STATISTICAL ANALYSIS PLAN FOR FOR EARLY PHASE ONCOLOGY STUDIES

A PHASE 1/2 STUDY OF BMS-986183 IN SUBJECTS WITH ADVANCED HEPATOCELLULAR CARCINOMA

VERSION # 1.0

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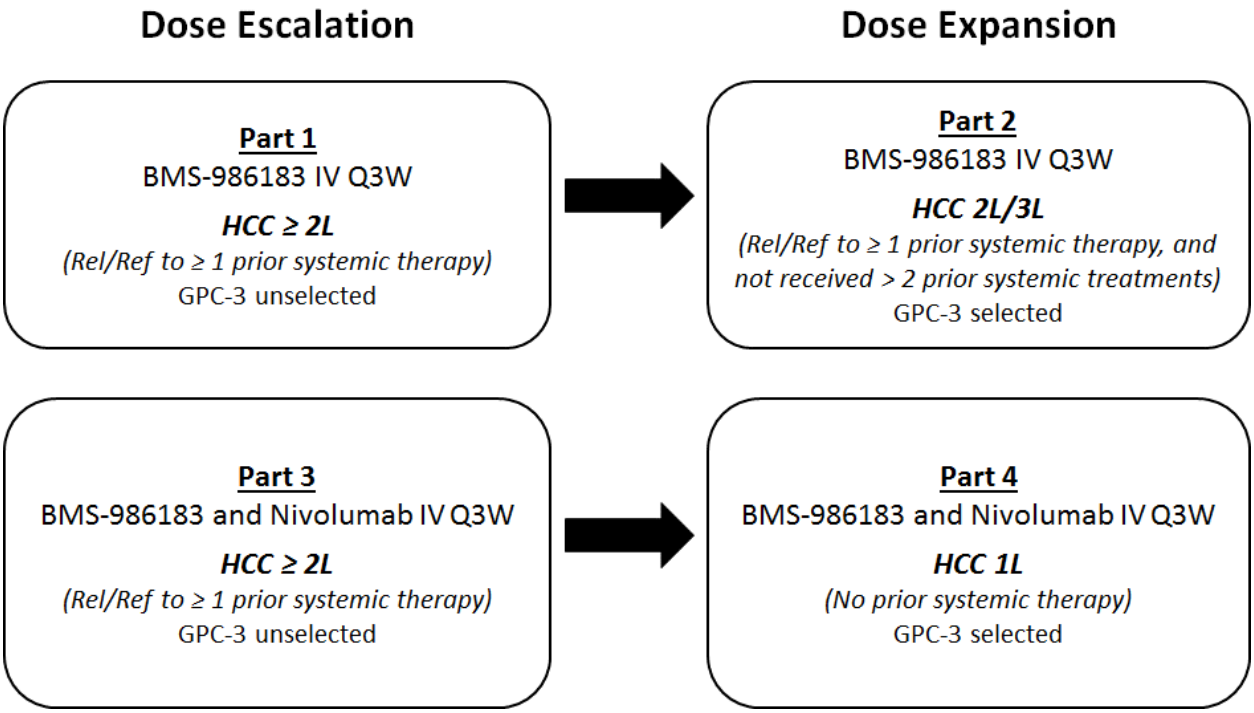
2 STUDY DESCRIPTION

2.1 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). See Figure 2.1- 1 below for a schematic of the study design

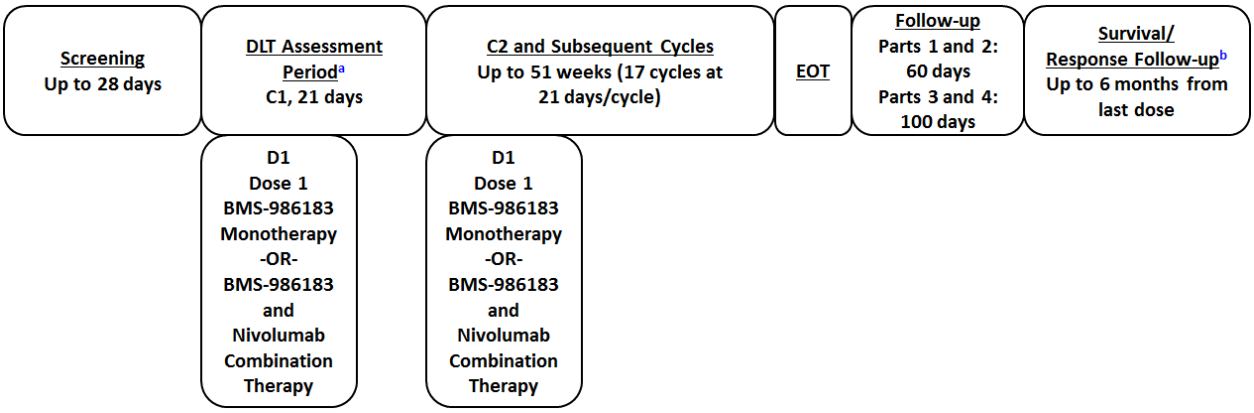
Figure 2.1- 1: Study Design



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

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. Only subjects in BMS-986183 dose expansion (Part 2) who have disease progression may be eligible for a combination therapy extension option (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)). 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 criteria specified in the protocol (Section 4.5.7). See Figure 2.1- 2: for a schematic of study periods

Figure 2.1- 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.

