic therapy for HCC AND with a plasma membrane or cytoplasmic H score ≥ 50 for GPC-3 expression in the tumor tissue. Subjects in BMS-986183 and nivolumab dose escalation (Part 3) and BMS-986183 and nivolumab dose expansion (Part 4) must not have an active, known, or suspected autoimmune disease. For details of biopsy requirements for all study parts, please refer to Section 3.3.1 of the protocol.

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

Study Drug: includes the following investigational [medicinal] product.

Study Drug for CA015-003

Medication	Potency	IP/NonIP
BMS-986183-01 for Injection	50 mg/vial	IP
Nivolumab Solution for Injection	100 mg/vial (10 mg/mL)	IP

IP = investigational product.

Study Assessments:

- Tumor measurements with computed tomography (CT) and/or magnetic resonance imaging (MRI), as appropriate, will be conducted at screening and every 6 weeks (± 1 week) during the treatment period. Tumor measurements should be conducted earlier, if clinically indicated. Subjects with stable disease, partial response (PR), or complete response (CR) at end of treatment undergo tumor assessment via CT/MRI scans every 3 to 4 months during survival follow-up until progression, death, or initiation of new treatment (whichever occurs first). Tumor measurements will be collected in all subjects until progression or the subject's discontinuation from the study. Tumor response and progression will be evaluated in this study using Response Evaluation Criteria in Solid Tumors version 1.1 (RECIST v1.1) (see protocol Appendix 6). Initial response assessment of PR or CR must be confirmed by a consecutive assessment no less than 4 weeks (28 days) later. De-identified scans and measurements will be collected and at the Sponsor's discretion may be reviewed by independent radiologists using RECIST v1.1 criteria at a later date or at any time during the study.
- Safety Outcome Measures: Safety assessments will be based on medical review of adverse event (AE) reports and the results of vital sign measurements, physical examinations, cardiac troponins, electrocardiograms (ECGs), echocardiogram/multigated acquisition scans, liver function tests, complete blood counts, and other clinical laboratory tests. In the event of Grade 3 or higher infusion or hypersensitivity reactions, samples for PK and ADA will be collected. The incidence of observed AEs will be tabulated and reviewed for potential significance and clinical importance.
- Pharmacokinetic Measures: PK parameters (maximum observed concentration [Cmax]; time of maximum observed concentration [Tmax]; area under the concentration-time curve from time 0 to T of the last measurable concentration [AUC(0-T)]; area under the concentration-time curve in 1 dosing interval [AUC(TAU)]; concentration at the end of a dosing interval [Ctau]; trough observed concentration, including predose concentrations and Ctau[Ctrough]; total body clearance [CLT]; apparent volume of distribution at steady-state [Vss]; volume of distribution of terminal phase [Vz]; Accumulation index, ratio of Cmax at steady-state to Cmax after the first dose [AI_Cmax]; Accumulation index, ratio of Ctau at steady-state to Ctau after the first dose [AI_Ctau]; accumulation index; ratio of AUC(TAU) at steady-state to AUC(TAU) after the first dose [AI_AUC(TAU)]; average concentration over a dosing interval calculated by dividing AUC(TAU) at steady-state by tau [Css,avg], and terminal half-life [T-HALF]) will be derived from serum or plasma concentration vs time data. PK of BMS-986183 as monotherapy (BMS-986183 dose escalation [Part 1] and BMS-986183 dose expansion [Part 2]) and in combination with nivolumab (BMS-986183 and nivolumab dose escalation [Part 3] and BMS-986183 and nivolumab dose expansion [Part 4]) will be based on serum concentrations of total antibody and active ADC in all subjects. PK assessments of BMS-986183 will also be based on plasma concentrations of conjugated tubulysin and unconjugated tubulysin in all subjects. Sparse nivolumab serum concentrations will be measured in BMS-986183 and nivolumab dose escalation (Part 3) and in BMS-986183 and nivolumab dose expansion (Part 4) and may be used in integrated population PK or exposure-response analyses along with data from other nivolumab studies, which would be the subject of a separate report.
- [redacted]
- [redacted]

Statistical Considerations:

Sample Size: Approximately 151 subjects, with up to 30 subjects in BMS-986183 dose escalation (Part 1), approximately 21 evaluable subjects in BMS-986183 and nivolumab dose escalation (Part 3); approximately 50 subjects in BMS-986183 dose expansion (Part 2) and approximately 50 subjects in BMS-986183 and nivolumab dose expansion (Part 4).

BMS-986183 dose escalation (Part 1) and BMS-986183 and nivolumab dose escalation (Part 3): The sample size per dose level cannot be precisely determined but depends on the observed dose-limiting toxicity (DLT) and the decision rules of modified toxicity probability interval (mTPI). An initial cohort of 1 to 2 subjects will be enrolled sequentially to dose level cohorts 1 to 3 in BMS-986183 dose escalation (Part 1) (as long as no DLTs are observed or criteria for transitioning from 2-fold increment to modified Fibonacci criteria are **not** met. Once the first DLT is observed or after the first 3 dose level cohorts with no DLT observed, then 3 to 4 subjects will be enrolled in each dose level cohort (including the current cohort). A modified Fibonacci based escalation will be triggered after dose level 4 and no further 2 fold increases in dose will be employed thereafter. For BMS-986183 and nivolumab dose escalation (Part 3), 3 to 4 evaluable subjects may be enrolled in each cohort. Then between 2 and up to 13 DLT evaluable subjects may be enrolled to a given cohort according to mTPI algorithm. Treating additional subjects beyond the 13 would be unlikely to alter the decision specified by the mTPI algorithm.

BMS-986183 dose expansion (Part 2) and BMS-986183 and nivolumab dose expansion (Part 4): An adaptive design will be used for the expansion cohort. During the dose expansion part of the study, approximately 50 subjects in BMS-986183 dose expansion (Part 2) and 50 subjects in BMS-986183 and nivolumab dose expansion (Part 4) with a plasma membrane or cytoplasmic H score of ≥ 50 for GPC-3 expression are expected to be treated at the maximally administered dose or the maximum tolerated dose (as determined from BMS-986183 dose escalation [Part 1] and BMS-986183 and nivolumab dose escalation [Part 3]). This number 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).

In a BMS-986183 monotherapy expansion cohort or combination expansion cohort of 50 marker-positive subjects, assuming no adaptation made, if 10 or 13 responses are observed, then the ORR 90% confidence intervals (CIs) are (11%, 32%) and (16%, 38%), respectively. These calculations are based on the Clopper-Pearson method for exact CIs.

In addition, 50 subjects in BMS-986183 dose expansion (Part 2) or BMS-986183 and nivolumab dose expansion (Part 4) provide the following FNR and FPR under assumptions of expected true ORR. For BMS-986183 dose expansion (Part 2), if the true ORR is 20%, then with 50 subjects in the cohort there is 95% and 90% chance of observing at least 5 or 6 responses, respectively, and there is a 5% chance of observing 4 or fewer responses (FNR). For BMS-986183 and nivolumab dose expansion (Part 4), if the true ORR is 30%, then with 50 subjects in the cohort there is a 96% and 92% chance of observing at least 10 or 11 responses, respectively, and there is a 4% chance of observing 9 or fewer responses (FNR).

Adaptive Design: BMS-986183 dose expansion (Part 2) and BMS-986183 and nivolumab dose expansion (Part 4) will begin enrolling subjects with plasma membrane or cytoplasmic H score ≥ 50. Decisions to change the H-score cutoff for BMS-986183 dose expansion (Part 2) will not be made until the following occur:

1. Approximately 10 response-evaluable subjects are available with membrane H-score (mH-score) ≥ 150, or
2. Approximately 10 response-evaluable subjects are available with mH-score < 50 and cytoplasmic H score ≥ 50.

Under 1) if 0 responses are observed with mH-score ≥ 150 (and no other responses in the study population for the expansion cohort are observed), then the expansion cohort may stop for futility. More generally, the statistical method to guide the determination of insufficient response is Bayesian predictive probability. Under 1), if predictive probability of success is less than a pre-specified futility threshold, where success means a posterior response rate is greater than the target null efficacy rate with a very high probability at end of study, the expansion cohort may stop for futility. A decision to stop the expansion cohort will be based not only on response but also on the totality of the safety, efficacy, and PK/pharmacodynamic data.

Under 2) if 0 responses are observed with mH-score < 50 and cytoplasmic H-score ≥ 50, then the study population may be restricted to mH-score ≥ 50. More generally, if predictive probability of success is less than a pre-specified futility threshold, where success means a posterior response rate is greater than the target null efficacy rate with a very high probability at the end of study, the expansion cohort may be restricted to mH-score ≥ 50.

Enrollment will continue while interim analyses are conducted. For the remainder of the dose expansion, assuming the study is not stopped for futility, ongoing assessment of the responses may result in 3 additional adaptations, depending on whether 1) or 2) is achieved first. If 1) occurs first, then when 2) occurs, if predictive probability is less than a pre-specified futility threshold, the study population may be restricted to mH-score ≥ 50. If 2) occurs first, then when 1) occurs, if predictive probability is less than the pre-specified futility threshold, the study may be stopped for futility.

The third possible adaptation may be considered once the population is restricted to mH-score ≥ 50. Depending on the number of responses in the mH-score < 150 (ie, if 0 responses) enrollment may be further restricted to subjects with mH-score ≥ 150.

Simulations were conducted to understand the operational characteristics of the design under a variety of scenarios, and the design has adequate power to detect a variety of alternative scenarios with response rates ≥ 20% in subpopulations while maintaining adequate control of Type 1 error with expected sample sizes < 50.

Endpoints: Primary endpoints are incidence of AEs at its worst grade, serious AEs at its worst grade, AEs leading to discontinuations, deaths, and frequency of laboratory test toxicity grade shifting from baseline. Secondary endpoints are best overall response (BOR), ORR, duration of response (DoR), PFS, PFS at week 't', PK measures, changes in Fridericia-corrected QT interval (ΔQTcF), and frequency of different subject immunogenicity status (eg, subject positive antidrug antibodies, persistent positive antidrug antibodies, and others). Exploratory endpoints will also be assessed.

Analyses: Only the safety analysis and efficacy endpoint analysis are described below. Please refer to Section 8 of the protocol for a complete description of statistical analyses.

Efficacy Analyses: Efficacy results will be presented by dose and regimen. Individual BOR, DoR, and PFS will be listed using RECIST v1.1. BOR outcomes will be tabulated by dose and regimen. The ORR and PFS rates (eg, at 24 weeks) and the CI will be provided by dose, if there is enough data. The DoR and PFS will be estimated by using 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. OS may also be assessed as part of exploratory efficacy analysis by K-M plots and medians and OS rates at specified times, and by tabulation, graphics, and/or medians as appropriate for the endpoints.

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 and time-matched PK, ΔQTcF interval, ECG intervals QRS and PR, and in heart rate will be tabulated by dose and study day. Frequency distributions of maximum Fridericia-corrected QT interval (QTcF) values, maximum ΔQTcF, maximum QRS, maximum PR interval, and maximum heart rate in prespecified categories will be tabulated by dose. Scatter plots of heart rate, change in heart rate, corrected QT interval, and ΔQTcF vs time-matched active ADC and unconjugated tubulysin concentrations will be provided. A concentration-response effect of BMS-986183 as monotherapy on QTcF may be assessed by a linear mixed effects regression model for ΔQTcF on serum and/or plasma concentrations, stratified by study day, as well as pooled across days. Additional modeling of exposure-response may also be explored.

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.

TABLE OF CONTENTS

[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 pharmacodynamics of BMS-986183 as monotherapy in BMS-986183 dose escalation (Part 1) and BMS-986183 dose expansion (Part 2) and in combination with nivolumab in BMS-986183 and nivolumab dose escalation (Part 3) and BMS-986183 and nivolumab dose expansion (Part 4) in subjects with HCC.

1.3 Objectives(s)

1.3.1 Primary Objectives

To assess the safety and tolerability of BMS-986183 administered as monotherapy and in combination with nivolumab in subjects with HCC.

1.3.2 Secondary Objectives

- To assess the preliminary anti-tumor activity of BMS-986183 administered 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 of BMS-986183 as monotherapy and in combination with nivolumab
- To assess the effect of dosage regimen and exposure (active ADC and unconjugated tubulysin) of BMS-986183 as monotherapy on the QT interval
- [redacted]

[redacted]

[73]

1.4.1 Pharmacology

1.4.1.1 BMS-986183

The unconjugated anti-GPC-3 monoclonal antibody (BMS-986182) binds specifically to cells expressing endogenous GPC-3. The median effective concentration (EC_{50}) for binding to GPC-3

positive HCC (Hep3B, Huh7D12, and HepG2) and small cell lung cancer (SCLC H446) cells ranged from 0.1 to 0.9 nM. BMS-986182 also binds to cynomolgus monkey, rat, and mouse GPC-3 with similar EC_{50} values (0.1 to 0.4 nM). ^{125}I-BMS-986182 Scatchard analysis was conducted to measure binding affinity; the estimated K_d was 0.8 and 2.1 nM using Hep3B and HepG2 cells, respectively. Collectively, these data support that the cross reactivity to cynomolgus protein is nearly identical to human GPC-3 and thus cynomolgus monkeys can be used as an appropriate toxicology species.

The internalization of the unconjugated antibody was demonstrated using fluorescently tagged BMS-986182 on Hep3B cells using a high-content fluorescent imager. After 30 minutes at 37°C, the majority of the labeled antibody appeared specifically bound to the cell surface. Following a 4-hour incubation at 37°C, the labeled antibody began to localize inside the cell, resulting in a punctate staining pattern. The kinetics of BMS-986182 internalization appeared slow, with maximum intracellular accumulation occurring at 12 hours.

The binding of the ADC, BMS-986183, and the unconjugated antibody to Hep3B cells resulted in an EC_{50} of 0.2 nM and similar levels of maximum binding as determined by flow cytometry. Thus, BMS-986183 retained full binding capacity to GPC-3 positive cells. In a 72-hour proliferation assay measuring ^{3}H-thymidine incorporation, BMS-986183 inhibited proliferation of Hep3B cells by 80% and HepG2 cells by 97% with an EC_{50} of 0.2 nM and 0.1 nM, respectively. BMS-986183 activity was comparable to that of unconjugated tubulysin payload, BMS-983518, suggesting efficient release of the active cytotoxic small molecule upon binding and subsequent internalization. Activity of BMS-986183 for GPC-3 positive cells was specific, as the potency of the non-binding isotype control (ADC antibody targeting human mesothelin) showed over 570-fold and 690-fold less potent activity on mesothelin negative Hep3B and HepG2 cells, respectively.

BMS-986183 exhibited potent, dose-dependent, specific anti-tumor efficacy on GPC-3-expressing HCC xenografts Hep3B, HuH7D12, and HepG2, and SCLC xenograft H446 grown in severe combined immunodeficiency mice. On established Hep3B xenografts, BMS-986183 dosed twice weekly at 1.3 mg/kg dose showed 104% tumor growth inhibition (TGI), and 7 out of 8 mice were tumor free on Day 57 post-treatment with 4.4 mg/kg of BMS-986183. BMS-986183 exhibits over 3-fold specific anti-tumor efficacy on Hep3B xenografts, and tumor regression and long-term tumor growth control were achieved with well-tolerated doses of BMS-986183.

BMS-986183 demonstrated dose-dependent TGI of Huh-7D12 HCC xenografts. Dosing with 5 mg/kg single dose or repeat dose (RD; every 7 days × 3) BMS-986183 resulted in 81% to 94% TGI, and tumor regression and long-term tumor growth control were achieved by 15 mg/kg single dose and 11 mg/kg every 8 days × 2 doses dose treatment arms. BMS-986183 demonstrated over 10-fold specificity over non-antigen binding isotype control-ADC, and treatment delayed onset of cachexia. All treatments did not have additional toxicity compared with vehicle treated mice.

HepG2 tumor-bearing mice treated with either a single dose, 2 doses (Days 0 and 7), or 3 doses (Days 0, 6, and 9) of 5 mg/kg of BMS-986183 resulted in a TGI of 70% to 90% with approximately

a 3-fold specificity over the non-binding isotype-control ADC. Tumor regression was not achieved, possibly due to the aggressive tumor growth. A higher loading dose regimen remains to be explored to induce long-term tumor growth control in the HepG2 model.

In addition to efficacy in HCC models, BMS-986183 exhibited potent, dose-dependent, and specific anti-tumor efficacy on GPC-3 expressing SCLC xenograft H446. On Day 35 posttreatment of established H446 tumors, BMS-986183 achieved 94% and 104% mean TGI at 5 and 15 mg/kg antibody given single dose, respectively. BMS-986183 achieved tumor regression and long-term tumor growth control. The 5 mg/kg single dose and every 7 days × 3 doses RD were well tolerated, while the 15 mg/kg single dose treatment group had significant transient, yet reversible median body weight loss. Body weight loss was mitigated by split dosing of 5 mg/kg (every 7 days ×3 doses), and importantly, the overall efficacy was similar to the 15 mg/kg single dose. While BMS-986183 demonstrated dose-dependent efficacy, the ADC exhibited a steep dose response from 1.7 to 5 mg/kg, possibly due to a non-linear PK in mice. Over 3-fold specificity was achieved over the non-binding isotype-control ADC.

More detailed information about the preclinical pharmacology of BMS-986183 can be found in the current version of the BMS-986183 IB.[14]

1.4.1.2 Nivolumab

The PK of nivolumab was studied in subjects over a dose range of 0.1 to 10 mg/kg administered as a single dose or as multiple doses Q2W or Q3W. The geometric mean (percent coefficient of variation [CV]%) CL was 9.5 mL/h (49.7%); geometric mean apparent volume of distribution at steady-state (Vss) was 8.0 L (30.4%); and geometric mean terminal half-life (T-HALF) was 26.7 days (101%). Steady-state concentrations of nivolumab were reached by 12 weeks when administered at 3 mg/kg Q2W, and systemic accumulation was approximately 3-fold. The exposure to nivolumab increased dose proportionally over the dose range of 0.1 to 10 mg/kg administered Q2W. The CL of nivolumab increased with increasing body weight. The PPK analysis suggested that the following factors had no clinically important effect on the CL of nivolumab: age (29 to 87 years), gender, race, baseline lactate dehydrogenase, and PD-L1 expression. The PPK analysis suggested no difference in CL of nivolumab based on age, gender, race, tumor type, baseline tumor size, and hepatic impairment. Although Eastern Cooperative Oncology Group (ECOG) status, baseline glomerular filtration rate (GFR), albumin, body weight, and mild hepatic impairment had an effect on nivolumab CL, the effect was not clinically meaningful. Additional details are also available in the nivolumab IB.[73]

1.4.2 Toxicity

1.4.2.1 BMS-986183

BMS-986183 is an ADC targeting GPC-3 that carries a synthetic small molecule microtubule polymerization inhibitor, tubulysin, and binds to both rat and monkey GPC-3. The safety profile of BMS-986183 was established in single- and repeat-dose (up to 1-month duration) IV toxicity studies. Tubulysin was also evaluated in a series of in vitro assays and single-dose toxicity studies to increase the understanding of the safety profile of the ADC. The monkey was considered the

most appropriate species to determine the MRSD because, similar to humans, GPC-3 expression is limited in adult monkey tissues and is not expressed in the heart. This contrasts to the rat, where GPC-3 is expressed in the heart, and this expression correlates with ADC-induced cardiac toxicity in that species. For more information, refer to the BMS-986183 IB.[14]

In the pivotal single-dose IV toxicity study in rats (0, 3, 6 or 9 mg/kg; 0, 0.06, 0.12, or 0.18 μmol/kg, tubulysin equivalent), BMS-986183 was clinically tolerated at the low dose of 3 mg/kg. The doses of 6 and 9 mg/kg were severely toxic and resulted in euthanasia on Days 7 to 8. The primary BMS-986183-related findings at all doses included increased mitotic figures and/or single-cell necrosis in a spectrum of tissues/organs. These findings were considered antigen-independent pharmacologic effects of tubulysin resulting in the inhibition of chromatin separation during cell mitosis (G2/M phase arrest) followed by single-cell necrosis. The primary targets were tissues with high mitotic rate including bone marrow, GI tract, liver, lymphoid tissues, and reproductive organs. These findings were generally dose dependent and reversible in surviving rats. Additionally, BMS-986183-related cardiac findings included subacute inflammation and increases in cTnI (6.76 to 54.79× highest individual control value) at ≥ 3 mg/kg and cardiomyocyte degeneration/necrosis of the right ventricle and a low incidence of atrioventricular valvulopathy (9 mg/kg only) at the severely toxic doses of ≥ 6 mg/kg. These cardiac findings were consistent with GPC-3 expression in the rat heart and were considered antigen dependent. Noteworthy changes in clinical chemistry included increased serum AST activity (1.79 to 11.49× control) and ALT activity (1.43 to 9.13× control) at all doses, likely due to liver toxicity. The MTD was 3 mg/kg (active ADC $AUC_{[0\text{-}168h]}$ = 1,370 μg•h/mL) and doses ≥ 6 mg/kg (active ADC $AUC_{[0\text{-}168h]}$ ≥ 2,930 μg•h/mL) were severely toxic.

In the pivotal single-dose IV toxicity study in monkeys (0, 6.9, 10 or 15 mg/kg; 0, 0.1, 0.2 or 0.3 μmol/kg, tubulysin equivalent), BMS-986183 was clinically tolerated at doses ≤ 10 mg/kg. One monkey at 15 mg/kg was euthanized due to clinical signs of toxicity on Day 3 characterized by decreased activity, abnormal gait, paresis, and low body temperature. The primary BMS-986183-related findings at all doses were a result of the nonspecific inhibition of microtubule polymerization in a spectrum of tissues. Considering the limited expression of GPC-3 in adult monkey tissues, these findings were considered to be antigen independent. At ≥ 6.9 mg/kg, these findings included minimal to moderate increases in mitotic figures (indicative of cell cycle arrest in G2/M phase) and associated single-cell necrosis in multiple tissues and minimal to mild lymphoid depletion in the thymus. These findings were dose related in incidence, severity, and numbers of tissues affected and were generally reversible or partially reversible following a 4-week recovery period. At the end of the study (Day 29), additional BMS-986183-related findings at ≥ 6.9 mg/kg included minimal to moderate vacuolation of the myocardial interstitium (likely fibroblasts and/or macrophages) with no morphologic evidence of cardiomyocyte degeneration, with moderate vacuolation noted in 1 monkey at 15 mg/kg accompanied by minimal fibrosis and, in this specific monkey, increased serum cTnI levels (described below). Notable changes in clinical chemistry included increased serum AST activity (2.05 to 33.63× pretest value) and ALT activity (2.33 to 21.36× pretest value) at all doses, likely due to liver toxicity (increased mitotic figures and single-cell necrosis), and increased serum cTnI in 2 monkeys at 15 mg/kg with no microscopic

evidence of cardiomyocyte degeneration (transient increase on Day 3 in 1 monkey; 25.55× highest pretest value and persistent increase on Days 15, 22 and 29 in the other monkey; 2.57 to 4.88× highest pretest value). Hematology changes reflecting bone marrow toxicity included decreased platelets (0.29 to 0.75× most recent pretest value) with increased mean platelet volume (1.58 to 1.78× most recent pretest value) at all doses and decreased red blood cells (RBCs; 0.76 to 0.85× most recent pretest value), hemoglobin (0.75 to 0.85× most recent pretest value), and hematocrit (0.72 to 0.88× most recent pretest value) at ≥ 10 mg/kg. The transient cTnI increase of 25.55 × in 1 monkey at 15 mg/kg was likely an incidental finding, and the persistent cTnI elevation of ≤ 4.88 × in the other monkey at 15 mg/kg occurred without any evidence of myocardial damage. The myocardial interstitial vacuolation occurred without any changes in cardiac myocytes, interstitial capillary endothelial cells, or interstitial collagen fibers. At tolerated doses in monkeys, myocardial vacuolation was minimal to mild in severity, occurred without any histological evidence of myocardial fibrosis or inflammation, and was considered nonadverse. Notably, the antigen-independent microscopic findings of myocardial interstitial vacuolation in monkeys are clearly different from the cardiomyocyte degeneration and subacute inflammation that occurred in rats, which were consistent with GPC-3 expression only in rat hearts. Accordingly, the dose of 10 mg/kg (active ADC $AUC_{[0\text{-}672h]}$ = 11,700 μg•h/mL) was considered the HNSTD with minimal clinical toxicity characterized by transient clinical observations, body weight loss in individual monkeys, decreases in red cell mass and platelets, and elevations in serum transaminases. BMS-986183 at 15 mg/kg (ADC; mean $AUC_{[0\text{-}672h]}$ value of 18,800 μg•h/mL) induced severe toxicity resulting in early euthanasia of 1 monkey on Day 3.

In the pivotal 1-month repeat-dose IV toxicity study in monkeys, Q1W (5 doses at 1 and 2 mg/kg; 3 doses at 3 mg/kg) (0, 0.02, 0.04 or 0.06 μmol/kg, tubulysin equivalent) BMS-986183 was clinically tolerated at 1 mg/kg. The doses of 2 and 3 mg/kg were severely toxic and resulted in euthanasia of monkeys after 3 weekly doses at 3 mg/kg and during the recovery period at 2 mg/kg. The primary antigen-independent findings were generally dose related in incidence, severity, and/or the numbers of tissues affected and included increased mitotic figures and single-cell necrosis in multiple tissues/organs, which were generally fully or partially resolved following a 4-week (1 mg/kg) or 6-week (3 mg/kg) recovery period. Minimal to mild myocardial interstitial vacuolation (fibroblasts and/or macrophages) similar to that observed in the single-dose monkey study occurred in individual monkeys that were euthanatized in poor clinical condition at ≥ 2 mg/kg (2 monkeys at 2 mg/kg; Week 6/7 and 1 monkey at 3 mg/kg; Week 4). At the end of the recovery period (Day 56), there were no findings of myocardial interstitial vacuolation at 3 mg/kg or in any monkeys at 1 mg/kg. Additionally, BMS-986183-related increases in heart rates (up to 48%) with corresponding decreases in PR and QT interval with no corresponding microscopic findings were noted at ≥ 2 mg/kg that persisted following a 6-week recovery period at 3 mg/kg. Nerve conduction velocity evaluations indicated that deficits in peroneal motor nerve conduction velocity, sural sensory amplitude, and delay in caudal nerve onset latency occurred following the 1-week recovery period (Week 4) at 3 mg/kg with slight prolongation of cauda equine latency persisting following the 5-week recovery period (Week 8). The nerve conduction deficit, although observed at nontolerated doses, is an expected tubulysin toxicity related to

microtubule polymerization inhibition. The clinical pathology changes included dose-dependent increased serum AST activity (1.6 to 11.3× pretest value) and fibrinogen (1.2 to 3× pretest value) at all doses, serum ALT activity (2.29× pretest value) for 1 monkey at 2 mg/kg on Day 25, and decreases in RBCs (0.74 to 0.84× pretest value), hemoglobin (0.74 to 0.87× pretest value), and hematocrit (0.72 to 0.89× pretest value) at ≥ 2 mg/kg that reflected bone marrow toxicity. Increases in cTnI (2.23 to 5.46× pretest value) were noted in 1 monkey at 1 mg/kg (Week 3), 1 monkey at 2 mg/kg (Week 6), and 4 monkeys at 3 mg/kg (Weeks 3 and/or 5) with no microscopic evidence of cardiomyocyte necrosis in the heart and no clear correlation with myocardial interstitial vacuolation. The myocardial vacuolation was minimal to mild in severity, was noted without any histological evidence of myocardial fibrosis or inflammation, and was considered nonadverse. The dose of 1 mg/kg (following the 4th dose of a 5-dose regimen the active ADC $AUC_{[0\text{-}168h]}$ = 842 μg•h/mL) was clinically tolerated with minimal toxicity and was considered to be the HNSTD in this study, whereas doses ≥ 2 mg/kg (active ADC $AUC_{[0\text{-}168h]}$ ≥ 2,090 μg•h/mL) resulted in severe clinical toxicity.

Single-dose toxicity studies of tubulysin in rats and cynomolgus monkeys also were conducted. In a pivotal single-dose IV toxicity study of tubulysin in rats (0, 0.03, 0.06 or 0.12 mg/kg; 0, 0.04, 0.08 or 0.16 μmol/kg), tubulysin was clinically tolerated at 0.03 mg/kg. The severely toxic doses at ≥ 0.06 mg/kg resulted in euthanasia of the majority of rats at 0.06 mg/kg by Day 5 and all rats at 0.12 mg/kg by Days 3 to 4. The primary histopathologic findings included increased mitotic figures and single-cell necrosis in a spectrum of tissues/organs, which was consistent with nonspecific inhibition of microtubule polymerization by tubulysin.[7] The most severely affected tissues/organs included bone marrow, GI tract, lymphoid tissues, liver and skeletal muscles. All findings were generally dose dependent and either completely or partially resolved in surviving rats. The dose of 0.03 mg/kg (area under the concentration vs time curve from 0 to 96 hours of the last measurable concentration [$AUC_{(0\text{-}96h)}$] = 0.996 ng•h/mL) was considered to be the MTD. In the initial single-dose IV toxicity study with the payload in monkeys (0, 0.075 or 0.15 mg/kg; 0, 0.1 or 0.2 μmol/kg), tubulysin was not tolerated in male monkeys at ≥ 0.075 mg/kg ($AUC_{[0\text{-}24h]}$ ≥ 45.5 ng•h/mL), and the study was terminated early on Day 2 due to poor clinical condition of these monkeys; the female monkeys were not dosed. In a subsequent pivotal single-dose IV toxicity study in monkeys (0, 0.025 or 0.05 mg/kg; 0, 0.03 or 0.06 μmol/kg), tubulysin was clinically tolerated at ≤ 0.05 mg/kg. The primary histopathologic findings included increased mitotic figures and single-cell necrosis in a spectrum of tissues/organs, most notably in the bone marrow, liver, GI tract, heart, and lymphoid tissues. All findings were generally dose dependent and either completely or partially resolved following a 4-week recovery period. The high dose of 0.05 mg/kg ($AUC_{[0\text{-}96h]}$ = 41.1 ng•h/mL) was considered the MTD in the study.

Safety pharmacology evaluations of potential BMS-986183 effects on the cardiovascular, nervous, and respiratory systems were conducted as part of the pivotal single-dose and repeat-dose toxicity studies in rats (nervous and respiratory, single-dose only) and monkeys (nervous, respiratory, and cardiovascular). There were no drug-related effects on these systems in these studies after single dosing at doses up to 9 mg/kg in rats (active ADC $AUC_{[0\text{-}168h]}$ = 4140 μg•h/mL) and 15 mg/kg in

cynomolgus monkeys (active ADC $AUC_{[0\text{-}672h]}$ = 18,800 μg•h/mL) as well as after repeat Q1W dosing (5 doses) at 1 mg/kg in monkeys (active ADC $AUC_{[0\text{-}168h]}$ = 842 μg•h/mL). However, increases in heart rates (up to 48%) with corresponding decreases in PR and QT interval were noted at the severely toxic doses of ≥ 2 mg/kg that persisted following 6-week recovery period at 3 mg/kg in the repeat-dose monkey study. Additionally, nerve conduction velocity evaluations indicated that deficits in peroneal motor nerve conduction velocity, sural sensory amplitude and delay in caudal nerve onset latency occurred following 1-week recovery period (Week 4; with no microscopic correlates) at the severely toxic dose of 3 mg/kg (BMS-986183 Day 1 active ADC $AUC_{[0\text{-}168h]}$ = 2,230 μg•h/mL) with slight prolongation of cauda equine latency persisting following 5-week recovery period (Week 8; with no microscopic correlates) in the repeat-dose monkey study.

The genotoxic potential of tubulysin was evaluated in an exploratory Ames bacterial reverse-mutation study. The study results indicated that tubulysin was not mutagenic. Tubulysin was also evaluated in an in vitro secondary pharmacology screen for its ability to modulate ligand interactions against a panel of 41 targets that consisted of G-protein coupled receptors, transporters, ion channels, nuclear hormone receptors, and enzymes. Except for the L-type calcium channel, tubulysin did not significantly alter ligand binding or functional activity against any of these unique pharmacological targets at maximum concentrations between 10 and 150 μM, depending on the individual assay. In subsequent patch-clamp assays (hERG, calcium and sodium channels) and the aortic ring assay, the study results suggested that BMS-983518 inhibited cardiac hERG/I_{Kr} potassium channel, cardiac SCN5A sodium channel and L-type calcium channel currents with low potency relative to the target potency (approximately 100 pM).

In conclusion, the nonclinical toxicity profile of BMS-986183 has been well characterized and it supports first-in-human (FIH) dosing in cancer patients.

1.4.2.2 Nivolumab

Nivolumab, both as monotherapy and in combination with other drugs, can cause clinically relevant AEs, including liver toxicities, thyroiditis, pneumonitis, myocarditis, and diarrhea. However, these toxicities are typically manageable or reversible with the management algorithms provided in Appendix 2 and the nivolumab IB.[73]

Please refer to the nivolumab IB for further details on the toxicity profile of nivolumab. For details on nivolumab in HCC, refer to Section 4.5.9 and Section 5.5.9 of the nivolumab IB.

[redacted]

[redacted]

1.4.4 Clinical Pharmacology and Safety

The current study is an FIH study. There is no previous clinical experience with BMS-986183; therefore, the clinical pharmacology and safety profiles have not been characterized.

