DF/HCC Protocol #: 19-040

TITLE: Phase 1 Study of the Bromodomain (BRD) and Extra-Terminal Domain (BET) Inhibitors BMS-986158 and BMS-986378 (CC-90010) in Pediatric Cancer

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Agents Supply: BMS-986158 and BMS-986378 (CC-90010) are supplied by Bristol-Myers Squibb.

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IND Sponsor: Steven DuBois, MD MS

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0 SCHEMA
This is an open-label, multicenter, pediatric, dose escalation and expansion phase 1 clinical trial of two BET inhibitors, assessed in two separate arms, each with two cohorts. Arm 1 will investigate BMS-986158 in patients with relapsed or refractory solid tumors or lymphoma. Within Arm 1, Cohort 1A will consist of patients with unselected relapsed or refractory solid tumors or lymphoma, while Cohort 1B will consist of patients with relapsed or refractory solid tumors or lymphoma that have defined molecular features predicted to increase sensitivity to BET inhibition (Table 1.1). Arm 2 will investigate a blood brain barrier penetrant BET inhibitor, BMS-986378 (CC-90010), in patients with relapsed or refractory CNS tumors / CNS metastatic disease. Within Arm 2, Cohort 2A will consist of patients with unselected relapsed or refractory CNS tumors, while Cohort 2B will consist of patients with relapsed or refractory CNS tumors that have defined molecular features predicted to increase sensitivity to BET inhibition (Table 1.2).

Table 1.1: Arm 1 - Cohort 1B enrichment cohort qualifications

<table>
<thead>
<tr>
<th>Arm 1: Enrichment Group</th>
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<tbody>
<tr>
<td>MYCN amplification or high copy number gain</td>
</tr>
<tr>
<td>MYC amplification or high copy number gain</td>
</tr>
<tr>
<td>Translocation involving MYC or MYCN</td>
</tr>
<tr>
<td>Translocation involving BRD3 or BRD4</td>
</tr>
<tr>
<td>BRD4 amplification or high copy number gain</td>
</tr>
<tr>
<td>Histologic diagnosis of NUT midline carcinoma</td>
</tr>
</tbody>
</table>

Table 1.2: Arm 2 - Cohort 2B enrichment cohort qualifications

<table>
<thead>
<tr>
<th>Arm 2: Enrichment Group</th>
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<tbody>
<tr>
<td>MYCN amplification or high copy number gain</td>
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<tr>
<td>MYC amplification or high copy number gain</td>
</tr>
<tr>
<td>Translocation involving MYC or MYCN</td>
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</tr>
<tr>
<td>Histologic diagnosis of NUT midline carcinoma</td>
</tr>
</tbody>
</table>

In Arm 1, patients will receive BMS-986158 monotherapy orally for 5 days on / 2 days off per week for 3 or 4 weeks in 28-day cycles, depending upon assigned dose level.

In Arm 2, patients will receive BMS-986378 (CC-90010) monotherapy orally for 4 days on / 24 days off in 28-day cycles.
In each Arm, patients who meet eligibility criteria will enroll into the main dose finding portion of the study if a treatment slot is available for that Arm, regardless of the patient’s Cohort. Patients who meet the eligibility criteria for either Cohort 1B or 2B are anticipated to be less common, and it is a high priority to allow such patients to enroll even if a treatment slot at the currently evaluated dose level is not available. Patients in Cohort 1B or 2B will enroll at the currently evaluated dose level if there is a slot available in their respective Arm, and otherwise will be able to enroll continuously at one dose level below the currently evaluated dose level of their respective Arm until the recommended pediatric phase 2 dose has been defined.

Once a recommended pediatric phase 2 dose (RP2D) has been defined for Arm 1, an additional 10 patients will enroll to Cohort 1B at the recommended pediatric phase 2 dose, with a minimum of 3 patients with MYCN amplified neuroblastoma to be included in the expansion cohort.

Separately within each Arm, dose escalation will proceed according to a modified continual reassessment method (CRM) utilizing cumulative DLT data from patients treated in Cohorts 1A/1B and 2A/2B, respectively.
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1 OBJECTIVES

1.1 Study Design

This is an open-label, multicenter, pediatric, dose escalation and expansion phase 1 clinical trial of two BET inhibitors, assessed in two separate arms, each with two cohorts. Arm 1 will investigate BMS-986158 in patients with relapsed or refractory solid tumors or lymphoma. Within Arm 1, Cohort 1A will consist of patients with unselected relapsed or refractory solid tumors or lymphoma, while Cohort 1B will consist of patients with relapsed or refractory solid tumors or lymphoma that have defined molecular features predicted to increase sensitivity to BET inhibition (Table 1.1). Arm 2 will investigate a blood brain barrier penetrant BET inhibitor, BMS-986378 (CC-90010), in patients with relapsed or refractory CNS tumors or CNS metastatic disease. Within Arm 2, Cohort 2A will consist of patients with unselected relapsed or refractory CNS tumors, while Cohort 2B will consist of patients with relapsed or refractory CNS tumors that have defined molecular features predicted to increase sensitivity to BET inhibition (Table 1.2).

Table 1.1: Arm 1 - Cohort B enrichment cohort qualifications

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<td>Histologic diagnosis of NUT midline carcinoma</td>
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Table 1.2: Arm 2 - Cohort 2B enrichment cohort qualifications

<table>
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<th>Arm 2: Enrichment Group (primary CNS tumor or known CNS metastases)</th>
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<tr>
<td>MYCN amplification or high copy number gain</td>
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Patients in Arm 1 will receive BMS-986158 monotherapy orally for 5 days on / 2 days off per week for 3 or 4 weeks in 28-day cycles, depending upon assigned dose level.

Patients in Arm 2 will receive BMS-986378 (CC-90010) monotherapy orally for 4 days on / 24 days off in 28-day cycles.

In each Arm, patients who meet eligibility criteria will enroll into the main dose finding portion of the study for that Arm, regardless of the patient’s Cohort, if a treatment slot is available.
Patients who meet the eligibility criteria for either Cohort 1B or 2B are anticipated to be less common and it is a high priority to allow such patients to enroll even if a treatment slot at the currently evaluated dose level is not available. Patients in either Cohort 1B or 2B will enroll at the currently evaluated dose level in their respective Arm if there is a slot available, and otherwise will be able to enroll continuously at one dose level below the currently evaluated dose level of their respective Arm until the recommended pediatric phase 2 dose has been defined.

Once a recommended pediatric phase 2 dose (RP2D) has been defined for Arm 1, an additional 10 patients will enroll to Cohort 1B at the recommended pediatric phase 2 dose, with a minimum of 3 patients with MYCN amplified neuroblastoma to be included in the expansion cohort.

Separately within each Arm, dose escalation on each arm will proceed according to a modified continual reassessment method (CRM) utilizing cumulative DLT data from patients treated in Cohorts 1A/1B and 2A/2B, respectively.
1.2 **Primary Objectives**

1.2.1 To determine the recommended pediatric phase 2 dose of BMS-986158 in children with relapsed or refractory solid tumors or lymphoma

1.2.2 To determine the recommended pediatric phase 2 dose of BMS-986378 (CC-90010) in children with relapsed or refractory CNS tumors or CNS metastatic disease

1.2.3 To describe the toxicities of BMS-986158 in children with relapsed or refractory solid tumors or lymphoma

1.2.4 To describe the toxicities of BMS-986378 (CC-90010) in children with relapsed or refractory CNS tumors or CNS metastatic disease

1.3 **Secondary Objectives**

1.3.1 To describe the objective response rate of BMS-986158

1.3.2 To describe the objective response rate to BMS-986378 (CC-90010)

1.3.3 To describe the pharmacokinetics and pharmacodynamics of BMS-986158 and BMS-986378 (CC-90010)

1.4 **Exploratory Objectives**

1.4.1 To investigate tumor, peripheral blood, and cerebrospinal fluid biomarkers associated with response to BMS-986158 or BMS-986378 (CC-90010)

1.4.2 To bank tumor material, germline DNA, peripheral blood, and cerebrospinal fluid for potential future research for participating subjects who provide additional consent.

2 **BACKGROUND**

2.1 **Relapsed and Refractory Pediatric Cancers**

Outcomes for patients with relapsed or refractory pediatric cancers remain poor. While significant progress has been made in the treatment of many pediatric malignancies at initial presentation, children with relapsed or refractory disease have seen little to no improvement in overall survival (OS). Relapsed and refractory solid tumors continue to herald particularly poor outcomes.  

Given the dismal outcomes of these advanced pediatric malignancies, new therapies are needed to improve outcomes and decrease treatment-related morbidity. Moreover, new approaches that show promise in the relapse setting may inform potential future studies in the newly diagnosed setting.
2.2 Bromodomain (BRD) and Extra-Terminal Domain (BET) Proteins

Bromodomain (BRD) and Extra-Terminal Domain (BET) proteins constitute a family of transcriptional modifiers, including BRD2, BRD3, BRD4, and BRDT. BET proteins are thought to function as epigenetic “readers” that bind acetylated lysines on histone H3 and H4 and thereby impact gene expression. BRD4 has been shown to be particularly critical in regulating transcription at super enhancer-associated genes, which are preferentially downregulated with BET inhibitors. Thus for cancers dependent on super enhancers (such as many tumors driven by Myc family proteins), BET inhibition provides an appealing strategy.

2.3 Role of Bromodomain (BRD) and Extra-Terminal Domain (BET) Proteins in Pediatric Malignancies

A large and growing body of preclinical investigation has identified BET inhibition as a potential therapeutic strategy in a number of pediatric cancers. Much of this work has highlighted the impact of this approach in tumors driven by Myc family proteins, though other tumor types may also be vulnerable to BET inhibition. Many pediatric cancers are genetically simple with mutations in epigenetic regulators serving as the main driver of transformation, suggesting a therapeutic opportunity.

Neuroblastoma: Neuroblastoma is the most common extracranial solid tumor in children. Approximately 16% of neuroblastomas harbor high-level MYCN amplification and the presence of MYCN amplification is associated with an aggressive clinical course. Given the role of MYCN in this disease, some of the earliest work investigating BET inhibition in pediatric indications focused on MYCN amplified neuroblastoma. The Stegmaier laboratory at Dana-Farber evaluated the BET inhibitor compound JQ1 and demonstrated that MYCN amplification was strongly associated with sensitivity to BET inhibition. BET inhibition downregulated the MYCN and its transcriptional program. JQ1 was associated with significant in vitro and in vivo activity, including in the context of a MYCN-driven genetically engineered neuroblastoma mouse model (Figure 1). JQ1 treatment decreased MYCN protein levels.

These findings in MYCN amplified neuroblastoma have been replicated by other groups using clinical grade BET inhibitors (OTX015 and GSK1324726A).

Ewing Sarcoma: Ewing sarcoma is driven by a characteristic fusion, most commonly
EWSR1/FLI1. Efforts to target the fusion directly have been challenging. It has recently been shown that EWSR1/FLI1 and related fusion oncoproteins depend upon BET proteins to alter gene expression patterns.\textsuperscript{8} Not surprisingly then, BET inhibition with JQ1 has been investigated in this context with promising results. In Ewing sarcoma cell lines, JQ1 reduced levels of EWSR1/FLI1 fusion transcript and fusion protein.\textsuperscript{9} JQ1 treatment was further associated with reduced viability of Ewing sarcoma cells \textit{in vitro} and reduced tumor growth in xenograft models \textit{in vivo}. This degree of activity was seen by two other groups who evaluated JQ1 in Ewing sarcoma preclinical experiments,\textsuperscript{10,11} including one group who highlighted a potential role for BET inhibition in combination with PI3K inhibition in this disease.\textsuperscript{11}

Alveolar Rhabdomyosarcoma: One group has investigated the role of BRD4 in the context of alveolar rhabdomyosarcoma driven by PAX3/FOXO1 translocation. They demonstrate that PAX3/FOXO1 is dependent upon BRD4 to mediate its transcriptional program. Treatment of PAX3/FOXO1-positive mouse rhabdomyosarcoma xenografts with JQ1 resulted in robust reductions in tumor volumes in this aggressive disease (Figure 2).\textsuperscript{12}

Other Solid Tumors: NUT midline carcinomas are aggressive tumors affecting children and young adults.\textsuperscript{13} These tumors are most commonly driven by translocations involving BRD4, which provided an ideal context for one of the first preclinical investigations of BET inhibition was in this context. Treatment with JQ1 abrogated the growth of NUT midline carcinoma \textit{in vitro} and \textit{in vivo}.\textsuperscript{14} These results have now been recapitulated in the clinic\textsuperscript{15}, though no clinical data are yet available on the use of BET inhibitors in children with these cancers.

At least two groups have investigated BET inhibition in osteosarcoma, with preclinical evidence of monotherapy antitumor activity using JQ1.\textsuperscript{16,17} In addition, these groups investigated potential combination strategies and identified additive or synergistic activity in combination with doxorubicin, rapamycin, or dinaciclib.

A recent report has also demonstrated that JQ1 is active in malignant rhabdoid tumors, which characteristically harbor inactivating mutations in SMARCB1.\textsuperscript{18} Moreover, synergistic activity was observed in combination with a CDK9 inhibitor. Whether these findings will be replicated in other tumors with SMARCB1 loss is not yet known.

Lymphoma: The main subtypes of non-Hodgkin lymphoma in pediatrics are diffuse large B cell lymphoma (DLBCL), Burkitt lymphoma, T cell lymphoblastic lymphoma, and anaplastic large cell lymphoma. BET inhibition has shown preclinical activity in each of these diseases and clinical activity in DLBCL.\textsuperscript{19-26} Specifically, a phase 1 trial of OTX015 included 33 adults with
lymphoma.\textsuperscript{19} Three patients with DLBCL had objective responses and two additional patients with DLBCL had evidence of clinical activity.

CNS Tumors: BET inhibition has shown promise in a number of pediatric CNS tumor models. For example, two groups have shown that JQ1 has \textit{in vitro} and \textit{in vivo} activity in medulloblastoma models with MYC amplification.\textsuperscript{27,28} As in MYCN amplified neuroblastoma, JQ1 decreased MYC protein levels. JQ1 has also demonstrated activity in another aggressive, embryonal brain tumor atypical teratoid rhabdoid tumors\textsuperscript{29}. Furthermore, BET inhibition has been reported by two groups to have significant antitumor activity in preclinical models of diffuse intrinsic pontine glioma\textsuperscript{30,31}, a uniformly fatal pediatric CNS tumor.

2.4 BMS-986158

2.4.1 BMS-986158 Nonclinical Studies

BMS-986158 is an oral investigational BET inhibitor. BMS-986158 inhibits binding to BRD4 with an IC\textsubscript{50} in the low nanomolar range. Likewise, BMS-986158 reduces MYC expression at exposures < 1 nM in a multiple myeloma cell line. The agent shows good oral bioavailability and is highly protein bound in nonclinical studies. BMS-986158 undergoes hydroxylation as its major metabolic pathway and biliary excretion of metabolites is the predominant route of excretion. CYP3A4 and CYP3A5 appear to play an important role in metabolizing BMS-986158 and therefore inhibitors or inducers of these enzymes have the potential to alter the metabolism of BMS-986158. BMS-986158 is a substrate for P-glycoprotein and BCRP. CNS penetration appears to be limited with this agent (BMS, personal communication).

In nonclinical toxicology studies, the main adverse events included enteropathy, hematologic toxicity, and depletion of lymphoid tissues. These findings were reversible.

2.4.2 Adult Experience with BMS-986158

Bristol-Myers Squibb (BMS) sponsored a now completed phase 1/2 trial of BMS-986158 (NCT02419417). The phase 1 portion of the trial includes adults \( \geq 18 \) years of age with relapsed/refractory solid tumors or lymphoma. This trial opened in June 2015 and a range of dose levels and dosing schedules have been investigated. In the 83 adults treated, the agent has been well tolerated. The only observed dose-limiting toxicities have been thrombocytopenia and nausea. At the maximum administered dose of 4.5 mg/dose once daily for 5 days on followed by 2 days off, 2 patients out of 13 reported a first cycle DLT (grade 4 thrombocytopenia in both patients). Following this DLT monitoring period, several other patients at this dose level required dose reduction due to toxicities in subsequent cycles. Although this dose level was below the set toxicity threshold for the trial, escalation beyond 4.5 mg/dose was not performed. As of data cut used for Investigator Brochure version 7, two patients had confirmed partial responses (one patients with NUT carcinoma, one patient with ovarian cancer). Two patients had unconfirmed partial responses (one patient with NUT carcinoma and one patient with adenoid cystic carcinoma). Additionally, there has been stable disease in 20 patients. Preliminary pharmacokinetic data demonstrate a dose proportional increase in exposure. The agent is
absorbed rapidly within 4 hours of oral administration. Pharmacodynamic effects on gene expression detectable in the peripheral blood have increased with increasing dose, peaking at 4-8 hours post-dose and then returning to baseline by 24 hours post-dose.

Based upon available toxicity data, future patients in the adult development program will be dosed with 4.5 mg/dose once daily for 5 days on followed by 2 days off each week for 2 weeks, followed by an empiric dose reduction for all patients to 3.75 mg/dose once daily for 5 days on followed by 2 days off for the remainder of their treatment.

2.4.3 Pediatric Experience with BMS-986158

Prior to this trial, no children had been treated with BMS-986158.

2.5 BMS-986378 (CC-90010)

2.5.1 BMS-986378 (CC-90010) Nonclinical Studies

BMS-986378 (also known as CC-90010) is an oral investigational BET inhibitor. BMS-986378 (CC-90010) demonstrated potent and selective binding to the BET BRD family (BRD2, BRD3, BRD4, and BRDT) with biochemical IC\(_{50}\)s in the low nanomolar range. BMS-986378 (CC-90010) has been studied in models of brain tumors. In glioblastoma multiforme (GBM) tumor models, BMS-986378 (CC-90010) inhibited colony formation with an average IC\(_{50}\) of 0.62 \(\mu\)M. BMS-986378 (CC-90010) demonstrated efficacy alone or in combination with temozolomide in several GBM mouse models. Additionally, BMS-986378 (CC-90010) downregulated GLI1 in GBM cell lines and in medulloblastoma mouse model tumors.

The agent shows good oral bioavailability and is highly protein bound in nonclinical studies. BMS-986378 (CC-90010) is P-glycoprotein substrate though this has not limited its absorption. BMS-986378 undergoes metabolism via multiple pathways including N-dealkylation, O-dealkylation, oxidation, glucuronidation of oxidative metabolites, and combinations of these pathways. Metabolism of BMS-986378 (CC-90010) is mediated primarily by CYP3A4/5. BMS-986378 (CC-90010) is not a substrate of efflux transporters (BCRP or MRPs) or uptake transporters (OAT1, OAT3, OCT2, OATP1B1, and OATP1B3). At clinically relevant concentrations, BMS-986378 (CC-90010) has minimal potential to cause drug-drug interactions with co-administered drugs that are CYP substrates or transporter substrates other than P-glycoprotein. BMS-986378 (CC-90010) has molecular properties typically associated with small-molecule CNS penetrance and it has been shown to have good CNS penetration with a brain to plasma ratio of 0.09-0.17 (BMS personal communication and reference\(^{32}\)).

In nonclinical toxicology studies, the primary organ for toxicity was the gastrointestinal (GI) tract. Additional target tissues were the bone marrow, lymphoid tissues, and testes. These findings were reversible after a 4-week rest period with the exception of the testes-related findings.
2.5.2 Adult Experience with BMS-986378 (CC-90010)

Celegene and subsequently Bristol-Myers Squibb (BMS) are sponsoring several clinical trials of BMS-986378 (CC-90010). CC-90010-ST-001 is a Phase 1a, open-label, multicenter, dose escalation (Part A) and expansion (Part B) first-in-human clinical trial which is currently evaluating the RP2D, PK, PD, preliminary efficacy and food effect (Part C) of oral BMS-986378 (CC-90010) in subjects with advanced or unresectable solid tumor and relapsed and/or refractory non-Hodgkin lymphoma. Part A explored escalating dose levels on several different dose schedules. Part B (dose expansion) of the study further evaluates the safety and efficacy of this drug administered at the RP2D (45 mg on a 4 days on/24 days off schedule) in selected expansion cohorts (DLBCL and advanced basal cell carcinoma). Part C evaluates the impact of food on BMS-986378 (CC-90010) in fasted and fed conditions in subjects with advanced solid tumors, with no significant food effect seen.

Final PK data from Part A of CC-90010-ST-001 are available from 69 patients, with PD data available for 68 of 69 patients. BMS-986378 (CC-90010) was administered in 3 different schedules over multiple cohorts, which affected the pharmacokinetics. Schedule A consisted of 3 days on/11 days off. Schedule C consisted of 2 days on/5 days off. Schedule B tested 3 doses of BMS986378 (CC-90010) administered for 4 days on /24 days off and was the preferred schedule. The $t_{\text{max}}$ was ~1-1.5 hours, with $\text{AUC}_{0-24}$ ranging from 12,065-21,606 ng*hr/mL. The recommended phase 2 dose level was 4B (45 mg flat dose), achieving a $C_{\text{max}}$ of 1303 at the last dose, $t_{\text{max}}$ of 1.5hr, and $\text{AUC}_{0-24}$ of 18,872 ng*hr/mL and $\text{AUC}_{0-\text{last}}$ of 47,960 ng*hr/mL.

Suppression of CCR1 (a known biomarker of BET inhibition) was observed with the first dose of BMS986378 (CC-90010), reaching 50% downregulation at 30 mg dose in all schedules tested. Maximal CCR1 decrease was observed after repeat dosing at doses $\geq$25mg with the lowest CCR1 levels achieved in schedule B of 17.7% of baseline expression with the 55mg dose (administered 4 days on /24 days off). Additionally, modelling of the platelet nadir showed the least drop and fastest recovery with Schedule B over Schedules A and C, thus Schedule B has been selected for further trials.

Preliminary efficacy data has been obtained in the course of the Phase 1 studies listed above. There was an overall response rate of 2.9% (n=2) while another 6 patients (8.8%) had stable disease for $\geq$11 months. There was one patient with a complete response (CR) who had a progressive grade II diffuse astrocytoma. Additionally, there was another patient with GBM who exhibited radiographic evidence of a minor response to BMS-986378 (CC-90010). For these reasons and for the confirmed brain penetration of BMS-986378 (CC-90010), BMS is continuing to study this agent in patients with brain tumors.

BMS is sponsoring an ongoing phase 1 trial of BMS-986378 (CC-90010) (NCT04047303) to determine the CNS penetration in patients with progressive/recurrent astrocytoma, anaplastic astrocytoma, or GBM. There have been 12 patients enrolled as of Nov 17th, 2020.

2.5.3 Pediatric Experience with BMS-986378 (CC-90010)

To date, no children have been treated with BMS-986378 (CC-90010).
2.6 **Rationale for Continual Reassessment Method Dose Escalation Design**

Dose escalation will utilize a modified continual reassessment method (CRM) design. The CRM is a Bayesian adaptive dose-escalation design that assumes a mathematical model of the dose-toxicity curve to predict the probability of a DLT at each dose level.\(^{34}\) As the trial proceeds, the model is updated and recommends the dose level as the one closest to the target DLT rate. Our modification of the CRM design will permit enrollment of patients from Cohort B to one dose below the current recommended dose when no enrollment slots are available at the currently evaluated dose level. An adaptive CRM design was selected rather than a conventional rule-based design (such as the 3+3 design) for two key reasons. First, the CRM has been shown to increase the chance of recommending the true maximum tolerated dose and increase the number of patients allocated to optimal dose levels.\(^{35}\) Second, a CRM design utilizes all DLT information collected to date to determine the next dose level, and this design feature is a major advantage as BMS-986158 and BMS-986378 (CC-90010) DLT information is derived simultaneously from Cohorts 1A and 1B of Arm 1 and Cohorts 2A and 2B of Arm 2 respectively over the course of the trial.

This design will allow continual enrollment of patients with specific genotypes with strong preclinical evidence for benefit from BMS-986158 and BMS-986378 (CC-90010) (i.e., Cohorts 1B and 2B of Arm 1 and Arm 2). Given that these pre-defined genotypes of interest are less common, making an enrollment slot available at the time such a patient presents is a high priority. This modified CRM design will permit enrollment of patients from Cohort B to one dose below the current recommended dose when no enrollment slots are available at the currently evaluated dose level. The modified CRM models will utilize observed DLT data from patients in Cohorts 1A/1B and separately from 2A/2B to safely and efficiently assign optimal dose levels and identify the MTD for BMS-986158 and BMS-986378 (CC-90010), respectively.

2.7 **Rationale for Planned Correlative Studies**

**Pharmacokinetic Studies:** Establishing the pharmacokinetic profiles of BMS-986158 and BMS-986378 (CC-90010) and their main circulating metabolites in a pediatric population is a key aim of the current study. Serial plasma samples will be obtained around the first doses of BMS-986158 and BMS-986378 (CC-90010) as well as at steady state to characterize standard pharmacokinetic parameters. CSF levels will be quantified for patients who have CSF sampling while on protocol therapy.

**Pharmacodynamic Studies:** BET inhibition results in profound changes in gene expression patterns. Evaluation of these changes in the peripheral blood can serve as a marker of pharmacodynamic effects of BMS-986158 and BMS-986378 (CC-90010). Use of this non-invasive marker is of particular interest in a pediatric population in whom serial research biopsies pose unique clinical and regulatory challenges.

**Markers of Response and Resistance:** Available data indicate that tumors with alterations in Myc family genes may be the most sensitive to BET inhibition. Some groups have found
differing patterns of resistance in different tumor models, such as PI3K signaling pathway 
activation, cell cycle alterations and cell differentiation. An integrative clinical sequencing 
platform will be used on archival tumor material to interrogate for mutations and copy number 
changes in Myc family genes, along with RNA-Seq to detect gene fusions and candidate gene 
expression profile, while also identifying other genomic alterations that may be associated with 
response or resistance to BMS-986158 and/or BMS-986378 (CC-90010).

In parallel, serial plasma samples will be used to isolate circulating tumor DNA (ctDNA) by next 
generation sequencing approaches. ctDNA will be quantified to provide a potential surrogate 
early marker of response. ctDNA will also be characterized over time to understand emergence 
of genomic changes in response to the selective pressure of BET inhibition. As proof of concept, 
the Crompton laboratory at Dana-Farber has utilized ultra-low passage whole genome 
sequencing (ULP-WGS) to detect copy number changes in plasma-derived cell free DNA. Dr. 
Crompton has been able to identify MYCN amplification in patients with high-risk 
neuroblastoma known to have tumors with MYCN amplification (Figure 3). Patients with 
primary CNS tumors who undergo standard of care CSF sampling will also have CSF collected 
for assessment of cell free DNA (cfDNA) in the CSF.

![Figure 3](image.png)

**Figure 3.** Output of ULP-WGS on cell free DNA identifying MYCN amplification in two 
patients with known MYCN amplified 
neuroblastoma (MRD0098 and MRD0100) 
compared to two patients with known MYCN 
wild type neuroblastoma (MRD0088 and 
MRD0096).

The protocol will include an optional banking 
sub-study in which patients may provide additional consent to obtain and store leftover material 
for potential future research.

2.8 Overall Summary of Rationale

Despite a large body of research that implicates BET proteins as a target in a number of pediatric 
cancers, no pediatric trials of BET inhibitors have been conducted. Given that the recommended 
adult phase 2 dose and schedules of BMS-986158 and BMS-986378 (CC-90010) have been 
defined, we are now poised to conduct a dedicated pediatric phase 1 trial of these agents. We 
hypothesize that BMS-986158 and BMS-986378 (CC-90010) will be both tolerable and active in 
children. The results of this trial will inform subsequent phase 2 studies in pediatric populations 
of greatest interest, while also enabling the development of novel combination approaches 
identified by laboratory studies focused on pediatric malignancies.

For BMS-986158, a flat dose of 4.5 mg/dose given orally on a 5-day on / 2-day off schedule in 
28-day cycles was the maximum administered dose in adults. Though tolerated in the DLT 
monitoring period, dose reductions were required in subsequent cycles in a subset of patients.
Thus, the recommended adult dosing program currently includes a 2-week initial dosing period at 4.5 mg/dose daily for 5-day on / 2-day off schedule. Following this 2-week period, the dose is reduced to 3.75 mg/dose daily on a 5-day on / 2-day off schedule for the remainder of treatment.

As the first dedicated pediatric phase 1 trial of a BET inhibitor and the first pediatric trial of BMS-986158, we will begin pediatric dose escalation at the equivalent of 75% of the maximum administered adult dose. Specifically, the maximum administered adult dose of 4.5 mg is equivalent to 2.6 mg/m$^2$, assuming an average adult BSA of 1.7m$^2$. 75% of 2.6 mg/m$^2$ is equal to 2 mg/m$^2$, which will serve as the starting dose level for this pediatric trial. Dosing will be based upon BSA, with a capped maximum absolute dose. Given the safety margin afforded by starting at 75% of the maximum adult absolute dose and the overall tolerability of the agent with DLTs mainly consisting of reversible thrombocytopenia, pediatric patients on this trial will receive the same assigned dose level throughout treatment, unless toxicity warrants intrapatient dose de-escalation or tolerability allows for intrapatient dose escalation during the expansion cohort (see below). Dose levels up to 130% of the adult dose will be explored based upon prior studies demonstrating that pediatric recommended phase 2 doses typically do not exceed this level.36

2.9 **Rationale for Amendment 4**

Based upon dose-limiting thrombocytopenia observed at dose levels 1 and -1 at September 2020, it is possible that administering BMS-986158 for 5 days every week of each cycle may not be feasible. This finding may reflect the intensive prior therapies that pediatric oncology patients typically receive prior to participating in an early phase clinical trial. As higher grade thrombocytopenia has most commonly been seen during the fourth week of dosing, Amendment 4 includes new dose levels that will evaluate an interrupted dosing schedule (5 days on / 2 days off for 3 weeks followed by a 1-week break). This pre-planned break in dosing may ultimately allow patients to recover platelet counts and move onto subsequent cycles on schedule. Since patients treated as part of the expansion cohort at the recommended phase 2 dose may be less heavily pretreated, this portion of the study will include an option for intrapatient dose escalation after the first cycle.

2.10 **Rationale for Amendment 5**

Based upon new information from BMS, it was determined that BMS-986158 had relatively poor blood brain barrier penetration in preclinical experiments. At the same time, another BET inhibitor in the company’s portfolio, BMS-986378 (CC-90010), demonstrated significant brain penetration in preclinical modelling. Pediatric patients with refractory brain tumors or tumors with CNS metastasis have dismal outcomes overall and those with certain aggressive histologies, such as high-grade gliomas or diffuse intrinsic pontine gliomas, are universally fatal. For this significant unmet medical need, any new agent with preclinical activity and documented brain penetration is eagerly sought to be assessed in a clinical trial. Given same in class drug toxicity, the statistical infrastructure established within this trial of BMS-986158 in children, as well as the significant embedded correlative biology, the most efficient path to assess BMS-986378 (CC-90010) in children with pediatric brain tumors is as an amendment to this existing trial.
As the first pediatric trial of BMS-986378 (CC-90010), we will begin pediatric dose escalation at the equivalent of 80% of the maximum administered adult dose. Specifically, the adult recommended phase 2 dose of 45 mg is equivalent to 27 mg/m², assuming an average adult BSA of 1.7m². The starting dose level for Arm 2 will be 21 mg/m², which is 80% of 27 mg/m². Dosing will be based upon BSA, with a capped maximum absolute dose. Given the safety margin afforded by starting at 80% of the maximum adult absolute dose and the overall tolerability of the agent with DLTs mainly consisting of reversible thrombocytopenia, pediatric patients on this trial will receive the same assigned dose level throughout treatment, unless toxicity warrants intrapatient dose de-escalation. Dose levels up to 130% of the adult dose will be explored based upon prior studies demonstrating that pediatric recommended phase 2 doses typically do not exceed this level.36

3 PARTICIPANT SELECTION

Prior to approaching a potential participant, treating sites must reserve a treatment slot by contacting the Study Coordinator. Upon reserving a treatment slot, an investigator may begin the informed consent process for that participant. Once informed consent has been obtained, the investigator may begin screening studies to confirm eligibility. Once all eligibility criteria have been satisfied, the investigator may enroll the participant according to Section 4.0.