2.2 Treatment Assignment

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.

In BMS 986183 monotherapy dose escalation (Part 1) and BMS 986183 and nivolumab combination therapy 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.

2.3 Blinding and Unblinding

Not Applicable.

2.4 Protocol Amendments

Table 2.4- 1: List of Protocol Amendments

Amendment number	Date	Summaries
1	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
2	21-Mar-2017	Added dose escalation and expansion arms combining BMS-986183 and nivolumab, including revision of the study objectives, select eligibility criteria, [redacted], 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] Updated BMS-986183 monotherapy product development and risk/benefit assessments with recent study data. Clarified age criteria to include subjects 18 or age of majority. 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 monotherapy dose expansion (Part 2). Updated the prior monotherapy analyses relevant to hepatocellular cancer and immune response, [redacted] and mandatory and optional tumor biopsy requirements. [redacted] 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 monotherapy dose escalation (Part 1) to satisfy regional/local requirements (e.g., 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 removed to reduce redundancy with 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. [redacted]. Changed additional research text so that prospective samples will not be collected. Changed the language describing when subjects will resume study therapy. Removed requirement for formalin-fixed, paraffin embedded tumor samples. 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.

3 OBJECTIVES

3.1 Primary Objective

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.

3.2 Secondary Objective

- 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]

4 ENDPOINTS

4.1 Primary Endpoints

Primary endpoints will include incidence of AEs at their worst grade, SAEs at their worst grade, AEs leading to discontinuations, deaths, and frequency of laboratory test toxicity grade shifting from baseline. Safety will be evaluated from the time that the subject signs the informed consent and for up to 60 days after the last dose of study drug for BMS-986183 monotherapy dose

escalation period (Part 1) and BMS-986183 monotherapy dose expansion period (Part 2) and up to 100 days after the last dose of study drug for BMS-986183 and nivolumab combination therapy dose escalation (Part 3) and BMS-986183 and nivolumab combination therapy dose expansion (Part 4). AEs and laboratory values will be graded according to the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) version 4.03.

4.2 Secondary Endpoints

4.2.1 Efficacy Endpoints

Efficacy endpoints that are based on tumor response data will be derived per RECIST v1.1 response criteria.

- **Best overall response (BOR)**, defined as the best response designation over the study as a whole, and recorded between the date of first dose until the last tumor assessment prior to subsequent anticancer therapy and the date of first objectively documented progression per RECIST v1.1, whichever occurs first. CR or PR determinations included in the BOR assessment must be confirmed by a second scan performed no less than 4 weeks after the criteria for response are first met. For those subjects who have surgical resection, only pre-surgical tumor assessments will be considered in the determination of BOR.
- **Objective Response Rate (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 anticancer therapy, duration of response will be censored on the date of last tumor assessment. For subjects who received subsequent anticancer therapy, duration of response will be censored on the date of last tumor assessment prior to initiation of subsequent anticancer therapy. Response duration will only be evaluated in participants with a BOR of CR or PR.
- **Progression Free Survival (PFS),** PFS for a subject is defined as the time from the first dose of study drug to the date of first objectively documented disease progression per RECIST v1.1 or death due to any cause, whichever occurs first. Clinical deterioration in the absence of radiographic evidence is not considered progression for the purpose of determining PFS. Participants who died without a reported prior progression will be considered to have progressed on the date of their death. Participants who remained alive and have not progressed will be censored on the last tumor assessment date. Participants who started subsequent anticancer therapy (defined as anticancer therapy initiated after the start of study treatment) without a prior reported progression will be censored at the last tumor assessment prior to initiation of the subsequent anticancer therapy. Participants who did not have any post-baseline tumor assessment and did not die will be censored the date of randomization. Censoring algorithm for PFS is listed in **Error! Reference source not found.**.
- **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.

Table 4.2.1- 1: Censoring Scheme for analysis of PFS

Situation	Date of Progression or Censoring	Outcome
No baseline tumor assessments	Treatment start date	Censored
No on study tumor assessments and no death[a]	Treatment start date	Censored
Subsequent anticancer therapy[b] started without a prior reported progression per RECIST v1.1 criteria	Date of last tumor assessment prior or on the date of initiation of the subsequent anticancer therapy[b]	Censored
No progression or clinical progression without evidence of progression per RECIST v1.1 criteria	Date of last tumor assessment[a] with no documented progression	Censored
Progression per RECIST v1.1 criteria documented between scheduled visits or at scheduled visit without prior subsequent anticancer therapy[b] started	Date of the first documented tumor progression per the RECIST v1.1 criteria	Progressed
Death without progression per RECIST v1.1 criteria and without prior subsequent anticancer therapy[b] started	Date of death	Progressed

[a] Tumor assessments and death if any, occurring after start of subsequent anticancer therapy are not considered.

[b] Subsequent anticancer therapy is 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.

4.2.2 Pharmacokinetic Endpoints

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 characterized using the following endpoints:

- Cmax: Maximum observed serum concentration
- Tmax: Time of maximum observed serum concentration
- AUC(0-T): Area under the concentration vs time curve from 0 to time of the last measurable concentration
- AUC(TAU): Area under the concentration vs time curve in 1 dosing interval
- Ctau: Concentration at the end of a dosing interval
- Ctrough: Trough observed serum and/or plasma concentration, including predose concentrations and Ctau concentrations
- CLT: Total body clearance calculated as dose divided by AUC(TAU)
- 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_AUCtau: Accumulation index; ratio of AUCtau at steady-state to AUCtau 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 serum half-life

4.2.3 ECG Endpoints

The effect of dosing 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

4.2.4 Immunogenicity Endpoints

The immunogenicity of BMS-986183 (as monotherapy and in combination with nivolumab) will be measured by assessment of the presence or absence of specific ADA to BMS-986183. The incidence of positive ADA will be calculated.