1.4.4.1 BMS-986183

BMS-986183 is predicted to have a systemic human CL and steady-state volume of distribution of 0.38 to 0.75 mL/h/kg and 0.04 to 0.06 L/kg, respectively. The projected human T-HALF is approximately 3 to 4 days. The projected T-HALF for tubulysin is approximately 24 hours.

As of 14-Feb-2017, 4 subjects have been administered BMS-986183 in BMS-986183 dose escalation (Part 1), at doses of 3 mg (n = 1), 9 mg (n = 2), and 18 mg (n = 1). No DLTs occurred. No Grade 4 related AEs or serious adverse events (SAEs) were reported. All related AEs were Grade 1 to Grade 3. The Grade 3 drug-related AE included a transient AST increase. It was noted in a subject who entered the study with a Grade 2 baseline AST level. AST levels decreased to baseline Grade 2 without intervention, and the subject was again dosed. The other Grade 1 and Grade 2 drug-related AEs included fatigue, fever, anorexia, back pain, and hypokalemia. There was no apparent relation in the incidence, severity, or causality of AEs to BMS-986183 at these dose levels.

1.4.4.2 Nivolumab

[redacted]

[redacted]

[redacted] [73].

1.5 Overall Risk/Benefit Assessment

[redacted]

or T and corrected QT interval (QTc) prolongation on ECG will be excluded from the study. Safety

As BMS-986183 is an experimental agent, it is possible that unforeseen, unknown, or

[redacted]

[redacted]

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 US Code of Federal Regulations (CFR), Title 21, Part 50 (21CFR50).

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

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

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

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

2.2 Institutional Review Board/Independent Ethics Committee

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

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

2.3 Informed Consent

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

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

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

Investigators must:

- Provide a copy of the consent form(s) and written information about the study in the language in which the subject is most proficient prior to clinical study participation. The language must be 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 ICF(s) and any other information to be provided to the subjects, prior to the beginning of the study, and after any revisions are completed for new information.
- If informed consent is initially given by a subject's legally acceptable representative or legal guardian, and the subject subsequently becomes capable of making and communicating his or her informed consent during the study, consent must additionally be obtained from the subject.
- Revise the informed consent whenever important new information becomes available that is relevant to the subject's consent. The investigator, or a person designated by the investigator, should fully inform the subject or the subject's legally acceptable representative or legal guardian, of all pertinent aspects of the study and of any new information relevant to the subject's willingness to continue participation in the study. This communication should be documented.

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

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

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

3 INVESTIGATIONAL PLAN

3.1 Study Design and Duration

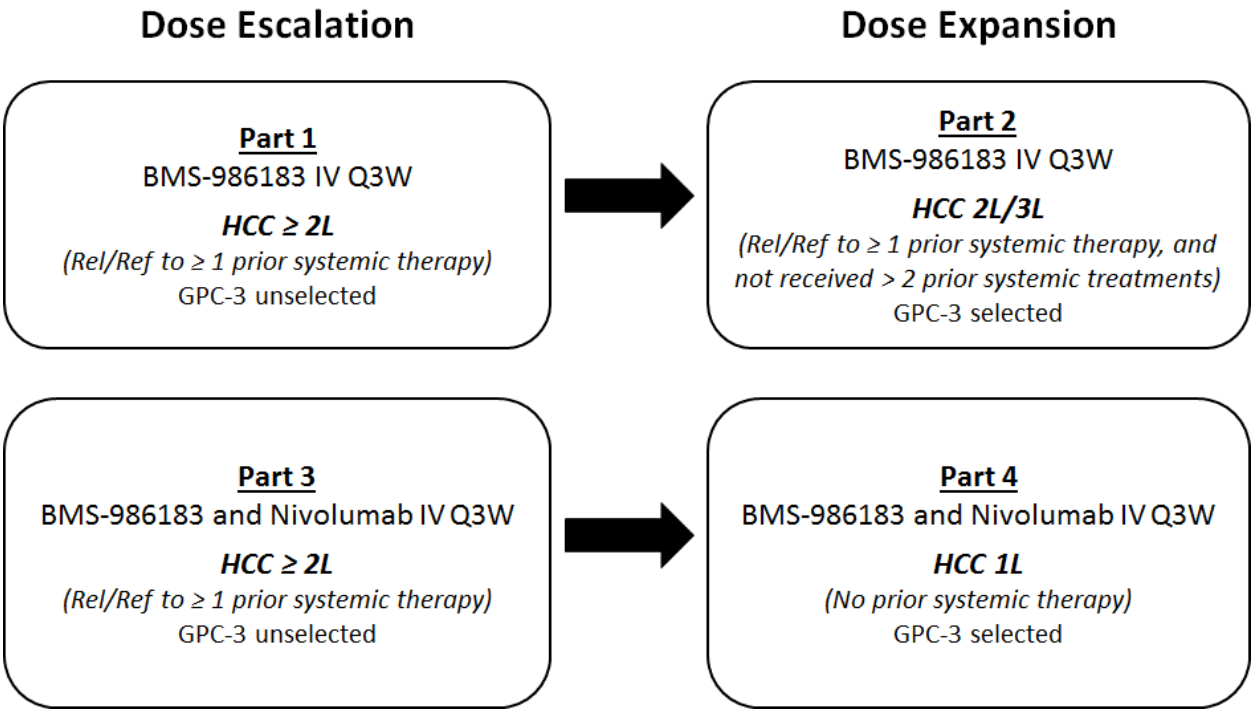
This is a Phase 1/2, open-label study to characterize the safety and tolerability of BMS-986183 administered as a single agent and in combination with nivolumab to subjects with HCC. The study has 4 parts: Part 1 (Phase 1 - BMS-986183 dose escalation), Part 2 (Phase 2 - BMS-986183 dose

expansion), Part 3 (Phase 1 - BMS-986183 and nivolumab dose escalation), and Part 4 (Phase 2 - BMS-986183 and nivolumab dose expansion). BMS-986183 dose escalation (Part 1) and BMS-986183 and nivolumab dose escalation (Part 3) will include subjects with HCC who have received and either progressed or been refractory or intolerant to at least 1 standard prior systemic treatment regimen. BMS-986183 dose expansion (Part 2) will include only subjects with HCC who have progressed or been refractory to at least 1 standard prior systemic treatment regimen (and not received more than 2 prior systemic treatments) AND with a plasma membrane or cytoplasmic H score ≥ 50 for GPC-3 expression in the tumor tissue. The dose chosen for BMS-986183 dose expansion (Part 2) will be based on results (safety, PK, and all available data) from BMS-986183 dose escalation (Part 1). BMS-986183 and nivolumab dose expansion (Part 4) will include subjects who have received no prior systemic therapy for HCC AND with a plasma membrane or cytoplasmic H score ≥ 50 for GPC-3 expression in the tumor tissue. The dose chosen for BMS-986183 and nivolumab dose expansion (Part 4) will be based on results (safety, PK, and all available data) from BMS-986183 and nivolumab dose escalation (Part 3).

All subjects will complete up to 4 study periods: screening (up to 28 days), treatment (for approximately 1 year or 17 cycles, with 21 days/cycle), safety follow-up (for a total of 60 days after the last dose of study drug for BMS-986183 dose escalation [Part 1] and BMS-986183 dose expansion [Part 2] and for a total of 100 days after the last dose of study drug for BMS-986183 and nivolumab dose escalation [Part 3] and BMS-986183 and nivolumab dose expansion [Part 4]), with simultaneous response and survival follow-up periods. All subjects will continue to be followed up to 6 months from last dose of study drug. Subjects in BMS-986183 and nivolumab dose escalation (Part 3) and BMS-986183 and nivolumab dose expansion (Part 4) may also be eligible for retreatment with their originally assigned dose regimen with disease progression during follow-up. Subjects in BMS-986183 dose expansion (Part 2) only who have disease progression may be eligible for a combination therapy extension option (see Section 3.1.2.1).

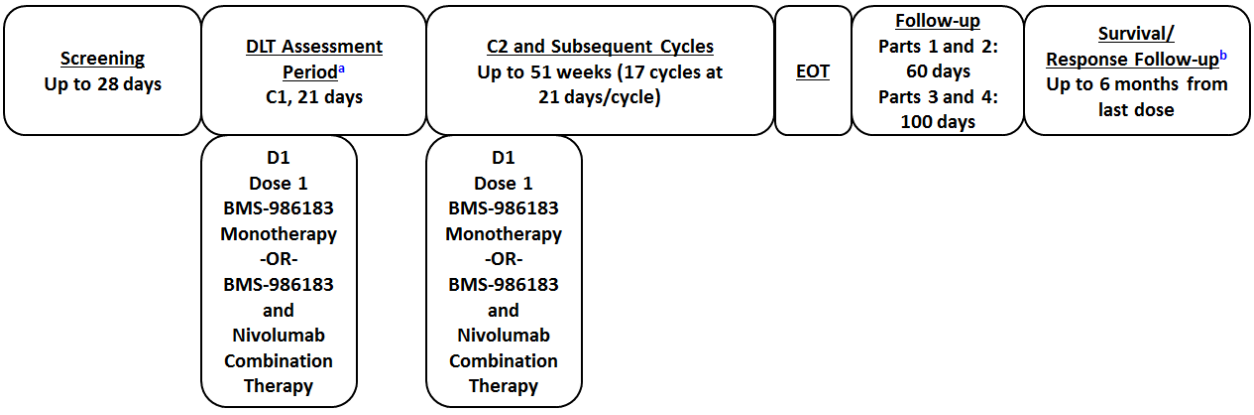
See Figure 3.1-1 and Figure 3.1-2 for a schematic of the study design and study periods, respectively.

Figure 3.1-1: Study Design



1L = first-line; 2L = second-line; Ref = refractory; Rel = relapse.

Figure 3.1-2: Dosing (Every 3 Weeks) and Study Periods



[a] DLT Assessment Period is only for BMS-986183 dose escalation (Part 1) and BMS-986183 and nivolumab dose escalation (Part 3).

[b] Response follow-up is simultaneous with survival follow-up. Only subjects with SD, PR, or CR will be followed for response at least every 3 to 4 months until progression, death, or initiation of new treatment (whichever occurs first).

C = Cycle 1 D = Day.

A total of approximately 151 subjects will be treated in the entire study, with approximately up to 30 subjects in BMS-986183 dose escalation (Part 1), approximately 50 subjects in BMS-986183

dose expansion (Part 2), approximately 21 subjects in BMS-986183 and nivolumab dose escalation (Part 3), and approximately 50 subjects in BMS-986183 and nivolumab dose expansion (Part 4). The approximate duration of the study is 4 years from the time of the first visit of the first subject to when the last subject has been followed for at least 6 months from his/her last date of treatment.

Screening Period:

The screening period will last for up to 28 days. Screening period begins after establishing the subject's initial eligibility and the subject's signing of the ICF. Specimens from tumor tissue must be provided (see Section 3.3.1 for details). The screening period either ends with confirmation of full eligibility and treatment assignment of the subject or with the confirmation that the subject is a screen failure. For information on re-screening, see Section 4.4. For details on re-enrollment, see Section 3.3.1.

Treatment Period:

Each treatment cycle consists of an IV infusion of BMS-986183 monotherapy (BMS-986183 dose escalation [Part 1] and BMS-986183 dose expansion [Part 2]) or BMS-986183 and nivolumab (BMS-986183 and nivolumab dose escalation [Part 3] and BMS-986183 and nivolumab dose expansion [Part 4]) once every 21 days. BMS-986183 monotherapy or BMS-986183 and nivolumab combination therapy will be given on Day 1 of each treatment cycle. The study drug is administered for approximately 1 year (17 cycles, with 21 days/cycle) or until complete remission, progression, unacceptable toxicity, withdrawal of consent, or study closure, whichever occurs first. Study assessments are to be collected as outlined in Table 5.1-1 and Table 5.1-2. Specific requirements for subjects treated with BMS-986183, including dose modifications, dose delays, and treatment discontinuation criteria are described in Section 4.5.2, Section 4.5.4, and Section 3.5, respectively. The treatment period ends when the subject is discontinued from study drug (see Section 3.5). Subjects will then enter the safety follow-up period.

Subjects with a response of SD, PR, or complete response (CR) at the end of a given cycle will continue to the next treatment cycle. Subjects with a confirmed CR at the end of the next cycle will discontinue treatment. Subjects will generally be allowed to continue study therapy for approximately 1 year (17 cycles, with 21 days/cycle) or until the subject meets criteria for discontinuation of study therapy as outlined in Section 3.5, whichever comes first.

Individual subjects with SD or PR may have 6 months (9 cycles, with 21 days/cycle) of extended treatment with BMS-986183 after the first treatment period (17 cycles, with 21 days/cycle) on a case-by-case basis after specific consultation and agreement between the investigator and BMS medical monitor.

Follow-up Period:

Safety Follow-up Period

All subjects will enter the safety follow-up period once the decision is made to discontinue the subject from treatment (eg, at end of treatment [EOT]).

After the EOT visit, all subjects will be evaluated for any new AEs for a total of 60 days after the last dose of study drug for BMS-986183 dose escalation (Part 1) and BMS-986183 dose expansion (Part 2) and for a total of 100 days after the last dose of study drug for BMS-986183 and nivolumab dose escalation (Part 3) and BMS-986183 and nivolumab dose expansion (Part 4). Follow-up visits should occur at 30 and 60 days (± 5 days) after the last dose. Subjects in BMS-986183 and nivolumab dose escalation (Part 3) and BMS-986183 and nivolumab dose expansion (Part 4) will have an additional visit at 100 days (± 10 days) after the last dose. All subjects will be required to complete their clinical safety follow-up visits regardless of whether they start new anti-cancer therapy, except those subjects who withdraw consent for study participation.

Subjects who develop toxicity requiring discontinuation of treatment will enter the safety follow-up period. The subject should be seen at least every 30 days, until the AE has resolved to baseline, stabilized, or been deemed irreversible.

Survival Follow-up Period

After completion of the safety follow-up period, all subjects will enter the survival follow-up period. All subjects will be followed by telephone contact, office visit, or documented clinic visit every 12 weeks (± 2 weeks) from his/her last dose of study drug for 6 months until progression or death. Both response and survival follow-up periods will occur simultaneously during the 6-month follow-up period. The duration of this period is up to 6 months following the subject's last dose of study drug. Subjects in the survival follow-up period who progress will be eligible to receive anti-cancer therapy as appropriate.

Retreatment during Survival Follow-up (Parts 3 and 4 only)

Retreatment may be allowed in BMS-986183 and nivolumab dose escalation (Part 3) and BMS-986183 and nivolumab dose expansion (Part 4) of this study for subjects with disease progression during follow-up. Subjects who complete approximately 1 year (17 cycles, with 21 days/cycle) of study therapy and 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 approximately 1 year (17 cycles, with 21 days/cycle) with the originally assigned dose regimen (eg, same dose and dose schedule administered during the first approximately 1 year [17 cycles, with 21 days/cycle]) 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. Subjects entering this phase will follow the schedule as outlined in Table 5.1-3. Samples for PK will be collected less frequently (Table 5.5.1-3).

Response Follow-up Period

Subjects with SD, PR, or CR at study drug discontinuation will continue to have radiologic and clinical tumor assessments at least every 3 to 4 months during the survival follow-up period (Section 3.1) until progression, death, or initiation of new treatment (whichever occurs first).

Radiological tumor assessments for subjects who have ongoing clinical benefit may continue to be collected after subjects complete the survival follow-up period of the study. Subjects who have disease progression following treatment with study drug will not be evaluated for response beyond the EOT visit and will be allowed to receive other tumor-directed therapy as required.

3.1.1 Dose Escalation (BMS-986183 Dose Escalation [Part 1] and BMS-986183 and Nivolumab Dose Escalation [Part 3])

3.1.1.1 BMS-986183 Dose Escalation (Part 1)

In BMS-986183 dose escalation (Part 1), BMS-986183 monotherapy will be administered Q3W (21 days/cycle), and BMS-986183 dose expansion (Part 2) may be initiated once the MTD or a tolerated dose below the MTD for BMS-986183 dose escalation (Part 1) is established.

BMS-986183 Dose Escalation (Part 1): (BMS-986183 administered every 3 weeks)

Approximately 30 subjects will be enrolled in ascending dose level cohorts starting with a flat dose of 3 mg (0.05 mg/kg based on a 60 kg body weight individual) of BMS-986183 monotherapy. BMS-986183 monotherapy will be administered Q3W in a 21-day cycle. The approach for selection of the next dose at each escalation step is presented below. For the rules for escalation decision based on DLT criteria, see Section 4.5.1.

BMS-986183 Dose Escalation (Part 1): Selection of Doses

BMS-986183 dose escalation (Part 1) will be conducted using an mTPI design. The decision governing when to escalate will follow the mTPI algorithm based on incidence of DLTs (Figure 3.1.1.1-1). The decision on what increment to increase the dose is based on DLTs, AEs, and PK and is explicitly described in Figure 3.1.1.1-2. In the mTPI design 1 to 2 subjects will be enrolled in each dose level cohort (up to 3 cohorts) until the first DLT is observed. Once the first DLT is observed or after the first 3 dose level cohorts with no DLT observed, then at least 3 subjects will be enrolled in each subsequent dose level cohort (including the current cohort).

The first dose level cohort will receive a starting dose of 3 mg (0.05 mg/kg based on a 60 kg body weight individual). This dose may produce ADC exposures below those projected for the human efficacious dose range for BMS-986183 (ie, 0.12 to 3.9 mg/kg and an ADC $AUC_{(0-\infty)}$ = 189 to 7,804 µg•h/mL). In addition, in the event that target-mediated drug disposition is observed for this compound, ADC exposures may be even lower than these target exposures. Therefore, dose escalation for each subsequent cohort of subjects will be guided first by the incidence of DLTs/AEs as graded by National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) version 4.03 (NCI CTCAE v4.03) in the first 3 weeks of dosing (DLT evaluation period) and then by available ADC exposure data.

Dose escalations based upon ADC exposure data:

In the absence of DLTs or AEs at the starting dose and in the initial dose level cohorts (1 to 2 subjects in the first 3 cohorts; at least 3 subjects in cohort 4 and subsequent cohorts), ADC exposure data will be used to guide dose escalations up to a maximum of 3-fold as long as exposures fall well below the safety margin (ie, active ADC $AUC_{(0-168h)}$ = 842 µg•h/mL)

determined for the HNSTD (1 mg/kg from the repeat-dose monkey toxicology study). A Bayesian model relating ADC exposure to dose will be derived to guide the next dose level selection. The prior information for the model is based upon target exposures derived from preclinical data (see Appendix 3 and Section 1.1.5.1 for details). Probabilities of ADC exposure at the next dose level will be calculated based upon both the prior information and actual PK data collected in the clinical study. The following criteria will be used to decide if the next dose level can be increased up to a maximum of 3-fold but within the safety margin: 1) the 90% quantile of the predicted next dose level exposure is less than the safety margin; 2) the 90% quantile of the predicted next dose level exposure is less than the target exposure; 3) the next dose level is no more than a 3-fold increase from the current dose level. The first criterion ensures with 90% probability that the next dose level exposures fall below the safety margin. In addition, a CV of 30% will be incorporated into the Bayesian model to ensure that as the dose levels increase, the distribution of next dose level exposures becomes wider and more likely to cover the safety margin, therefore making it less likely to allow dose escalations up to a maximum of 3-fold at higher doses. Once the next dose level exposures are near the safety margin or there is a first occurrence of DLTs/AEs, 3-fold increments will cease and further dose escalations will be based upon mTPI and modified Fibonacci as described previously. Of note, in the absence of DLTs or AEs at the starting dose and in the initial dose level cohorts *and* in the event that ADC exposure data are not available (e.g. samples weren't drawn at the site or there are significant delays in sample shipping) the next dose level will be a 2-fold increase from the current dose level. See Figure 3.1.1.1-2 for a summary of the decision rules for choice of dose-escalation increments, including use of PK. More details and operating simulation results illustrating the Bayesian model approach are provided in Appendix 3.

Intermediate doses may also be evaluated by safety, PK, and pharmacodynamic if agreed upon by the Sponsor/medical monitor and investigators. If there are dose levels with insufficient data to characterize BMS-986183 monotherapy PK, additional subjects may be enrolled at that dose level upon agreement of the Sponsor/medical monitor and investigators.

Dose escalations based on incidence of DLTs/AEs:

In the absence of ADC exposure data or if the exposure does not fall below the limits described above, initial dose escalations will be in increments of up to 2-fold 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

Two subjects with similar ≥ Grade 2 AEs that are considered related to BMS-986183 in a single dose level cohort, with the following exceptions: asymptomatic electrolyte abnormalities that can be managed with appropriate supplements and Grade 2 alopecia, fatigue, or nausea (Grade 2 fatigue or nausea that is less than 2 grades from baseline [ie, from Grade 1 to Grade 2] will not trigger a Fibonacci sequence). If 1 or more of the above occur, a modified Fibonacci dose escalation based upon DLTs will be employed for any subsequent dose escalations, and the next immediate escalation increment will be a maximum of 67% of the current dose followed by

increments of 50%, 40%, and 33% respectively for each subsequent dose escalation. If the mTPI algorithm indicates that escalation should continue beyond the first 33% increase, any further dose escalations will be in increments of 33% of the current dose.

In the absence of DLTS or AEs, in the initial four dose levels during dose escalation, then dose escalation will proceed as above. A modified Fibonacci based escalation will be triggered after dose level 4 and no further 2 fold increase in dose will be employed thereafter.

BMS-986183 Dose Escalation (Part 1): Dose Escalation Decision Rules

Enrollment in dose escalation and selection of the MTD will adhere to an mTPI design. The mTPI design provides a simple algorithm for decisions on escalation, expanding at the same dose, and de-escalation, depending on the number of observed toxicities after each dose level cohort (see Figure 3.1.1.1-1). The mTPI method utilizes a target toxicity (DLT) rate and equivalence interval (EI) to make decisions on escalation after each cohort and to estimate the MTD. For this study the target DLT rate is 27% and the EI is 25% to 29%.

Dose escalation will begin at a dose of 3 mg flat dose (0.05 mg/kg based on a 60 kg body weight individual; 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 1 to 2 subjects will be enrolled sequentially to dose level cohorts 1 to 3 in BMS-986183 dose escalation (Part 1) (as long as no DLTs are observed or criteria above for transitioning from 2-fold increment to modified Fibonacci criteria are **not** met). If a DLT is observed or at dose level cohort 4, the design requires at least 3 subjects per cohort (including the current cohort). A fourth subject may be enrolled in that initial cohort following agreement between the investigator and the Sponsor/medical monitor if the subject is 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 decision of the mTPI design is to expand the same dose, 3 or 4 more subjects will be enrolled to that cohort. If a decision to treat more subjects at a given dose level is specified by the mTPI algorithm when there are already at least 13 DLT evaluable subjects treated at the same dose level or the total of all treated DLT evaluable subjects reaches 30, the dose escalation will be stopped.

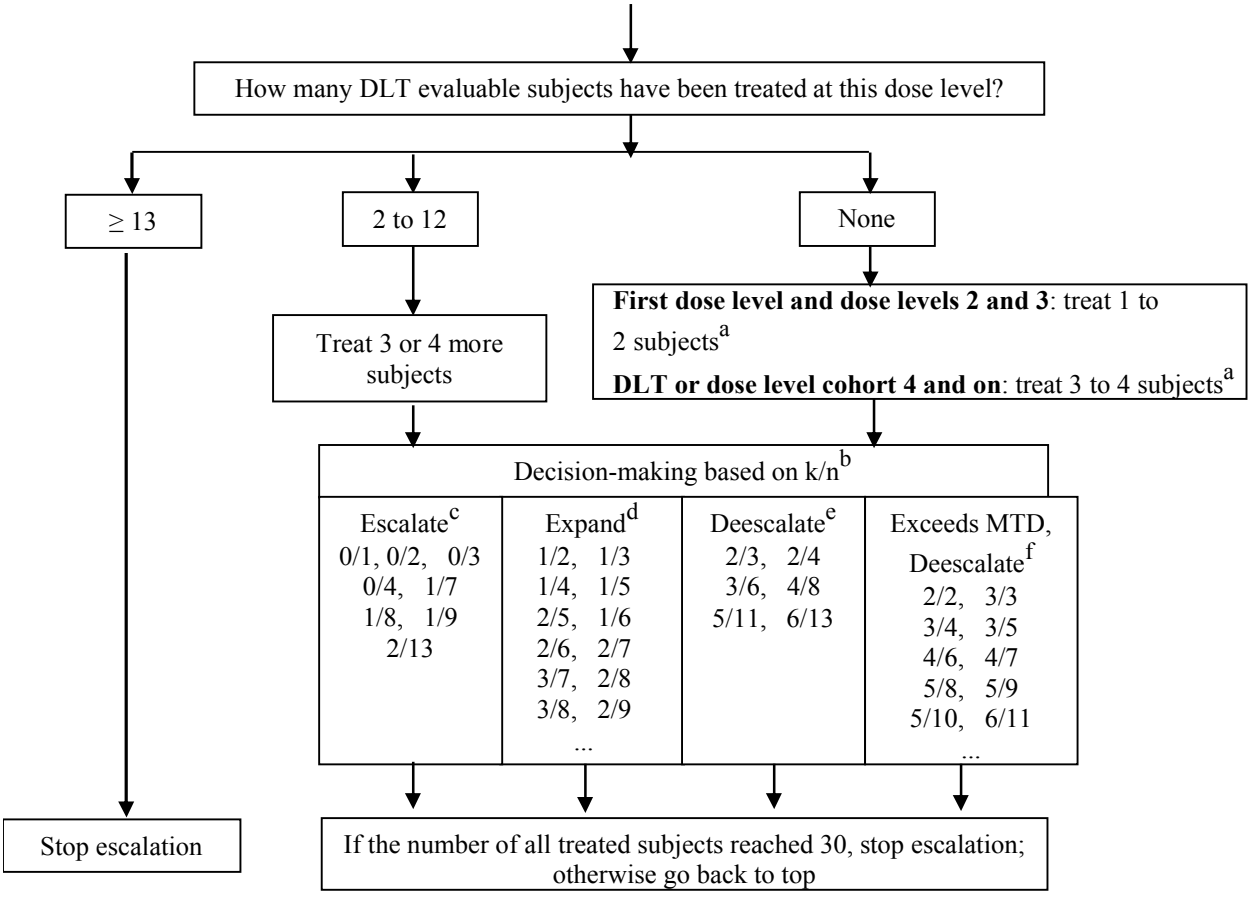
Decisions to escalate, add more subjects to the current dose, de-escalate, or de-escalate and declare the current dose as unacceptable (exceeding the MTD) will be based on the rate of DLTs in evaluable subjects within the 21-day DLT evaluation period for BMS-986183 dose escalation (Part 1) (Figure 3.1.1.1-1, and Appendix 1). Subjects with insufficient data to establish safety during the DLT evaluation period at the dose tested may be replaced upon agreement of the Sponsor/medical monitor and investigators.

There will be no intra-subject dose escalation of BMS-986183 monotherapy.

Figure 3.1.1.1-1 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 3.1.1.1-1 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 3.1.1.1-1: BMS-986183 Dose Escalation (Part 1) Algorithm



[a] Dose level cohorts 1 to 3: Treat 1 to 2 subjects initially if no DLTs and criteria for transitioning from 2-fold increment to modified Fibonacci are not met; after DLT is observed or dose level cohort 4 and on: Treat 3 to 4 subjects initially in that cohort and subsequent.

[b] At the same dose, n = cumulative number of DLT evaluable subjects, k= cumulative number of subjects who experienced DLT. Decision making based on other combinations of k/n are shown in Appendix 1.

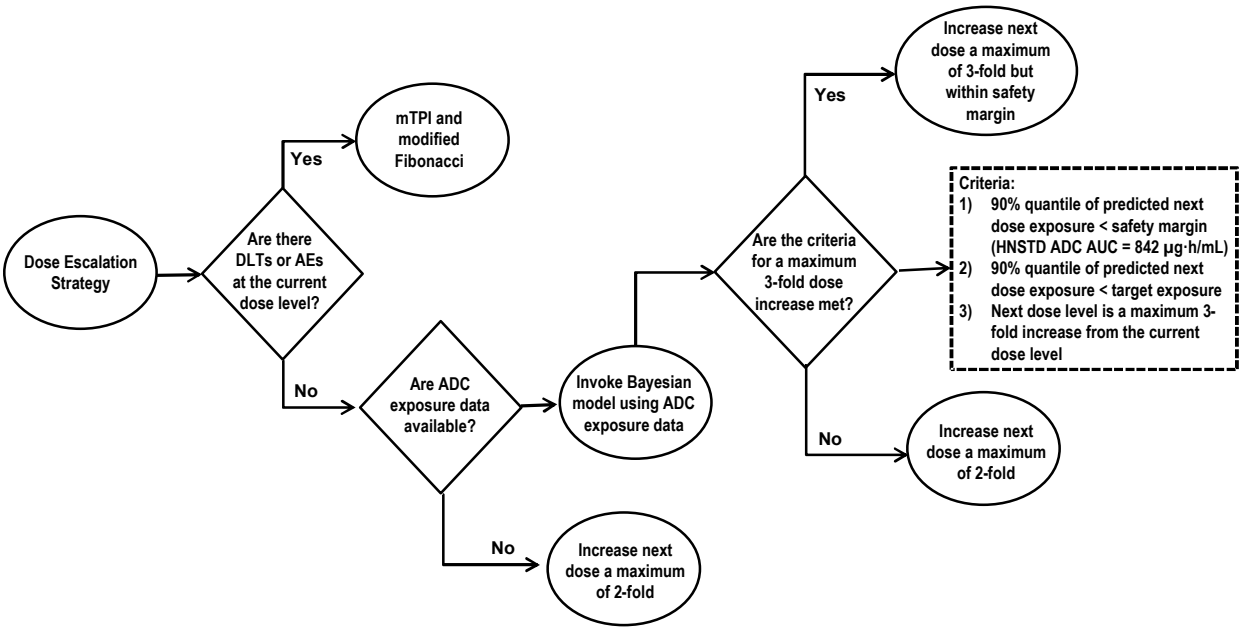
[c] Treat the next cohort of subjects at the next higher dose

[d] Treat 3 to 4 more subjects at the current dose

[e] Treat 3 to 4 more subjects at the next lower dose

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

Figure 3.1.1.1-2: Decision Tree for BMS-986183 Dose Escalation (Part 1) Increments in Starting and Initial Dose Cohorts



BMS-986183 Dose Escalation (Part 1): MTD 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.

Once the safety (during DLT evaluation) of a dose level has been established (BMS-986183 dose escalation [Part 1]), additional subjects may be added at that dose to better characterize the PK, safety, and pharmacodynamic profile or to satisfy regional/local requirements (eg, in Chinese subjects where weight or genetic factors may play a role in safety, PK, and pharmacodynamics).

3.1.1.2 BMS-986183 and Nivolumab Dose Escalation (Part 3)

Dose escalation with BMS-986183 and nivolumab combination therapy will follow the same guidelines as described in Section 3.1.1.1. An mTPI design similar to that described for BMS-986183 monotherapy (see Section 3.1.1.1) will guide dose-escalation decisions. A total of approximately 21 evaluable subjects will be treated across 4 dose levels (3 to 6 subjects for each dose level). Additional subjects may be treated if additional dose levels are required as described in "Selection of Dose Levels" below.

Selection of Dose Levels to be Evaluated

The starting dose of BMS-986183 to be combined with nivolumab at 360 mg Q3W will be at least 1 dose level below the dose that is currently considered tolerated in BMS-986183 dose escalation (Part 1) of this study (Combination Dose Level 1). The subsequent combination doses will not exceed the monotherapy dose currently considered tolerated.

Approximately 21 subjects will be enrolled in ascending dose cohorts starting with a dose of BMS-986183 (Combination Dose Level 1) with nivolumab 360 mg administered Q3W in a 21-day

cycle. Subsequent escalation to Combination Dose Level 2 and onward (or MTD determined from BMS-986183 dose escalation [Part 1]) 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-986183 is determined to exceed the MTD in combination with 360 mg Q3W of nivolumab, a lower BMS-986183 dose tested in monotherapy escalation may be explored based on available safety, PK, and biomarker information. Nivolumab will be administered as 360 mg IV Q3W in all dose cohorts.