Baseline studies used to meet eligibility for the relevant patient cohort must be completed within 14 days prior to the date of enrollment as outlined in Section 10. Baseline disease assessments (such as MRIs, CT scans, bone marrow biopsies, and nuclear medicine studies) must be performed within 28 days prior to the date of enrollment.

See Section 5.4.2 for specific studies that may need to be repeated within key windows prior to initiation of study drug.

3.1 Eligibility Criteria

3.1.1 Age ≤ 21 years at time of enrollment. Note the requirement in section 3.1.6 that all patients must be able to swallow intact capsules.

3.1.2 Karnofsky performance status ≥ 50% for patients ≥16 years of age or Lansky ≥ 50% for patients <16 years of age (see Appendix A)

3.1.3 Diagnosis requirement

1. Participants must have evaluable or measurable disease (see Section 11).

2. Must have disease that is relapsed or refractory and for which standard curative measures do not exist or are no longer effective.

3. For Arm 1 - Cohort 1A, participants must have histologically confirmed non-CNS primary solid tumors or lymphoma based upon biopsy or surgery at
relapse/progression. Patients without biopsy or surgery at relapse/progression and with tissue only available from initial diagnosis may still be considered after discussion with the overall Primary Investigator.

4. For Arm 1 - Cohort 1B, participants must have histologically confirmed solid tumors, lymphoma, based upon biopsy or surgery at relapse/progression as well as documentation of one of the following confirmed tumor molecular features obtained in a laboratory certified to return results for clinical purposes. Patients without biopsy or surgery at relapse/progression and with tissue only available from initial diagnosis may still be considered after discussion with the overall Primary Investigator.

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<thead>
<tr>
<th>MYCN amplification or high copy number gain</th>
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<tr>
<td>MYC amplification or high copy number gain</td>
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<tr>
<td>Translocation involving MYC or MYCN</td>
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<tr>
<td>Translocation involving BRD3 or BRD4</td>
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<tr>
<td>BRD4 amplification or high copy number gain</td>
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<tr>
<td>Histologic diagnosis of NUT midline carcinoma</td>
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</table>

5. For Arm 2 – Cohort 2A, participants must have histologically confirmed primary CNS tumors or solid tumors with untreated CNS metastases based upon biopsy or surgery at relapse/progression. Patients without biopsy or surgery at relapse/progression and with tissue only available from initial diagnosis may still be considered after discussion with the overall Primary Investigator.

6. For Arm 2 - Cohort 2B, participants must have histologically confirmed primary CNS tumor or solid tumor with untreated CNS metastases based upon biopsy or surgery at relapse/progression as well as documentation of one of the following confirmed tumor molecular features obtained in a laboratory certified to return results for clinical purposes. Patients without biopsy or surgery at relapse/progression and with tissue only available from initial diagnosis may still be considered after discussion with the overall Primary Investigator.

<table>
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</tr>
<tr>
<td>Histologic diagnosis of NUT midline carcinoma</td>
</tr>
</tbody>
</table>

3.1.4 Patients must have fully recovered from the acute toxic effects of all prior anti-cancer therapy except organ function as noted in Section 3.1.5. Patients must meet the following minimum washout periods prior to enrollment:
3.1.4.1 Myelosuppressive chemotherapy: At least 21 days after the last dose of myelosuppressive chemotherapy (42 days for nitrosourea or mitomycin C).

3.1.4.2 Radiotherapy:
- At least 14 days after local XRT (small port, including cranial radiation);
- At least 90 days must have elapsed after prior TBI or if >50% radiation of pelvis;
- At least 180 days must have elapsed after prior craniospinal XRT;
- At least 42 days must have elapsed if other substantial BM radiation;
- At least 42 days must have passed since last MIBG or other radionuclide therapy.

3.1.4.3 Small molecule biologic therapy: At least 7 days following the last dose of a small molecule biologic agent. For agents with known adverse events occurring beyond 7 days, this duration must be extended beyond the time in which adverse events are known to occur. If extended duration is required, this must be discussed with and approved by the overall PI.

3.1.4.4 Monoclonal antibody: At least 28 days must have elapsed after the last dose of therapeutic monoclonal antibody.

3.1.4.5 Myeloid growth factors: At least 14 days following the last dose of long-acting growth factor (e.g. Neulasta) or 7 days following short-acting growth factor.

3.1.4.6 Autologous hematopoietic stem cell transplant and stem cell boost: Patients must be at least 60 days from day 0 of an autologous stem cell transplant or autologous stem cell boost.

3.1.4.7 Cellular therapies (including CAR-T cells) and other non-cellular, non-antibody immunotherapies (e.g., vaccines): At least 42 days must have elapsed after last dose.

3.1.4.8 Major Surgery: At least 2 weeks from prior major surgical procedure. Note: Major surgical procedure will be considered all surgical procedures aside from the following: Biopsy; central line placement/removal; bone marrow aspirate/biopsy; lumbar puncture; dental procedures; gastrostomy tube placement; and VP shunt placement/revision.

3.1.4.9 BET inhibitors: Patients must not have received prior treatment with a BET inhibitor, except patients with CNS tumors or CNS metastasis previously treated on Arm 1 of the trial who discontinued protocol therapy due to disease progression and not due to toxicity. Such patients may participate in Arm 2 of the trial.
3.1.5 Participants must have normal organ function as defined below.

3.1.5.1 Bone Marrow Function
A. For Patients without Documented Bone Marrow Involvement by Disease:
   • Hemoglobin \( \geq 8 \text{ g/dL} \) (may be transfused)
   • Absolute neutrophil count \( \geq 1,000 \text{ /uL} \)
   • Platelets \( \geq 100,000 \text{ /uL} \) and transfusion independent, defined as not receiving a platelet transfusion for at least 5 days prior to CBC documenting eligibility.

B. For Patients with Documented Bone Marrow Involvement by Disease:
   • Hemoglobin \( \geq 8 \text{ g/dL} \) (may be transfused)
   • Absolute neutrophil count \( \geq 750 \text{ /uL} \)
   • Platelets \( \geq 75,000 \text{ /uL} \) and transfusion independent, defined as not receiving a platelet transfusion for at least 5 days prior to CBC documenting eligibility.

3.1.5.2 Hepatic Function:
   • Total bilirubin \( \leq 1.5 \text{ x upper limit of normal for age} \)
     (patients with known Gilbert’s may be considered after discussion with overall PI and if direct bilirubin is at or below the upper limit of normal for age)
   • ALT (SGPT) \( \leq 3 \text{ x upper limit of normal} \)
   • Serum albumin \( \geq 2 \text{ g/dL} \)

3.1.5.3 Adequate Pancreatic Function:
   • Lipase < upper limit of normal

3.1.5.4 Adequate GI Function:
   • Diarrhea \( \leq \text{ grade 1 by CTCAE version 5} \)

3.1.5.5 Coagulation Factors:
   • International Normalized Ratio (INR) \( \leq 1.5 \)
   • Partial thromboplastin time (PTT) \( \leq 1.5 \text{ times upper limit of normal} \)
   Note: For patients having labs drawn via heparinized catheters, it is important to request heparin-absorbed values.

3.1.5.6 Adequate Cardiac Function:
   • QTc \( \leq 480 \text{ msec} \)
3.1.5.7 Renal Function:

- A serum creatinine based on age/sex as follows:

<table>
<thead>
<tr>
<th>Age</th>
<th>Maximum Serum Creatinine (mg/dL)</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>Male</td>
</tr>
<tr>
<td>1 to &lt; 2 years</td>
<td>0.6</td>
</tr>
<tr>
<td>2 to &lt; 6 years</td>
<td>0.8</td>
</tr>
<tr>
<td>6 to &lt; 10 years</td>
<td>1</td>
</tr>
<tr>
<td>10 to &lt; 13 years</td>
<td>1.2</td>
</tr>
<tr>
<td>13 to &lt; 16 years</td>
<td>1.5</td>
</tr>
<tr>
<td>≥ 16 years</td>
<td>1.7</td>
</tr>
</tbody>
</table>

OR

Creatinine clearance ≥ 60 mL/min/1.73 m² for participants with creatinine levels greater than the above age/sex maximum allowed values.

3.1.6 Able to swallow intact capsules (BMS-986158) or tablets (BMS-986378, also known as CC-90010).

3.1.7 Patient (or parent or legally authorized representative, if minor) is able to understand and willing to provide informed consent, using an institutionally approved informed consent procedure.

3.1.8 Participants of childbearing or child-fathering potential must agree to use adequate contraception throughout their participation following the guidance in Appendix H.

3.2 Exclusion Criteria

3.2.1 Prior solid organ or allogeneic stem cell transplantation.

3.2.2 Patients with primary or metastatic CNS tumors are not eligible for Arm 1, except:
   a. Patients with a history of CNS metastatic disease that has been resected and/or radiated without evidence of active CNS disease for 3 months preceding enrollment;
      NOTE: patients with primary CNS tumors or solid tumors with active CNS metastases will be eligible for Arm 2

3.2.3 Patients receiving any of the following prohibited foods and medications:
   a. Agents listed in Appendix B within 7 days prior to enrollment (note separate tables for patients enrolling to Arm 1 vs. patients enrolling to Arm 2)
   b. Grapefruit or Seville oranges and/or their juices within 7 days prior to enrollment
   c. Non-steroidal anti-inflammatory drugs, oral anticoagulants, and therapeutic heparins (unfractionated or low molecular weight heparin) at the time of
enrollment. Note: Use of heparin to maintain patency of a central or peripheral catheter is allowed.

d. Other investigational agents being administered under an IND.

3.2.4 Pregnant participants will not be entered on this study given that the effects of BMS-986158 and BMS-986378 (CC-90010) on the developing human fetus are unknown. Female participants of childbearing potential must have a documented negative pregnancy exam within 24 hours prior to dosing.

3.2.5 Breastfeeding mothers are not eligible, because there is an unknown risk for adverse events in nursing infants secondary to treatment of the mother with BMS-986158 or BMS-986378 (CC-90010).

3.2.6 History of allergic reactions attributed to compounds of similar chemical or biologic composition to BMS-986158 or BMS-986378 (CC-90010).

3.2.7 Uncontrolled intercurrent illness including, but not limited to, ongoing or uncontrolled infection, symptomatic congestive heart failure, unstable angina pectoris, cardiac arrhythmia, or psychiatric illness/social situations that would limit compliance with study requirements.

3.2.8 Patients with a known history of HIV, hepatitis B, and/or hepatitis C (testing not required as part of screening).

3.2.9 Patients with gastrointestinal disease or disorder that could interfere with absorption of BMS-986158 or BMS-986378 (CC-90010), such as bowel obstruction or inflammatory bowel disease.

3.2.10 For Arm 1: Patients with BSA < 0.3 m² for all dose levels except Dose Level -2 or -2i for which patients with BSA < 0.71 m² will be excluded due to dose rounding constraints.

3.2.11 For Arm 2: Patients with BSA < 0.65 m².

3.3 **Inclusion of Children and Minorities**

Both male and female children of all races and ethnic groups are eligible for this trial.
4 REGISTRATION PROCEDURES

4.1 General Guidelines for Dana-Farber/Boston Children’s

DF/HCC Policy for Human Subject Research Titled *Subject Protocol Registration* (Policy #: REGIST-101) must be followed.

An investigator will confirm eligibility criteria and will complete and sign the protocol-specific eligibility checklist.

Dana-Farber/Boston Children’s study staff will then register eligible participants in the Clinical Trials Management System (CTMS) OnCore. Registrations must occur prior to the initiation of protocol therapy. Any participant not registered to the protocol before protocol therapy begins will be considered ineligible and registration will be denied.

Following registration, participants may begin protocol therapy and must begin protocol therapy within 5 days. Unless the delay is approved by the Overall Principal Investigator, if a participant does not receive protocol therapy within 5 days following registration, the participant must be taken off-study in the CTMS (OnCore) with an appropriate date and reason entered.

4.2 General Guidelines for Other Investigative Sites

All sites must contact the Study Coordinator to verify an available slot before initiating the informed consent and screening processes (see Section 3). Eligible participants will be entered on study centrally at Dana-Farber by the Study Coordinator (or designee).

Following registration, participants may begin protocol therapy and must begin protocol therapy within 5 days. Issues that would cause treatment delays must be discussed with the Overall PI. Unless the delay is approved by the Overall Principal Investigator, if a participant does not receive protocol therapy within 5 days following registration, the participant must be taken off-study in the central CTMS (OnCore) by the DFCI Study Coordinator with an appropriate date and reason entered.

4.3 Registration Process for Other Investigative Sites

To register a participant, the following documents will be e-mailed via a secure portal to the DFCI Study Coordinator and to the e-mail address pediatricBMS-986158@dfci.harvard.edu.

- Copy of the following source documents confirming eligibility:
  - Eligibility lab results in Section 3.1.5;
  - ECG;
  - Pregnancy test, urine or serum (if female of childbearing potential);
  - Pathology report;
  - Imaging and/or pathology reports demonstrating evaluable or measurable disease;
  - Most recent clinician note, including medication list;
• Documentation to confirm one of the following qualifying molecular features:

Arm 1 - Cohort 1B only:

| MYCN amplification or high copy number gain |
| MYC amplification or high copy number gain  |
| Translocation involving MYC or MYCN         |
| Translocation involving BRD3 or BRD4       |
| BRD4 amplification or high copy number gain|
| Histologic diagnosis of NUT midline carcinoma|

Arm 2 - Cohort 2B only:

| MYCN amplification or high copy number gain |
| MYC amplification or high copy number gain  |
| Translocation involving MYC or MYCN         |
| Translocation involving BRD3 or BRD4       |
| BRD4 amplification or high copy number gain|
| Histologic diagnosis of NUT midline carcinoma|

• Signed participant consent form
• HIPAA authorization (if separate from informed consent document)
• Protocol-specific eligibility checklist signed by site investigator.

The research nurse or study coordinator at the participating site will then contact the DFCI Study Coordinator to verify eligibility and consent. To complete the registration process, the DFCI Study Coordinator will register the participant on the study with the DF/HCC Clinical Trial Management System (CTMS), OnCore. The DFCI Study Coordinator will e-mail the participant study number, assigned cohort, and assigned dose treatment level to the participating site in a registration e-mail. The site must receive this registration e-mail prior to initiating protocol therapy.

5 TREATMENT PLAN

5.1 Treatment Regimen

5.1.1 Overview of Treatment Regimen – Arm 1 (BMS-986158 in solid tumors)
BMS-986158 will be administered orally at the dose level assigned at registration. For continuous dosing levels, BMS-986158 will be administered once daily on a five day on / two day off schedule in 28-day cycles (Figure 4a). For interrupted dosing levels, BMS-986158 will be administered once daily on a five day on / two day off schedule for 3 weeks of a 4-week cycle (Figure 4b).

| Day | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 0 | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 0 | 1 | 2 | 3 | 4 | 5 |
| BMS-986158 | * | * | * | * | * | * | * | * | * | * | * | * | * | * | * | * | * | * | * | * | * | * | * | * | * |

**Figure 4a**: Dosing schedule for one cycle of BMS-986158 – continuous dosing.
Participants are recommended to begin therapy on Monday through Thursday to facilitate collection of pharmacokinetic and pharmacodynamic blood draws on day 2.

Appropriate dose modifications are described in Section 6. Reported adverse events and potential risks are described in Section 7. No investigational or commercial agents or therapies other than those described below may be administered with the intent to treat the participant's malignancy.

In the absence of criteria for removal from protocol therapy (see Section 5.8), participants may continue to receive protocol therapy for up to 26 cycles (approximately two years of therapy).

5.1.2 Overview of Treatment Regimen – Arm 2 [BMS-986378 (CC-90010) in CNS tumors]
BMS-986378 (CC-90010) will be administered orally at the dose level assigned at registration. BMS-986378 (CC-90010) will be administered once daily on a four day on / twenty-four day off schedule in 28-day cycles (Figure 4c).

Participants are recommended to begin therapy on Monday through Thursday to facilitate collection of pharmacokinetic and pharmacodynamic blood draws on day 2.

Appropriate dose modifications are described in Section 6. Reported adverse events and potential risks are described in Section 7. No investigational or commercial agents or therapies other than those described below may be administered with the intent to treat the participant's malignancy.

In the absence of criteria for removal from protocol therapy (see Section 5.8), participants may continue to receive protocol therapy for up to 26 cycles (approximately two years of therapy).

5.2 Dose Escalation Overview
Separately within each Arm, dose escalation will proceed according to a modified CRM dose-escalation model (see Section 13), with DLTs in cycle 1 informing dose escalation decisions.

5.2.1 Dose Escalation for Arm 1 - BMS-986158 in solid tumors
The starting dose level will be 2 mg/m² (75% of the adult maximum administered dose). Doses for Arm 1 will be capped as shown in Table 2. Eligible Cohort 1B patients will enroll at one
level below the currently evaluated dose level only if there are no available treatment slots at the currently evaluated dose level; otherwise they will enroll at the currently evaluated dose level. If the currently evaluated dose level is dose level -2i and there are no open slots, then a patient meeting criteria for Cohort 1B will not be able to enroll until additional slots are opened. Patients in Cohort 1A will always enroll at the currently evaluated dose level. Dose levels are shown in Table 2. In Arm 1, the initial version of the protocol included Dose Levels -1, 1, 2, and 3. With Amendment 3, Dose Levels 1S and -2 were added to Arm 1 based upon dose-limiting thrombocytopenia seen at Dose Level 1. With Amendment 4, Dose Levels 2, 3, and 1S were removed and interrupted dose levels 1i, -1i, and -2i were added to Arm 1.

Table 2: Dose escalation strategy for BMS-986158 (Arm 1).

<table>
<thead>
<tr>
<th>Dose Level*</th>
<th>Daily Dose of BMS-986158</th>
<th>Percent of Adult Maximum Administered Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Level -2i</td>
<td>1.3 mg/m²/dose (max 2.25 mg) for 3 weeks followed by 1 week break</td>
<td>50% dose x 3 weeks</td>
</tr>
<tr>
<td>Level -2</td>
<td>1.3 mg/m²/dose (max 2.25 mg)</td>
<td>50%</td>
</tr>
<tr>
<td>Level -1i</td>
<td>1.6 mg/m²/dose (max 2.75 mg) for 3 weeks followed by 1 week break</td>
<td>60% dose x 3 weeks</td>
</tr>
<tr>
<td>Level -1</td>
<td>1.6 mg/m²/dose (max 2.75 mg)</td>
<td>60%</td>
</tr>
<tr>
<td>Level 1i</td>
<td>2 mg/m²/dose (max 3.5 mg) for 3 weeks followed by 1 week break</td>
<td>75% dose x 3 weeks</td>
</tr>
<tr>
<td>Level 1 – Starting Dose</td>
<td>2 mg/m²/dose (max 3.5 mg)</td>
<td>75%</td>
</tr>
</tbody>
</table>

*Dose levels ending in an “i” are considered interrupted dose levels.

5.2.2 Dose Escalation for Arm 2 - BMS-986378 (CC-90010) in CNS tumors
The starting dose level will be 21 mg/m²/dose (80% of the adult recommended phase 2 dose of 45 mg normalized to average adult BSA of 1.7 m²). Doses will be capped in Arm 2 as outlined in Table 3. Eligible Cohort 2B patients will enroll at one dose level below the currently evaluated dose level only if there are no available treatment slots at the currently evaluated dose level. Otherwise, they will enroll at the currently evaluated dose level. If the currently evaluated dose level is Dose Level -1 and there are no open slots, then a patient meeting criteria for Cohort 2B will not be able to enroll until additional slots are opened. Patients in Cohort 2A will always enroll at the currently evaluated dose level. Dose levels are shown in Table 3.

Table 3: Dose escalation strategy for BMS-986378 (CC-90010) (Arm 2).

<table>
<thead>
<tr>
<th>Dose Level</th>
<th>Daily Dose of BMS-986378 (CC-90010)</th>
<th>Percent of Adult Recommended Phase 2 Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Level -1</td>
<td>15 mg/m²/dose (max 25 mg)</td>
<td>60%</td>
</tr>
<tr>
<td>Level 1</td>
<td>21 mg/m²/dose (max 35 mg)</td>
<td>80%</td>
</tr>
<tr>
<td>Level 2</td>
<td>27 mg/m²/dose (max 45 mg)</td>
<td>100%</td>
</tr>
<tr>
<td>Level 3</td>
<td>35 mg/m²/dose (max 60 mg)</td>
<td>130%</td>
</tr>
</tbody>
</table>
5.3 **Dose Escalation Determination**

Decisions for dose escalation will be made by the Study Investigators, including the Overall Principal Investigator and the study biostatisticians following the dose escalation rules given in Section 13.

5.4 **Pre-Treatment Criteria**

5.4.1 Screening Assessments
See Section 10 for details of required screening studies.

5.4.2 Cycle 1, Day 1

If screening laboratory studies for registration were obtained > 5 days prior to Cycle 1, Day 1, then the following laboratory studies must be repeated within 5 days prior to proceeding with the Cycle 1, Day 1 BMS-986158 or BMS-986378 (CC-90010) dose: CBC with differential; creatinine or creatinine clearance; bilirubin; ALT; albumin; lipase; INR; and PTT. If screening pregnancy test > 24 hours old, it will need to be repeated prior to administration of study drug on Cycle 1, Day 1.

If any of these repeat laboratory studies do not meet organ function requirements in Section 3.1.5, then the patient must not receive protocol therapy. In this case, laboratory studies may be repeated within 5 days. If these repeat laboratory studies meet eligibility requirements, the patient may proceed with protocol therapy, otherwise the patient will be removed from study.

5.4.3 Subsequent Cycles

Prior to the start of subsequent cycles of therapy, patients must meet all of the following criteria:
- No clinical, pathologic, or radiographic evidence of disease progression (see Section 11 for required assessments);
- Meet hematologic, renal, hepatic, pancreatic and GI organ function requirements listed in Section 3.1.5 (ECG and coags do not need to be repeated each cycle unless clinical concern), with the following exception:
  1. Bone Marrow Function Regardless of ANC, Platelets, and Bone Marrow Disease Involvement at Enrollment:
     - Absolute neutrophil count \( \geq 750/\mu L \)
     - Platelets \( \geq 75,000/\mu L \) and transfusion independent, defined as not receiving a platelet transfusion for at least 5 days prior to CBC used for starting the cycle.
- Documentation of a negative pregnancy test in female participants of childbearing potential within 24 hours of start of each cycle.
- All other adverse events at baseline or \( \leq \) grade 2.
- Have not completed 26 total cycles.
• No criteria met for permanent discontinuation of BMS-986158 or BMS-986378 (CC-90010) (Section 5.8).

Laboratory studies to meet these requirements may be obtained within 3 days prior to Day 1 of each subsequent cycle (with the exception of pregnancy test which must be obtained with 24 hours prior to Day 1 of each subsequent cycle).

5.5 **Investigational Agent Administration**

5.5.1 **BMS-986158 Administration**

BMS-986158 is administered orally dosed based upon the participant’s weight and height within 7 days prior to the start of each cycle and their assigned dose level (Section 5.1). Dose adjustments for toxicity are provided in Section 6. There is no adjustment for obesity. Doses must not be adjusted throughout the course of a cycle for changes in BSA. See Appendix C for dosing nomograms as a function of dose level and BSA.

There is no intra-patient dose escalation during the dose-finding portion of the study. During the 10-patient expansion phase only, if the recommended phase 2 dose level to be evaluated is dose level -1i or lower, then patients in the expansion cohort will be eligible at investigator discretion for intrapatient dose escalation by no more than one dose level starting with cycle 2 if they meet all of the following criteria:

- No DLT in cycle 1;
- Thrombocytopenia ≤ grade 2 during cycle 1; AND
- No delay in start of cycle 2 due to toxicity observed during cycle 1.

BMS-986158 is administered once daily on a five day on / two day off schedule in 28-day cycles (i.e. on days 1-5, 8-12, 15-19, and 22-26 of each 28-day cycle for continuous dosing dose levels or days 1-5, 8-12, and 15-19 for interrupted dosing dose levels). BMS-986158 should be administered at approximately the same time each day (dosing window of ± 4 hours). A dose should be considered missed if more than 4 hours have passed from usual dosing time (e.g., if usual dosing time is noon, then a dose not given by 4pm should be considered missed). A missed dose should not be made up and should be recorded as such on the patient diary.

BMS-986158 should be administered on an empty stomach (1 hour prior to or 2 hours after a meal). Capsules must be swallowed intact and not opened, chewed, or otherwise altered prior to administration. If a patient vomits within 1 hour of BMS-986158 administration AND all capsules are intact and accounted for, then BMS-986158 may be redosed. Otherwise, the dose should not be repeated.

5.5.2 **BMS-986378 (CC-90010) Administration**

BMS-986378 (CC-90010) is administered orally based upon the participant’s weight and height within 7 days prior to the start of each cycle and their assigned dose level (Section 5.2.2). Dose adjustments for toxicity are provided in Section 6. There is no adjustment for obesity. Doses
must not be adjusted throughout the course of a cycle for changes in BSA. See Appendix C for dosing nomograms as a function of dose level and BSA.

There is no intrapatient dose escalation of BMS-986378 (CC-90010).

BMS-986378 (CC-90010) is administered once daily for 4 days on / 24 days off schedule in 28-day cycles. BMS-986378 (CC-90010) should be administered at approximately the same time each day (dosing window of ± 4 hours). A dose should be considered missed if more than 4 hours have passed from usual dosing time (e.g., if usual dosing time is noon, then a dose not given by 4pm should be considered missed). A missed dose on Days 2, 3, or 4 may be made up on Day 5 and should be recorded as such on the patient diary.

BMS-986378 (CC-90010) should be administered without regard to timing of last meal. Tablets must be swallowed intact and are not to be chewed or otherwise altered prior to administration. If a patient vomits within 1 hour of BMS-986378 (CC-90010) administration AND all tablets are intact and accounted for, then BMS-986378 (CC-90010) may be redosed. Otherwise the dose should not be repeated.

5.6 Definition of Dose-Limiting Toxicity (DLT)

5.6.1 Definition of Dose-Limiting Toxicity for Arms 1 and 2

Toxicity will be graded using the CTCAE criteria, version 5. The CTCAE provides descriptive terminology and a grading scale for each adverse event listed. A copy of the CTCAE can be downloaded from the CTEP home page (http://ctep.cancer.gov). Any dose-limiting toxicity must be reported immediately via email to the Overall Principal Investigator and to the DFCI Study Coordinator.

Definition of Dose-Limiting Toxicity

DLT is defined as any of the following events determined to be possibly, probably, or definitely related to BMS-986158 or BMS-986378 (CC-90010). A DLT may occur in any cycle, but only DLTs occurring in the first cycle will be used for dose escalation/expansion decisions.

Non-Hematological DLT:
- Any Grade 3 or higher non-hematological toxicity with the specific exclusion of:
  - Grade 3 fatigue resolving to ≤ grade 2 within 7 days using standard supportive measures.
  - Grade 3 nausea, vomiting, or diarrhea resolving to ≤ grade 2 within 72 hours using standard supportive measures, unless hospitalization is required to manage the adverse event.
  - Grade 3 AST, ALT, alkaline phosphatase, or GGT liver enzyme elevation as long as both of the following criteria are met: a) levels return to ≤ grade 2 within 4 days; AND b) bilirubin is < grade 1 or baseline (if bilirubin was grade 1 at baseline).
  - Grade 3 amylase or lipase elevation as long as both of the following criteria are met: a) levels return to ≤ grade 2 within 4 days; AND b) no clinical signs/symptoms of pancreatitis.
  - Grade 3 fever or febrile neutropenia lasting ≤ 5 days in the absence of clinical or...
laboratory documentation of infection.
  
  o Grade 3 hypophosphatemia, hypokalemia, hypocalcemia, or hypomagnesemia responsive to oral supplementation within 72 hours.
  
  o Grade 3 hyponatremia not associated with clinical adverse events (e.g., lethargy, altered mental status, seizures, or other clinical adverse events attributable to hyponatremia) and that resolves within 72 hours (study drug does not need to be held unless DLT criteria are met)

- Any Grade 2 non-hematological toxicity that persists for ≥ 7 days and is considered sufficiently medically significant or sufficiently intolerable by patients that it requires treatment interruption.
- Any non-hematologic toxicity that results in delay in start of subsequent cycle by > 14 days.

**Hematological DLT:**

Note: the hematological DLT criteria differ for patients with and without known bone marrow metastatic disease as follows:

- Hematological dose limiting toxicity for patients **without known bone marrow metastatic disease**:
  
  o Grade 4 thrombocytopenia or grade 4 neutropenia of any duration. If clinical concern that the thrombocytopenia or neutropenia may be attributable to progressive bone marrow metastatic disease, recommend bone marrow evaluation. Grade 4 thrombocytopenia or grade 4 neutropenia attributable to progressive bone marrow metastatic disease and not to study drug will not be considered DLT; or
  
  o Grade 3 thrombocytopenia of any duration that is associated with grade > 2 bleeding or purpura (study drug does not need to be held unless DLT criteria are met); or
  
  o Grade 3 thrombocytopenia that persists for ≥ 7 days and requires platelet transfusion on ≥ 2 separate days within a 7-day period (study drug does not need to be held unless DLT criteria are met); or
  
  o Grade 3 or higher hemolysis; or
  
  o Neutropenia or thrombocytopenia that results in delay in start of subsequent cycle by > 14 days.

- Hematological dose limiting toxicity for patients **with known bone marrow metastatic disease**:
  
  o Grade 4 thrombocytopenia or grade 4 neutropenia of any duration. If clinical concern that the thrombocytopenia or neutropenia may be attributable to progressive bone marrow metastatic disease, recommend bone marrow evaluation. Grade 4 thrombocytopenia or grade 4 neutropenia attributable to progressive bone marrow metastatic disease and not to study drug will not be considered DLT; or
  
  o Grade 3 or higher hemolysis; or
  
  o Neutropenia or thrombocytopenia that results in delay in start of subsequent cycle by > 14 days.

Any Grade 5 toxicity will be considered a DLT unless unrelated to BMS-986158 or BMS-986378 (CC-90010).
Allergic reactions of any grade are considered to be idiosyncratic and not dose-related. Therefore, these events will not be considered DLT.

Management and dose modifications associated with the above adverse events are outlined in Section 6.

5.7 General Concomitant Medication and Supportive Care Guidelines

5.7.1 Concomitant Medications

5.7.1.1 No other cancer chemotherapy, radiotherapy, tumor-directed surgery (biopsy acceptable), or immunomodulating agents are allowed.

5.7.1.2 Appropriate antibiotics, blood products, anti-emetics (see Section 5.7.2.2), fluids, electrolytes and general supportive care are to be used as necessary (see Section 5.7.2).

5.7.1.3 Non-steroidal anti-inflammatory drugs, oral anticoagulants, and therapeutic heparins are prohibited while on protocol therapy. Note: Use of heparin to maintain patency of a central or peripheral catheter is allowed.

5.7.1.4 BMS-986158 is a substrate for efflux transporters and CYP3A4/CYP3A5. Therefore, there is a potential for drug-drug interactions with strong inducers/inhibitors of P-glycoprotein and CYP3A. The agents in Appendix B are prohibited while a patient is on protocol therapy with BMS-986158 (Arm 1). This is not a comprehensive list and any medications in question should be discussed with the Overall Principal Investigator.

BMS-986378 (CC-90010) is an inhibitor of P-glycoprotein. P-glycoprotein substrates with a narrow therapeutic index are listed in Appendix B and are prohibited while a patient is on protocol therapy on Arm 2. BMS-986378 (CC-90010) is primarily metabolized by CYP3A4/CYP3A5. Strong inducers/inhibitors of CYP3A4/5 are listed in Appendix B and are prohibited while a patient is on protocol therapy on Arm 2. These are not comprehensive lists and any medications in question should be discussed with the Overall Principal Investigator.

BMS-986378 (CC-90010) inhibits phosphodiesterase type 5 and 6. Unless listed as prohibited in Appendix B, protease inhibitors, anti-hypertensives, nitrates, guanylate cyclase stimulators, and PDE5 inhibitors should be used with caution for patients on Arm 2.