Validated ADA test methods enable characterization of samples into ADA-positive vs ADA-negative. To classify the ADA status of a participant using data from an in vitro test method, each sample from a participant is categorized based on the following definitions:

Table 4.2.4- 1: Sample ADA Status

Sample ADA Status	Definition
Baseline ADA-positive sample	ADA is detected in the last sample before initiation of treatment
Baseline ADA-negative sample	ADA is not detected in the last sample before initiation of treatment
ADA-positive sample	1) an ADA detected (positive seroconversion) sample in a participant for whom ADA is not detected at baseline, or (2) an ADA detected sample with ADA titer to be at least *4*-fold or greater (≥) than baseline positive titer
ADA-negative sample	After initiation of treatment, ADA not positive sample relative to baseline

Next, using the sample ADA status, participant ADA status is defined as follows:

Table 4.2.4- 2: Participant ADA Status

ADA Status	Definition
Baseline ADA-positive	A participant with baseline ADA-positive sample
ADA-positive	A participant with at least one ADA positive-sample relative to baseline at any time after initiation of treatment
• *Persistent Positive (PP)*	ADA-positive sample at 2 or more consecutive timepoints, where the first and last ADA-positive samples are at least 16 [c] weeks apart
• *Not PP-Last Sample Positive*	Not persistent positive with ADA-positive sample at the last

ADA Status	Definition
	sampling timepoint
• *Other Positive*	Not persistent positive with ADA-negative sample at the last sampling timepoint
Neutralizing Positive:	At least one ADA-positive sample with neutralizing antibodies detected.
ADA-negative	A participant with no ADA-positive sample after the initiation of treatment

[c] 16 week threshold was chosen based on the planned ADA blood sampling every four cycles of study therapy.

[redacted]

4.3.4 ADME-related genes

DNA variants in ADME-related genes from the Core and Extended ADME gene lists may be determined.

[redacted]

5 SAMPLE SIZE AND POWER

Dose Escalation (Parts 1 and 3): 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.

Dose Expansion (Part 2 and 4): 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 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 $\geq$ 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.[1] 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 (i.e., 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%. 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.

6 STUDY PERIODS, TREATMENT REGIMENS AND POPULATIONS FOR ANALYSES

6.1 Study Periods

Subjects will complete up to 4 periods in the study: Screening, Treatment, Safety Follow Up, Simultaneous Response and Survival Follow-up. For the purpose of the analysis the periods are grouped into Baseline (includes Screening) and Post-Baseline (includes Treatment and Safety Follow Up for Safety analyses and Treatment and all follow up periods for efficacy analyses only).

6.1.1 Baseline Period

Baseline evaluations or events will be defined as evaluations or events that occur before the date and time of the first dose of study.

The following definitions will apply:

- Pre-treatment AEs will be defined as AEs with an onset date and time prior to but not including the day and time of the first dose of study treatment (or with an onset date prior to the day of first dose of study treatment if time is not collected or is missing)
- Baseline evaluations (laboratory tests, pulse oximetry and vital signs) will be defined as evaluations with a date and time on or prior to the day and time of first dose of study treatment (or with an onset date on or prior the day of first dose of study treatment if time is not collected or is missing)

If there are multiple valid assessments, the assessment that is closest to day (and time if collected) of the first dose of study treatment will be used as the baseline in the analyses. If multiple assessments are collected at the same date (and time, if recorded and not missing), the assessment with the latest database entry date (and time, if recorded and not missing) will be considered as baseline. If same database entry date (and time, if recorded and not missing) or database entry date not available, the assessment with the latest modification date will be considered as baseline.

Tumor assessments will be slotted in the baseline period if assessments are before or on start of the treatment date. Baseline tumor assessment is the last assessment in the baseline period.

6.1.2 Post-baseline period

- On-treatment AEs will be defined as AEs with an onset date and time on or after the date and time of the first dose of study treatment (or with an onset date on or after the day of first dose of study treatment if time is not collected or is missing). For subjects who are off study treatment, AEs will be included in summaries if event occurred within a safety window of 60 days after the last dose of study for BMS-986183 monotherapy dose escalation period (Part 1) and BMS-986183 monotherapy dose expansion period (Part 2) and of 100 days after the last dose of study drug for BMS-986183 and nivolumab combination therapy dose escalation (Part 3) and BMS-986183 and nivolumab combination therapy dose expansion (Part 4).
- On-treatment evaluations (laboratory tests, pulse oximetry and vital signs) will be defined as evaluations taken after the day (and time, if collected and not missing) of first dose of study treatment. For subjects who are off study treatment, summaries will include measurements

within a safety window of 60 days after the last dose of study for BMS-986183 monotherapy dose escalation period (Part 1) and BMS-986183 monotherapy dose expansion period (Part 2) and of 100 days after the last dose of study drug for BMS-986183 and nivolumab combination therapy dose escalation (Part 3) and BMS-986183 and nivolumab combination therapy dose expansion (Part 4).

