Official Title of Study:

A Phase I/IIa Trial With BMS-986158, a Small Molecule Inhibitor of the Bromodomain and Extra-Terminal (BET) Proteins, as Monotherapy or in Combination with Nivolumab in Subjects with Selected Advanced Solid Tumors or Hematologic Malignancies

NCT Number: NCT02419417

Document Date (Date in which document was last revised): 23 Aug 2021

STATISTICAL ANALYSIS PLAN
FOR CLINICAL STUDY REPORT

A PHASE I/IIA TRIAL WITH BMS-986158, A SMALL MOLECULE INHIBITOR OF THE BROMODOMAIN AND EXTRA-TERMINAL (BET) PROTEINS, AS MONOTHERAPY OR IN COMBINATION WITH NIVOLUMAB IN SUBJECTS WITH SELECTED ADVANCED SOLID TUMORS OR HEMATOLOGIC MALIGNANCIES

PROTOCOL(S) CA011001

VERSION # 2.0

TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

1 BACKGROUND AND RATIONALE

The scope of this SAP is limited to Part 1 and Part 2 Initial expansion, and only relevant objectives are included.

Patients with relapsed or refractory haematologic and solid tumors have a very poor prognosis[1]. Despite advances in multimodal therapy, increases in overall survival in these patient populations have been limited. The unmet need resides in the lack of effective treatments to deliver long term survival, hence the need to test compounds that have novel mechanisms of action in clinical studies.

The bromodomain and extra-terminal (BET) family of adaptor proteins is comprised of 4 members (BRD2, BRD3, BRD4, and BRDT), each of which contain two conserved N-terminal bromodomains (BD1 and BD2) and an extra terminal (ET) protein interaction motif[2,3]. Bromodomain-mediated interactions with acetylated chromatin result in the localization of BET proteins to discrete chromosome regions, where they recruit additional regulatory complexes to influence gene transcription[4,5,6]. BRD4 is dysregulated by chromosomal translocation to form in-frame fusions with the NUT (nuclear protein in testis) gene in NUT-midline carcinoma (NMC);[7] it is also overexpressed in many solid tumors. Early BET inhibitors, JQ1 and I-BET, demonstrated therapeutic effects in multiple tumor models of hematologic malignancies[8,9] including multiple myeloma (MM),[10] as well as in solid tumors.[11] The therapeutic activity of BET inhibitors in hematologic malignancies correlates with transcriptional suppression of key proto-oncogenes, including MYC and BCL2.[12,13] c-MYC is the most frequently amplified oncogene and is deregulated in 40% to 70% of all cancers;[14] however, efforts to target MYC inhibition have not been successful to date.[15,16]

BET inhibitors have the potential to provide an effective strategy for targeting the MYC oncogene in the treatment of cancer. Examination of BRD4 occupancy at genes whose transcription is highly sensitive to JQ1, led to the observation that BRD4 (and potentially other BET family members) localizes to the core promoter regions of many oncogenes.[17] Additionally, BRD4 is enriched in enhancer regions, leading to high expression levels of many growth promoting genes, in addition to MYC. Recent studies demonstrated that key lineage-specific survival genes are regulated by these super-enhancer regions.[18]

Because tumor cells are frequently highly reliant on high oncogene expression for survival, selective disruption of super-enhancers by a BET inhibitor may represent an effective strategy for the treatment of multiple tumor types with an acceptable safety profile.

Cooperative interactions between BET inhibitors and PD-1 inhibitors may involve different molecular pathways. Inflammatory cytokines, including IFNγ, are expressed within the tumor microenvironment and upregulate PD-L1 levels contributing to immunosuppression.[19,20] Induction of PD-L1 expression in tumor cells, as a downstream effect of canonical IFNγ signaling, is BRD4-dependent.[21]

Cancer immunotherapy rests on the premise that tumors can be recognized as foreign rather than as self and can be effectively attacked by an activated immune system. An effective immune response in this setting is thought to rely on immune surveillance of tumor antigens expressed on cancer cells that ultimately result in immune responses and cancer cell death. Meanwhile, tumor progression may depend upon acquisition of traits that allow cancer cells to evade immunosurveillance and escape effective innate and adaptive immune responses.[22,23,24] Current immunotherapy efforts attempt to break the apparent tolerance of the immune system to tumor cells and antigens by either introducing cancer antigens by therapeutic vaccination or by modulating regulatory checkpoints of the immune system. T-cell stimulation is a complex process involving the integration of numerous positive as well as negative co-stimulatory signals in addition to antigen recognition by the T-cell receptor.[25] Collectively, these signals govern the balance between T-cell activation and tolerance.

In the pivotal 1-month oral toxicity studies, the highest non-severely toxic dose (HNSTD) in dogs was 0.15 mg/kg. The dog was considered the most appropriate species for calculation of the maximum recommended starting dose (MRSD) because a nontolerated dose was attained in dog but not rat and the toxicity profile was similar in both species. The starting dose of 0.75 mg/day was selected based upon the human equivalent dose (HED; scaled by body-surface area) of the HNSTD in dogs (the more sensitive species between dogs and rats) with a safety factor of 1/6. The projected human efficacious dose is estimated to be 2 mg/day.

To assure safety of human subjects, the initial dose of BMS-986158 tested in this study was 0.75 mg/day. Part 1 of this study also evaluates different administration schedules: monotherapy given 5 consecutive days on with 2 days off each week of a 4-week cycle (Schedule A of Part 1); monotherapy given 14 consecutive days on with 7 days off of a 3-week cycle (Schedule B of Part 1); and monotherapy given 7 days on and 14 days off of a 3-week cycle (Schedule C of Part 1). The rationale for the 3 schedules is based on the human half-life of 39 hours. Schedule A effectively provides continuous drug exposure, while Schedules B and C provide intermittent exposure with a break to allow for platelet recovery as needed at higher doses in human trials of other compounds in this class.[26,27,28,29]

For Part 2, Schedule A, has been selected considering the safety, [redacted] and PK obtained during Part 1. In addition to adult subjects, adolescent subjects will be included in Part 2.

The increment in the dose levels used in dose escalation especially in the first schedule tested (Schedule A), will be guided by the modified Fibonacci to help mitigate the potential risk inherent in the steep dose/toxicity curve and/or the low therapeutic index seen in preclinical studies. Dose escalation decisions will utilize a modified toxicity probability interval (mTPI) design. Rationale for selection of an mTPI over a 3+3 design includes a more accurate determination of MTD, provides flexibility in cohort size, and allows de-escalation and re-escalation to a previously tried dose. The design provides a simple dose escalation decision algorithm, and in addition to the higher accuracy of MTD selection, it treats fewer subjects at suboptimal doses.

Drug development strategies in oncology continue to evolve with the advent of histology-agnostic biomarkers correlating with the clinical activity of targeted anticancer drugs. Tumors with genetic rearrangements that engage molecular pathways regulated by BRD proteins, including gene translocations, mutations, or amplifications, have been selected for Part 2 of this study to identify early clinical activity in these preselected patient populations. The results of this study may help to understand whether the activity of BMS-986158 depends on specific genetic alterations observed in selected histologies or may be tumor agnostic.

Translocations

Chromosomal translocations may lead to the formation of fusion proteins with oncogenic properties. Examples of these genetic abnormalities include BRD3,4-NUT fusion (in 75% of cases of NMC), EWS/FLI1 fusion (in 85% of cases of Ewing sarcoma [ES]), and IGH/L-MYC and IGH-BCL-2/6 fusions (in Burkitt's lymphoma [BL] and double-hit lymphoma [DHL]).

Detection of these fusion proteins is required for diagnosis and is a routine clinical practice. Initially, only subjects with NMC carrying BRD3,4-NUT fusion will be selected to participate in Part 2.

Mutations

SWI/SNF functions as a tumor suppressing complex and mutations in subunits contribute to malignant transformation.[30] The KRAS protein is required for signaling in normal cells, and the mutation of a KRAS gene contributes to the development of many cancers. Similarly, Gnaq and Gnaq/11 mediate the intracellular signal transduction pathway, and mutations in these genes lead to oncogenesis.

- Renal cell carcinoma (RCC): Approximately 40% of patients with RCC harbor mutations within the SWI/SNF complex, including ARID1A, ARID1B, SMARCA4, SMARCA2, SMARCB1, ARID2, PBRM1 (BAF180) ,[31] and BET inhibitors induced RCC cell apoptosis and repressed tumor growth in vitro and in vivo.[32]
- Non-small cell lung cancer (NSCLC): BMS-986158 suppressed proliferation of NSCLC cell lines with SWI/SNF mutations (BMS, data on file). In vitro and in vivo antitumor activity of other BET inhibitors has also been reported in NSCLC cells harboring KRAS mutations, although this effect was abrogated by concurrent alterations of LKB1, also known as STK11.[33] According to TCGA database, 30% of patients with NSCLC harbor SWI/SNF mutations, and 15% harbor KRAS mutations of which approximately 75% express wild type LKB1.
- Uveal melanoma (UM): BET inhibitor demonstrated cytotoxic activity in UM cells carrying Gnaq/11 mutations and inhibited tumor growth in xenograft models.

Amplifications

- BRD: In patients with OC, BRD amplification is associated with worse overall survival. BRD gene amplification correlates with overexpression of BRD RNA (TCGA database) and is necessary for proliferation and survival of some tumor cell types, including OC and triple negative breast cancer (TNBC). Blocking hyperactivity of BRD proteins with a BET inhibitor results in growth inhibition of xenografts obtained from patients with OC and from patients

with TNBC.[34,35] Approximately 43% of patients with TNBC, 55% of patients with neuroendocrine prostate cancer (NEPC), and 17% of patients with OC harbor BRD4 amplifications (TCGA database).

- MYC: Forty-one percent of patients with castration-resistant prostate cancer (CRPC) and 47% of patients with OC harbor MYC amplifications (TCGA database). BET inhibition results in reduced MYC expression and inhibition of tumor growth in PDX models with high MYC expression and inhibition of AR signaling.[36] High frequency of MYC amplification (approximately 30%) has also been observed in patients with uterine carcinosarcoma (UCS) (TCGA database). Also, the non-germinal center subtype of diffuse large B-cell lymphoma (non-GC-DLBCL) is often associated with MYC (and BCL2) overexpression.[37] A recent Phase I study of a BET inhibitor in patients with relapsed and refractory lymphoma reported objective clinical responses in the non-GC-DLBCL subtype, in particular in patients with activated B cell (ABC)-DLBCL.[38]
- AR: Among other genetic abnormalities sensitive to BET regulation is AR amplification. AR promotes ligand-independent prostate cancer (PC) progression through c-MYC upregulation.[39] BET inhibitors decreased MYC levels and proliferation viability of castration-resistant prostate cancer (CRPC) cells, and inhibited growth of PC xenografts. Approximately 67% of CRPC patients harbor AR amplification, and 25% to 30% harbor both MYC and AR amplifications (TCGA database).

BRD, MYC, and AR amplifications will be detected in tumor biopsies using Foundation Medicine diagnostic platform. Subjects with TNBC, non-GC-DLBCL and CRPC with any of these gene amplifications/overexpressions will be eligible to participate in Part 2 as part of the Initial Expansion.

These genetically defined tumor cohorts/patient populations have one or more qualifying characteristics:

- NMC: NUT-midline carcinoma
- DHL and non-GC-DLBCL: double hit lymphoma and non-germinal center subtype of diffuse large B-cell lymphoma
- TNBC: Triple negative breast cancer
- CRPC: castrate-resistant prostate cancer

Biomarkers are increasingly playing a key role in the development of cancer therapeutics. By interrogating BET-inhibitor-induced PD/gene signature changes in molecular markers measured in tissue and body fluids, the activity of this drug may be addressed and may be informative in identifying appropriate doses, treatment schedules, as well as potential prediction of responses.

