Abbreviated Title: BMS-986253 in MDS

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Title: A Phase I/II Trial of BMS-986253 in Myelodysplastic Syndromes

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Drug Name:	BMS-986253	DNMTi (decitabine and cedazuridine)
IND Number:	157591	157591
Sponsor:	Center for Cancer Research	Center for Cancer Research
Manufacturer:	BMS	Otsuka Pharmaceutical Co. Ltd
Supplier:	BMS	CC Pharmacy

PRÉCIS

Background:

- The myelodysplastic syndromes (MDS) are a group of clonal bone marrow neoplasms characterized by ineffective hematopoiesis, cytopenia, and high risk for transformation to acute myeloid leukemia (AML).
- MDS is primarily a disease of the elderly, with about 80% of participants being older than 65-years of age; with 10,000 new diagnoses per year in the U.S.
- The only curative treatment for participants with MDS is allogeneic hematopoietic stem cell transplantation (HSCT) and only a small portion of participants are eligible. Depending on risk stratification, the median survival of high- and low-risk MDS participants is 1.5 to 5.9 years, respectively.
- DNA methyltransferase inhibitors (DNMTi) are the standard of care therapy for high-risk MDS. However, less than half of participants respond to DNMTi, and even the best responses are transient and non-curative. More effective and less toxic therapies are needed.
- Interleukin-8 (IL-8) is a proinflammatory chemokine from the CXC family and a potent chemoattractant of granulocytes and related cells to the site of inflammation. IL-8 is uniquely upregulated and found at high levels in both the peripheral blood and bone marrow aspirates of MDS participants. In purified MDS/AML long-term/short term stem cells and granulocyte-macrophage progenitor cells both IL-8 and the IL-8 receptor, CXCR2, are overexpressed.
- Preclinical data showed that CXCR2 inhibition led to significantly reduce proliferation of leukemic cell lines. In addition, MDS $CD34^+$ cell cultures treated with neutralizing anti-IL-8 showed improvement in erythroid colony formation.
- BMS-986253 is a fully human IgG1 neutralizing antibody that showed a favorable safety profile in participants with advanced solid tumors.
- Concomitant treatment with DNMTi and BMS-986253 may improve treatment responses in participants with MDS by attenuating chemoattraction of myeloid derived suppressor cells to the bone marrow, indirectly disinhibiting NK- and T-cell responses against MDS stem cells, reducing neoangiogenesis, and improving cytopenia.

Objectives:

Primary objectives:

- Phase I: To determine the optimal biological dose (OBD) and RP2D of BMS-986253 with or without DNMTi (decitabine and cedazuridine) therapy in MDS participants, and to describe the safety and tolerability of BMS-986253.
- Phase II: To determine ORR to BMS-986253 with or without DNMTi (decitabine and cedazuridine) therapy in MDS, measured according to the proposed revised IWG 2018 response criteria.

Eligibility:

- Participants must have histologically or cytologically confirmed MDS according to 2016 WHO criteria[1], and

  - have higher risk (HR) MDS (R-IPSS ≥ 3.5) and received a minimum of 2 and maximum of 8 cycles of DNMTi for Phase I (and a maximum of 4 cycles for Phase 2), or
  - have lower risk (LR) MDS(R-IPSS <3.5) and at least one cytopenia (for both Phases I and II).
- Age ≥ 18 years
- ECOG performance status ≤ 2 (KPS ≥ 60%)

Design:

This study consists of two phases:

- Phase I: safety evaluation with determination of OBD of BMS-986253 with or without DNMTi (decitabine and cedazuridine), and
- Phase II: efficacy evaluation of BMS-986253 with or without DNMTi (decitabine and cedazuridine)

In both Phase I and II, participants will be enrolled into two cohorts:

- A) Higher-risk cohort (HR-MDS), including high-risk and higher intermediate-risk disease, defined as those with R-IPSS ≥ 3.5: treatment with BMS-986253 in combination with DNMTi (decitabine and cedazuridine)
- B) Lower-risk cohort (LR-MDS), including low-risk and lower intermediate-risk disease participants, defined as those with R-IPSS <3.5: treatment with BMS-986253 given as monotherapy

For Phase I, the safety endpoint will be DLT by D28 with the objective of defining the OBD and RP2D for BMS-986253. In addition, follow up for safety will be assessed 100 days after the end of the treatment cycle. For Phase II, the primary endpoint will be overall response rate after 6 cycles, reported separately by cohort.