- Tumor assessments will be slotted in the post-baseline period if assessments are after start of the treatment date.

6.2 Treatment Regimens

Study treatments (as treated) are the dose level assignments of BMS-986183 in monotherapy, and BMS-986183 in combination with nivolumab, and are administered in one of four parts:

- BMS-986183 monotherapy dose escalation (Part 1)
- BMS-986183 monotherapy dose expansion (Part 2)
- BMS-986183 and nivolumab combination therapy dose escalation (Part 3)
- BMS-986183 and nivolumab combination therapy dose expansion (Part 4)

6.3 Populations for Analyses

- All Enrolled Subjects: All subjects who sign an ICF.
- All Treated Subjects: All subjects who receive at least 1 dose of study drug.
- PK Subjects: All subjects who receive at least 1 dose of BMS-986183 monotherapy (and nivolumab in the combination therapy) and have available serum and/or plasma concentration data.
- Biomarker Subjects: All treated subjects for whom PD measurements are available at both baseline and at least 1 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 1 other tumor measurement after treatment, clinical progression, or death prior to the first on-treatment tumor assessment.
- Nivolumab subjects treated beyond progression: All subjects who received at least one dose of nivolumab after the date of initial progression per RECIST v1.1.

7 STATISTICAL ANALYSES

All analyses will be performed in SAS using version 9.2 or higher.

7.1 General Methods

Continuous variables will be summarized using descriptive statistics, i.e., medians, minimums, maximums, and means with standard deviations of the mean and quartiles. Categorical variables will be summarized by frequencies and percentages. Percentages will be rounded and may not always add up to 100.

Confidence intervals for binomial proportions will be derived using the Clopper-Pearson method[2].

Time to event distributions (i.e., progression free survival, overall survival) will be estimated using Kaplan Meier techniques. When appropriate, the median along with 95% CI will be estimated based on Brookmeyer and Crowley methodology[3] (using log-log transformation for constructing the confidence intervals). Rates at fixed time points (e.g., PFS at 24 weeks) will be estimated using 95% CIs with Greenwood formula[4].

Laboratory results, adverse events, and other symptoms will be graded using the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE), version 4.03, except where CTCAE grades are not available. Adverse events will be categorized using the most current version of Medical Dictionary for Regulatory Activities (MedDRA), by system organ class and preferred term.

7.2 Study Conduct

7.2.1 Study Information

Listing:

- Batch numbers

7.2.2 Accrual

Summary:

- Number (%) of subjects accrued by country and investigational site based on All Enrolled population by treatment and overall.
- Number of subjects accrued by month based on All Enrolled population.

Listing:

- Subjects accrued by country and investigational site based on All Enrolled population

7.2.3 Protocol Deviation

The following programmable deviations will be considered as relevant protocol deviations. Nonprogrammable relevant eligibility and on-treatment protocol deviations, as well as significant (both programmable and non-programmable) eligibility and on-treatment protocol deviations will be reported through ClinSIGHT listings.

Table 7.2.3- 1: Relevant Protocol Deviations

Timing	Part	Deviation Items
At entrance	All Parts	Subjects with ECOG PS > 1
		Subjects without evaluable disease at baseline
		Subjects with absolute neutrophil count (ANC) <1500 /μL
		Subjects with platelet count < 60×10^3/μL
		Subjects with hemoglobin < 8.5 g/dL
		Subjects with Prothrombin time (PT)-international normalized ratio (INR) > 2.3 or PT > 6 seconds above control

Timing	Part	Deviation Items
		Subjects with serum albumin < 2.8 g/dL
		Subjects with total bilirubin > 3 mg/dl
		Subjects with AST > 5 x the institutional ULN
		Subjects with ALT > 5 x the institutional ULN
		Subject with confirmed ECG QTcF > 480 msec prior to study treatment administration
		Subjects with with a serum creatinine of >= 1.5 × ULN and a creatinine clearance (CrCl) <=40 mL/min using Cockcroft-Gault equation
		Subjects with co-infection of HBV and HCV or HBV and HDV
		Child-Pugh score of 7 points or higher
	Part 1, 2 and 3	Subject received <1 line of prior therapy
	Part 2	Subject received >2 line of prior therapy
		Subjects with both plasma membrane and cytoplasmic H score < 50 for GPC-3 expression in the tumor tissue
	Part 4	Subject received any prior therapy
		Subjects with both plasma membrane and cytoplasmic H score < 50 for GPC-3 expression in the tumor tissue
On-Study	All Parts	Subjects receiving concurrent anticancer therapy (defined as systemic therapy or any investigational drug, non-systemic therapy for HCC, chemo radiation, curative surgery, palliative radiotherapy/surgery on any target lesion) that not allowed per protocol.
		Subjects treated differently than as assigned (subjects who received the wrong treatment, excluding the never treated)

A summary table and a by subject listing will be produced.