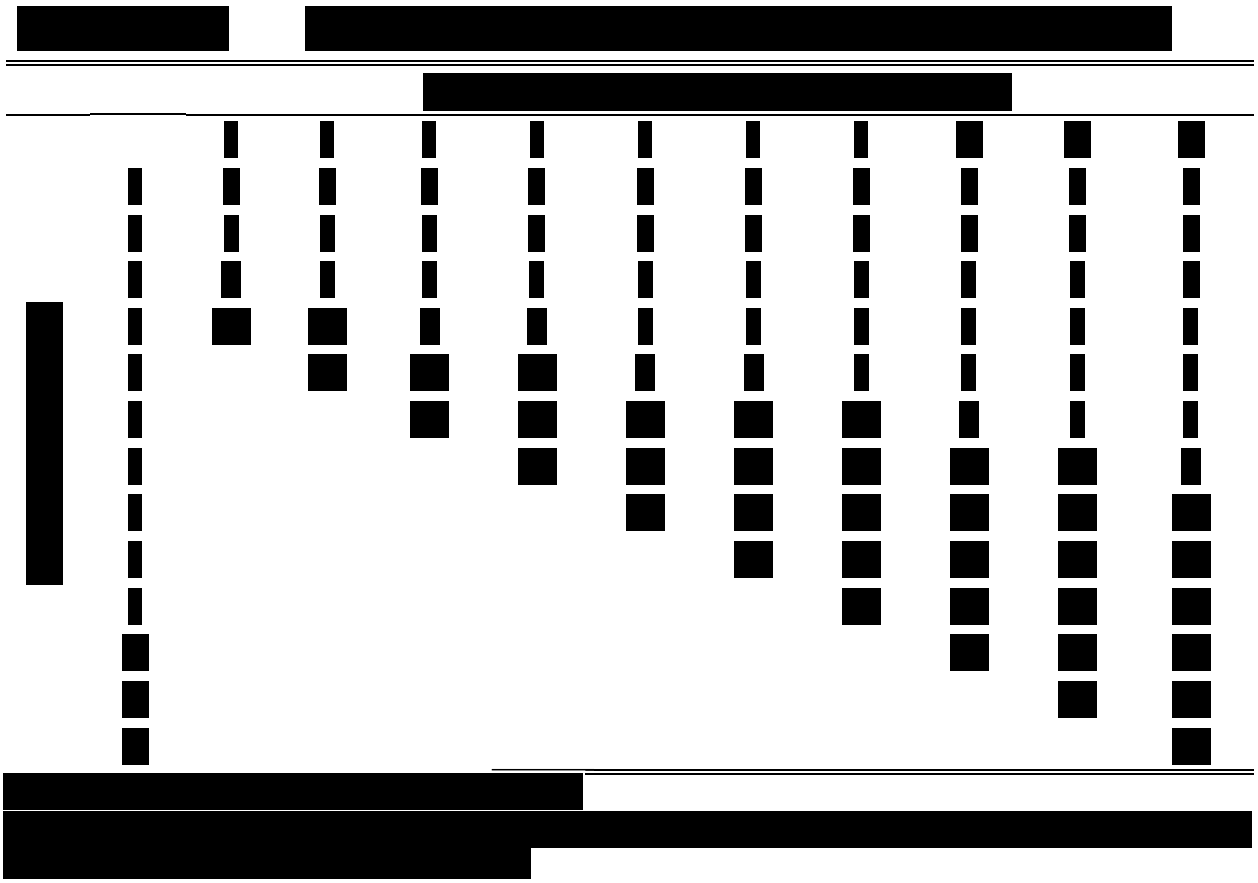
Intermediate doses of BMS-986183 in combination with nivolumab 360 mg Q3W may be evaluated if agreed upon by the BMS Medical Monitor and investigators. The next dose level will not exceed 100% of the dose increment.

No intra-subject dose escalation of BMS-986183 or nivolumab is allowed at any dose level.

Dose Escalation Decision Guide

As in BMS-986183 dose escalation (Part 1), an mTPI design (Table 3.1.1.2-1) will be used to guide dose-escalation decisions and to select the MTD. A DLT target rate of 29% (EI = [27%, 31%]) will be used for combination therapy to guide escalation decisions. Dose-escalation decisions will be based on the total number of subjects in a dose level who are DLT evaluable and the number of DLTs observed at that dose level, guided by the mTPI Bayesian model and posterior inference.

The number of subjects in the initial cohort of each dose level will be 3 to 4. The fourth subject may be enrolled following agreement between the investigator and the Sponsor/Medical Monitor if able to start the first day of dosing within approximately 1 week of the third subject in the same dose-escalation cohort. The DLT evaluation period will be 21 days. See Section 4.5.1 for further details of DLT evaluation. 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 at each of the dose levels in BMS-986183 and nivolumab dose escalation (Part 3) 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 (ie, exceeding the MTD). Subjects with insufficient data to establish safety during the DLT evaluation period at a dose level may be replaced upon agreement of the BMS Medical Monitor and investigators.



Dose Selection for BMS-986183 and Nivolumab Dose Expansion (Part 4)

At the end of the BMS-986183 and nivolumab dose-escalation period, the cumulative number of subjects who experience a DLT at each dose level will be used to estimate the MTD of BMS-986183 in combination with nivolumab using isotonic regression. The MTD will be selected as the dose level with the smaller difference of estimated toxicity rate and the target DLT rate among the dose levels explored.

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 pharmacodynamic profile or to satisfy regional/local requirements (eg, in Chinese subjects where weight or genetic factors may play a role in safety, PK, and pharmacodynamics).

3.1.2 Dose Expansion (BMS-986183 Dose Expansion [Part 2] and BMS-986183 and Nivolumab Dose Expansion [Part 4])

3.1.2.1 BMS-986183 Dose Expansion (Part 2)

The purpose of the BMS-986183 dose expansion (Part 2) will be to assess expanded safety experience, PK, preliminary anti-tumor efficacy, and pharmacodynamic effects of BMS-986183 monotherapy. Enrollment in cohort expansion will be determined by the GPC-3 expression of the subject's tumor sample (archival or fresh tumor sample). (See Section 3.3.1 for details regarding

tumor sample requirements; refer to the Laboratory Manual for procedures for collecting fresh tumors; and see Section 8.1.2 for adaptive design of subject enrollment during BMS-986183 dose expansion [Part 2].) Dose expansion will include subjects who are progressors or refractory on first-line treatment (see Section 3.3.1 for criteria).

Safety monitoring of subjects enrolled in BMS-986183 dose expansion (Part 2) of the study will be the same as conducted during BMS-986183 dose escalation (Part 1). During BMS-986183 dose expansion (Part 2), if the incidence of study drug-related AEs that require dose modification exceeds 29% (of treated subjects), then further enrollment to BMS-986183 dose expansion (Part 2) will be interrupted and the findings will be discussed between the Sponsor/medical monitor and investigators. An agreement will be reached as to whether a lower dose or an alternate dose schedule of BMS-986183 monotherapy should be examined, or whether any additional treatment guidelines should be implemented prior to enrollment of additional subjects on study.

Combination Therapy Extension Option

In BMS-986183 dose expansion (Part 2) only, subjects who have disease progression on BMS-986183 monotherapy will be able to receive combination treatment (their current BMS-986183 dose + flat dose of nivolumab, provided that this combination dose has been found to be safe from BMS-986183 and nivolumab dose escalation [Part 3]). This combination therapy option is not applicable during BMS-986183 dose escalation (Part 1). Eligible subjects may receive the combination option 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 approximately 1 year (17 cycles, with 21 days/cycle) with a dose regimen of the combination of BMS-986183 and nivolumab at the MTD or below the MTD that has been found to be safe from BMS-986183 and nivolumab dose escalation (Part 3). Such subjects must meet the eligibility criteria for receiving the combination of BMS and nivolumab as specified in Table 5.1-3.

If subjects in BMS-986183 dose expansion (Part 2) agree to receive the combination therapy, they must consent to a mandatory biopsy at clinically documented disease progression (see Section 3.3.1). In addition, subjects must wait at least 21 days since their last dose of BMS-986183 before receiving the combination therapy option, but they must receive their first dose of combination therapy within 6 weeks of their last study drug administration. These subjects will follow the assessment schedules in Table 5.1-3 and Table 5.5.1-3.

Subjects who agree to receive the combination therapy will be included in the main analysis up to and including disease progression. After disease progression, subjects who agree to receive the combination therapy will also be analyzed in a subanalysis.

3.1.2.2 BMS-986183 and Nivolumab Dose Expansion (Part 4)

The purpose of the BMS-986183 and nivolumab dose expansion (Part 4) will be to assess expanded safety experience, PK, preliminary anti-tumor efficacy, and pharmacodynamic effects of BMS-986183 and nivolumab combination therapy. Enrollment in cohort expansion will be determined by the GPC-3 expression of the subject's tumor sample (archival or fresh tumor sample). (See Section 3.3.1 for details regarding tumor sample requirements; refer to the

Laboratory Manual for procedures for collecting fresh tumors; and see Section 8.1.2 for adaptive design of subject enrollment during BMS-986183 and nivolumab dose expansion [Part 4].) Dose expansion will include subjects who have received no prior systemic therapy for HCC (see Section 3.3.1 for criteria). The dose levels of BMS-986183 and nivolumab selected for BMS-986183 and nivolumab dose expansion (Part 4) will not exceed the MTD or maximum administered dose (MAAD) of BMS-986183 and nivolumab dose escalation (Part 3) or at an alternate dose below the MTD as agreed upon by the BMS Medical Monitor and investigators.

Safety monitoring of subjects enrolled in BMS-986183 and nivolumab dose expansion (Part 4) of the study will be the same as conducted during BMS-986183 and nivolumab dose escalation (Part 3). During BMS-986183 and nivolumab dose expansion (Part 4), if the combined incidence of study drug-related AEs that require dose modification exceeds 31% (of treated subjects), then further enrollment to BMS-986183 dose expansion (Part 2) will be interrupted and the findings will be discussed between the Sponsor/Medical Monitor and investigators. An agreement will be reached as to whether a lower dose or an alternate dose schedule of BMS-986183 in combination with nivolumab should be examined or whether any additional treatment guidelines should be implemented prior to enrollment of additional subjects on study.

3.2 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 following criteria MUST be met prior to dosing on Day 1. No exceptions will be granted.

3.3.1 Inclusion Criteria

1) Signed Written Informed Consent

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

2) Target Population

a) Subjects with advanced HCC not amenable for management with curative intent by surgery or local therapeutic measures.

b) Histological confirmation of HCC. Subjects with radiological diagnosis may be enrolled for screening in the study but histological confirmation is mandatory prior to initiation of study therapy.

c) Subjects must fulfill the criteria for prior therapy and GPC-3 expression as follows:

i) **For BMS-986183 dose escalation (Part 1) and BMS-986183 and nivolumab dose escalation (Part 3)**: Subjects with HCC must have received and either progressed or been refractory or intolerant to at least 1 standard prior systemic treatment regimen. Subjects who refuse or are ineligible for standard therapy will be allowed to enroll provided their refusal/ineligibility is documented in medical records.

ii) **For BMS-986183 dose expansion (Part 2)**: Only subjects with HCC who have progressed or been refractory to at least 1 standard prior systemic treatment regimen (and not received more than 2 prior systemic treatments) AND with a plasma membrane or cytoplasmic H score ≥ 50 for GPC-3 expression (as defined in Section 5.6.1) in the tumor tissue.

iii) **BMS-986183 and nivolumab dose expansion (Part 4)**: No prior systemic therapy for HCC AND with a plasma membrane or cytoplasmic H score ≥ 50 for GPC-3 expression (as defined in Section 5.6.1) in the tumor tissue.

d) **For BMS-986183 dose escalation (Part 1) and BMS-986183 and nivolumab dose escalation (Part 3)**: A tumor tissue block or unstained slides of tumor sample (archival or recent and not older than 3 months from time of slide preparation) must be provided for biomarker evaluation, as described in Section 5.6.

i) Subjects must consent to allow the acquisition of tumor block or a minimum of 10 slides for performance of correlative studies; attempts should be made to collect a maximum of 20 unstained slides. Individual sample availability should be discussed with the Sponsor if at least 10 slides are not available for any subject.

ii) Subjects have the option to also provide fresh pre- and post-treatment biopsies. The post-treatment biopsy should be obtained on Cycle 2, 24 to 48 hours post dose and at any other time an investigator chooses to obtain a biopsy during the study period. These biopsies are not mandatory but are highly encouraged. If a subject opts to have the post-treatment biopsy taken, then a fresh tumor biopsy at screening will be mandatory because it will serve as a baseline sample with which data from the post-treatment biopsy will be compared. For both biopsies, subjects must have a soft tissue tumor lesion that can be biopsied at acceptable clinical risk (as judged by the investigator).

iii) If archival slides do not meet the requirements (minimum 10 slides and not older than 3 months from time of slide preparation) or are not available, then slides from a fresh biopsy will be used to assess GPC-3 expression.

e) **For BMS-986183 dose expansion (Part 2) and BMS-986183 and nivolumab dose expansion (Part 4)**: A tumor tissue block or unstained slides of tumor sample (archival or recent and not older than 3 months from time of slide preparation) is mandatory for biomarker evaluation, as described in Section 5.6.

i) Subjects must consent to allow the acquisition of existing tumor block or a minimum of 10 slides for performance of correlative studies; attempts should be made to collect a maximum of 20 slides. Individual sample availability should be discussed with the Sponsor if at least 10 slides are not available for any subject.

ii) In addition to archived samples, a fresh biopsy sample is mandatory at screening. For this biopsy, subjects must have a soft tissue tumor lesion that can be biopsied at acceptable clinical risk (as judged by the investigator) at baseline. Subjects must consent to the pretreatment fresh biopsy as a condition of protocol participation. In this setting, if adequate tissue is not obtained during the first procedure then a repeat biopsy should be considered based on the investigator's assessment of clinical risk. However, a repeat biopsy is not required to meet eligibility in BMS-986183 dose escalation (Part 1).

iii) Both archived biopsy/slides and slides from fresh biopsy will be used for determining eligibility in BMS-986183 dose expansion dose expansion (Part 2) or BMS-986183 and nivolumab dose expansion (Part 4) based on GPC-3 expression (see Section 5.6 for details regarding GPC-3 expression cut-off required for eligibility). If the fresh biopsy meets defined cut-off criteria for GPC-3 expression, then the subject will be eligible. If the fresh biopsy does not meet defined cut-off criteria for GPC-3 expression, then the subject will not be eligible. If the archival slides meet defined cut-off criteria for GPC-3 expression and data from the fresh sample are not evaluable, then the subject will be eligible. If the archival slides do not meet the requirements (a minimum of 10 slides and not older than 3 months from time of slide preparation) and data from the fresh sample are not evaluable, then the subject will not be eligible. If archival tissue is not available and only fresh tumor biopsy can be obtained for assessing eligibility, such subjects can be enrolled in study after discussion with the Sponsor.

iv) A mandatory fresh post-treatment biopsy is to be obtained at Cycle 2, 24 to 48 hours post dose from 20 subjects enrolled in BMS-986183 dose expansion (Part 2) and from 20 subjects enrolled in BMS-986183 and nivolumab dose expansion (Part 4). The biopsy is optional but highly encouraged for the other 30 subjects enrolled in BMS-986183 dose expansion (Part 2) and BMS-986183 and nivolumab dose expansion (Part 4). If 20 subjects out of the first 30 subjects enrolled in BMS-986183 dose expansion (Part 2) and BMS-986183 and nivolumab dose expansion (Part 4) do not opt to provide a biopsy at Cycle 2, 24 to 48 hours post dose, then this biopsy will be mandatory for the remaining 20 subjects to be enrolled in BMS-986183 dose expansion (Part 2) and BMS-986183 and nivolumab dose expansion (Part 4). Post-treatment biopsies can also be obtained at any other time an investigator chooses to obtain a biopsy during the study period. For tumor biopsies, subjects must have a soft tissue tumor lesion that can be biopsied at an acceptable clinical risk (as judged by the investigator).

v) Lesions selected for biopsy should be large enough to allow for the collection of tumor tissue using a minimum 18-gauge or larger needle with an expected core sample length of 5 mm. A minimum of 2 passages of the needle core should be obtained. If adequate tissue is not obtained following initial passages of the needles, repeat passages of the needle should be performed if clinically feasible. Smaller lesions may be biopsied or smaller gauge needles may be used provided adequate tissue can be collected (similar quantity to amount collected using 18-gauge thickness and 5-mm core length). Refer to the Laboratory Manual for further details on procedures for collecting fresh tumors.

vi) Biopsies at clinically documented disease progression are optional but highly encouraged. At the time of clinically documented disease progression, if a subject enrolled in BMS-986183 dose expansion (Part 2) agrees to receive combination therapy, then the biopsy at clinically documented disease progression is mandatory (see also Section 3.1.2.1).

vii) The immediate confirmation (eg, touch imprint cytopathology) for presence of viable tumor cells from collected tissue samples is strongly recommended.

f) Cirrhotic status of Child-Pugh Class A, that is, Child-Pugh Score of 6 points or less (Appendix 4).

g) ECOG Performance Status of 0 to 1 (Appendix 5).

h) Subjects are eligible to enroll if they have nonviral-HCC or if they have HBV- or HCV-HCC, defined as follows:

   i) HBV-HCC: Resolved HBV infection (as evidenced by detectable HBV surface antibody, detectable HBV core antibody, undetectable HBV deoxyribonucleic acid [DNA], and undetectable hepatitis B surface antigen [HBsAg]) or chronic HBV infection (as evidenced by detectable HBsAg, hepatitis B e antigen [HBeAg], or HBV DNA). Subjects with chronic HBV infection must have HBV DNA < 500 IU/mL and must be on antiviral therapy per regional standard of care guidelines prior to initiation of study therapy. All subjects enrolled with HBV must continue antiviral therapy through the follow-up period of the study. Both HBeAg-positive and -negative subjects will be included. Subjects with chronic HBV who are not on antiviral therapy at screening cannot be enrolled in the study.

   ii) HCV-HCC: Active or resolved HCV infection as evidenced by detectable HCV ribonucleic acid (RNA) or antibody, respectively. Subjects on antiviral therapy for hepatitis C are permitted and should continue treatment during the study up to the follow-up period. Subjects with active HCV who are not on antiviral therapy at screening cannot be enrolled in the study.

i) At least 1 RECIST v1.1 previously untreated, unidimensionally measurable lesion by contrast-enhanced tri-phasic computed tomography (CT ≥ 10 mm or contrast-enhanced dynamic magnetic resonance imaging (MRI) scan ≥ 10 mm (malignant lymph nodes must be ≥ 15 mm on short axis) (additional details are included in Appendix 6)[81]

   i) The lesion can be accurately measured unidimensionally according to RECIST v1.1

   ii) The lesion has not been previously treated with surgery, radiotherapy, and/or locoregional therapy (eg: radiofrequency ablation, percutaneous ethanol or acetic acid injection, cryoablation, high-intensity focused ultrasound, transarterial chemoembolization, transarterial embolization, etc.)

   iii) Previously treated lesions can be considered target lesions if there is clear evidence of progression.

   iv) Bone metastases are not considered measurable lesions, unless there is a measurable soft tissue component per RECIST v1.1 (see Appendix 6).[81]

   v) The measurable lesion cannot be biopsied during treatment (if there is only 1 lesion).

j) For subjects who progressed after locoregional therapy, locoregional therapy for HCC must be completed at least 4 weeks prior to the baseline scan. All acute toxic effects of any prior local treatment must have resolved to NCI CTCAE v4.03 Grade ≤ 1 or been deemed irreversable.

Screening laboratory values must meet the following criteria:

   i) Adequate hematologic function:

      (1) Neutrophils ≥ 1500/μL

(2) Platelets $\geq 60 \times 10^3/\mu L$ (transfusion to achieve this level is not permitted within 2 weeks of first study drug administration)

(3) Hemoglobin $\geq$ 8.5 g/dL (may be transfused to meet this requirement within 2 weeks of first study drug administration)

(4) Prothrombin time (PT)-international normalized ratio (INR) $\leq$ 2.3 or PT $\leq$ 6 seconds above control.

ii) Adequate hepatic function

(1) Albumin $\geq$ 2.8 g/dL

(2) Total bilirubin $\leq$ 3 mg/dL

(3) AST $\leq 5 \times$ the institutional ULN

(4) ALT $\leq 5 \times$ the institutional ULN

iii) Adequate renal function with a serum creatinine of $< 1.5 \times$ ULN or a creatinine clearance (CrCl) > 40 mL/min using Cockcroft-Gault formula below:

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

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

k) Ability to comply with treatment, PK and research sample collection (when indicated), and required study follow-up.

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

3) Age and Reproductive Status

a) Males and Females, ages 18 or 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 gonadotropin) within 24 hours prior to the start of study drug.

c) Women must not be breastfeeding.

d) WOCBP must agree to follow instructions for method(s) of contraception for the duration of treatment with study drug (s) BMS-986183 monotherapy plus 5 half-lives of study drug plus 30 days (duration of ovulatory cycle) for a total of 90 days post-treatment completion (BMS-986183 dose escalation [Part 1] and BMS-986183 dose expansion [Part 2]). WOCBP must agree to follow instructions for method(s) of contraception for the duration of study treatment with nivolumab and 5 months (150 days) after the last dose of study drug (ie, 30 days [duration of ovulatory cycle] plus the time required for the study drug to undergo approximately 5 half-lives) (BMS-986183 and nivolumab dose escalation [Part 3] and BMS-986183 and nivolumab dose expansion [Part 4]).

e) Males who are sexually active with WOCBP must agree to follow instructions for method(s) of contraception for the duration of treatment with study drug (s) BMS-986183 plus 5 half-lives of the study drug plus 90 days (duration of sperm turnover) for a total of 150 days post-treatment completion (BMS-986183 dose escalation [Part 1] and BMS-986183 dose expansion [Part 2]). Males who are sexually active with WOCBP must agree to follow instructions for method(s) of contraception for the duration of study treatment with nivolumab and 7 months (210 days) after the last dose of study drug (ie, 90 days [duration of sperm turnover] plus the time required for the study drug to undergo approximately 5 half-lives). In all study parts, male subjects must be willing to refrain from sperm donation during the time described above.

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

Investigators shall counsel WOCBP and male subjects who are sexually active with WOCBP on the importance of pregnancy prevention and the implications of an unexpected pregnancy. Investigators shall advise on the use of highly effective methods of contraception, which have a failure rate of < 1% when used consistently and correctly. Refer to Appendix 7.

3.3.2 Exclusion Criteria

1) Target Disease Exceptions

a) Known fibrolamellar HCC, sarcomatoid HCC, or mixed cholangiocarcinoma are excluded.

b) Prior liver transplant

c) History of hepatic encephalopathy

d) Clinically significant ascites as defined by:

i) Any ascites by full PE at screening

OR

ii) Current clinically significant ascites that requires active paracentesis for control or required paracentesis in the prior 6 months

e) Evidence of portal hypertension with bleeding esophageal or gastric varices within the past 6 months

f) Active brain metastases or leptomeningeal metastases. Subjects with treated brain metastases are eligible if the following criteria are fulfilled:

i) The brain lesions have been treated and there is no MRI evidence of progression for at least 4 weeks after treatment is complete and within 28 days prior to the first dose of study drug administration. (If an MRI is contraindicated, a CT scan is acceptable after discussion with the study medical monitor.)

ii) There is no requirement for immunosuppressive doses of corticosteroids (> 10 mg/day prednisone equivalents) for at least 2 weeks prior to study drug administration.

iii) The case is discussed with the study medical monitor

2) Medical History and Concurrent Diseases

a) Infections:

i) Active coinfection with

(1) Both hepatitis B and C as evidenced by detectable HBV surface antigen, HBeAg, or HBV DNA and HCV RNA, OR

(2) Hepatitis D infection in subjects with hepatitis B.

ii) Known history of positive test for human immunodeficiency virus (HIV) or known acquired immunodeficiency syndrome. No HIV testing is required during screening. NOTE: Testing for HIV must be performed at study sites where mandated locally.

iii) Active bacterial, viral, or fungal infections requiring systemic treatment within 7 days prior to screening.

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

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

ii) Uncontrolled angina within the past 3 months

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

iv) History of other clinically significant heart disease (eg, cardiomyopathy, congestive heart failure with NYHA functional classification 3 to 4, pericarditis, myocarditis, or significant pericardial effusion). See Appendix 8.

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

vi) QTcF prolongation > 480 msec

vii) Valvular heart disease > CTCAE Grade 2

viii) Cardiac Troponin T (cTnT) or I $\geq 2 \times$ institutional ULN. Subjects with cTnT or cTnI levels between > 1 to 2 × ULN will be permitted if repeat levels within 24 hours are $\leq 1 \times$ ULN.

ix) LVEF < 50% as measured by 2-D echocardiography.

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

d) Thrombotic or embolic events (except HCC tumor thrombus) within the past 6 months, such as cerebrovascular accident (including transient ischemic attacks), pulmonary embolism

e) Any other hemorrhage/bleeding event ≥ CTCAE Grade 3 within 8 weeks except for esophageal or gastric varices (Target disease exception 1.e.)

f) Major surgical procedure, open biopsy, or significant traumatic injury within 4 weeks prior to start of investigational product (IP) administration or those who receive minor surgical procedures (eg, core biopsy or fine needle aspiration) within 1 week prior to the start of IP.

g) Prior malignancy active within the previous 3 years except for locally curable cancers that have been apparently cured, such as basal or squamous cell skin cancer, superficial bladder cancer, or carcinoma in situ of the prostate, cervix, or breast.

h) Any serious or uncontrolled medical, psychiatric, and/or social reason that in the opinion of the investigator may increase the risk associated with study participation or study drug administration, impair the ability of the subject to receive protocol therapy, or interfere with the interpretation of study results.

i) Subjects in all study parts except BMS-986183 and nivolumab dose expansion (Part 4): All toxicities attributed to prior anti-cancer therapy other than alopecia, and fatigue must have resolved to Grade 1 (NCI CTCAE v4.03) or baseline before administration of study drug.

j) Subjects in BMS-986183 and nivolumab dose escalation (Part 3) and BMS-986183 and nivolumab dose expansion (Part 4): Prior organ allograft or allogeneic bone marrow transplantation.

k) Subjects in BMS-986183 and nivolumab dose escalation (Part 3) and BMS-986183 and nivolumab dose expansion (Part 4) with an active, known, or suspected autoimmune disease. Subjects with type I diabetes mellitus, hypothyroidism only requiring hormone replacement, skin disorders (such as vitiligo, psoriasis, or alopecia) not requiring systemic treatment, or conditions not expected to recur in the absence of an external trigger are permitted to enroll.

l) Subjects in BMS-986183 and nivolumab dose escalation (Part 3) and BMS-986183 and nivolumab dose expansion (Part 4) with a condition requiring systemic treatment with either corticosteroids (> 10 mg daily prednisone equivalent) or other immunosuppressive medications within 14 days of start of study drug. Inhaled or topical steroids, and adrenal replacement steroid doses > 10 mg daily prednisone equivalent, are permitted in the absence of active autoimmune disease.

m) Subjects in BMS-986183 and nivolumab dose escalation (Part 3) and BMS-986183 and nivolumab dose expansion (Part 4) with interstitial lung disease that is symptomatic or may interfere with the detection and management of suspected drug-related pulmonary toxicity.

3) Prior and Current Therapies

a) Subjects with more than 2 prior systemic treatments are excluded in BMS-986183 dose expansion (Part 2), and subjects with any prior systemic treatments are excluded in BMS-986183 and nivolumab dose expansion (Part 4)

b) Prior use of systemic investigational agents for HCC other than anti-PD-1/PD-L1 therapy and/or anti-CTLA-4 during BMS-986183 dose expansion (Part 2)

c) Prior participation in an anti GPC-3 study or GPC-3 vaccination study

d) Current therapeutic anticoagulation therapy

e) Treatment with anti-platelet therapy (aspirin at dose ≥ 300 mg/day, clopidrogrel at dose ≥ 75 mg/day)

f) Radiotherapy within 4 weeks prior to start of study drug. Palliative radiotherapy for symptomatic control is acceptable if completed at least 2 weeks prior to study drug administration) and no additional radiotherapy for the same lesion is planned.

g) Concomitant medications known to be strong inhibitors of CYP3A4 metabolism.

4) Physical and Laboratory Test Findings

a) Laboratory evidence of any underlying medical conditions that, in the investigator's opinion, will make the administration of study drug hazardous or obscure the interpretation of toxicity determination or AEs.

b) Positive pregnancy test.

c) Subjects in BMS-986183 and nivolumab dose escalation (Part 3) and BMS-986183 and nivolumab dose expansion (Part 4) with baseline serum sodium < 130 mmol/L.

d) Subjects in BMS-986183 and nivolumab dose escalation (Part 3) and BMS-986183 and nivolumab dose expansion (Part 4) with baseline serum potassium < 3.5 mmol/L (potassium supplementation may be given to restore the serum potassium above this level prior to study entry).

5) Allergies and Adverse Drug Reaction

a) History of allergy or hypersensitivity to GPC-3 directed antibodies, tubulysin, monoclonal antibodies, or study drug components.

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

c) Subjects in BMS-986183 and nivolumab dose escalation (Part 3) with history of life-threatening toxicity related to prior immune therapy (eg, anti-CTLA-4 or anti-PD-1/PD-L1 treatment or any other antibody or drug specifically targeting T-cell co-stimulation or immune checkpoint pathways) except those that are unlikely to recur with standard countermeasures (eg, hormone replacement after adrenal crisis).

6) Prohibited Treatments or Therapies

a) Prior exposure to GPC-3-directed monoclonal antibodies, GPC-3 vaccines, 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 Sponsor/medical monitor is mandatory.

d) Exposure to any investigational drug concurrent with study drug administration

e) Use of medications causing Torsades de Pointes within 1 week or 5 half-lives (whichever is longer)

7) Other Exclusion Criteria

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

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

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

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

3.3.3 Women of Childbearing Potential

WOCBP is defined as any female who has experienced menarche and who has not undergone surgical sterilization (hysterectomy or bilateral oophorectomy) and is not postmenopausal. Menopause is defined as 12 months of amenorrhea in a woman over age 45 in the absence of other biological or physiological causes. In addition, females under the age of 55 years must have a documented serum follicle stimulating hormone (FSH) level > 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 durations of the washout periods below are suggested guidelines and the investigators should use their judgment in checking serum FSH levels.

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

Other parenteral products may require washout periods as long as 6 months. If the serum FSH level is > 40 mIU/ml at any time during the washout period, the woman can be considered postmenopausal.

[redacted]

3.4.1 Antiviral Treatment

Subjects on antiviral therapy for hepatitis B or C should continue treatment during the study. Changing of dosage and regimens of antiviral therapy will be at the discretion of the investigator.

If a subject has a > 1 log IU/mL increase in HBV DNA, then virologic breakthrough should be considered and HBV DNA confirmed. Adherence to current antiviral therapy should be assessed, and resistance testing performed according to local practices. If a subject has documented virologic breakthrough due to antiviral resistance, then this should be managed based on standardized regional guidelines and treatment with BMS-986183 temporarily held. The subject may resume treatment with study drug once virologic control is reestablished (HBV DNA < 500 IU/mL), according to protocol-defined criteria, provided that both the principal investigator and the BMS medical monitor assess the benefit-risk ratio to be in the best interest of the subject.

For any subject who continues to be HCV RNA positive after receiving BMS-986183, current guidelines for management of chronic HCV infection, including those from American Association for the Study of Liver Diseases, European Association for the Study of the Liver, or Asian Pacific Association for the Study of the Liver may be consulted. Initiation of direct acting antivirals for HCV is allowed at the discretion of the investigator after discussion with the BMS medical monitor.

3.4.2 Palliative Local Therapy

Palliative local therapy for clinically symptomatic tumor sites (eg bone pain) including palliative (limited-field) radiation and palliative surgical resection may be considered if the following criteria are met:

- The subject is considered to have progressed at the time of palliative therapy
- The lesion for palliative local therapy is a nontarget lesion
- The case is discussed with the BMS medical monitor. Palliative therapy must be clearly documented as such in the study record.
- Tumor lesions requiring palliative local therapy should be evaluated for objective evidence of disease progression prior to the initiation of such therapy.
  - Palliative therapy must be clearly documented in the source records and electronic case report form (eCRF). Details in the source records should include: dates of treatment, anatomical site, dose administered and fractionation schedule, and AEs.

3.4.3 Prohibited and/or Restricted Treatments

Prohibited and/or restricted medications taken prior to study drug administration in the study are described below. Medications taken within 4 weeks and all anti-viral medications taken for any length of treatment prior to study drug administration must be recorded on the case report form (CRF). For subjects receiving combination therapy who are in retreatment or subjects in BMS-986183 dose expansion (Part 2) who agree to receive the combination therapy extension option, concomitant medications and all antiviral medications taken for any length of treatment are to be collected within 4 weeks of dosing through 100 days after the last dose of study drug.

Specific medications that may not be administered concomitantly with BMS-986183 include:

- Locoregional therapy for HCC.
- Concurrent antineoplastic therapy, such as chemotherapy, molecular targeted therapy, hormonal therapy, immunotherapy, botanical formulations with an approved indication for

cancer treatment (eg, traditional Chinese medicines), or radiation therapy (except for palliative local therapy described in Section 3.4.2).

- Exposure to noncytotoxic investigational drug within 4 weeks or 5 half-lives (whichever is shorter) is prohibited. If 5 half-lives is shorter than 4 weeks, agreement with Sponsor/medical monitor is mandatory.
- Medications known to be strong inhibitors of CYP 3A4 metabolism.

Additional criteria that apply only to the BMS-986183 and nivolumab combination therapy (BMS-986183 and nivolumab dose escalation [Part 3] and BMS-986183 and nivolumab dose expansion [Part 4]) include the following, which are prohibited during the study (unless utilized to treat a drug-related AE):

- Immunosuppressive agents
- Immunosuppressive doses of systemic corticosteroids (except as stated in Section 3.4)

All concomitant therapies must be recorded on the CRF.

3.4.4 Other Restrictions and Precautions

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 GFR < 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 study site radiologist, the investigator and the standard set by the local ethics committee.

Subjects with a condition requiring systemic treatment with either corticosteroids (> 10 mg daily prednisone equivalent) or other immunosuppressive medications within 14 days of treatment assignment 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.

3.5 Discontinuation of Subjects following any Treatment with Study Drug

Subjects MUST discontinue IP 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 v1.1 (see Appendix 6)[81]
- Disease progression
- 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 Sponsor or designee of this event. In most cases, the study drug will be permanently discontinued in an appropriate manner (eg, dose tapering if necessary for subject safety). Please call the Sponsor or designee within 24 hours of awareness of the pregnancy. If the investigator determines a possible favorable benefit/risk ratio that warrants continuation of study drug, a discussion between the investigator and the Sponsor or designee must occur.