5.7.1.5 Consumption of grapefruit or Seville oranges and/or their juices is prohibited while on protocol therapy on either arm of the trial.
5.7.1.6 No other investigational agents (administered under an IND) may be given while on protocol therapy.

5.7.2 Supportive Care Guidelines

5.7.2.1 Use of Antidiarrheal Agents

All patients should be provided with loperamide and instructed in its use at the initial treatment visit in the event that a patient develops diarrhea. The following guidelines for the management of diarrhea should be used along with the clinical judgment of the treating physician.

Dietary recommendations should include eating small, frequent meals, diet modification (avoiding milk products, spicy and/or fatty foods, and caffeine).

Loperamide is recommended to be started at the earliest sign of 1) poorly formed or loose stool, 2) the occurrence of 1 to 2 more bowel movements than usual in 1 day, or 3) an increase in stool volume or liquidity. Loperamide may be taken in the following manner according to weight:

Under 13 kg: take 0.5 mg after the first loose bowel movement, followed by 0.5 mg every 3 hours. During the night, the patient may take 0.5 mg every 4 hours. Do not exceed 4 mg per day.

From 13 kg to less than 20 kg: Take 1 mg after the first loose bowel movement, followed by 1 mg every 4 hours. During the night, the patient may take 1 mg every 4 hours. Do not exceed 6 mg per day.

From 20 kg to less than 30 kg: Take 2 mg after the first loose bowel movement, followed by 1 mg every 3 hours. During the night, the patient may take 2 mg every 4 hours. Do not exceed 8 mg per day.

From 30 kg to less than 43 kg: Take 2 mg after the first loose bowel movement, followed by 1 mg every 2 hours. During the night, the patient may take 2 mg every 4 hours. Do not exceed 12 mg per day.

For adolescents ≥ 43 kg: Take 4 mg after the first loose bowel movement, followed by 2 mg after each loose stool. During the night, the patient may take 4 mg every 4 hours. Do not exceed 16 mg per day.

For subjects who cannot take loperamide or who do not get adequate relief with maximum doses, standard doses of Lomotil (diphenoxylate/atropine) may be added or used instead of loperamide.

Additional antidiarrheal measures, such as octreotide, may be used at the
discretion of the investigator or treating physician.

5.7.2.2 Use of Antiemetics

All patients should have an antiemetic available per institutional guidelines while receiving BMS-986158 or BMS-986378 (CC-90010), given that nausea is a frequently reported adverse event associated with the study drug. The recommended regimen is to receive a 5-HT₃ antagonist (i.e. ondansetron) per institutional standard as needed for nausea/vomiting. If 5-HT₃ antagonist use is contraindicated, substitution with another antiemetic is advised.

5.7.2.3 Use of Myeloid Growth Factors

Myeloid growth factors are only to be utilized in the setting of grade 3 or 4 neutropenia together with documented invasive fungal infection, bacteremia, or fever with sepsis physiology. The Overall Principal Investigator must be notified in the event of myeloid growth factor use. Patients who receive myeloid growth factor for treatment-related grade 4 neutropenia will be included as a DLT as per its definition in Section 5.6.1. Patients who received myeloid growth factor for treatment-related grade 3 neutropenia will be excluded from assessment of dose-limiting neutropenia in that cycle.

5.8 Criteria for Taking a Participant Off Protocol Therapy

Duration of therapy will depend on individual response, evidence of disease progression, and tolerance. Treatment may continue for up to 26 cycles or until one of the following criteria applies:

- Clinical or radiographic evidence of disease progression
- Intercurrent illness that prevents further administration of treatment
- Dose-limiting or other toxicity that meets criteria for removal from protocol therapy (see Section 6.1)
- Participant demonstrates an inability or unwillingness to comply with the medication regimen and/or documentation requirements
- Participant or parent/legal guardian decides to withdraw from the protocol therapy
- General or specific changes in the participant’s condition or protocol compliance render the participant unacceptable for further treatment in the judgment of the treating investigator
- Pregnancy

Participants will be removed from the protocol therapy when any of these criteria apply. The reason for removal from protocol therapy, and the date the participant was removed, must be documented in the case report form (CRF).

When a participant is removed from protocol therapy and/or is off of the study, the relevant Off-Treatment/Off-Study information will be updated in OnCore.
5.9 **Duration of Follow Up**

Participants will be followed for 30 days from last dose of protocol therapy or until death, whichever occurs first. Participants who start a new therapy will still be followed for 30 days from last dose of BMS-986158 or BMS-986378 (CC-90010). This period will be extended until resolution of any ongoing adverse events unless determined to be unrelated to BMS-986158 or BMS-986378 (CC-90010). Participants removed from protocol therapy for unacceptable adverse event(s) will be followed until resolution or stabilization of the adverse event.

For participants unable to return to the study center for the planned 30-day follow-up visit, documentation of a clinical evaluation at their referring center is acceptable.

For participants of reproductive potential, a telephone follow-up will be performed 7 months after last dose of BMS-986158 or BMS-986378 (CC-90010) to ascertain pregnancy status of participants and their partners, if such information is not already known by study team. For participants who are discovered to be pregnant or may have been pregnant at the time of exposure to BMS-986158 or BMS-986378 (CC-90010) (or within 5 half-lives of last dose), or female partners of male participants who become pregnant or had unprotected vaginal intercourse while pregnant (even if the male participant has had a vasectomy), follow-up information should be obtained on pregnancy outcomes for one year following the birth of the offspring. Follow-up information regarding the course of the pregnancy, including perinatal and neonatal outcome and, where applicable, offspring information must be reported in an expedited manner (see Section 7.8.2).

5.10 **Criteria for Taking a Participant Off Study**

Participants will be removed from study when any of the following criteria apply:
- Completion of 30-day follow-up (this period will be extended until resolution of any ongoing possibly, probably, or definitely related adverse events);
- Found to be ineligible, including participants who have repeat organ function laboratory studies obtained within 5 days prior to Cycle 1, Day 1 that do not meet entry eligibility requirements;
- Lost to follow-up;
- Withdrawal of consent for data submission;
- Death.

The reason for taking a participant off study, and the date the participant was removed, must be documented in the case report form (CRF). In addition, the study team will ensure Off Treatment/Off Study information is updated in OnCore in accordance with DF/HCC policy REGIST-101.

6 **DOsing DELays/DOse ModIficATions**
Dose delays and modifications will be made as indicated in the following text and table(s). The descriptions and grading scales found in the revised NCI Common Terminology Criteria for Adverse Events (CTCAE) version 5.0 will be utilized for guiding dose delays and dose modifications.

6.1 **Dose modification for dose-limiting toxicity**

Patients with protocol-defined DLT (Section 5.6) during the DLT evaluation period (Cycle 1) will discontinue treatment with BMS-986158 or BMS-986378 (CC-90010) unless deriving clinical benefit. With overall PI approval, those patients deriving benefit will be allowed to continue on protocol therapy with a dose reduction as described in the next paragraph.

Patients with protocol-defined DLT (Section 5.6) during Cycle $\geq 2$ will have investigational agent, either BMS-986158 or BMS-986378 (CC-90010), held until resolution of toxicity to $\leq$ grade 1 (or baseline, whichever is higher). Investigational agent will then be resumed at one dose level below assigned initial dose level. Patients with recurrent DLT (regardless of category of DLT) despite this dose reduction will be removed from protocol therapy. Patients already receiving therapy at the lowest dose level at the time of DLT will be removed from protocol therapy. If the patient requires $> 21$ days for resolution of toxicity to $\leq$ grade 1 (or baseline, whichever is higher), then the patient will be removed from protocol therapy.

For Arm 1, patients in the 10-patient expansion phase who undergo intrapatient dose escalation during Cycle $\geq 2$ and have DLT on the higher dose level will have BMS-986158 resumed at their original assigned initial dose level once toxicity has resolved to $\leq$ grade 1. Such patients who have recurrent DLT at their original assigned initial dose level will be managed according to the preceding paragraph.

Patients experiencing $\geq$ Grade 3 hypersensitivity reactions that are related to BMS-986158 or BMS-986378 (CC-90010) should be discontinued from study treatment and not rechallenged.

7 **ADVERSE EVENTS: LIST AND REPORTING REQUIREMENTS**

7.1 **Introduction to Adverse Event Reporting**

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

Adverse event (AE) monitoring and reporting is a routine part of every clinical trial. The following list of reported and/or potential AEs (Section 7.2) and the characteristics of an observed AE (Section 7.3) will determine whether the event requires expedited reporting in
addition to routine reporting.

7.2 Adverse Event List for Investigational Agents

7.2.1 Adverse Event List for BMS-986158 (Arm 1)
The following adverse event list reflects adverse events reported in adults treated with BMS-986158 monotherapy on one adult clinical trial, CA011-001 (see also current version of Investigator Brochure).

≥10% Incidence
- Diarrhea
- Nausea
- Thrombocytopenia
- Anemia
- Lymphopenia
- Fatigue
- Decreased appetite
- Vomiting
- Constipation
- Cough
- Dyspnea
- Increased AST
- Hyperbilirubinemia
- Neutropenia
- Decreased white blood cells
- Increased ALT
- Elevated GGT
- Elevated lipase
- Elevated amylase
- Hypomagnesemia
- Hyponatremia
- Hyponatremia
- Hypophosphatemia
- Hyperuricemia
- Increased creatinine
- Increased PTT

Additional Rare But Serious Adverse Events
- Small intestinal obstruction
- Myocardial infarction
- Stroke
- Respiratory tract infection

7.2.2 Adverse Event List for BMS-986378 (CC-90010) (Arm 2)
The following adverse event list reflects adverse events reported in adults treated with BMS-
986378 (CC-90010) monotherapy on one adult clinical trial, CC-90010-ST-001 (see also current version of Investigator Brochure).

>10% Incidence
- Thrombocytopenia
- Diarrhea
- Nausea
- Asthenia
- Dysgeusia
- Stomatitis
- Vomiting
- Fatigue
- Decreased appetite
- Hyperglycemia
- Anemia
- Abdominal pain
- Increased ALT
- Dermatitis acneiform
- Constipation
- Headache
- Maculopapular rash
- Neutropenia
- Pyrexia
- Hypomagnesemia
- Hypophosphatemia

<10% Incidence
- Arthralgia
- Cognitive disorder
- Dyspnea

7.3 Adverse Event Characteristics

Investigators are to provide the following adverse event characteristics for all adverse events experienced from start of protocol therapy until 30 days after last dose of BMS-986158 or BMS-986378 (CC-90010), unless extended according to Section 5.9:

- **CTCAE term (AE description) and grade:** The descriptions and grading scales found in the revised NCI Common Terminology Criteria for Adverse Events (CTCAE) version 5.0 will be utilized for AE reporting. All appropriate treatment areas should have access to a copy of the CTCAE version 5.0. A copy of the CTCAE version 5.0 can be downloaded from the CTEP web site, [http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm](http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm).

- **Attribution of the AE:**
  - Definite – The AE is clearly related to the study treatment.
  - Probable – The AE is likely related to the study treatment.
Possible – The AE *may be related* to the study treatment.

Unlikely – The AE *is doubtfully related* to the study treatment.

Unrelated – The AE *is clearly NOT related* to the study treatment.

- **Seriousness of the AE:** An AE is to be classified as “serious” (SAE) if it meets any of the following criteria:

<table>
<thead>
<tr>
<th>Death of Patient</th>
<th>An event that results in the death of a patient.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Life-Threatening</td>
<td>An event that, in the opinion of the investigator, would have resulted in immediate fatality if medical intervention had not been taken. This does not include an event that would have been fatal if it had occurred in a more severe form.</td>
</tr>
<tr>
<td>Hospitalization</td>
<td>An event that results in an admission to the hospital for any length of time. This does not include an emergency room visit or admission to an outpatient facility.</td>
</tr>
<tr>
<td>Prolongation of Hospitalization</td>
<td>An event that occurs while the study patient is hospitalized and prolongs the patient’s hospital stay.</td>
</tr>
<tr>
<td>Congenital Anomaly</td>
<td>An anomaly detected at or after birth or any anomaly that result in fetal loss.</td>
</tr>
<tr>
<td>Persistent or Significant Disability/Incapacity</td>
<td>An event that results in a condition that substantially interferes with the activities of daily living of a study patient. Disability is not intended to include experiences of relatively minor medical significance such as headache, nausea, vomiting, diarrhea, influenza, or accidental trauma (e.g., sprained ankle).</td>
</tr>
<tr>
<td>Important Medical Event Requiring Medical or Surgical Intervention to Prevent Serious Outcome</td>
<td>An <em>important medical event</em> that may not be immediately life-threatening or result in death or hospitalization, but based on medical judgment may jeopardize the patient and may require medical or surgical intervention to prevent any of the outcomes listed above (<em>i.e.</em>, death of patient, life-threatening, hospitalization, prolongation of hospitalization, congenital anomaly, or persistent or significant disability/incapacity). Examples of such events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse.</td>
</tr>
</tbody>
</table>

An AE that meets none of the above criteria is considered “non-serious”.

**Note:** Seriousness is independent of attribution or expectedness of the AE.

- **Expectedness of the AE:** In addition to term, grade, attribution, and seriousness, adverse events that have the potential to qualify for expedited reporting (see Section 7.5) are to be designated as “expected” or “unexpected”.

### 7.4 Routine Adverse Event Reporting

All Adverse Events in Cohorts A and B of the study **must** be reported in routine study data submissions to the Overall Principal Investigator on the toxicity case report forms. AE collection will begin following the participant’s written consent to participate in the study. **AEs that also meet criteria for expedited reporting (see Section 7.5) must also be reported in**
routine study data submissions.

All non-serious adverse events (not only those deemed to be treatment-related) should be collected continuously during the treatment period and for a minimum of 30 days following the last dose of study treatment.

Non-serious AEs should be followed to resolution or stabilization, or reported as SAEs if they become serious. Follow-up is also required for non-serious AEs that cause interruption or discontinuation of study drug and for those present at the end of study treatment as appropriate.

All laboratory test results captured as part of the study should be recorded following institutional procedures. Test results that constitute SAEs should be documented and reported as such (including to BMS, see Section 7.8.1).

The following laboratory abnormalities should be documented and reported appropriately:

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

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

7.5 Expedited Adverse Event Reporting

7.5.1 Criteria for Expedited Adverse Event Reporting

Investigators must report to the Overall Principal Investigator in an expedited manner any adverse events (AE) that occur after the initial dose of study treatment, during treatment, or within 30 days of the last dose of treatment if they meet any of the following criteria and are not listed as adverse events exempt from expedited reporting in Section 7.5.3:

- Serious adverse event, including grade 5 adverse events;
- Pregnancy in a female participant treated with BMS-986158 or BMS-986378 (CC-90010) or pregnancy in a female partner of a male participant treated with BMS-986158 or BMS-986378 (CC-90010);
- Potential drug-induced liver injury (see definition in section 7.8.3);
- Other adverse events (serious or not serious) that meet DFCI Institutional Review Board Adverse Event Reporting policy for expedited reporting:
  - Grade 2 or 3 unexpected adverse events that are attributed as at least possibly related to BMS-986158 or BMS-986378 (CC-90010);
  - All Grade 4 adverse events, regardless of attribution, unless listed as both expected (see Section 7.2) and not reportable (see Section 7.5.3)
Note: Grade 2 and Grade 3 laboratory abnormalities that are considered by the investigator to be clinically insignificant and do not require therapy, or adjustment in prior therapy, do not need to be reported to the Overall Principal Investigator or the DFCI IRB.

Regardless of treating institution, these expedited reports will be submitted to the Overall Principal Investigator using a DF/HCC AE Reporting form.

The treating institution must notify the Overall Principal Investigator by phone or email of any serious adverse event within 24 hours of learning of the event, with a formal written report within 3 business days.

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

For non-serious AE’s that nevertheless meet the above DF/HCC definition for expedited reporting, the following timelines apply for submission of a DF/HCC AE Reporting form to the Overall Principal Investigator.

<table>
<thead>
<tr>
<th>Attribution</th>
<th>Gr. 2 &amp; 3 AE Expected</th>
<th>Gr. 2 &amp; 3 AE Unexpected</th>
<th>Gr. 4 AE Expected</th>
<th>Gr. 4 AE Unexpected</th>
<th>Gr. 5 AE Expected or Unexpected</th>
</tr>
</thead>
<tbody>
<tr>
<td>Unrelated Unlikely</td>
<td>Not required</td>
<td>Not required</td>
<td>5 calendar days</td>
<td>5 calendar days</td>
<td>24 hours*</td>
</tr>
<tr>
<td>Possible Probable</td>
<td>Not required</td>
<td>5 calendar days</td>
<td>5 calendar days</td>
<td>5 calendar days</td>
<td>24 hours*</td>
</tr>
<tr>
<td>Definite</td>
<td></td>
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<td></td>
</tr>
</tbody>
</table>

#Events that are expected and listed within the protocol and/or current consent form do not need to be reported in an expedited manner.

* For participants enrolled and actively participating in the study or for AEs occurring within 30 days of the last intervention, the AE should be reported within 24 hours of learning of the event.

**Please follow these reporting timelines only if the event qualifies as non-serious. The treating institution must notify the Overall Principal Investigator by phone or email of any serious adverse event within 24 hours of learning of the event, with a formal written report within 3 business days.

7.5.2 Guidelines for Multicenter Expedited AE Reporting
For multi-institution studies where a DF/HCC investigator is serving as the Overall Principal Investigator, each participating institution must abide by the reporting requirements set by the DF/HCC. This applies to any adverse event meeting the criteria for expedited reporting as defined in section 7.5.1.

Investigative sites within DF/HCC will report expedited AEs directly to the DFCI Office for Human Research Studies (OHRS) per the DFCI IRB reporting policy.

Other investigative sites will report expedited AEs to their respective IRB according to the local IRB’s policies and procedures in reporting adverse events. These sites will also complete a DF/HCC AE Reporting form to the Overall Principal Investigator within the timeframes detailed above. The Overall Principal Investigator will then submit the DF/HCC AE Reporting form from outside institutions to the DFCI OHRS according to DFCI IRB policies and procedures in reporting adverse events. Outside sites should also provide the Overall Principal Investigator with a copy of any local AE reporting form required to be submitted to their local IRB.

7.5.3 Protocol-Specific Expedited Adverse Event Reporting Exclusions

Unless the adverse event meets the definition of serious, the following grade 2 adverse events do not require expedited reporting to the Overall Principal Investigator or the DFCI IRB: nausea; vomiting; fatigue; anemia; anorexia; headache; constipation; and diarrhea.

Unless the adverse event meets the definition of serious, lymphopenia of any grade does not require expedited reporting to the Overall Principal Investigator or the DFCI IRB.

These AEs still must be reported through the routine reporting mechanism (i.e. case report form).

7.6 Expedited Reporting to the Food and Drug Administration (FDA)

The Overall Principal Investigator, as study sponsor and IND holder, will be responsible for all communications with the FDA. The Overall Principal Investigator will report to the FDA, regardless of the site of occurrence, any serious adverse event that meets the FDA’s criteria for expedited reporting following the reporting requirements and timelines set by the FDA.

Specifically, the Overall Principal Investigator will notify the FDA and all participating investigators in a written IND safety report of any adverse experience associated with use of the drug that is both serious and unexpected. Each written notification shall be made as soon as possible, and in no event later than 15 calendar days after the sponsor’s initial receipt of the information. Each written notification may be submitted on FDA Form 3500A (MedWatch) or in a narrative format and must bear prominent identification of its contents, i.e., “IND Safety Report”. Follow-up information to a safety report should be submitted as soon as the relevant information is available.

The sponsor must also notify FDA of any unexpected fatal or life-threatening experience associated with use of the drug in the clinical studies conducted under the IND as soon as
possible but in no event later than 7 calendar days after initial receipt of the information. Notification may occur via telephone, facsimile, or other mode of transmission. In the event a 7-day report is required, the Overall Principal Investigator or designee will consult with the assigned FDA Project Manager and follow the preferred mode of communication for reporting the event.

The Overall Principal Investigator will determine whether any AE’s reported in an expedited manner on an Expedited AE Reporting form meet criteria for submission as an expedited report to the FDA. The Overall Principal Investigator will prepare the FDA expedited report using information provided by the treating investigator on the Expedited AE Reporting form.

7.7 Expedited Reporting to Hospital Risk Management

Participating investigators will report to their local Risk Management office any participant safety reports or sentinel events that require reporting according to institutional policy.

7.8 Reporting to Bristol-Myers Squibb

7.8.1 SAE Reporting to Bristol-Myers Squibb

The Overall Principal Investigator or his designee will report any serious adverse events from time of consent until 30 days after last dose of BMS-986158 or BMS-986378 (CC-90010) - regardless of expectedness or attribution - to Bristol-Myers Squibb. The initial report must be within 24 hours of notification of such events. If only limited information is initially available, a follow-up report is required. All serious adverse events should be followed to resolution or stabilization.

Initial and follow-up safety reports will utilize the DF/HCC AE Reporting form and will be sent electronically to: Worldwide.Safety@BMS.com

7.8.2 Reporting Pregnancy to Bristol-Myers Squibb

Any pregnancy in a female participant treated with BMS-986158 or BMS-986378 (CC-90010) or any pregnancy in a female partner of a male participant treated with BMS-986158 or BMS-986378 (CC-90010) will be reported to BMS in an expedited manner following the same guidelines used for reporting SAEs (section 7.8.1).

In addition, any adverse events associated with maternal exposure and pregnancy outcomes must be reporting using SAE reporting guidelines (Section 7.8.1). Follow-up information should be obtained on pregnancy outcomes for one year following the birth of the offspring. Follow-up information regarding the course of the pregnancy, including perinatal and neonatal outcome and, where applicable, offspring information must be reported in an expedited manner.

Since BMS-986158 and BMS-986378 (CC-90010) has been detected in seminal fluid in non-clinical studies, any sexual activity between a male participant without the use of a condom
(even if a male participant is azoospermic) and a female partner who is already pregnant must be reported to BMS following the same guidelines used for reporting SAEs (section 7.8.1).

7.8.3 Reporting Potential Drug-Induced Liver Injury to Bristol-Myers Squibb

Potential drug-induced liver injury is defined as:
1) ALT or AST elevation > 3 times upper limit of normal (ULN)
   AND
2) Total bilirubin > 2 times ULN, without initial findings of cholestasis (elevated serum alkaline phosphatase)
   AND
3) No other immediately apparent possible causes of ALT or AST elevation and hyperbilirubinemia, including, but not limited to, viral hepatitis, pre-existing chronic or acute liver disease, or the administration of other drug(s) known to be hepatotoxic.

Any episode of potential drug-induced liver injury is to be reported to Bristol-Myers Squibb in an expedited manner following the same guidelines used for reporting SAEs (section 7.8.1).

7.8.4 Quarterly Non-Serious Adverse Event Reporting to Bristol-Myers Squibb

Routine non-serious adverse events not submitted to BMS in an expedited manner will be submitted to BMS every three (3) months by the last working day of the third month. Adverse event information required will be sent to BMS using the “Bristol-Myers Squibb Early Asset Investigator Sponsored Research (ISR) Import Plan.” The file will be submitted to BMS via the following mailbox with a note that the file contains all non-serious adverse events (only adverse events not previously submitted to BMS with the 3 months):

MG-RD-GPVE-PHARMACOVIGILANCE@bms.com

7.9 External Safety Reports Received from Bristol-Myers Squibb

In accordance with local regulations, BMS will notify sponsor investigators of all reported SAEs that are suspected (related to the investigational product) and unexpected (i.e., not previously described in the IB). An event meeting these criteria is termed a Suspected, Unexpected Serious Adverse Reaction (SUSAR). Sponsor investigator notification of these events will be in the form of either a SUSAR Report or a Semi-Annual SUSAR Report.

8 PHARMACEUTICAL INFORMATION

A list of the adverse events and potential risks associated with BMS-986158 and BMS-986378 (CC-90010) can be found in Section 7.2.

8.1 BMS-986158

8.1.1 Description Including Pharmacokinetics, Metabolism and Drug-Interactions
The molecular formula of BMS-986158 is C$_{30}$H$_{33}$N$_5$O$_2$ and the molecular weight is 495.62 amu. BMS-986158 is a chemically synthesized small molecule inhibitor of the bromodomain (BRD) and extraterminal (BET) family of transcription modulators.

BMS-986158 has a plasma t$_{1/2}$ of 1.8 hours in mice and a projected t$_{1/2}$ of 9 hours in humans. After four weeks of 5 days on/2 days off daily dosing there was no accumulation of the primary drug in rats. BMS-986158 is primarily metabolized by oxidation, glucuronidation, and glucuronidation of oxidative metabolites. The major metabolite is BMS-161485. Hepatobiliary metabolism and fecal excretion are the primarily clearance pathways for BMS-986158.

*In vitro* metabolic reaction phenotyping studies, using individually expressed recombinant human CYP enzymes, demonstrated that the oxidative metabolism of BMS-986158 was primarily mediated by CYP3A4 (66%) and CYP3A5 (23%). Glucuronidation of BMS-986158 is primarily mediated via UGT1A4 with minor contribution by UGT2B17. These data suggest that the potential exists of drug-drug interactions if BMS-986158 is co-administered with an inhibitor of inducer of these enzymes. Pre-clinical data also suggests that BMS-986158 is a substrate of efflux transporter(s) such as P-gp and BCRP, therefore levels of BMS-986158 may be impacted by inhibitors of these transporters.

8.1.2 Form

BMS-986158 capsules containing drug substance and polyethylene glycol 1450 have been developed for clinical studies. There are 2 capsule strengths: grey size #0 capsules contain 2 mg of BMS-986158 and white size #2 capsules contain 0.25 mg of BMS-986158. The 2-piece hard gelatin capsules are supplied in a tightly closed, high-density polyethylene bottle with a cotton coil and child-resistant closure with a heat induction seal. Each bottle contains 33 capsules. BMS-986158 should be dispensed in the original bottle.

8.1.3 Storage and Stability

BMS-986158 capsules should be stored in a tightly closed container refrigerated at 2$^\circ$C to 8$^\circ$C (36$^\circ$F to 46$^\circ$F) and protected from light.

8.1.4 Handling

Qualified personnel, familiar with procedures that minimize undue exposure to themselves and the environment, should undertake the handling and safe disposal of BMS-986158 in a self-contained and protective environment.

8.1.5 Availability

BMS-986158 is an investigational agent and is only available to participants in clinical trials being conducted under an IND.
8.1.6 Preparation

No preparation is required for BMS-986158 capsules. Capsules must be swallowed intact and not opened, chewed, or otherwise altered prior to administration.

8.1.7 Administration

See Section 5 for full administration instructions.

8.1.8 Ordering

Initial and follow-up supplies of BMS-986158 capsules will be obtained using a drug order form from Bristol-Myers Squibb. The initial shipment will only be shipped once all regulatory requirements have been satisfied.

For drug re-supply orders, please submit requests at least 7 business days in advance of full depletion in order to ensure that the site is re-supplied in a timely manner.

8.1.9 Accountability

The investigator, or a responsible party designated by the investigator, should maintain a careful record of the inventory and disposition of the agent using the NCI Drug Accountability Record Form (DARF) or another comparable drug accountability form.

8.1.10 Destruction and Return

At the conclusion of the study, the Overall Principal Investigator will provide participating institutions with guidance on final disposition (destruction vs. return of drug to Bristol-Myers Squibb) of BMS-986158 that has not been administered to participants.

8.2 BMS-986378 (CC-90010)

8.2.1 Description Including Pharmacokinetics, Metabolism and Drug-Interactions

BMS-986378 (CC-90010) is a reversible small molecule inhibitor of the bromodomain (BRD) and extraterminal (BET) family of transcription modulators including BRD2, BRD3, BRD4 and BRDT. The molecular formula of BMS-986378 is C_{21}H_{21}NO_4S.

Following oral dosing, BMS-986378 (CC-90010) is rapidly and well absorbed in mice, rats, and dogs with a median $t_{\text{max}}$ ranging from 0.25 to 2 hours post-dose. Oral bioavailability is 71%, 40% and 76% for mice, rats, and dogs, respectively. BMS-986378 (CC-90010) has a $t_{1/2}$ of 40-70 hours in humans when administered on a 4 days on/24 days off schedule. BMS-986378 (CC-90010) is primarily metabolized by oxidation, glucuronidation, dealkylation and combinations of these pathways. Rat studies indicate that metabolism plays a significant role in the elimination of BMS-986378 (CC-90010) and excretion of intact drug is not the primary mode of elimination.
In vitro metabolic reaction phenotyping studies, demonstrated that BMS-986378 metabolism is primarily catalyzed by CYP3A4/5 with minor involvement of CYP2C8. These data suggest that the potential exists of drug-drug interactions if BMS-986378 (CC-90010) is co-administered with an inhibitor of inducer of these enzymes. Pre-clinical data also suggests that BMS-986378 (CC-90010) is a substrate of efflux transporter P-gp, therefore levels of BMS-986378 (CC-90010) may be impacted by inhibitors of these transporters.

8.2.2 Form

BMS-986378 (CC-90010) is supplied as white to off-white, round (10 mg and 15 mg) and oval (50 mg) tablets containing the active pharmaceutical ingredient. Tablets also contain the following excipients: hydroxypropylmethylcellulose acetate succinate, microcrystalline cellulose, lactose monohydrate, croscarmellose sodium, colloidal silicon dioxide, and magnesium stearate.

8.2.3 Storage and Stability

BMS-986378 (CC-90010) tablets should be stored as directed on the product label and must be used within the individual assigned expiry date on the label.

8.2.4 Handling

Qualified personnel, familiar with procedures that minimize undue exposure to themselves and the environment, should undertake the handling and safe disposal of BMS-986378 (CC-90010) in a self-contained and protective environment.

Patients should not extensively handle BMS-986378 (CC-90010) tablets and should maintain storage in the original packaging until ingestion.

8.2.5 Availability

BMS-986378 (CC-90010) is an investigational agent and is only available to participants in clinical trials being conducted under an IND.

8.2.6 Preparation

No preparation is required for BMS-986378 (CC-90010) tablets. Tablets must be swallowed intact and not chewed, or otherwise altered prior to administration.

8.2.7 Administration

See Section 5 for full administration instructions.

8.2.8 Ordering
Initial and follow-up supplies of BMS-986378 (CC-90010) tablets will be obtained using a drug order form from Bristol-Myers Squibb. The initial shipment will only be shipped once all regulatory requirements for Amendment 5 have been satisfied.

For drug re-supply orders, please submit requests **at least 7 business days** in advance of full depletion in order to ensure that the site is re-supplied in a timely manner.

8.2.9 Accountability

The investigator, or a responsible party designated by the investigator, should maintain a careful record of the inventory and disposition of the agent using the NCI Drug Accountability Record Form (DARF) or another comparable drug accountability form.

8.2.10 Destruction and Return

At the conclusion of the study, the Overall Principal Investigator will provide participating institutions with guidance on final disposition (destruction vs. return of drug to Bristol-Myers Squibb) of BMS-986378 (CC-90010) that has not been administered to participants.

9 BIOMARKER, CORRELATIVE, AND SPECIAL STUDIES

9.1 Pharmacokinetic Study for Arms 1 and 2

The goal of the pharmacokinetic studies are to define the plasma concentration-time profiles of BMS-986158 and BMS-986378 (CC-90010) and their primary circulating metabolites following the first dose (Cycle 1, Day 1) as well as trough concentrations later in the treatment course.

To better understand the levels of BMS-986378 (CC-90010) in the CSF, CSF will be collected each time patients with CNS tumors undergo lumbar puncture as part of standard of care procedures. Likewise, patients with an Ommaya present who can undergo unsedated Ommaya taps and provide additional consent will provide a single CSF sample following administration of BMS-986378 (CC-90010).

When planning the start date for Cycle 1, note the timing of required PK draws relative to staff availability to obtain and process the PK samples.

PK kits will be provided to participating sites and sites are advised to be sure to have sufficient, non-expired, PK kits available prior to starting a new patient on therapy.