7.3 Study Population

7.3.1 Subject Disposition

Summary:

- Pre-treatment period: The number (%) of subjects of the following will be based on All Enrolled Subjects.
    - All enrolled into the study
    - Entering the treatment period, i.e. All treated subjects
    - Enrolled but not entering the treatment period together with the reasons
- End of treatment period: The number (%) of subjects of the following will be summarized by treatment and overall based on All Treated Subjects
    - All treated subjects
    - Subjects continuing in treatment period
    - Subjects not continuing in treatment period
        - Reasons for not continuing in treatment period

  - Subjects continuing in the study
    - Subject continuing into the survival/response follow-up period
    - Subject continuing into the safety follow-up period
  - Subject not continuing in the study
    - Reasons for not continuing in the study
    -

- End of safety follow-up: The number (%) of subjects of the following will be summarized by treatment and overall based on All Treated Subjects
  - Subjects continued into safety follow-up
  - Subject not continuing to the survival/response follow-up
  - Subject not continuing to the survival/response follow-up
    - Reasons for not continuing to the survival/response follow-up
- End of the survival/response follow-up period: The number (%) of subjects of the following will be summarized by treatment and overall, based on the All Treated Subjects.
  - Subjects continuing in the survival/response follow-up period
  - Subjects not continuing in the survival/response follow-up period
    - Reasons for not continuing in the survival/response follow-up period

Listing:

- Pre-treatment period: Subjects who discontinued from the study before treatment (for screen failures)
- End of treatment period: Treated subjects who discontinued from the study treatment with the specific reason for discontinuation.
- End of safety follow-up or survival/response follow-up: Treated subjects who discontinued from safety follow-up or survival/response follow-up with the reason for not being followed.

7.3.2 Demographics and Other Baseline Characteristics

Summary:

Descriptive statistics will be summarized for the following baseline characteristics for all treated subjects by treatment and overall. All baseline presentations will identify subjects with missing measurements.

- Age (in years); age category (< 65, ≥ 65 - < 75, ≥ 75)
- Gender (Male, Female)

- Race (White, Black or African American, Asian (Asian Indian, Chinese, Japanese, Korean, Taiwanese, Asian Other), American Indian or Alaska Native, Native Hawaiian or Other Pacific Islander, Other)
- Ethnicity (Hispanic/Latino , Not Hispanic/Latino)
- Height (descriptive statistics)
- Weight (descriptive statistics)
- ECOG PS (0, 1, >1)
- Tobacco use (cigarettes, cigars, pipe, chewing tobacco/snuff)

Listing:

- All data listed above by treatment

7.3.3 Baseline Disease Characteristics

Summary:

The following (source CRF) baseline disease characteristics will be summarized for all treated subjects by treatment and overall.

- Disease etiology (Non-viral/HCV/HBV)
- Time from initial diagnosis to treatment (< 1 year, 1-< 2 year, 2 - < 3 year, 3 -< 4 year, 4 - < 5 year, ≥ 5 year)
- HCC risk factors (Alcoholic, and others as shown on the CRF)
- Alpha-fetoprotein (AFP) (descriptive statistics)
- AFP category (AFP < 400 ng/ml vs. ≥ 400 ng/ml, < 200 ng/ml vs. ≥ 200 ng/ml)
- Child-Pugh class (A/B/C) and Score (5 - 15, categorical) (see Appendix 1 for the details)
- Vascular invasion (VI)
- Extrahepatic spread (EHS)
- VI or EHS
- Sites of diseases (all lesions, target lesions); number of disease sites per subject (all lesions); number of target lesions, non-target lesions and disease sites at baseline; tumor burden: sum of the diameters of target lesions at baseline; number of liver nodules; tumor invasion in liver above 50%

Listing:

- All data above listed by treatment

7.3.4 Physical Measurements

Physical measurements such as body weight, height, body mass index (BMI) and ECOG PS will be listed for all treated subjects.

7.3.5 Medical History

General medical history will be listed by subject.

7.3.6 Prior Sorafenib Therapy

A subject is deemed to have prior sorafenib therapy if the subject has at least one record of sorafenib treatment in prior systemic therapy or has been checked "Yes" for the question of "prior HCC medication" on the CRF. Subjects may have multiple records of sorafenib treatments.

The following will be summarized:

- Summary of sorafenib prior treatment (Naïve/Treated/Intolerant)
- Summary of best overall response from sorafenib therapy (All unique sorafenib records per subject)
- Summary of duration of prior sorafenib therapy (All sorafenib records)
- Summary of prior sorafenib therapy setting of regimen (All sorafenib records)
- Summary of time from last sorafenib stop date to start of the study medication
- Summary of primary reason for sorafenib discontinuation (All unique sorafenib discontinuation reasons per subject will be counted)

[redacted]

7.3.8 Pre-treatment Events

Liver, HCC and sorafenib-related pre-treatment events will be summarized by worst CTC grade, system organ class and preferred term. A by-subject listing will be provided.

7.4 Extent of Exposure

The extent of exposure will be characterized according to the number of subjects exposed, the duration of exposure, and the dose to which they were exposed. Analyses in this section will be performed on all treated subjects "as treated".

7.4.1 Study Therapy

Summary:

Duration of treatment will be presented by treatment using a Kaplan-Meier curve whereby the last dose date will be the event date for those subjects who are off study therapy. Median duration of treatment and associated 95% CI will be provided. Subjects who are still on study therapy will be censored on their last dose date.

Descriptive statistics will be provided by study drug (i.e. BMS-986183, Nivolumab) for the following.

- Number of doses received (summary statistics)
- Duration of therapy (weeks)
- Cumulative dose
- Dose intensity
  - Relative dose intensity (%) using the following categories: <50%; 50 - < 70%; 70 - < 90%; 90 - < 110%; ≥ 110%

Error! Reference source not found. summarizes the key parameters used to calculate dosing data for each study.