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

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

3.6 Post Study Drug Follow-up

In this study, assessing the safety and tolerability of BMS-986183 in subjects with HCC is a key endpoint of the study. Post study follow-up is of critical importance and is essential to preserving subject safety and the integrity of the study. Subjects who discontinue study drug must continue to be followed for collection of outcome and/or survival follow-up data as required and in line with Section 5 until death or the conclusion of the study.

BMS may request that survival data be collected on all treated/randomized subjects outside of the protocol defined window (Table 5.1-2). 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.

Safety follow-up Visit 1 will should occur 30 days from the last dose (± 5 days) or coinciding with the date of discontinuation of study drug (± 5 days). Safety follow-up Visit 2 will occur 60 days from the last dose (± 5 days). For BMS-986183 and nivolumab dose escalation (Part 3) and BMS-986183 and nivolumab dose expansion (Part 4) only, safety follow-up Visit 3 will occur 100 days from the last dose (± 10 days). Survival follow-up visits for all subjects will occur approximately every 12 weeks from their last follow-up visit. Survival follow-up visits may be performed by telephone contact, office visit, or documented clinic visit. Response follow-up visits (only for subjects with SD, PR, or CR) occur at least every 3 to 4 months during the survival follow-up period until progression, death, or initiation of new treatment (whichever occurs first).

3.6.1 Withdrawal of Consent

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

3.6.2 Lost to Follow-up

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

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

3.7 Treatment 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 Sponsor/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 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 drugs 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 all study drugs.
- Begin an IV infusion of normal saline and treat the subject as follows: Recommend bronchodilators, epinephrine 0.2 to 1 mg of a 1:1,000 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. All study drugs will be permanently discontinued.
- 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

study drug administrations. Remain at bedside and monitor subject until recovery from symptoms.

- For 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).

All Grade 3 or 4 infusion reactions should be reported within 24 hours to the BMS Medical Monitor and reported as an SAE if criteria are met. Additional samples for PK and immunogenicity assessments, referred to as "Grade 3+ Infusion Reaction Event" samples, will be drawn in cases of Grade 3 to 4 infusion or hypersensitivity reactions (see Section 5.5.1).

If a subject discontinues treatment for an AE, both study drugs should be stopped. If there is an infusion reaction with only 1 study drug and it resolves quickly and is low grade, then the subject can continue both study drugs.

4 STUDY DRUG

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

Table 4-1: Study Drugs for CA015003

Product Description Class and Dosage Form	Potency	IP/NonIMP	Blinded or Open Label	Packaging/Appearance	Storage Conditions (per label)
BMS-986183-01 for Injection	50 mg/vial	IP	Open label	Primary Packaging: Glass vial Secondary Packaging: Outer carton 10 cc vial/White to off-white, whole or fragmented cake in a vial Lyophilized	Protect from light Store at 2 to 8ºC
Nivolumab Solution for Injection	100 mg/vial (10 mg/mL)	IP	Open label	Primary Packaging: 10 mL (10 cc) glass vial Secondary Packaging: Outer carton Appearance: Vial containing 10 mL clear to opalescent, colorless to pale yellow liquid, light (few) particulates may be present.	2°C to 8°C (36°F to 46°F). Protect from light. Protect from freezing.

IMP = investigational medicinal product.

Approved v6.0 930091072 6.0

4.1 Investigational Product

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

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

In this protocol, the IPs are BMS-986183-01 for injection, 50 mg/vial, and nivolumab for injection, 100 mg/vial.

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 as non-IPs. 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 contact BMS immediately.

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

IP documentation (whether supplied by BMS or not) must be maintained that includes all processes required to ensure drug is accurately administered. This includes documentation of drug storage, administration and, as applicable, storage temperatures, reconstitution, and use of required processes (eg, required diluents, administration sets).

4.3.1 BMS-986183

There will be no individual subject dose escalations of BMS-986183 allowed. Subjects should be carefully monitored for infusion reactions during BMS-986183 administration. If an infusion reaction is noted, subjects should be managed according to the guidance provided in Section 3.7.

Doses of BMS-986183 may be interrupted, delayed, or discontinued as described in Sections 3.7 and 4.5.

BMS-986183 Preparation:

BMS-986183 is supplied as a sterile, nonpyrogenic, single-use, preservative-free, lyophilized cake. Study drug is supplied as 50 mg/vial that must be reconstituted and diluted prior to dosing the subjects as an IV injection formulation. A sufficient excess of BMS-986183-01 is incorporated into each vial to account for withdrawal losses.

Solution for infusion is prepared by reconstituting BMS-986183-01 followed by further dilution to concentrations appropriate for the dosing cohort.

Prepared BMS-986183-01 infusion is administered to subjects as IV infusion.

BMS-986183 Administration:

Appropriate volume of prepared BMS-986183-01 solution should be administration through IV infusion set (using 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.

Final diluted solutions of BMS-986183-01 for injection is stable for up to 24 hours at refrigerated conditions (2° to 8°C [36° to 46°F]) and protected from light (diluted solution may also be stored at room temperature conditions, 15 to 25°C [59° to 77°F] under ambient light for a total of up to 4 hours out of the total 24 hour storage period). The constituted vial and diluted bag should not be shaken. Equilibration to room temperature is recommended for drug product infusion fluid and their combination prior to administration. Infusion of BMS-986183-01 injection must be completed within 24 hours of dilution. The start of drug infusion equals 0 hour.

Detailed instructions for drug product preparation, administration, and storage are provided in separate dosing instruction manual.

4.3.2 Nivolumab

Subjects should receive nivolumab at a dose of 360 mg as a 30-minute infusion on Day 1 of each treatment cycle until progression, unacceptable toxicity, withdrawal of consent, or the study ends, whichever occurs first.

For combination treatment in BMS-986183 and nivolumab dose escalation (Part 3) and BMS-986183 and nivolumab dose expansion (Part 4), BMS-986183 will be administered as an infusion for up to 60 minutes. The infusion line containing BMS-986183 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-986183. The nivolumab dose would then be infused not less than 30 minutes from the completion of the BMS-986183 infusion, which would then be infused over a period of 30 minutes.

There will be no individual subject dose escalations or reductions of nivolumab allowed. Subjects may be dosed no less than 18 days from the previous dose during Q3W cycles. For Q3W dosing cycles, subjects may be dosed within a ± 3-day window. Premedications are not recommended for the first dose of nivolumab.

Subjects should be carefully monitored for infusion reactions during nivolumab administration. If an infusion reaction is noted, subjects should be managed according to Section 4.5.2.2.

Doses of nivolumab may be interrupted, delayed, or discontinued depending on how well the subject tolerates the treatment.

Nivolumab Injection, 100 mg/10 mL (10 mg/mL) is to be administered as an IV infusion through a 0.2- to 1.2-micron pore size, low-protein binding in-line filter at the protocol-specified doses. It is not to be administered as an IV push or bolus injection. Nivolumab Injection can be infused undiluted (10 mg/mL) or diluted with 0.9% Sodium Chloride Injection, USP or 5% Dextrose Injection, USP to protein concentrations as low as 1 mg/mL. Instructions for dilution and infusion of Nivolumab Injection may be provided in the pharmacy manual. Care must be taken to assure sterility of the prepared solution because the product does not contain any antimicrobial preservative or bacteriostatic agent.

Nivolumab infusions are compatible with polyvinyl chloride (or polyolefin containers and infusion sets) and glass bottles.

Separate infusion bags and filters should be used when administering nivolumab and BMS-986183 on the same day.

4.4 Method of Assigning Subject Identification

After informed consent has been obtained, the subject must be enrolled into the study by using an interactive response technology (IRT) to obtain the subject number. The exact procedure for using the IRT will be detailed in a separate document.

In BMS-986183 dose escalation (Part 1) and BMS-986183 and nivolumab dose escalation (Part 3), if a subject discontinues treatment with BMS-986183 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 Sponsor/medical monitor and investigators.

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 BMS-986183 dose escalation (Part 1) and BMS-986183 and nivolumab dose escalation (Part 3) (see Section 3.1.1). Subjects in BMS-986183 dose expansion (Part 2) and BMS-986183 and nivolumab dose expansion (Part 4) will be enrolled at or below the MTD (or MAAD for BMS-986183 and nivolumab dose expansion [Part 4]) as agreed upon by the Sponsor/medical monitor and investigators (Section 3.1.2).

4.5.1 Dose Limiting Toxicities

For the purpose of guiding dose escalation, DLTs will be defined based on incidence, intensity, and duration of AEs for which no clear alternative cause is identified. The DLT evaluation period for dose escalation in BMS-986183 dose escalation (Part 1) and BMS-986183 and nivolumab dose escalation (Part 3) 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 Sponsor/medical monitor and investigators, if they are determined to have no clear alternative cause and are not related to disease progression.

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

Hepatic DLT

Hepatic DLT for which no clear alternative cause is identified (e.g. disease progression, hepatitis flare, other concomitant medications) and meets the following criteria

- AST or ALT > 10 × ULN for > 2 weeks
- AST or ALT > 15 × ULN irrespective of duration
- Total bilirubin > 8 × ULN irrespective of duration for subjects with elevated total bilirubin at study entry or > 5 × ULN for those with normal total bilirubin at entry
- Concurrent ALT ≥ 10 × ULN AND total bilirubin ≥ 2 × ULN or baseline value (if elevated bilirubin at study entry), AND no other immediately apparent possible causes of ALT elevation and hyperbilirubinemia. (For definition of potential drug-induced liver injury [p-DILI], see Section 6.6.)
- Clinical deterioration manifested by drug-related hepatic decompensation not identified above

Nonhematologic DLT

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

- ≥ Grade 3 infusion-related reactions that recur despite appropriate medical management as in Section 3.7.
- (BMS-986183 and nivolumab dose escalation [Part 3] only) ≥ Grade 2 episcleritis, uveitis, or iritis.
- (BMS-986183 and nivolumab dose escalation [Part 3] only) Grade 2 or greater eye pain or reduction of visual acuity that does not respond to topical therapy and does not improve to Grade 1 severity within 2 weeks of starting therapy or requires systemic treatment.
- ≥ 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 nausea, vomiting or diarrhea that lasts less than 48 hours and either resolves spontaneously or responds to conventional medical intervention
- Isolated Grade 3 fever not associated with hemodynamic compromise (ie, hypotension, clinical or laboratory evidence of impaired end-organ perfusion)
- Grade 3 or 4 elevation of amylase or lipase not associated with clinical or radiographic evidence of pancreatitis

- Grade 3 endocrinopathy that is well controlled by hormone replacement
- Grade 3 fatigue for ≤ 7 days
- Grade 3 infusion reaction that returns to Grade 1 in less than 6 hours

Hematologic DLT

- Grade 4 neutropenia ≥ 7 days in duration
- Grade 4 febrile neutropenia of any duration
- Grade 3 febrile neutropenia that lasts > 48 hours
- Grade 4 thrombocytopenia or Grade ≥ 3 thrombocytopenia associated with clinically significant bleeding
- 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 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 Sponsor/medical monitor.
- Dose reductions should be to the previous lower dose level.
- If several AEs of varying grade or severity occur simultaneously, the dose modification applied should be the greatest reduction 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 vs discontinuation of the subject from further protocol therapy will be discussed and agreed upon by the Sponsor/medical monitor and investigators.
- Subjects who experience a Grade 4 nonhematologic AE, except for Grade 4 electrolyte abnormalities (see Table 4.5.2-1), will not receive additional protocol-related therapy and will be removed from study unless discussed and agreed upon by the Sponsor/medical monitor and investigators that it is in the best interest of the subject to receive additional therapy with BMS-986183 (for example, if the subject has demonstrated a response to therapy).
- No more than 2 dose reductions 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 Sponsor/medical monitor and investigators.

- For an AE requiring dose modification, BMS-986183 should be interrupted to allow recovery from the AE. Re-initiation of study drug cannot occur until AE decreases to ≤ Grade 1 or baseline assessment. In case of delayed recovery to ≤ Grade 1 or baseline (except for alopecia or fatigue) from treatment-related AEs that results in a delay of treatment for > 6 weeks, the subject will not receive additional protocol-related therapy and will be removed from study unless discussed and agreed upon by the Sponsor/medical monitor and investigators that it is in the best interest of the subject to receive additional therapy with BMS-986183 (for example, if the subject has demonstrated a response to therapy).
- 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.
- Dose reductions for nivolumab will not be permitted for individual subjects.

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

Table 4.5.2-1: Dose Modifications

Dose Modification Criteria for Drug-Related Adverse Events	BMS-986183 (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 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-986183, if necessary), discontinue.
Grade 1 Troponin I or T confirmed when repeated in 72 hours	Discontinue
Grade 3 Troponin I or T	Discontinue
AST/ALT/total bilirubin elevation per Section 4.5.3	Decrease 1 level
≥ Grade 3 infusion-related reaction	See Section 3.7
≥ Grade 3 peripheral neuropathy	Discontinue
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	Decrease 1 level

4.5.2.1 Intra-subject Dose Escalation

Intra-subject dose escalation of BMS-986183 monotherapy or BMS-986183 and nivolumab combination therapy is not permitted.

4.5.2.2 Management Algorithms for Immuno-oncology Agents: BMS-986183 and Nivolumab Combination Therapy Only

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

- GI
- Renal
- Pulmonary
- Hepatic
- Endocrinopathy
- Skin
- Neurological

The above algorithms are found in the nivolumab IB[73] and Appendix 2 of this protocol. In addition to the guidance provided in these algorithms, it is recommended that consultation with a nephrologist be obtained for subjects with Grade 2 or 3 renal I-O-related AEs. Also, the use of infliximab for I-O-related AEs has the most data for treatment of colitis/diarrhea, whereas use in other AEs has not been well established. Infusion reaction management is provided in Section 3.7.

Immune-mediated adverse reactions are specific events occurring within 100 days of the last dose [which includes pneumonitis, diarrhea/colitis, hepatitis, nephritis/renal dysfunction, rash, and endocrine abnormalities (adrenal insufficiency, hypothyroidism/thyroiditis, hyperthyroidism, diabetes mellitus, and hypophysitis)], regardless of causality, for which subjects received immunosuppressive medication for treatment of the event. The exception to the immunosuppressive medication criteria for IMARs is endocrine events (hypothyroidism/thyroiditis, hyperthyroidism, hypophysitis, diabetes mellitus, adrenal insufficiency), which are included regardless of treatment since these events are often managed without immunosuppression.

4.5.3 Protocol-Specific Recommendation for Management of Hepatic Events

Subjects with advanced HCC generally have underlying cirrhosis with decreased hepatic function. They may also have a concomitant chronic viral infection. For CA015003, the upper limits for inclusion were therefore adjusted to account for baseline liver dysfunction. Subjects with AST or ALT elevations within the CTCAE Grade 2 range can be enrolled. This requires a protocol-specific approach for the management of hepatic events, outlined as follows.

For subjects in BMS-986183 and nivolumab dose escalation (Part 3) and BMS-986183 and nivolumab dose expansion (Part 4), the protocol-specific approach for the management of hepatic events is as follows:

- If AST or ALT levels do not improve with a dose delay of 3 to 5 days or if the levels worsen, initiate steroid therapy at 0.5 to 2 mg/kg/day methylprednisolone or oral equivalent.

- For ALT or AST levels > 8× ULN, initiate steroid therapy promptly at 1 to 2 mg/kg/day methylprednisolone or oral equivalent.
- For all subjects initiating steroids, consult the BMS Medical Monitor within 24 hours after initiation of steroids. Gastroenterology consult is recommended.
- If AST or ALT levels do not improve within 3 to 5 days or the levels worsen after the start of steroid therapy, discuss with the BMS Medical Monitor the possibility of adding mycophenolate mofetil at 1 g twice daily.
- Tapering of steroids can start once AST or ALT levels have declined by 1 CTCAE grade. Taper steroids slowly over no less than 1 month.

As outlined in Section 4.5.3.2, nivolumab and BMS-986183 combination therapy may resume when AST or ALT have returned to near baseline unless the criteria for permanent discontinuation are reached (Section 4.5.6).

4.5.3.1 Criteria for Dose Modifications or Delay for Changes in AST, ALT or Total Bilirubin

Subjects who experience the following must have dose of study drug delayed:

- If a subject has a baseline AST, ALT or total bilirubin that is within normal limits, delay dosing for drug-related ≥ Grade 2 toxicity (2 grade shift)
- If a subject has baseline AST, ALT or total bilirubin within the Grade 1 toxicity range, delay dosing for drug-related ≥ Grade 3 toxicity (2 grade shift)
- If a subject has baseline AST, ALT or total bilirubin within the Grade 2 toxicity range, delay dosing for a 2-fold drug-related increase in AST, ALT or total bilirubin or for AST or ALT values 8 × ULN (whichever is lower)
- Hepatic DLT as defined in Section 4.5.1.

It is recommended to monitor elevations in AST, ALT or total bilirubin approximately every 3 days until levels peak and begin to decline. BMS-986183 dosing can be resumed where treatment criteria are met (Section 4.5.3.2)

If AST, ALT or total bilirubin levels do not improve with a dose delay of 3 to 5 days or if the levels worsen, or for ALT or AST levels > 8 × ULN, a gastroenterology/hepatology consult and discussion with BMS medical monitor is recommended.

4.5.3.2 Criteria to Resume Treatment for Elevations of AST or ALT or Total Bilirubin

Subjects who experience the following are eligible to resume study drug administration:

- Subjects with baseline Grade 1 AST, ALT, or total bilirubin who require dose delays for reasons other than a study drug-related hepatic event may resume treatment in the presence of Grade 2 AST, ALT, or total bilirubin.
- Subjects who require dose delays for drug-related increased AST, ALT, or total bilirubin may resume treatment when hepatic parameters are at baseline or CTCAE Grade 1 and after discussion with BMS Medical Monitor.

- Subjects with AST, ALT, and bilirubin values meeting discontinuation parameters (Section 4.5.6) should have treatment permanently discontinued.

Subjects meeting criteria to resume treatment will undergo dose modification with BMS-986183 as outlined in Section 4.5.2.

4.5.4 Dose Delays Due to Toxicity

Subjects who experience the following must have study drug held:

- Potential DLTs (DLT per definition, are related to study drug), until DLT relatedness is defined. In BMS-986183 and nivolumab dose escalation (Part 3) and BMS-986183 and nivolumab dose expansion (Part 4), every attempt must be made to assign relationship to BMS-986183, to nivolumab, or to both.
- Elevated AST or ALT as defined in Section 4.5.3.1.
- Grade 1 Troponin T or I elevation until confirmation (until repeat Troponin is ≤ 1× ULN) within 24 hours. (Subjects with repeat Troponin I or T > 1× ULN will be discontinued.)
- AE, laboratory abnormality, or concurrent illness that, in the judgment of the Investigator, warrants delaying the dose of study drug.

Nivolumab in combination with BMS-986183 administration should be delayed for the following:

- Any > Grade 2 non-skin, drug-related AE, with the exception of fatigue
- Any > Grade 3 skin, drug-related AE
- Any > Grade 3 drug-related laboratory abnormality (excluding AST/ALT or total bilirubin), with the following exceptions:
  - 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 BMS-986183 and/or nivolumab should be re-evaluated weekly or more frequently if clinically indicated and resume study drug dosing when retreatment criteria are met.

Subjects eligible to resume study therapy can resume treatment(s) after at least 21 days from the last dose. Subjects who meet criteria listed in Section 4.5.6 are required to permanently discontinue study drug. All other subjects will be permitted to resume therapy with study drug following resolution of the AE as described in Section 4.5.2.

Extensions to the period of dose delays > 6 weeks may be granted for individual subjects on a case-by-case basis after specific consultation and agreement between the investigator and BMS medical monitor in settings where benefit/risk may justify continued study therapy (eg, subject deriving clinical benefit who requires prolonged steroid taper for the management of non-DLT drug related AEs, or experiences delays for the management of a non-drug-related AE).

The end of cycle tumor assessments will continue every 6 weeks (Q6W; ± 1 week) relative to the subject's first dose regardless of any treatment delay incurred.

4.5.5 Criteria to Resume Treatment

Subjects experiencing AEs not meeting the criteria for permanent discontinuation as outlined in Section 4.5.6 may resume treatment with study medication under the following criteria:

Subjects may resume treatment after dose modification with study drug when the drug-related non-DLT AE(s) resolve to ≤ Grade 1 or baseline value with the following exceptions:

- Subjects may resume treatment in the presence of Grade 2 fatigue
- Subjects who have not experienced a Grade 3 drug-related skin AE may resume treatment in the presence of Grade 2 skin toxicity
- For AST/ALT/total bilirubin elevation (see hepatic criteria in Section 4.5.3.2)
- For subjects in BMS-986183 and nivolumab dose escalation (Part 3) and BMS-986183 and nivolumab dose expansion (Part 4), 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 the BMS Medical Monitor.
- Subjects in BMS-986183 and nivolumab dose escalation (Part 3) and BMS-986183 and nivolumab dose expansion (Part 4) with drug-related endocrinopathies adequately controlled with only physiologic hormone replacement may resume treatment after consultation with the BMS Medical Monitor. Adrenal insufficiency requires discontinuation regardless of control with hormone replacement.
- If the criteria to resume treatment are met, the subject should restart treatment after at least 21 days from the last dose.
- Tumor assessments should continue as per protocol even if dosing is delayed.

The consideration to re-initiate study therapy under these exceptions will be made on a case-by-case basis after considering the overall benefit/risk profile and in consultation between the investigator and the Sponsor.

- Any dosing delay lasting > 6 weeks from the previous dose requires discontinuation, with the following exceptions:
  - Dosing delays to allow for prolonged steroid tapers to manage drug-related AEs are allowed.
  - Dosing delays lasting > 6 weeks from the previous dose that occur for non-drug-related reasons may be allowed if approved by the BMS Medical Monitor.
  - Prior to re-initiating treatment in a subject with a dosing delay lasting > 6 weeks, the BMS Medical Monitor must be consulted. Tumor assessments should continue as per protocol even if dosing is delayed. Periodic study visits to assess safety and laboratory studies should also continue Q6W or more frequently if clinically indicated during such dosing delays.

4.5.6 Guidelines for Permanent Discontinuation

Subjects will be required to permanently discontinue study drug for the following criteria:

- Clinical deterioration, as assessed by the investigator
- Progressive disease (PD)
- For subjects in BMS-986183 and nivolumab dose escalation (Part 3) and BMS-986183 and nivolumab dose expansion (Part 4), any Grade 2 drug-related uveitis, eye pain, or blurred vision that does not respond to topical therapy and does not improve to Grade 1 severity within the retreatment period OR requires systemic treatment
- 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-986183.
- Grade 3 drug-related uveitis, pneumonitis, bronchospasm, hypersensitivity reaction, neurological toxicity, or infusion reaction of any duration requires discontinuation.
- Any Grade 3 non-skin, drug-related AE lasting > 7 days or recurs.
- Any Grade 3 or 4 AE that meets DLT criteria as outlined in Section 4.5.1; however, an exception may be made for the following upon consultation between the investigator and BMS medical monitor:
  - Grade 3 infusion reaction that returns to Grade 1 in less than 6 hours
  - 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 with medical intervention
  - Grade 3 or 4 electrolyte imbalances/abnormalities that are not associated with clinical sequelae and are corrected with supplementation/appropriate management within 72 hours
  - Grade 4 neutropenia < 7 days in duration
  - Grade 4 lymphopenia or leukopenia
  - Grade 3 or 4 amylase or lipase abnormalities that are not associated with symptoms or clinical manifestations of pancreatitis
  - Grade 3 or 4 drug-related endocrinopathy AEs, such as hyper- or hypothyroidism, or glucose intolerance, which resolve or are adequately controlled with physiologic hormone replacement (corticosteroids, thyroid hormones) or glucose-controlling agents, respectively, may not require discontinuation after discussion with and approval from the BMS Medical Monitor. Adrenal insufficiency requires discontinuation regardless of control with hormone replacement.
  - Grade 3 drug-related laboratory abnormalities do not require treatment discontinuation except:
    - Grade 3 drug-related thrombocytopenia > 7 days or associated with bleeding requires discontinuation
    - AST or ALT > 10 × ULN for > 2 weeks
    - AST or ALT > 15 × ULN irrespective of duration

  - Total bilirubin > 8 × ULN irrespective of duration for subjects with elevated bilirubin at study entry or > 5 × ULN for those with normal total bilirubin at entry
  - Concurrent AST or ALT > 3 × ULN and total bilirubin > 5 × ULN for subjects entering treatment with a normal bilirubin and up to 8 × ULN for subjects with elevated bilirubin
- Any AE, laboratory abnormality, or intercurrent illness that, in the judgment of the investigator, presents a substantial clinical risk to the subject with continued dosing of study treatment(s).
- Confirmed CR
- Completion of 1 year (17 cycles, with 21 days/cycle) of treatment

All subjects who discontinue IP should comply with protocol-specified follow-up procedures as outlined in Section 5.1. The only exception to this requirement is when a subject withdraws consent for all study procedures including post-treatment study follow-up or loses the ability to consent freely (eg, is imprisoned or involuntarily incarcerated for the treatment of a psychiatric or physical illness).

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

If the investigator determines a possible favorable benefit/risk ratio that warrants continuation of study drug(s), a discussion between the investigator and the BMS Medical Monitor/designee must occur including during BMS-986183 and nivolumab combination therapy. If there is toxicity requiring discontinuation and the toxicity is considered related to 1 study drug while clinical benefit has been observed (eg, pneumonitis due to nivolumab), treatment with the study drug to which the toxicity is attributed must be discontinued, but may be resumed for the other study drug, but only after discussion and agreement with the BMS Medical Monitor (or designee).

The consideration to re-initiate study therapy under these exceptions will be made on a case-by-case basis after considering the overall benefit/risk profile and in consultation between the investigator and the study Sponsor.

4.5.7 Treatment Beyond Disease Progression in BMS-986183 and Nivolumab Combination Therapy

Accumulating evidence indicates a minority of subjects treated with immunotherapy may derive clinical benefit despite initial evidence of PD.[46]

Subjects treated with BMS-986183 and nivolumab combination therapy may be permitted to continue combination therapy beyond initial RECIST v1.1-defined PD, as assessed by the investigator, as long as they meet the following criteria:

- Investigator-assessed clinical benefit
- Tolerance of study drug
- Stable performance status

- Treatment beyond progression will not delay an imminent intervention to prevent serious complications of disease progression (eg, central nervous system [CNS] metastases).
- Subject provides written informed consent prior to receiving additional combination treatment. All other elements of the main consent including description of reasonably foreseeable risks or discomforts, or other alternative treatment options will still apply.

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

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

Discontinuation due to Further Progression (Confirmed Progression)

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

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

4.6 Blinding/Unblinding

Not applicable.

4.7 Treatment Compliance

Study drug will be administered in the clinical facility by 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-986183 and nivolumab 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 will be at the completion of the study. Any discrepancy should be brought to the attention of the Sponsor.

4.8 Destruction of Study Drug

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

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

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

- On-site disposal practices must not expose humans to risks from the drug.
- On-site disposal practices and procedures are in agreement with applicable laws and regulations, including any special requirements for controlled or hazardous substances.
- Written procedures for on-site disposal are available and followed. The procedures must be filed with the site's 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 study period.

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

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

4.9 Return of Study Drug

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

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

[redacted].

5 STUDY ASSESSMENTS AND PROCEDURES

5.1 Flow Chart/Time and Events Schedule

Study assessments and procedures are presented in Table 5.1-1, Table 5.1-2, and Table 5.1-3. In limited instances, scheduled events can occur outside of the indicated timeframes, but BMS should be notified.

Table 5.1-1: Screening and Cycle 1 Procedural Outline (CA015003)

Procedure [a]	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 BMS-986183 dose expansion (Part 2) and BMS-986183 and nivolumab dose expansion (Part 4), if allowed by institutional practices, sites are encouraged to use a prescreening consent for the GPC-3-expressing tumor analysis. Other screening procedures should not be performed before the GPC-3-expressing tumor analysis is available for the determination of subject eligibility. Refer to Section 3.1 for additional details on screening.
IRT Assignment	X						
Inclusion/Exclusion Criteria	X						Assessed during screening period. All inclusion/exclusion criteria must be met for subjects to participate in the study.
ECOG	X	X					Refer to Appendix 5 and Section 3.3.1. For Screening, must be within 14 days prior to treatment assignment.
Medical History	X						Include any toxicities or allergy related to previous treatments, smoking history, asthma, chronic obstructive pulmonary disease, history of hepatic encephalopathy. Includes detailed medical history of potential risk factors for potential events such as pulmonary-related events, cardiovascular history, neurological toxicity, infusion or hypersensitivity reactions, and smoking history. Ensure documentation of hepatitis risk factors.
History of Alcohol use	X						
Child-Pugh Score	X	X					See Appendix 4 for scale
Prior Treatments	X						Including prior cancer treatment regimens
Safety Assessments							
Full PE	X	X					For Screening, must be within 14 days prior to treatment assignment. If the screening full PE is performed within 24 hours prior to dosing on Day 1, then a single exam may count as both the screening and predose evaluation.

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Table 5.1-1: Screening and Cycle 1 Procedural Outline (CA015003)

Procedure [a]	Screening Visit D-28 to D-1	C1D1	C1D2	C1D4 [b]	C1D8	C1D15	Notes
Targeted PE					X	X	Targeted examination must include at a minimum the following body systems, performed within 72 hours prior to dosing: cardiovascular, gastrointestinal, pulmonary, and skin. The targeted examination also includes signs and symptoms of peripheral neuropathy.
Physical Measurements	X	X					Height (screening only), weight (for Screening, must be within 14 days prior to treatment assignment).
Vital Signs [c]	X	X			X	X	Body temperature, blood pressure, and heart rate (for Screening, must be within 14 days prior to treatment assignment).
ECGs	X	X	X		X		ECGs should be recorded after the subject has been supine for at least 5 minutes. ECGs will be taken prior to dosing. For ALL subjects in BMS-986183 dose escalation (Part 1) and at least 20 subjects in BMS-986183 dose expansion (Part 2): Time matched for PK; triplicate ECG evaluations at C1D1 predose and EOI, C1D2 (24 hours post dose), and C1D8 (168 hours post dose) QTcF assessment > 480 msec must be confirmed on repeat ECG.
ECHO or MUGA	X						Must include a quantitative assessment of left ventricular ejection fraction and utilize the same modality for any subsequent assessments. ECHO/MUGA may be assessed up to 72 hours prior to the first dose.
Laboratory Tests	X	X	X	X	X	X	Screening laboratory values should be obtained within 14 days prior to the start of study drug. If the screening laboratory tests are performed within 72 hours prior to dosing on Day 1 then a single exam may count as both the screening and predose evaluation. Urine - screening only, unless clinically indicated FSH - screening only, if needed to document post-menopausal status C1D4: CBC and LFT only, collection to be time-matched with PK collection See Section 5.3.2.

Approved v6.0 930091072 6.0

Table 5.1-1: Screening and Cycle 1 Procedural Outline (CA015003)

Procedure [a]	Screening Visit D-28 to D-1	C1D1	C1D2	C1D4 [b]	C1D8	C1D15	Notes
Thyroid Panel including TSH, free T3, and free T4	X						Required for BMS-986183 and nivolumab combination therapy only. See Section 5.3.2. Free T3 and free T4 are required at screening and then taken reflexively if TSH is abnormal.
Coagulation Panel	X	X			X		See Section 5.3.2.
Serology (Hepatitis B, Hepatitis C)	X						HBV DNA viral load (PCR), HCV RNA (HCV antibody testing with HCV RNA reflex), hepatitis D antibody, HBV core antibody HBeAg, HBeAb, HBsAb, and HBsAg.
Viral biomarkers (for HCV and HBV)		X					For HCV infected, HCV RNA on treatment For HBV infected, HBV DNA on treatment
Troponin T or I	X	X			X	X	The same evaluation (assay) must be performed throughout the study
Pregnancy Test	X	X					For WOCBP only; see Section 5.3.2
Whole blood sample for ADME		X					See Section 5.7.3
PK and Immunogenicity Assessments See Section 5.5.							
Biomarker Assessments See Section 5.6.							
Tumor Sample	X						See Section 3.3.1.
Tumor Assessment Tumor Imaging (See Section 5.3.1)	X						Baseline must be within approximately 30 days of C1D1 Scans must be de-identified. See Section 5.3.1.
Concomitant Treatments		X	X	X	X	X	Medications administered within 4 weeks of dosing and all anti-viral medications taken for any length of treatment through 60 days post-study drug discontinuation for BMS-986183 dose escalation (Part 1) and BMS-986183 dose expansion (Part 2) and for 100 days after the last dose of study drug for BMS-986183 and nivolumab dose escalation (Part 3) and BMS-986183 and nivolumab dose expansion (Part 4).