BET pathway inhibition induces parallel transcriptional changes of multiple genes in tumor cell lines, xenografts and in vitro treated mouse and human blood. [redacted]

In preclinical models, BET pathway inhibition induces parallel transcriptional changes of multiple genes in tumor cell lines and patient-derived xenografts.[46,47,48,49,50]. Some BET-regulated proteins are known to play important roles in tumor development and maintenance. and treatment with BET inhibitors resulted in downregulation of MYC or BCL2 transcription in many preclinical tumor models. [redacted]

BMS-986158 treatment also induced differential gene expression in mouse and human blood. [redacted]

Exclusion of adolescent subjects from adult trials may slow the investigation of novel therapies in adolescent subjects and delay the delivery of novel efficacious drugs to this patient population. Thus, it has been recommended to consider adolescent subjects for tumor type- and molecular target-appropriate adult oncology trials.[51]

Some cancers, including rare diseases such as NMC affect both children and adults. While NMC was initially thought to be a childhood cancer, recent studies have shown that it affects people of all ages with 30% of new cases reported in pediatric patients. Similar to adult patients, NMC is highly lethal in children and adolescent patients with an average of 10 months survival time, despite intensive therapies.[52] Thus, there is an unmet medical need for new therapeutic approaches for patients with NMC across all ages.

During the dose expansion part of this study, BMS-986158 will initially be tested in subjects with TNBC, CRPC, DHL, non-GC-DLBCL, and NMC. These cancers are rare in children.[53,54,55,56] Some predictors of poor outcome were shared among all age groups, such as multiple primary tumor sites and advanced stage disease.[57] Because patient numbers are low, there are no randomized trials comparing different relapse regimens. These results provide rationale for development of alternative treatment approaches focusing on targeted therapy to circumvent chemotherapy-resistant disease by providing alternative therapeutic targets across different ages.

Current experience with BMS-986158 did not identify drug-related adverse events (AEs) that warrant exclusion of adolescent subjects from this study. Thus, the balance of benefit to risk may be favorable in adolescent subjects with advanced cancers and poor treatment options. Therefore, adolescent subjects with NMC will be eligible to participate in this study. Additional indications will be allowed at the discretion of the Sponsor if the tumor contains similar genetic abnormalities sensitive to regulation by the BET family proteins.

This SAP supersedes the statistical considerations identified in the protocol; where considerations are substantially different, they will be identified as such in this document. In the event that the protocol has amendment(s) that do not have an impact on the statistical analysis methodology, this SAP will not require an amendment. [redacted]

[redacted]

Research Hypothesis

There is no formal primary research hypothesis for this study to be statistically tested. It is anticipated that BMS-986158 as monotherapy will demonstrate adequate safety and tolerability at pharmacologically relevant doses, so as to permit further clinical development (at a recommended dose range).

Schedule of Analyses:

Data emerging from this study may be needed to for timely decisions about adjustments to procedures in subsequent parts of the study. Therefore, data from each part of the study will be examined prior to the final lock of the study database. Additional interim analyses may also be performed for administrative purposes, early termination of the study or publications. No formal inferences requiring any adjustment to statistical significance level will be performed. Efficacy analyses based on interim data may use the Response Evaluable Subjects population or the All Treated Subjects population depending on the purpose of the analysis.

An interim analysis to summarize safety, PK, and efficacy data may be performed when sufficiently treated participants become available. Additional interim analyses on safety and efficacy may be performed at various times prior to study completion in order to facilitate program decisions and to support scientific publications or presentations.

2 STUDY DESCRIPTION

2.1 Study Design

This is a phase 1/2a, open label study to characterize the safety and tolerability of BMS-986158 monotherapy in subjects with advanced solid tumors and hematologic malignancies. The study has two segments Part 1 (Phase 1 study - dose escalation, with Schedules A, B and C enrolling at different dosing schedules) and Part 2 (Initial Expansion including subjects with a limited set of tumor types) (see Figure 2.1-1). In Part 1 and Part 2, BMS-986158 will be studied as monotherapy.

In Part 1, the continuous dosing Schedule A enrolled first. Each subject in Schedules A, B and C of Part 1 is administered a single dose of BMS-986158 on Cycle 1 Day 1 and no additional doses are administered until Cycle 2 Day 1. For subjects in Schedule A on Cycle 2 Day 1, and on each subsequent cycle, subjects receive QD dosing for 5 consecutive days of each week, followed by a 2-day rest period, on a 28-day cycle. For subjects in Schedule B on Cycle 2 Day 1, and on each subsequent cycle, subjects receive QD dosing for 14 consecutive days, followed by a 7-day rest period, on a 21-day cycle. For subjects in Schedule C on Cycle 2 Day 1, and on each subsequent cycle, subjects receive QD dosing for 7 consecutive days, followed by a 14-day rest period, on a 21-day cycle.

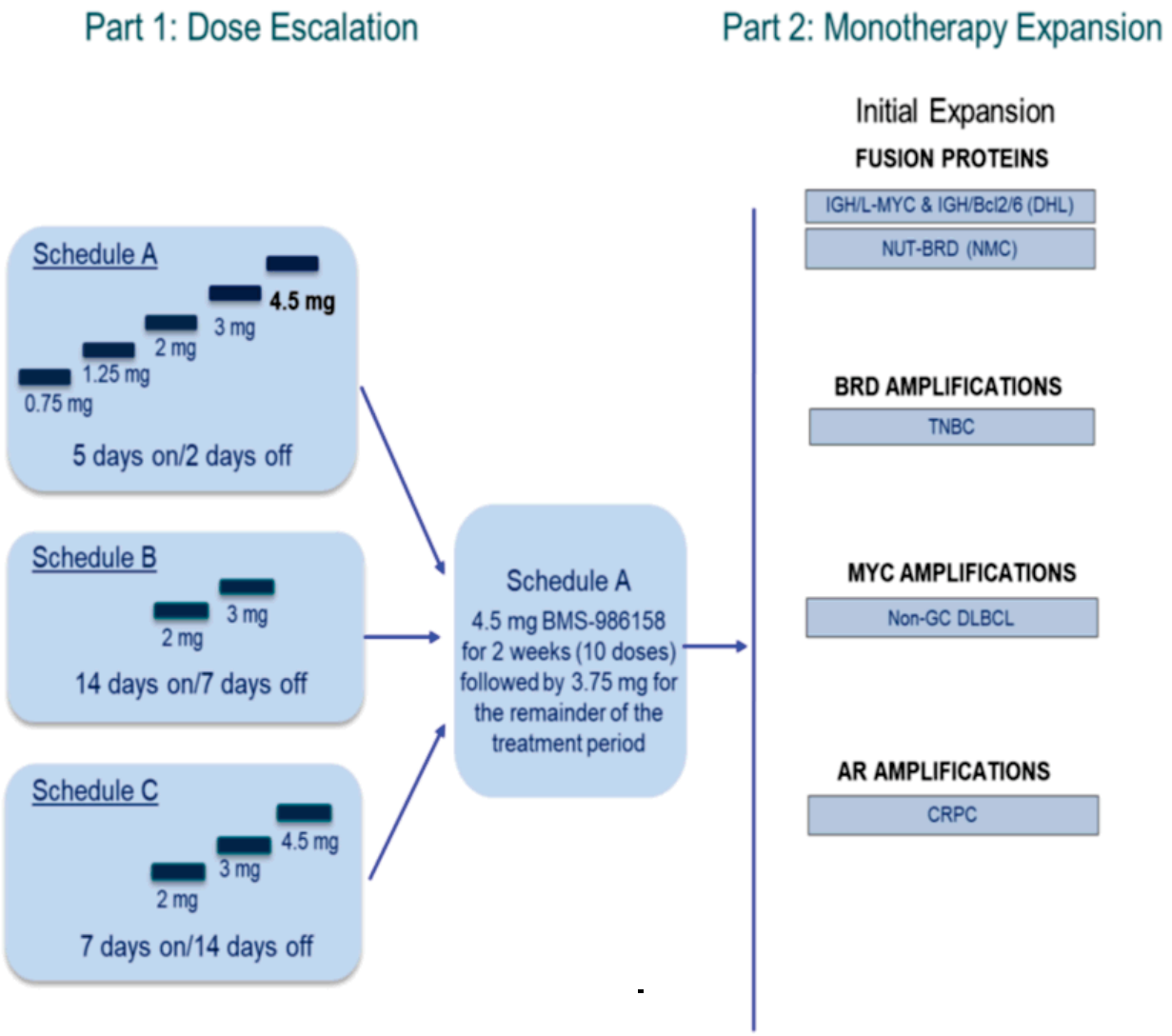
In Part 2, Schedule A for BMS-986158 administration has been selected for expansion of the 4.5 mg dose, which will be administered for 2 weeks (10 doses) followed by 3.75 mg for the remainder of the treatment period. Adult and adolescent subjects weighing ≥ 40 kg will be

administered a flat dose of BMS-986158. Using Schedule A with a loading period of 2 weeks at 4.5 mg followed by 3.75 mg for the remainder of the treatment period, BMS-986158 will be tested as monotherapy, in a limited set of tumor types (NMC, CRPC, DHL, Non-DC-DLBCL, and TNBC; Initial Expansion).

Enrollment in Part 1 and selection of the monotherapy MTD will adhere to a modified Toxicity Probability Interval (mTPI) design. 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%-29%. During Parts 1, the monotherapy MTD will be selected as the dose levels with the smaller difference between estimated toxicity and the target DLT rate among the dose levels administered based on the mTPI design. See Protocol Appendix 1.

Figure 2.1-1 shows a graphical depiction of the study design, which shows only Part 1 and Part 2 initial expansion as clarified in the scope of this SAP document in the beginning.

Figure 2.1-1: Study Overview

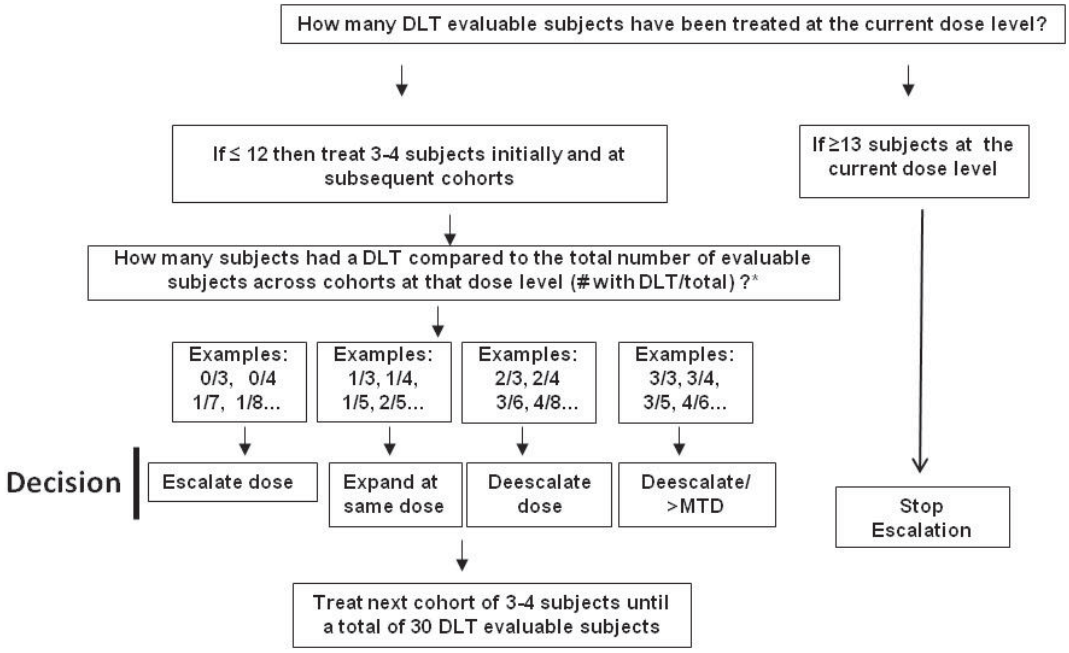


Abbreviations: CRPC = castrate-resistant prostate cancer; DHL = double-hit lymphoma; NMC = NUT-midline carcinoma; Non-GC-DLBCL = Non-germinal center diffuse large B-cell lymphoma; NSCLC = non-small cell lung cancer; Res = response; SOC = standard of care; TNBC = triple negative breast cancer;

Subjects will complete up to 5 study periods: Screening (up to 28 days for Part 1 and up to 40 days for Part 2), Treatment (up to 2 years, until disease progression or other protocol-specified criteria), Clinical Follow-up (30 days for BMS-986158 monotherapy), and Survival Follow-up [redacted].