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STATEMENT OF COMPLIANCE

The trial will be carried out in accordance with International Conference on Harmonisation Good Clinical Practice (ICH GCP) and the following:

- United States (US) Code of Federal Regulations (CFR) applicable to clinical studies (45 CFR Part 46, 21 CFR Part 50, 21 CFR Part 56, 21 CFR Part 312, and/or 21 CFR Part 812)

National Institutes of Health (NIH)-funded investigators and clinical trial site staff who are responsible for the conduct, management, or oversight of NIH-funded clinical trials have completed Human Subjects Protection and ICH GCP Training.

The protocol, informed consent form(s), recruitment materials, and all participant materials will be submitted to the Institutional Review Board (IRB) for review and approval. Approval of both the protocol and the consent form must be obtained before any participant is enrolled. Any amendment to the protocol will require review and approval by the IRB before the changes are implemented to the study. In addition, all changes to the consent form will be IRB-approved; an IRB determination will be made regarding whether a new consent needs to be obtained from participants who provided consent, using a previously approved consent form.

1 INTRODUCTION

1.1 STUDY OBJECTIVES

1.1.1 Primary Objective

1.1.1.1 Phase I

- To determine the optimal biological dose (OBD) and recommended phase 2 dose (RP2D) of BMS-986253 in combination with and without DNMTi in participants with high- and low-risk myelodysplastic syndromes (MDS), respectively; and to describe the safety and tolerability of BMS-986253 in participants with MDS. OBD will be the lowest tolerated dose leading to maximal suppression of serum free IL-8 levels*.

  *Maximal suppression of serum free IL-8 levels will be monitored for a goal of achieving IL-8 levels below the lower limit of detection of the assay in real time as outlined in Section **5.1.3.2** [ultrasensitive immunoassay based on Quanterix Simoa technology (lower limit of quantification = 0.86 pg/mL) by Myriad-RBM]

1.1.1.2 Phase II

- To determine the overall response rate (ORR) to BMS-986253 in combination with and without DNMTi in participants with high- and low-risk MDS respectively, measured according to the proposed revised International Working Group (IWG) 2018 response criteria.

1.1.2 Secondary Objectives

1.1.2.1 Phase I

- To describe pharmacokinetic properties of BMS-986253 with or without DNMTi in MDS participants.

1.1.2.2 Phase II

- To evaluate safety and tolerability of BMS-986253 with or without DNMTi in MDS participants, as well as clinical outcomes including overall improvement rate (OIR), transfusion-independence (TI), cytogenetic response rate, time to best response (CR, PR, marrow CR + HI, HI) , disease free survival (DFS: definition: time to relapse for participants who achieve CR), progression-free survival (PFS; definition: disease progression or death from MDS), leukemia-free survival (LFS; definition: progression to AML or death from any cause), and overall survival (OS: definition: death from any cause).

1.1.3 Exploratory Objectives

- To evaluate changes in serum cytokine levels pre- and post-treatment with BMS-986253.
- To evaluate the cell composition in the peripheral blood and bone marrow microenvironment before and after treatment with BMS-986253.
- To evaluate changes in the transcriptome and proteome in response to treatment with BMS-986253.
- To determine the degree of bone marrow myeloid-derived suppressor cell (MDSC) infiltration.
- To describe changes in genetic clonal diversity during treatment with BMS-986253 in combination with DNMTi.
- To assess cell-autonomous effects on the MDS clone by measuring biomarkers in the Akt pathway (i.e. pS743) in MDS blasts.
- To evaluate cell-autonomous and microenvironment dependent activity of BMS-986253 using ex vivo culture of participant-derived hematopoietic stem and progenitor cells.
- To assess quality of life improvement by participant reported outcomes using the EORTC QLQC30 score.