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Table 5.1-1: Screening and Cycle 1 Procedural Outline (CA015003)

Procedure [a]	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 Nonserious Adverse Events		X	X	X	X	X	**BMS-986183 dose escalation (Part 1) and BMS-986183 dose expansion (Part 2):** From first dose of study drug until a total of 60 days post discontinuation of dosing or subject's participation in the study if the last scheduled visit occurs at a later time. **BMS-986183 and nivolumab dose escalation (Part 3) and BMS-986183 and nivolumab dose expansion (Part 4):** From first dose of study drug until a total of 100 days post discontinuation of dosing or subject's participation in the study if the last scheduled visit occurs at a later time. See Section 5.3.
Monitor for SAEs	X	X	X	X	X	X	**BMS-986183 dose escalation (Part 1) and BMS-986183 dose expansion (Part 2):** From the time of consent until a total of 60 days post discontinuation of dosing. **BMS-986183 and nivolumab dose escalation (Part 3) and BMS-986183 and nivolumab dose expansion (Part 4):** From the time of consent until a total of 100 days post discontinuation of dosing. See Section 5.3.
Clinical Drug Supplies							
Dose Level Assignment	X						At the completion of screening procedures and eligibility determined
Dispense Study Drug		X					Those supplied by BMS; the start and stop time of the study drug infusion should be documented (start of drug infusion = 0 hour). Subjects in BMS-986183 dose escalation (Part 1) and BMS-986183 dose expansion (Part 2) receive BMS-986183 monotherapy. Subjects in BMS-986183 and nivolumab dose escalation (Part 3) and BMS-986183 and nivolumab dose expansion (Part 4) receive BMS-986183 and nivolumab combination therapy.

Approved v6.0 930091072 6.0

[a] In the event that multiple procedures are required at a single timepoint, the ECG may be obtained up to 15 minutes earlier, vital signs may be obtained up to 10 minutes earlier or later, and clinical laboratory sample may be obtained up to 5 minutes earlier than the nominal PK timepoint, ensuring the PK samples can be collected on time.

[b] C1D4 visit: ± 1 day.

[c] During C1: vital signs will be obtained before the BMS-986183 infusion and then every 15 minutes (± 5 minutes) until 60 minutes after completion of the infusion. After C1 vital signs may be obtained predose, 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).

C = cycle, D = day; EOI = end of infusion; HBeAb = hepatitis B e antibody; HBsAb = hepatitis B surface antibody; PCR = polymerase chain reaction; T3 = triiodothyronine; T4 = thyroxine; TSH = thyroid stimulating hormones.

Approved v6.0 930091072 6.0

Table 5.1-2: Cycle 2 to Off Study Visit Procedural Outline (CA015003)

Procedure [a]	C2 and C3			C4					C5 to C17 [b]	EOT	Follow-up (30 and 60 Days After Last Dose)	Follow-up (100 Days After Last Dose) [c]	Survival Follow-up [d]	Notes
	D1	D8	D15	D1	D2	D4 [e]	D8	D15	D1		(± 5 days)	(± 10 days)	(± 2 weeks)	
Safety Assessments														
Child-Pugh Score	X			X					X	X	X	X		See Appendix 4 for scale
Full PE										X				
Targeted PE	X	X	X	X					X		X	X		See note in Table 5.1-1.
Physical Measurements	X			X					X	X	X	X		Weight only
Vital Signs [f]	X	X	X	X					X	X	X	X		See note in Table 5.1-1.
ECGs	X			X	X		X		X	X	X	X		See note in Table 5.1-1. ALL subjects in BMS-986183 dose escalation (Part 1) and at least 20 subjects in BMS-986183 dose expansion (Part 2) will have time matched for PK; triplicate evaluations at C4D1 predose and EOI, C4D2 (24 hour post dose), and C4D8 (168 hours post dose)
Laboratory Tests	X	X	X	X		X	X	X	X	X	X	X		See note in Table 5.1-1 and Section 5.3.2. C4D4 (CBC only) collection to be time matched with PK collection C4D8, C4D15: LFTs only

Approved v6.0 930091072 6.0

Table 5.1-2: Cycle 2 to Off Study Visit Procedural Outline (CA015003)

Procedure [a]	C2 and C3			C4					C5 to C17 [b]	EOT	Follow-up (30 and 60 Days After Last Dose)	Follow-up (100 Days After Last Dose) [c]	Survival Follow-up [d]	Notes
	D1	D8	D15	D1	D2	D4 [e]	D8	D15	D1		(± 5 days)	(± 10 days)	(± 2 weeks)	
Thyroid Function Testing	X								X See note	X	X	X		Required for BMS-986183 and nivolumab combination therapy only. Free T3 and free T4 will be taken reflexively if TSH is abnormal. To be performed every other cycle after Cycle 3 (ie, Cycles 5, 7, etc). See Section 5.3.2.
Coagulation Panel	X	X	X	X			X	X	X	X	X	X		See Section 5.3.2
Troponin T or I														As clinically indicated
ECHO or MUGA									C5 only	X				At other times as clinically indicated
Tumor Biopsy (Fresh)	See assessment schedules in Section 5.6.1 for details.													C2, 24 to 48 hours post dose and at any other time an investigator chooses to obtain a biopsy during the study period. See Section 3.3.1 for further details.
Viral biomarkers (for HCV and HBV)	X			X					X	X	X	X		For HCV infected, HCV RNA on treatment For HBV infected, HBV DNA on treatment
Pregnancy Test	X			X					X	X				See Table 5.1-1

Approved v6.0 930091072 6.0

Table 5.1-2: Cycle 2 to Off Study Visit Procedural Outline (CA015003)

Procedure [a]	C2 and C3			C4					C5 to C17 [b]	EOT	Follow-up (30 and 60 Days After Last Dose)	Follow-up (100 Days After Last Dose) [c]	Survival Follow-up [d]	Notes
	D1	D8	D15	D1	D2	D4 [e]	D8	D15	D1		(± 5 days)	(± 10 days)	(± 2 weeks)	
Concomitant treatments	X	X	X	X	X	X	X	X	X	X	X [g]	X		See Table 5.1-1
Adverse Event Reporting														
Monitor for Nonserious Adverse Events	X	X	X	X	X	X	X	X	X	X	X	X		See note in Table 5.1-1.
Monitor for Serious Adverse Events	X	X	X	X	X	X	X	X	X	X	X	X		See note in Table 5.1-1.
PK and Immunogenicity Assessments See Section 5.5.														
Biomarker Assessments See Section 5.6.														
Efficacy Assessments														
Tumor Assessment	At the start of Cycle 3 and then Q6W, thereafter (±1 week)									X	X [h]	X [h]	X [i]	Scans must be de-identified. See Sections 5.3.1, 5.4.1
Clinical Drug Supplies														
BMS-986183 Administration	X			X					X					The start and stop time of the study drug infusion should be documented (start of drug infusion = 0 hour). See Section 4 for administration details.
Nivolumab Administration	X			X					X					For BMS-986183 and nivolumab dose escalation (Part 3) and BMS-986183 and nivolumab dose

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Table 5.1-2: Cycle 2 to Off Study Visit Procedural Outline (CA015003)

Procedure [a]	C2 and C3			C4					C5 to C17 [b]	EOT	Follow-up (30 and 60 Days After Last Dose)	Follow-up (100 Days After Last Dose) [c]	Survival Follow-up [d]	Notes
	D1	D8	D15	D1	D2	D4 [e]	D8	D15	D1		(± 5 days)	(± 10 days)	(± 2 weeks)	
														expansion (Part 4) only. BMS-986183 is infused first followed by nivolumab. See Section 4 for administration details. See Section 3.1.1.2 for observation times. The start and stop time of the study drug infusion should be documented (start of drug infusion = 0 hour).
Other														
Other Anti-cancer Therapies													X [j]	
Subject Status													X	Also see tumor assessment schedule above

[a] In the event that multiple procedures are required at a single timepoint, the ECG may be obtained up to 15 minutes earlier, vital signs may be obtained up to 10 minutes earlier or later, and clinical laboratory sample may be obtained up to 5 minutes earlier than the nominal PK timepoint, ensuring the PK samples can be collected on time.

[b] Individual subjects with SD or PR may have 6 months (9 cycles, with 21 days/cycle) of extended treatment with BMS-986183 after the first treatment period (17 cycles, with 21 days/cycle) on a case-by-case basis after specific consultation and agreement between the investigator and BMS medical monitor. These subjects, as well as any subjects in BMS-986183 and nivolumab dose escalation (Part 3) or BMS-986183 and nivolumab dose expansion (Part 4) who meet the criteria to continue combination therapy beyond progression (see Section 4.5.7), will follow the assessment/procedure schedule for C5 to C17 subjects.

[c] BMS-986183 and nivolumab dose escalation (Part 3) and BMS-986183 and nivolumab dose expansion (Part 4) only.

Approved v6.0 930091072 6.0

[d] For all subjects, subject status will be assessed by telephone contact, office visit, or documented clinic visit every 12 weeks (± 2 weeks) up to 6 months from his or her last dose of study drug.

[e] C4D4: ± 1 day.

[f] Vital signs will be obtained before the BMS-986183 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).

[g] Only anti-cancer treatments.

[h] Only at the 60-day follow-up visit (BMS-986183 dose escalation [Part 1] or BMS-986183 dose escalation [Part 2]) or the 100-day follow-up visit (BMS-986183 and nivolumab dose escalation [Part 3] or BMS-986183 and nivolumab dose expansion [Part 4]).

[i] Subjects with SD, PR, or CR at the EOT visit should undergo tumor assessment via CT/MRI scans at least every 3 to 4 months during the survival follow-up period (Section 3.1) until progression, death, or initiation of new treatment (whichever occurs first).

[j] 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 who have progressed will be permitted to receive other anti-cancer therapies as appropriate, including investigational agents, during this follow-up period once the 60-day (BMS-986183 dose escalation [Part 1] or BMS-986183 dose escalation [Part 2]) or the 100-day follow-up visit (BMS-986183 and nivolumab dose escalation [Part 3] or BMS-986183 and nivolumab dose expansion [Part 4]) follow-up visit is completed.

C = cycle; D = day.

Approved v6.0 930091072 6.0

Table 5.1-3: Retreatment Day 0 and Cycle 1 Onwards (Parts 3 and 4 only) or Combination Therapy Extension Option (Part 2 only): 21-Day Cycle Procedural Outline (CA015003)

Procedure [a]	Day 0 [b,c]	C1 and Beyond D1	EOT	FU (30, 60, and 100 Days after Last Dose) (30- and 60-day FU: ± 5 days) (100-day FU: ± 10 days)	Survival FU [d] (±2 weeks)	Notes
Eligibility Assessments						
Inclusion/Exclusion Criteria	X					Same criteria as in screening
ECOG	X	X				Refer to Appendix 5 and Section 3.3.1. For Day 0, must be within 14 days prior to treatment assignment.
Medical History	X					Interim history (medical, AE or SAE) that occurred during the survival FU period that was not previously reported.
Child-Pugh Score	X					See Appendix 4 for scale.
Prior Treatments	X					Including prior cancer treatment regimens.
Safety Assessments						
Full PE	X	X				For Day 0, must be within 14 days prior to treatment assignment. If the screening full PE is performed within 24 hours prior to dosing on Day 1, then a single exam may count as both the screening and predose evaluation.
Targeted PE			X	X	X	See note in Table 5.1-1.
Physical Measurements	X	X	X	X		Height (Day 0 only), weight (for Day 0, must be within 14 days prior to treatment assignment).

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Table 5.1-3: Retreatment Day 0 and Cycle 1 Onwards (Parts 3 and 4 only) or Combination Therapy Extension Option (Part 2 only): 21-Day Cycle Procedural Outline (CA015003)

Procedure [a]	Day 0 [b,c]	C1 and Beyond D1	EOT	FU (30, 60, and 100 Days after Last Dose) (30- and 60-day FU: ± 5 days) (100-day FU: ± 10 days)	Survival FU [d] (±2 weeks)	Notes
Vital Signs [e]	X	X	X	X		Body temperature, blood pressure, and heart rate (if Day 0 and C1D1 coincide, record vital signs once).
ECGs	X	X	X	X		ECGs should be recorded after the subject has been supine for at least 5 minutes.
ECHO or MUGA	X		X			Must include a quantitative assessment of left ventricular ejection fraction and utilize the same modality for any subsequent assessments. ECHO/MUGA may be assessed up to 72 hours prior to the first dose. Also perform as clinically indicated.
Laboratory Tests	X	X	X	X		Day 0 laboratory values should be obtained within 14 days prior to the start of study drug. If the Day 0 laboratory tests are performed within 72 hours prior to dosing on Day 1 then a single exam may count as both the Day 0 and predose evaluation. Repeat the following if > 6 months since last treatment: hepatitis B surface antigen and hepatitis C antibody (if hepatitis C antibody is positive reflex to hepatitis C RNA) or hepatitis 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.

Approved v6.0 930091072 6.0

Table 5.1-3: Retreatment Day 0 and Cycle 1 Onwards (Parts 3 and 4 only) or Combination Therapy Extension Option (Part 2 only): 21-Day Cycle Procedural Outline (CA015003)

Procedure [a]	Day 0 [b,c]	C1 and Beyond D1	EOT	FU (30, 60, and 100 Days after Last Dose) (30- and 60-day FU: ± 5 days) (100-day FU: ± 10 days)	Survival FU [d] (±2 weeks)	Notes
						Urine - Day 1 only, unless clinically indicated. See Section 5.3.2.
Viral Biomarkers(for HBV and HCV)	X	X	X	X		For HCV infected, HCV RNA on treatment For HBV infected, HBV DNA on treatment
Coagulation Panel	X	X	X	X		
Troponin T or I	X					As clinically indicated
Thyroid Panel including TSH, free T3, and free T4	X	X See note				To be done Q6W. See Section 5.3.2.
Pregnancy Test	X	X	X	X		For WOCBP only; see Section 5.3.2.
PK and Immunogenicity Assessments See Section 5.5.						
Biomarker Assessments See Section 5.6.						
Tumor Assessment Tumor Imaging (See Section 5.3.1)	X		X	X [f]	X [g]	Day 0 must be within approximately 30 days of C1D1. Then at the start of Cycle 3 and then Q6W thereafter (± 1 week). Scans must be de-identified. See Section 5.3.1.
Concomitant Treatments	X	X	X	X [h]		Medications administered within 4 weeks of dosing and all antiviral medications taken for any length of treatment 100 days after the last dose of study drug.

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Table 5.1-3: Retreatment Day 0 and Cycle 1 Onwards (Parts 3 and 4 only) or Combination Therapy Extension Option (Part 2 only): 21-Day Cycle Procedural Outline (CA015003)

Procedure [a]	Day 0 [b,c]	C1 and Beyond D1	EOT	FU (30, 60, and 100 Days after Last Dose) (30- and 60-day FU: ± 5 days) (100-day FU: ± 10 days)	Survival FU [d] (±2 weeks)	Notes
Adverse Event Reporting						
Clinical Complaints		X				See note in Table 5.1-1; only if subject entered survival FU.
Monitor for Nonserious Adverse Events		X	X	X		From first dose of study drug until a total of 100 days post discontinuation of dosing or subject's participation in the study if the last scheduled visit occurs at a later time. See Section 5.3.
Monitor for SAEs	X	X	X	X		From the time of consent until a total of 100 days post discontinuation of dosing. See Section 5.3.
Clinical Drug Supplies						
Dose Level Assignment	X					At the completion of Day 0 procedures and eligibility determined.
BMS-986183 Administration		X				The start and stop time of the study drug infusion should be documented (start of drug infusion = 0 hour). See Section 4 for administration details. Subjects in BMS-986183 dose escalation (Part 2) Combination Therapy Extension Option must receive their first dose of combination therapy within 6 weeks of their last study drug administration.

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Table 5.1-3: Retreatment Day 0 and Cycle 1 Onwards (Parts 3 and 4 only) or Combination Therapy Extension Option (Part 2 only): 21-Day Cycle Procedural Outline (CA015003)

Procedure [a]	Day 0 [b,c]	C1 and Beyond D1	EOT	FU (30, 60, and 100 Days after Last Dose) (30- and 60-day FU: ± 5 days) (100-day FU: ± 10 days)	Survival FU [d] (±2 weeks)	Notes
Nivolumab Administration		X				BMS-986183 is infused first followed by nivolumab. See Section 4 for administration details. See Section 3.1.1.2 for observation times. The start and stop time of the study drug infusion should be documented (start of drug infusion = 0 hour). Subjects in BMS-986183 dose escalation (Part 2) Combination Therapy Extension Option must receive their first dose of combination therapy within 6 weeks of their last study drug administration.
Other						
Survival FU					X [i]	

[a] In the event that multiple procedures are required at a single timepoint, the ECG may be obtained up to 15 minutes earlier, vital signs may be obtained up to 10 minutes earlier or later, and clinical laboratory sample may be obtained up to 5 minutes earlier than the nominal PK timepoint, ensuring the PK samples can be collected on time.

Abbreviations: C = cycle, D = day; FU = follow=up; PE = physical examination; T3 = triiodothyronine; T4 = thyroxine; TSH = thyroid stimulating hormone.

[b] Day 0 is first day of assessment for either retreatment or combination therapy extension.

[c] For BMS-986183 dose expansion (Part 2), BMS-986183 and nivolumab dose escalation (Part 3), and BMS-986183 and nivolumab dose expansion (Part 4), if the Day 0 and C1 visits occur on the same day, then only a single examination or procedure is needed.

[d] Subjects will be followed up for up to 6 months after their last dose.

[e] During C1: vital signs will be obtained before the BMS-986183 infusion and then every 15 minutes (± 5 minutes) until 60 minutes after completion of the infusion. After C1, vital signs may be obtained predose, every 30 minutes (± 10 minutes) until 30 minutes following completion of the infusion. If any vital sign

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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 at the 60- and 100-day FU visits, unless discontinued for disease progression.

[g] Subjects with SD, PR, or CR at the EOT visit should undergo tumor assessment via CT/MRI scans at least every 3 to 4 months during the survival FU period (Section 3.1) until progression, death, or initiation of new treatment (whichever occurs first).

[h] Only anti-cancer treatments.

[i] Subject status will be assessed by telephone contact, office visit, or documented clinic visit every 12 weeks (± 2 weeks) up to 6 months from his or her last dose of study drug. 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 who have progressed will be permitted to receive other anti-cancer therapies as appropriate, including investigational agents, during this FU period once the 100-day FU visit is completed.

Approved v6.0 930091072 6.0

5.1.1 Retesting During Screening or Lead-in Period

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

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

5.2 Study Materials

The site will provide all required materials for the tests performed locally (ie, relevant clinical laboratory tests). The site will have available a well-calibrated scale for recording body weight, a 12-lead ECG machine (provided by the central vendor), and a calibrated sphygmomanometer and thermometer for vital signs assessments. A current and fully-stocked advanced cardiac life support cart will be immediately available on the premises. 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 samples. The site will provide all materials required for preparation and administration of IV study drug and accurate source documentation of study activities and for housing the subjects during the study.

BMS will provide a BMS-approved protocol and any amendments or administrative letters (if required), and IB. CRFs (electronic or hard copy) will be provided by BMS. BMS/the Central Laboratory will provide labels and tubes for the collection of blood samples for PK/biomarker. NCI CTCAE criteria may be provided to study sites prior to site initiation.

5.3 Safety Assessments

All subjects who receive at least 1 dose of BMS-986183 will be evaluated for safety parameters. Additionally, any occurrence of an SAE will be documented and any occurrence of nonserious AEs will be collected as described in Table 5.1-1.

AEs will be coded using the most current version of the Medical Dictionary for Regulatory Activities and reviewed for potential significance and importance. AEs 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 to study drug 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 (full and targeted), cardiac troponins, ECGs, ECHO/MUGA scans, LFTs, CBCs, and other clinical laboratory tests. In the event of Grade 3 or higher infusion or hypersensitivity reactions, samples for PK and anti-drug antibody (ADA) will be collected. The incidence of AEs will be tabulated and reviewed for potential significance and clinical importance. The schedule of required visits, tests, procedures, and assessments are described in Table 5.1-1 and Table 5.1-2. In limited instances, scheduled events (including events other than safety assessments) can occur outside of the indicated timeframes but the sponsor should be notified.

Some of the assessments referred to in this section may not be captured as data in the eCRF. They are intended to be used as safety monitoring by the treating physician. Additional testing or

assessments may be performed as clinically necessary or where required by institutional or local regulations. 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 ± 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 AE or SAE page.

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. Pregnancy testing (serum or urine) for WOCBP must be performed within 24 hours prior to the initial administration of IP at baseline and then prior to administration of study drug during study therapy (Q3W) and at the follow-up visit. Sensitivity of test must be at least 25 IU/L or equivalent units of 1.human chorionic gonadotropin. CBC plus differential, serum chemistry, and thyroid 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. Any increase in LFTs from baseline must be monitored every 3 days until levels peak and begin to decline. Grade 3 decreases in neutrophil and thrombocytopenia must be repeated within 72 hours. Additional laboratory tests should be performed as per standard of care.

The cTnT or cTnI will be monitored as described in Table 5.1-1 and Table 5.1-2. Grade 1 elevation requires dose interruption of BMS-986183 and nivolumab and repeat assessment within 24 hours. If there is persistent elevation, further dosing should be discontinued. Grade 3 elevation of cTnI or cTnT requires discontinuation of BMS-986183 and nivolumab, and prompt consultation and management with a cardiologist are recommended until it resolves.

If a subject shows pulmonary-related signs (hypoxia, fever) or symptoms (eg, dyspnea, cough, 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.

Additional measures, including nonstudy required laboratory tests, should be performed as clinically indicated or to comply with local regulations. Laboratory toxicities (eg, suspected drug induced liver enzyme elevations) will be monitored during the safety follow-up period via on-site/local labs until all study drug toxicities for which no clear alternative cause is identified other than to BMS-986183 resolve, return to baseline, or are deemed irreversible.

Chest X-Ray, ECHO/MUGA, urinalysis, cTnT or cTnI, or ECG may also be performed on-treatment as clinically indicated.

Safety assessments may be shared with investigators at periodic safety teleconferences.

5.3.1 Imaging Assessment for the Study

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

De-identified scans and measurements will be collected and at the Sponsor's discretion may be reviewed by independent radiologists using RECIST v1.1 criteria at a later date or at any time during the study. Tumor measures must be documented in the CRF.

Tumor response assessment will be done by RECIST v1.1 (Appendix 6).[81]

If a nontarget lesion is managed with local treatment such as radiotherapy or surgery, that lesion will not be counted in the radiologic response assessment.

CT/MRI

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 5.1-1 and Table 5.1-2. Triphasic CT of the liver is acquired with 2.5-mm (preferred) to 5-mm contiguous axial slices.

Should a subject have a contraindication for CT IV contrast, a noncontrast CT of the chest and a contrast-enhanced MRI of the abdomen (including a 4-phase MRI of the liver) 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 timepoints.

Note: Use of CT component of a positron emission tomography (PET)/CT scanner:

Combined modality scanning such as with [18^{F}]-fluorodeoxyglucose (FDG)-PET/CT is increasingly used in clinical care, and is a modality/technology that is in rapid evolution; therefore, the recommendations outlined here may change rather quickly with time. At present, low dose or attenuation correction CT portions of a combined FDG-PET/CT are of limited use in anatomically based efficacy assessments and it is therefore suggested that they should not be substituted for dedicated diagnostic contrast-enhanced CT scans for anatomically based RECIST v1.1 measurements (for details on RECIST v1.1, see Appendix 6).[81]

MRI Brain

Contrast-enhanced MRI of brain is required at screening for subjects with a history of brain metastases in order to rule out active metastatic disease. Subjects with a history of brain metastasis should have surveillance MRI approximately every 12 weeks, or sooner if clinically indicated.

MRI brain scans during on-study treatment and follow-up periods are required only if there is a prior history of lesions present at screening, or as clinically indicated for new signs and symptoms that suggest CNS involvement.

Bone Scan

Bone scans can be used to evaluate metastatic disease as clinically indicated.

5.3.2 Laboratory Test Assessments

A central/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. For retreatment and the BMS-986183 dose expansion (Part 2) combination therapy extension option, screening laboratory assessments must be repeated.

The following clinical laboratory tests will be performed:

Hematology

Hemoglobin	Hematocrit
Total leukocyte count, including differential	Platelet count
Coagulation panel (including PT/INR, activated partial thromboplastin time, and fibrinogen)	

Serum Chemistry

AST	Total Protein
ALT	Albumin
Total bilirubin	Sodium
Direct bilirubin	Potassium
Alkaline phosphatase	Chloride
GGT, if alkaline phosphatase is > Grade 2	Calcium
Lactate dehydrogenase	Phosphorus
Creatinine	Magnesium
Blood urea nitrogen or urea	Creatine kinase (with reflex measurement of isoenzymes if elevated)
eGFR	CrCl - screening and Day 0 only (Cockcroft-Gault formula)
Glucose	Bicarbonate or equivalent (if locally available)
cTnT or cTnI (the same assay must be performed throughout the study)	AFP
Lipase/amylase (screening and Day 0 only)	
TSH*	
Free triiodothyronine*	
Free thyroxine*	

** BMS-986183 and nivolumab combination therapy only (BMS-986183 and nivolumab dose escalation [Part 3] and BMS-986183 and nivolumab dose expansion [Part 4])*

Note: Free triiodothyronine and free thyroxine are required at screening and then taken reflexively if TSH is abnormal. For BMS-986183 and nivolumab combination therapy only (BMS-986183 and nivolumab dose escalation [Part 3] and BMS-986183 and nivolumab dose expansion [Part 4], during retreatment TSH, free triiodothyronine, and free thyroxine are also done Q6W.

FSH at screening and Day 0 only, for women only (Section 3.3.3)

Urinalysis at screening and Day 0 only (unless clinically indicated)

Protein	Leukocyte esterase

Glucose	Specific gravity
Blood	pH

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

Serology

At Screening: Serum for HBV DNA viral load (polymerase chain reaction), HCV RNA (HCV antibody testing with HCV RNA reflex), hepatitis D antibody, HBV core antibody, HBsAg, hepatitis B e antibody, hepatitis B surface antibody, and hepatitis B e antigen.

On Treatment: Viral Biomarkers:

For HCV infected, HCV RNA Q3W on treatment

For HBV infected, HBV DNA Q3W on treatment

Other Analyses

Pregnancy test (WOCBP only: screening/Day 0 retreatment, predose [each dose of BMS-986183 whether monotherapy or in combination with nivolumab], EOT and follow-up)

ECHO or MUGA (at screening and if clinically indicated [retreatment: Day 0, Cycle 3, and Q3W thereafter and as clinically indicated]; must include a quantitative assessment of left ventricular ejection fraction and utilize the same modality for any subsequent assessments)

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 Section 5.1) 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 study sponsor.

5.4.1 Primary Efficacy Assessment

Tumor measurements with CT and/or MRI, as appropriate, will be conducted at screening and Q6W (± 1 week) during the treatment period. Tumor measurements should be conducted earlier, if clinically indicated. Subjects with SD, PR, or CR at EOT undergo tumor assessment via CT/MRI scans every 3 to 4 months during survival follow-up until progression, death, or initiation of new treatment (whichever occurs first). Tumor measurements will be collected in all subjects until progression or the subject's discontinuation from the study as per Table 5.1-1 and Table 5.1-2. Tumor response and progression will be evaluated in this study using RECIST v1.1 (Appendix 6).[81] Initial response assessment of PR or CR must be confirmed by a consecutive assessment no less than 4 weeks (28 days) later.

5.4.2 Secondary Efficacy Assessments

Not applicable.

[redacted]

5.5 Pharmacokinetic Assessments

PK assessments of BMS-986183 for BMS-986183 as monotherapy (BMS-986183 dose escalation [Part 1] and BMS-986183 dose expansion [Part 2]) and in combination with nivolumab (BMS-986183 and nivolumab dose escalation [Part 3] and BMS-986183 and nivolumab dose expansion [Part 4]) will be based on serum concentrations of total antibody and active ADC in all subjects. PK assessments of BMS-986183 will also be based on plasma concentrations of conjugated tubulysin and unconjugated tubulysin in all subjects. The PK parameters that will be determined following intensive PK collection, if data permit, include:

Cmax	Maximum observed concentration
Tmax	Time of maximum observed concentration
AUC(0-T)	Area under the concentration-time curve from time 0 to T of the last measurable concentration
AUC(TAU)	Area under the concentration-time curve in 1 dosing interval
Ctau	Concentration at the end of a dosing interval
Ctrough	Trough observed concentration, including predose concentrations and Ctau
CLT	Total body clearance
Vss	Apparent volume of distribution at steady-state
Vz	Volume of distribution of terminal phase
AI_Cmax	Accumulation index; ratio of Cmax at steady-state to Cmax after the first dose
AI_Ctau	Accumulation index; ratio of Ctau at steady-state to Ctau after the first dose
AI_AUC(TAU)	Accumulation index; ratio of AUC(TAU) at steady-state to AUC(TAU) after the first dose
Css,avg	Average concentration over a dosing interval calculated by dividing AUC(TAU) at steady-state by tau
T-HALF	Terminal half-life

Individual subject PK parameter values will be derived by noncompartmental methods by a validated PK analysis program. Actual times will be used for the final analyses. Additional PK parameters may be computed as appropriate. The PK data from this study may also be pooled with PK data from other studies to enhance the PK characterization of BMS-986183 and would be part of a separate report. Sparse nivolumab serum concentrations will be measured in BMS-986183 and nivolumab dose escalation (Part 3) and in BMS-986183 and nivolumab dose expansion (Part 4) and may be used in integrated PPK or exposure-response analyses along with data from other nivolumab studies, which would be the subject of a separate report. Serum samples to evaluate the development of ADAs to BMS-986183 and to nivolumab will also be collected in this study.

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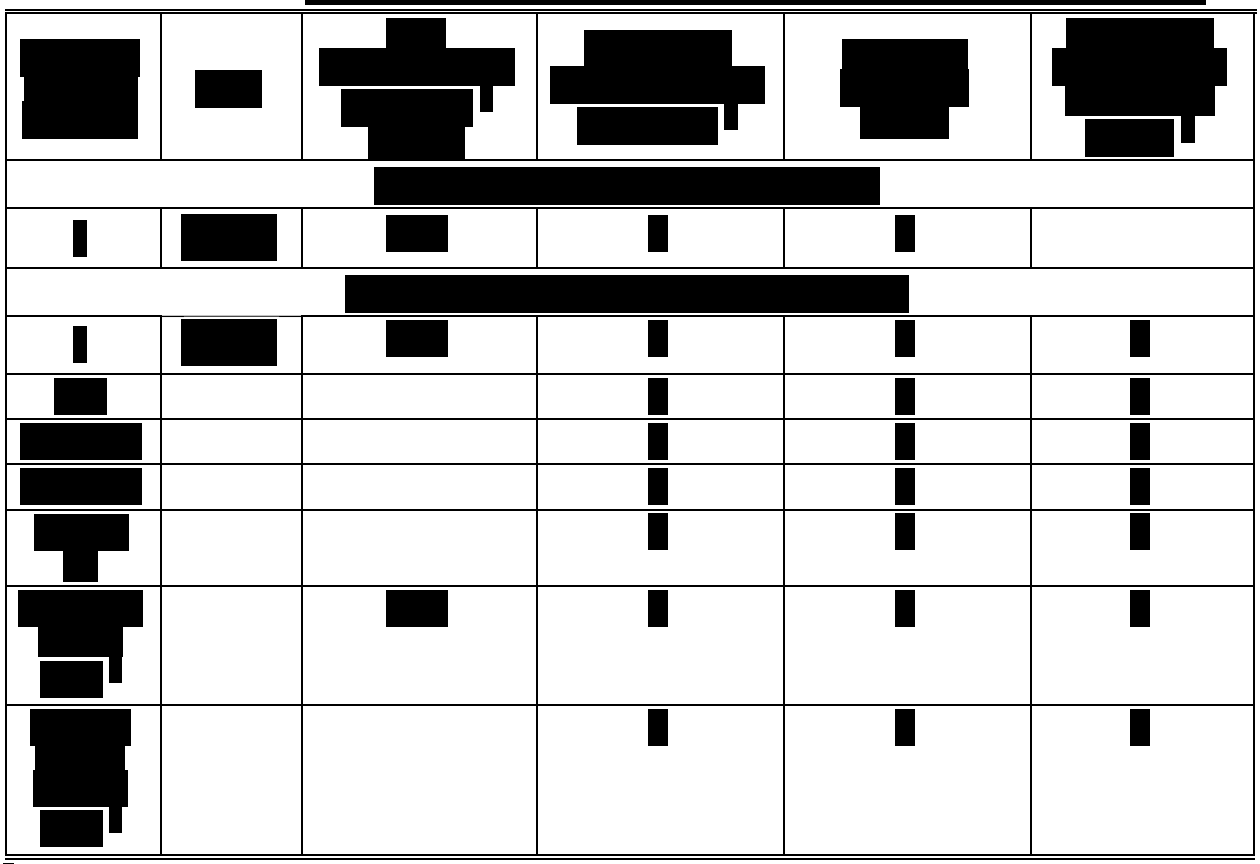

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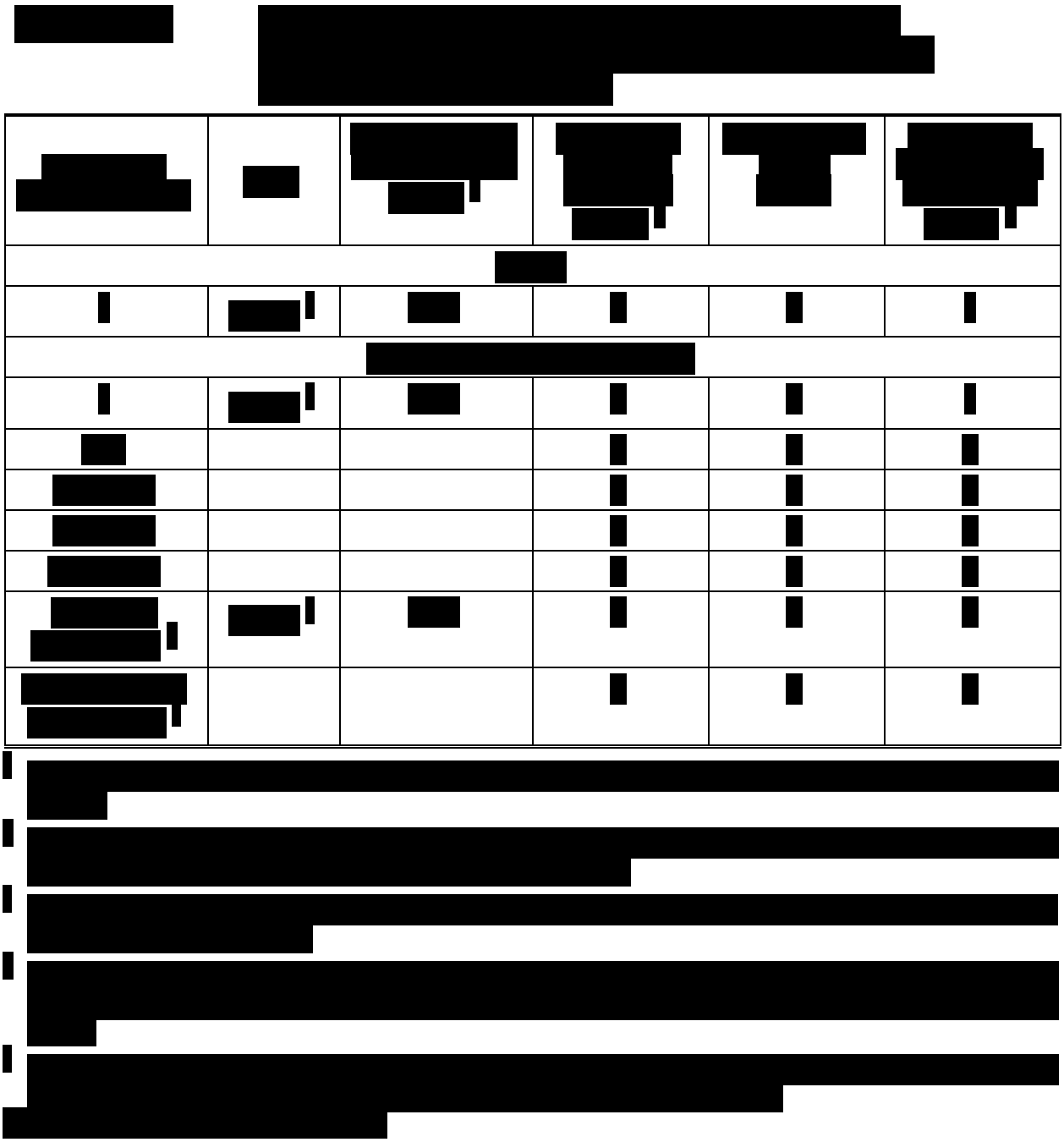

5.5.2 Pharmacokinetic Sample Analyses

Serum samples for total antibody, active ADC concentrations, and nivolumab, and plasma samples for unconjugated and conjugated tubulysin concentrations will be analyzed using a series of validated assays. Treatment assignments will be released to the bioanalytical laboratory in order to minimize unnecessary analysis of samples.