Figure 2.1-3 shows the mPTI dose escalation decisions for Part 1 based on scenarios that may be encountered during dose escalation with respect to the number of DLT-evaluable subjects and the number of subjects with a DLT. Schedule A, B, and C subjects will be evaluated independently for establishment of DLTs, MTDs and MAADs in each part.

Figure 2.1-2: Dose Escalation Decision Scheme



DLT-evaluable subjects are defined as subjects who received at least 16 of 21 doses of BMS-986158 in Schedule A; at least 17 of 22 doses of BMS-986158 in Schedule B ; and at least 12 of 15 doses in Schedule C of Part 1 during the DLT evaluation period and will be considered for dose escalation decisions. Subjects who developed a DLT during the DLT period are considered evaluable regardless of the number of received doses.

At the end of dose escalation, the MTD for one evaluated dosing schedule (Schedules A, B, or C) will be selected as the dose with the smaller difference between estimated toxicity and the target DLT rate (27%), among the dose levels used, with an isotonic regression model of the accumulated DLT data based on the mTPI design.

Treatment in Part 2 can be initiated before Part 1 is completed and when the MTD (or maximum administered dose if no MTD is determined) for Part 1 has been determined. Schedule A (QD dosing for 5 consecutive days of each week, followed by a 2-day rest period, on a 28-day cycle) has been chosen for expansion. This regimen was selected after considering safety, PK [redacted] data generated during Part 1. The initial dose level of BMS-986158 selected for Part 2 is 4.5 mg with a loading period of 2 weeks (10 doses or half a cycle) with subsequent dose level of 3.75 mg for the duration of study treatment for each subject.

BMS-986158 will be first evaluated as monotherapy. The Initial Expansion will enroll a maximum of 45 subjects with tumors harboring specific genetic alterations including fusion proteins (NMC, DHL), BRD amplifications (TNBC), MYC amplifications (Non-GC DLBCL) and AR amplification (CRPC).

Adolescent subjects will be treated with a dose and schedule selected from Part 1 (dose escalation) in adult subjects. The safety of this selected BMS-986158 dose will be evaluated in adolescents (≥12 to <18 years of age) as part of the dose expansion phase (Part 2) in subjects with NMC. Initially, 3 to 4 adolescent subjects across different tumor types may be enrolled in the Initial Expansion and monitored for DLT. Based on safety and other available data, the Sponsor may consider decreasing the dose level of BMS-986158 for adolescent subjects.

Once the safety and tolerability profile is established at the selected dose of BMS-986158 alone during the dose evaluation phase, enrollment in the expansion phase will initiate at this dose level to assess a preliminary efficacy signal, and to obtain additional data, such as [redacted] safety information across the selected tumors.

Enrollment in the Part 2 expansion will start in the initial BMS-986158 monotherapy cohorts. Although a 2-stage (Fleming) design will be used to guide assessment of preliminary anti-tumor activity in each of the monotherapy cohorts, up to 9 subjects may be enrolled in each of the initial cohorts to better characterize the PK, safety [redacted] profiles. The decision to continue or discontinue enrollment in one or more cohorts or discontinue treatment in existing cohorts will be made by the Sponsor/Medical Monitor based on a comprehensive assessment of the accruing on-treatment evidence.

Clinical safety monitoring of subjects during dose expansion phase will continue throughout the study. If at a selected BMS-986158 dose level, the combined incidence exceeds 33% for study drug related toxicity requiring treatment discontinuation, further enrollment to that dose level may be interrupted and a decision to continue dosing will be based on discussions of the observed aggregate (acute and chronic) toxicities between the investigator(s) and the Sponsor, if needed.

Table 2.2-1 shows the planned number of subjects per tumor type and setting (Part 2 Initial monotherapy) in the expansion phase.

Table 2.1-1: Dose Expansion Planned Sample Size

Tumor Cohort and Group	Initial Monotherapy
FUSION PROTEINS	
DHL	5 to 9
NMC	5 to 9
BRD AMPLIFICATIONS	
TNBC	5 to 9
MYC AMPLIFICATIONS	
Non-GC-DLBCL	5 to 9
AR AMPLIFICATIONS	
CRPC	5 to 9
All Cohorts	**25 to 45**

The minimum overall planned sample sizes are based on initial enrollment subject counts per cohort. The maximums are determined similarly.

Therefore, the potential total for expansion will be approximately up to 45 subjects if only initial monotherapy is pursued.

Administration of Additional Treatment Cycles:

Subjects may discontinue treatment due to disease progression, unacceptable AEs, or at the subject's request. Treatment decisions related to subject management will be based exclusively on RECIST version 1.1 or the Lugano 2014 criteria, or PCWG3 criteria (including PSA assessments). Subjects with an objective response of CR, partial response (PR) or stable disease, will continue therapy until they develop progressive disease (PD, unless in case of treatment beyond progression), experience clinical deterioration, develop AEs requiring discontinuation of treatment or withdraw consent.

Subjects who develop toxicity requiring discontinuation of treatment will enter the Clinical Follow-up Period. The subject should be seen in follow-up at least every 30 days, until the AE has resolved to baseline, stabilized, or been deemed irreversible. After completion of the Clinical Follow-up Period, subjects will then enter the Survival Follow-up Period. [redacted]

The overall duration of the study is expected to be approximately 6 years from the time of the first visit of the first subject to the required survival follow-up of the last subject enrolled. Subjects may discontinue treatment due to disease progression, unacceptable AEs, or withdrawal of consent. The Clinical Follow-up visits will occur approximately 30 days (for subjects who receive monotherapy) after the subject discontinues study treatment. For subjects in PR or CR who discontinue treatment for AEs, tumor assessments will be performed every 12 weeks for the first year then every 6 months for the second year. If a subject discontinues treatment due to an AE, the subject should be seen in Clinical Follow-up every 30 days until the AEs either resolved to baseline or Grade 1, stabilized, or been deemed irreversible. After completing the Clinical Follow-up Period, subjects will continue on to a Survival Follow-up Period. [redacted] The end of the study will occur after the last treated subject completes their Clinical Follow-up, unless a subject discontinues prematurely. Subjects in Survival Follow-up Period who have progression of disease will be eligible to receive anticancer therapy as appropriate.

2.2 Treatment Assignment

This is an open-label study. Enrolled subjects, including those not dosed, will be assigned sequential subject numbers starting with 00001, eg, 00001, 00002, 00003.... 00010. Those enrolled subjects meeting eligibility criteria will be eligible to be dosed. Sequential numbering may restart

at 00001 for each participating site as the distinct subject identification number (PID) will ultimately be comprised of the site number and subject number, eg, 0002 00001.

During Part 1, once informed consent has been obtained, the investigator (or designee) will register the subject by transmitting a copy of the completed enrollment worksheet (registration form) to the Sponsor. Treatment groups and/or dose levels will be provided to the site study team after the subject has registered and eligibility for the study confirmed.

In Part 2, during the screening visit, the investigative site will call into the enrollment option of the interactive response technology (IRT) designated by BMS. Enrolled participants, including those not dosed, will be assigned sequential participant numbers for their site starting with 00001, (eg, 00001, 00002, 00003.... 00010). The patient identification number (PID) will ultimately be comprised of the site number and participant number. Once it is determined that the participant meets the eligibility criteria following the screening visit, the investigative site will call the IRT to centrally assign the participant into the appropriate monotherapy cohort.

2.3 Blinding and Unblinding

This study is a non-randomized open-label study for Part 1 and Part 2. Interactive Response Technology **(**IRT) will be used in Part 2 for treatment assignment. Data emerging from this exploratory study may be necessary to inform timely decisions for adjusting procedures in subsequent portions of the study, including early termination of the study. Additionally, availability of the open label treatment assignments may facilitate optimization of the bioanalytical analysis of samples.

2.4 Protocol Amendments

This SAP incorporates the following protocol amendments (Table 2.4-1).

Table 2.4-1: Protocol Amendments

Document	Date of Issue	Summary of Major Changes
Amendment 01	10-Aug-2015	Revisions to Inclusion/Exclusion criteria, T&E table, and minor typographical edits
Amendment 04	03-Mar-2016	Incorporates new dosing regimens, revisions to the inclusion/exclusion criteria, T&E table and minor typographical edits
Amendment 05	12-Apr-2016	Removes Parts 1B & 2B and pertaining language from the protocol; incorporates revisions to the inclusion/exclusion criteria, T&E table, and minor typographical edits.
Revised Protocol 04	06-Sep-2017	Adds nivolumab to Part 2 escalation phase and updates to biomarker driven study design with additional tumor types added. Includes revisions to rationales, inclusion/exclusion criteria, T&E table, sample collection tables and statistics; and minor typographical edits.
Revised Protocol 05	01-Mar-2018	Incorporates Administrative Letter 04 and the following changes:1) clarify the acceptable prior lines of therapy for participants with Non-Small Cell Lung Cancer (NSCLC) in Part 2; 2) update Exclusion Criteria for subjects participating in Part

Table 2.4-1: Protocol Amendments

		2; and 3) provide updated contraception and protection requirements based on recent non-clinical reproductive toxicology study. Study design elements including time and events schedules, sample collections, laboratory analyses and additional safety measures have been added to align with these changes.
Revised Protocol 06	17-Jul-2018	Updates schedules for mandatory biopsies during Part 2, updates imaging requirements for tumor assessments; updates inclusion criteria for subjects with NSCLC, corrects dose-limiting toxicity period for Part 2, updates schedules for PK sample collections, includes language to allow for release of IRT codes to facilitate ongoing data review, and added PROSTATE CANCER WORKING GROUP 3 (PCWG3) appendix.
Revised Protocol 07	18-Mar-2019	Identifies the dose and schedule for Part 2 and updates the study design for Part 2. Includes revisions to rationales, inclusion/exclusion criteria, T&E tables, sample collection tables and statistics; minor typographical edits, and an update to Appendix 4 RECIST 1.1. [redacted]

3 OBJECTIVES

3.1 Primary

- To assess the safety and tolerability and to assess the DLTs, MTD, and recommended Phase 2 dose (RP2D) of BMS-986158 as monotherapy for subjects with advanced solid tumors and hematologic malignancies

3.2 Secondary

- To assess the preliminary anti-tumor activity of BMS-986158 monotherapy as measured by ORR, and response duration based on response evaluation criteria in solid tumors (RECIST) v1.1, prostate cancers using PCWG3 criteria, or hematologic malignancies using criteria from Lugano 2014.
- To characterize PK of BMS-986158 and metabolite in monotherapy.
- To assess the dose-response and exposure-response effect of BMS-986158 monotherapy on the ECG (QT interval).

[redacted]

[redacted]

4 ENDPOINTS

4.1 Safety Endpoint(s)

The assessment of safety will be based on the incidence of adverse events (AEs), serious adverse events (SAEs), adverse events leading to discontinuation, deaths and frequency of laboratory test toxicity grade shifting from baseline.

Toxicities will be graded using the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) version 4.03 in the first 32-35 days of dosing (DLT evaluation period for Schedule A) and in the first 35 days of dosing (DLT evaluation period for Schedules B and C).

4.2 Secondary Endpoints

Secondary endpoints comprise preliminary antitumor activity, PK, and electrocardiogram (ECG) results and are described below.

4.2.1 Preliminary Antitumor Activity

Changes in solid tumor measurements and tumor response will be assessed by the RECIST v1.1 (Response Evaluation Criteria in Solid Tumors version 1.1)[58](Protocol Appendix 4), or PCWG3 for prostate cancer (Protocol Appendix 12). PCWG3 criteria is intended for Part 2 subjects and not Part 1 subjects. Changes in hematologic malignancies will be assessed using Lugano 2014 criteria (Protocol Appendix 9). In Schedule A (Part 1), tumor assessments will occur 8 weeks (± 1 week) after treatment begins and continue every 8 weeks (± 1 week) until investigator-assessed disease progression or treatment discontinuation. In Schedules B and C (Part 1), tumor assessments will occur 9 weeks (± 1 week) after treatment begins and continue every 9 weeks (± 1 week) until investigator-assessed disease progression or treatment discontinuation. In Part 2, Schedule A, tumor assessments will occur 8 weeks (± 1 week) after treatment begins and continue every 8 (± 1 week) until investigator-assessed disease progression or treatment discontinuation.