1.2 BACKGROUND AND RATIONALE

1.2.1 Myelodysplastic syndromes

The myelodysplastic syndromes (MDS) are a group of heterogenous clonal neoplasms of hematopoietic stem cells, characterized by dysplastic changes in at least one myeloid lineage, recurrent genetic aberrations, presence of up to 20% myeloblasts in the bone marrow, and high risk of evolution to acute myelogenous leukemia (AML).[1] Myelodysplasia results in ineffective hematopoiesis with consequential peripheral blood cytopenia(s). Anemia is the most common clinical presentation of MDS, but other cytopenias are also often present. Cytopenia, together with ineffective maturation of neutrophils and platelets, often result in severe and/or recurrent infections and/or bleeding episodes, respectively. In general, it is estimated that up to 1/3 of participants with MDS will die from cytopenia-related complications, up to 1/3 have

disease progression into a secondary AML with poor prognosis, and the remaining 1/3 may die from causes unrelated to their MDS.[2, 3]

MDS is a disease of the elderly, with a median age at diagnosis of approximately 75 years, with ~80% of participants being ≥65 years.[4] Based on cancer registry data, about 10,000 new MDS cases are diagnosed per year in the United States,[5, 6] but the number is probably underestimated[7] and may be as high as >40,000 based on Medicare claims analyses.[8] There is a slight predominance of males.[4]

Most MDS participants (~90%) have sporadic disease and the remainder are therapy-related MDS (t-MDS), the latter often presenting in participants younger than 60 years of age. In the last decade, familial related myeloid neoplasia in persons with germ-line mutations (i.e. *RUNX1, GATA2, DDX41, CEPBA, ANKRD26, ETV6*) is recognized as a predisposing condition for earlier acquisition of additional MDS-related mutations and MDS development.[9] Additionally, MDS can also develop from the rare inherited bone marrow failure disorders, such as Fanconi and Diamond-Blackfan anemia, which can present in childhood and adolescence.[10]

A conceptual model of MDS evolution[11] presumes an initiating somatic driver mutation in the hematopoietic stem cell with subsequent formation of the mutant stem cell clone. The most commonly affected genes involve RNA splicing, DNA methylation, histone modification, transcription regulators, DNA-repair control, signaling and cohesin complex. Six genes are commonly affected and have been reported to be mutant in at least 10% of participants: *SF3B1, TET2, SRSF2, DNMT3A, ASXL1,* and *RUNX1*.[12] In the second phase, the mutant clone expands and when it reaches approximately 4% of the total hematopoiesis, clonal hematopoiesis of indeterminate potential (CHIP) arises. The duration of the first phase and potential of further progression to the third phase (MDS or clonal cytopenia of undetermined significance [CCUS] – cytopenia with presence of a clonal population without morphologic evidence of dysplastic changes) seems to be related to the genes affected by mutations and the size of the clonal population.[13] Most participants with CHIP and mutations in *DNMT3A, TET2,* or *ASXL1* will slowly progress to the third phase, while those harboring spliceosome gene mutations (i.e. *SF3B1, SRSF2, U2AF1*) will usually progress faster into MDS.[13] The spliceosome gene mutations are collectively present in more than 50% of the participants with MDS and are mutually exclusive.[14, 15] They are most commonly present in MDS participants when compared to the participants with other malignancies. In the third phase, clonal predominance of the mutant clone is established with further acquisitions of additional mutations (median of 3).[16, 17] The fourth phase is initiated with the selection of a clone that usually harbors AML-driving mutations (i.e. *FLT3, PTPN11, WT1, IDH1, NPM1, IDH2* and *NRAS*) leading to progression into secondary AML (s-AML) with ≥20% blasts in the bone marrow (Figure 1).

According to World Health Organization (WHO) 2016 classification of myeloid neoplasms and acute leukemia,[1] based on the number of lineages affected by dysplastic changes, the percentage of blasts in bone marrow, the existence of ring sideroblasts and genetic changes, several different MDS-related entities can be discriminated (**Figure 1**) with defined diagnostic criteria. Apart from that, MDS precursor conditions, such as CHIP and CCUS, are defined (**Figure 1**) by expert panels through a consensus process.[18-21]

Figure 1. Spectrum from non-malignant states to MDS and aggressive secondary AML with current treatment options.