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

[redacted]

5.5.3 Labeling and Shipping of Biological Samples

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

5.6 Biomarker Assessments

5.6.1 Glypican-3 Immunohistochemistry on Tumor Samples

Differential clinical response to BMS-986183 is anticipated to be associated with the expression level of GPC-3 on the plasma membrane of tumor cells. The distribution of GPC-3 expression in HCC was assessed in commercially procured HCC tumor samples using H scores generated with a clinically validated IHC assay. H scores were calculated as the sum of the product of protein expression (strong = 3, moderate = 2, weak = 1, or none = 0) by the percentage of cells expressing GPC-3 protein at each of these levels. Analysis of the distribution of H scores revealed expression of GPC-3 in both the plasma membrane and the cytoplasm at varying levels. High, medium, and low plasma membrane GPC-3 expressions were defined as plasma membrane H-score (mH-score) ≥ 150, ≥ 100 but < 150, and ≥ 50 but < 100, respectively. High cytoplasmic GPC-3 expression was defined as cytoplasmic H score ≥ 50. BMS-986183 is expected to target GPC-3 expressed on the plasma membrane and therefore elicit objective responses in subjects whose tumors have high plasma membrane GPC-3 expression. However, BMS-986183 may also be efficacious in subjects whose tumors have lower plasma membrane GPC-3 expression (plasma mH-scores ≥ 50 but < 150). Therefore, all subjects with plasma membrane GPC-3 H scores ≥ 50 will be enrolled in the dose-expansion parts (BMS-986183 dose expansion [Part 2] and BMS-986183 and nivolumab dose expansion [Part 4]). In addition, it is unclear whether high expression of GPC-3 expressed in the cytoplasm impacts in any way the levels of GPC-3 expressed on the plasma membrane. Therefore, subjects with cytoplasmic GPC-3 expression (cytoplasmic H score ≥ 50) will also be enrolled in BMS-986183 dose expansion (Part 2) and BMS-986183 and nivolumab dose expansion (Part 4) for assessing the efficacy of BMS-986183 as monotherapy and in combination with nivolumab. In order to efficiently assess the efficacy of BMS-986183 with respect to these varying H score cut-offs, an adaptive design for both H score cutoff selection and subject enrollment will be employed (see Section 8.1 for full details).

In addition to tumor-based biomarkers, the blood-based biomarkers outlined in Table 5.6.1-1, Table 5.6.1-2, and Table 5.6.1-3 below will also be assessed.

Table 5.6.1-1: Sampling Timepoints for Blood- and Tumor-Based Biomarkers for BMS-986183 dose escalation (Part 1)

Study Day of Sample Collection	Event	Time (Relative to Start of Infusion of BMS-986183) Hour: Min	sGPC-3	AFP and PIVKA-II	CK18	Tumor Sampling for Immuno-histochemistry	Serum and/or Plasma Samples for Biomarkers Related to Hepatic Adverse Events
Screening							
-28 to -1		00:00				X [a]	
Cycle 1							
1	predose	0:00	X	X	X		X
		4:00			X		
2		24:00:00			X		
4 [b]		72:00:00	X		X		
8		168:00:00	X		X		
15		336:00:00	X		X		
Cycle 2							
2 [c]		24:00:00 to 48:00:00				X	
Cycle 3							
1	predose	0:00	X	X			
Cycle 4							
1	predose	0:00	X		X		
		4:00			X		
2		24:00:00			X		
4 [b]		72:00:00	X		X		
8		168:00:00	X		X		
15		336:00:00	X		X		
Dose Delay Biomarker Event [d]		00:00	X	X	X		
At Tumor Assessments (Q6W [± 1 week] starting at Cycle 5) (see Table 5.1-1 and Table 5.1-2)			X	X	X		

Table 5.6.1-1: Sampling Timepoints for Blood- and Tumor-Based Biomarkers for BMS-986183 dose escalation (Part 1)

Study Day of Sample Collection	Event	Time (Relative to Start of Infusion of BMS-986183) Hour: Min	sGPC-3	AFP and PIVKA-II	CK18	Tumor Sampling for Immuno-histochemistry	Serum and/or Plasma Samples for Biomarkers Related to Hepatic Adverse Events
Event-driven Sample Collection at the Time of Hepatic Adverse Event)			X	X	X	X	X

[a] Archived biopsy/slides are mandatory. Fresh sample is optional but highly encouraged. If a subject opts to have a post-treatment biopsy taken, then a fresh tumor biopsy at screening will be mandatory because it will serve as a baseline sample with which data from the post-treatment biopsy will be compared.

[b] ± 1 day, PK sample should be collected at the same time.

[c] 24 to 48 hours post dose and at any other time an investigator chooses to obtain a biopsy during the study period. Sample is optional but highly encouraged. Any subject on the study can opt to have a post-treatment biopsy. If a subject opts to have a post-treatment biopsy taken, then a fresh tumor biopsy at screening will be mandatory because it will serve as a baseline sample with which data from the post-treatment biopsy will be compared.

[d] In the event dose is delayed; please refer to lab manual.

Table 5.6.1-2: Sampling Timepoints for Blood- and Tumor-Based Biomarkers for BMS-986183 Dose Expansion (Part 2)

Study Day of Sample Collection	Event	Time (Relative to Start of Infusion of BMS-986183) Hour: Min	sGPC-3	AFP and PIVKA-II	CK18	Serum Samples for Inflammatory Cytokines	Tumor Sampling for DNA-RNA Extraction	Tumor Sampling for Immuno-histochemistry	Serum and/or Plasma Samples for Biomarkers Related to Hepatic Adverse Events	Whole Blood for Biomarkers
Screening										
-28 to -1		00:00					X [a]	X [b]		
Cycle 1										
1	predose	0:00	X	X	X	X			X	X
		4:00			X					
2		24:00:00			X	X				
4 [c]		72:00:00	X		X					
8		168:00:00	X		X					
15		336:00:00	X		X					
Cycle 2										
1	predose	0:00				X				
2		24:00:00 to 48:00:00						X [d]		
Cycle 3										
1	predose	0:00	X	X		X				
Cycle 4										
1	predose	0:00	X		X	X				

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Table 5.6.1-2: Sampling Timepoints for Blood- and Tumor-Based Biomarkers for BMS-986183 Dose Expansion (Part 2)

Study Day of Sample Collection	Event	Time (Relative to Start of Infusion of BMS-986183) Hour: Min	sGPC-3	AFP and PIVKA-II	CK18	Serum Samples for Inflammatory Cytokines	Tumor Sampling for DNA-RNA Extraction	Tumor Sampling for Immuno-histochemistry	Serum and/or Plasma Samples for Biomarkers Related to Hepatic Adverse Events	Whole Blood for Biomarkers
		4:00			X					
2		24:00:00			X					
4 [c]		72:00:00	X		X					
8		168:00:00	X		X					
15		336:00:00	X		X					
Dose Delay Biomarker Event [e]		00:00	X	X	X					
At Clinically Documented Disease Progression							X [f]	X [g]		
At Tumor Assessments (Q6W [± 1 week] starting at Cycle 5) (see Table 5.1-1 and Table 5.1-2)			X	X	X	X				
Event-driven Sample Collection at the Time of Hepatic Adverse Event			X	X	X		X[h]	X[h]	X	

[a] Mandatory for the 20 subjects who provided fresh tumor biopsy for immunohistochemistry at the same timepoint, provided ample tumor tissue is available after tumor sample for immunohistochemistry is obtained. Biopsy should be taken from same lesion used for immunohistochemistry analysis. Only if this is not possible will a biopsy from another lesion be acceptable. Complete details for required sample size and the collection, processing, storage, shipment, and analysis of samples will be provided in a separate Laboratory Manual.

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[b] Archived biopsy/slides and fresh biopsy are both mandatory. Both archived biopsy/slides and slides from fresh biopsy will be used for determining eligibility based on GPC-3 expression. If the fresh biopsy meets defined cut-off criteria for GPC-3 expression, then the subject will be eligible. If the fresh biopsy does not meet defined cut-off criteria for GPC-3 expression, then the subject will not be eligible. If the archival slides meet defined cut-off criteria for GPC-3 expression and data from the fresh sample are not evaluable, then the subject will be eligible. If the archival slides do not meet the requirements (a minimum of 10 slides and not older than 3 months from time of slide preparation), and data from the fresh sample are not evaluable, then the subject will not be eligible. If archival tissue is not available and only fresh tumor biopsy can be obtained for assessing eligibility, such subjects can be enrolled in study after discussion with the Sponsor.

[c] ± 1 day, PK sample should be collected at the same time.

[d] 24 to 48 hours post dose and at any other time an investigator chooses to obtain a biopsy during the study period. Sample at Cycle 2, 24 to 48 hours post dose is mandatory for 20 subjects enrolled in BMS-986183 dose expansion (Part 2). The biopsy is optional but highly encouraged for the other 30 subjects enrolled in BMS-986183 dose expansion (Part 2). If 20 subjects out of the first 30 subjects enrolled in BMS-986183 dose expansion (Part 2) do not opt to provide a biopsy at Cycle 2, 24 to 48 hours post dose, then this biopsy will be mandatory for the remaining 20 subjects to be enrolled in BMS-986183 dose expansion (Part 2).

[e] In the event dose is delayed; please refer to lab manual.

[f] Sample is optional but highly encouraged. At the time of clinically documented disease progression, if a subject enrolled in BMS-986183 dose expansion (Part 2) agrees to receive combination therapy, then the biopsy at clinically documented disease progression is mandatory but only if ample tumor tissue is available after tumor sample for immunohistochemistry is taken. Biopsy should be taken from same lesion used for immunohistochemistry analysis. Only if this is not possible will a biopsy from another lesion be acceptable. Complete details for required sample size and the collection, processing, storage, shipment, and analysis of samples will be provided in a separate Laboratory Manual.

[g] Sample is optional but highly encouraged. At the time of clinically document disease progression, if subject agrees to receive combination therapy, then this sample is mandatory.

[h] Sample is optional but is highly encouraged.

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Table 5.6.1-3: Sampling Timepoints for Blood- and Tumor-Based Biomarkers for BMS-986183 and Nivolumab Dose Escalation (Part 3) and BMS-986183 and Nivolumab Dose Expansion (Part 4)

Study Day of Sample Collection	Event	Time (Relative to Start of Infusion of BMS-986183) Hour: Min	sGPC-3	AFP and PIVKA -II	CK18	Serum Samples for Inflammatory Cytokines	Tumor Sampling for DNA-RNA Extraction	Tumor Sampling for Immuno-histochemistry	Serum and/or Plasma Samples for Biomarkers Related to Hepatic Adverse Events	Whole Blood for Biomarkers
Screening										
-28 to -1		00:00					X [a]	X [b]		
Cycle 1										
1	predose	0:00	X	X	X	X			X	X [c]
		4:00			X					
2		24:00:00			X	X				
4 [d]		72:00:00	X		X					
8		168:00:00	X		X					
Cycle 2										
1	predose	0:00				X				
2		24:00:00 to 48:00:00						X [e]		
Cycle 3										
1	predose	0:00	X	X		X				
Cycle 4										
1	predose	0:00	X		X	X				
		4:00			X					

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Table 5.6.1-3: Sampling Timepoints for Blood- and Tumor-Based Biomarkers for BMS-986183 and Nivolumab Dose Escalation (Part 3) and BMS-986183 and Nivolumab Dose Expansion (Part 4)

Study Day of Sample Collection	Event	Time (Relative to Start of Infusion of BMS-986183) Hour: Min	sGPC-3	AFP and PIVKA-II	CK18	Serum Samples for Inflammatory Cytokines	Tumor Sampling for DNA-RNA Extraction	Tumor Sampling for Immuno-histochemistry	Serum and/or Plasma Samples for Biomarkers Related to Hepatic Adverse Events	Whole Blood for Biomarkers
2		24:00:00			X					
4 [d]		72:00:00	X		X					
8		168:00:00	X		X					
15		336:00:00	X		X					
Dose Delay Biomarker Event [f]		00:00	X	X	X					
At Clinically Documented Disease Progression							X [g]	X [g]		
At Tumor Assessments (Q6W [± 1 week] starting at Cycle 5) (see Table 5.1-1 and Table 5.1-2)			X	X	X	X				
Event-driven Sample Collection at the Time of Hepatic Adverse Event			X	X	X		X [h]	X [h]	X	

[a] Applies only to subjects enrolled in BMS-986183 and nivolumab dose expansion (Part 4) of the study. Sample is mandatory for the 20 subjects who provided fresh tumor biopsy for immunohistochemistry at the same timepoint, provided ample tumor tissue is available after tumor sample for immunohistochemistry is obtained. Biopsy should be taken from same lesion used for immunohistochemistry analysis. Only if this is not possible will a biopsy from another lesion be acceptable. Complete details for required sample size and the collection, processing, storage, shipment, and analysis of samples will be provided in a separate Laboratory Manual.

Approved v6.0 930091072 6.0

[b] **BMS-986183 and nivolumab dose escalation (Part 3)**: archived biopsy/slides are mandatory, and fresh biopsy is optional but highly encouraged. If a subject in BMS-986183 and nivolumab dose escalation (Part 3) opts to have a post-treatment biopsy taken, then a fresh tumor biopsy at screening will be mandatory because it will serve as a baseline sample with which data from the post-treatment biopsy will be compared. **BMS-986183 and nivolumab dose expansion (Part 4)**: archived biopsy/slides and fresh biopsy are both mandatory. Both archived biopsy/slides and fresh biopsy will be used for determining eligibility based on GPC-3 expression. If the fresh biopsy meets defined cut-off criteria for GPC-3 expression, then the subject will be eligible. If the fresh biopsy does not meet defined cut-off criteria for GPC-3 expression, then the subject will not be eligible. If the archival slides meet defined cut-off criteria for GPC-3 expression and data from the fresh sample are not evaluable, then the subject will be eligible. If the archival slides do not meet the requirements (a minimum of 10 slides and not older than 3 months from time of slide preparation), and data from the fresh sample are not evaluable, then the subject will not be eligible. If archival tissue is not available and only fresh tumor biopsy can be obtained for assessing eligibility, such subjects can be enrolled in study after discussion with the Sponsor.

[c] Applies only to subjects enrolled in BMS-986183 and nivolumab dose expansion (Part 4) of the study.

[d] ± 1 day, PK sample should be collected at the same time.

[e] 24 to 48 hours post dose and at any other time an investigator chooses to obtain a biopsy during the study period. **BMS-986183 and nivolumab dose escalation (Part 3)**: post-treatment biopsy is optional but highly encouraged. If a subject opts to provide a post-treatment biopsy then a fresh tumor biopsy at screening will be mandatory because it will serve as a baseline sample with which data from the post-treatment biopsy will be compared. **BMS-986183 and nivolumab dose expansion (Part 4)**: biopsy at Cycle 2, 24 to 48 hours post dose is mandatory for 20 subjects enrolled. The biopsy is optional but highly encouraged for the other 30 subjects enrolled. If 20 subjects out of the first 30 subjects enrolled in BMS-986183 and nivolumab dose expansion (Part 4) do not opt to provide a biopsy at Cycle 2, 24 to 48 hours post dose, then this biopsy will be mandatory for the remaining 20 subjects to be enrolled.

[f] In the event dose is delayed; please refer to lab manual.

[g] Applies only to subjects enrolled in BMS-986183 and nivolumab dose expansion (Part 4) of study and is optional but highly encouraged.

[h] Sample is optional but is highly encouraged.

Approved v6.0 930091072 6.0

[redacted]

5.7.1 Serum-based biomarkers

5.7.1.1 Soluble Glypican-3

Table 5.6.1-1, Table 5.6.1-2, and Table 5.6.1-3 indicate the sampling timepoints for this biomarker.

5.7.1.2 Alpha-Fetoprotein

Table 5.6.1-1, Table 5.6.1-2, and Table 5.6.1-3 indicate the sampling timepoints for this biomarker.

5.7.1.3 Cytokeratin 18

Table 5.6.1-1, Table 5.6.1-2, and Table 5.6.1-3 indicate the sampling timepoints for this biomarker.

5.7.1.4 Prothrombin induced by vitamin K absence-II

Table 5.6.1-1, Table 5.6.1-2, and Table 5.6.1-3 indicate the sampling timepoints for this biomarker.

5.7.2 Additional Tumor and Serum-Based Biomarkers

Tumor and serum specimens may be used for identification of potentially predictive and pharmacodynamic markers of study drug activity or to enhance the understanding around disease biology and mechanism of action of BMS-986183 and nivolumab. In addition to the biomarkers outlined above, tumor tissue will be used to assess immune cell markers, such as, but not limited to, CD4, CD8, FoxP3, PD-1, PD-L1, CD68, and CD163. RNA and DNA from tumor tissue may be used for gene expression analysis and assessment of tumor mutational load.

[redacted]

5.8 Outcomes Research Assessments

Not applicable.

5.9 Other Assessments

Not applicable.

5.10 Additional Research Collection

All residual blood and tissue samples will be retained by the BMS Biorepository for additional research purposes. Additional research collections are mandatory for all subjects, except where prohibited by local laws and regulations or where specific waiver is provided by the BMS Medical Monitor (or designee); if one of these exceptions occur, participation in additional research collection should be encouraged but will not be a condition of overall study participation. Details of sample collection and processing will be provided to the site in the procedure manual. See also Section 1.1.9.7.

6 ADVERSE EVENTS

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

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

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

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

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

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

Immune-mediated adverse events (IMAEs) are AEs consistent with an immune-mediated mechanism or immune-mediated component for which noninflammatory etiologies (eg, infection or tumor progression) have been ruled out. IMAEs can include events with an alternate etiology that were exacerbated by the induction of autoimmunity. Information supporting the assessment will be collected on the subject's CRF.

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 one of the other serious outcomes listed in the definition above.) Examples

of such events include, but are not limited to, intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalization.) 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 6.4 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 an SAE (see Section 6.1.1 for reporting details).

NOTE:

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

- a visit to the emergency room or other hospital department < 24 hours, that does not result in admission (unless considered an important medical or life-threatening event)
- elective surgery, planned prior to signing consent
- admissions as per protocol for a planned medical/surgical procedure
- routine health assessment requiring admission for baseline/trending of health status (eg, routine 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[14] represent the Reference Safety Information to determine expectedness of SAEs for expedited reporting. Following the subject's written consent to participate in the study, all SAEs, whether related or not related to study drug, must be collected, including those thought to be associated with protocol-specified procedures. All SAEs must be collected that occur during the screening period and within a total of 60 days of discontinuation of dosing for BMS-986183 dose escalation (Part 1) and BMS-986183 dose expansion (Part 2) and within a total of 100 days of discontinuation of dosing for BMS-986183 and nivolumab dose escalation (Part 3) and BMS-986183 and nivolumab dose expansion (Part 4). If applicable, SAEs must be collected that relate to any later protocol-specified procedure (eg, a follow-up skin biopsy).

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

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

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

SAEs, whether related or not related to study drug, and pregnancies must be reported to BMS or designee within 24 hours of awareness of the event. SAEs must be recorded on the SAE Report Form; pregnancies on a Pregnancy Surveillance Form (electronic or paper forms). The preferred method for SAE data reporting collection is through the 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, electronic submission is the required method for reporting. In the event the electronic system is unavailable for transmission, paper forms must be used and submitted immediately. When paper forms are used, the original paper forms are to remain on site.

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

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

If an ongoing SAE changes in its intensity or relationship to study drug or if new information becomes available, the SAE report must be updated and submitted within 24 hours to BMS (or designee) using the same procedure used for transmitting the initial SAE report.

All SAEs must be followed to resolution or stabilization.

6.2 Nonserious Adverse Events

A ***nonserious AE*** is an AE not classified as an SAE.

6.2.1 Nonserious Adverse Event Collection and Reporting

The collection of nonserious AE information should begin at initiation of study drug. Nonserious AE information should also be collected from the start of a placebo lead-in period or other observational period intended to establish a baseline status for the subjects.

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

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

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

6.3 Laboratory Test Result Abnormalities

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

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

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

6.4 Pregnancy

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

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

The investigator must immediately notify the BMS medical monitor or designee of this event and complete and forward a Pregnancy Surveillance Form to BMS (or designee) within 24 hours of awareness of the event and in accordance with SAE reporting procedures described in Section 6.1.1.

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).

p-DILI is defined as:

- Concurrent ALT ≥ 10 × ULN AND total bilirubin ≥ 2 × ULN or baseline value (if elevated bilirubin at study entry), AND
- No other immediately apparent possible causes of ALT elevation and hyperbilirubinemia, including, but not limited to, tumor progression, acute viral hepatitis, cholestasis, pre-existing hepatic disease or the administration of other drug(s), herbal medications and substances known to be hepatotoxic.

This is the standard drug-induced liver injury definition across the BMS HCC program.

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, total bilirubin, alkaline phosphatase). Any subject with an abnormal Hepatic Laboratory Panel that meets p-DILI criteria 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 HCC), autoimmune 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 nonserious AE or SAE, as appropriate, and reported accordingly.

7 DATA MONITORING COMMITTEE AND OTHER EXTERNAL COMMITTEES

Not applicable.

8 STATISTICAL CONSIDERATIONS

8.1 Sample Size Determination

8.1.1 BMS-986183 Dose Escalation (Part 1) and BMS-986183 and Nivolumab Dose Escalation (Part 3) Sample Size

A total of approximately 30 evaluable subjects are expected to be treated during BMS-986183 dose escalation (Part 1), and approximately 21 evaluable subjects in BMS-986183 and nivolumab dose escalation (Part 3), assuming 4 dose levels (3 to 6 subjects for each dose level) will be evaluated. In BMS-986183 dose escalation (Part 1) of the study, the sample size per dose level cannot be precisely determined but depends on the observed DLT and the decision rules of mTPI. An initial cohort of 1 to 2 subjects will be enrolled sequentially to dose level cohorts 1 to 3 in BMS-986183 dose escalation (Part 1) (as long as no DLTs are observed or criteria for transitioning from 2-fold increment to modified Fibonacci criteria are **not** met). Once the first DLT is observed or after the first 3 dose level cohorts with no DLT observed, then 3 to 4 subjects will be enrolled in each dose level cohort (including the current cohort). For the first dose level cohorts of BMS-986183 and nivolumab dose escalation (Part 3), 3 to 4 evaluable subjects may be enrolled. Then between 2 and up to 13 DLT evaluable subjects may be enrolled to a given cohort according to mTPI algorithm. Treating additional subjects beyond the 13 would be unlikely to alter the decision specified by the mTPI algorithm.

8.1.2 BMS-986183 Dose Expansion (Part 2) and BMS-986183 and Nivolumab Dose Expansion (Part 4) Sample Size

An adaptive design will be used for the expansion cohorts. Approximately 50 subjects in BMS-986183 dose expansion (Part 2) and 50 subjects in BMS-986183 and nivolumab dose expansion (Part 4) with a plasma membrane or cytoplasmic H score of ≥ 50 for GPC-3 expression are expected to be treated in the BMS-986183 monotherapy expansion cohort at the maximally administered dose or the MTD (as determined from BMS-986183 dose escalation [Part 1] and BMS-986183 and nivolumab dose escalation [Part 3]). This number 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).

In a BMS-986183 monotherapy expansion cohort or BMS-986183 combination expansion cohort of 50 marker-positive subjects, assuming no adaptation made, if 10 or 13 responses are observed, then the ORR 90% confidence intervals (CIs) are (11%, 32%) and (16%, 38%), respectively. These calculations are based on the Clopper-Pearson method for exact CIs.

In addition, 50 subjects in BMS-986183 dose expansion (Part 2) or BMS-986183 and nivolumab dose expansion (Part 4) provide the following FNR and FPR under assumptions of expected true ORR. For BMS-986183 dose expansion (Part 2), if the true ORR is 20%, then with 50 subjects in the cohort there is 98% and 95% chance of observing at least 5 or 6 responses, respectively, and there is a 2% chance of observing 4 or fewer responses (FNR). If the true ORR is only 5%, then there is 10% and 4% chance respectively of observing at least 5 and at least 6 responses among 50 subjects (FPR). For BMS-986183 and nivolumab dose expansion (Part 4), if the true ORR is 30%, then with 50 subjects in the cohort there is a 96% and 92% chance of observing at least 10 or 11 responses, respectively, and there is a 4% chance of observing 9 or fewer responses (FNR). If the true ORR is only 15%, then there is 21% and 12% chance respectively of observing at least 10 and at least 11 responses among 50 subjects (FPR).

For more details on the H score cutoff, see Section 5.6.1.

Adaptive Design: BMS-986183 dose expansion (Part 2) and BMS-986183 and nivolumab dose expansion (Part 4) will begin enrolling subjects with plasma membrane or cytoplasmic H score ≥ 50. Decisions to change the H-score cutoff for BMS-986183 dose expansion (Part 2) will not be made until the following occur:

1) Approximately 10 response-evaluable subjects are available with mH-score ≥ 150, or
2) Approximately 10 response-evaluable subjects are available with mH-score < 50 and cytoplasmic H score ≥ 50.

Under 1) if 0 responses are observed with mH-score ≥ 150 (and no other responses in the study population for the expansion cohort are observed), then the expansion cohort may stop for futility. More generally, the statistical method to guide the determination of insufficient response is Bayesian predictive probability.[82] Under 1), if predictive probability of success is less than a pre-specified futility threshold, where success means a posterior response rate is greater than the target null efficacy rate with a very high probability at the end of study, the expansion cohort may stop for futility. A decision to stop the expansion cohort will be based not only on response but also on the totality of the safety, efficacy, and PK/pharmacodynamic data.

Under 2) if 0 responses are observed with mH-score < 50 and cytoplasmic H-score ≥ 50, then the study population may be restricted to mH-score ≥ 50. More generally, if predictive probability of success is less than a pre-specified futility threshold, where success means a posterior response rate is greater than the target null efficacy rate with a very high probability at the end of study, the expansion cohort may be restricted to mH-score ≥ 50.

Enrollment will continue while interim analyses are conducted. For the remainder of the dose expansion, assuming the study is not stopped for futility, ongoing assessment of the responses may result in 3 additional adaptations, depending on whether 1) or 2) is achieved first. If 1) occurs first, then when 2) occurs, if predictive probability is less than a pre-specified futility threshold, the study population may be restricted to mH-score ≥ 50. If 2) occurs first, then when 1) occurs, if predictive probability is less than the pre-specified futility threshold, the study may be stopped for futility.

The third possible adaptation may be considered once the population is restricted to mH-score ≥ 50. Depending on the number of responses in the mH-score < 150 (ie, if 0 responses) enrollment may be further restricted to subjects with mH-score ≥ 150. Once the biomarker threshold is identified, the cohort may be expanded to ensure adequate subjects from the finalized population of interest for achieving a reasonable precision of ORR.

Simulations were conducted to understand the operational characteristics of the design under a variety of scenarios. For example, assuming a target null efficacy rate of 5%, in the scenario where response rates in all subpopulations were no better than 5%, the observed false positive rate was 8.6% using a 1-sided test, indicating control of Type 1 error. In addition, the average sample size across simulations was 36 subjects. In the scenario where response rate in the mH-score ≥ 50 was 20% and response rate in the mH-score < 50 and cytoplasmic H-score ≥ 50 is 5%, the observed power was 80.6%. Full simulation results will be presented in the Statistical Analysis Plan (SAP). In short, the design has adequate power to detect a variety of alternative scenarios with response rates ≥ 20% in subpopulations while maintaining adequate control of Type 1 error with expected sample sizes < 50.

8.2 Populations for Analyses

- All Enrolled Subjects: All subjects who sign an ICF.
- All Treated Subjects: All subjects who receive at least one dose of study drug.
- PK Subjects: All subjects who receive at least one dose of BMS-986183 monotherapy (or BMS-986183 and nivolumab combination therapy) and have available serum and/or plasma concentration data.
- Biomarker Subjects: All treated subjects for whom pharmacodynamic measurements are available at both baseline and at least one other time after treatment.
- 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 one other tumor measurement after treatment, clinical progression, or death prior to the first on-treatment tumor assessment.

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

All available data from subjects who receive BMS-986183 monotherapy (or BMS-986183 and nivolumab combination therapy) will be included in the PK data set.

All available data from subjects for whom pharmacodynamic measurements are available at baseline and at least one other time will be included in the pharmacodynamic data set.

8.3 Endpoints

8.3.1 Primary Endpoint(s)

The primary objective (to assess the safety and tolerability of BMS-986183 administered as monotherapy and in combination with nivolumab in subjects with HCC) will be measured by the

primary endpoint(s) of incidence of AEs at its worst grade, SAEs at its worst grade, AEs leading to discontinuations, deaths, and frequency of laboratory test toxicity grade shifting from baseline. Safety will be evaluated as described in Table 5.1-1.