Table 7.4.1- 1: Study Therapy Parameter Definition

	BMS-986183	Nivolumab
Dosing Schedule per Protocol	At the assigned dose (for Part 1 and 3) or at the recommended dose (for Part 2 and 4) every 21 days	360 mg every 21 days for Part 3 and 4
Dose	Dose (mg) is defined as Total Dose administered (mg) collected on the CRF.	Dose (mg) is defined as Total Dose administered (mg) collected on the CRF.
Cumulative Dose	Cum Dose (mg) is the sum of the doses (mg) administered to a subject during the treatment period.	Cum Dose (mg) is the sum of the doses (mg) administered to a subject during the treatment period.
Dose Intensity	Cum dose (mg)/[(Last dose date[a] - Start dose date + 21)] × 21	Cum dose (mg)/[(Last dose date[a] - Start dose date + 21)] × 21
Relative Dose Intensity (%)	Cum dose (mg)/[(Last dose date - Start dose date + 21) × (planned dose/21)] × 100	Cum dose (mg)/[(Last dose date - Start dose date + 21) × (planned dose/21)] × 100
Duration of Therapy	Last dose date - Start dose date +21.	Last dose date - Start dose date +21

[a] Last observed dosing date regardless of retreatment status.

Listing:

- Administration of each study drug
- Duration, cumulative dose, dose intensity and relative dose intensity of each study drug

7.4.2 Modification of Study Therapy

Summary:

The following will be provided by cohort.

- Number (%) of subjects with dose delay, omission and discontinuation along with the reason
- Number(%) of subjects with dose reduction along with the reason
- Infusion interruptions
  - Number (%) of subjects with at least one infusion interruption along with the reason
  - Number of infusion interruptions per subject
  - Number (%) of subjects with at least one IV infusion rate reduction along with the reason

Listing:

- All relevant information on dose modification listed above

[redacted]

7.5 Safety

Safety analyses will be performed primarily on All Treated Subjects and presented by treatment ("as treated") and overall. In addition, SAE analyses will be produced using All Enrolled Subjects.

Adverse events (AEs) will be coded according to the most current version of MedDRA and be graded using the NCI Common Terminology Criteria for Adverse Events (CTCAE) version 4.03. Drug-related AEs are those events with relationship to study drug "Related" as recorded on the CRF. If the relationship to study drug is missing, the AE will be considered as drug-related. Serious adverse events consist of AEs deemed serious by the Investigator and flagged accordingly in the CRF and clinical database. Adverse events leading to study drug discontinuation are AEs with action taken = "Drug was discontinued". Adverse events leading to dose delay are AEs with action taken = "Dose was delayed".

Listing of adverse events will include all enrolled subjects as SAEs and deaths are collected pretreatment. Summaries of adverse events will include events occurring from the date of first study medication and for up to 60 days (inclusive) after the last dose of study drug for Part 1 and 2 and up to 100 days (inclusive) after the last dose of study drug for Part 3 and 4. Listing of serious adverse events will include all enrolled subjects as SAEs and deaths are collected pretreatment. Listing of non-serious adverse events will include all treated subjects.

When reporting adverse events by CTC grade, summary tables will be provided based on the event with worst CTC grade (independent of relationship to study medication). Subjects will only be counted (1) once at the preferred term (PT) level, (2) once at the system organ class (SOC) level, and (3) once in the 'Total subject' row at their worst CTC grade, regardless of SOC or PT.

The analysis of laboratory results will be based on All Treated Subjects. Laboratory results will be categorized according to NCI CTCAE (version 4.03) grade. Baseline is defined as the last non-missing measurement prior to or on the first treatment's dosing date and time. Summaries of laboratory results include baseline and post-baseline results up to 60 days (inclusive) after the last dose of study drug for Part 1 and 2 and up to 100 days (inclusive) after the last dose of study drug for Part 3 and 4 for subjects who are off treatment.

For retreated subject in Part 3 and 4, the initial off-treatment period is included in all safety analysis as if the retreated subject were still on treatment in that period of time.

For the analyses (during original assigned treatments) of subjects treated with the combination therapy extension option in Part 2, all the safety assessment will be truncated at the first dose date of the combination therapy. All others will follow regular counting rules. For the analysis of subjects treated with the combination therapy extension option during the combination period, all the safety assessments will be counted from the first dose of combination therapy and up to 100 days after last dose (optional analyses).

7.5.1 Deaths

Summary:

Deaths will be summarized by treatment:

- All deaths, reasons for death
- Deaths within 60 days of last dose received, reasons for death
- Deaths within 100 days of last dose received, reasons for death

Listing:

All recorded deaths for All Enrolled subjects will be listed by subject.

7.5.2 Serious Adverse Events

Summary:

Serious adverse events will be summarized by treatment:

- Overall summary of SAEs by worst CTC grade (grade 1, 2, 3, 4, 5, unknown) presented by SOC/PT
- Overall summary of drug-related SAEs by worst CTC grade (grade 1, 2, 3, 4, 5, unknown) presented by SOC/PT
- Overall summary of SAEs by worst CTC grade (any grade, grade 3-4, grade 5) presented by SOC/PT.
- Overall summary of drug-related SAEs by worst CTC grade (any grade, grade 3-4, grade 5) presented by SOC/PT.