	ICUS	CHIP	CCUS	"Low-risk" MDS	"High-risk" MDS	sAML
Clonality	-	+	+	+	+	+
Dysplasia	-	-	-	+	+	+
Cytopenias	+	-	+	+	+	+
BM% blasts	<5%				5-19%	≥20%
*OR-tAML**	Very low (0.5%/year)		?	Low	High	Adverse prognostic risk
Treatments	Obs/SUP	Obs	Obs/SUP/GF	Obs/SUP/GF/IMiD/IST	HMA/AML-like ind.	IC/HMA ± venetoclax/IDH1/2 inh./FLT3 inh.
HSCT	NO				YES	

ICUS - idiopathic cytopenia of undetermined significance; CHIP - clonal hematopoiesis of indeterminate potential; CCUS - clonal cytopenia of undetermined significance; BM—bone marrow; OR-tAML - overall risk for transformation; Obs - observation; SUP - supportive care; GF - growth factors, IMiD - immunomodulatory drugs; IST - immunosuppression; HMA - hypomethylating agents; ind. - induction, IC - intensive chemotherapy, inh. - inhibitor; IDH—isocitrate dehydrogenase; FLT3—FMS-like tyrosine kinase 3

The prognosis of MDS depends on disease- and participant-related characteristics. The disease-specific factors with major influence on the prognosis of participants with MDS are the number and depth of cytopenias, the percentage of bone marrow blasts and the cytogenetic aberrations. These factors are incorporated in Revised International Prognostic Scoring System (R-IPSS) - currently the most relevant prognostic index that stratifies MDS participants in the 5 prognostic groups predicting OS and time-to-progression to AML.[22] For the purposes of clinical practice, an R-IPSS score of 3.5 is accepted as a cutoff for stratifying the participants into "higher-risk" MDS (HR-MDS) versus "lower-risk" MDS (LR-MDS) with corresponding median OS of 1.5 versus 5.9 years, respectively (see Appendix C).[23] About 1/3 of participants with MDS will be classified as HR-MDS. Apart from classic cytogenetics already incorporated into R-IPSS, somatic mutations can also be independent prognostic factors, such as *TP53* mutations, which are associated with poor prognosis.[24] Participant-specific factors also play important prognostic roles. Older age was found to be an independent negative risk factor on OS, particularly in participants with LR-MDS.[25] The time-dependent MDS-specific comorbidity index (MDS-CI) showed good predictive value for non-leukemic death and survival in LR-MDS participants (see **Appendix E**).[26] For HR-MDS, comorbidities are usually the limiting factor for more intensive treatment including HSCT, and therefore, represents an indirect factor predictive of poor outcome due to increased treatment-related mortality.[27]

1.2.2 Interleukin 8 (IL-8) in MDS

A defining feature of MDS is aberrant and/or chronic inflammation, and recent work has solidified the notion that cytokine mis-regulation is a hallmark of the disease. IL-8 (CXCL8) is a proinflammatory chemokine from the CXC family and a potent chemoattractant of granulocytes and related cells to the site of inflammation.[28] Its non-constitutive production is triggered by inflammatory stimuli such as tumor necrosis factor alpha (TNFα) and interleukin-1b (IL-1b).[29] The main activity of IL-8 is mediated by its two specific cell surface G protein-coupled receptors, CXCR1 and CXCR2.[30] The latter one is likely responsible for the proangiogenic effect of IL-8, independent of vascular endothelial growth factor (VEGF).[31, 32] Based on the research in prostatic cancer,[33] signaling through CXCR1 could play an important role in tumorigenesis by increasing proliferation of malignant cells.