8.3.2 Secondary Endpoint(s)

The first secondary objective (to assess the preliminary anti-tumor activity of BMS-986183 administered as monotherapy and in combination with nivolumab as measured by ORR, response duration, and PFS) will be measured by 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 presurgical 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 (DoR): 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, DoR will be censored on the date of last tumor assessment
- PFS: defined as the time from the first dose of study drug 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 drug. Subjects who started any subsequent anti-cancer therapy without a prior reported progression will be censored at the last tumor assessment prior to initiation of the subsequent anti-cancer therapy. Subsequent anti-cancer therapy will be defined as the following therapy, which started after the treatment start date: systemic anti-cancer/anti-neoplastic therapy, any investigational drug, or palliative local therapy.
- PFS rate at week ‘t’: defined as the proportion of subjects who remain progression free and surviving at ‘t’ weeks (t=12, 24, 36, etc). The proportion will be calculated by the product-limit method (Kaplan-Meier [K-M] estimate) which takes into account censored data.
- The second secondary objective (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) of BMS-986183 as monotherapy and in combination with nivolumab will be measured by the following secondary endpoints, when applicable (see Section 5.5 for details):
- Cmax
- Tmax
- AUC(0-T)
- AUC(TAU)
- Ctau

- Ctrough
- CLT
- Vss
- Vz
- AI_Cmax
- AI_Ctau
- AI_AUC(TAU)
- Css,avg
- T-HALF

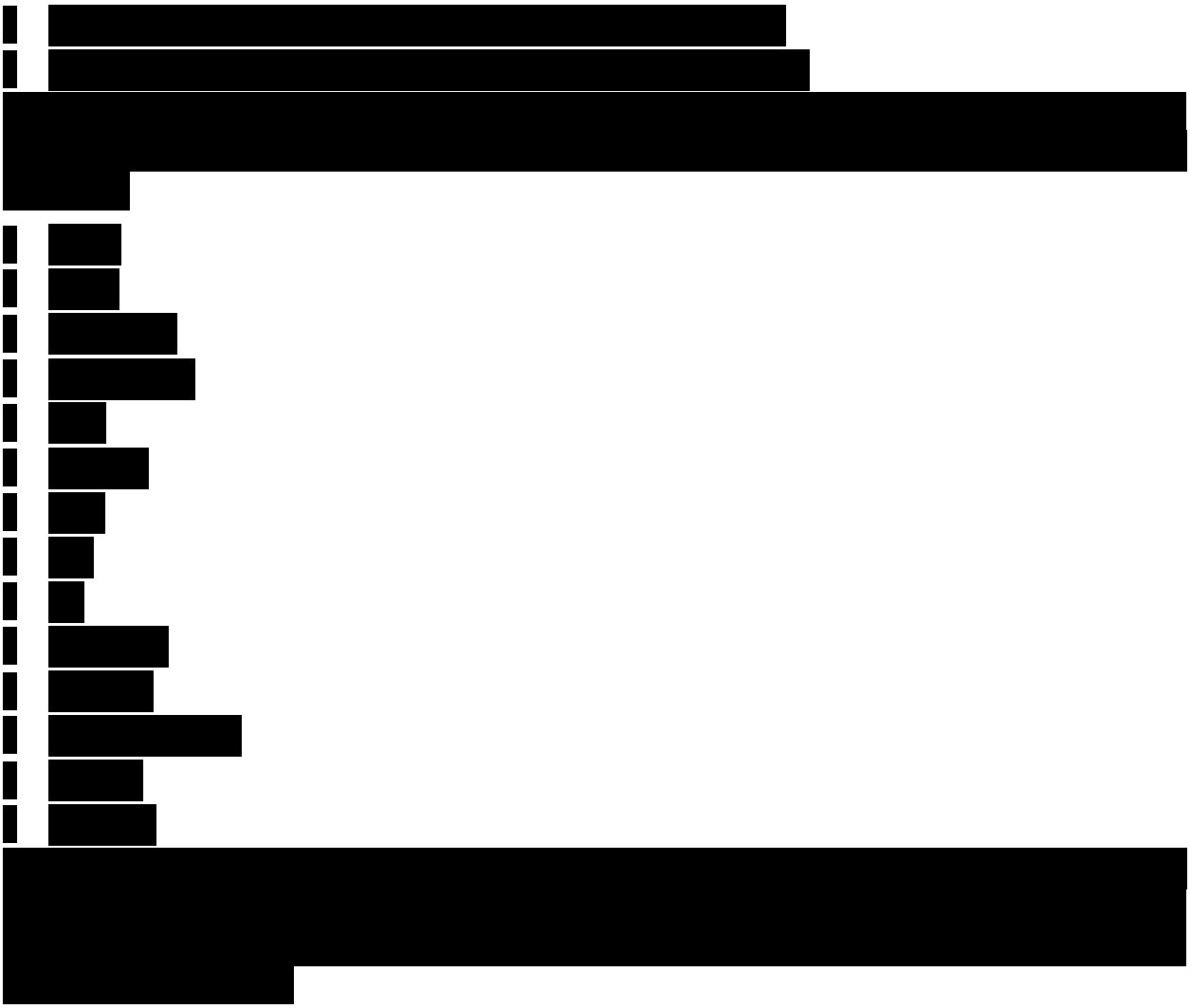
The third secondary objective (To assess the effect of dosage regimen and exposure [active ADC and unconjugated tubulysin] of BMS-986183 as monotherapy on the QT interval) will be measured by the following secondary endpoints:

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

The fourth secondary objective (to characterize the immunogenicity of BMS-986183 as monotherapy and in combination with nivolumab) will be measured by the following secondary endpoints:

- The endpoints of immunogenicity of BMS-986183 as monotherapy and in combination with nivolumab include frequency of different subject immunogenicity status, eg, subject positive ADA, persistent positive ADA and others. Definitions of all the immunogenicity endpoints will be provided in the SAP.

[redacted]



8.4 Analyses

8.4.1 Demographics and Baseline Characteristics

Frequency distributions of gender and race will be tabulated. Summary statistics for age, body weight, height, and Body Mass Index will be tabulated.

8.4.2 Efficacy Analyses

Efficacy results will be presented by dose and regimen. Individual BOR, DoR, and PFS will be listed using RECIST v1.1 criteria (Appendix 6).[81] 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 if there is enough data. The DoR and PFS will be estimated by 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. OS may also be assessed as part of exploratory efficacy analysis, by K-M plots and medians and OS rates at specified times, and by tabulation, graphics, and/or medians as appropriate for the endpoints.

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 (full or targeted) 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, ΔQTcF, ECG intervals QRS and PR, and in heart rate will be tabulated by dose and study day. Frequency distributions of maximum QTcF values, maximum ΔQTcF, maximum QRS, maximum PR interval, and maximum heart rate in prespecified categories will be tabulated by dose. Scatter plots of heart rate, change in heart rate, QTc, and ΔQTcF vs time-matched active ADC and unconjugated tubulysin concentrations will be provided. A concentration-response effect of BMS-986183 as monotherapy 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, active ADC, conjugated tubulysin, and unconjugated tubulysin will be calculated using noncompartmental analysis.

PK analysis will be provided separately for each of the above analytes. 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) vs dose will be provided, on indicated study days for each dose regimen. In addition, exploratory assessment of dose proportionality will be based on a power model and a CI around the power will be calculated. To assess the attainment of steady-state geometric mean trough observed concentration values will be plotted vs study day by dose and dose regimen.

Associations between PK and select safety and efficacy measures may be explored.

PPK and exposure-response analyses for BMS-986183 and for nivolumab may be conducted, which would be presented in a separate report.

[redacted]

8.4.6 Biomarker Analyses

Boxplot of baseline GPC-3 expression via IHC will be shown, and distribution of expression will be assessed. Association between efficacy measures and GPC-3 expression may be assessed by graphs and/or summary statistics.

[redacted]

8.4.8 Outcomes Research Analyses

Not applicable.

8.4.9 Other Analyses

Not applicable.

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.

9 STUDY MANAGEMENT

9.1 Compliance

9.1.1 Compliance with the Protocol and Protocol Revisions

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

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

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

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

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

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

9.1.2 Monitoring

BMS representatives will review data centrally to identify potential issues to determine a schedule of on-site visits for targeted review of study records.

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

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

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

9.1.2.1 Source Documentation

The investigator is responsible for ensuring that the source data are accurate, legible, contemporaneous, original and attributable, whether the data are hand-written on paper or entered electronically. If source data are created (first entered), modified, maintained, archived, retrieved, or transmitted electronically via computerized systems (and/or any other kind of electronic devices) as part of regulated clinical study 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, eCRFs, study documentation, informed consent, and enrollment of WOCBP.

9.2 Records

9.2.1 Records Retention

The investigator must retain all study records and source documents for the maximum period required by applicable regulations and guidelines, or institution procedures, or for the period specified by BMS, whichever is longer. The investigator must contact BMS prior to destroying any records associated with the study and BMS will notify the investigator when the study records are no longer needed.

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

9.2.2 Study Drug Records

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

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

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

9.2.3 Case Report Forms

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

For sites using the BMS electronic data capture tool, eCRFs will be prepared for all data collection fields except for fields specific to SAEs and pregnancy, which will be reported on the paper or electronic SAE form and Pregnancy Surveillance form, respectively. If electronic SAE form is not available, a paper SAE form can be used. Spaces may be left blank only in those circumstances permitted by study-specific CRF completion guidelines provided by BMS.

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

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

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

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

9.3 Clinical Study Report and Publications

A Signatory Investigator must be selected to sign the clinical study report.

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

- Subject recruitment (eg, among the top quartile of enrollers)
- Involvement in study 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	Complete Abstinence is defined as complete avoidance of heterosexual intercourse and is an acceptable form of contraception for all study drugs. This also means that abstinence is the preferred and usual lifestyle of the patient. This does not mean periodic abstinence (eg, calendar, ovulation, symptothermal, profession of abstinence for entry into a clinical study, post-ovulation methods) and withdrawal, which are not acceptable methods of contraception. Women must continue to have pregnancy tests. Acceptable alternate methods of highly or less effective contraceptives 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 study design, for which we would like to collect and/or retain samples from study participants. Examples of additional 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
ΔQTcF	change in Fridericia-corrected QT interval
ADA	anti-drug antibody
ADC	antibody drug conjugate
ADME	absorption, distribution, metabolism, and excretion
AE	adverse event
AFP	alpha-fetoprotein
AI_AUC(TAU)	Accumulation index; ratio of AUC(TAU) at steady-state to AUC(TAU) after the first dose
AI_Cmax	accumulation index; ratio of Cmax at steady-state to Cmax after the first dose
AI_Ctau	accumulation index; ratio of Ctau at steady-state to Ctau after the first dose
ALT	alanine aminotransferase
AST	aspartate aminotransferase
AUC	area under the concentration-time curve
AUC(0-T)	area under the concentration-time curve from time 0 to T of the last quantifiable concentration
$AUC_{(0-96h)}$	area under the concentration vs time curve from 0 to 96 hours of the last measurable concentration
$AUC_{(0-168h)}$	area under the concentration vs time curve from 0 to 168 hours of the last measurable concentration
$AUC_{(0-672h)}$	area under the concentration vs time curve from 0 to 672 hours of the last measurable concentration
$AUC_{(0-\infty)}$	area under the concentration-time curve from time 0 to infinity
AUC(TAU)	area under the concentration-time curve in 1 dosing interval
BMS	Bristol-Myers Squibb
BOR	best overall response
BTLA	B and T lymphocyte attenuator
BV	brentuximab vendotin
C	cycle
Cavg	average concentration over a dosing interval calculated by dividing AUC(TAU) by tau
CBC	complete blood count
CD	cluster of differentiation
CFR	Code of Federal Regulations
CI	confidence interval
CK18	cytokeratin 18

Term	Definition
CL	clearance
CLT	total body clearance
Cmax	maximum observed concentration
CMV	cytomegalovirus
CNS	central nervous system
CR	complete response
CrCl	creatinine clearance
CRF	case report form
Css,avg	Average concentration over a dosing interval calculated by dividing AUC(TAU) at steady state by tau
CT	computed tomography
CTA	clinical trial agreement
Ctau	concentration at the end of a dosing interval
CTCAE	Common Terminology Criteria for Adverse Events
CTLA-4	cytotoxic T lymphocyte antigen 4
cTnI	cardiac Troponin I
cTnT	cardiac Troponin T
Ctrough	trough observed concentration, including predose concentrations and Ctau
CV	coefficient of variation
CYP	cytochrome P450
D	day
DCR	disease control rate
DLT	dose limiting toxicity
DMC	data monitoring committee
DNA	deoxyribonucleic acid
DoR	duration of response
EC_{50}	median effective concentration
ECG	electrocardiogram
ECHO	echocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	electronic case report form
EI	equivalence interval
EOI	end of infusion
EOT	end of treatment

Term	Definition
FDG	[18^{F}]fluorodeoxyglucose
FFPE	formalin-fixed, paraffin-embedded
FIH	first-in-human
FNR	false negative rate
FPFV	first patient, first visit
FPR	false positive rate
FSH	follicle stimulating hormone
GCP	Good Clinical Practice
GFR	glomerular filtration rate
GI	gastrointestinal
GPC-3	glypican-3
HBeAb	hepatitis B e antibody
HBeAg	hepatitis B e antigen
HBsAb	hepatitis B surface antigen antibody
HBsAg	hepatitis B surface antigen
HBV	hepatitis B virus
HCC	hepatocellular carcinoma
HCV	hepatitis C virus
HED	human equivalent dose
HER2	human epidermal growth factor receptor 2
hERG	human ether-a-go-go-related gene
HFSR	hand-foot-skin reaction
HIV	human immunodeficiency virus
HNSTD	highest nonseverely toxic dose
HRT	hormone replacement therapy
IB	Investigator's Brochure
ICF	informed consent form
ICH	International Conference on Harmonisation
ICOS	inducible T-cell co-stimulator
IFN-γ	interferon gamma
Ig	immunoglobulin
IHC	immunohistochemistry
I_{Kr}	rapid delayed rectifier current

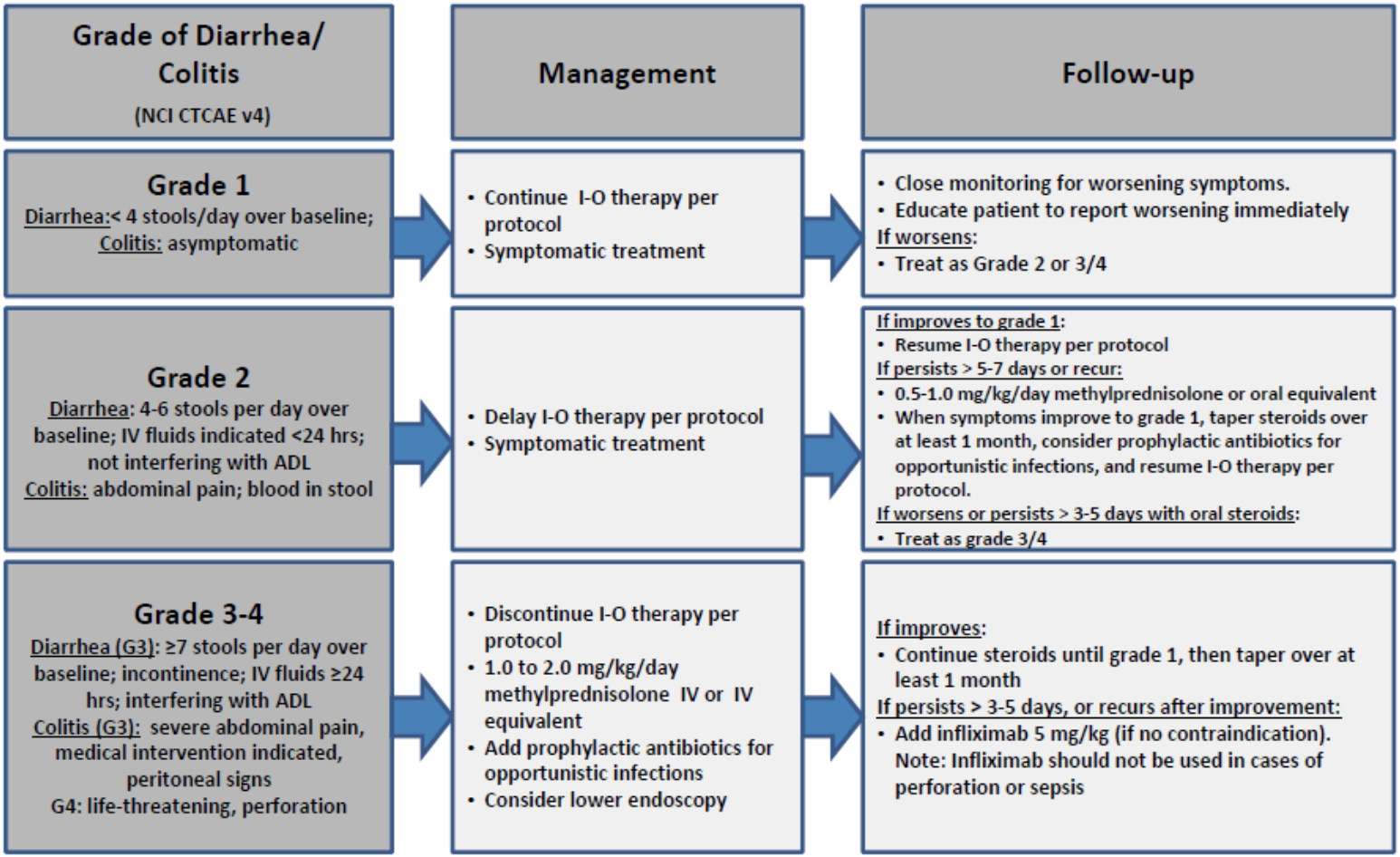
Term	Definition
IL	interleukin
IMAE	immune-mediated adverse event
IMP	investigational medicinal product
INR	international normalized ratio
I-O	immuno-oncology
IP	investigational product
IRB/IEC	Institutional Review Board/Independent Ethics Committee
IRT	interactive response technology
IUD	intrauterine device
IV	intravenous
K-M	Kaplan-Meier
LFT	liver function test
LLOQ	lower limit of quantification
LVEF	left ventricular ejection fraction
MAAD	maximum administered dose
mH-score	membrane H-score
MI	myocardial infarction
MRI	magnetic resonance imaging
MRSD	maximum recommended starting dose
MTD	maximum tolerated dose
mTPI	modified toxicity probability interval
MUGA	multigated acquisition scan
NCI	National Cancer Institute
NSCLC	non-small cell lung cancer
NYHA	New York Heart Association
ORR	objective response rate
OS	overall survival
PCR	polymerase chain reaction
p-DILI	potential drug-induced liver injury
PD	progressive disease
PD-1	programmed cell death protein-1
PD-L1	programmed cell death ligand 1
PD-L2	programmed cell death ligand 2
PE	physical examination

Term	Definition
PET	positron emission tomography
PFS	progression-free survival
PI	prediction interval
PIVKA-II	prothrombin induced by vitamin K absence-II
PK	pharmacokinetic(s)
PPK	population pharmacokinetic
PR	partial response
PT	prothrombin time
Q1W	once weekly
Q2W	every 2 weeks
Q3W	every 3 weeks
Q6W	every 6 weeks
QTc	corrected QT interval
QTcF	Fridericia-corrected QT interval
RBC	red blood cell
RCC	renal cell carcinoma
RD	repeat dose
RECIST	Response Evaluation Criteria in Solid Tumors
RNA	ribonucleic acid
SAE	serious adverse event
SAP	statistical analysis plan
SCLC	small cell lung cancer
SCN5A	sodium channel, voltage gated, type V alpha subunit
SD	stable disease
SGBS1	type 1 Simpson–Golabi–Behmel syndrome
sGPC-3	soluble glypican-3
STD10	severe toxicity to 10%
T3	triiodothyronine
T4	thyroxine
T-DM1	ado-trastuzumab emtansine
TGI	tumor growth inhibition
T-HALF	terminal half-life
TIL	tumor-infiltrating lymphocyte
TMA	tissue microarray

Term	Definition
Tmax	time of maximum observed concentration
Treg	T regulatory cell
ULN	upper limit of normal
UC	urothelial carcinoma
US	United States
Vss	Apparent volume of distribution at steady-state
Vz	volume of distribution of terminal phase
WOCBP	women of childbearing potential

Figure 1: Gastrointestinal Adverse Event Management Algorithm

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



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

ADL = activities of daily living; CTCAE = Common Terminology Criteria for Adverse Events; IV = intravenous; NCI = National Cancer Institute.

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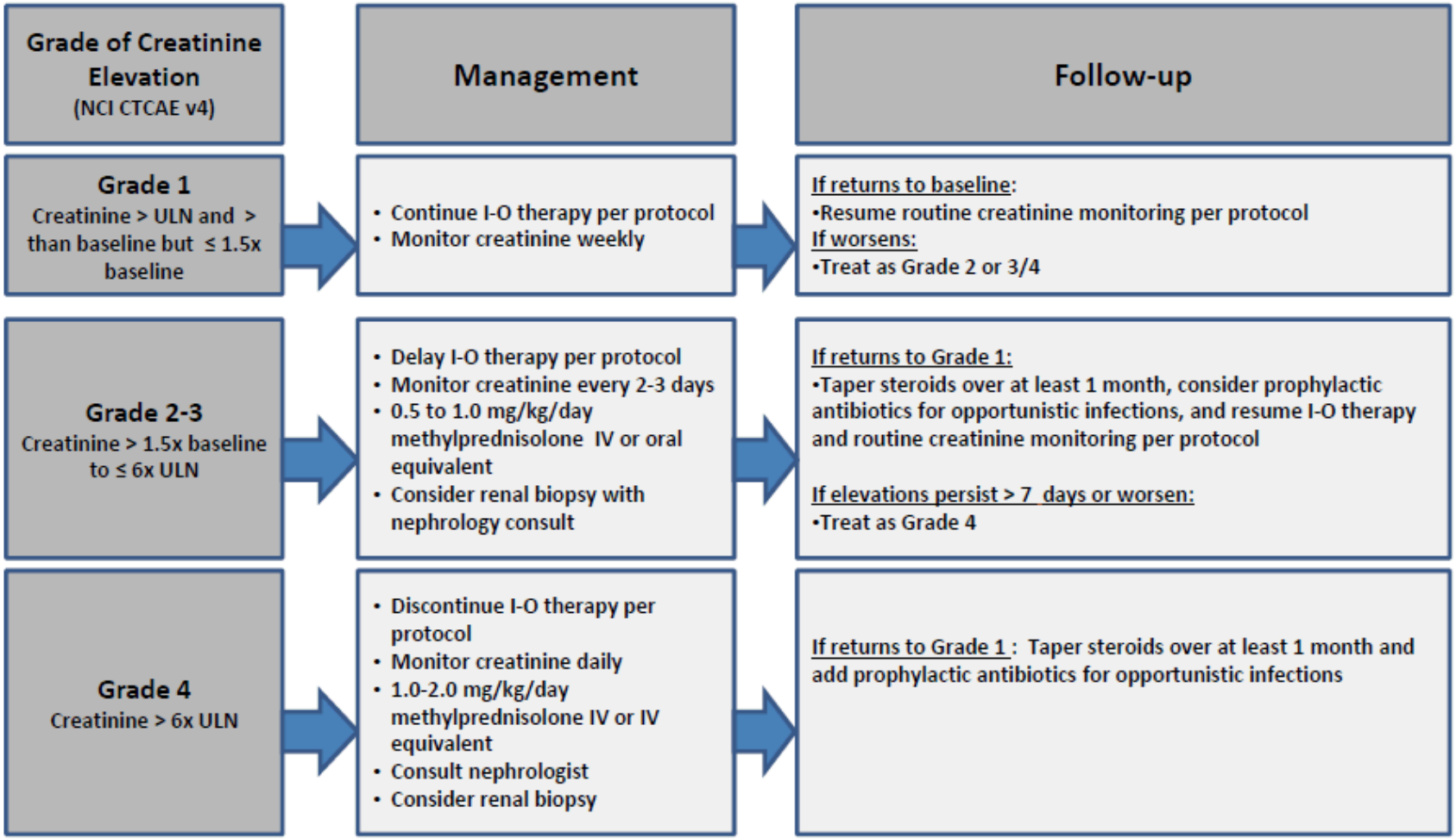
Figure 2: Renal Adverse Event Management Algorithm

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



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

CTCAE = Common Terminology Criteria for Adverse Events; IV = intravenous; NCI = National Cancer Institute; ULN = upper limit of normal.

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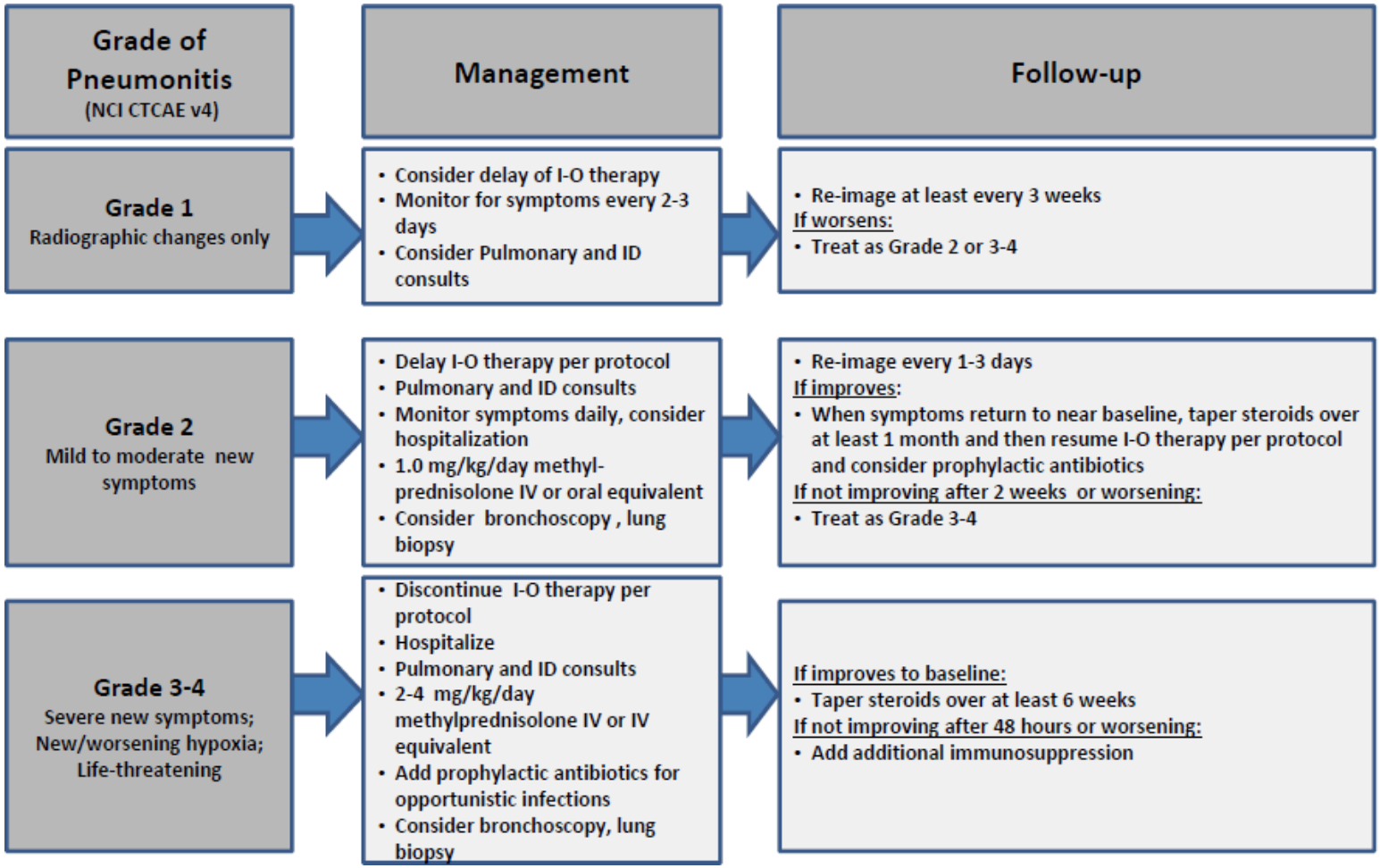
Figure 3: Pulmonary Adverse Event Management Algorithm

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



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

CTCAE = Common Terminology Criteria for Adverse Events; ID = infectious disease; IV = intravenous; NCI = National Cancer Institute.

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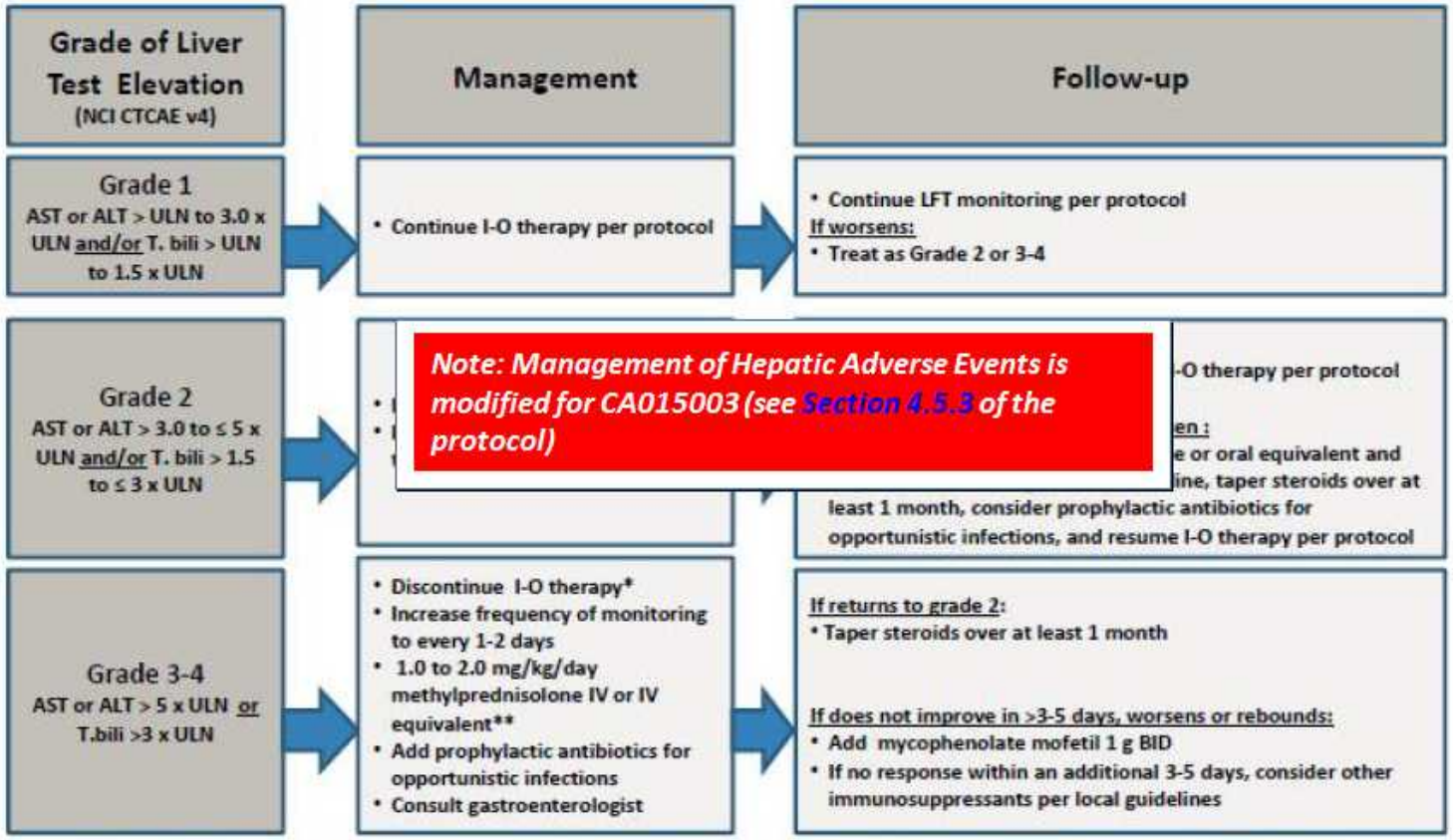
Figure 4: Hepatic Adverse Event Management Algorithm

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



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

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

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

ALT = alanine aminotransferase; AST = aspartate aminotransferase; BID = twice daily; CTCAE = Common Terminology Criteria for Adverse Events; IV = intravenous; LFT = liver function test; NCI = National Cancer Institute; ULN = upper limit of normal.

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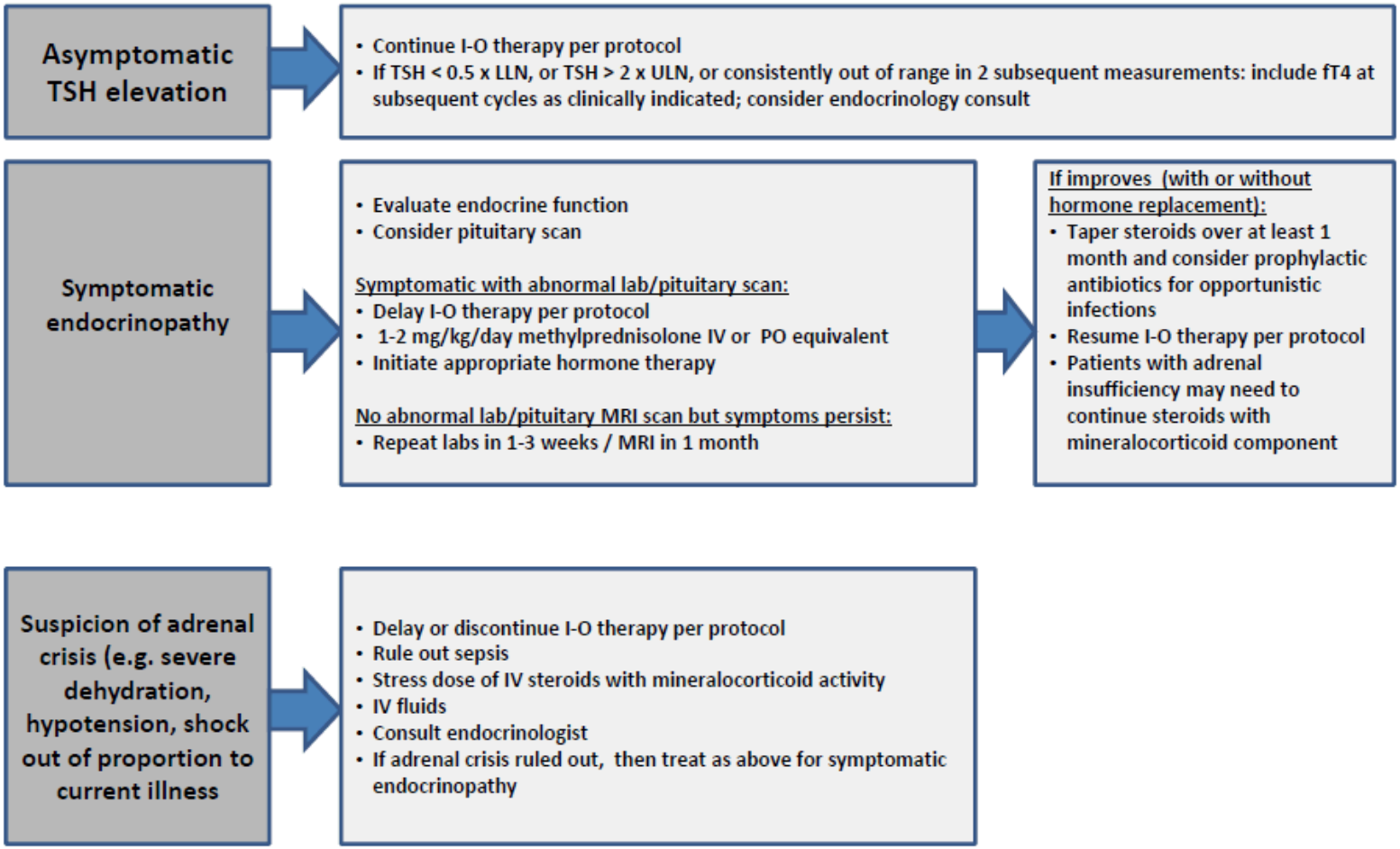
Figure 5: Endocrinopathy Management Algorithm

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



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

IV = intravenous; MRI = magnetic resonance imaging; PO = oral; TSH = thyroid stimulating hormones; ULN = upper limit of normal.