9.1.1 Sampling Schedule

9.1.1.1 Plasma Sampling Strategy (required for all participants in all parts of the study)
At each time point, 1 mL of blood is to be collected into a 1 mL K2EDTA (usually purple top) tube. For patients with a central catheter, samples may be obtained centrally or peripherally.

Sites are encouraged to utilize a digital timer/stopwatch programmed to operate continuously as a 24-h clock in order to accurately monitor drug administration and sample collection times. The same timer should be allowed to run without interruption until the last blood specimen has been obtained from the patient during that cycle of therapy. The exact time of each draw must be recorded on the Pharmacokinetic Worksheet in Appendix D.

The following sampling schedule will be used in Arm 1 - Cycle 1. All draws may be completed within the designated window, with exact time recorded on the Pharmacokinetic Worksheet.

Arm 1 with BMS-986158 - Cycle 1:

Day 1:
- Prior to first orally administered dose
- 30 minutes after dose (± 10 minutes)
- 1 hour after dose (± 10 minutes)
- 2 hours after dose (± 10 minutes)
- 3 hours after dose (± 10 minutes)
- 4 hours after dose (± 15 minutes)
- 6 hours after dose (± 15 minutes)
- 8 hours after dose (± 1 hours)

Day 2:
- 24 hours after Day 1 dose (± 4 hours) before the Day 2 dose

Day 4 or 5:
- 24 hours after dose on preceding day (± 4 hours) but prior to the dose on the day of the PK draw.

Day 8:
- Untimed draw any time prior to administration of Day 8 dose

Day 11, 12, 18, or 19:
- 24 hours after dose on preceding day (± 4 hours) but prior to the dose on the day of the PK draw.

For patient and site flexibility, this sample may be obtained pre-dose on Day 11, 12, 18, or 19. The intent is to obtain a pre-dose trough sample on the fourth or fifth dosing day of one of these five-day dosing weeks.

Day 15 or 22:
Untimed draw any time prior to administration of Day 15 or Day 22 dose (or at any time on Day 22 for patients on interrupted dose level who do not receive drug on Day 22)

The following sampling schedule will be used in Arm 2 - Cycle 1. All draws may be completed within the designated window, with exact time recorded on the Pharmacokinetic Worksheet.

Arm 2 with BMS-986378 (CC-90010) - Cycle 1:

Day 1:
- Prior to first orally administered dose
- 30 minutes after dose (± 10 minutes)
- 1 hour after dose (± 10 minutes)
- 2 hours after dose (± 10 minutes)

Day 2:
- 24 hours after Day 1 dose (± 4 hours) before the Day 2 dose

Day 4:
- Prior to Day 4 dose
- 30 minutes after dose (± 10 minutes)
- 1 hour after dose (± 10 minutes)
- 2 hours after dose (± 10 minutes)
- 3 hours after dose (± 10 minutes)
- 4 hours after dose (± 15 minutes)
- 6 hours after dose (± 15 minutes)
- 8 hours after dose (± 1 hours)
- 24 hours after dose on preceding day (± 4 hours) but prior to the dose on the day of the PK draw if dose due that day

Day 8 (±/± 1 day)
- Untimed draw

Day 15 (±/± 1 day)
- Untimed draw

The Pharmacokinetic Worksheet in Appendix D is to be completed in real time by site staff.

9.1.1.2 CSF Sampling Strategy

9.1.1.2.1 Patients Having Standard of Care Lumbar Puncture (Required submission on Arm 2)
Patients who undergo planned standard of care lumbar puncture (e.g., for
staging/disease assessment) will provide a 3 mL CSF sample at the time of each standard of care lumbar puncture (may be during or after Cycle 1). If clinically feasible, it is recommended that lumbar puncture procedures be scheduled on a BMS-986378 (CC-90010) dosing day, with the procedure occurring any time after that day’s dose of BMS-986378 (CC-90010). The sample should be collected into a standard plastic CSF collection tube without additive. A simultaneous (± 15 minutes) paired plasma sample should be obtained as well (collect 1 mL of blood in K2EDTA tube and process as per section 9.1.2.1). The CSF (Lumbar Puncture) Worksheet in Appendix D is to be completed in real time by site staff.

9.1.1.2 Patients with Ommaya Reservoir Sampling Schedule (Optional)
Patients with Ommaya reservoirs on Arm 2 who provide additional consent and who do not require anesthesia to access the Ommaya will provide a single 3 mL CSF sample via Ommaya on Cycle 1 Day 2 or 4. The sample must be obtained within 4 hours of administration of medication on these days. The sample should be collected into a standard plastic CSF collection tube without additive. A simultaneous (± 15 minutes) paired plasma sample should be obtained as well (collect 1 mL of blood in K2EDTA tube and process as per section 9.1.2.1). The CSF (Ommaya) Worksheet in Appendix D is to be completed in real time by site staff.

9.1.2 Processing Instructions

9.1.2.1 Plasma Processing Instructions

Immediately after obtaining each sample, tubes are to be gently inverted 8-10 times to mix the blood with the anticoagulant. Tubes are to be placed on wet ice within 5 minutes of the draw and remain on wet ice until they are centrifuged. Within 30 minutes of collection, samples are to be centrifuged at 1500 x g for 10 minutes at 4°C. Next, a disposable pipette (provided in PK kit) will be used to transfer two equal aliquots of the plasma, without disturbing the blood cells, into two (2) 2.0 mL self-standing polypropylene cryogenic storage vial with external threads (provided in PK kit). Affix a pre-printed barcode label onto the cryovials by wrapping the label around the tube and flagging the long sticky ends together. Write patient’s study ID number, collection date (mm/dd/yyyy) and time (hh:mm-24 hr clock) on label provided. No other identifiers should be included on the label. Store the plasma samples in a freezer at ≤ -70°C until packaged for shipment to the reference laboratory.

9.1.2.1 CSF Processing Instructions

CSF samples should be placed onto wet ice until arrival in the specimen processing laboratory. Once there, the CSF should be split into two equal aliquots of 1.5 mL each into 2.0 mL polypropylene cryovials (not provided). Write the patient’s study
ID number, collection date (mm/dd/yyyy), collection time (hh:mm-24 hr clock), and the word “CSF” on a standard label. No other identifiers should be included on the label. Store the CSF samples in a freezer at ≤ -70°C until requested by the study team.

9.1.3 Shipping Instructions

**NOTE THAT SHIPPING LOCATIONS AND CONTACTS DIFFER BETWEEN ARM 1 AND ARM 2**

For each time point, there will be a primary aliquot and a back-up aliquot. Retain one back-up aliquot at the site until instructed to ship the back-up aliquot. Do NOT ship both aliquots from a time point in the same shipment.

Send the primary aliquot samples in one batch once requested by the DFCI Study Coordinator. Ship samples by next day delivery to the address listed below.

Place the sample cryovials in a zip lock or self-adhesive plastic biohazard bag containing absorbent material sufficient to absorb the entire contents of all cryovials. Package samples in a seamless styrofoam container. Place the sample bag over at least 3-4 inches of dry ice on the bottom of the container and completely cover with an additional 3-4 inches or more of dry ice. Seal the styrofoam container within a tight-fitting cardboard shipping box which allows the escape of CO₂ gas.

Insert copies of the Pharmacokinetic Worksheet for each set of samples into a separate zip lock plastic bag placed on top of the styrofoam container before the external shipping box is sealed. Please retain one copy of the worksheet at the study center and send a copy of the worksheet via email to the DFCI Study Coordinator.

Send the plasma samples from Monday to Wednesday by FedEx for delivery by 10 a.m. on the following day. Samples should not be shipped on a Thursday or Friday.

**For Arm 1 with BMS-986158:** Please provide notification of the sample shipment by e-mail to pediatricBMS-986158@dfci.harvard.edu, JessicaR_Clymer@dfci.harvard.edu, LiMajor.Pittman@ppdi.com, RichmondSMOpeners@ppdi.com, and Richmond_data@ppdi.com. Reference “Pediatric BMS-986158” in your email.

Please use this FedEx account number 361615042 for these shipments and be sure to also provide reference number 9618307.

Sample Management
PPD Bioanalytical Lab
2246 Dabney Road
Richmond, VA 23230
USA
For Arm 2 with BMS-986378 (CC-90010): Please provide notification of the sample shipment by e-mail to pediatricBMS-986158@dfci.harvard.edu, JessicaR_Clymer@dfci.harvard.edu, and sample@qps.com Reference “Pediatric BMS-986378 (CC-90010)” in your email.

Please use this FedEx account number 361615042 for these shipments and be sure to also provide reference number 9618307.

QPS, LLC
Attn: Sample Team (SCG)
3 Innovation Way, Suite 240
Newark, DE 19711
USA
Phone: (302) 369-5182
Email: sample@qps.com

9.1.4 Methodology

The concentrations of BMS-986158, BMS-986378 (CC-90010), and their major circulating metabolites will be determined by a validated analytical method using LC-MS/MS. Individual patient plasma concentration-time curves will be analyzed by non-compartmental methods. Pharmacokinetic parameters and variables will be calculated according to standard equations.

9.2 Laboratory Correlative Studies for Both Arms 1 and 2

9.2.1 Pharmacodynamic Effects (required for all participants in all parts of the study)

The main pharmacodynamic marker is changes in peripheral blood gene expression profile.

9.2.1.1 Sampling Strategy

At each time point, 2.5 mL of blood is to be collected into provided PAXgene blood RNA tubes. For patients with a central catheter, samples may be obtained centrally or peripherally.

The following sampling schedule will be used in Cycle 1. All draws may be completed within the designated window, with exact time recorded on the Pharmacodynamic Worksheet in Appendix E.
• Cycle 1: Day 1 – prior to administration of drug
• Cycle 1: Day 1 – 4 hours after dose (± 15 minutes)
• Cycle 1: Day 1 – 8 hours after dose (± 1 hours)
• Cycle 1: Day 2 – 24 hours after the Day 1 dose (± 4 hours) prior to Day 2 dose

Note that these time points align with some but not all of the required PK time points.

9.2.1.2 Sample Processing Instructions
After collecting blood into a PAXgene tube, the tube should be gently inverted 8-10 times. Keep the tube at room temperature for 2 - 72 hours and then freeze upright in a wire rack (not Styrofoam holder) for 24 hours at -20°C and then transfer to -70 or -80°C freezer until batch shipment.

9.2.1.3 Sample Labeling Instructions

PAXgene tubes should be labeled with the patient’s study ID number, the words “Pediatric BMS-986158” if on Arm 1, or “Pediatric BMS-986378” if on Arm 2, the date of blood draw, the time of blood draw, and one of the following indicators of the sample timing:
• Cycle 1, Day 1, pre-dose
• Cycle 1, Day 1, 4 hours
• Cycle 1, Day 1, 8 hours
• Cycle 1, Day 2

No other identifiers should be included on the label.

9.2.1.4 Sample Shipment

Frozen PAXgene tubes from all draws for a patient should be batch shipped after all samples have been obtained. These samples should be shipped frozen on dry ice. Place the PAXgene tubes in a zip lock or self-adhesive plastic biohazard bag containing absorbent material sufficient to absorb the entire contents of all tubes. Ensure adequate dry ice to keep the samples frozen.

Sample shipment must include a copy of the Pharmacodynamic Worksheet (Appendix E). Please retain a copy of the worksheet at the site and email a copy of the worksheet to the DFCI Study Coordinator.
Samples should be shipped by Federal Express Priority Overnight to:

ATTN: Myriam Armant, TransLab
Boston Children’s Hospital
61 Binney Street
ENDERS Room 428
Boston, MA 02115

Please use this FedEx account number 361615042 for these shipments and be sure to also provide reference number 9618307.

Samples should only be shipped on Mondays-Thursdays to allow for weekday delivery. Email pediatricBMS-986158@dfci.harvard.edu, JessicaR_Clymer@dfci.harvard.edu, and myriam.armant@childrens.harvard.edu with the tracking number at the time of sample shipment.

9.2.1.5 Description of Assay

Total mRNA will be isolated from PAXgene tubes, using the commercial PAXgene Blood RNA kit. RNA expression will be quantified, with an emphasis on key target genes known to be modulated after BET inhibition: *HEXIM1* (upregulated) and *MYC* (downregulated).

9.2.2 Putative Biomarkers Associated with Response or Resistance

A series of markers summarized in Table 3 will be assessed to identify potential biomarkers associated with response or primary or secondary resistance to BMS-986158 and BMS-986378 (CC-90010).

**Table 3.** Putative predictive biomarkers to be evaluated.

<table>
<thead>
<tr>
<th>Biomarker</th>
<th>Tissue Source</th>
<th>Assay</th>
</tr>
</thead>
<tbody>
<tr>
<td>MYC, MYCN, Tuj1, BCL2L1, PTEN, and pAKT protein levels</td>
<td>Archival tumor material</td>
<td>Immunohistochemistry</td>
</tr>
<tr>
<td>MYC, MYCN, Tuj1, and BCL2L1 mRNA expression</td>
<td>Archival tumor material</td>
<td>RNA sequencing</td>
</tr>
<tr>
<td>MYC/MYCN copy number, translocation involving MYC, MYCN, BRD3, or BRD4</td>
<td>Archival tumor material</td>
<td>Next generation sequencing</td>
</tr>
<tr>
<td>MYC/MYCN copy number</td>
<td>Serial cell-free DNA samples</td>
<td>Next generation sequencing</td>
</tr>
</tbody>
</table>
9.2.3  Circulating Tumor DNA (ctDNA) – Required

9.2.3.1  Sampling Strategy

Collect blood in a provided Streck Cell-Free DNA blood collection tube (BCT). For patients ≥ 25 kg, collect 10 mL in one tube; for patients ≥ 15 and < 25 kg collect 5 to 10 ml of blood in one tube; for patients ≥ 5 kg but < 15 kg, collect 5 to 7 mL in one tube. As close to the maximum range blood volume as possible is requested for each time point. Samples are not required for patients weighing less than 5 kg. Streck tubes specifications require > 5 ml of blood for optimal sample handling.

All draws must be completed with exact time recorded on the Correlative Biology Worksheets in Appendix E.

Samples may be obtained on any day of the week and should be drawn at the following time points for Arm 1:

- Prior to Cycle 1, Day 1 dose
- Prior to Cycle 1, Day 15 or 22 dose (or untimed draw on Day 22 for patients on interrupted dose level as they do not receive drug on Day 22)
- Cycle 2, Day 1, pre-dose
- Within ±5 days of every subsequent disease assessment
- At time of disease progression or other reason off protocol therapy

Samples may be obtained on any day of the week and should be drawn at the following time points for Arm 2:

- Prior to Cycle 1, Day 1 dose
- Cycle 2, Day 1, pre-dose
- Within ±5 days of every subsequent disease assessment
- At time of disease progression or other reason off protocol therapy

9.2.3.2  Sample Handling Instructions

Blood should be drawn directly into Streck tubes. Tubes should be completely inverted 8-10 times after sample collection. No other on-site processing is required. Sample should be kept at room temperature until shipped. Samples must NOT be refrigerated.

9.2.3.3  Sample Labeling Instructions
Streck tubes should be labeled with the patient’s study ID number, the words “Pediatric BMS-986158 ctDNA” for Arm 1 patients, and “Pediatric BMS-986378 ctDNA” for Arm 2 patients, the date of blood draw, and one of the following indicators of the sample timing:

- Baseline
- Cycle 1, Day 15 or 22
- Cycle 2, Day 1
- Cycle XX, Day XX
- Off protocol therapy

No other identifiers should be included on the label.

9.2.3.4 Sample Shipment

Each sample should be sent on the day the sample was obtained, unless obtained on a Friday, Saturday or Sunday. Pre-treatment and Cycle 1, Day 2 samples may be shipped together if obtained one day apart. If obtained on a Friday, Saturday or Sunday, sample should be STORED AT ROOM TEMPERATURE until shipment the following Monday. Sample should be SHIPPED AT ROOM TEMPERATURE. Sample shipment must include a copy of the ctDNA Worksheet (Appendix E). Please retain a copy of the worksheet at the site and also email a copy of the worksheet to the DFCI Study Coordinator.

Samples should be shipped by Federal Express Priority Overnight to:

Brian Crompton  
Dana-Farber Cancer Institute  
450 Brookline Ave, Dana 604  
Boston, MA 02215  
617-632-4468

Please use this FedEx account number 361615042 for these shipments and be sure to also provide reference number 9618307.

Samples should only be shipped on Mondays-Thursdays to allow for weekday delivery. Email pediatricBMS-986158@dfci.harvard.edu, briand_crompton@dfci.harvard.edu, KellyS_Klega@dfci.harvard.edu, and JessicaR_Clymer@dfci.harvard.edu with the tracking number at the time of sample shipment.

9.2.3.5 Description of Assay

A next generation sequencing approach will be used to detect ctDNA extracted from approximately 2 milliliters of plasma for each patient using a commercial
kit. After extraction, sequencing of cell free DNA will be performed utilizing oligonucleotides complementary to the genomic regions of interest. Sequencing and analysis of samples will be done at Dana-Farber and the Broad Institute under the supervision of Dr. Brian Crompton.

9.2.4 CSF Cell Free DNA – Optional

9.2.4.1 Sampling Strategy

A. Patients Having Standard of Care Lumbar Puncture or Other CSF Access Procedure (Required)

Patients who undergo planned standard of care lumbar puncture (e.g., for staging/disease assessment) or another standard of care procedure in which CSF can be obtained (e.g., ventriculoperitoneal shunt placement) who agree to participate in the optional CSF cell free DNA study will provide a 1-5 mL CSF sample at the time of each procedure (may be during or after Cycle 1). The sample should be collected into a Streck cell-free DNA tube. Use Form 4 in Appendix E to document Cycle, day, date, and time of CSF collection.

B. Patients with Ommaya Reservoir Sampling Schedule (Optional)

Patients with Ommaya reservoirs who provide additional consent and who do not require anesthesia to access the Ommaya will provide a single 1-5 mL CSF sample via Ommaya on Cycle 1, Day 2 or 4 (timed with CSF PK sample). The sample should be collected into a Streck cell-free DNA tube. Use Form 4 in Appendix E to document Cycle, day, date, and time of CSF collection.

9.2.4.2 Sample Handling Instructions

CSF should be collected in Streck cell-free DNA tubes. Gently invert the tube 10 times to ensure proper mixing of stabilization agent. No other on-site processing is required. Sample should be kept at room temperature until shipped. Samples must NOT be refrigerated.

9.2.4.3 Sample Labeling Instructions

Streck tubes should be labeled with the patient’s study ID number, the words “Pediatric BMS-986158 cfDNA CSF” for Arm 1 patients, and “Pediatric BMS-986378 cfDNA CSF” for Arm 2 patients, the date CSF was obtained, the type of draw, and an indicator of the sample timing such as:

- Cycle XX, Day XX

No other identifiers should be included on the label.
9.2.4.4 Sample Shipment

Samples should be shipped by Federal Express Priority Overnight to:

Broad Institute
Attn: Genomics Platform – Samples Lab
320 Charles St – Lab 181
Cambridge, MA 02141
Phone: (617) 714-8952

Please use this FedEx account number 361615042 for these shipments and be sure to also provide reference number 9618307.

Samples should only be shipped on Mondays-Thursday to allow for weekday delivery. Email pediatricBMS-986158@dfci.harvard.edu, Pratiti_Bandopadhayay@dfci.harvard.edu, and JessicaR_Clymer@dfci.harvard.edu with the tracking number at the time of sample shipment. Sample shipment must include a copy of the CSF Cell Free DNA Worksheet (Appendix E). Please retain a copy of the worksheet at the site and also email a copy of the worksheet to the DFCI Study Coordinator.

9.2.4.5 Description of Assay

A next generation sequencing approach will be used to detect cell free DNA present in the CSF. After extraction, sequencing of cell free DNA will be performed utilizing oligonucleotides complementary to the genomic regions of interest. Sequencing and data analysis will be performed at the Broad Institute under the supervision of Dr. Pratiti Bandopadhayay.

9.2.5 Archival Tissue Markers – Required (if tissue available)

9.2.5.1 Requested Samples

Sites are requested to provide one of the following sources of archival tumor material:

Option 1: Formalin fixed paraffin embedded (FFPE) tumor block, OR

Option 2: 20 to 25 scrolls of 4-5 micron thick unstained tissue sections along with 5 unstained slides (4-5 microns thick), OR

Option 3: 15 to 35 unstained tumor slides, 4-5 microns thick, OR
Option 4: 5 unstained slides (4-5 microns thick) PLUS 25 mg or 0.25 cm$^3$ flash frozen tumor.

Material obtained from biopsy to diagnose or treat recurrent or progressive disease is strongly preferred. If not available, material from biopsy/resection to obtain initial diagnosis will be submitted. If not available, material from resection of tumor after neoadjuvant chemotherapy will be submitted, taking care to submit material representing viable tumor. Material from primary tumor or metastatic deposits is acceptable. Materials obtained during bone marrow biopsy or fine needle aspirate procedure are not acceptable to support this evaluation.

For patients who undergo clinically-indicated biopsy or surgical resection while on therapy or within 30-days after last dose of either investigational agent, an additional set of materials meeting Options 1-4 above is requested.

For patients without available tumor material, the site investigator should notify the Overall Principal Investigator.

9.2.5.2 Sample Handling
No additional processing is required at the treating institution.

9.2.5.3 Sample Labeling
Materials should be labeled with the patient’s assigned study ID number, the word “BMS-986158” for arm 1 patients and “BMS-986378” for arm 2 patients, and the date of biopsy/resection.

No other identifiers should be included on the label.

9.2.5.4 Sample Shipment
Slides should be shipped by Federal Express Priority Overnight to the following address:

Kim Stegmaier, MD  
Dana-Farber Cancer Institute  
360 Longwood Avenue, 6th Floor  
Boston, MA 02215

FedEx account number 361615042 should be used for all shipments and be sure to also provide reference number 9618307.

Samples should only be shipped on Mondays-Thursdays to allow for weekday delivery. Email pediatricBMS-986158@dfci.harvard.edu, JessicaR_Clymer@dfci.harvard.edu, and jennifer_perry@dfci.harvard.edu with the tracking number at the time of sample shipment.
Sample shipment must include a copy of the Tissue Biomarker Worksheet (Appendix E) and a redacted copy of the pathology report with patient’s study ID number in place of identifiers. Please retain a copy of the worksheet at the site and also send a copy of the worksheet to the DFCI Study Coordinator.

9.2.5.5 Description of Assay
Immunohistochemistry will be used to quantify expression of MYC, MYCN, TUJ1, BCL2L1, PTEN, and pAKT protein on archival materials using a semiquantitative scoring system (0 to 3+).

If not already completed, DNA will be extracted from archival tumor material and sequenced using a next generation sequencing panel (OncoPanel) at the Center for Advanced Molecular Diagnostics at the Department of Pathology at Brigham and Women’s Hospital.

Depending upon tissue quality and quantity, RNA will be extracted from archival tumor material and sequenced using RNA-Seq, including but not limited to MYC and MYCN.

The Stegmaier Laboratory at Dana-Farber will oversee this work, some of which may be completed at the Broad Institute.

9.3 Banking for Potential Future Research (Optional)
For patients who provide additional consent, remaining tumor material, blood, CSF, and extracted nucleic acids will be stored for up to 5 years after the completion of the trial for potential future correlative biology studies.

9.4 Summary of Blood Volumes for Research Blood Draws
The volume needed for the required pharmacokinetic draws is 13 mL in Cycle 1 for Arm 1 and 16 mL in Cycle 1 for Arm 2. The volume needed for the required pharmacodynamic draws is 10 mL in Cycle 1 for Arm 1 and 10 mL in Cycle 1 for Arm 2. The volume needed for the required ctDNA draws is 20 mL in Cycle 1 and 10 mL in Cycle 2 and at each subsequent draw associated with a disease evaluation or disease progression.

If a treating site or investigator has concerns about this volume of blood for a specific patient, then the ctDNA samples in 9.2.3 should be omitted for that patient.
## 10 STUDY CALENDAR

### 10.1 Study calendar for both Arms and both Chorts

Baseline observations with the exception of disease evaluations must be completed within 14 days prior to the date of enrollment. Laboratory tests used to meet eligibility requirements may be completed within 14 days prior to date of enrollment, but must be repeated prior to Cycle 1, Day 1 if obtained > 5 days prior to Cycle 1, Day 1 (except pregnancy test required within 24 hours). Baseline disease assessments, such as MRIs, CT scans and nuclear medicine studies, must be performed within 28 days prior to the date of enrollment.

Once enrolled, required observations due at the start of a cycle may be obtained within 3 days prior to starting the cycle. Other observations must be obtained within \( \pm 3 \) days of the protocol-specified date, unless otherwise noted. Start of subsequent cycles may be delayed by up to 3 days for logistical reasons without being considered a protocol violation.

<table>
<thead>
<tr>
<th>Observation</th>
<th>Screening</th>
<th>Cycle 1(^1)</th>
<th>Cycle 2</th>
<th>Subsequent Cycles</th>
<th>End of Therapy(^2)</th>
<th>30-Day Follow-up(^3)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Physical Exam (Includes Ht, Wt, BSA, Vital signs(^4),(^5); Performance status(^6) (only during screening)</td>
<td>X</td>
<td>Weekly</td>
<td>Start of cycle</td>
<td>Start of cycle</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>CBC, Diff, Platelets(^6)</td>
<td>X</td>
<td>Twice weekly(^7)</td>
<td>Start of cycle and weekly(^7)</td>
<td>Start of cycle and weekly(^7)</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Electrolytes, Calcium, Magnesium, Phosphorus, BUN, Serum Creatinine(^6)</td>
<td>X</td>
<td>Weekly(^7)</td>
<td>Start of cycle(^7)</td>
<td>Start of cycle(^7)</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>AST, ALT, Alk Phos, Total + Direct Bilirubin, Albumin, Lipase(^6)</td>
<td>X</td>
<td>Weekly(^7)</td>
<td>Start of cycle(^7)</td>
<td>Start of cycle(^7)</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>PT/INR and PTT(^6)</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ECG(^6)</td>
<td>X</td>
<td>Day 4 or 5 (untimed)</td>
<td>Start of cycle (untimed)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Serum or urine pregnancy test(^6),(^8)</td>
<td>X</td>
<td>Within 24 hours of start of cycle</td>
<td>Within 24 hours of start of cycle</td>
<td>Within 24 hours of start of cycle</td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>Disease evaluation(^9),(^10)</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td>X(^10)</td>
<td>X(^10)</td>
</tr>
<tr>
<td>Blood for pharmacokinetic assays (required)</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td>X(^10)</td>
<td>X(^10)</td>
</tr>
<tr>
<td>CSF for pharmacokinetic assay (only for patients with Ommaya or undergoing LP as part of routine care)</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Blood for pharmacodynamic markers and ctDNA (required)</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CSF for cell free DNA (optional)</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tissue for biomarker studies (required)</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**OBTAIN OTHER STUDIES AS NEEDED FOR GOOD PATIENT CARE.**
1. Laboratory studies obtained within 5 days prior to C1D1 dosing may count toward the first set of biweekly labs during week 1 of Cycle 1. If laboratory studies for screening were obtained > 5 days prior to Cycle 1 Day 1, repeat according to Section 5.4.2.

2. End of therapy visit and observations should be performed within 7 days after day 28 of the final cycle of protocol therapy.

3. 30-day follow-up observations must be collected 30 days ± 7 days after last dose. For participants who are unable to return to the study center, observations may be performed at referring center. All patients will be monitored for adverse events through the full 30 days post-treatment discontinuation. This follow-up period may be extended per Section 5.9. In addition, a telephone follow-up call will be made to male or female participants of reproductive potential 7 months after the last dose of BMS-986158 or BMS-986378 to ascertain pregnancy status and to determine if unprotected vaginal intercourse occurred with a pregnant partner.

4. Vital signs include temperature, heart rate, blood pressure, respiratory rate, and oxygen saturation.

5. A full physical exam must be completed on Day 1 (-3 days) prior to administration of BMS-986158 or BMS-986378. Height, weight, and BSA are only required during week 1.

6. Required for verification of eligibility. All results should be emailed to the DFCI Study Coordinator prior to registration. Creatinine clearance may be required at screening if creatinine does not meet criteria in Section 3.1.5.

7. More frequent CBCs and chemistries may be needed as part of good patient care, particularly if adverse events are noted.

8. Obtain for females 12 years of age and older or post-pubertal. Must be obtained within 24 hours prior to the start of all cycles, including Cycle 1.

9. Studies obtained as part of disease evaluation will depend upon underlying histology and sites of disease involvement. Studies may include anatomic imaging, nuclear imaging, bone marrow biopsies, urine catecholamines, and other tumor markers. Baseline disease status tests must be performed ≤ 28 days prior to study registration and subsequent to any intervening therapy.

10. Perform disease re-staging during Week 4 of all even cycles (every 8 weeks) until after 6 cycles. Patients who remain on protocol therapy beyond 6 cycles will have disease re-staging after every 3rd cycle (end cycle 9, 12, etc). Confirmatory scans will also be obtained at least 4 weeks following initial documentation of an objective response (partial response or better).

11. MEASUREMENT OF EFFECT

Although response is not the primary endpoint of this trial, participants with measurable or evaluable disease will be assessed by standard criteria. For the purposes of this study, participants should be re-evaluated according to the schedule outlined in Section 10. Confirmatory scans will also be obtained 4 weeks following initial documentation of an objective response.

11.1 Arm 1 (Cohorts 1A and 1B) and Arm 2 (Cohorts 2A and 2B)

11.1.1 Definitions

Duration of overall response: The duration of overall response is measured from the time measurement criteria are met for ≥ PR until the first date that recurrent or progressive disease is objectively documented (taking as reference for progressive disease the smallest measurements recorded since the treatment started), or death due to any cause. Participants without an event reported are censored at the last disease evaluation.

Duration of overall complete response: The duration of overall CR is measured from the time measurement criteria are first met for CR until the first date that progressive disease is
objectively documented, or death due to any cause. Participants without an event reported are censored at the last disease evaluation.

Duration of stable disease: Stable disease is measured from the start of the treatment until the criteria for progression are met (taking as reference the smallest measurements recorded since the treatment started, including the baseline measurements), or death due to any cause. Participants without an event reported are censored at the last disease evaluation.

11.1.2 Antitumor Effect –Solid Tumors Other Than CNS Tumors or Neuroblastoma

For non-CNS non-neuroblastoma solid tumors, response and progression will be evaluated using Response Evaluation Criteria in Solid Tumors (RECIST) guideline (version 1.1). Changes in the largest diameter (unidimensional measurement) of the tumor lesions and the shortest diameter in the case of malignant lymph nodes are used in the RECIST criteria.

11.1.2.1 Definitions

Measurable disease: For lesions other than lymph nodes, measurable lesions are defined as those that can be accurately measured in at least one dimension (longest diameter to be recorded) as ≥ 20 mm by chest x-ray or ≥10 mm with CT scan, MRI, or calipers by clinical exam. All tumor measurements must be recorded in millimeters (or decimal fractions of centimeters).

For malignant lymph nodes to be considered pathologically enlarged and measurable, a lymph node must be ≥15 mm in short axis when assessed by CT scan (CT scan slice thickness recommended to be no greater than 5 mm). At baseline and in follow-up, only the short axis will be measured and followed.

Non-measurable evaluable disease: All other lesions (or sites of disease), including small lesions (longest diameter <10 mm or pathological lymph nodes with ≥10 to <15 mm short axis), are considered non-measurable disease. Leptomeningeal disease, ascites, pleural/pericardial effusions, lymphangitis cutis/pulmonitis, inflammatory breast disease, and cystic lesions are all considered non-measurable. Bone lesions are considered non-measurable unless associated with a soft tissue lesion that itself meets criteria for measurable disease.

Important notes: Tumor lesions that are situated in a previously irradiated area are not considered measurable or evaluable unless that site meets criteria for progression after completion of radiation.

Cystic lesions that meet the criteria for radiographically defined simple cysts should not be considered as malignant lesions (neither measurable nor non-measurable) unless biopsy proven since they are, by definition, simple cysts.

‘Cystic lesions’ thought to represent cystic metastases, particularly if biopsy proven, can be considered as measurable lesions, if they meet the definition of measurability described above. However, if non-cystic lesions are present in the same participant, these are preferred for
selection as target lesions.