The following set of study-level efficacy endpoints will be used.

- Objective Response Rate (ORR): defined as the total number of subjects whose best overall response (BOR) is either a CR or PR divided by the total number of subjects in the population of interest.
  - Best overall response (BOR): defined as the best response designation recorded between the dates of first dose and the date of first objectively documented progression per Investigator assessed RECIST v1.1 (or Lugano 2014 criteria for hematologic malignancies or PCWG3 for prostate cancer) or the date of subsequent therapy, whichever occurs first.

Investigator reported CR or PR was not always confirmed by a second scan. Therefore, ORR summaries will be presented regardless of confirmation. For subjects without documented progression or subsequent therapy, all available response designations will contribute to the BOR assessment. For subjects who continue treatment beyond progression or begin subsequent therapy, the BOR should be determined based on response designations recorded up to the time of the initial RECIST v1.1 (or by Lugano 2014 criteria for hematologic malignancies, or PCWG3 criteria for prostate cancer [CRPC or NEPC]) defined progression or subsequent therapy, whichever occurs first. For those subjects who have surgical resection, only pre-surgical tumor assessments will be considered in the determination of BOR.

- Duration of Response (DOR): defined as the time between the date of first response (CR or PR) and the date of the first objectively documented disease progression (as determined using RECIST v1.1 for solid tumors, Lugano 2014 criteria for hematologic malignancies, or PCWG3 (including PSA assessments) for prostate cancer [CRPC or NEPC]), or death due to any cause, whichever occurs first. For those subjects who remain alive and have not progressed , duration of response will be censored on the date of last evaluable tumor assessment. Subjects who started subsequent therapy without a prior reported progression will be censored at the last evaluable tumor assessment prior to initiation of the subsequent anticancer therapy. Response duration will only be evaluated in subjects with a BOR of CR or PR. Duration of response will be reported if there are more than 5 CR or PR in a tumor type
- Progression Free Survival (PFS): defined as the time from the first dose of study medication to the date of the first objective documentation of tumor progression or death due to any cause. Clinical deterioration in the absence of radiographic evidence is not considered progression for the purpose of determining PFS. Subjects who neither progressed nor died will be censored on the date of their last evaluable tumor assessment. Subjects who did not have any evaluable on-study tumor assessments will be censored on the date of the first dose of study medication. Subjects who started subsequent therapy without a prior reported progression will be censored at the last evaluable tumor assessment prior to initiation of the subsequent anticancer therapy.
- Progression Free Survival Rate (PFSR) at week ‘t’: defined as the proportion of subjects who remain progression free and surviving at ‘t’ weeks (t=12, 24). The proportion will be calculated by the product-limit method (Kaplan-Meier estimate) which takes into account censored data.

4.2.2 Pharmacokinetic Endpoints

Pharmacokinetics of BMS-986158 monotherapy (parent and metabolite, as data permits) will be derived from plasma concentrations versus time data.

Throughout the SAP, TAU was replaced by 24 hours or 0-24. This is because it is more meaningful to compare PK of first 24 hours following single dose kinetics on cycle 1 day 1, and the dosing interval of 24 hours on cycle 2 NCA (Cycle 2 Day 5 for schedule A, Cycle 2 Day 14 for schedule B and Cycle 2 Day 7 for schedule C). Therefore, with reference to the protocol, the following PK parameters were replaced in the SAP: Ctau was replaced by C24, AUC(TAU) was replaced by AUC(0-24), AI_AUC(Tau) was replaced by AI_AUC(0-24), AI_Ctau was replaced by AI_C24 and MR_AUC(TAU) was replaced by MR_AUC(0-24).

The PK parameters to be assessed following single and multiple dose administration are shown in Tables 4.2.2-1 through 4.2.2-4 below.

Table 4.2.2-1: Single Dose Pharmacokinetic Endpoints

Parameter	Definition
Cmax	Maximum observed plasma concentration
Tmax	Time of maximum observed plasma concentration
AUC(0-T)	Area under the plasma concentration-time curve from time zero to time of last quantifiable concentration
AUC(0-24)	Area under the concentration-time curve from time zero to time 24 hours
Cmax/D	Maximum observed plasma concentration; Dose normalized
AUC(0-24)/D	Area under the concentration-time curve from time zero to time 24 hours; Dose normalized
AUC(INF)/D	Area under the plasma concentration-time curve from time zero extrapolated to infinite time; Dose normalized

In addition, the following PK parameters may also be assessed after single dose administrations, if data permit:

Table 4.2.2-2: Extended Single and Multi-dose Pharmacokinetic Endpoints

Parameter	Definition
T-HALF	Apparent terminal phase half-life
AUC(INF)	Area under the plasma concentration-time curve from time zero extrapolated to infinite time
CLT/F	Apparent total body clearance, reported only for parent, not for metabolite
Vz/F	Apparent volume of distribution of terminal phase, reported only for parent, not for metabolite

The PK parameters to be assessed following multiple dose administration include:

Table 4.2.2-3: Multi-dose Pharmacokinetic Endpoints

Parameter	Definition
Cmax	Maximum observed plasma concentration
Tmax	Time of maximum observed plasma concentration
AUC(0-T)	Area under the plasma concentration-time curve from time zero to time of last quantifiable concentration
AUC(0-24)	Area under the concentration-time curve from time zero to time 24 hours
Cmin	The minimum observed concentration within a dosing interval
C24	Observed concentration at 24 hours
Ctrough	Trough observed plasma concentration (this includes predose concentrations (C0) and concentrations at the end of dosing interval (C24));

Table 4.2.2-3: Multi-dose Pharmacokinetic Endpoints

AI_AUC(0-24)	Accumulation Index; ratio of an exposure measure at steady-state to that after the first dose (exposure measure includes AUC(0-24)).
AI_Cmax	Accumulation Index; ratio of Cmax at steady-state to Cmax after the first dose
AI_C24	Accumulation Index; ratio of an C24 at steady-state to C24 after the first dose
T-HALFeff	Effective elimination half-life that explains the degree of accumulation observed for a specific exposure measure

In addition, the following PK parameters may also be assessed after single and multiple dose administrations, if data permit:

Table 4.2.2-4: Extended Single and Multi-dose Pharmacokinetic Endpoints

Parameter	Definition
MR_Cmax	Ratio of metabolite Cmax to parent Cmax, corrected for molecular weight
MR_AUC(0-T)	Ratio of metabolite AUC(0-T) to parent AUC(0-T), corrected for molecular weight
MR_AUC(INF)	Ratio of metabolite AUC(INF) to parent AUC(INF), corrected for molecular weight (following single dose only)
MR_AUC(0-24)	Ratio of metabolite AUC(0-24) to parent AUC(0-24), corrected for molecular weight

Individual subject pharmacokinetic parameter values will be derived by non-compartmental methods by a validated pharmacokinetic program. Actual times will be used for the analyses.

4.2.3 ECG/QTc

Changes in QTcF (ΔQTcF) from baseline, at selected times in relation to BMS-986158 monotherapy will be evaluated in the context of dose- or exposure-response as observed. This may also be evaluated in relation to Metabolite BMT-161485.

[redacted]

[redacted]

5 SAMPLE SIZE AND POWER

5.1 Dose Escalation

In the dose escalation part of the study, i.e., Part 1, the sample size per dose level and schedule cannot be precisely determined but depends on the observed DLT and the decision rule of mTPI. Between 3 and up to 13 DLT evaluable subjects may be enrolled to a given dose level and schedule. Treating additional subjects beyond the 13 at a dose level in a dose schedule would be unlikely to alter the decision specified by the mTPI algorithm. A total of approximately 30 subjects is expected to be treated per schedule, with a total of 90 planned across schedules for the dose escalation phase. More subjects may be added at a specific schedule if additional dose levels need to be evaluated. Similarly, fewer than 30 subjects may be needed for a different schedule if a smaller number of dose levels are evaluated.

Assuming a 27% acceptable DLT rate, which corresponds to a Beta(1, 2.7) distribution, the risk associated with selecting a dose level as safe given the number of DLTs observed at that dose level based on the posterior probability associated with an observed DLT is dependent on the number of subjects evaluable for DLT at that dose level at the time of the event.

5.2 Dose-expansion Cohort

The purpose of cohort expansion is to gather additional safety, tolerability, preliminary efficacy, PK, [redacted] information regarding BMS-986158 alone. However, the sample size is strictly based on efficacy, specifically based on the target ORR relative to historic response rate.

During this part of the study, the efficacy signal assessment in each tumor cohort in monotherapy regimens will be guided by a Fleming 2-stage design. The Stage 1 and total (Stages 1 and 2) sample size for each cohort is calculated based on assumptions of true (target) and historic ORR for each tumor type in the studied population. Using a 2-stage design provides an option to stop early for futility, as well as an early signal of preliminary strong antitumor activity. Approximately 5 to 9 subjects will be treated in each of the 5 parallel cohorts. Enrollment may continue during the initial

Stage 1 efficacy evaluation (while the planned number of participants for Stage 1 are followed for evaluable tumor assessments) to ensure that sufficient subjects are response evaluable in case of early drop outs and to account for design parameters changes (eg, historical rate update).

The total sample size for each expansion cohort will be calculated to provide a reasonable false-positive rate (FPR < 10%) and false-negative rate (FNR < 10%) based on assumptions of true (target) and historic ORR for each indication. The assumed historic and target response rates may change over time and may need to be adjusted by the time of response data from this study are available. Enrollment may continue into stage 2 while the planned number of participants for stage 1 are followed for efficacy evaluable tumor assessments. There will be no stopping of a disease cohort for efficacy, although early planning for the next stage of clinical development may be initiated.

If one or more of the 5 subjects in a Stage 1 cohort respond to therapy, the Fleming Stage 1 futility boundary will have been exceeded and enrollment will continue in Stage 2. If 2 or fewer of 9 subjects enrolled through Stage 2 respond to therapy, the cohort will have failed to evidence the targeted ORR (Table 5.2-1).

Table 5.2-1: Characteristics for Initial Monotherapy Expansion Cohorts Signal assessment when guided by a Two-Stage Design

Tumor Cohort and Group	Target ORR %	SOC ORR %	Stage 1 / Total N	Stage 1 Res Futility/ Efficacy Boundary	Stage 2 Res Futility/ Efficacy Boundary	FPR/FNR (%)
FUSION PROTEINS						
NMC	50	10	5/9	0/2	2/3	10/10
DHL	50	10	5/9	0/2	2/3	10/10
BRD AMPLIFICATIONS						
TNBC	50	10	5/9	0/2	2/3	10/10
MYC AMPLIFICATIONS						
Non-GC-DLBCL	35	10	5/9	0/2	1/2	20/20
AR AMPLIFICATIONS						
CRPC	35	10	5/9	0/2	1/2	20/20

Abbreviations: CRPC = castrate-resistant prostate cancer; DHL = double-hit lymphoma; FNR = false negative rate; FPR = false positive rate; N = number of subjects; NMC = NUT-midline carcinoma; ORR = objective response rate; RCC = renal cell carcinoma; Res = response; SOC = standard of care; TNBC = triple negative breast cancer; Non-GC-DLBCL = Non-germinal center diffuse large B-cell lymphoma;

The planned sample size consists of up to approximately 90 subjects for Part 1 and up to approximately 45 subjects for Part 2 Initial expansion for a total of up to approximately 135 subjects in the entire study (up to Part 2 Initial expansion, as clarified in the scope of this SAP document in the beginning).

6 STUDY PERIODS, TREATMENT REGIMENS AND POPULATIONS FOR ANALYSES

6.1 Study Periods

This study consists of four periods: Screening (up to 28 days for Part 1 and up to 40 days for Part 2), Treatment, Clinical Follow-up (30 days), and Survival Follow-up.

6.1.1 Baseline Period

- The screening period is up to 28 days for Part 1 and up to 40 days for Part 2 and is immediately prior to the first study drug administration. The screening period begins by establishing the participant's initial eligibility and signing of the informed consent form (ICF).