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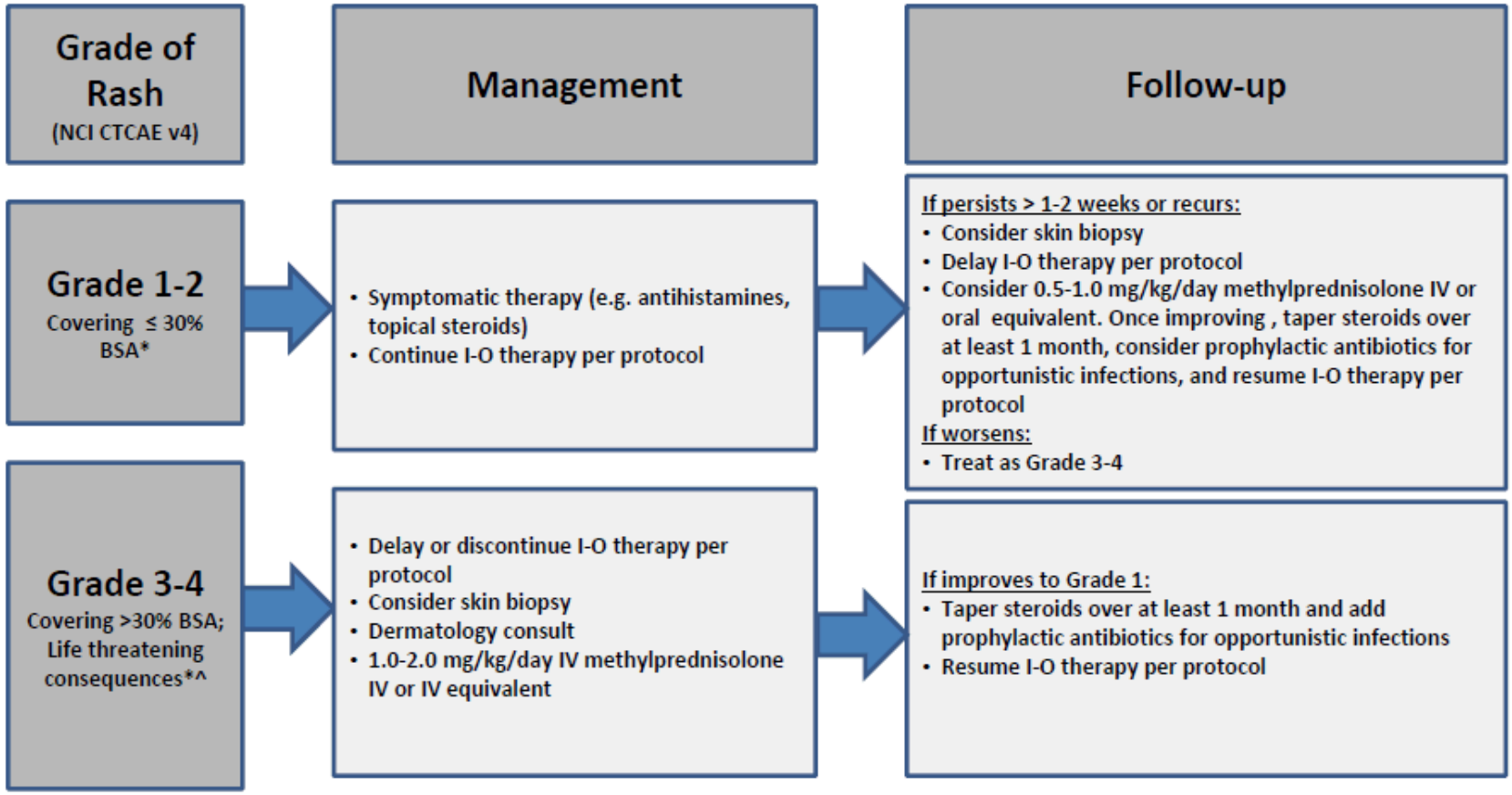
Figure 6: Skin Adverse Event Management Algorithm

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



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

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

^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.

BSA = body surface area; CTCAE = Common Terminology Criteria for Adverse Events; IV = intravenous; NCI = National Cancer Institute; SJS = Stevens Johnson Syndrome; TEN = toxic epidermal necrolysis.

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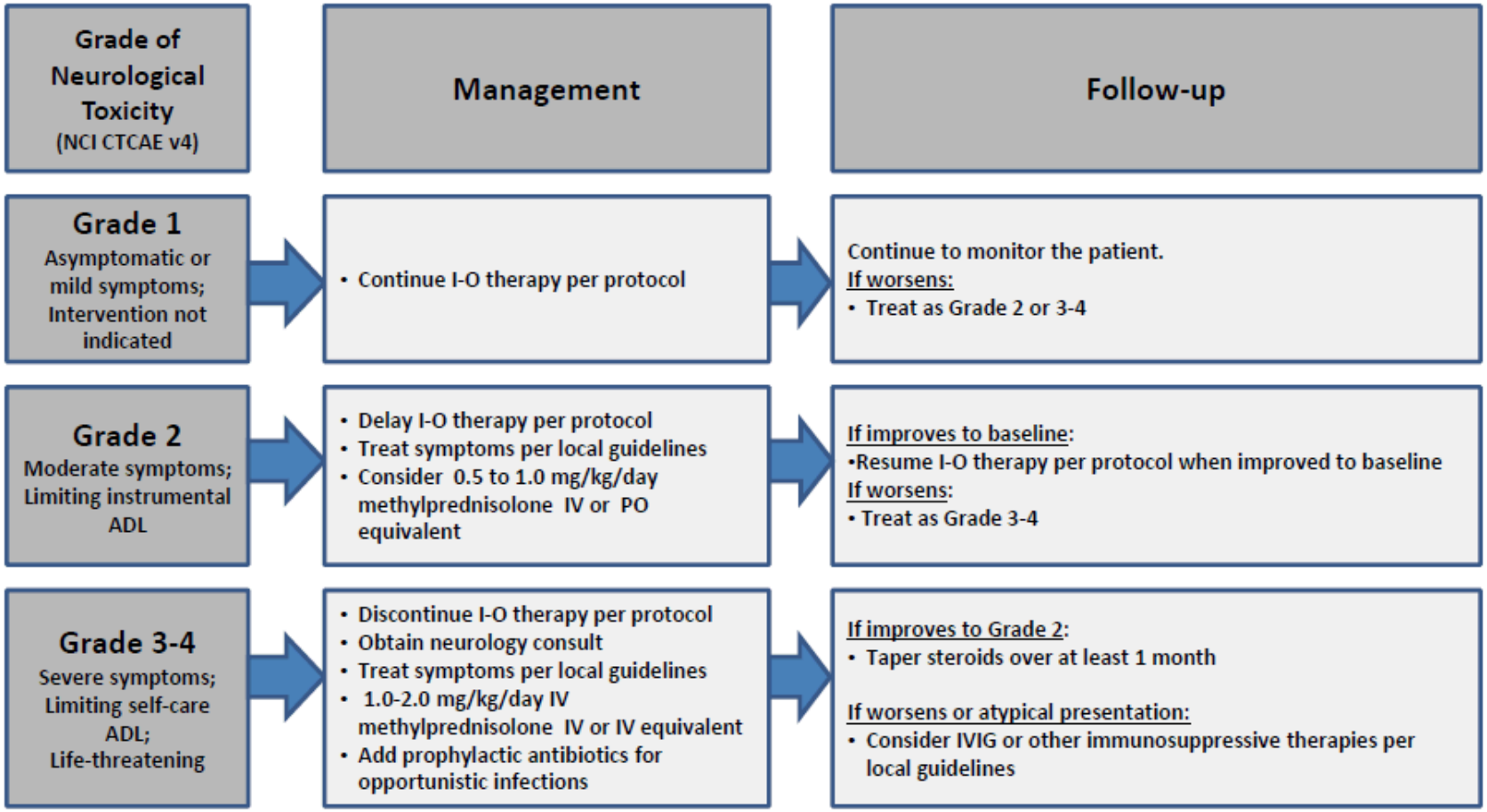
Figure 7: Neurological Adverse Event Management Algorithm

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



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

ADL = activities of daily living; CTCAE = Common Terminology Criteria for Adverse Events; IV = intravenous; IVIG = intravenous immunoglobulin therapy; NCI = National Cancer Institute; PO = oral

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APPENDIX 3 PHARMACOKINETIC-GUIDED DOSE ESCALATION ALGORITHM AND OPERATING CHARACTERISTICS

In the event that there are no dose-limiting toxicities or relevant adverse events in the initial dose cohorts and pharmacokinetic (PK) data are available and informative, a Bayesian model for exposure versus dose will be fit to the accrued data, and Bayesian posterior probabilities will be derived to guide the next dose selection. To illustrate the methodology, the model discussed in this appendix is assumed to be linear, although the final parametric model may be adjusted to account for nonlinearity in PK, which may occur in the event of target-mediated drug disposition. The prior for the model is informative and based on preclinical animal models (details below). Posterior probabilities of exposure at the next dose are calculated based on the prior and actual data collected in the study. If the posterior probability of exposure meets the prespecified criteria (see below), then the prespecified dose will be used in the next cohort; otherwise, a new dose will be calculated using PK data.

To illustrate the methodology, the PK endpoint used in this model is the area under the concentration-time curve from time 0 to infinity (AUC[0,∞]); however, depending upon the available PK data, other endpoints such as the maximum observed serum and/or plasma concentration (C_{max}) can also be used. From Section 1.1.5.1 in the protocol, the human projected AUC(0,∞) is 79 µg•h/mL at the starting dose of 0.05 mg/kg (equivalent to 3 mg in a 60-kg individual). Assuming linear PK, the target area under the concentration-time curve as function of dose follows a linear model with a slope B of 1,580. Then the Bayesian linear model takes the form

1) Exposure ~ B•dose + σ(dose),
   B ~ Normal(µ = 1,580, 316.2)
   σ(dose) = 0.30•µ•dose (CV of 30%)

An informative prior is chosen for the slope B because of limited data in the first few cohorts. Also relevant in the decision rules is the safety margin derived from the repeat-dose monkey study (Section 1.1.5.1 in the protocol). The highest nonseverely toxic dose from that study is 1 mg/kg with an area under the concentration-time curve from 0 to 168 hours of 842 µg•h/mL. Then, after updating the Bayesian model with the observed data to date and assuming no dose-limiting toxicities or relevant adverse events are observed to date, the following criteria for the next dose will be used to decide if the dose can be increased beyond the default 2-fold increase:

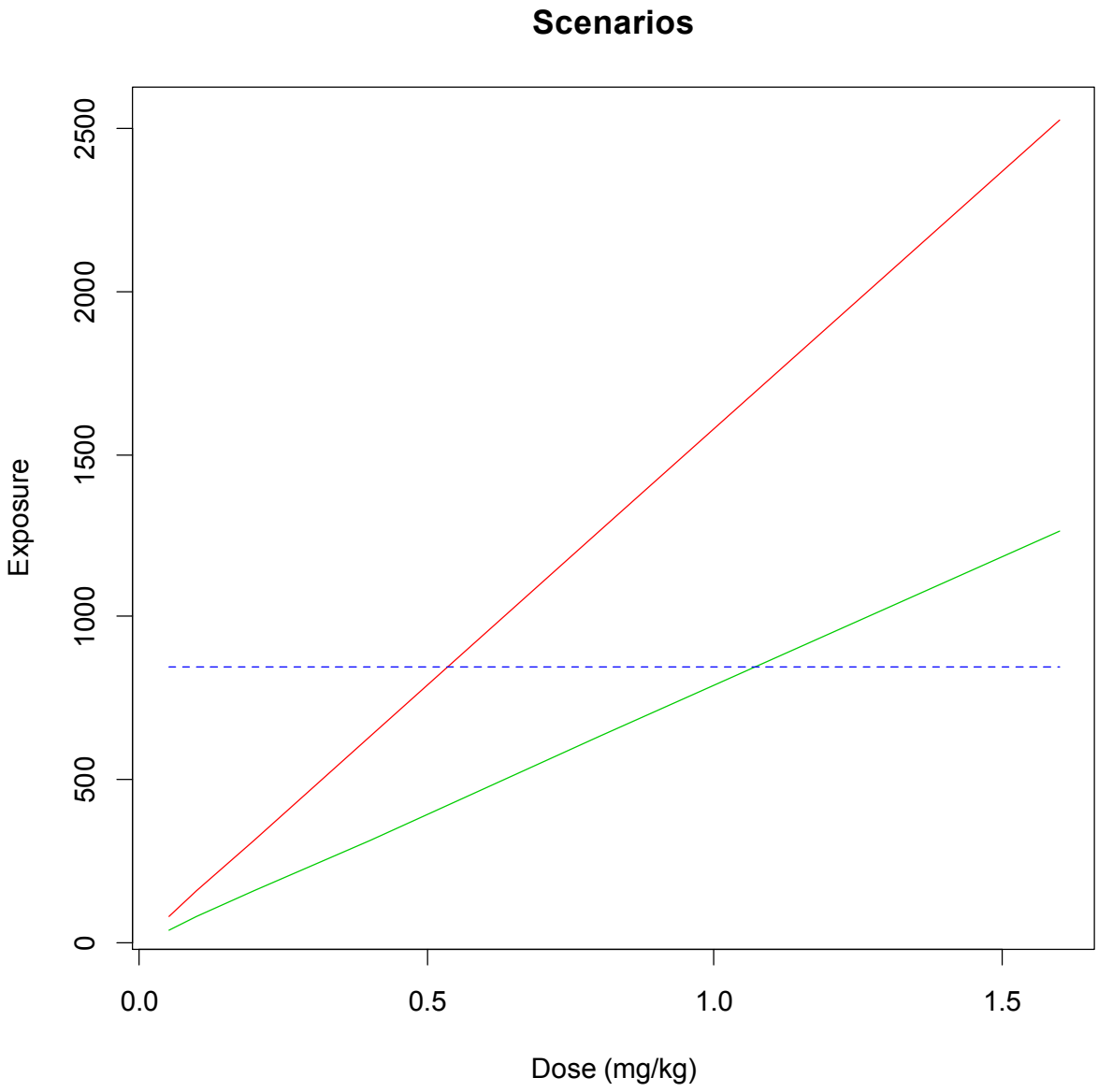
2) Posterior probability of next dose exposure > safety margin is less than 10%, AND
   90% quantile of posterior next dose exposure < target exposure, AND
   Next dose is ≤ 3-fold increase from the current dose

If 2) holds for a dose that is beyond the default 2-fold increase, then that dose may be chosen for the next dose cohort; otherwise, the next dose will default to 2-fold increase.

Simulations were conducted to understand the operating characteristics of the PK-guided dose escalation algorithm. Two scenarios were considered: 1) exposures at each dose match the target exposures (79 µg•h/mL at the starting dose of 0.05 mg/kg, and then 2-fold increases in dose and

exposure), and 2) exposures at each dose are lower than expected, specifically one-half the level of the target exposures. See Figure 1.

Figure 1: Scenarios



Software for the Bayesian model was written in R v3.2.2 and OpenBugs v3.2.3. Markov chain Monte Carlo was used to fit the model. Twenty simulated trials were generated. Under Scenario 1

(red line), 50% of the trials allowed at least one 3-fold dose increase and 35% allowed two 3-fold dose increases. All 3-fold dose increases occurred in the first 2 escalations. Under Scenario 2 (green line), 100% of the trials allowed two 3-fold increases, all in the first 2 escalations. Note that with a coefficient of variation of 30%, the standard deviation of exposure increases with dose. With increasing dose, the posterior distribution of the next dose exposure therefore becomes wider and more likely to cover the safety margin. It becomes less likely to allow dose escalations beyond 2-fold at higher does. These simulations indicate that the PK-guided dose-escalation model, while safeguarding against high exposures, allows greater increases in dose and achieves accelerated escalation decisions, especially at lower doses.

APPENDIX 6 RECIST V1.1

This Appendix has been excerpted from the full Response Evaluation Criteria in Solid Tumors Version 1.1 (RECIST v1.1).[1] For information pertaining to RECIST v1.1 not contained in the study protocol or in this Appendix, please refer to the full publication.[1]

1 ASSESSMENT OF OVERALL TUMOR BURDEN AND MEASURABLE DISEASE

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 ≥ 1 measurable lesion.

1.1 Measurability of Tumor

At baseline, tumor lesions/lymph nodes will be categorized measurable or nonmeasurable as follows. All baseline evaluations should be performed as close as possible to the treatment start and never more than 4 weeks before the beginning of the treatment.

Measurable lesions must be accurately measured in at least 1 dimension (longest diameter in the plane of the measurement to be recorded) with a minimum size of:

- 10 mm by computed tomography (CT) scan (CT scan slice thickness ≤ 5 mm)
- 10 mm caliper measurement by clinical examination (lesions that cannot be accurately measured with calipers should be recorded as nonmeasurable)
- 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 ≤ 5 mm). At baseline and in follow-up, only the short axis will be measured and followed.

All measurements should be recorded in metric notation, using calipers if clinically assessed.

Special considerations regarding lesion measurability

Bone lesions:

- Bone scan, positron emission tomography 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 magnetic resonance imaging (MRI) can be considered as measurable lesions if the soft tissue component meets the definition of measurability described above.
- Blastic bone lesions are nonmeasurable.

Cystic lesions:

- Lesions that meet the criteria for radiographically defined simple cysts should not be considered as malignant lesions (neither measurable nor nonmeasurable) 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 noncystic lesions are present in the same patient, these are preferred for selection as target lesions.

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.

Nonmeasurable lesions are all other lesions, including small lesions (longest diameter < 10 mm or pathological lymph nodes with ≥ 10 to < 15 mm short axis), as well as nonmeasurable lesions. Lesions considered nonmeasurable include leptomeningeal disease, ascites, pleural or pericardial effusion, inflammatory breast disease, lymphangitic involvement of skin or lung, and abdominal masses/abdominal organomegaly identified by physical examination that is not measurable by reproducible imaging techniques.

1.2 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 performed rather than clinical examination unless the lesion(s) being followed cannot be imaged but are assessable by clinical examination.

CT, MRI: CT is the best currently available and reproducible method to measure lesions selected for response assessment. Measurability of lesions on CT scan is based on the assumption that CT slice thickness is 5 mm or less. When CT scans have slice thickness > 5 mm, the minimum size for a measurable lesion should be twice the slice thickness.

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.

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 noted above, when lesions can be evaluated by both clinical examination and imaging, imaging evaluation should be undertaken since it is more objective and may be reviewed at the end of the study.

Ultrasound: Ultrasound is not useful in the assessment of lesion size and should not be used as a method of measurement. If new lesions are identified by ultrasound in the course of the study, confirmation by CT or MRI is advised.

Endoscopy, laparoscopy: The utilization of these techniques for objective tumor evaluation is not advised.

Tumor markers: Tumor markers alone cannot be used to assess objective tumor response.

2 BASELINE DOCUMENTATION OF 'TARGET' AND 'NONTARGET' LESIONS

Target lesions: When more than 1 measurable lesion is present at baseline, all lesions up to a maximum of 5 lesions total (and a maximum of 2 lesions per organ) representative of all involved organs should be identified as target lesions and will be recorded and measured at baseline.

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

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. All other pathological nodes (those with short axis ≥ 10 mm but < 15 mm) should be considered nontarget lesions. Nodes that have a short axis < 10 mm are considered nonpathological and should not be recorded or followed.

A sum of the diameters (longest for nonnodal lesions, short axis for nodal lesions) for all target lesions will be calculated and reported as the baseline sum diameters. The baseline sum diameters will be used as reference to further characterize any objective tumor regression in the measurable dimension of the disease.

Nontarget lesions: All other lesions (or sites of disease) including pathological lymph nodes should be identified as nontarget lesions and should also be recorded at baseline. Measurements are not required, and these lesions should be followed as 'present,' 'absent,' or 'unequivocal progression.' In addition, it is possible to record multiple nontarget lesions involving the same organ as a single item on the case record form (eg, 'multiple enlarged pelvic lymph nodes' or 'multiple liver metastases').

3 TUMOR RESPONSE EVALUATION AND RESPONSE CRITERIA

3.1 Evaluation of Target Lesions

Complete Response (CR): Disappearance of all target lesions. Any pathological lymph nodes (whether target or nontarget) must have reduction in short axis to < 10 mm.

Partial Response (PR): ≥ 30% decrease in the sum of diameters of target lesions, taking as reference the baseline sum diameters.

Progressive Disease (PD): ≥ 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 ≥ 5 mm. Note: The appearance of 1 or more new lesions is also considered progression.

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

Special notes on the assessment of target lesions

- **Lymph nodes:** Lymph nodes identified as target lesions should always have the actual short axis measurement recorded and should be measured in the same anatomical plane as the baseline examination, even if the nodes regress to below 10 mm on study. This means that when lymph nodes are included as target lesions, the 'sum' of lesions may not be zero even if CR criteria are met since a normal lymph node is defined as having a short axis of < 10 mm.
- **Target lesions that become 'too small to measure':** All lesions (nodal and nonnodal) recorded at baseline should have their actual measurements recorded at each subsequent evaluation, even when very small (eg, 2 mm). If the radiologist is able to provide an actual measure, 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:

(i) if it is the opinion of the radiologist that the lesion has likely disappeared, the measurement should be recorded as 0 mm.

(ii) 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).

Lesions that split or coalesce on treatment: When nonnodal lesions 'fragment,' the longest diameters of the fragmented portions should be added together to calculate the target lesion sum. Similarly, as lesions coalesce, a plane between them may be maintained that would aid in obtaining maximal diameter measurements of each individual lesion. If the lesions have 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 Nontarget Lesions

While some nontarget lesions may actually be measurable, they need not be measured and instead should be assessed only qualitatively at the timepoints specified in the protocol.

CR: Disappearance of all nontarget lesions and normalization of tumor marker level. All lymph nodes must be nonpathological in size (< 10 mm short axis).

Non-CR/NonPD: Persistence of 1 or more nontarget lesion(s) and/or maintenance of tumor marker level above the normal limits.

PD: Unequivocal progression of existing nontarget lesions. Note: The appearance of 1 or more new lesions is also considered progression.

- The concept of progression of nontarget disease requires additional explanation as follows:
- *When the patient also has measurable disease*: To achieve 'unequivocal progression' on the basis of the nontarget disease, there must be an overall level of substantial worsening in nontarget 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 1 or more nontarget lesions is usually not sufficient to qualify for unequivocal progression status.
- *When the patient has only nonmeasurable disease*: To achieve 'unequivocal progression' on the basis of the nontarget disease, there must be an overall level of substantial worsening such that the overall tumor burden has increased sufficiently to merit discontinuation of therapy. A modest 'increase' in the size of 1 or more nontarget lesions is usually not sufficient to qualify for unequivocal progression status. Because worsening in non-target disease cannot be easily quantified (by definition: if all lesions are nonmeasurable), a useful test that can be applied when assessing patients for unequivocal progression is to consider if the increase in overall disease burden based on the change in nonmeasurable disease is comparable in magnitude to the increase that would be required to declare PD for measurable disease, ie, an increase in tumor burden representing an additional 73% increase in 'volume' (which is equivalent to a 20% increase diameter in a measurable lesion). Examples include an increase in a pleural effusion from 'trace' to 'large,' an increase in lymphangitic disease from localized to widespread, or may be described in protocols as 'sufficient to require a change in therapy.' If 'unequivocal progression' is seen, the patient should be considered to have had overall PD at that point.

3.3 New Lesions

The appearance of new malignant lesions denotes disease progression. The finding of a new lesion should be unequivocal, ie, not attributable to differences in scanning technique, change in imaging modality, or findings thought to represent something other than tumor (eg, some 'new' bone lesions may be simply healing or flare of pre-existing lesions). This is particularly important when the patient's baseline lesions show PR or CR. For example, necrosis of a liver lesion may be reported on a CT scan report as a 'new' cystic lesion, which it is not.

A lesion identified on a follow-up study in an anatomical location that was not scanned at baseline is considered a new lesion and will indicate disease progression. An example of this is the patient who has visceral disease at baseline and while on study has a CT or MRI brain ordered, which reveals metastases. The patient's brain metastases are considered to be constituted 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 new disease. If repeat scans confirm that there is a new lesion, then progression should be declared using the date of the initial scan.

3.4 Tumor Markers

Tumor markers alone cannot be used to assess objective tumor responses. If markers are initially above the upper normal limit, however, they must normalize in order for a patient to be considered as having attained a CR.

4 EVALUATION OF BEST OVERALL RESPONSE

4.1 Timepoint Response

A response assessment should occur at each timepoint specified in the protocol.

For patients who have measurable disease at baseline, Table 4.1-1 provides a summary of the overall response status calculation at each timepoint.

Table 4.1-1: Summary of the Overall Response Status Calculation [Timepoint Response: Patients with Target (+/-) Nontarget Disease]

Target Lesions	Nontarget 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

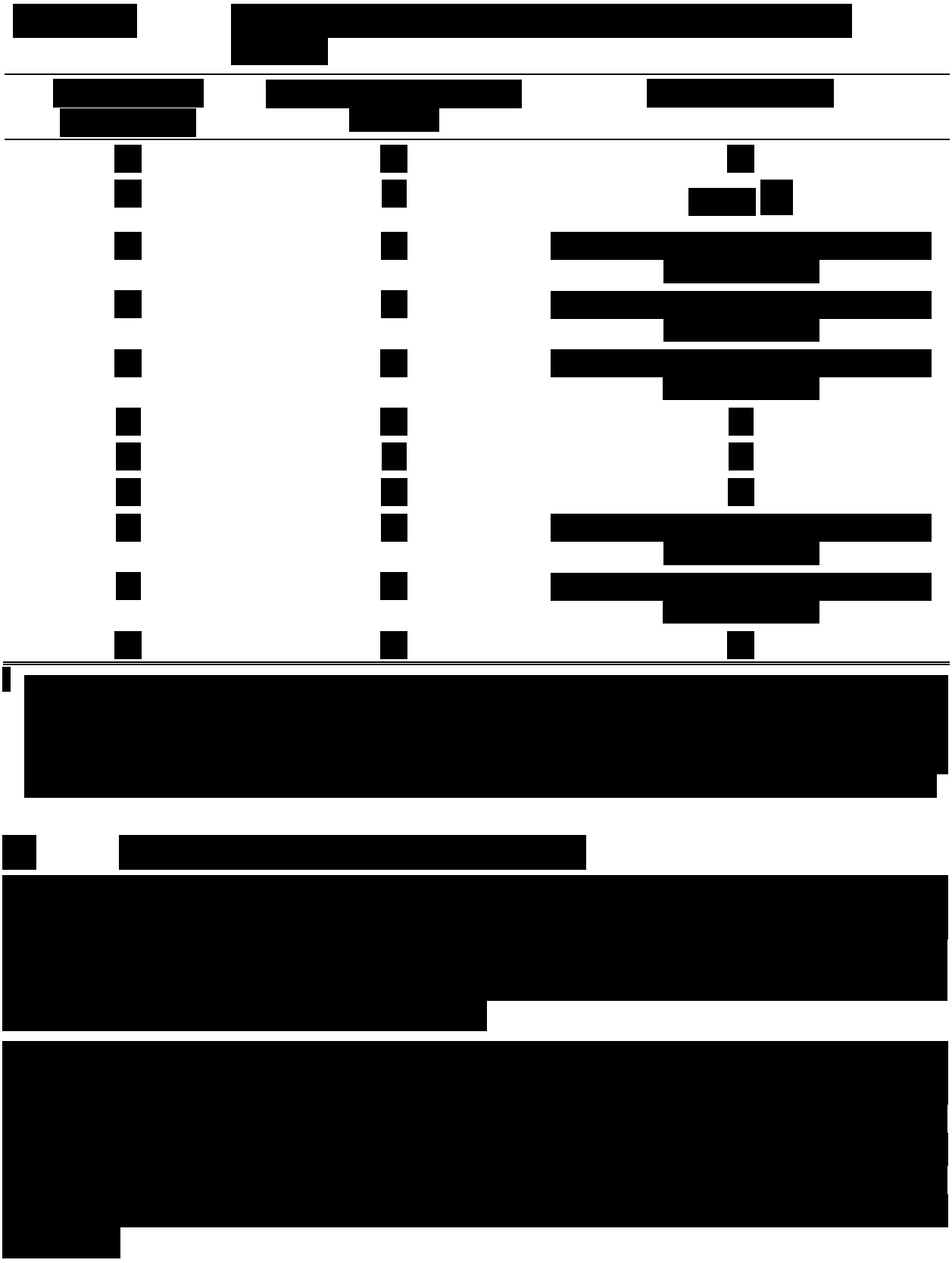
NE = not evaluable.

4.2 Missing Assessments and Inevaluable Designation

When no imaging/measurement is done at all at a particular timepoint, the patient is not evaluable (NE) at that timepoint. If only a subset of lesion measurements is made at an assessment, usually the case is also considered NE at that timepoint, unless a convincing argument can be made that the contribution of the individual missing lesion(s) would not change the assigned timepoint response. This would be most likely to happen in the case of PD.

4.3 Best Overall Response - All Timepoints

Best response determination in trials where confirmation of CR or PR **is** required: CRs or PRs may be claimed only if the criteria for each are met at a subsequent timepoint as specified in the protocol. In this circumstance, the best overall response can be interpreted as in Table 4.3-1. In the case of SD, measurements must have met the SD criteria at least once after study entry at a minimum interval of 7 weeks or approximately 8 weeks.



For equivocal findings of progression (eg, very small and uncertain new lesions; cystic changes or necrosis in existing lesions), treatment may continue until the next scheduled assessment. If at the next scheduled assessment, progression is confirmed, the date of progression should be the earlier date when progression was suspected.

5 ADDITIONAL CONSIDERATIONS

5.1 Duration of Response

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 PD is objectively documented (taking as reference for PD the smallest measurements recorded on study).

The duration of overall CR is measured from the time measurement criteria are first met for CR until the first date that recurrent disease is objectively documented.

Duration of SD: SD is measured from the start of the treatment (in randomized trials, from date of randomization) until the criteria for progression are met, taking as reference the smallest sum on study (if the baseline sum is the smallest, this is the reference for calculation of PD).

5.2 Lesions that Disappear and Reappear

If a lesion disappears and reappears at a subsequent timepoint, measurement should be continued. However, the patient's response at the point in time when the lesion reappears will depend upon the status of his/her other lesions. For example, if the patient's tumor had reached a CR status and the lesion reappeared, then the patient would be considered PD at the time of reappearance. In contrast, if the tumor status was a PR or SD and 1 lesion that had disappeared then reappears, its maximal diameter should be added to the sum of the remaining lesions for a calculated response; in other words, the reappearance of an apparently 'disappeared' single lesion among many that remain is not in itself enough to qualify for PD; this requires the sum of all lesions to meet the PD criteria. The rationale for such a categorization is based upon the realization that most lesions do not actually 'disappear' but are not visualized because they are beyond the resolving power of the imaging modality employed.

Reference:

[1] Eisenhauer EA, Therasse P, Bogaerts J, et al. New response evaluation criteria in solid tumours: Revised RECIST guideline (version 1.1). Eur J Cancer 2009;45:228-47.

APPENDIX 7 WOMEN OF CHILDBEARING POTENTIAL DEFINITIONS AND METHODS OF CONTRACEPTION

At a minimum, subjects must agree to use one highly effective method of contraception as listed below:

HIGHLY EFFECTIVE METHODS OF CONTRACEPTION

Highly effective methods of contraception have a failure rate of < 1% when used consistently and correctly. Women of childbearing potential (WOCBP) and female partners of male subjects, who are WOCBP, are expected to use 1 of the highly effective methods of contraception listed below. 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:

1. 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®
2. Non-hormonal IUDs, such as ParaGard®
3. Bilateral tubal occlusion
4. 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.
5. Intrauterine hormone-releasing system.
6. 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 investigational drug plus 30 days).
   - It is not necessary to use any other method of contraception when complete abstinence is elected.
   - Subjects who choose complete abstinence 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.
   - 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.

UNACCEPTABLE METHODS OF CONTRACEPTION

1. Periodic abstinence (calendar, symptothermal, post-ovulation methods)
2. Withdrawal (coitus interruptus)

3. Spermicide only
4. Lactation amenorrhea method

APPENDIX 8 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.

NYHA = New York Heart Association.