In cancer cells, the effect of IL-8 is autocrine and paracrine, promoting type 3 endothelial-to-mesenchymal transition (EMT) and cancer stem cell renewal shown across different solid cancers[34-36] and AML.[37] EMT is the process in which epithelial cells are transformed to

into mesenchymal cells[38] and is associated with tumor invasion, metastasis and chemotherapy resistance.[39] There is emerging evidence that EMT transcription factors, such as Twist1, Snail1/2 and ZEB play an important role in myeloid malignancies by promoting proliferation, cell renewal/stemness and therapy-resistance,[39] including progression of MDS to AML.[40-42]

Dysregulated immune pathways play an important role in the pathogenesis of MDS. Cytokine profiles in peripheral blood and bone marrow identified the chemokines IL-8 and CXCL10 as showing a strong correlation with the MDS phenotype, and IL-8 was unique among 19 other cytokines in showing upregulation in both peripheral blood and bone marrow aspirates.[43] Moudra et al.[44] measured cytokine levels before and after lenalidomide treatment and DNMTi, and found that IL-8, IL-27, CXCL10, and MCP1 were elevated in the bone marrow of all groups of MDS participants. Surprisingly, the levels increased with DNMTi therapy, but the IL-8 expression was much higher in DNMTi non-responders than responders. The latter observation suggests that IL-8 overexpression may play a role in DNMTi treatment resistance. In participants with MDS and concurrent autoimmune disorders (AD) IL-8 expression levels are even more pronounced than in those without AD. AD were identified in a third of MDS participants in one study,[45] and together with the R-IPSS,[22] concurrent AD is an independent adverse prognostic factor for overall survival (OS). Relapsed/refractory AML participants also have high levels of IL-8.[46, 47] In the preclinical experiments done in Laboratory of Receptor Biology and Gene Expression (NCI/CCR),[46] heterozygous U2AF1 mutation was found to be necessary and sufficient for elevated IL-8 secretion, supporting an association between the genotype and phenotype. IL-8 levels were found to be upregulated by ~20 times of baseline levels in isogenic cell lines with heterozygous U2AF1 mutation. The same effect was visible in the human cancer cell lines corrected by clustered regularly interspaced short palindromic repeats (CRISPR) and in the NKM1-cell line derived from a participant with AML harboring a U2AF1 mutation.[46] The underlying mechanism for elevated levels of cytokines is not well-understood, but there is some inclination that a history of infection or autoimmune disease is associated with increased risk of MDS.[48, 49]

Both IL-8 and CXCR2 are overexpressed in purified MDS/AML long-term/short-term stem cells and granulocyte-macrophage progenitor cells.[37] *In vitro* inhibition of CXCR2 leads to a significant reduction in the proliferation of several leukemic cell lines and primary AML/MDS cells through cell cycle arrest. Moreover, *in vivo* inhibition of CXCR2 led to significant improvement in survival of U937 xenografted NOD scid gamma (NSG) mice. In addition, IL-8 knockdown results in decreased proliferation and colony forming ability along with increased apoptosis of HL60, NB4, and THP1 AML cell lines.[47] Anemia is one of the hallmarks of MDS and lower levels of hemoglobin, i.e. worsening anemia, increase R-IPSS and adverse prognosis.[22] MDS CD34+ cell cultures treated with neutralizing IL-8 antibody showed improvement in erythroid colony formation.[50] Also, higher CXCR2 gene expression levels in MDS participants were demonstrated to correlate with lower hemoglobin levels and with increased transfusion requirements.[37]

The indirect mechanism of action is not well studied at present - partly due to the lack of MDS models in humanized mice, but also due to the fact that mice do not secrete IL-8 or an IL-8 homolog, as the gene encoding IL-8 has been lost from the rat/mouse (muroid rodent) lineage.[51] Nevertheless, there is a reason to postulate a role for IL-8 in creating a microenvironment conducive to MDS development. IL-8 enhances endothelial cell proliferation

and capillary tube organization[52] and higher microvascular density (MVD) has been found in the bone marrow of participants with MDS in comparison to normal controls, a finding that seems to be VEGF-independent.[53] Although both AML cells and stromal cells secrete IL-8, the bone marrow stromal cells are the main source of IL-8. IL-8 produced by stromal cells protects AML cells against apoptosis in co-culture experiments *in vitro*.[47, 54] Similarly, endothelial cells in AML participants secrete IL-8, which increases expansion of the AML blasts. This also leads to resistance to the chemotherapy agent cytarabine, which is the front-line therapy for AML and sometimes for high-risk MDS with excess blasts. Nevertheless, a small molecule inhibitor of IL-8 inhibited AML cell growth in tissue culture.[55] Moreover, Dr. Larson's lab has shown in a lung xenograft model that tumorigenic cells lines containing splicing factor mutations (U2AF1 – S34F) show reduced nodule formation in NOG mice when treated with IL-8 neutralizing Ab compared to mice treated with control IgG. [46]