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

6.1.2 Post-Baseline Period

- The On-treatment period starts at the time of the first dose of study medication and ends when the decision to discontinue a subject from study therapy is made.
- The clinical follow-up period begins when the decision to discontinue a subject from study therapy is made, and for subjects treated with BMS-986158 in monotherapy extends until 30 days after a subject discontinues.
- The survival follow-up period begins 30 days after a subject discontinues from study therapy, and ends 2 years after the first dose of study drug unless continuing on study treatment for more than 2 years, or 6 months after his/her last treatment date, whichever occurs later.

6.2 Treatment Regimens

The treatment group "as assigned" will be retrieved from the IRT system, if applicable. The treatment group "as treated" will be the same as the arm as assigned by IRT. However, if a participant received an incorrect treatment for the entire period of treatment, the participant's treatment group will be defined as the incorrect treatment the participant actually received.

Statistical analysis and reporting will be performed based on the treatment regimen assigned to subjects at the time of study therapy initiation unless otherwise specified. For Part 1 Schedule A the 5 days on / 2 days off regimen will be considered as the assigned treatment, even though subjects are expected to receive a single dose in Cycle 1 (i.e., the first week of therapy), with the exception of the PK analysis where the single dose PK will be presented separately for the Cycle 1 Week 1 schedule. The regimens administered in Part 1 via Schedules B and C will be handled equivalently. Part 2 Schedule A (QD dosing for 5 consecutive days of each week, followed by a 2-day rest period, on a 28-day cycle) has been chosen for expansion. The initial dose level of BMS-986158 selected for Part 2 is 4.5 mg with a loading period of 2 weeks (10 doses or half a cycle) with subsequent dose level of 3.75 mg for the duration of study treatment for each subject.

6.3 Populations for Analyses

- All Enrolled: All participants who provided an informed consent form.
- All Treated: All participants who received at least one dose of any study medication.
- Pharmacokinetic: All participants who received at least one dose of BMS-986158 and have available serum or plasma concentration data for the corresponding analyte
- Pharmacokinetic evaluable: Subset of Pharmacokinetic population with adequate PK Profiles who have at least 1 valid PK parameter. Pharmacokinetic summaries and statistical analyses will be based on this dataset.
- [redacted]
- ECG Evaluable: all treated participants who had a baseline ECG and at least one on study ECG.
- Response-evaluable: all treated participants with measurable disease at baseline and at least one of the following: 1) at least one post-baseline tumor assessment, 2) clinical progression, or 3) death.

All subjects who receive study medication will be included in the safety population.

7 STATISTICAL ANALYSES

All analyses will be performed using the SAS System Version 9.2 or later. Some figures will be generated using S-Plus or R.

7.1 General Methods

Continuous variables will be summarized using descriptive statistics including mean, standard deviation (SD), standard errors of the mean (SEM), median, minimum, and maximum. PK endpoints will also report geometric means, standard deviations, and standard errors of the mean. Categorical variables will be summarized using frequencies and percentages. Percentages will be rounded to one decimal precision and may sum to more or less than 100.0. Percentages less than 0.1 will be indicated as '< 0.1'. For summaries, tumor types that have less than 5 participants may be grouped together with "Other".

Time-to-event (TTE) endpoints will be evaluated using Kaplan-Meier (K-M) methods. Regimen describes BMS-986158 monotherapy**Study Conduct**

7.2.1 Study Information

- **Listing**:
- Batch number listing for all treated subjects will be provided.

7.2.2 Accrual

The following will be presented using the All Enrolled population.

Summary:

- Number (%) of participants accrued by country and investigational site: include country, site number, number of subjects enrolled, and number of participants treated
- **Listing**:

- Participants accrued by country and investigational site

7.2.3 Relevant Protocol Deviations

Non-programmable relevant eligibility and on-treatment protocol deviations, as well as significant (both programmable and non-programmable) deviations will be reported through ClinSIGHT listings. The following programmable deviations from inclusion and exclusion criteria will be considered as relevant protocol deviations and a listing will be provided, based on data availability.

At entrance:

- Participants with baseline ECOG performance status > 1
- Participants who used strong inhibitors of CYP3A4 or P-gp within 2 weeks or strong inducers of CYP3A4 or P-gp within 2 weeks.
- Participants with inadequate hepatic function:
  - Aspartate aminotransferase (AST) > 3x ULN
  - Alanine aminotransferase (ALT) > 3x ULN
  - Total bilirubin > 1.5 x ULN (except known Gilbert's syndrome)
- Participants with inadequate bone marrow function:
  - Absolute neutrophil count (ANC) < 1,500 cells/mm^3;
  - Platelet count < 100,000 cells/mm^3;
  - Hemoglobin < 8 g/dL
- Participants with abnormal blood coagulation parameters:
  - PT such that international normalized ratio (INR) is > 1.5 (or > 3, if a subject is on a stable dose of therapeutic warfarin) and a PTT > 1.2x upper limit of normal (ULN).
- Participants with positive blood screen for hepatitis C antibody or hepatitis B surface antigen

On-Study:

- Participants receiving concurrent anti-cancer therapy (defined as chemotherapy, hormonal immunotherapy, non palliative radiation therapy, standard or investigational agents for treatment of NSCLC).
- Participants who received the wrong dose level

7.3 Study Population

7.3.1 Participant Disposition

Status of participants at the end of pre-treatment period will be summarized and listed by including all enrolled participants. Status of participants at the end of treatment period will be summarized by treatment and overall, based on All Treated population. In addition, status of participants at the end of each study period will be summarized as appropriate. A listing will be provided for those participants who were treated and reason for discontinuation of treatment or not being followed will be described.

7.3.2 Demographics and Other Baseline Characteristics

Summary:

Descriptive statistics will be summarized the following baseline characteristics for all treated subjects by treatment and overall, and may also be presented by tumor type.

- Age (in years) ; age category (<65, 65 - 84,≥85),
- Sex at Birth
- Race
- Ethnicity (if applicable)
- Country
- Physical characteristics
  - Height
  - Weight
- ECOG PS

Listing:

- All relevant data, generally the variables listed above by treatment.
- General medical history

7.3.3 Prior Anti-Cancer Therapy

Summary:

Summary statistics will be provided by treatment and overall for each tumor type for:

- Prior systemic cancer therapy
  - Number of prior therapies and lines of therapy
- Prior surgery
  - Number of subjects with prior surgery
- Prior radiotherapy therapy
  - Number of subjects with prior radiotherapy

Listing:

- Prior surgery and radiotherapy
- Prior systemic cancer therapy
  - Best response to therapy

7.3.4 Baseline Disease Diagnosis

Summary:

Summary statistics will be provided by treatment and overall and also separately by tumor type.

- Baseline Disease Diagnosis, and disease characteristics (e.g. stage)

Listing:

- Baseline Disease Diagnosis

7.4 Extent of Exposure

Subjects' extent of BMS-986158 exposure will be characterized using the number of subjects exposed, and the duration of exposure by the BMS-986158 dose levels assigned. Analyses in this section will be performed using the All Treated population.

Three BMS-986158 dosing schedules in Part 1 will be described: monotherapy single weekly dosing followed by 1) five consecutive daily doses per week, 2) 14 consecutive daily doses followed by 7 days of non-dosing per three week period, 3) 7 consecutive daily doses followed by 14 days of non-dosing per three week period. BMS-986158 schedule A will be administered in Part 2 initial expansion as BMS-986158 Monotherapy.

Extent of exposure to BMS-986158 will be characterized by the number of oral dosings, duration of therapy, cumulative exposure, and absolute and relative dose intensity.

7.4.1 Study Therapy

7.4.1.1 Therapy with BMS-986158

Summary 1:

Descriptive statistics will be provided by treatment and overall for the following.

- Number (%) of treated subjects exposed for specified periods of time such as less than or equal to 1 week, more than 1 but less than 4 weeks, etc.

Summary 2:

Descriptive statistics will be provided by treatment and overall for the following.

- **Number of actual BMS-986158 doses**
- **BMS-986158 Duration of therapy (weeks)**
  - The (last dosing date - the first dosing date + DI) / 7, where DI is the dosing interval between the end of the scheduled dose(s) and the start of the next dose(s) in days for the study part and dosing schedule(s) administered; the denominator (7) scales the duration to units of weeks.
  - As Part 1 consists of a single dose delivered in the first 7 days (Cycle 1), without plan to be repeated, a dosing interval in this schedule is not defined, and Part 1 Cycle 1 will not be included in the summary of the exposure.
  - **Dosing Interval (DI)** number of days between planned set of doses per a schedule is:
    - Part 1 and Part 2, while "on" dose during the "on cycle", DI=1 day
    - Part 1, Schedule A, Cycle 2 and beyond, and Part 2, Schedule A: (5 single daily doses followed by 2 days of no dosing per week), after 4th consecutive dose for 7 day cycle, DI=2 days

  - Part 1, Schedule B (Three Week dosing schedule), after 13th consecutive dose for 14 day cycle, DI=7 days
  - Part 1, Schedule C (Three Week dosing schedule), after 6th consecutive dose for 7 day cycle, DI=14 days
- The duration of therapy will be adjusted for subjects who are known to have died prior to receiving the next dose by using instead of DI the number of days between the death date and the last dose date. For subjects who discontinued or were lost to follow-up, DI will be
  - Parts 1, 2, using Schedule A, DI= 1 day if they received <=3 of the 5 doses, and DI= 2 if they received 4 or 5 doses.
  - Part 1, using Schedule B, DI will still be set to 7 days if discontinued or lost to followup.
  - Part 1, using Schedule C, DI will still be set to 14 days if discontinued or lost to followup.
- Duration of therapy for subjects admitted to Study Part 1 will be left censored to exclude the single dose administered on Cycle 1 Day 1. The dose administered on Cycle 2 Day 1 will be considered to establish the date of first dose for dose intensity and relative dose intensity calculation.

- **BMS-986158 cumulative dose (mg)** is the sum of the actual doses administered to a subject
- **BMS-986158 dose intensity (mg/week)** per subject is the ratio of the cumulative dose (mg) to the duration of therapy (weeks) for the study part to which the subject is enrolled:
- **BMS-986158 relative dose intensity (%)** is the ratio of the dose intensity (mg/week) to the planned dose level per week and is scaled to units of percent for presentation.
  - Relative dose intensity will be summarized using categories: <50%; 50 - < 70%; 70 - < 90%; 90 - < 110%; ≥ 110%

Listing:

- Drug administration of BMS-986158
- Duration of therapy (weeks) , cumulative dosing, dosing intensity, and relative dose intensity

7.4.1.2 Modification of BMS-986158 Therapy

Summary:

- Descriptive statistics will be provided by treatment and overall for:
  - Number (%) of subjects with dose modifications with reasons.

7.4.2 Concomitant Medications

Concomitant medications, defined as medications other than study medications which are taken at any time on-treatment (i.e. on or after the first day of study therapy and within 100 days following the last dose of study therapy), will be coded using the UMC WHO Drug Global Dictionary. Concomitant medication by-subject listing will be provided.

7.5 Efficacy

- PCWG3 criteria is intended for Part 2 subjects and not Part 1 subjects. Lugano and PCWG3 criteria will be used if relevant data is available.
- The primary efficacy analyses will be performed on All Treated Population for the final analysis. Efficacy analyses based on the Response-evaluable Population may be performed as supportive analyses. If the majority of All Treated Population is included in Response-evaluable Population, limited efficacy analyses will be performed on Response-evaluable Population (e.g., ORR).
- For interim analyses when the minimum follow-up period is less than sufficient to warrant adequate interpretation of the result, efficacy analyses may be performed on Response-evaluable Population.
- Efficacy results will be presented by treatment and overall, for each tumor type. For efficacy endpoints, treatment comprises dose schedule.
- Efficacy will be reported based on investigator BOR. Investigator reported CR or PR was not always confirmed by a second scan. Therefore, ORR summaries will be presented regardless of confirmation.

Time-to-event distributions (e.g. for progression free survival, [redacted] and duration of response) will be estimated using K-M methodology. When appropriate, the median along with 95% CI will be provided using Brookmeyer and Crowley methodology[59] (i.e., using log-log transformations for the construction of confidence intervals).