11.1.2.2 Requirements for Disease Assessments
Investigators are to determine the optimal mode of disease assessment at baseline, including anatomic imaging studies, nuclear medicine studies, clinical measurements, tumor markers, and bone marrow biopsies. The same method of assessment and the same technique should be used to characterize each identified and reported lesion at baseline and during follow-up. Imaging-based evaluation is preferred to evaluation by clinical examination unless the lesion(s) being followed cannot be imaged but are assessable by clinical exam.

All measurements must be taken and recorded in metric notation using a ruler, calipers, or a digital measurement tool. All baseline evaluations should be performed as closely as possible to the beginning of treatment and never more than 4 weeks before enrollment.

11.1.2.3 Response Criteria

1. Evaluation of Target Lesions

**Target lesions:** All measurable lesions up to a maximum of 2 lesions per organ and 5 lesions in total, representative of all involved organs, should be identified as target lesions and recorded and measured at baseline. Target lesions should be selected on the basis of their size (lesions with the longest diameter), be representative of all involved organs, but in addition should be those that lend themselves to reproducible repeated measurements. It may be the case that, on occasion, the largest lesion does not lend itself to reproducible measurement in which circumstance the next largest lesion which can be measured reproducibly should be selected. A sum of the diameters (longest axis for non-nodal lesions, short axis for nodal lesions) for all target lesions will be calculated and reported as the baseline sum diameters. If lymph nodes are to be included in the sum, then only the short axis is added into the sum. The baseline sum diameters will be used as reference to further characterize any objective tumor regression in the measurable dimension of the disease.

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

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

**Progressive Disease (PD):** At least a 20% increase in the sum of the diameters of target lesions, taking as reference the smallest sum on study (this includes the baseline sum if that is the smallest on study). In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 5 mm. (Note: the appearance of one or more new lesions is also considered
progressions).

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

2. **Evaluation of Non-Target Lesions**

**Non-target lesions.** All other lesions (or sites of disease) including any measurable lesions over and above the 5 target lesions should be identified as non-target lesions and should also be recorded at baseline. Measurements of these lesions are not required, but the presence, absence, or in rare cases unequivocal progression of each should be noted throughout follow up.

**Complete Response (CR):** Disappearance of all non-target lesions and normalization of tumor marker level. All lymph nodes must be non-pathological in size (<10 mm short axis).

Note: If tumor markers are initially above the upper normal limit, they must normalize for a patient to be considered in complete clinical response.

**Non-CR/Non-PD:** Persistence of one or more non-target lesion(s) and/or maintenance of tumor marker level above the normal limits.

**Progressive Disease (PD):** Appearance of one or more new lesions and/or unequivocal progression of existing non-target lesions. **Unequivocal progression** should not normally trump target lesion status. It must be representative of overall disease status change, not a single lesion increase.

Although a clear progression of “non-target” lesions only is exceptional, the opinion of the treating physician should prevail in such circumstances.

3. **Evaluation of New Lesions**

The finding of a new lesion should be unequivocal (i.e. not due to difference in scanning technique, imaging modality, or findings thought to represent something other than tumor (for example, some ‘new’ bone lesions may be simply healing or flare of pre-existing lesions). However, a lesion identified on a follow-up scan in an anatomical location that was not scanned at baseline is considered new and will indicate PD. If a new lesion is equivocal (because of small size etc.), follow-up evaluation will clarify if it truly represents new disease and if PD is confirmed, progression should be declared using the date of the initial scan on which the lesion was discovered.

4. **Need for confirmatory testing**

RECIST criteria specify the need for confirmation of response a minimum of 4
weeks from the disease evaluation that first demonstrated a response. Responses will be reported as confirmed or unconfirmed based upon the results of this restaging.

5. Evaluation of Best Overall Response
The best overall response is the best response recorded from the start of the treatment until disease progression/recurrence (taking as reference for progressive disease the smallest measurements recorded since the treatment started). The patient’s best response assignment will depend on the achievement of both measurement and confirmation criteria.

For Participants with Measurable Disease (i.e., Target Disease)

<table>
<thead>
<tr>
<th>Target Lesions</th>
<th>Non-Target Lesions</th>
<th>New Lesions*</th>
<th>Overall Response</th>
<th>Best Overall Response when Confirmation is Required</th>
</tr>
</thead>
<tbody>
<tr>
<td>CR</td>
<td>CR</td>
<td>No</td>
<td>CR</td>
<td>≥4 wks Confirmation</td>
</tr>
<tr>
<td>CR</td>
<td>Non-CR/Non-PD</td>
<td>No</td>
<td>PR</td>
<td></td>
</tr>
<tr>
<td>CR</td>
<td>Not evaluated</td>
<td>No</td>
<td>PR</td>
<td>≥4 wks Confirmation</td>
</tr>
<tr>
<td>PR</td>
<td>Non-CR/Non-PD/not evaluated</td>
<td>No</td>
<td>PR</td>
<td></td>
</tr>
<tr>
<td>SD</td>
<td>Non-CR/Non-PD/not evaluated</td>
<td>No</td>
<td>SD</td>
<td>Documented at least once ≥4 wks from baseline</td>
</tr>
<tr>
<td>PD</td>
<td>Any</td>
<td>Yes or No</td>
<td>PD</td>
<td>no prior SD, PR or CR</td>
</tr>
<tr>
<td>Any</td>
<td>PD**</td>
<td>Yes or No</td>
<td>PD</td>
<td></td>
</tr>
<tr>
<td>Any</td>
<td>Any</td>
<td>Yes</td>
<td>PD</td>
<td></td>
</tr>
</tbody>
</table>

* See RECIST 1.1 manuscript for further details on what is evidence of a new lesion.
** In exceptional circumstances, unequivocal progression in non-target lesions may be accepted as disease progression.

Note: Participants with a global deterioration of health status requiring discontinuation of treatment without objective evidence of disease progression at that time should be reported as “symptomatic deterioration.” Every effort should be made to document the objective progression even after discontinuation of treatment.
For Participants with Non-Measurable Disease (i.e., Non-Target Disease)

<table>
<thead>
<tr>
<th>Non-Target Lesions</th>
<th>New Lesions</th>
<th>Overall Response</th>
</tr>
</thead>
<tbody>
<tr>
<td>CR</td>
<td>No</td>
<td>CR</td>
</tr>
<tr>
<td>Non-CR/non-PD</td>
<td>No</td>
<td>Non-CR/non-PD*</td>
</tr>
<tr>
<td>Not all evaluated</td>
<td>No</td>
<td>not evaluated</td>
</tr>
<tr>
<td>Unequivocal PD</td>
<td>Yes or No</td>
<td>PD</td>
</tr>
<tr>
<td>Any</td>
<td>Yes</td>
<td>PD</td>
</tr>
</tbody>
</table>

*‘Non-CR/non-PD’ is preferred over ‘stable disease’ for non-target disease since SD is increasingly used as an endpoint for assessment of efficacy in some trials so to assign this category when no lesions can be measured is not advised

11.1.3 Antitumor Effect – Neuroblastoma

This study will use the revised International Neuroblastoma Response Criteria for disease assessment. The updated response criteria incorporate current approaches to imaging of neuroblastoma, including functional imaging. Furthermore, a standardized approach to assessment of bone marrow involvement is included. The current INRC do not include methods of disease assessment that are less sensitive and/or specific for neuroblastoma (99Tc bone scan and catecholamine levels).

11.1.3.1 Definitions

Key sites and terms

Primary site: The primary site will be identified as a measurable lesion ≥ 10 mm in diameter as assessed by cross sectional imaging (CT or MRI scan). Primary site measurements must be recorded in millimeters (or decimal fractions of centimeters). The longest diameter of the primary tumor will be recorded at baseline. Serial measurements of the primary tumor will include assessment of tumor size in the same orthogonal plane at the time of each evaluation. In patients with bilateral adrenal lesions, response will be based on the sum of the longest dimensions of both adrenal lesions unless biopsy proves one to be ganglioneuroma rather than neuroblastoma/ganglioneuroblastoma. In patients with multi-focal non-adrenal disease, the largest tumor will be considered the primary tumor. Response in additional lesions will be assessed as described below for metastatic lesions.

Tracer avidity (123I-MIBG or FDG-PET) in the primary site will be recorded at baseline. The scan appropriate for serial disease assessments should be used at each disease re-evaluation timepoint (e.g. 123I-MIBG avid primary lesions should be followed using 123I-MIBG scans during therapy).

Malignant lymph nodes: To be considered pathologically enlarged and measurable, a metastatic lymph node must be ≥ 15 mm in short axis when assessed by CT or MRI scan (CT scan slice thickness recommended to be no greater than 5 mm). At baseline and in follow-up, only the short
axis of a discreet lymph node will be measured and followed as per RECIST criteria. Patients with neuroblastoma may have conglomerate masses of non-discrete lymph nodes (i.e. multiple contiguous retroperitoneal nodes). When a short axis of a discreet node cannot be identified, a lymph node conglomerate can be measured using the longest diameter of the composite lesion. Tracer avidity of metastatic nodes will be recorded at baseline and during disease evaluations.

For the purposes of response assessment, target lesions are disease sites that are measurable (non-nodal soft tissue mass \( \geq 10 \) mm in longest dimension or lymph node \( \geq 15 \) mm in short axis) and tracer avid OR are biopsy positive for neuroblastoma or ganglioneuroblastoma. The sum of diameters of target lesions is defined as the sum of the short axis of discrete lymph nodes (i.e., cervical, axillary nodes) added to the sum of the longest diameters of non-lymph node soft tissue metastases.

Non-measurable disease: All other lesions (or sites of disease), including small lesions (longest diameter < 10 mm or pathological lymph nodes < 15 mm short axis), are considered non-measurable disease. Bone lesions, leptomeningeal disease, ascites, pleural/pericardial effusions are considered non-measurable.

Bone lesions: Osteomedullary disease will be assessed using \(^{123}\)I-MIBG scans or FDG-PET scans. Technitium bone scans are no longer used as part of the revised INRC and are not included as part of disease reassessments during this trial. The extent of tracer avid disease will be evaluated using the Curie scoring system. SPECT may be used to confirm the presence or absence of lesions in a given segment of the body. The absolute Curie score should be reported at baseline. A relative score (Curie score at the time of disease assessment divided by baseline Curie score) should be recorded at the time of each disease evaluation.

Bone marrow disease: Bilateral bone marrow aspirates and trephine biopsies are encouraged during dose escalation portion and required during dose expansion portion for patients with neuroblastoma. These samples should be obtained at disease assessment timepoints. The extent of marrow involvement in all four samples should be recorded. Use of immunohistochemical staining for evaluation of trephine biopsies is strongly encouraged. The percentage of tumor infiltration of bone marrow space is assessed by histologic evaluation of trephine/biopsies or counting the number of tumor cells in aspirates by cytology or immunocytochemistry (recommended if available) divided by the number of hematopoietic/mononuclear cells evaluated to obtain a percentage involvement (methodology described by Burchill et al.).\(^{40}\) The bone marrow sample with the highest percentage of tumor infiltration is used for response assessment. If > 0% to \( \leq 5\% \) tumor infiltration is the highest percentage seen among samples obtained, the result should be recorded as minimal.
11.1.3.2 Response Criteria

**Primary (Soft Tissue) Tumor Response**

<table>
<thead>
<tr>
<th>RESPONSE</th>
<th>Anatomical Imaging + MIBG (FDG-PET) Imaging</th>
</tr>
</thead>
<tbody>
<tr>
<td>Complete Response (CR)</td>
<td>• &lt; 10 mm residual soft tissue at primary site, AND &lt;br&gt;• complete resolution of MIBG or FDG-PET uptake (for MIBG non-avid tumors) at primary site</td>
</tr>
<tr>
<td>Partial Response (PR)</td>
<td>• ≥ 30% decrease in longest diameter (LD) of primary site &lt;br&gt;• MIBG or FDG-PET uptake at primary site stable, improved or resolved</td>
</tr>
<tr>
<td>Progressive Disease (PD)</td>
<td>• &gt; 20% increase in longest diameter taking as reference the smallest sum on study (this includes the baseline sum if that is the smallest on study), AND &lt;br&gt;• a minimum absolute increase of 5 mm in longest dimension</td>
</tr>
<tr>
<td>Stable Disease (SD)</td>
<td>Neither sufficient shrinkage for PR nor sufficient increase for PD at the primary site</td>
</tr>
</tbody>
</table>

1Not for use in assessment of metastatic sites  
2 For $^{123}$I-MIBG non-avid tumors  
3 A mass that has not met PD measurement criteria but has fluctuating $^{123}$I-MIBG avidity will not be considered progressive disease.

**Response at Metastatic Soft Tissue and Bone Sites**

<table>
<thead>
<tr>
<th>RESPONSE</th>
<th>ANATOMICAL IMAGING + MIBG (FDG-PET) Imaging</th>
</tr>
</thead>
<tbody>
<tr>
<td>Complete Response (CR)</td>
<td>• Resolution of all sites of disease defined as: &lt;br&gt;• Non-primary target and non-target lesions measure &lt; 10 mm AND &lt;br&gt;• Lymph nodes identified as target lesions decrease to a short axis &lt; 15 mm, AND &lt;br&gt;• MIBG uptake or FDG-PET uptake (for MIBG non-avid tumors) of non-primary lesions resolves completely</td>
</tr>
<tr>
<td>Partial Response (PR)</td>
<td>• ≥ 30% decrease in sum of diameters of non-primary target lesions compared to baseline, AND all of the following: &lt;br&gt;• Non-target lesions may be stable or smaller in size AND &lt;br&gt;• No new lesions AND &lt;br&gt;• ≥ 50% reduction in MIBG absolute bone score</td>
</tr>
<tr>
<td><strong>Progressive Disease (PD)</strong></td>
<td>Any of the following⁵:</td>
</tr>
<tr>
<td>---</td>
<td>---</td>
</tr>
<tr>
<td></td>
<td>• Any new soft tissue lesion detected by CT or MRI that is also MIBG avid or FDG-PET avid;</td>
</tr>
<tr>
<td></td>
<td>• Any new soft tissue lesion seen on anatomic imaging that is biopsied and confirmed to be a neuroblastoma or ganglioneuroblastoma;</td>
</tr>
<tr>
<td></td>
<td>• Any new bone site that is MIBG avid;</td>
</tr>
<tr>
<td></td>
<td>• A new bone site that is FDG-PET avid (for MIBG non-avid tumors) AND has CT or MRI findings consistent with tumor OR has been confirmed histologically to be neuroblastoma or ganglioneuroblastoma;</td>
</tr>
<tr>
<td></td>
<td>• &gt; 20% increase in longest diameter taking as reference the smallest sum on study (this includes the baseline sum if that is the smallest on study), AND a minimum absolute increase of 5 mm in sum of diameters of target soft tissue lesions;</td>
</tr>
<tr>
<td></td>
<td>• Relative MIBG score ≥ 1.2⁴</td>
</tr>
</tbody>
</table>

| **Stable Disease (SD)** | Neither sufficient shrinkage for PR nor sufficient increase for PD of non-primary lesions |

---

¹ Used for MIBG non-avid tumors

² Sum of diameters is defined as the sum of the short axis of discrete lymph nodes (i.e., cervical, axillary nodes) added to the sum of the longest diameters of non-lymph node soft tissue metastases. Masses of conglomerate non-discrete lymph nodes will be measured using longest diameter.

³ For patients with soft tissue metastatic disease, resolution of MIBG and/or FDG-PET uptake at the soft tissue sites is not required; all size reduction criteria must be fulfilled.

⁴ Relative Curie score is the absolute score for bone lesions at time of response assessment divided by the absolute score for bone lesions at entry onto a clinical trial. MIBG-SPECT or MIBG-SPECT/CT may be used for scoring purposes, but the same imaging methodology should be used for all evaluations.

⁵ The post-infusion MIBG scan is not considered a diagnostic study for the purposes of response assessment. Progressive disease should NOT be designated on the basis of this scan.
## Bone Marrow Response

<table>
<thead>
<tr>
<th>RESPONSE</th>
<th>Bone marrow status $^1$</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Complete response (CR)</strong></td>
<td>Bone marrow with no tumor infiltration upon reassessment, independent of baseline tumor involvement</td>
</tr>
</tbody>
</table>
| **Progressive disease (PD)** | Any of the following:  
  - Bone marrow without tumor infiltration that becomes $> 5\%$ tumor infiltration upon reassessment; or  
  - Bone marrow with tumor infiltration that increases by $> 2$-fold and has $> 20\%$ tumor infiltration upon reassessment. |
| **Minimal disease (MD)** | Any of the following:  
  - Bone marrow with $\leq 5\%$ tumor infiltration and remains $> 0 - \leq 5\%$ tumor infiltration upon reassessment; or  
  - Bone marrow with no tumor infiltration that becomes $\leq 5\%$ tumor infiltration upon reassessment; or  
  - Bone marrow with $> 20\%$ tumor infiltration that has $> 0 - \leq 5\%$ tumor infiltration upon reassessment. |
| **Stable disease (SD)** | Bone marrow with tumor infiltration that remains positive with $> 5\%$ tumor infiltration upon reassessment but does not meet CR, MD or PD criteria |

$^1$Immunohistochemistry strongly encouraged

## Determination of Overall Response

<table>
<thead>
<tr>
<th>Response</th>
<th>Criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>Complete Response (CR)</td>
<td>All components meet criteria for CR</td>
</tr>
<tr>
<td>Partial Response (PR)</td>
<td>PR in at least one component and all other components are either CR, MD (Bone marrow), PR (Soft tissue or Bone) or Not involved (NI); no component with PD.</td>
</tr>
<tr>
<td>Minor Response (MR)</td>
<td>PR or CR in at least one component but at least one other component with SD; no component with PD.</td>
</tr>
<tr>
<td>Stable Disease (SD)</td>
<td>SD in one component with no better than SD or NI in any other component; no component with PD.</td>
</tr>
<tr>
<td>Progressive Disease (PD)</td>
<td>Any component with PD</td>
</tr>
</tbody>
</table>

NI = Not involved, site not involved at study entry and remains not involved; MD = Minimal Disease, for bone marrow assessment only.
11.1.4 Antitumor Effect – CNS Tumors

For patients with primary CNS tumors or CNS metastasis, the modified RANO criteria, in line with RAPNO disease specific consensus statements, will be used to assess sites of CNS disease evaluated by MRI. RAPNO criteria will be used to assess CSF cytology for patients with leptomeningeal seeding tumors (e.g., medulloblastoma).

11.1.4.1 Definitions

**Measurable disease:** Bi-dimensionally contrast-enhancing or non-enhancing lesions with clearly defined margins by MRI scan, with two perpendicular diameters of at least 10 mm, visible on two or more axial slices that are preferably, at most, 5 mm apart with 0-mm skip. As with RECIST version 1.1, in the event the MRI is performed with thicker slices, the size of a measurable lesion at baseline should be two times the slice thickness. In the event there are interslice gaps, this also needs to be considered in determining the size of measurable lesions at baseline. Measurement of tumor around a cyst or surgical cavity represents a particularly difficult challenge. In general, such lesions should be considered non-measurable unless there is a nodular component measuring ≥10 mm in diameter. The cystic or surgical cavity should not be measured in determining response.

A measurable lesion is evaluated by contrast-enhancing MRI and:

- Has clearly defined margins;
- Is visible on two or more axial slices, preferably < 5 mm thick;
- At least 10 mm in size if slice thickness is < 5 mm (or 2x slice thickness if > 5 mm); and
- Does not measure a cystic cavity.

Measurements are calculated by summing the products of perpendicular diameters of all measurable enhancing lesions. If there are multiple contrast-enhancing lesions, a minimum of the two largest lesions should be measured. However, emphasis should be placed on selecting lesions that allow reproducible repeated measurements. For patients who have multiple lesions for which only one or two are increasing in size, the enlarging lesions should be considered the target lesions for evaluation of response.

**Non-measurable disease:** Either unidimensionally measurable lesions, masses with margins not clearly defined, or lesions with maximal perpendicular diameters less than 10 mm. Non-measurable lesions are those that do not fit the criteria above, and specifically lesions that are cystic, necrotic, or include a surgical cavity should not be considered measurable.

11.1.4.2 Requirements for Disease Assessments

Investigators are to determine the optimal mode of disease assessment at baseline, including anatomic imaging studies, nuclear medicine studies, clinical measurements, lumbar punctures and bone marrow biopsies. The same method of assessment and the same technique should be used to characterize each identified and reported lesion at baseline and during follow-up. Imaging-based evaluation is preferred to evaluation by clinical examination unless the lesion(s)
being followed cannot be imaged but are assessable by clinical exam. For patients with primary CNS tumors, disease evaluations should always include contrast-enhanced MRI scans.

All measurements must be taken and recorded in metric notation using a ruler, calipers, or a digital measurement tool. All baseline evaluations should be performed as closely as possible to the beginning of treatment and never more than 4 weeks before enrollment.

11.1.4.3 Response Criteria

1. Response criteria for lesions assessed by MRI are summarized in the following table:

<table>
<thead>
<tr>
<th>RESPONSE CATEGORY</th>
<th>CRITERIA</th>
</tr>
</thead>
<tbody>
<tr>
<td>Complete Response</td>
<td>Complete resolution of both target and non-target lesions</td>
</tr>
<tr>
<td></td>
<td>No new lesions</td>
</tr>
<tr>
<td></td>
<td>Clinically stable or improved with no reliance on corticosteroids (except for physiological replacement)</td>
</tr>
<tr>
<td>Partial Response</td>
<td>≥ 50% decrease from baseline of target lesions</td>
</tr>
<tr>
<td></td>
<td>No progression of non-measurable disease</td>
</tr>
<tr>
<td></td>
<td>No new lesions</td>
</tr>
<tr>
<td></td>
<td>Clinically stable or improved, with stable or reduced corticosteroids compared to baseline</td>
</tr>
<tr>
<td>Progressive Disease</td>
<td>≥ 25% increase from baseline of target lesions; clear increase in size of non-measurable disease or non-target lesions from baseline or from time of best response</td>
</tr>
<tr>
<td></td>
<td>Any new lesions</td>
</tr>
<tr>
<td></td>
<td>Clinical deterioration not attributable to other nontumor causes and not due to steroid decrease</td>
</tr>
<tr>
<td>Stable Disease</td>
<td>Does not meet other criteria for response or progression</td>
</tr>
<tr>
<td></td>
<td>Clinically stable with stable or reduced corticosteroids compared to baseline</td>
</tr>
</tbody>
</table>

2. Response Criteria for CSF Cytology

Note that medulloblastoma is a histology of particular interest in this study, given the role of Myc and Mycn in this disease. Evaluation for leptomeningeal disease in these patients with spine MRI and CSF cytology is strongly encouraged at each disease evaluation. For patients with measurable leptomeningeal disease by MRI, the criteria in section 11.1.4.3.1 should be used to assess response at these sites. CSF cytology should be assessed following recent consensus guidelines from the RAPNO group as follows:

- Complete Response by CSF: If tumor cells are present at baseline, must be negative x 2 (sampling at least 2 weeks apart).
- Partial Response by CSF: If absent (negative) at baseline, must remain absent. If present at baseline, can be present or absent.
- Stable Disease by CSF: If absent (negative) at baseline, must remain absent. If present at baseline, can be present or absent.
- Progressive Disease by CSF: Previously absent tumor cells in CSF now present (positive).
Patients with disease evaluated by CSF can have an overall response that is no better than their response in the CSF (e.g., a patient with CR in measurable disease but still positive CSF will be coded as having an overall PR). Likewise, progression in the CSF will be classified as an overall response of Progressive Disease regardless of MRI response. See RAPNO consensus guidelines for additional details.42

3. Need for confirmatory testing

The RANO Criteria specify the need for confirmation of response at a minimum of 4 weeks from the disease evaluation that first demonstrated a response. Responses will be reported as confirmed or unconfirmed based upon the results of this restaging.

11.1.5 Antitumor Effect – Non-Hodgkin Lymphoma

For patients with non-Hodgkin lymphoma, the International Pediatric Non-Hodgkin Lymphoma Response Criteria will be used.43

11.1.5.1 Definitions

Measurable disease: These response criteria rely upon two-dimensional measurements of sites of bulk tumor, but do not specify a minimum diameter. For the purposes of this protocol, a lesion is considered measurable if it can be accurately measured in both longest diameter and perpendicular diameter AND the longest diameter measures at least 15 mm.

Non-measurable evaluable disease: All other sites of disease that do not meet the above definition of measurable disease will be considered evaluable disease. In pediatric non-Hodgkin lymphoma, evaluable sites of disease will most commonly include bone marrow metastatic disease, involvement of the central nervous system as measured by cerebrospinal fluid (CSF) cytology, and smaller lesions evaluable by FDG-PET imaging.

11.1.5.2 Requirements for Disease Assessments

Investigators are to determine the optimal mode of disease assessment at baseline, including anatomic imaging studies, nuclear medicine studies, clinical measurements, lumbar punctures and bone marrow biopsies. The same method of assessment and the same technique should be used to characterize each identified and reported lesion at baseline and during follow-up. Imaging-based evaluation is preferred to evaluation by clinical examination unless the lesion(s) being followed cannot be imaged but are assessable by clinical exam. For patients who have bone marrow and/or CSF staging at enrollment who do not have bone marrow or CSF involvement, repeat bone marrow and/or CSF restaging is not required at subsequent time points unless there is a clinical concern for disease progression. Likewise, if disease clears in marrow and/or CSF, a confirmatory evaluation should be obtained with next disease evaluation. Thereafter, that site does not require repeat evaluation unless clinical suspicion for recurrence at one of these sites.
All measurements must be taken and recorded in metric notation using a ruler, calipers, or a digital measurement tool. All baseline evaluations should be performed as closely as possible to the beginning of treatment and never more than 4 weeks before enrollment.

11.1.5.3 Response Criteria

1. Evaluation of measurable disease
   The International Pediatric Non-Hodgkin Lymphoma Response Criteria utilize two-dimensional measures of disease burden. Up to six nodal or extra-nodal sites of disease are specified. For each lesion, the product of the longest diameter and its perpendicular diameter is determined and the sum of these products calculated as the overall disease measure (known as the SPD).

2. Evaluation of evaluable disease
   For either bone marrow or CSF sites of disease, the percentage of lymphoma cells involved should be determined and recorded.

   For FDG-PET imaging, a standardized approach to grading uptake should be used, such as the Deauville criteria or use of standardized uptake values.

3. Determination of overall response
   - Complete response: Defined as disappearance of all disease and may include any of the following categories:
     - CR: No residual disease or new lesions by CT or MRI; any resected residual mass is morphologically negative for disease involvement; bone marrow and CSF are free of disease
     - CRb: A residual mass is presented, but core biopsy shows no morphologic evidence of disease; bone marrow and CSF are free of disease; no new sites of disease
     - Cru: A residual mass is presented, but negative by FDG-PET imaging; bone marrow and CSF are free of disease; no new sites of disease
   - Partial response: At least a 50% decrease in the SPD; FDG-PET scan may be positive, but must be improved; disease may be present in bone marrow and/or CSF, but there must be at least a 50% decrease in percentage of lymphoma cells involved; no new sites of disease.
   - Minor response: Decrease in SPD by more than 25%, but less than 50%; disease may be present in bone marrow and/or CSF, but there must be a decrease in percentage of lymphoma cells involved of 25-50%; no new sites of disease.
   - No response: Not meeting criteria for complete response, partial response, minor response, or progressive disease.
   - Progressive disease: Any of the following constitute disease progression:
     - > 25% increase in SPD;
     - Positive FDG-PET scan (Deauville category 4 or 5) with increase in
FDG uptake (NOTE: increased FDG-PET should not be used as the only indication of progressive disease. See Section 11.1); or
  o New site of disease involvement.

4. Need for confirmatory testing

The International Pediatric Non-Hodgkin Lymphoma Response Criteria do not specify the need for confirmation of response. For the purposes of this protocol, patients with partial or complete response should have confirmatory restaging studies performed a minimum of 4 weeks from the disease evaluation that first demonstrated a response. Responses will be reported as confirmed or unconfirmed based upon the results of this restaging.

11.2 Response Review

Patients with confirmed objective response (partial response or better) will have de-identified imaging studies and/or pathology reports submitted to the Study Coordinator for central confirmation of response. Imaging studies to be submitted include baseline scans, initial scans documenting response, and second set of scans confirming response. When relevant to the patient’s response assessment, de-identified copies of bone marrow pathology reports and tumor marker lab reports will be submitted as well.

12 DATA REPORTING / REGULATORY REQUIREMENTS

Adverse event lists, guidelines, and instructions for AE reporting can be found in Section 7.0.

12.1 Data Reporting

12.1.1 Method for Data Submission

All sites will submit data using the electronic data capture system, InForm.

The DFCI Office of Data Quality (ODQ) will perform quality checks on the data for this study.

12.1.2 Timelines for Data Submission

All investigative sites are expected to submit data in InForm according to the following timelines. Note that a cycle and reporting period are identical. Patients who do not meet criteria to proceed to subsequent cycle at Day 28 remain in the preceding cycle/reporting period until criteria to proceed to the next cycle are met (or criteria for removal from protocol therapy are met).
<table>
<thead>
<tr>
<th><strong>Form</strong></th>
<th><strong>Submission Timeline</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>Eligibility Checklist</td>
<td>Complete prior to registration</td>
</tr>
<tr>
<td>On Study Form</td>
<td>Within 14 days of registration</td>
</tr>
<tr>
<td>Toxicity Log (Baseline Adverse events)</td>
<td>Within 14 days of registration</td>
</tr>
<tr>
<td>Baseline Disease Assessment Form</td>
<td>Within 14 days of registration</td>
</tr>
<tr>
<td>Cycle 1 Rapid Toxicity Form</td>
<td>Weekly in Cycle 1 and immediately upon notification of a DLT (reporting Monday-Friday acceptable)</td>
</tr>
</tbody>
</table>
| Reporting Period Forms                        | Cycle 1: Within 5 business days of the last day of the cycle  
Other Cycles: Within 10 days of the last day of the cycle |
| Toxicity Log                                  | Cycle 1: Within 5 business days of the last day of the cycle  
Other Cycles: Within 10 days of the last day of the cycle |
| Response Assessment Form                      | Within 14 days of the completion of cycles in which disease evaluated    |
| Off Protocol Therapy Form                     | Within 14 days of completing treatment                                   |
| Follow-up Form                                | Within 14 days of the protocol defined follow up visit date              |
| Off Study Form                                | Within 14 days of being taken off study for any reason                  |
| Outcome Form                                  | Within 14 days of being taken off study for any reason                  |

12.1.3 Submission of Source Documentation and Imaging Studies

Aside from submission of data in InForm, investigative sites are expected to submit to the Overall PI at Dana-Farber the source materials listed in Section 4.3 and de-identified imaging studies that meet criteria given in Section 11.2.

12.2 Data Safety Monitoring

The DF/HCC Data and Safety Monitoring Committee (DSMC) will review and monitor toxicity and accrual data from this study. The committee is composed of medical oncologists, research nurses, pharmacists and biostatisticians with direct experience in cancer clinical research. Information that raises any questions about participant safety will be addressed with the Overall PI and study team.

The DSMC will review this protocol up to four times a year or more often if required to review toxicity and accrual data. Information to be provided to the committee may include: up-to-date participant accrual; current dose level information; DLT information; all grade 2 or higher unexpected adverse events that have been reported; summary of all deaths occurring within 30 days of intervention; any response information; audit results; and a summary provided by the study team. Other information (e.g. scans, laboratory values) will be provided upon request.

12.3 Multicenter Guidelines

This protocol will adhere to the policies and requirements of the DF/HCC Multi-Center Data and Safety Monitoring Plan. The specific responsibilities of the Overall PI, Coordinating Center, and Participating Institutions and the procedures for monitoring and auditing are presented in
Appendix G.

- The Overall PI/Coordinating Center is responsible for distributing all IND Action Letters or Safety Reports to all participating institutions for submission to their individual IRBs for action as required.
- Registration procedures for all sites are provided in Section 4.
- Mechanisms will be in place to ensure quality assurance, protocol compliance, and adverse event reporting at each site.
- Each participating institution will order the study agent(s) directly from Bristol-Myers Squibb. A participating site may order the agent(s) only after the initial IRB approval for the site has been forwarded to the Coordinating Center AND the site has been activated by the Coordinating Center.