Several preclinical studies have reported findings supporting IL-8's direct role as a chemoattractant for MDSCs. [56-58] Increased chemotaxis of both granulocytic and monocytic MDSCs were seen in response to recombinant IL-8 and IL-8 derived from cancer cell lines.[58] Further, a neutralizing anti-IL-8 antibody could potentially be used in combination with recently developed MDS chimeric antigen receptor T-cell (CAR-T) therapies.[59] Specifically, MDSCs (LIN–HLA-DR–CD33+), which are a cell population that is distinct from the neoplastic clone, accumulate in the bone marrow of MDS participants and impair hematopoiesis, and are derived from myeloid progenitors.[60] MDSCs repress T-cell immunity through multiple metabolic pathways,[61] and their reduction could be therapeutically beneficial.[62] A comprehensive proteomics profiling study[63] identified IL-8 as the central molecule in the network of more than 150 dysregulated proteins in the bone marrow of participants with AML, suggesting IL-8 is a promising therapeutic target. All the above studies suggest a paracrine interaction between MDS/AML cells and the microenvironment, mediated largely by IL-8.

Inflammatory cytokines are also controlled at the post-transcriptional level. [46, 64] Moreover, translational regulation is a hallmark of hematopoiesis[65, 66] and is mis-regulated in CD123+ progenitor cells from MDS participants.[67] In line with this observation, germline mutations in the translation machinery (*RPS19, RPS26, RPS17, RPL5, RPL11*) manifest as defects in myelopoiesis, and the MDS del(5q) subtype results in haploinsufficiency of *RPS14.*[68] Yet somatic mutations in the translation machinery are largely absent in the disease, and there is little understanding of the relationship between driver mutations in MDS and subsequent translational misregulation. In the preclinical experiments done in Laboratory of Receptor Biology and Gene Expression (NCI/CCR), a heterozygous U2AF1 mutation was found to lead to widespread changes in translation such that mutant cells showed a 'non-oncogene addiction' to the ribosome biogenesis machinery.[69] These data indicate an unanticipated functional connection between a splicing factor mutation and the ribosome biogenesis machinery.

The preceding observations necessitate clinical correlates which specifically interrogate post-transcriptional regulation in MDS. Although there has been exhaustive DNA and RNA sequencing in MDS, there has been little if any quantitative measurements of translational regulation. Indeed, despite the fact that measurements of translational activity are technically feasible and reveal widespread regulation across healthy human tissues,[70] the only extant ribosome footprinting analyses remotely relevant to MDS have been carried out in T-ALL cell lines[71] or in CLL primary cells cultured *ex vivo.*[72]

1.2.3 Current treatment options for the participants with MDS

Currently, the only curative treatment modality for the participants with MDS is allogeneic hematopoietic stem cell transplantation (HSCT). Since HSCT is associated with high incidence of mortality and morbidity, only a small portion of fit participants are eligible to undergo a transplant.[73, 74] There is an estimate that only 6 of 100 MDS participants will receive HSCT (2 will be cured, 3 will relapse and 1 will die from the HSCT-related complications).[3]