Rates at fixed time points (e.g. PFSR at 24 weeks or OS at 12 months) will be derived from the K-M estimates and corresponding confidence intervals will be derived based on the Greenwood formula. Confidence intervals for binomial proportions will be derived using the Clopper-Pearson method. Additional time points will be considered based on data availability.

Summary:

The following will be summarized by treatment and overall, for each tumor type.

- ORR with corresponding 2-sided 95% CI based on Clopper-Pearson method along with each category of BOR
- Duration of response (DOR) with median (95% CI using the log-log transformation method) and range (min, max) by K-M method. The number of subjects still in response at the time of database lock will be indicated. If the number of responders per tumor type is too small (e.g., 5 or less confirmed CR or PR in a tumor type), DOR will not be presented.
- PFS with median (95% CI) and range (min, max) by K-M method. The number of subjects still progression free at the time of database lock will be indicated.
- PFSR at specified timepoints (e.g., Week 24, Week 48) by K-M method using the Greenwood formula for confidence intervals

[redacted]

Figure:

- Percent change from baseline in target lesions over time (aka spider plot)

- Best change in baseline target lesions (aka waterfall plot)
- K-M plot of duration of response for responders only (if sufficient number of responders, i.e. more than 5 confirmed CR or PR in a tumor type)
- Swimmer plot of time to response, duration of response and tumor progression for all participants
- K-M plot of PFS
- K-M plot of OS

Listing:

The following will be listed by treatment and tumor type as appropriate.

- Tumor lesion measurements
- Tumor evaluation at each visit
- Participant level efficacy for all treated participants- tumor best overall response (BOR), best change in tumor burden, PFS, death indicator
- Duration of response for responders - BOR, time to response, time on therapy, response duration

[redacted]

- Subsequent therapy

7.6 Safety

Analyses of safety will be based on All Treated population and will be presented principally by treatment ("as treated") and overall unless otherwise indicated. Deaths will be summarized by schedule.

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 to be drug-related.

Listing of AEs will include all enrolled subjects as well as SAEs and deaths, which are collected pretreatment. Summaries of AEs will include (1) events occurring from the first dose date to 30 days (inclusive) after the last dose of BMS-986158 monotherapy for subjects who are off study treatment and (2) all events occurring from first dose date for subjects who are still on study medication. AEs and treatment-related AEs will be tabulated by descending frequency of SOC and descending frequency of PT within each SOC, unless specified otherwise.

When reporting adverse events by CTC grade, summary tables will be provided based on events' worst CTC grade (independently 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.

Unless otherwise specified, the AE summary tables will be restricted to on-treatment events regardless of the causality.

The analysis of laboratory results will be based on the All Treated population in participants with data. Laboratory results will be categorized according to NCI CTCAE (version 4.03) grade. Baseline is defined as the last non-missing measurement prior to the first dosing date and time. Summaries of laboratory results include baseline and (1) post-baseline results up to 30 days (inclusive) after the last dose of BMS-986158 monotherapy for subjects who are off study treatment and (2) all available post-baseline results for subjects who are still on study medication. Vital signs and clinical laboratory test results will be listed and summarized by treatment. Any significant physical examination findings and clinical laboratory results will be listed. ECG readings will be evaluated by the investigator and abnormalities, if present, will be listed.

7.6.1 Deaths

- **Summary**:

All deaths during the study and within 30 days after the last dose of BMS-986158 monotherapy will be summarized for causes of death by schedule.

- **Listing**:

All recorded deaths for All Enrolled subjects will be listed.

7.6.2 Serious Adverse Events

- Overall summary of SAEs and treatment-related SAEs by worst CTC grade will be presented by SOC/PT. By- participant SAE listing will be provided for the All Enrolled population.
- **Summary**:
- Overall summary of SAEs by worst CTC grade (grade 1, 2, 3, 4, 3-4, 5, unknown) presented by SOC/PT
- Overall summary of treatment-related SAEs by worst CTC grade (Grade 1, 2, 3, 4, 3-4, 5) presented by SOC/PT
- **Listing**:

A by-subject SAE listing will be provided for the All Enrolled population.

7.6.3 Adverse Events Leading to Discontinuation of Study Therapy

Adverse events leading to study drug discontinuation are AEs with action taken classification of "Drug was discontinued". Overall summary of AEs leading to discontinuation and treatment-related AEs leading to discontinuation by worst CTC grade will be presented by SOC/PT. By-participant AEs leading to discontinuation listing will be provided.

Summary:

- Overall summary of AEs leading to discontinuation by worst CTC grade (grade 1, 2, 3, 4, 3-4, 5, unknown) presented by SOC/PT
- Overall summary of treatment-related AEs leading to discontinuation by worst CTC grade (any grade, grade 3-4, grade 5) presented by SOC/PT.
- **Listing**:
- A by-participant AEs leading to discontinuation listing will be provided.

7.6.4 Adverse Events Leading to Dose Modification or Delay

AEs leading to dose delay/reduction/interruption will be summarized by treatment and overall if sufficient data are available.

Summary:

- Overall summary of AEs leading to dose reduction by worst CTC grade (grade 1, 2, 3, 4, 3-4, 5, unknown) presented by SOC/PT.
- **Listing**:
- A by-subject listing of AEs leading to dose delay/reduction/interruption will be provided.

7.6.5 Overall Adverse Events

- AEs and drug-related AEs will be tabulated by descending frequency of SOC and descending frequency of PT within each SOC.

Summary:

- Overall summary of any AEs by worst CTC grade (grade 1, 2, 3, 4, 3-4, 5, unknown) presented by SOC/PT
- Overall summary of treatment-related AEs by worst CTC grade (grade 1, 2, 3, 4, 3-4, 5) presented by SOC/PT.
- Overall summary of AEs occurring in at least 5% of subjects across treatments. This table will be restricted to events with an incidence greater or equal to 5% in any treatment group.
- Overall summary of non-serious AEs presented by SC/PT. This table will be restricted to events with an incidence greater or equal to 5% in any treatment group.
- **Listing**:
- All recorded Adverse Events occurring in the screening, on-treatment, and clinical follow-up periods will be listed.

7.6.6 Multiple Events

Analyses that take into account the multiple occurrences of a given adverse event will be conducted. In order to prepare these analyses, the CRF data will be processed according to standard BMS algorithms[60] 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 subject-years of exposure. This analysis will take into account all on-treatment events (allowing more than 1 event per subject) and the total duration of exposure. The subject-years exposure will be computed as the sum over the subjects' exposure expressed in years where the duration of exposure is defined as:

- Date of last dose of study treatment - date of first dose of study treatment + 3*0+1* days, for subject who are off study treatment and were followed at least 3*0* days after last dose of study medication. Units for this calculation are subject-days.
- Last known date alive - date of first dose of study medication +1, for subjects who are still on-treatment or who are off study treatment and were followed less than 3*0* days after last dose of study medication. Units for this calculation are subject-days.

- Subject-years are defined as the sum of subject-days divided by 365.25 and are rounded to a single decimal place of precision.

Summary:

The following summary tables will be provided by treatment and overall and may also be provided by schedule.

- Total number and rate (exposure adjusted, i.e., patient-year event rate) of occurrences for all AEs

Listing:

- Unique instances of all AEs, i.e., after duplicates have been eliminated and overlapping and contiguous occurrences of the same event (i.e., having the same PT) have been collapsed into the worst severity observed.

7.6.7 Clinical Laboratory Evaluations

Clinical laboratory data will be analyzed using International System of Units (SI). Analyses will be repeated using US conventional units.

Summary:
The number (%) of subjects with the following will be summarized by treatment and overall, if appropriate, using the worst CTC grade on-treatment per subject.

- Post-baseline grade
- Grade change from baseline
- Descriptive statistics of laboratory test result and their changes from baseline

Listing:

A by-subject listing of these laboratory parameters will be provided. Laboratory abnormality criteria and laboratory results outside of normal range will be listed.

7.6.7.1 Abnormal Hepatic Test

Summary:

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

- ALT or AST > 3 x ULN, > 5 x ULN, > 10 x ULN and > 20 x ULN
- Total bilirubin > 2 x ULN
- Concurrent (within 1 day) ALT or AST > 3 x ULN and total bilirubin > 2 x ULN
- Concurrent (within 30 days) ALT or AST > 3 x ULN and total bilirubin > 2 x ULN

Figure:

- Scatter plot of Total bilirubin peak vs. AST peak
- Scatter plot of Total bilirubin peak vs. ALT peak

On-treatment peak total bilirubin and on-treatment peak AST/ALT within 30 days of liver testing will be plotted.

Listing:

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

7.6.8 Vital Signs, and Other Safety Evaluation

Summary:

Vital sign measurements will be summarized by treatment.

- Vital signs summary and changes from baseline

Listing:

- Vital signs
- Echocardiogram measurements and findings
- Physical examination findings

7.6.9 DLT information

Available DLT data as per the database will be listed.

7.7 Pharmacokinetics

All available plasma/serum concentration-time data from participants who receive BMS-986158 will be reported. The Pharmacokinetic (PK) population will be used for all listings. Evaluable PK population will be used for summaries and statistical analyses. Only Part 1 participants will be summarized unless there are more than 5 participants in Part 2.

7.7.1 Pharmacokinetic Concentrations

Participant concentration-time profiles will be listed and summarized by treatment and nominal collection time for BMS-986158 and Metabolite BMT-161485. Plot of individual concentration profiles over time will be provided. Plots of mean (+SD) concentration profiles versus time will be presented by treatment (ie, dose schedule, dose and visit) on the same plot. The concentration-time data will be handled by CPAR&O group.

7.7.2 Pharmacokinetic Parameters

PK parameters for plasma concentrations from subjects who receive BMS-986158 will be calculated using non-compartmental analysis. All available plasma concentration-time data from subjects who receive BMS-986158 will be reported. All available derived PK parameter values will be included in the PK dataset and reported, but only subjects with adequate PK profiles will be included in summary statistics and statistical analysis.

PK parameters will be provided separately for parent compound BMS-986158 and Metabolite BMT-161485. In general, summary statistics will be tabulated for the pharmacokinetics parameters by dose schedule, dose and visit for each select analyte. To assess the attainment of steady state, geometric mean Ctrough values will be plotted versus study day by dose schedule and dose.

Effective plasma half life, T-HALFeff will be calculated for Accumulation Index (AI) values of AUC(0-24). The formula is as shown in Figure 7.7.2-1 below.

Figure 7.7.2-1: Effective Half Life

$$Effective\ T-HALF = \frac{\tau \ln(2)}{\ln\left[\frac{AI}{AI-1}\right]}$$

, where τ is the length of one dosing interval in hours, AI>1.

Summary:

- Summary statistics will be provided for all parameters listed in Section 4.2.2 by treatment, for each dosing schedule.
- Geometric means and coefficients of variation will be presented for all parameters (including Cmax, AUC(0-T), AUC(0-24), AUC(INF), C24, CLT/F, AI_AUC, and T-HALFeff except for Tmax). Median, minimum, and maximum will be presented for Tmax.
- Dose proportionality analysis for Cmax, AUC(INF) (single dose only) and AUC(0-24) will be presented by analyte as warranted by completeness of the data.
- Means and standard deviations will be presented for other PK parameters like T-HALF.
- **Figure:**
- Plot of geometric mean Ctrough vs. study day will be presented by dose level for each dose schedule.
- Scatter plot of AUC(INF) vs. dose level in log-log scale by dose schedule and superposed with the regression line from the power model
- Scatter plot of AUC(0-24) vs. dose level in log-log scale by dose schedule and superposed with the regression line from the power model
- Scatter plot of Cmax vs. dose level in log-log scale by dose schedule and superposed with the regression line from the power model
- **Listing**:
- All individual PK parameters will be listed including any exclusions and reasons for exclusion from summaries.

7.7.3 Ctrough

Ctrough values will be listed and summarized by dose and time point. To evaluate the steady state of BMS-986158 concentration in the body, the geometric means of Ctrough vs. cycle will be plotted by dose level for each dose schedule.