Listing:

- All recorded SAEs for All Enrolled Subjects.

7.5.3 Adverse Events

Summary:

Adverse events will be summarized by treatment:

- Overall summary of any AEs by worst CTC grade (grade 1, 2, 3, 4, 5, unknown) presented by SOC/PT
- Overall summary of any AEs by worst CTC grade (any grade, grade 3-4, grade 5) presented by SOC/PT.
- Overall summary of drug-related AEs by worst CTC grade (grade 1, 2, 3, 4, 5, unknown) presented by SOC/PT
- Overall summary of drug-related AEs by worst CTC grade (any grade, grade 3-4, grade 5) presented by SOC/PT.
- Overall summary of any non-serious AEs presented by SOC/PT.

The analyses will be conducted using the 60 days safety window.

Listing:

- All recorded Adverse Events for All Treated Subjects.
- All drug-related Adverse Events for All Treated Subjects.

7.5.4 Adverse Events Leading to Discontinuation of Study Therapy

Summary:

Adverse Events leading to discontinuation will be summarized by treatment:

- Overall summary of AEs leading to discontinuation by worst CTC grade (grade 1, 2, 3, 4, 5, unknown) presented by SOC/PT
- Overall summary of AEs leading to discontinuation by worst CTC grade (any grade, grade 3-4, grade 5) presented by SOC/PT.
- Overall summary of drug-related AEs leading to discontinuation by worst CTC grade (grade 1, 2, 3, 4, 5, unknown) presented by SOC/PT
- Overall summary of drug-related AEs leading to discontinuation by worst CTC grade (any grade, grade 3-4, grade 5) presented by SOC/PT.

Listing:

- All AEs leading to discontinuation for All Treated Subjects.

7.5.5 Adverse Events Leading to Dose Modification

Summary:

AEs leading to dose delay/interruption/reduction will be summarized for each treatment:

- Overall summary of AEs leading to dose delay/ interruption/reduction by worst CTC grade (grade 1, 2, 3, 4, 5, unknown) presented by SOC/PT
- Overall summary of drug-related AEs leading to dose delay/interruption/reduction by worst CTC grade (grade 1, 2, 3, 4, 5, unknown) presented by SOC/PT

Listing:

By-subject AEs leading to dose delay/interruption/reduction listing will be provided.

- All AEs leading to dose delay/interruption/reduction for All Treated Subjects.

7.5.6 Multiple Events

Analyses that take into account the multiple occurrences of a given adverse event will be conducted. To prepare these analyses, the CRF data will be processed according to standard BMS algorithms[5] in order to collapse adverse event records into unique records based on the preferred term. This data will be presented as the rate per 100 person-years of exposure. These analyses will take into account all on-treatment events (allowing more than 1 event per subject) and the total exposure time. The person-year exposure will be computed as the sum over the subjects' exposure expressed in years where the exposure time is defined as

- Date of last dose of study treatment - date of first dose of study treatment + 61 days (+ 101 days for Part 3 and 4), for subject who are off study treatment and were followed for at least 60 days (100 days for Part 3 and 4) after last dose of study treatment.
- Last known date alive- date of first dose of study treatment + 1, for subjects who are still on-treatment or who are off study treatment and were followed less than 60 days (or 100 days for Part 3 and 4) after last dose of study treatment.

When specified the 95%CI of the rate per 100 person-year of exposure will be derived using normal approximation and variance estimation proposed in Cook and Lawless[6] (optional).

Summary:

The following summary tables will be provided for each treatment:

- Total number and rate (exposure adjusted) of occurrences for all AEs occurring in at least 5% of the subjects treated per study treatment.

Listing:

- Listing displaying the unique instances of all AEs, i.e., after duplicates have been eliminated and overlapping and contiguous occurrences of the same event (i.e. same PT) have been collapsed will be provided.

7.5.7 Adverse Events of Special Interest

The Adverse Events of Special Interest (AEOSIs) consist of a list of preferred terms grouped by specific category which have been identified of interest for BMS-986183. Nivolumab AEOSI (also referred to as 'Select AE') consist of a list of preferred terms grouped by specific category (e.g., pulmonary events, gastrointestinal events categories). These AEs and the categories are defined by the Sponsor and the list that is the most current at the time of analysis will be used.

AEOSI for BMS-986183 and Nivo will be analyzed separately, if there is any identified as the program matures and more safety data is collected.

Summary:

AEOSIs will be summarized by treatment for each category:

- Overall summary of any AEs by worst CTC grade presented by Category/PT (any grade, grade 3-4, grade 5)
- Overall summary of drug-related AEs by worst CTC grade presented by Category/ PT (any grade, grade 3-4, grade 5)
- Overall summary of any AEs leading to discontinuation by worst CTC grade presented by Category/PT (any grade, grade 3-4, grade 5)
- Overall summary of drug-related select AEs leading to discontinuation by worst CTC grade presented by Category/PT (any grade, grade 3-4, grade 5)
- Overall summary of any AEs by worst CTC grade presented by Category/PT (grade 1, 2, 3, 4, 5, unknown)
- Overall summary of drug-related AEs by worst CTC grade presented by Category/ PT (grade 1, 2, 3, 4, 5, unknown)

Listing:

By-subject AEOSI listing will be provided by category.