DNMTi, 5-azacitidine (AZA) and decitabine (DAC), are the standard of care therapies in HR-MDS. However, less than a half of participants respond to DNMTi, and even the best responses are transient, non-durable, and non-curative.[75] Although the benefit on OS was significant in the AZA registration trial, [75] in real-life practice the impact on OS is not reproducible and prolongs OS for just a few months.[76].[77] Numerous combination therapies with DNMTi have been explored in treatment of MDS/AML. The BCL-2-inhibitor, venetoclax, in combination with DNMTi has emerged as a promising therapeutic combination with good safety and efficacy in AML,[78] though remains under clinical investigation in MDS.[79-81] Two presentations on early data from ongoing clinical trials of venetoclax in combination with DNMTi were presented at this past year's 2020 American Society of Hematology conference: (a) a Phase 1b trial by Garcia et al. that explored use of venetoclax plus azacitidine in 57 high-risk MDS participants, and reported an ORR of 77% with a 13 month median follow-up, and high rates of grade 3 AEs in 97% of participants, including febrile neutropenia in 46% and neutropenia and thrombocytopenia in 51% and 30%, respectively;[80] and (b) a Phase 1b trial of venetoclax plus azacitidine by Zeidan et al for treatment of MDS in the relapsed/refractory setting; Of the 38 participants enrolled, with a median follow up of 6.8 months, there was a clinical response of CR + mCR in 40%, and HI in 25%. Common grade 3-4 AEs included neutropenia and thrombocytopenia in 50% and 42% of participants, respectively.[81] While reported efficacy is promising for this combination, the side effect profile and complications due to cytopenias appear significant based on these preliminarily data and this regimen may require further optimization in the MDS setting.

LR-MDS is generally not an indication for HSCT, although some participants may be eligible.[73, 74] At the time of diagnosis, participants with LR-MDS have several treatment options based on the characteristics of the disease. The primary objective in the treatment approach to participants with LR-MDS is to preserve quality of life and improve cytopenia.[82] Erythropoiesis stimulating agents (ESA) are indicated in participants with LR-MDS and anemia, with a ~70% overall response rate (ORR) in participants with endogenous erythropoietin (EPO) levels < 500 mU/L, but ORR is < 10% in those with EPO > 500 mU/L.[83] The duration of response is up to ~24 months. As a second line treatment after ESA failure for participants with MDS with ring sideroblasts, an ORR of 38% is reported in the luspatercept registration trial.[84] According to International Working Group (IWG) 2018 Response Criteria,[85] 28% of participants remained transfusion-independent for 48 weeks. The 5q syndrome is the subtype of MDS with isolated 5q deletion without other cytogenetic abnormalities accounting for about 15% of all MDS cases.[86] Due to the specific haploinsufficiency in 5q syndrome, treatment with lenalidomide targets selectively aberrant signaling pathways[87] and even complete cytogenetic remission can be induced with a median time to progression of 2-3 years.[88] After the progression, usually there is an emergence of clone with additionally acquired mutations with an adverse prognostic significance (i.e. TP53 or RUNX1). Lenalidomide was also evaluated via a randomized phase III trial in treatment of non-del5q LR-MDS participants who were ineligible

or refractory to ESAs, which resulted in a 26.9% RBC transfusion independence (RBC-TI) rate and improved HRQoL as measured by EORTC QLQ-C30.[89] While not considered standard of care for LR-MDS, DNMTis have been explored in this setting, including a randomized phase 2 trial evaluating low-dose decitabine vs azacitidine in this participant population with reported ORR between 40-70%, which are now being confirmed in a larger trial.[90] A meta-analysis explored azacitidine efficacy in LR-MDS with a reported RBC-TI rate of 38.9%.[91] A recent phase II trial of imetelstat, a telomerase inhibitor, in 53 RBC-transfusion dependent LR-MDS participants reported 8- and 24-week RBC-TI rates of 42% and 29%, respectively, that were durable for a median of 87 weeks.[92] Participants with hypoplastic MDS are candidates for immunosuppressive therapy with cyclosporine with or without anti-thymocyte gamma globulin (ATG, only for younger fit participants).[93] A substantial number of participants with LR-MDS, other than those mentioned above will be candidates for a "watch-and-wait" approach with supportive transfusion treatment or administration of granulocyte stimulating colony factor (G-CSF) agents when required. Most such participants will eventually develop regular dependence on red-cell transfusions and be at great risk of parenchymal iron overload and related organ toxicity.[94]

1.2.4 BMS-986253

1.2.4.1 Background and safety

BMS-986253 (HuMax-Immune) is a fully human IgG1 kappa neutralizing monoclonal antibody against IL-8. It binds the IL-8 epitope on both IL-8 isoforms (72 and 78 amino acids), important for CXCR1/2 binding, and prevents IL-8 from binding to its corresponding receptors. Since BMS-986253 cannot bind receptor-bound IL-8, it shows no antibody dependent cell-mediated cytotoxicity (ADCC) or complement-dependent cytotoxicity (CDC). It shows no cross-reactivity with other human tissues or chemokines.[95]