7.7.4 Dose Proportionality

To assess the dose proportionality, the power model described by Gough et al.[61]

$$\text{PK Parameter} = A*\text{Dose}^{\beta}$$

will be estimated by the simple linear regression of the natural log of the PK Parameter (Cmax, AUC) on the natural log of Dose:

$$E[\log(\text{PK Parameter})|\ \text{Dose}] = \alpha + \beta*\log(\text{Dose}).$$

A slope (β) equal to 1 would indicate perfect dose proportionality. For each PK parameters (Cmax, AUC), the point estimates and 90% CI of the slopes will be provided.

Plots of individual BMS-986158 PK parameter (Cmax, AUC) values versus dose with fitted regression line on a log-log scale will be presented.

Note that dose proportionality analysis may not be performed if there are too few different dose levels (e.g. <=2) under some dose schedule.

As MAD studies are neither optimally designed nor powered to confirm the presence or absence of meaningful departures from dose proportionality, these results should be interpreted with caution. The estimated regression line will be overlaid on the individual points in the corresponding scatter plot. For MAD studies, these dose proportionality assessments can be done for each day of serial PK sampling, but, unless there are differences from one day to another, only the assessments on the last such day will be discussed.

7.9 Electrocardiogram (ECG)

All of the available ECG parameter values, single and triplicates, from each participant will be included in the ECG data set. Although all recorded ECG parameter values will be included in the data listings, only ECG parameters with scheduled visits will be included in the summary statistics, graphs, and statistical analysis. Only Part 1 participants will be summarized unless there are more than 5 participants in Part 2.

The triplicate measurements will be averaged at each scheduled measurement timepoints. Baseline values are defined as the average of last recorded triplicate values prior to the first dosing. If triplicate values are not the last recorded values prior to the first dosing, the last recorded value

prior to the first dosing will be used as baseline. For ECG parameters such as QTcF, QT, QTcB, heart rate (HR), QRS, and PR, summary measures (n, mean, standard deviation, median, minimum, and maximum) will be provided.

Summary:

ECG measurements will be summarized by treatment and study day, for each dose schedule separately and across dose schedule.

- ECG measurements will be summarized as follows:
  - The frequency distribution of subjects' maximum recorded post-dose QTcF, PR, QRS, ΔQTcF will be summarized and tabulated for the following ranges:
    - For QTcF: QTcF ≤ 450 msec, 450 msec < QTcF ≤ 480 msec, 480 msec < QTcF ≤ 500 msec, QTcF > 500 msec
    - For PR: PR ≤ 200 msec, PR > 200 msec
    - For QRS: QRS ≤ 120 msec, QRS > 120 msec
    - For ΔQTcF: ΔQTcF ≤ 30 msec, 30 msec < ΔQTcF ≤ 60 msec, ΔQTcF > 60 msec
  - The frequency distribution of subjects' maximum recorded post-dose HR and ΔHR and of minimum recorded post-dose HR and ΔHR will be summarized and tabulated for the following ranges:
    - HR and ΔHR: HR Value >100 bpm with ΔHR > 30 bpm or
    - HR value < 55 bpm with ΔHR < –15 bpm
  - Summary statistics (n, mean, standard deviation, median, minimum, and maximum) will be presented for each ECG parameter and the corresponding changes from baseline by treatment and time point.
  - Linear mixed effects regression model of ΔQTcF vs. BMS-986158 will be provided across dose schedules at Cycle 1 Day 1 (single dose), and may also be provided separately by dose schedule at steady state. The same model will be repeated on the active metabolite plasma concentrations if the latter is sufficiently measured
    - The plot of ΔQTcF versus drug concentrations will include the estimated linear regression taken from the results of fitting a mixed effect model, if available. Mixed effect model with random intercept and slope will be used to explore the relationship between the ΔQTcF and plasma concentration data. The following SAS® code is recommended.

      proc mixed data=Data Set Name method=reml;
      class usubjid;
      model ΔQTcF =concentration/solution cl alpha=0.10 ddfm=kenwardroger;
      random intercept concentration/subject=usubjid type=un;
    - Use of option "empirical" will provide more robust estimate; Start with "type=un", and then examine the covariance structure and adjust to reduce the number of parameters to be estimated, as needed. If, however, the SAS log file contains the "Note: Estimated G matrix is not positive definite.", then the variances of the random intercepts or slopes may be so small that one or both should be replaced by fixed effects, i.e., dropped from

the random statement. The point estimate and 90% confidence interval for the slope will be reported within the CSR text

Figure:

- ECG measures
  - Scatter plot and regression of ΔQTcF on BMS-986158 concentration (with fitted line) on each study day. Scatter plots of QTcF, HR, ΔHR on BMS-986158 concentration on each study day.

Listing:

- ECG measures
  - Individual QTcF, PR, QRS, HR, ΔHR, and ΔQTcF values will be listed.
- ECG abnormalities

8 CONVENTIONS

8.1 Date Conventions

The following conventions may be used for imputing missing or partial dates for analyses requiring dates:

AE onset date following Adverse Event Domain Requirements Specification[62]

AE resolution/end date (these conventions may change)

- If only the day of the month is missing, the last day of the month will be used to replace the missing day. If the imputed date is after the death date or the last known alive date, then the latest known alive date or death date is considered as the resolution date.
- If the day and month are missing or a date is completely missing, it will be considered as missing

Non-study medication date following Non-Study Medication Domain Requirements Specification[63].

- Missing and partial radiotherapy and surgery dates will be imputed using algorithm described in APPENDIX 1.

Death date

- 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 and the maximum will be considered as the death date.
- If month or the year is missing, the death date will be imputed as the last known date alive.
- 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.

Disease progression date

- 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 case of 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 dates, the following conventions apply:

- 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-to onset, time-to resolution) will be calculated as follows:

Duration = (Last date - first date + 1)

Last known alive date will be defined based on all appropriate dates collected on the CRF.

All statistical analyses will be carried out using SAS (Statistical Analysis System software, SAS Institute, North Carolina, USA) unless otherwise noted.

8.2 Recurrent Events

In order to prepare adverse events for recurrent or multiple event analyses (Section 7.6.6), the CRF data will be processed according to standard BMS algorithms[64] 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 subject-years of exposure. This analysis will take into account all on-treatment events (allowing more than 1 event per subject) and the total duration of exposure. The subject-years exposure will be computed as the sum over the subjects' exposure expressed in years where the duration of exposure is defined as:

- Date of last dose of study treatment - date of first dose of study treatment + 100 (or *30* for monotherapy)+*1* days, for subject who are off study treatment and were followed at least 100 (or *30* for monotherapy) days after last dose of study medication. Units for this calculation are subject-days.
- Last known date alive - date of first dose of study medication +1, for subjects who are still on-treatment or who are off study treatment and were followed less than 100 (or *30* for monotherapy) days after last dose of study medication. Units for this calculation are subject-days.

Subject-years are defined as the sum of subject-days divided by 365.25 and are rounded to a single decimal place of precision.

8.3 Pharmacokinetic Summaries

In-text Tables

For in-text pharmacokinetic tables, coefficient of variation (%CV) will be reported as integers. For other statistics except for standard deviations, values of 100 or higher will be presented as integers, values of 10 - <100 will be displayed to one decimal place, and values of 1 - < 10 will be displayed to two decimal places. Values less than 1 will be displayed to three decimal places. Ratios will also be displayed to three decimal places. Standard deviations will be reported to a precision of 1 decimal place more than the mean.

Handling of Non-Quantifiable Concentrations

For the summaries of concentration-time data, concentrations that are less than the lower limit of quantification (LLOQ) should be displayed as "< LLOQ" in the listings and be treated as missing in summary tables and plots. For the purpose of calculating PK parameters, other than Ctrough, pre-dose concentrations that are less than LLOQ and concentrations prior to the first quantifiable concentration that are less than LLOQ will be set to zero, and all other concentrations less than LLOQ will be set to missing.

Summary statistics for Ctrough concentrations, analyses of PD-concentrations and ECG-concentrations relationships will be calculated by imputing values less than LLOQ as ½ * LLOQ. This imputation is done for Ctrough concentrations because it is treated like a PK parameter; the imputation is not done for Day 1 pre-dose concentrations. Individual Ctrough listings will display these concentrations as "< LLOQ."

All available concentration-time data and derived pharmacokinetic parameter values will be included in the PK data set and listed accordingly.

PK Exclusions

PK Analysis, Reporting, and Exclusion criteria should following the BMS PK Harmonization document Version 4.0. Specific guideline for exclusionary criteria for half-life and how other PK parameters are affected for exclusion is under section 9.2 of the BMS PK Harmonization document.

Exclusion of one or more parameters or the entire dataset may be considered due to incomplete profile such as AUC(INF) or when T-HALF cannot be reliably calculated, or there is no sample around the suspected Cmax.

9 CONTENT OF REPORTS

One or more interim analysis reports may be prepared. [redacted] No formal adjustments for multiplicity will be employed.

The clinical study report will be prepared to address the clinical objectives and endpoints identified in the protocol following closure and locking of the clinical database (CDBL).

All analyses describe in this SAP will be included in final Clinical Study Report (per data availability). Refer to the Data Presentation Plan for mock-ups of all tables and listings.

10 DOCUMENT HISTORY

The history of this document is as shown below in Table 10-1 below.

Table 10-1: Document History

Version Number	Author(s)	Description
1.0	[redacted]	Initial approved version
2.0	[redacted]	Revisions to align with revprot02-revprot07 Scope of this SAP is limited to Part 1 and Part 2 Initial expansion

APPENDIX 1 MISSING AND PARTIAL RADIOTHERAPY AND SURGERY DATES IMPUTATION ALGORITHMS

Procedures – Imputation Rules.

If reported procedure start date is a full valid date then set start date equal to the date part of procedure start date.

In case of partial date use imputation rules described below:

- If only day is missing then
  - If month and year of procedure match month and year of first dose date then impute as date of first dose;
  - If month and year of procedure don't match month and year of first dose date then impute as first day of that month and year.
- If both day and month are missing, then impute as maximum between 01JAN of the year and date of the first dose;
- If date is completely missing or invalid then leave missing.

Note: Imputation is not applicable to data where start date is not collected (for example "PRIOR RADIOTHERAPY" CRF). Set start date to missing in this case.

If reported end date is a full valid date then set end date equal to the date part of the reported end date.

In case of partial date use imputation rules described below:

- If reported end date is partial then set end date equal to the last possible reported end date based on the partial entered reported end date.
- If reported end date is missing, continuing, unknown or invalid then set end date equal to the most recent database extraction date.

If end date was imputed then compare end date to the death date or last known alive date if subject is not dead. If posterior then end date should be imputed to death date (or last known alive date if subject not dead).

Note: Imputation of partial dates only applies to data entered on "RADIOTHERAPY" CRF page. For other CRF pages in case of partial dates set end date to missing.

Surgeries – Imputation Rules.

If reported surgery date is a full valid date then set start date equal to the date part of surgery date.

In case of partial date, use one of the two imputation rules described below:

A. For data collected on "PRIOR SURGERY RELATED TO CANCER" CRF page:

- If only day is missing then impute as the first day of the month;
- If both day and month are missing then then impute as 01JAN of the year;

- If date is completely missing or invalid then leave missing.

B. For data collected on other CRF pages (deemed to be on-treatment/subsequent surgeries):

- If only day is missing then
  - If month and year of surgery match month and year of first dose date then impute the missing date as the date of first dose;
  - If month and year of surgery don't match month and year of first dose date then impute as first day of that month and year;
- If both day and month are missing then impute as maximum between 01JAN of the year and date of the first dose;
- If date is completely missing or invalid then leave missing.

11 REFERENCES

1 http://seer.cancer.gov/

2 Haynes SR, et al. The bromodomain: a conserved sequence found in human, Drosophila and yeast proteins. Nucl Acids Res 1992; 20:2603

3 Jeanmougin F, Wurtz JM, Le Douarin B, et al. The bromodomain revisited. Trends Biochem Sci 1997; 22:151–153.

4 Dey A, Nishiyama A, Karpova T, et al. Brd4 marks select genes on mitotic chromatin and directs postmitotic transcription. Mol. Biol. Cell 2009; 20, 4899–4909.