7.5.8 Clinical Laboratory Evaluations

Clinical laboratory data will be analyzed using International System of Units (SI). Analyses will be repeated using US conventional units for the clinical study report. Relevant parameters will be fully toxicity graded per CTCAE v4.03.

Summary:

Laboratory parameters will be summarized by treatment as worst CTC grade on-treatment per subject and as shift table of worst on-treatment CTC grade compared to baseline CTC grade per subject.

Listing:

A by-subject listing of laboratory parameters will be provided.

7.5.8.1 Abnormal Hepatic Function Tests

Summary:

The number of subjects with the following laboratory abnormalities from on-treatment evaluations will be summarized by treatment:

- AST or ALT > 3, 5, 10, 15, or 20 x ULN
- Total bilirubin > 2 or 8 x ULN
- AST or ALT > 10 × ULN for > 2 weeks
- Total bilirubin > 8 × ULN for subjects with elevated total bilirubin at study entry or > 5 × ULN for those with normal total bilirubin at entry or
- Concurrent (within 1 day)
    - ALT >= 10 x ULN and
    - total bilirubin >= 2 x ULN or baseline if elevated total bilirubin at entry

Figure:

The following scatterplots will be produced for the following hepatic laboratory parameters:

- Total bilirubin peak vs. AST peak
- Total bilirubin peak vs. ALT peak

On-treatment peak total bilirubin and on-treatment peak AST/ALT may or may not happen on the same day of liver testing.

Listing:

A by-subject listing of these specific abnormalities will be provided.

7.5.8.2 Abnormal Thyroid Function Test

Summary:

The number of subjects with the following laboratory abnormalities from on-treatment evaluations will be summarized by treatment group for Part 3 and 4:

- TSH value > ULN and
  - with baseline TSH value <= ULN
  - at least one FT3/FT4 test value < LLN
- TSH < LLN and
  - with baseline TSH value >= LLN
  - at least one FT3/FT4 test value > ULN

Listing:

A by-subject listing of these specific abnormalities will be provided.

7.5.9 Vital Signs and Physical Examination Abnormalities

Listing:

- Vital signs for all treated subjects
- Physical examination abnormalities for all treated subjects
- Diagnostic procedures for all treated subjects

7.5.10 Electrocardiogram

Summary:

- For heart rate (HR), QT, ΔQTcF, and PR, summary measures (n, mean, standard deviation, median, minimum, and maximum) and the corresponding changes from baseline will be provided by treatment and study date.
- Frequency distribution of maximum QTcF, maximum ΔQTcF, maximum QRS, maximum PR interval and maximum heart rate by treatment within pre-specified intervals:
  - For QTcF: QTcF ≤ 450 msec, 450 msec < QTcF ≤ 480 msec, 480 msec < QTcF ≤ 500 msec, QTcF > 500 msec
  - For ΔQTcF: ΔQTcF ≤ 30 msec, 30 msec < ΔQTcF ≤ 60 msec, ΔQTcF > 60 msec
  - For PR: PR ≤ 200 msec, PR > 200 msec
  - For QRS: QRS ≤ 120 msec, QRS > 120 msec

Figure:

- Scatter plot and regression of ΔQTcF on active ADC, conjugated tubulysin, and unconjugated tubulysins, respectively.

Listing:

- ECG measures through EOT
- ECG abnormalities

7.5.11 Pregnancy

Listing:

- By-subject listing of pregnancy tests results will be provided for all treated female subjects.

7.6 Other analyses

Additional exposure response analysis may be performed to explore associations of exposure with biomarkers, selected safety measures, and/or efficacy measures.

8 CONVENTIONS

The following conventions may be used for imputing partial dates for analyses requiring dates: For missing and partial adverse event onset dates, imputation will be performed using the Adverse Event Domain Requirements Specification[7]. Missing and partial Non-Study Medication Domain dates will be imputed using the derivation algorithm described in 4.3.3 of BMS Non-Study Medication Domain Requirements Specification[8].

For death dates, the following conventions will be used for imputing partial dates:

- If only the day of the month is missing, the 1st of the month will be used to replace the missing day. The imputed date will be compared to the last known date alive day and the maximum will be considered as the death date.
- If the month or the year is missing, the death date will be imputed as the last known date alive day
- If the date is completely missing but the reason for death is present the death date will be imputed as the last known date alive day

For date of progression, the following conventions will be used for imputing partial dates:

- If only the day of the month is missing, the 1st of the month will be used to replace the missing day*.
- If the day and month are missing or a date is completely missing, it will be considered as missing.

*In cases where the date of death is present and complete, the imputed progression date will be compared to the date of death. The minimum of the imputed progression date and date of death will be considered as the date of progression.

For other partial/missing dates, the following conventions may be used:

- If only the day of the month is missing, the 15th of the month will be used to replace the missing day.
- If both the day and the month are missing, “July 1” will be used to replace the missing information.
- If a date is completely missing, it will be considered as missing.

The following conversion factors will be used to convert days to months or years: 1 month = 30.4375 days and 1 year = 365.25 days.

Duration (e.g. time from first diagnosis to first dosing date, duration of response, and time to response) will be calculated as follows:

Duration = (Last date - first date + 1)

8.1 Glossary of Terms

Table 8.1- 1: Glossary of Terms

Term	Definition

Term	Definition

9 CONTENT OF REPORTS

The complete list of analyses contributing to the clinical study report is given in the Data Presentation Plan.