13 STATISTICAL CONSIDERATIONS

In this protocol, there are two treatment Arms: Arm 1 – BMS-986158 and Arm 2 – BMS-986378 (CC-90010). Within each treatment Arm, a separate prospective, multicenter, pediatric phase 1 evaluation will be conducted. Each Arm has two cohorts. Evaluation of Arm 1 and Arm 2 will occur in parallel in each Arm. Arm 1 will include an expansion cohort at the RP2D, but Arm 2 not have an expansion cohort. In Arm 1, Cohort 1A will be open to patients with relapsed/refractory solid tumors or lymphoma and Cohort 1B will consist of patients with specific genotypes/diagnoses anticipated to be more likely to respond to treatment. All Arm 1 patients will receive BMS-986158 monotherapy and dose escalation will proceed according to a modified CRM design. The original Arm 1 design evaluated 4 dose levels (see Table 2: dose levels -1, 1, 2, and 3). With Amendment 3, two additional dose levels were added (Table 2: new dose levels -2 and 1S) based upon dose-limiting thrombocytopenia at dose level 1, for a total of 6 dose levels in Arm 1. With Amendment 4, Dose Levels 2, 3, and 1S were removed and interrupted dose levels 1i, -1i, and -2i were added to Arm 1.

Arm 2 will evaluate BMS-986378 in children with relapsed/refractory CNS tumors. Cohort 2A will be open to patients with relapsed or refractory primary CNS tumors or solid tumors with untreated CNS metastases, while Cohort 2B will consist of patients with specific genotypes/diagnoses anticipated to be more likely to respond to treatment. All Arm 2 patients will receive BMS-986378 (CC-90010) monotherapy and dose escalation will proceed according to a modified CRM design. The Arm 2 design will evaluate 4 dose levels (see Table 3).

13.1 Definitions of evaluability

13.1.1 Definition of Evaluability for Dose Escalation Evaluation for Arm 1

Eligible patients on non-interrupted dose levels will be evaluable for inclusion in dose escalation consideration if they have received at least 16 of 20 planned doses of BMS-986158 in Cycle 1 AND are followed until Day 28 of the first cycle of therapy without starting an alternative therapy, or until non-disease related criteria in Section 5.4.3 to proceed to start Cycle 2 are met, whichever occurs last (even if patients do not move on to Cycle 2). Eligible patients on
interrupted dose levels will be evaluable for inclusion in dose escalation consideration if they have received at least 12 of 15 planned doses BMS-986158 in Cycle 1 AND are followed until Day 28 of the first cycle of therapy without starting an alternative therapy, or until non-disease related criteria in Section 5.4.3 to proceed to start Cycle 2 are met, whichever occurs last (even if patients do not move on to Cycle 2). In addition, eligible patients who experience first cycle DLT at any time after the first dose of BMS-986158 are evaluable for inclusion in dose escalation consideration.

Patients in Cohort 1A who do not receive the adequate number of planned doses of BMS-986158 defined above in Cycle 1 and do not experience a DLT in Cycle 1 will be replaced for the purposes of evaluating the dose level for dose escalation/de-escalation purposes.

During the dose-finding portion of the trial, patients in Cohort 1B enrolling to the current active dose level who do not receive at least 16 of 20 planned doses (or 12 of 15 planned doses at interrupted dose levels) of BMS-986158 in Cycle 1 and do not experience a DLT in Cycle 1 will be replaced for the purposes of evaluating the dose level for dose escalation/de-escalation purposes. During the dose finding portion of the trial, patients in Cohort 1B enrolling one dose level below the current active dose level will not be replaced.

13.1.2 Definition of Evaluability for Dose Escalation Evaluation for Arm 2

Eligible patients will be evaluable for inclusion in dose escalation consideration if they have received at least 3 of 4 planned doses of BMS-986378 in Cycle 1 AND are followed until Day 28 of the first cycle of therapy without starting an alternative therapy, or until non-disease related criteria in Section 5.4.3 to proceed to start Cycle 2 are met, whichever occurs last (even if patients do not move on to Cycle 2). In addition, eligible patients who experience first cycle DLT at any time after the first dose of BMS-986378 are evaluable for inclusion in dose escalation consideration.

Patients in Cohort 2A who do not receive the adequate number of planned doses of BMS-986378 defined above in Cycle 1 and do not experience a DLT in Cycle 1 will be replaced for the purposes of evaluating the dose level for dose escalation/de-escalation purposes.

During the dose-finding portion of the trial, patients in Cohort 2B enrolling to the current active dose level who do not receive at least 3 of 4 planned doses of BMS-986378 in Cycle 1 and do not experience a DLT in Cycle 1 will be replaced for the purposes of evaluating the dose level for dose escalation/de-escalation purposes. During the dose finding portion of the trial, patients in Cohort 2B enrolling one dose level below the current active dose level will not be replaced.

13.1.3 Patients to be Included in Reporting Toxicities

Eligible patients will be included in reporting toxicities if they have received at least one dose either investigational agent.
13.1.4 Patients to be Included in Reporting Objective Response Rate

Eligible patients will be included in reporting objective response rate if they have evaluable or measurable disease present at baseline, have received at least one dose of either investigational agent AND meet either of the following criteria:
1. Have had at least one follow-up disease assessment, or
2. Have had clinical evidence of disease progression after starting protocol therapy, or
3. Early death due to toxicity prior to first disease assessment.

Patients who do not meet this definition will not be replaced except during the final 10-patient expansion cohort at the maximum tolerated dose.

13.2 Study Design/Endpoints

13.2.1 Primary and secondary endpoints and the modified CRM design

The primary endpoint driving dose escalation and informing objectives 1.2.1 and 1.2.2 will be DLT during cycle 1 as defined in Section 5.6.

For the secondary endpoint, “responder” will be defined as having a partial response or better based on central review of responding patients. Patients who start protocol therapy and progress prior to the first disease assessment will be classified as non-responders.

Separately within Arm 1 and Arm 2, this study will utilize a modified CRM dose escalation model; two parallel phase 1 evaluations will be conducted within this protocol. To simplify the presentation of the study design/conduct in this section and Appendix F of the protocol, “Cohort A” will designate either Cohorts 1A or 2A, and “Cohort B” will designate either Cohorts 1B or 2B. This is acceptable because the identical design is applied within each Arm. Dose escalation will utilize a modified continual reassessment method (CRM) design. Our modification of the CRM design will permit enrollment of patients from Cohort B to one dose below the current recommended dose when no enrollment slots are available at the currently evaluated dose level. The CRM is a Bayesian adaptive dose-escalation design that assumes a mathematical model of the dose-toxicity curve to predict the probability of a DLT at each dose level.34,35

This design will allow continual enrollment of patients with specific genotypes/histologies with strong pre-clinical evidence for benefit from BMS-986158 (Cohort 1B) and BMS-986378 (CC-90010) (Cohort 2B). Given that these pre-defined genotypes of interest are less common, it is a high priority to make an enrollment slot available at the time such a patient presents. The modified CRM model will utilize observed DLT data from patients in Cohorts A and B to safely and efficiently assign optimal dose levels and identify the MTD for BMS-986158 and BMS-986378 (CC-90010), respectively.

The following dose escalation rules will be applied within participants evaluable for dose escalation assessment, based on DLTs experienced in the first cycle. Toxicity as graded by CTCAE v5.0 will continue to be recorded and monitored throughout all cycles of therapy.
For both Arm 1 and Arm 2, the target DLT rate in the modified CRM dose escalation model is 20%. For Arm 1, the original estimated prior DLT probabilities were based on clinical experience from the adult BMS-986158 trial. With Amendment 4, the updated prior DLT probabilities for Arm 1 are listed in Table 4a1. For the existing dose levels 1, -1, and -2, the prior probabilities were estimated based on the estimated posterior probabilities from the CRM model using original prior and the trial data for Arm 1 as of September 22, 2020. For new dose levels 1i, -1i, and -2i, the prior probabilities were selected by interpolating between priors of the other dose levels. Prior DLT probabilities for Arm 2 are listed in Table 4a.2.

Table 4a1: Prior toxicity probabilities for the modified CRM model for Arm 1.

<table>
<thead>
<tr>
<th>Arm 1 Dose Level</th>
<th>Dose Schedule</th>
<th>Prior toxicity probabilities</th>
</tr>
</thead>
<tbody>
<tr>
<td>Level -2i</td>
<td>Interrupted</td>
<td>8%</td>
</tr>
<tr>
<td>Level -2</td>
<td>Continuous</td>
<td>17%</td>
</tr>
<tr>
<td>Level -1i</td>
<td>Interrupted</td>
<td>20%</td>
</tr>
<tr>
<td>Level -1</td>
<td>Continuous</td>
<td>22%</td>
</tr>
<tr>
<td>Level 1i</td>
<td>Interrupted</td>
<td>32%</td>
</tr>
<tr>
<td>Level 1 – Starting Dose</td>
<td>Continuous</td>
<td>38%</td>
</tr>
</tbody>
</table>

Table 4a.2: Prior toxicity probabilities for the modified CRM model for Arm 2

<table>
<thead>
<tr>
<th>Arm 2 Dose Level</th>
<th>Dose Schedule</th>
<th>Prior toxicity probabilities</th>
</tr>
</thead>
<tbody>
<tr>
<td>Level -1</td>
<td>4-day</td>
<td>10%</td>
</tr>
<tr>
<td>Level 1</td>
<td>4-day</td>
<td>17%</td>
</tr>
<tr>
<td>Level 2</td>
<td>4-day</td>
<td>25%</td>
</tr>
<tr>
<td>Level 3</td>
<td>4-day</td>
<td>30%</td>
</tr>
</tbody>
</table>

We will assume a power dose-toxicity function in the CRM model. We begin by enrolling a cohort of 3 patients (from Cohort A or B) on dose level 1 and proceed in cohorts of 3 patients following subsequent dose escalations or de-escalations.

While each cohort of 3 patients are being evaluated for DLTs in the first cycle of treatment, no enrollment slots are available and patients for Cohort A will enter a waitlist. However, when no enrollment slots are available, patients from Cohort B may enroll at one dose level below the currently evaluated dose level of the cohort of 3 patients under observation. No more than 6 patients from Cohort B may be concurrently treated in Cycle 1 at one dose level below the currently evaluated dose level. If the lowest dose level (-2i for Arm 1; -1 for Arm 2) is being evaluated as the current dose level, enrollment for patients from Cohort B at one dose level below the current dose will not be permitted.

Dose escalation decisions will occur once all three patients from the current cohort are evaluable.
for DLT assessment. The recommended dose for the next cohort of 3 patients will be based on updated posterior probabilities from the CRM utilizing DLT data from all Cohort A and B patients who are evaluable for DLT assessment, including evaluable Cohort B patients treated at one dose below the current dose. However, we will not delay dose escalation decisions for the next cohort of 3 patients to wait for the completion of the observation period for any Cohort B patients treated at one dose below the current dose level. These patients will enter the CRM model in subsequent dose escalation decisions. Patient DLT information will be collected on a weekly basis during Cycle 1 to ensure up-to-date DLT information for patients who remain in Cycle 1 therapy at the time of dose escalation decision.

If the first or second patient in the current cohort of 3 patients experiences a DLT, we will update the CRM model using all available DLT data from all preceding patients who are evaluable for DLT assessment to determine if an intra-cohort dose de-escalation is recommended. If the CRM model recommends an intra-cohort dose de-escalation, a new cohort of 3 patients will be assigned the recommended lower dose. Otherwise, the subsequent patient in the current cohort of 3 patients will be treated at the same, current dose. Intra-cohort dose escalation is not permitted.

The recommended dose level for the next cohort of 3 patients will be the dose with the toxicity probability closest to the toxicity threshold. For dose escalation, the recommended dose level can never be more than one sequential dose level above the current dose level; for dose de-escalation, the recommended dose may be one or two dose levels below the current dose level. While the modified CRM will use Cycle 1 DLT data to recommend a dose level for the next cohort of 3 patients, the study committee will review all available toxicity and PK data before opening the next dose level recommended by the model.

When determining the dose level for the next cohort of 3 patients, if the posterior probability of toxicity for the lowest dose level (-2i for Arm 1; -1 for Arm 2) is greater than 60%, we will recommend a review by the study committee and the DSMC for consideration of protocol amendment or early study termination.

Dose escalation with a given Arm will continue until the following termination rules are achieved:
1. A minimum of 18 patients have been treated in total for Cohorts A and B; AND,
2. A minimum of 6 Cohort A or B patients have been treated at a single dose level.

Once the termination rules have been triggered within a given Arm, study enrollment to Cohorts A and B will be paused for that Arm. Once all enrolled patients to Cohorts A and B are evaluable for DLT assessment, we will run the CRM model for a final time for that Arm. The MTD for a given Arm is the dose level with the posterior toxicity probability closest to the target toxicity level of 20%. The RP2D for a given Arm is the dose recommended by the study team per the final run of the CRM model and evaluation of study data including PK, PD, response, and subsequent cycle DLTs.

In Arm 1, once the RP2D has been identified, we will enroll 10 additional Cohort 1B patients at the RP2D (see toxicity monitoring rules for these additional 10 patients in Section 13.5). Because
the MTD and RP2D will have already been determined, the CRM will not be rerun on the data for these 10 additional Cohort 1B patients. The primary focus of Cohort 1B will be to describe the objective response rate of BMS-986158 in this selected cohort based on the response criteria outlined in Section 11. A minimum of 3 slots will be reserved for patients with MYCN amplified neuroblastoma, leaving up to 7 slots for Cohort 1B patients with diseases other than MYCN amplified neuroblastoma. Data from Cohort 1B will also contribute to pharmacokinetic and correlative biology analyses.

13.2.2 Operating characteristics for the modified CRM design

A detailed description of the simulation methods used to evaluate the operating characteristics of the modified CRM for Cohorts A and B can be found in Appendix F. An abbreviated summary is provided herein. To evaluate the performance of the modified CRM design, we conducted simulated trials across multiple scenarios where we specified the true underlying toxicity probabilities per dose (Table 4b.1 for Arm 1; Table 4b.2 for Arm 2). Dose escalation in each simulated trial followed the modified CRM design as described in section 13.2.1. We assumed patient inter-arrival times were distributed as a Poisson process with an average rate of 1 patient arrival per 15 days. We assumed that 33.33% of arriving patients were from Cohort B. When no enrollment slots were available, patients from Cohort A entered onto a waitlist and had 50% chance to enroll when slots became available. We performed 2,000 simulated trials for each scenario and parameter setting.

Table 4b.1: Prior toxicity probabilities and true toxicity probabilities for simulations for Arm 1. The true MTD is bolded for each simulation scenario, assuming the target toxicity probability is 20%.

<table>
<thead>
<tr>
<th>Dose Level</th>
<th>Prior toxicity probabilities</th>
<th>True toxicity probabilities</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Scenario 1</td>
</tr>
<tr>
<td>Level -2i</td>
<td>8%</td>
<td>1%</td>
</tr>
<tr>
<td>Level -2</td>
<td>17%</td>
<td>5%</td>
</tr>
<tr>
<td>Level -1i</td>
<td>20%</td>
<td>10%</td>
</tr>
<tr>
<td>Level -1</td>
<td>22%</td>
<td>13%</td>
</tr>
<tr>
<td>Level 1i</td>
<td>32%</td>
<td>16%</td>
</tr>
<tr>
<td>Level 1 – Starting Dose</td>
<td>38%</td>
<td>20%</td>
</tr>
</tbody>
</table>
Table 4b.2: Prior toxicity probabilities and true toxicity probabilities for simulations for Arm 2. The true MTD is bolded for each simulation scenario, assuming the target toxicity probability is 20%.

<table>
<thead>
<tr>
<th>Dose Level</th>
<th>Prior toxicity probabilities</th>
<th>Scenario 1</th>
<th>Scenario 2</th>
<th>Scenario 3</th>
</tr>
</thead>
<tbody>
<tr>
<td>-1</td>
<td>10%</td>
<td>12%</td>
<td>8%</td>
<td>6%</td>
</tr>
<tr>
<td>1</td>
<td>17%</td>
<td>20%</td>
<td>14%</td>
<td>10%</td>
</tr>
<tr>
<td>2</td>
<td>25%</td>
<td>27%</td>
<td>20%</td>
<td>15%</td>
</tr>
<tr>
<td>3</td>
<td>30%</td>
<td>32%</td>
<td>32%</td>
<td>20%</td>
</tr>
</tbody>
</table>

Tables 5.1 and 5.2 display the operating characteristics of the modified CRM design for Arm 1 and Arm 2, respectively. For Arm 1, the proportion of trials that recommend the true MTD is highest in scenario 1 (49.7%) and lowest in scenario 3 (13.2%) and ranges from 56.1% down to 27.8% for Arm 2 scenarios. The overall proportion of patients experiencing a DLT ranges from 14.2% to 21.9% for Arm 1 and 13.2 to 19.3% for Arm 2, with DLT rates higher in scenarios in which dose de-escalation was needed, as expected. The proportion of trials with one or more patients from Cohort B enrolled at one dose level below the current dose ranges from 52.3% to 87.5% for Arm 1, and 61.3% and 81.1% for Arm 2. Across these scenarios, there are an average of 0.81 to 1.76 Cohort 1B patients and 1.03 to 1.57 Cohort 2B patients enrolled per trial at one dose level below the current dose. Given that 33.33% of arriving patients are from Cohort B (e.g. an average of N=6 Cohort B patients per trial with total N=18), the modified CRM design enrolls ~24% of all arriving Cohort B patients at one dose level below the current dose. Furthermore, nearly every arriving Cohort B patient will be able to enroll in the trial.

Table 5.1: Operating characteristics of the modified CRM design for Arm 1 in four scenarios (defined in Table 4b.1) based on 2,000 simulated trials.

<table>
<thead>
<tr>
<th>Scenario</th>
<th>Total sample size (median [range])</th>
<th>Proportion of trials that recommend the true MTD</th>
<th>Proportion patients experiencing DLT</th>
<th>% trials with ≥1 Cohort 1B patients enrolled at one dose level below the current dose</th>
<th># Cohort 1B patients enrolled per trial at one dose level below the current dose [mean (SD)]</th>
<th># of Cohort 1B patients enrolled per trial overall [mean (SD)]</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>18 (18-27)</td>
<td>49.7%</td>
<td>14.2%</td>
<td>87.5%</td>
<td>1.76 (1.13)</td>
<td>6.78 (2.21)</td>
</tr>
<tr>
<td>2</td>
<td>18 (18-27)</td>
<td>28.7%</td>
<td>18.2%</td>
<td>74.2%</td>
<td>1.36 (1.12)</td>
<td>6.44 (2.23)</td>
</tr>
<tr>
<td>3</td>
<td>18 (18-27)</td>
<td>13.2%</td>
<td>19.2%</td>
<td>71.1%</td>
<td>1.17 (1.01)</td>
<td>6.28 (2.13)</td>
</tr>
<tr>
<td>4</td>
<td>18 (18-27)</td>
<td>34.3%</td>
<td>21.9%</td>
<td>52.3%</td>
<td>0.81 (0.95)</td>
<td>5.90 (2.09)</td>
</tr>
</tbody>
</table>
Table 5.2: Operating characteristics of the modified CRM design for **Arm 2** in three scenarios (defined in Table 4b.2) based on 2,000 simulated trials.

<table>
<thead>
<tr>
<th>Scenario</th>
<th>Total sample size (median [range])</th>
<th>Proportion of trials that recommend the true MTD</th>
<th>Proportion patients experiencing DLT</th>
<th>% trials with ≥ 1 Cohort 2B patients enrolled at one dose level below the current dose</th>
<th># Cohort 2B patients enrolled per trial at one dose level below the current dose [mean (SD)]</th>
<th># of Cohort 2B patients enrolled per trial overall [mean (SD)]</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>18 (18-19)</td>
<td>33.5%</td>
<td>19.3%</td>
<td>61.3%</td>
<td>1.03 (1.05)</td>
<td>5.90 (2.10)</td>
</tr>
<tr>
<td>2</td>
<td>18 (18-20)</td>
<td>27.8%</td>
<td>16.7%</td>
<td>74.4%</td>
<td>1.38 (1.14)</td>
<td>5.21 (2.06)</td>
</tr>
<tr>
<td>3</td>
<td>18 (18-20)</td>
<td>56.1%</td>
<td>13.2%</td>
<td>81.1%</td>
<td>1.57 (1.13)</td>
<td>6.42 (2.06)</td>
</tr>
</tbody>
</table>

Additional details regarding the simulations are presented in Appendix F.

13.3 **Sample Size, Accrual Rate and Study Duration**

A given Arm will require a minimum of 3 evaluable patients for dose escalation and determination of the MTD (i.e., first patient has a DLT, followed by two patients at the lowest dose level also experiencing a DLT). Simulations indicate a maximum of 27 evaluable patients for Arm 1 and 20 patients for Arm 2. However, given the termination rules for the modified CRM, simulation results show that the expected maximum accrual should not exceed 18 evaluable patients in either Arm 1 or Arm 2.

In each Arm, we have assumed that 33.33% of enrolled patients are from Cohort B and 66.67% are from Cohort A; therefore, Cohort B is not expected to enroll more than 12 evaluable patients for the dose escalation portion of a given Arm. Specifically, simulations across the scenarios shown in Table 4b demonstrate that the mean number of Cohort B patients enrolled during dose escalation is approximately 6 with a standard deviation of 2. In Arm A, after the RP2D has been determined, Cohort B is expected to enroll an extra 10 patients at the RP2D. Thus, Cohort 1B is not expected to enroll more than 22 evaluable patients overall and Cohort 2B in Arm 2 is not expected to enroll more than 12 evaluable patients overall.

**Total Sample Size:** In Arm 1, up to 37 eligible and evaluable patients will be enrolled (Cohort A+B dose escalation N=27; Cohort B expansion N=10). In order to account for potentially ineligible or non-evaluable Arm 1 patients, a maximum sample size of up to 43 Arm 1 patients is anticipated (assuming 6 patients are ineligible or non-evaluable).

In Arm 2, up to 20 eligible and evaluable patients will be enrolled (Cohort A+B dose escalation N=20; no expansion cohort). In order to account for potentially ineligible or non-evaluable Arm 2 patients, a maximum sample size of up to 23 Arm 1 patients is anticipated (assuming 3 patients...
are ineligible or non-evaluable). Thus, the total protocol sample size for Arm 1+Arm 2 is up to 66 patients (43 + 23).

**Study Duration:** To facilitate completion of the trial, the study will be open at multiple centers. Arm 1 and Arm 2 will accrue in parallel.

**Arm 1:** At an estimated rate of 2 patients (Cohort A or B) per month in Arm 1, accrual of up to 32 patients to the dose escalation portion of Arm 1 should complete in less than 16 months. During expansion for Cohort 1B on Arm 1, Cohort 1B will enroll approximately 1 patient every other month and will complete in 22 months. Hence, accrual of 43 patients to Arm 1 should be completed in about 38 months.

**Arm 2:** Assuming an accrual rate of 1 patient (Cohort A or B) per month in Arm 2, accrual of up to 23 patients on Arm 2 should complete in less than 2 years.

### 13.4 Stratification Factors

Patients will be stratified by genomic features into Cohort A or B within each Arm.

### 13.5 Interim Monitoring Plan

The modified CRM model and the CRM model include inherent safety stopping rules. In addition, each death on study not due to tumor will be reviewed by the Study Committee, reported to the DSMC, and a decision in consultation with DSMC will be made to close the trial, modify the trial, or continue unchanged. This event may also require the addition of new information to the informed consent document. Each death occurring within 30 days of completing the last dose of BMS-986158, regardless of cause, will be reviewed and reported to the DSMC according to standard procedure.

Toxicities observed in either Arm during the dose-finding portion of the trial will be factored into the respective CRM model; however, toxicities observed in Arm 1 during the 10-patient expansion will not be analyzed by the CRM model. Instead, the following toxicity-monitoring rule will be applied. Cycle 1 DLTs in this 10-patient cohort will result in a pause in enrollment and trigger a formal review of all the toxicities, with the possibility of reducing the dose:

- If 2 patients on Arm 1 experience a cycle 1 DLT at the RP2D in the 1st 6 patients enrolled; or
- If 3 patients experience a cycle 1 DLT at the RP2D in the 1st 9 patients.

With the exception of pausing enrollment due to meeting one of the rules above, enrollment to the Arm 1 10-patient expansion at the RP2D will be continuous.
Adverse events in cycles 2+ for any patients in the expansion cohort who have undergone intrapatient dose escalation will be reported descriptively. The experience in these patients will not impact assessment of the above monitoring rule used to monitor toxicity during the 10-patient expansion as this rule is based upon toxicities observed during cycle 1.

This phase 1 clinical trial does not include an efficacy or futility-stopping rule.

13.6 **Analysis of Primary Endpoints**

13.6.1 Toxicity endpoint

Primary objectives 1.2.1 and 1.2.2, to determine the MTD and RP2D, will be assessed by application of the CRM separately within Arm 1 and Arm 2.

To assess primary objective 1.2.3 and 1.2.4, all toxicities observed will be summarized in terms of type (organ affected or laboratory determination), severity (by NCI CTCAE v5.0), and attribution, separately for each treatment Arm. By Arm, tables will be created to summarize the proportion of patients experiencing toxicity by Cohort (A vs. B) and by dose level. Patients who undergo intrapatient dose escalation will be analyzed according to their original assigned dose level.

### Table 6: Probability of Early Pausing of the Arm 1 Expansion Cohort (before 10 Evaluable Cohort 1B Patients are Enrolled to the the RP2d) to Review Safety of BMS-986158 Based on the Monitoring Criteria Above

<table>
<thead>
<tr>
<th>True Probability of DLT</th>
<th>0.05</th>
<th>0.10</th>
<th>0.15</th>
<th>0.20</th>
<th>0.25</th>
<th>0.30</th>
<th>0.35</th>
<th>0.40</th>
<th>0.45</th>
</tr>
</thead>
<tbody>
<tr>
<td>Probability of Observing 2+ DLTs in 1st 6 or 3+ DLT’s in 1st 9 Patients</td>
<td>0.03</td>
<td>0.12</td>
<td>0.25</td>
<td>0.39</td>
<td>0.52</td>
<td>0.65</td>
<td>0.75</td>
<td>0.84</td>
<td>0.90</td>
</tr>
</tbody>
</table>

Adverse events in cycles 2+ for any patients in the expansion cohort who have undergone intrapatient dose escalation will be reported descriptively. The experience in these patients will not impact assessment of the above monitoring rule used to monitor toxicity during the 10-patient expansion as this rule is based upon toxicities observed during cycle 1.

This phase 1 clinical trial does not include an efficacy or futility-stopping rule.

13.6 **Analysis of Primary Endpoints**

13.6.1 Toxicity endpoint

Primary objectives 1.2.1 and 1.2.2, to determine the MTD and RP2D, will be assessed by application of the CRM separately within Arm 1 and Arm 2.

To assess primary objective 1.2.3 and 1.2.4, all toxicities observed will be summarized in terms of type (organ affected or laboratory determination), severity (by NCI CTCAE v5.0), and attribution, separately for each treatment Arm. By Arm, tables will be created to summarize the proportion of patients experiencing toxicity by Cohort (A vs. B) and by dose level. Patients who undergo intrapatient dose escalation will be analyzed according to their original assigned dose level.

13.7 **Analysis of Secondary Efficacy Endpoints**

To address objectives 1.3.1 and 1.3.2, patients who meet the definition of evaluability in Section 13.1.3 will be included in the calculation of the objective response rate, by treatment Arm.

The overall response rate will be calculated as the number of responders divided by the number of evaluable patients, with exact two-sided 95% confidence intervals. The objective response rate will be tabulated overall for each Arm, and within each Arm by Cohort. Among responders, the duration of response will be calculated, and an exact two-sided 95% confidence interval will be placed on the response duration.
13.8 Analysis of Secondary Pharmacokinetic Endpoint

To address objective 1.3.3, routine pharmacokinetic parameters, including area under the curve (AUC), and $C_{\text{max}}$ for BMS-986158, BMS-986378 and their main metabolites, will be calculated using standard methods and reported descriptively, in aggregate and by assigned dose level. A population pharmacokinetic analysis for BMS-986158 and BMS-986378 may be conducted to explore the inter-individual variability of plasma drug exposure and the contributing factors (covariates) across adult and pediatric patients.

13.9 Analysis of Exploratory Objectives: Correlative Biology Endpoints

To address objective 1.4.1, the correlative biomarkers will largely be analyzed descriptively, by treatment Arm. To address the pharmacodynamic endpoint in objective 1.3.2, the relative change from baseline will be calculated for key RNA transcripts detected in the peripheral blood, with results displayed by dose level for qualitative comparisons. Association between modulation of these markers versus a) occurrence of DLT (no DLT, $\geq$1 DLT); and, b) any clinical response ($\geq$PR, <PR) will then be examined qualitatively using box and whisker plots. Evaluation of tumor protein, RNA, and genomic features as well as cell-free DNA results will be presented overall and according to clinical response category ($\geq$PR, <PR). No formal inferential statistical analyses are planned. No formal inferential statistical analyses are planned.

To address objective 1.4.2, a database will be created to track the banked specimens.

14 PUBLICATION PLAN

The results are expected to be made public within 24 months of reaching the end of the study. The end of the study is the time point at which the last data items are to be reported. The initial release may be an abstract to be presented at a relevant scientific meeting. A full report of the outcomes should be made public no later than three (3) years after the end of the study.
15 REFERENCES


patients (pts) with advanced solid tumours (aSTs) and relapsed/refractory (R/R) diffuse large B-cell lymphoma (DLBCL): Longer follow-up from parts A & B and first reporting of part C of a phase I study, ESMO Targeted Anticancer Therapies Virtual Congress 2021, 2021


44. R T, 2015

45. Cheung K: dfcrm: Dose-finding by the continual reassessment method. R package version 0.2-2., 2013
APPENDIX A: PERFORMANCE STATUS SCALES/SCORES

Performance Status Criteria
Karnofsky and Lansky performance scores are intended to be multiples of 10

<table>
<thead>
<tr>
<th>Score</th>
<th>ECOG (Zubrod)</th>
<th>Karnofsky Description</th>
<th>Score</th>
<th>Description</th>
<th>Score</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>100</td>
<td>Fully active, able to carry on all pre-disease performance without restriction.</td>
<td>Normal, no complaints, no evidence of disease</td>
<td>90</td>
<td>Able to carry on normal activity, minor signs or symptoms of disease.</td>
<td>90</td>
<td>Minor restrictions in physically strenuous activity.</td>
</tr>
<tr>
<td>80</td>
<td>Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light housework, office work.</td>
<td>Normal activity with effort; some signs or symptoms of disease. Cares for self, unable to carry on normal activity or do active work.</td>
<td>70</td>
<td>Both greater restriction of and less time spent in play activity.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>60</td>
<td>Ambulatory and capable of all self-care but unable to carry out any work activities. Up and about more than 50% of waking hours</td>
<td>Required occasional assistance, but is able to care for most of his/her needs. Requires considerable assistance and frequent medical care.</td>
<td>50</td>
<td>Up and around, but minimal active play, keeps busy with quieter activities. Gets dressed, but lies around much of the day; no active play, able to participate in all quiet play and activities.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>40</td>
<td>Capable of only limited self-care, confined to bed or chair more than 50% of waking hours.</td>
<td>Disabled, requires special care and assistance. Severely disabled, hospitalization indicated. Death not imminent.</td>
<td>30</td>
<td>Mostly in bed; participates in quiet activities. In bed; needs assistance even for quiet play.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>20</td>
<td>Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair.</td>
<td>Very sick, hospitalization indicated. Death not imminent. Moribund, fatal processes progressing rapidly.</td>
<td>10</td>
<td>Often sleeping; play entirely limited to very passive activities. No play; does not get out of bed.</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*The conversion of the Lansky to ECOG scales is intended for NCI reporting purposes only.
APPENDIX B: PROHIBITED CONCOMITANT MEDICATIONS

The following medications are prohibited within 7 days of enrollment to Arm 1 and while patients are on protocol therapy on Arm 1.