5 Florence B, Faller DV. You bet-cha: a novel family of transcriptional regulators. Front Biosci 2001; 6:D1008–D1018.

6 Rahman S, Sowa ME, Ottinger M, et al. The Brd4 extraterminal domain confers transcription activation independent of pTEFb by recruiting multiple proteins, including NSD3. Mol Cell Biol 2011; 31, 2641–2652.

7 French CA, et al. BRD4-NUT fusion oncogene: a novel mechanism in aggressive carcinoma. Cancer Res 2003; 63:304–307.

8 Dawson MA, et al. Inhibition of BET recruitment to chromatin as an effective treatment for MLL-fusion leukaemia. Nature 2011; 478(7370):529–533.

9 Mertz JA, et al. Targeting MYC dependence in cancer by inhibiting BET bromodomains. Proc Natl Acad Sci USA 2011; 108(40):16669–16674.

10 Aristeidis C, Valentina C, Goudevenou K, et al. Potent anti-myeloma activity of the novel bromodomain inhibitors I-BET151 and I-BET762. Blood First Edition Paper, prepublished online December 13, 2013.

11 Lockwood WW, Zejnullahu K, Bradner JE, et al. Sensitivity of human lung adenocarcinoma cell lines to targeted inhibition of BET epigenetic signaling proteins. Proc Natl Acad Sci USA 2012; 109(47):19408–19413.

12 Wyce A, et al. BET inhibition silences expression of MYCN and BCL2 and induces cytotoxicity in neuroblastoma tumor models. PLoS ONE 2013; 8(8):e72967.

13 Delmore JE1, Issa GC, Lemieux ME, et al. BET bromodomain inhibition as a therapeutic strategy to target c-Myc. Cell. 2011;146(6):904-17.

14 Dang CV. MYC on the path to cancer. Cell 2012;149(1):22-35.

15 Vita M, Henriksson M. The Myc oncoprotein as a therapeutic target for human cancer. Semin Cancer Biol. 2006; 16(4):318-30.

16 Ponzielli R, Katz S, Barsyte-Lovejoy D, et al. Cancer therapeutics: Targeting the dark side of Myc. Eur J of Cancer 2005; 41(16): 2485–2501.

[17] Lovén J, Hoke HA, Lin CY, et al. Selective inhibition of tumor oncogenes by disruption of super-enhancers. Cell 2013;153(2):320-34.

[18] Chapuy B, McKeown MR, Lin CY, et al. Discovery and Characterization of Super-Enhancer-Associated Dependencies in Diffuse Large B Cell Lymphoma Cancer Cell, 2014; 25(4) 14: 545-546.

[19] Liu J, Hamrouni A, Wolowiec D, Coiteux V, Kuliczkowski K, Hetuin D, Saudemont A, Quesnel B. Plasma cells from multiple myeloma patients express B7-H1 (PD-L1) and increase expression after stimulation with IFN-{gamma} and TLR ligands via a MyD88-, TRAF6-, and MEK-dependent pathway. Blood 2007;110:296-304.

[20] Lu C, Redd PS, Lee JR Savage N, Liu K The expression profiles and regulation of PD-L1 in tumor-induced myeloid-derived suppressor cells. OncoImmunology 2016 Oct 20;5(12):e1247135.

[21] Hogg SJ, Vervoort SJ, Deswal S, Ott CJ, Li J, Cluse LA, Beavis PA, Darcy PK, Martin BP, Spencer A, Traunbauer AK, Sadovnik I, Bauer K, Valent P, Bradner JE, Zuber J, Shortt J, Johnstone RW. BET-Bromodomain Inhibitors Engage the Host Immune System and Regulate Expression of the Immune Checkpoint Ligand PD-L1. Cell Rep. 2017 Feb 28:18(9):2162-2174.

[22] Pardoll D. Does the immune system see tumors as foreign or self? Annu Rev Immunol. 2003;21:807-39.

[23] Zitvogel L, Tesniere A, Kroemer G. Cancer despite immunosurveillance: immunoselection and immunosubversion. Nat Rev Immunol. 2006;6:715-27.

[24] Dunn GP, Bruce AT, Ikeda H, et al. Cancer immunoediting: from immunosurveillance to tumor escape. Nat Immunol. 2002;3:991-8.

[25] Greenwald RJ, Freeman GH, Sharpe AH. The B7 family revisited. Annu Rev Immunol. 2004;23:515-48.

[26] Berthon C, Raffoux E, Thomas X, et al. Bromodomain inhibitor OTX015 in patients with acute leukaemia: a dose-escalation, phase 1 study. Lancet Haematol. 2016 Apr;3(4):e186-95.

[27] Amorim S, Stathis A, Gleeson M, et al. Bromodomain inhibitor OTX015 in patients with lymphoma or multiple myeloma: a dose-escalation, open-label, pharmacokinetic, phase 1 study. Lancet Haematol. 2016:3(4):e196-204.

[28] Massard C, Penttinen HM, Vjaters E, Bono P, Lietuvietis V, Tammela TL, Vuorela A, Nykänen P, Pohjanjousi P, Snapir A, Fizazi K. Pharmacokinetics, Antitumor Activity, and Safety of ODM-201 in Patients with Chemotherapy-naive Metastatic Castration-resistant Prostate Cancer: An Open-label Phase 1 Study. Eur Urol. 2016 May;69(5):834-40.

[29] Odore E, Lokiec F, Cvitkovic E, Bekradda M, Herait P, Bourdel F, Kahatt C, Raffoux E, Stathis A, Thieblemont C, Quesnel B, Cunningham D, Riveiro ME, Rezaï K. Phase I Population Pharmacokinetic Assessment of the Oral Bromodomain Inhibitor OTX015 in Patients with Haematologic Malignancies. Clin Pharmacokinet 2016;55:397–405.

[30] St. Pierre R and Kadoch C. Mammalian SWI/SNF complexes in cancer: emerging therapeutic opportunities. Curr Opin Genet Dev. 2017 Feb;42:56-67.

[31] The Cancer Genome Atlas, available from http://cancergenome.nih.gov. Accessed Aug 2017.

[32] Wu Q, Lian JB, Stein JL, Stein GS, Nickerson JA, Imbalzano AN. The BRG1 ATPase of human SWI/SNF chromatin remodeling enzymes as a driver of cancer. Epigenomics. 2017 Jun;9(6):919-931.

[33] Shimamura T, Chen Z, Soucheray M, Carretero J, Kikuchi E, Tchaicha JH, Gao Y, Cheng KA, Cohoon TJ, Qi J, Akbay E, Kimmelman AC, Kung AL, Bradner JE, Wong KK. Efficacy of BET bromodomain inhibition in Kras-mutant non-small cell lung cancer. Clin Cancer Res. 2013 Nov 15;19(22):6183-92.

[34] Pérez-Peña J, Serrano-Heras G, Montero JC, Corrales-Sánchez V, Pandiella A, Ocaña A. In Silico Analysis Guides Selection of BET Inhibitors for Triple-Negative Breast Cancer Treatment. Mol Cancer Ther. 2016 Aug;15(8):1823-33.

[35] da Motta LL, Ledaki I, Purshouse K, Haider S, De Bastiani MA, Baban D, Morotti M, Steers G, Wigfield S, Bridges E, Li JL, Knapp S, Ebner D, Klamt F, Harris AL, McIntyre A. The BET inhibitor JQ1 selectively impairs tumour response to hypoxia and downregulates CA9 and angiogenesis in triple negative breast cancer. Oncogene. 2017 Jan 5;36(1):122-132.

[36] Welti J, Sharp A, Yuan W, Dolling K, et al. Targeting bromodomain and extra-terminal (BET) family proteins in castration-resistant prostate cancer. Clin Cancer Res 2018; 24(13):3149-62.

[37] Ennishi D, Mottok A, Ben-Neriah S, Shulha HP, et al. Genetic profiling of MYC and BCL2 in diffuse large B-cell lymphoma determines cell-of-origin-specific clinical impact. Blood 2017;129(20):2760-70.

[38] Blum KA, Abramson J, Maris, Flinn I, et al. A phase I study of CPI-0610, a bromodomain and extra terminal protein (BET) inhibitor in patients with relapsed or refractory lymphoma. Annals of Oncology 2018;29(suppl 3): mdy048.

[39] Gao L, Schwartzman J, Gibbs A, Lisac R, Kleinschmidt R, Wilmot B, Bottomly D, Coleman I, Nelson P, McWeeney S, Alumkal J. Androgen receptor promotes ligand-independent prostate cancer progression through c-Myc upregulation. PLoS One. 2013 May 21;8(5):e63563.

[redacted]

[redacted]

46 Shao Q, Kannan A, Lin Z, et al. BET Protein Inhibitor JQ1 Attenuates Myc-Amplified MCC Tumor Growth In Vivo. Cancer Res. 2014;74(23):7090-102.

47 Bhadury J, Nilsson LM, Muralidharan SV, et al. BET and HDAC inhibitors induce similar genes and biological effects and synergize to kill in Myc-induced murine lymphoma. Proc Natl Acad Sci U S A 2014;111(26):E2721-30.

48 Roderick JE, Tesell J, Shultz LD, et al. c-Myc inhibition prevents leukemia initiation in mice and impairs the growth of relapsed and induction failure pediatric T-ALL cells. Blood. 2014; 123(7):1040-50.

49 Bandopadhayay P, Bergthold G, Nguyen B, et al. BET bromodomain inhibition of MYC-amplified medulloblastoma. Clin Cancer Res. 2014;20(4):912-25.

50 Puissant A, Frumm SM, Alexe G, et al. Targeting MYCN in neuroblastoma by BET bromodomain inhibition. Cancer Discov 2013; 3(3):308-23.

51 Chuk MK, Mulugeta Y, Roth-Cline M, et al. Enrolling adolescents in disease/target appropriate adult oncology clinical trials of investigational agents. Clin Cancer Res. 2017; 23: 9-12.

52 French CA, Kutok JL, Faquin WC, et al. Midline Carcinoma of Children and Young Adults with NUT Rearrangement. 2004, J Clin Oncol 22:4135-4139.

53 Shields CL, Kaliki S, Arepalli S, et al. Uveal melanoma in children and teenagers. Saudi Journal of Ophthal 2013 Jul;27(3):197-201.

54 Indolfi P, Terenziani M, Casale F, et al. Renal cell carcinoma in children: a clinicopathological study. J Clin Oncol. 2003;21:530-535.

55 Kayton ML, He M, Zakowski MF, et al. Primary lung adenocarcinomas in children and adolescents treated for pediatric malignancies. J Thorac Oncol. 2010 Nov;5(11):1764-71.

56 Gualco G, Weiss LM, Harrington WJ Jr, et al. Nodal diffuse large B-cell lymphomas in children and adolescents: immunohistochemical expression patterns and c-MYC translocation in relation to clinical outcome. Am J Surg Pathol. 2009 Dec; 33(12):1815–1822.

57 Mukhtar F, Bofetta P, Risch HA, et al. Survival predictors of Burkitt's lymphoma in children, adults and elderly in the United States during 2000-2013. Int J Cancer. 2017 Apr 1;140(7):1494-1502.

[58] Eisenhauer EA, Therasse P, Bogaerts J, et al. New Response Evaluation Criteria in Solid Tumors: Revised RECIST Guideline (version 1.1). European Journal of Cancer 2009;45:228-247.

[59] Brookmeyer R. and Crowley J. A confidence interval for the median survival time. Biometrics 38:29-41, 1982.

[60] Adverse Event Domain Requirements Specification. Bristol Myers Squibb Co. PRI. Version 2.1. April 23, 2012.

[61] Gough K, Hutchison M, Keene O, Byrom B, Ellis S, Lacey L, McKellar J: Assessment of dose proportionality: Report from the statisticians in the Pharmaceutical Industry/Pharmacokinetics UK Joint Working Party. Drug Information J. 1995; 29: 1039-1048.

[62] Adverse Event Domain Requirements Specification Bristol Myers Squibb Co. PRI. Version 2.3.0 April 23, 2018

[63] Non-Study Medication Domain Requirements Specification Bristol Myers Squibb Co. PRI. Version 2.10.0 April 23, 2018

[64] Adverse Event Domain Requirements Specification. Bristol Myers Squibb Co. PRI. Version 2.1. April 23, 2012.