<table>
<thead>
<tr>
<th>CYP3A4/5 Strong Inhibitors</th>
<th>CYP3A4/5 Strong Inducers</th>
<th>PGP Strong Inhibitors</th>
</tr>
</thead>
<tbody>
<tr>
<td>Atazanavir</td>
<td>Barbiturates</td>
<td>Amiodarone</td>
</tr>
<tr>
<td>Boceprevir</td>
<td>Carbamazepine</td>
<td>Carvedilol</td>
</tr>
<tr>
<td>Clarithromycin</td>
<td>Efavirenz</td>
<td>Clarithromycin</td>
</tr>
<tr>
<td>Cobicistat</td>
<td>Enalutamide</td>
<td>Cyclosporine</td>
</tr>
<tr>
<td>Darunavir</td>
<td>Fosphenytoin</td>
<td>Dronedarone</td>
</tr>
<tr>
<td>Delavirdine</td>
<td>Nevirapine</td>
<td>Itraconazole</td>
</tr>
<tr>
<td>Idelalisib</td>
<td>Phenobarbital</td>
<td>Lopinavir/ritonavir</td>
</tr>
<tr>
<td>Indinavir</td>
<td>Phenytoin</td>
<td>Ketoconazole</td>
</tr>
<tr>
<td>Itraconazole</td>
<td>Primidone</td>
<td>Propafenone</td>
</tr>
<tr>
<td>Ketoconazole</td>
<td>Rifabutin</td>
<td>Quinidine</td>
</tr>
<tr>
<td>Lopinavir/ritonavir</td>
<td>Rifampin</td>
<td>Ranolazine</td>
</tr>
<tr>
<td>Nefazodone</td>
<td>St. John’s wort</td>
<td>Ritonavir</td>
</tr>
<tr>
<td>Nelfinavir</td>
<td></td>
<td>Saquinavir</td>
</tr>
<tr>
<td>Posaconazole</td>
<td></td>
<td>Tacrolimus</td>
</tr>
<tr>
<td>Ritonavir</td>
<td></td>
<td>Telaprevir</td>
</tr>
<tr>
<td>Saquinavir</td>
<td></td>
<td>Tipranavir</td>
</tr>
<tr>
<td>Suboxone</td>
<td></td>
<td>Verapamil</td>
</tr>
<tr>
<td>Telaprevir</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Telithromycin</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Voriconazole</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
The following medications are prohibited within 7 days of enrollment to **Arm 2** and while patients are on protocol therapy on **Arm 2**.

<table>
<thead>
<tr>
<th>CYP3A4/5 Strong Inhibitors</th>
<th>CYP3A4/5 Strong Inducers</th>
<th>P-glycoprotein substrates with narrow therapeutic windows*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Atazanavir</td>
<td>Barbiturates</td>
<td>Amitriptyline</td>
</tr>
<tr>
<td>Boceprevir</td>
<td>Carbamazepine</td>
<td>Baricitinib</td>
</tr>
<tr>
<td>Clarithromycin</td>
<td>Efavirenz</td>
<td>Cabergoline</td>
</tr>
<tr>
<td>Cobicistat</td>
<td>Enzalutamide</td>
<td>Calcium channel blockers (e.g., amlodipine and nifidenipine)</td>
</tr>
<tr>
<td>Darunavir</td>
<td>Fosphenytoin</td>
<td>Chloramphenicol</td>
</tr>
<tr>
<td>Delavirdine</td>
<td>Nevirapine</td>
<td>Colchicine</td>
</tr>
<tr>
<td>Idelalisib</td>
<td>Phenobarbital</td>
<td>Cyclosporine</td>
</tr>
<tr>
<td>Indinavir</td>
<td>Phenytoin</td>
<td>Digoxin</td>
</tr>
<tr>
<td>Itraconazole</td>
<td>Primidone</td>
<td>Fexofenadine</td>
</tr>
<tr>
<td>Ketoconazole</td>
<td>Rifabutin</td>
<td>Flecainide</td>
</tr>
<tr>
<td>Lopinavir/ritonavir</td>
<td>Rifampin</td>
<td>Imipramine</td>
</tr>
<tr>
<td>Nefazodone</td>
<td>St. John’s wort</td>
<td>Nortriptyline</td>
</tr>
<tr>
<td>Nelfinavir</td>
<td></td>
<td>Indinavir</td>
</tr>
<tr>
<td>Posaconazole</td>
<td></td>
<td>Nortriptyline</td>
</tr>
<tr>
<td>Ritonavir</td>
<td></td>
<td>Phenobarbital</td>
</tr>
<tr>
<td>Saquinavir</td>
<td></td>
<td>Phenytoin</td>
</tr>
<tr>
<td>Suboxone</td>
<td></td>
<td>Quinidine</td>
</tr>
<tr>
<td>Telaprevir</td>
<td></td>
<td>Sirolimus</td>
</tr>
<tr>
<td>Telithromycin</td>
<td></td>
<td>Tacrolimus</td>
</tr>
<tr>
<td>Voriconazole</td>
<td></td>
<td>Tolvaptan</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Trimipramine</td>
</tr>
</tbody>
</table>

*Anticoagulants and other anticancer agents are prohibited for all patients on trial and are therefore not included in this list.
APPENDIX C: DOSING NOMOGRAMS

ARM 1 PATIENTS WITH BMS-986158

Dose Assignment: 1.3 mg/m$^2$/day
(Dose Level -2 or -2i)

<table>
<thead>
<tr>
<th>BSA (m$^2$)</th>
<th>Total Daily Dose (mg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.71 – 0.86</td>
<td>1.0</td>
</tr>
<tr>
<td>0.87 – 1.05</td>
<td>1.25</td>
</tr>
<tr>
<td>1.06 – 1.24</td>
<td>1.5</td>
</tr>
<tr>
<td>1.25 – 1.44</td>
<td>1.75</td>
</tr>
<tr>
<td>1.45 – 1.63</td>
<td>2.0</td>
</tr>
<tr>
<td>1.64 – 2.00</td>
<td>2.25</td>
</tr>
</tbody>
</table>

Note that Dose Level -2 / -2i nomogram begins at a BSA of 0.71 m$^2$ due to dose rounding constraints. Patients who are < 0.71 m$^2$ and require a dose reduction to Dose Level -2 should receive their original dose minus 0.25 mg per dose. For example, a 0.5 m$^2$ patient originally receiving 0.75 mg on Dose Level -1 who requires dose reduction will receive 0.5 mg with dose reduction.

Dose Assignment: 1.6 mg/m$^2$/day
(Dose Level -1 or -1i)

<table>
<thead>
<tr>
<th>BSA (m$^2$)</th>
<th>Total Daily Dose (mg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.30 – 0.39</td>
<td>0.5</td>
</tr>
<tr>
<td>0.40 – 0.54</td>
<td>0.75</td>
</tr>
<tr>
<td>0.55 – 0.70</td>
<td>1.0</td>
</tr>
<tr>
<td>0.71 – 0.85</td>
<td>1.25</td>
</tr>
<tr>
<td>0.86 – 1.01</td>
<td>1.5</td>
</tr>
<tr>
<td>1.02 – 1.17</td>
<td>1.75</td>
</tr>
<tr>
<td>1.18 – 1.32</td>
<td>2.0</td>
</tr>
<tr>
<td>1.33 – 1.48</td>
<td>2.25</td>
</tr>
<tr>
<td>1.49 – 1.64</td>
<td>2.5</td>
</tr>
<tr>
<td>1.65 – 2.00</td>
<td>2.75</td>
</tr>
</tbody>
</table>
**Dose Assignment: 2.0 mg/m\(^2\)/day**  
(Dose Level 1 or 1i)

<table>
<thead>
<tr>
<th>BSA (m(^2))</th>
<th>Total Daily Dose (mg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.30 – 0.31</td>
<td>0.5</td>
</tr>
<tr>
<td>0.32 – 0.43</td>
<td>0.75</td>
</tr>
<tr>
<td>0.44 – 0.56</td>
<td>1.0</td>
</tr>
<tr>
<td>0.57 – 0.68</td>
<td>1.25</td>
</tr>
<tr>
<td>0.69 – 0.81</td>
<td>1.5</td>
</tr>
<tr>
<td>0.82 – 0.93</td>
<td>1.75</td>
</tr>
<tr>
<td>0.94 – 1.06</td>
<td>2.0</td>
</tr>
<tr>
<td>1.07 – 1.18</td>
<td>2.25</td>
</tr>
<tr>
<td>1.19 – 1.31</td>
<td>2.5</td>
</tr>
<tr>
<td>1.32 – 1.43</td>
<td>2.75</td>
</tr>
<tr>
<td>1.44 – 1.56</td>
<td>3.0</td>
</tr>
<tr>
<td>1.57 – 1.68</td>
<td>3.25</td>
</tr>
<tr>
<td>1.69 – 2.00</td>
<td>3.5</td>
</tr>
</tbody>
</table>
**ARM 2 PATIENTS WITH BMS-986378 (CC-90010)**

**Dose Assignment: 15 mg/m²/dose**

**Dose Level -1**

<table>
<thead>
<tr>
<th>BSA (m²)</th>
<th>Total Daily Dose (mg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.65 – 0.83</td>
<td>10</td>
</tr>
<tr>
<td>0.84 – 1.16</td>
<td>15</td>
</tr>
<tr>
<td>1.17 – 1.50</td>
<td>20</td>
</tr>
<tr>
<td>&gt;1.50</td>
<td>25</td>
</tr>
</tbody>
</table>

**Dose Assignment: 21 mg/m²/dose**

**Dose Level 1**

<table>
<thead>
<tr>
<th>BSA (m²)</th>
<th>Total Daily Dose (mg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.65 – 0.83</td>
<td>15</td>
</tr>
<tr>
<td>0.84 – 1.07</td>
<td>20</td>
</tr>
<tr>
<td>1.08 – 1.30</td>
<td>25</td>
</tr>
<tr>
<td>1.31 – 1.54</td>
<td>30</td>
</tr>
<tr>
<td>&gt;1.54</td>
<td>35</td>
</tr>
</tbody>
</table>

**Dose Assignment: 27 mg/m²/dose**

**Dose Level 2**

<table>
<thead>
<tr>
<th>BSA (m²)</th>
<th>Total Daily Dose (mg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.65 – 0.83</td>
<td>20</td>
</tr>
<tr>
<td>0.84 – 1.01</td>
<td>25</td>
</tr>
<tr>
<td>1.02 – 1.20</td>
<td>30</td>
</tr>
<tr>
<td>1.21 – 1.38</td>
<td>35</td>
</tr>
<tr>
<td>1.39 – 1.57</td>
<td>40</td>
</tr>
<tr>
<td>&gt;1.57</td>
<td>45</td>
</tr>
</tbody>
</table>

**Dose Assignment: 35 mg/m²/dose**

**Dose Level 3**

<table>
<thead>
<tr>
<th>BSA (m²)</th>
<th>Total Daily Dose (mg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.65 – 0.78</td>
<td>25</td>
</tr>
<tr>
<td>0.79 – 0.92</td>
<td>30</td>
</tr>
<tr>
<td>0.93 – 1.07</td>
<td>35</td>
</tr>
<tr>
<td>1.08 – 1.21</td>
<td>40</td>
</tr>
<tr>
<td>1.22 – 1.35</td>
<td>45</td>
</tr>
<tr>
<td>1.36 – 1.50</td>
<td>50</td>
</tr>
<tr>
<td>1.51 – 1.64</td>
<td>55</td>
</tr>
<tr>
<td>&gt;1.64</td>
<td>60</td>
</tr>
</tbody>
</table>
APPENDIX D: PHARMACOKINETIC WORKSHEET

For Arm 1:
Complete this worksheet for plasma samples collected following the Cycle 1, Day 1 dose (Section 9.1).

<table>
<thead>
<tr>
<th>Patient ID:</th>
<th>Sex:</th>
<th>Dose Level:</th>
<th>Weight:</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Arm 1 – BMS-986158</td>
<td></td>
</tr>
</tbody>
</table>

| Height: | 1 mL in K2EDTA (purple top) tube |

<table>
<thead>
<tr>
<th>Cycle</th>
<th>Day</th>
<th>Sample Time Points</th>
<th>Volume</th>
<th>Date and Time</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>1</td>
<td>Pre-dose</td>
<td>1 mL</td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>1</td>
<td>Dose administered:</td>
<td>______ mg</td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>1</td>
<td>30 minutes (± 10 mins) after dose</td>
<td>1 mL</td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>1</td>
<td>1 hour (±10 mins) after dose</td>
<td>1 mL</td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>1</td>
<td>2 hours (± 10 mins) after dose</td>
<td>1 mL</td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>1</td>
<td>3 hours (± 10 mins) after dose</td>
<td>1 mL</td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>1</td>
<td>4 hours (±15 mins) after dose</td>
<td>1 mL</td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>1</td>
<td>6 hours (±15 mins) after dose</td>
<td>1 mL</td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>1</td>
<td>8 hours (± 1 hours) after dose</td>
<td>1 mL</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td></td>
<td>24 hours (± 4 hours) after dose</td>
<td>1 mL</td>
<td></td>
</tr>
</tbody>
</table>

Total blood volume for PK samples this worksheet: 9 mL

Signature of site staff responsible for sample collection: ____________________
Date: ____________________

INCLUDE A COPY OF THIS WORKSHEET WITH EACH SAMPLE SHIPMENT AND RETAIN A COPY AT THE STUDY SITE.
Arm 1: Complete this worksheet for plasma samples collected later in Cycle 1 (Section 9.1).

For all patients on Arm 1, complete the row for Day 5 administration and collect samples for Day 4 or 5 AND Day 8 AND Day 11, 12, 18, or 19 AND Day 15 or 22.

<table>
<thead>
<tr>
<th>Patient ID:</th>
<th>Sex:</th>
<th>Dose Level:</th>
<th>Weight:</th>
</tr>
</thead>
<tbody>
<tr>
<td>Arm 1 – BMS-986158</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Height:</td>
<td>1 mL in K2EDTA (purple top) tube</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Cycle</th>
<th>Day</th>
<th>Sample Time Points</th>
<th>Volume</th>
<th>Date and Time</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>☐ 4</td>
<td>24 hours (± 4 hours) after prior day’s dose</td>
<td>1 mL</td>
<td>Date of Prior Dose:</td>
</tr>
<tr>
<td></td>
<td>☐ 5</td>
<td>Date of Prior Dose:</td>
<td></td>
<td>Time of Prior Dose:</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Prior Dose: ______ mg</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

24 hours (± 4 hours) after prior day’s dose

Dose administered: ______ mg

Complete this row for all patients.

Any time pre-dose

Obtain this sample for all patients regardless of timing of other draws.

<table>
<thead>
<tr>
<th>Cycle</th>
<th>Day</th>
<th>Sample Time Points</th>
<th>Volume</th>
<th>Date and Time</th>
</tr>
</thead>
<tbody>
<tr>
<td>8</td>
<td>☐ 11</td>
<td>24 hours (± 4 hours) after prior day’s dose</td>
<td>1 mL</td>
<td>Date of Prior Dose:</td>
</tr>
<tr>
<td></td>
<td>☐ 12</td>
<td>Date of Prior Dose:</td>
<td></td>
<td>Time of Prior Dose:</td>
</tr>
<tr>
<td></td>
<td>☐ 18</td>
<td>Prior Dose: ______ mg</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>☐ 19</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Obtain one sample pre-dose for all patients regardless of timing of other draws.

<table>
<thead>
<tr>
<th>Cycle</th>
<th>Day</th>
<th>Sample Time Points</th>
<th>Volume</th>
<th>Date and Time</th>
</tr>
</thead>
<tbody>
<tr>
<td>15</td>
<td>☐ 15</td>
<td>Date of Prior Dose:</td>
<td>1 mL</td>
<td></td>
</tr>
<tr>
<td></td>
<td>☐ 22</td>
<td>Time of Prior Dose:</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Prior Dose: ______ mg</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Total blood volume for PK samples this worksheet: 4 mL

Signature of site staff responsible for sample collection: 
Date: 

INCLUDE A COPY OF THIS WORKSHEET WITH EACH SAMPLE SHIPMENT AND RETAIN A COPY AT THE STUDY SITE.
For Arm 2:
Complete this worksheet for plasma samples collected following the Cycle 1, Day 1 dose (Section 9.1).

<table>
<thead>
<tr>
<th>Patient ID:</th>
<th>Sex:</th>
<th>Dose Level:</th>
<th>Weight:</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Arm 2 – BMS-986378 (CC-90010)</th>
<th>Height:</th>
<th>1 mL in K2EDTA (purple top) tube</th>
</tr>
</thead>
</table>

<table>
<thead>
<tr>
<th>Cycle</th>
<th>Day</th>
<th>Sample Time Points</th>
<th>Volume</th>
<th>Date and Time</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>1</td>
<td>Pre-dose</td>
<td>1 mL</td>
<td></td>
</tr>
<tr>
<td></td>
<td>1</td>
<td>Dose administered:</td>
<td>_____ mg</td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>1</td>
<td>30 minutes (± 10 mins) after dose</td>
<td>1 mL</td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>1</td>
<td>1 hour (±10 mins) after dose</td>
<td>1 mL</td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>1</td>
<td>2 hours (± 10 mins) after dose</td>
<td>1 mL</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>2</td>
<td>24 hours (± 4 hours) after dose</td>
<td>1 mL</td>
<td></td>
</tr>
</tbody>
</table>

**Total blood volume for PK samples this worksheet: 5 mL**

**Signature of site staff responsible for sample collection**

INCLUDE A COPY OF THIS WORKSHEET WITH EACH SAMPLE SHIPMENT AND RETAIN A COPY AT THE STUDY SITE.
For Arm 2:
Complete this worksheet for plasma samples collected following the Cycle 1, Day 4 dose (Section 9.1).

<table>
<thead>
<tr>
<th>Patient ID:</th>
<th>Sex:</th>
<th>Dose Level:</th>
<th>Weight:</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Arm 2 – BMS-986378 (CC-90010)</th>
<th>Height:</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 mL in K2EDTA (purple top) tube</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Cycle</th>
<th>Day</th>
<th>Sample Time Points</th>
<th>Volume</th>
<th>Date and Time</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>4</td>
<td>Pre-dose</td>
<td>1 mL</td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>4</td>
<td>Dose administered:</td>
<td>______ mg</td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>4</td>
<td>30 minutes (± 10 mins) after dose</td>
<td>1 mL</td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>4</td>
<td>1 hour (±10 mins) after dose</td>
<td>1 mL</td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>4</td>
<td>2 hours (± 10 mins) after dose</td>
<td>1 mL</td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>4</td>
<td>3 hours (± 10 mins) after dose</td>
<td>1 mL</td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>4</td>
<td>4 hours (±15 mins) after dose</td>
<td>1 mL</td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>4</td>
<td>6 hours (±15 mins) after dose</td>
<td>1 mL</td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>4</td>
<td>8 hours (± 1 hours) after dose</td>
<td>1 mL</td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>5</td>
<td>24 hours (± 4 hours) after dose</td>
<td>1 mL</td>
<td></td>
</tr>
</tbody>
</table>

Total blood volume for PK samples this worksheet: 9 mL

Signature of site staff responsible for sample collection

Date

INCLUDE A COPY OF THIS WORKSHEET WITH EACH SAMPLE SHIPMENT AND RETAIN A COPY AT THE STUDY SITE.
For Arm 2:
Complete this worksheet for plasma samples collected later in Cycle 1 (Section 9.1).

<table>
<thead>
<tr>
<th>Patient ID:</th>
<th>Sex:</th>
<th>Dose Level:</th>
<th>Weight:</th>
</tr>
</thead>
<tbody>
<tr>
<td>Arm 2 – BMS-986378 (CC-90010)</td>
<td></td>
<td></td>
<td>Height:</td>
</tr>
</tbody>
</table>

1 mL in K2EDTA (purple top) tube

<table>
<thead>
<tr>
<th>Cycle</th>
<th>Day</th>
<th>Sample Time Points</th>
<th>Volume</th>
<th>Date and Time</th>
</tr>
</thead>
<tbody>
<tr>
<td>8</td>
<td>Any time</td>
<td>Obtain this sample for all patients regardless of timing of other draws.</td>
<td>1 mL</td>
<td>10/27/17 @ 1401</td>
</tr>
<tr>
<td>15</td>
<td>Any time</td>
<td>Obtain this sample for all patients regardless of timing of other draws</td>
<td>1 mL</td>
<td></td>
</tr>
</tbody>
</table>

Total blood volume for PK samples this worksheet: 2mL

Signature of site staff responsible for sample collection

Date

INCLUDE A COPY OF THIS WORKSHEET WITH EACH SAMPLE SHIPMENT AND RETAIN A COPY AT THE STUDY SITE.
Complete this worksheet for patients who have CSF sampled via Ommaya in Cycle 1 (Section 9.1) – Arm 2 only.

<table>
<thead>
<tr>
<th>Patient ID:</th>
<th>Sex:</th>
<th>Dose Level:</th>
<th>Weight:</th>
</tr>
</thead>
<tbody>
<tr>
<td>Arm 2 – BMS-986378 (CC-90010)</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Cycle</th>
<th>Day</th>
<th>Sample Time Points</th>
<th>Volume</th>
<th>Date and Time</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>2*</td>
<td>BMS-986378 (CC-90010) dose administered: _______ mg</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>2*</td>
<td>CSF within 4 hours of dose</td>
<td>CSF: 3 mL</td>
<td></td>
</tr>
<tr>
<td></td>
<td>2*</td>
<td>Blood in EDTA tube within ±15 mins of CSF collection</td>
<td>Blood: 1 mL</td>
<td></td>
</tr>
<tr>
<td></td>
<td>4*</td>
<td>BMS-986378 (CC-90010) dose administered: _______ mg</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>4*</td>
<td>CSF within 4 hours of dose</td>
<td>CSF: 3 mL</td>
<td></td>
</tr>
<tr>
<td></td>
<td>4*</td>
<td>Blood in EDTA tube within ±15 mins of CSF collection</td>
<td>Blood: 1 mL</td>
<td></td>
</tr>
</tbody>
</table>

*Collection on either Day 2 or 4. Collection is optional.

**Total blood volume for this worksheet: 1 mL**

Signature of site staff responsible for sample collection | Date

---

INCLUDE A COPY OF THIS WORKSHEET WITH EACH SAMPLE SHIPMENT AND RETAIN A COPY AT THE STUDY SITE.
Complete this worksheet for patients who have CSF sampled via lumbar puncture (Section 9.1) – Arm 2 only.

For patients who undergo multiple lumbar punctures, use a new worksheet for each procedure.

<table>
<thead>
<tr>
<th>Patient ID:</th>
<th>Sex:</th>
<th>Dose Level:</th>
<th>Weight:</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>Height:</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Cycle</th>
<th>Day</th>
<th>Sample Time Points</th>
<th>Volume</th>
<th>Date and Time</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Last BMS-986378 (CC-90010) administered prior to lumbar puncture:</td>
<td></td>
<td>(use 24-hour clock for times; e.g. 1401 instead of 2:01 PM)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>CSF sample collection</td>
<td>CSF: 3 mL</td>
<td>Example: 10/27/17 @ 1401</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Blood in EDTA tube within ±15 mins of CSF collection</td>
<td>Blood: 1 mL</td>
<td></td>
</tr>
</tbody>
</table>

Total blood volume for PK samples: 1 mL

Signature of site staff responsible for sample collection  Date

INCLUDE A COPY OF THIS WORKSHEET WITH EACH SAMPLE SHIPMENT AND RETAIN A COPY AT THE STUDY SITE.
APPENDIX E: CORRELATIVE BIOLOGY WORKSHEETS

Form 1: PAXGENCE RNA EXPRESSION PHARMACODYNAMIC WORKSHEET (Section 9.2.1) – Arms 1 and 2

<table>
<thead>
<tr>
<th>Patient ID:</th>
<th>Dose Level:</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>2.5 mL in PAXgene RNA blood tube (provided)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Cycle</th>
<th>Day</th>
<th>Sample Time Points (See Section 9.2 for allowable windows for blood draws)</th>
<th>Volume</th>
<th>Date and Time (use 24-hour clock for times; e.g. 1622 instead of 4:22)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>1</td>
<td>Pre-dose</td>
<td>2.5 mL</td>
<td>Example: 12/30/16 @ 1622</td>
</tr>
<tr>
<td>1</td>
<td>1</td>
<td>Study drug dose administered:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td></td>
<td>4 hours (±15 mins) after dose</td>
<td>2.5 mL</td>
<td></td>
</tr>
<tr>
<td>1</td>
<td></td>
<td>8 hours (± 1 hours) after dose</td>
<td>2.5 mL</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td></td>
<td>24 hours (± 4 hours) after dose</td>
<td>2.5 mL</td>
<td></td>
</tr>
</tbody>
</table>

Total blood volume for PD samples for this worksheet: 10 mL

Signature of site staff responsible for sample collection Date

INCLUDE A COPY OF THIS WORKSHEET WITH EACH SAMPLE SHIPMENT AND RETAIN A COPY AT THE STUDY SITE.
### Form 2: ctDNA WORKSHEET – Cycles 1 and 2 (Section 9.2.3) – Arms 1 and 2

<table>
<thead>
<tr>
<th>Cycle</th>
<th>Day</th>
<th>Sample Time Points</th>
<th>Volume</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>1</td>
<td>Pre-dose</td>
<td>5 - 10 mL</td>
</tr>
<tr>
<td>1</td>
<td>15</td>
<td>Day 15 (pre-dose on Arm 1; untimed on Arm 2)</td>
<td>5 - 10 mL</td>
</tr>
<tr>
<td></td>
<td>22</td>
<td>OR</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Day 22 (pre-dose on Arm 1 if dosed during all 4 weeks;</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>untimed on Arm 1 interrupted schedules; untimed on Arm 2)</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>1</td>
<td>Pre-dose</td>
<td>5 - 10 mL</td>
</tr>
</tbody>
</table>

**Total blood volume for ctDNA samples for this worksheet:** 15 - 30 mL

**Cycle 1:**

Signature of site staff responsible for sample collection

Date

**Cycle 2:**

Signature of site staff responsible for sample collection

Date

INCLUDE A COPY OF THIS WORKSHEET WITH EACH SAMPLE SHIPMENT AND RETAIN A COPY AT THE STUDY SITE.
Form 3: ctDNA WORKSHEET – Disease Evaluation and Off Protocol Time Points
(Section 9.2.3)

<table>
<thead>
<tr>
<th>Patient ID:</th>
<th>Dose Level:</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>5 - 10 mL in Streck Cell Free DNA BCT (provided)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Diagnosis:</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
</tr>
</tbody>
</table>

Date of Disease Evaluation (MM/DD/YY):

<table>
<thead>
<tr>
<th>Cycle</th>
<th>Day</th>
<th>Sample Time Points</th>
<th>Volume</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Within ±5 days of every disease assessment</td>
<td>5 - 10 mL</td>
</tr>
<tr>
<td></td>
<td></td>
<td>At time of disease progression or other reason off protocol therapy</td>
<td>5 - 10 mL</td>
</tr>
</tbody>
</table>

Total blood volume for ctDNA samples per worksheet: 10 - 20 mL

Signature of site staff responsible for sample collection   Date  

INCLUDE A COPY OF THIS WORKSHEET WITH EACH SAMPLE SHIPMENT AND RETAIN A COPY AT THE STUDY SITE.
**Form 4: CSF CELL FREE DNA WORKSHEET (Section 9.2.4) – Arm 2 only**

<table>
<thead>
<tr>
<th>Patient ID:</th>
<th>Dose Level:</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>1 – 5 mL in Streck Cell Free DNA BCT (provided)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Cycle</th>
<th>Day</th>
<th>Sample Time Point</th>
<th>CSF Volume</th>
<th>Date and Time</th>
</tr>
</thead>
<tbody>
<tr>
<td>_____</td>
<td>___</td>
<td>See section 9.2.4.1</td>
<td>1 – 5 mL</td>
<td><strong>12/30/16 @ 1622</strong></td>
</tr>
</tbody>
</table>

Signature of site staff responsible for sample collection  

Date

INCLUDE A COPY OF THIS WORKSHEET WITH EACH SAMPLE SHIPMENT AND RETAIN A COPY AT THE STUDY SITE.
Form 5: TISSUE BIOMARKER WORKSHEET (Section 9.2.5)

<table>
<thead>
<tr>
<th>Patient ID:</th>
<th>Dose Level:</th>
</tr>
</thead>
<tbody>
<tr>
<td>Time point</td>
<td></td>
</tr>
<tr>
<td></td>
<td>[ ] Pre-enrollment</td>
</tr>
<tr>
<td></td>
<td>[ ] Initial diagnosis</td>
</tr>
<tr>
<td></td>
<td>[ ] Second look surgery</td>
</tr>
<tr>
<td></td>
<td>[ ] Biopsy or surgery at time of relapse</td>
</tr>
<tr>
<td></td>
<td>[ ] Post-enrollment</td>
</tr>
<tr>
<td></td>
<td>[ ] Biopsy or surgery at time of progression</td>
</tr>
<tr>
<td></td>
<td>[ ] Biopsy or surgery in setting of response</td>
</tr>
<tr>
<td>Source of material</td>
<td>[ ] Primary tumor</td>
</tr>
<tr>
<td>Date of biopsy/surgery</td>
<td>[ ] Metastatic lesion</td>
</tr>
<tr>
<td>Material Submitted</td>
<td>[ ] Formalin fixed paraffin embedded block</td>
</tr>
<tr>
<td>(check all that apply)</td>
<td>Number of blocks__________</td>
</tr>
<tr>
<td></td>
<td>[ ] Tissue section scrolls (4-5 micron)</td>
</tr>
<tr>
<td></td>
<td>Number of scrolls__________</td>
</tr>
<tr>
<td></td>
<td>[ ] Unstained slides (4-5 micron)</td>
</tr>
<tr>
<td></td>
<td>Number of slides__________</td>
</tr>
<tr>
<td></td>
<td>[ ] Flash frozen tumor</td>
</tr>
<tr>
<td></td>
<td>Quantity__________</td>
</tr>
</tbody>
</table>

Signature of site staff responsible for sample collection  
Date

INCLUDE A COPY OF THIS WORKSHEET WITH EACH SAMPLE SHIPMENT ALONG WITH A REDACTED COPY OF THE PATHOLOGY REPORT. RETAIN A COPY OF THIS WORKSHEET AT THE STUDY SITE.
APPENDIX F: CONTINUAL REASSESSMENT METHOD SIMULATION ALGORITHM

All simulations were conducted using the R version 3.4.3. For each set of simulations, we set the random seed to a specific value so that our simulations are reproducible.

Simulations for Cohorts A and B followed the modified CRM dose-escalation design as described in section 13.2.1. We began each simulated trial by enrolling a cohort of 3 patients (from Cohort A and/or B) on the starting dose level and proceeded in cohorts of 3 patients following subsequent dose escalations or de-escalations. We simulated patient arrival times as a Poisson process with a mean inter-arrival time of 15 days. Arriving patients had a 33.33% chance to be from Cohort B and a 66.67% chance to be from Cohort A. For each patient, we simulated the occurrence of a DLT as a Bernoulli random variable with DLT probability equal to the true toxicity probability for the patient’s assigned dose (Table 4a.1 and 4a.2). If a patient experienced a DLT, the time of occurrence of the DLT was selected from a uniform distribution between Day 0 and Day 28. Patients who did not experience a DLT were observed for the full 28-day cycle.

While each cohort of 3 patients were being evaluated for DLTs in the first cycle of treatment, patients from Cohort A entered a waitlist with 50% probability to enroll immediately when slots became available. However, when no enrollment slots were available, patients from Cohort B were enrolled at one dose level below the dose level of the current cohort of 3 patients under observation. If the lowest dose level was being evaluated as the current dose level, enrollment for patients from Cohort B at one dose lower was not permitted.

Dose escalation decisions were made once all three patients from the current cohort were evaluable for DLT assessment. We used the `crm` function from the `dfcrm` R package to determine the next dose recommended by the CRM. The input parameters to the `crm` function are presented in Table F1.

Table F1: Input parameters for the `crm` function

<table>
<thead>
<tr>
<th>Input parameter</th>
<th>Description</th>
<th>Value(s)</th>
</tr>
</thead>
<tbody>
<tr>
<td>prior</td>
<td>Prior toxicity probabilities</td>
<td>Arm 1: c(0.08, 0.17, 0.20, 0.22, 0.32, 0.38)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Arm 2: c(0.10, 0.17, 0.25, 0.30)</td>
</tr>
<tr>
<td>target</td>
<td>Target DLT rate</td>
<td>0.20</td>
</tr>
<tr>
<td>tox</td>
<td>A vector of patient outcomes</td>
<td>Include all outcomes from evaluable patients</td>
</tr>
<tr>
<td>level</td>
<td>A vector of dose levels assigned to patients</td>
<td>Include all levels from evaluable patients</td>
</tr>
<tr>
<td>n</td>
<td>Number of patients enrolled</td>
<td>length(level)</td>
</tr>
<tr>
<td>dosename</td>
<td>Vector containing names of doses used</td>
<td>NULL</td>
</tr>
<tr>
<td>include</td>
<td>A subset of patients to include</td>
<td>Include all evaluable patients</td>
</tr>
<tr>
<td></td>
<td>in the dose calculation</td>
<td></td>
</tr>
<tr>
<td>----------------</td>
<td>-----------------------------------------------------------------------------------------</td>
<td></td>
</tr>
<tr>
<td>pid</td>
<td>Patient ID provided</td>
<td></td>
</tr>
<tr>
<td>conf.level</td>
<td>Confidence level for probability interval of returned dose-toxicity curve</td>
<td></td>
</tr>
<tr>
<td>method</td>
<td>Method for parameter estimation</td>
<td></td>
</tr>
<tr>
<td>Model</td>
<td>Working model for the dose-toxicity function</td>
<td></td>
</tr>
<tr>
<td>scale</td>
<td>Standard deviation of the normal prior of the model parameter</td>
<td></td>
</tr>
</tbody>
</table>

Include all evaluable patients

Baseline: 0.90

If the first or second patient in the current cohort of 3 patients experienced a DLT, we updated the CRM model using all available DLT data from all evaluable patients to determine if an intra-cohort dose de-escalation was recommended. The next patient in the current cohort of 3 patients was assigned the recommended dose from the updated CRM model: either the same dose or a lower dose. Subsequent patients in the current cohort of 3 patients were treated at the new currently evaluated dose.

The recommended dose level for the next cohort of 3 patients was the dose with the toxicity probability closest to the toxicity threshold, as calculated by the `crm` function. For dose escalation, the recommended dose level was never more than one sequential dose level above the current dose level; for dose de-escalation, the recommended dose was one or two dose levels below the current dose level.

Dose escalation continued until the following termination rules were achieved:

1. A minimum of 18 patients were treated in total for Cohorts A and B; AND,
2. A minimum of 6 Cohort A or B patients were treated at a single dose level.

Once the termination rules were triggered, study enrollment to Cohorts A and B was terminated. Once all enrolled patients to Cohorts A and B were evaluable for DLT assessment, the CRM model was run for the final time. The MTD was the dose level with the posterior toxicity probability closest to the target toxicity level.

For each simulated trial, we recorded a number of trial metrics including the: (1) selected MTD; (2) number of patients assigned per dose level; (3) number of DLTs per dose level; (4) total number of patients enrolled; (4) number of Cohort B patients enrolled at one dose below the current dose; and (5) number of Cohort B patients enrolled overall.
APPENDIX G: MULTICENTER GUIDELINES

Dana-Farber/Harvard Cancer Center Multi-Center Data and Safety Monitoring Plan

G.1 INTRODUCTION

The Dana-Farber/Harvard Cancer Center Multi-Center Data and Safety Monitoring Plan (DF/HCC DSMP) outlines the procedures for conducting a DF/HCC Multi-Center research protocol. The DF/HCC DSMP serves as a reference for any sites external to DF/HCC that are participating in a DF/HCC clinical trial.

G.1.1 Purpose

To establish standards that will ensure that a Dana-Farber/Harvard Cancer Center Multi-Center protocol will comply with Federal Regulations, Health Insurance Portability and Accountability Act (HIPAA) requirements and applicable DF/HCC Standard Operating Procedures.

G.1.2 Multi-Center Data and Safety Monitoring Plan Definitions

**DF/HCC Multi-Center Protocol:** A research protocol in which one or more outside institutions are collaborating with Dana-Farber/Harvard Cancer Center where a DF/HCC investigator is the sponsor. DF/HCC includes Dana-Farber/Partners Cancer Care (DF/PCC) Network Clinical Trial Affiliates.

**Lead Institution:** One of the Dana-Farber/Harvard Cancer Center consortium members (Dana-Farber Cancer Institute (DFCI), Massachusetts General Hospital (MGH), Beth Israel Deaconess Medical Center (BIDMC), Boston Children’s Hospital (BCH), Brigham and Women’s Hospital (BWH) responsible for the coordination, development, submission, and approval of a protocol as well as its subsequent amendments per the DFCI IRB and applicable regulatory guidelines (CTEP, Food and Drug Administration (FDA), Office of Biotechnology Activities (OBA) etc.). The Lead Institution is typically the home of the DF/HCC Sponsor. The Lead Institution also typically serves as the Coordinating Center for the DF/HCC Multi-Center Protocol.

**DF/HCC Sponsor:** The person sponsoring the submitted Multi-Center protocol. Within DF/HCC, this person is the Overall Principal Investigator who takes responsibility for initiation, management and conduct of the protocol at all research locations. In applicable protocols, the DF/HCC Sponsor will serve as the single liaison with any regulatory agencies (i.e. the FDA). The DF/HCC Sponsor has ultimate authority over the protocol and is responsible for the conduct of the study at DF/HCC and all Participating Institutions. In most cases the DF/HCC Sponsor is the same person as the DF/HCC Overall Principal Investigator; however, both roles can be filled by two different people.

**Participating Institution:** An institution that is outside the DF/HCC and DF/PCC consortium that is collaborating with DF/HCC on a protocol where the sponsor is a DF/HCC
Investigator. The Participating Institution acknowledges the DF/HCC Sponsor as having the ultimate authority and responsibility for the overall conduct of the study. **Coordinating Center:** The entity (i.e. Lead Institution, Medical Monitor, Contract Research Organization (CRO), etc) that provides administrative support to the DF/HCC Sponsor in order that he/she may fulfill the responsibilities outlined in the protocol document and DSMP, and as specified in applicable regulatory guidelines (i.e. CTEP Multi-Center Guidelines). In general, the Lead Institution is the Coordinating Center for the DF/HCC Multi-Center Protocol.

**DF/HCC Office of Data Quality (ODQ):** A group within DF/HCC responsible for ensuring high-quality standards are used for data collection and the ongoing management of clinical trials, auditing, and data and safety monitoring. ODQ also coordinates quality assurance efforts related to multi-center clinical research.

**DF/HCC Research Informatics for Operations (RIO):** A group within DF/HCC responsible for providing a comprehensive data management platform for managing clinical trial data.

G.2 GENERAL ROLES AND RESPONSIBILITIES

For DF/HCC Multi-Center Protocols, the DF/HCC Sponsor, the Coordinating Center, and the Participating Institutions are expected to adhere to the following general responsibilities:

**G.2.1 DF/HCC Sponsor**

The DF/HCC Sponsor, Steven DuBois, MD, will accept responsibility for all aspects of conducting a DF/HCC Multi-Center protocol which includes but is not limited to:

- Oversee the coordination, development, submission, and approval of the protocol as well as subsequent amendments.
- Ensure that the investigators, study team members, and Participating Institutions are qualified and appropriately resourced to conduct the protocol.
- Include the Multi-Center Data and Safety Monitoring Plan as an appendix to the protocol.
- Ensure all Participating Institutions are using the correct version of the protocol.
- Ensure that each participating investigator and study team member receives adequate protocol training (and/or a Site Initiation Visit prior to enrolling participants) and throughout trial’s conduct as needed.
- Ensure the protocol will be provided to each participating site in a language understandable to all applicable site personnel when English is not the primary language.
- Monitor progress and overall conduct of the study at all Participating Institutions.
- Ensure all DFCI Institutional Review Board (IRB), DF/HCC and other applicable (i.e. FDA) reporting requirements are met.
- Review data and maintain timely submission of data for study analysis.
- Act as the single liaison with the FDA.
- Ensure compliance with all requirements as set forth in the Code of Federal Regulations, applicable DF/HCC requirements, HIPAA requirements, and the approved protocol.
- Commit to the provision that the protocol will not be rewritten or modified by anyone other than the DF/HCC Sponsor.
- Identify and qualify Participating Institutions and obtain accrual commitments prior to extending the protocol to that site.
- Monitor accrual and address Participating Institutions that are not meeting their accrual requirements.

G.2.2 Coordinating Center (Dana-Farber Cancer Institute)

The general responsibilities of the Coordinating Center may include but are not limited to:
- Assist in protocol development.
- Maintain FDA correspondence, as applicable.
- Review registration materials for eligibility and register participants from Participating Institutions in the DF/HCC clinical trial management system (CTMS).
- Distribute protocol and informed consent document updates to Participating Institutions as needed.
- Oversee the data collection process from Participating Institutions.
- Maintain documentation of Serious Adverse Event (SAE) reports and deviations/violation submitted by Participating Institutions and provide to the DF/HCC Sponsor for timely review and submission to the DFCI IRB, as necessary.
- Distribute serious adverse events reported to the DF/HCC Sponsor that fall under the DFCI IRB Adverse Event Reporting Policy to all Participating Institutions.
- Provide Participating Institutions with information regarding DF/HCC requirements that they will be expected to comply with.
- Carry out plan to monitor Participating Institutions either by on-site or remote monitoring.
- Maintain Regulatory documents of all Participating Institutions which includes but is not limited to the following: local IRB approvals/notifications from all Participating Institutions, confirmation of Federal Wide Assurances (FWAs) for all sites, all SAE submissions, Screening Logs for all sites, IRB approved consents for all sites
- Conduct regular communications with all Participating Institutions (conference calls, emails, etc) and maintain documentation of all relevant communications.

G.2.3 Participating Institution

Each Participating Institution is expected to comply with all applicable federal regulations and DF/HCC requirements, the protocol and HIPAA requirements.
The general responsibilities for each Participating Institution may include but are not limited to:

- Document the delegation of research specific activities to study personnel.
- Commit to the accrual of participants to the protocol.
- Submit protocol and/or amendments to their local IRB of record.
- Maintain regulatory files as per sponsor requirements.
- Provide the Coordinating Center with regulatory documents or source documents as requested.
- Participate in protocol training prior to enrolling participants and throughout the trial as required (i.e. teleconferences).
- Update Coordinating Center with research staff changes on a timely basis.
- Register participants through the Coordinating Center prior to beginning research related activities.
- Submit Serious Adverse Event (SAE) reports to local IRB per institutional requirements and to the Coordinating Center, in accordance with DF/HCC requirements.
- Submit protocol deviations and violations to local IRB per institutional requirements and to the DF/HCC Sponsor in accordance with DF/HCC requirements.
- Order, store and dispense investigational agents and/or other protocol mandated drugs per federal guidelines and protocol requirements.
- Have office space, office equipment, and internet access that meet HIPAA standards.
- Participate in any quality assurance activities and meet with monitors or auditors at the conclusion of a visit to review findings.
- Promptly provide follow-up and/or corrective action plans for any monitoring queries or audit findings.

G.3 DF/HCC REQUIREMENTS FOR MULTI-CENTER PROTOCOLS

The following section will clarify DF/HCC Requirements and further detail the expectations for participating in a DF/HCC Multi-Center protocol.

G.3.1 Protocol Distribution

The Coordinating Center will distribute the final DFCI IRB approved protocol and any subsequent amended protocols to all Participating Institutions.

G.3.2 Protocol Revisions and Closures

The Participating Institutions will receive notification of protocol revisions and closures from the Coordinating Center. It is the individual Participating Institution’s responsibility to notify its IRB of these revisions.

- **Non life-threatening revisions**: Participating Institutions will receive written notification of protocol revisions regarding non life-threatening events from the
Coordinating Center. Non-life-threatening protocol revisions must be IRB approved and implemented within 90 days from receipt of the notification.

- **Revisions for life-threatening causes:** Participating Institutions will receive immediate notification from the Coordinating Center concerning protocol revisions required to protect lives with follow-up by fax, mail, e-mail, etc. Life-threatening protocol revisions will be implemented immediately followed by IRB request for approval.

- **Protocol closures and temporary holds:** Participating Institutions will receive notification of protocol closures and temporary holds from the Coordinating Center. Closures and holds will be effective immediately. In addition, the Coordinating Center, will update the Participating Institutions on an ongoing basis about protocol accrual data so that they will be aware of imminent protocol closures.

### G.3.3 Informed Consent Requirements

The DF/HCC approved informed consent document will serve as a template for the informed consent for Participating Institutions. The Participating Institution consent form must follow the consent template as closely as possible and should adhere to specifications outlined in the DF/HCC Guidance Document on Model Consent Language for Investigator-Sponsored Multi-Center Trials. This document will be provided separately to each Participating Institution upon request.

Participating Institutions are to send their version of the informed consent document and HIPAA authorization, if a separate document, to the Coordinating Center for review and approval prior to submission to their local IRB. The approved consent form must also be submitted to the Coordinating Center after approval by the local IRB for all consent versions.

The Principal Investigator (PI) at each Participating Institution will identify the physician members of the study team who will be obtaining consent and signing the consent form for therapeutic protocols. Participating institutions must follow the DF/HCC requirement that for all interventional drug, biologic, or device research, only attending physicians may obtain initial informed consent and any re-consent that requires a full revised consent form.

### G.3.4 IRB Documentation

The following must be on file with the Coordinating Center:
- Initial approval letter of the Participating Institution's IRB.
- Copy of the Informed Consent Form(s) approved by the Participating Institution’s IRB.
- Participating Institution’s IRB approval for all amendments.
- Annual approval letters by the Participating Institution's IRB.
G.3.5  IRB Re-Approval

Verification of IRB re-approval from the Participating Institutions is required in order to continue research activities. There is no grace period for continuing approvals.

The Coordinating Center will not register participants if a re-approval letter is not received from the Participating Institution on or before the anniversary of the previous approval date.

G.3.6  Participant Confidentiality and Authorization Statement

In 1996, congress passed the first federal law covering the privacy of health information known as the Health Insurance Portability and Accountability Act (HIPAA). Any information, related to the physical or mental health of an individual is called Protected Health Information (PHI). HIPAA outlines how and under what circumstances PHI can be used or disclosed.

In order for covered entities to use or disclose protected health information during the course of a study, the study participant must sign an authorization statement. This authorization statement may or may not be separate from the informed consent document. The Coordinating Center, with the approval from the DFCI IRB will provide a consent template, with information regarding authorization for the disclosure of protected health information.

The DF/HCC Sponsor will use all efforts to limit its use of protected health information in its trials. However, because of the nature of these trials, certain protected health information must be collected. DF/HCC has chosen to use authorizations, signed by the participant in the trial, rather than limited data sets with data use agreements.

G.3.6.1  DF/HCC Multi-Center Protocol Confidentiality

All documents, investigative reports, or information relating to the participant are strictly confidential. Whenever reasonably feasible, any participant specific reports (i.e. Pathology Reports, MRI Reports, Operative Reports, etc.) submitted to the Coordinating Center should be de-identified. It is recommended that the assigned protocol case number (as described below) be used for all participant specific documents. Participant initials may be included or retained for cross verification of identification.

G.3.7  DF/HCC Multi-Center Protocol Registration Policy

Requirements and procedures for patient registration are given in protocol Section 4. The Overall PI, Dr. DuBois will make no exceptions to the eligibility requirements for a protocol without DFCI IRB approval. All Participating Institutions are required to fully comply with this requirement.
G.3.7.1 Participant Registration

To register a participant, the following documents should be completed by the Participating Institution and e-mailed to the Coordinating Center Study Coordinator and to the email address pediatricBMS-986158@dfci.harvard.edu:

- Copy of the following source documents confirming eligibility:
  - Eligibility lab results listed in Section 3.1.5;
  - ECG;
  - Pregnancy test, urine or serum (if female and of childbearing potential);
  - Pathology report;
  - Imaging and/or pathology reports demonstrating evaluable or measurable disease;
  - Most recent clinician note, including medication list;
  - Documentation to confirm one of the following qualifying molecular features (Cohort B only):
    - MYCN amplification or high copy number gain
    - MYC amplification or high copy number gain
    - Translocation involving MYC or MYCN
    - Translocation involving BRD3 or BRD4

- Signed informed consent document
- HIPAA authorization form (if separate from the informed consent document)
- Completed Eligibility Checklist

The Coordinating Center will review the submitted documents in order to verify eligibility and consent. To complete the registration process, the Coordinating Center will:

- Register the participant on the study the DF/HCC Clinical Trial Management System (CTMS).
- Upon receiving confirmation of registration, the Coordinating Center will inform the Participating Institution and provide the study specific participant case number, and, if applicable, assigned treatment and/or dose level.

Treatment or other protocol-specific interventions may not begin without confirmation from the Coordinating Center that the participant has been registered.

G.3.7.2 Initiation of Therapy

Participants must be registered with the DF/HCC CTMS before the initiation of treatment or other protocol-specific interventions. Treatment and other protocol-specific interventions may not be initiated until the Participating Institution receives confirmation of the participant’s registration from the Coordinating Center. The DF/HCC Sponsor and DFCI IRB must be notified of any violations to this policy.
G.3.7.3 Eligibility Exceptions

No exceptions to the eligibility requirements for a protocol without DFCI IRB approval will be permitted. All Participating Institutions are required to fully comply with this requirement. The process for requesting an eligibility exception is defined below.

G.3.8 DF/HCC Protocol Case Number

At the time of registration, the following identifiers are required for all subjects: initials, date of birth, gender, race and ethnicity. Once eligibility has been established and the participant successfully registered, the participant is assigned a unique protocol case number. Participating Institutions should submit all de-identified subsequent communication and documents to the Coordinating Center, using this case number to identify the subject.

G.3.8.1 Protocol Deviations, Exceptions and Violations

Federal Regulations require an IRB to review proposed changes in a research activity to ensure that researchers do not initiate changes in approved research without IRB review and approval, except when necessary to eliminate apparent immediate hazards to the participant. DF/HCC requires all departures from the defined procedures set forth in the IRB approved protocol to be reported to the DF/HCC Sponsor, who in turn is responsible for reporting to the DFCI IRB.

For reporting purposes, DF/HCC uses the terms “violation”, “deviation” and “exception” to describe departures from a protocol. All Participating Institutions must adhere to these requirements for reporting to the DF/HCC Sponsor and will follow their institutional policy for reporting to their local IRB.

G.3.8.2 Definitions

**Protocol Deviation:** Any departure from the defined procedures set forth in the IRB-approved protocol which is *prospectively approved* prior to its implementation.

**Protocol Exception:** Any protocol deviation that relates to the eligibility criteria, e.g. enrollment of a participant who does not meet all inclusion/exclusion criteria.

**Protocol Violation:** Any protocol departure that was not *prospectively approved* by the IRB prior to its initiation or implementation.

G.3.8.3 Reporting Procedures

**DF/HCC Sponsor:** is responsible for ensuring that clear documentation is available in the medical record and/or regulatory documents to describe all protocol exceptions, deviations
and violations. The DF/HCC Sponsor will also be responsible for ensuring that all protocol violations/deviations are promptly reported per DFCI IRB guidelines.

**Participating Institutions:** Protocol deviations require prospective approval from the DFCI IRB. The Participating Institution must submit the deviation request to the Coordinating Center who will then submit the deviation request to the DFCI IRB. Upon DFCI IRB approval the deviation is submitted to the Participating Institution IRB, per institutional policy. A copy of the Participating Institution’s IRB report and determination will be forwarded to the Coordinating Center within 10 business days after the original submission. The deviation may not be implemented without all required approvals.

All protocol violations must be sent to the Coordinating Center in a timely manner. The Coordinating Center will provide training for the requirements for the reporting of violations.

**Coordinating Center:** Upon receipt of the violation/deviation report from the Participating Institution, the Coordinating Center will submit the report to the DF/HCC Sponsor for review. Subsequently, the Participating Institution’s IRB violation/deviation report will be submitted to the DFCI IRB for review per DFCI IRB reporting guidelines.

**G.3.9 Safety Assessments and Toxicity Monitoring**

The study teams at all participating institutions are responsible for protecting the safety, rights and well-being of study participants. Recording and reporting of adverse events that occur during the course of a study help ensure the continuing safety of study participants.

All participants receiving investigational agents and/or other protocol mandated therapy will be evaluated for safety. The safety parameters include all laboratory tests and hematological abnormalities, physical examination findings, and spontaneous reports of adverse events reported by participants. All toxicities encountered during the study will be evaluated according to the NCI criteria specified in the protocol. Life-threatening toxicities must be reported immediately to the DF/HCC Sponsor via the Coordinating Center.

Additional safety assessments and toxicity monitoring will be outlined in the protocol.

**G.3.9.1 Guidelines for Reporting Serious Adverse Events**

Guidelines for reporting Adverse Events (AEs) and Serious Adverse Events (SAEs) are detailed in protocol Section 7.0.

Participating Institutions must report the SAEs to the DF/HCC Sponsor and the Coordinating Center following the DFCI IRB Adverse Event Reporting Policy: http://www.dfhcc.harvard.edu/crs-resources/DFHCC_SOP_Library/RCO-204.pdf
The Coordinating Center will maintain documentation of all Participating Institution Adverse Event reports and be responsible for communicating to all participating investigators, any observations reportable under the DFCI IRB Reporting Requirements. Participating Institutions will review and submit to their IRB according to their institutional policies and procedures.

G.3.9.2 Guidelines for Processing IND Safety Reports

The DF/HCC Sponsor will review all IND Safety Reports and ensure that all IND Safety Reports are distributed to the Participating Institutions. Participating Institutions will review/submit to the IRB according to their institutional policies and procedures.

G.3.10 Data Management

DF/HCC RIO develops case report forms (CRF/eCRFs), for use with the protocol. These forms are designed to collect data for each study. DF/HCC RIO provides a web based training for all eCRF users.

G.3.10.1 Data Forms Review

Data submissions are monitored for timeliness and completeness of submission. If study forms are received with missing or questionable data, the submitting institution will receive a written or electronic query from the DF/HCC Office of Data Quality, Coordinating Center, or designee.

Responses to all queries should be completed and submitted within 14 calendar days.

Responses may be returned on the written query or on an amended paper case report form, or in the case of electronic queries, within the electronic data capture (eDC) system. In the case of a written query for data submitted on a paper case report form, the query must be attached to the specific data being re-submitted in response.

If study forms are not submitted on schedule, the Participating Institution will periodically receive a Missing Form Report from the Coordinating Center noting the missing forms.

G.4 REQUISITIONING INVESTIGATIONAL DRUG

Detailed instructions for ordering BMS-986158 from Bristol-Myers Squibb are specified in the protocol Section 8.

Participating Institutions should order their own agent.

Ensure that the pharmacy will be able to receive and store the agent according to state and federal requirements. The local IRB should be kept informed of who will supply the agent so that any regulatory responsibilities can be met in a timely fashion.
G.5 MONITORING: QUALITY CONTROL

The quality control process for a clinical trial requires verification of protocol compliance and data accuracy. The Coordinating Center, with the aid of the DFCI Clinical Trials Monitoring group, provides quality control oversight for the protocol.

G.5.1 Ongoing Monitoring of Protocol Compliance

The Participating Institutions may be required to submit participant source documents to the Coordinating Center for monitoring. Participating Institutions may also be subject to on-site monitoring conducted by the Coordinating Center.

The Coordinating Center will implement ongoing monitoring activities to ensure that Participating Institutions are complying with regulatory and protocol requirements, data quality, and participant safety. Monitoring will occur before the clinical phase of the protocol begins, continue during protocol performance and through study completion. Additional monitoring practices may include but are not limited to source data verification, and review and analysis of the following: eligibility requirements of all participants; informed consent procedures; adverse events and all associated documentation, review of study drug administration/treatment, regulatory files; protocol departures reporting; pharmacy records, response assessments, and data management.

On-Site Monitoring: On-site monitoring will occur during the dose escalation cohort and during the dose expansion cohort. Participating Institutions will be required to provide access to participants’ complete medical record and source documents for source documentation verification during the on-site visit. In addition, upon request from a monitor or auditor, Participating Institutions should provide access to regulatory documents, pharmacy records, local policies related to the conduct of research, and any other trial-related documentation maintained by the participating site. If there are concerns for protocol compliance, issues that impact subject safety or the integrity of the study are found, or trends identified based on areas of need, additional monitoring visits may be scheduled.

Remote Monitoring: Remote monitoring will occur on a regular basis, approximately every 6 months. The Coordinating Center will request source documentation from participating Institutions as needed to complete monitoring activities. Participating Institutions will be required to forward de-identified copies of participants’ medical record and source documents to the Coordinating Center to aid in source verification.

G.5.2 Monitoring Reports

The DF/HCC Sponsor will review all monitoring reports to ensure protocol compliance. The DF/HCC Sponsor may increase the monitoring activities at Participating Institutions that are unable to comply with the protocol, DF/HCC Sponsor requirements or federal and local regulations.
G.5.3 Accrual Monitoring

Prior to extending a protocol to an external site, the DF/HCC Sponsor will establish accrual requirements for each participating institution. Accrual will be monitored for each participating institution by the DF/HCC Sponsor or designee. Sites that are not meeting their accrual expectations may be subject to termination.

G.6 AUDITING: QUALITY ASSURANCE

Auditing is a method of Quality Assurance and involves the systematic and independent examination of all trial related activities and documents. Audits determine if evaluated activities were appropriately conducted and whether data was generated, recorded and analyzed, and accurately reported per the protocol, applicable Policies, and the Code of Federal Regulations (CFR).

G.6.1 Audit Plan: DF/HCC Sponsored Trials

The DFCI ODQ will be asked to conduct an audit of a participating site if all of the following criteria are met:
- At least 4 participants enrolled at the site;
- Monitoring identified major violations in more than 1 participant; and
- Site not yet audited for this trial (such that sites are audited no more than once during the conduct of the trial).

G.6.2 DF/HCC Internal Audits

All Participating Institutions are subject to audit by the DF/HCC Office of Data Quality (ODQ). Typically, approximately 3-4 participants would be audited at the site over a 2-day period. If violations which impact participant safety or the integrity of the study are found, more participant records may be audited.

G.6.3 Audit Notifications

It is the Participating Institution’s responsibility to notify the Coordinating Center of all external audits or inspections (e.g., FDA, EMA) that involve this protocol. All institutions will forward a copy of final audit and/or re-audit reports and corrective action plans (if applicable) to the Coordinating Center, within 12 weeks after the audit date.

G.6.4 Audit Reports

The DF/HCC Sponsor will review all final audit reports and corrective action plans, if applicable. The Coordinating Center must forward any reports to the DF/HCC ODQ per DF/HCC policy for review by the DF/HCC Audit Committee. For unacceptable audits, the
DF/HCC Audit Committee would forward the final audit report and corrective action plan to the DFCI IRB as applicable.

**G.6.5 Participating Institution Performance**

The DF/HCC Sponsor and the IRB of record are charged with considering the totality of an institution’s performance in considering institutional participation in the protocol.

Participating Institutions that fail to meet the performance goals of accrual, submission of timely and accurate data, adherence to protocol requirements, and compliance with state and federal regulations, may be recommended for a six-month probation period. Such institutions must respond with a corrective action plan and must demonstrate during the probation period that deficiencies have been corrected, as evidenced by the improved performance measures. Participating Institutions that fail to demonstrate significant improvement will be considered by the DF/HCC Sponsor for revocation of participation. A DF/HCC Sponsor and/or the DFCI IRB may terminate a site’s participation if it is determined that a site is not fulfilling its responsibilities as described above.
APPENDIX H: CONTRACEPTION GUIDANCE

1. CONTRACEPTION GUIDANCE FOR FEMALE PARTICIPANTS OF CHILD BEARING POTENTIAL

One of the highly effective methods of contraception listed below is required during study duration and until the end of relevant systemic exposure, defined as 5 months after the end of study treatment.

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

Highly Effective Contraceptive Methods that are User Dependent
(Failure rate of <1% per year when used correctly)\(^a\)

- Combined (estrogen- and progestogen-containing) hormonal contraception associated with inhibition of ovulation started at least 30 days before first dose of study drug\(^b\)
  - Oral
  - Intravaginal
  - Transdermal
- Progestogen-only hormonal contraception associated with inhibition of ovulation\(^b\)
  - Oral
  - Injectable

Highly Effective Methods That Are User Independent

- Implantable progestogen-only hormonal contraception associated with inhibition of ovulation\(^b\)
- Intrauterine device (IUD)\(^c\)
- Intrauterine hormone-releasing system (IUS)\(^c\)
- Bilateral tubal occlusion
- Vasectomized partner

A vasectomized partner is a highly effective contraception method provided that the partner is the sole male sexual partner of the woman of childbearing potential and the absence of sperm has been confirmed. If not, an additional highly effective method of contraception should be used.

- Sexual abstinence (continuous abstinence must begin at least 30 days prior to first dose of study drug)

Sexual abstinence, defined as complete absence of heterosexual intercourse, is considered highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the study treatment. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the study and the preferred and usual lifestyle of the participant.
  - It is not necessary to use any other method of contraception when complete abstinence is elected.
  - Women of childbearing potential participants who choose complete abstinence must continue to have pregnancy tests as outline in the protocol.
Acceptable alternative methods of highly effective contraception must be discussed in the event that women of childbearing potential participants chooses to forego complete abstinence.

NOTES:

a. Typical use failure rates may differ from those when used consistently and correctly. Use should be consistent with local regulations regarding the use of contraceptive methods for participants participating in clinical studies.

b. Hormonal contraception may be susceptible to interaction with the study treatment, which may reduce the efficacy of the contraceptive method. Hormonal contraception is permissible only when there is sufficient evidence that the IMP and other study medications will not alter hormonal exposures such that contraception would be ineffective or result in increased exposures that could be potentially hazardous. In this case, alternative methods of contraception should be utilized.

c. Intrauterine devices and intrauterine hormone releasing systems are acceptable methods of contraception in the absence of definitive drug interaction studies when hormone exposures from intrauterine devices do not alter contraception effectiveness.

Listed below are the Less Than Highly Effective and Unacceptable Contraceptive Methods that are NOT acceptable methods of contraception or protection for participants in this study:

**Less Than Highly Effective Contraceptive Methods That Are User Dependent**

(Failure rate of >1% per year when used consistently and correctly)

- Male of female condom with or without spermicide. Male and female condoms cannot be used simultaneously
- Diaphragm with spermicide
- Cervical cap with spermicide
- Vaginal sponge with spermicide
- Progestogen-only oral hormonal contraception where inhibition of ovulation is not the primary mechanism of action

**Unacceptable Methods of Contraception**

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

2. **CONTRACEPTION GUIDANCE FOR MALE PARTICIPANTS WITH PARTNER(S) OF CHILD BEARING POTENTIAL**

Male participants with female partners of childbearing potential are eligible to participate if they agree to the following during the treatment and until the end of relevant systemic exposure.

- Inform any and all partner(s) of their participation in a clinical drug study and the need to comply with contraception instructions as directed by the investigator.
- All male participants will be required to always use a latex or other synthetic condom during any sexual contact with a woman of childbearing potential; even if the participants have undergone a successful vasectomy or if their partner is already pregnant or breastfeeding. Males should continue to use a condom while on study and until the end.
of relevant systemic exposure defined as 7 months after the end of study treatment.

- Female partners of males participating in the study to consider use of effective methods of contraception until the end of relevant systemic exposure, defined as 7 months after the end of treatment in the male participant.

- Male participants with a pregnant or breastfeeding partner must agree to remain abstinent from penile vaginal intercourse or use a male condom during each episode of penile penetration during the treatment and until 7 months after the end of treatment.

- Refrain from donating sperm for the duration of the study treatment and until 7 months after the end of treatment.