BMS-986253 has been tested in a single dose PK study in monkeys at 20 and 160 mg/kg. The dosing was clinically tolerable in the monkeys. A reduction of serum IL-8 to below the lower limit of detection was seen for the total follow-up period of 6 weeks. A larger multiple dose toxicokinetic study in cynomolgus monkeys at doses 20, 80 and 160 mg/kg/week for 12 weeks has been completed and showed no safety issues.

A phase I/II clinical trial[96] designed to evaluate safety and efficacy in palmoplantar pustulosis (PPP), a rare chronic inflammatory skin disorder, enrolled 31 participants. For PPP, BMS-986253 showed efficacy in reducing disease activity. The antibody was well-tolerated, with no serious adverse events (SAE) attributed to treatment. The most frequently reported mild or moderate adverse events included nausea, nasopharyngitis, and headache. Moreover, no antihuman antibodies developed after administration of BMS-986253.[96] In the phase I trial of BMS-986253 in advanced solid tumors as monotherapy,[97] 11/15 subjects achieved the best response of stable disease (4 subjects had progressive disease). Reduction of serum IL-8 levels were observed across all dose levels (4, 8, 16 and 32 mg/kg every 2 weeks) without reaching a dose-limiting toxicity (DLT) or defining maximum tolerated dose (MTD). Treatment with BMS-986253 reversed EMT process measured by the EMT markers and inhibited IL-8 induced peripheral blood cells migration isolated from subjects post-treatment. The most common adverse events (AE), regardless of causality, were constipation (n=5), nausea (n=4) and anemia (n=4). Six subjects (40%) had grade 3 AEs with increased ALP (n=2) and anemia (n=2) being the most common. Treatment-related AEs occurred in one-third of the subjects and were all

grade 1 and 2 (anemia and fatigue as the most common). Four subjects experienced SAE non-related to the treatment (grade 3 pain, abdominal infection, fall, decreased ALP, hyponatremia [n=5]; grade 2 pulmonary embolism [n=1]). The pharmacokinetic (PK) analysis showed an approximate linear correlation between increasing dose and exposure for the dose range of 4 mg/kg to 32 mg/kg.[97]

In the currently ongoing clinical trial phase I/IIa (CA027-002, ClinicalTrials.gov NCT03400332), testing various flat doses of BMS-986253 in combination with nivolumab, treatment-related AEs were observed in 30/92 participants with solid cancer at the time of the preliminary analysis (data cut-off date of 16-Jan-2020). The most common treatment-related AEs in combination with nivolumab were fatigue (n=9), nausea (n=7), rash (n=3), and decreased appetite (n=3). Based on preliminary clinical data from that trial BMS-986253 does not appear to significantly increase the rate of nivolumab-induced AEs.[95]

Based on currently available clinical data from prior trials including 158 participants,[95-97] only 3 participants had infusion reactions. One participant received 8 mg/kg BMS-986253 monotherapy and experienced a grade 1 infusion reaction on Cycle 1 Day 1, which did not recur with subsequent infusions. Two participants treated with 2,400 mg BMS-986253 Q2W + 480 mg nivolumab Q4W experienced infusion reactions: one grade 2 infusion reaction on Cycle 1, Day 15 and continued to receive subsequent infusion of study therapy and tolerated well, and one experienced a grade 4 infusion reaction on Cycle 2, Day 15 that led to drug discontinuation.

Of note, there has been a higher-than-expected incidence of hemophagocytic lymphohistiocytosis (HLH) in participants receiving ipilimumab + nivolumab + blinded study drug (BMS-986253 or placebo) in Part 2 of Study CA027-002. As of 31 Jan 2023, 144 participants were treated in Part 1 with the nivolumab + BMS-986253 doublet, across different dose levels and/or schedules of BMS-986253. No dose-dependent toxicities were identified. In Part 1C, 15 participants were treated with BMS-986253 (3600 mg Q2W) in combination with nivolumab (1 mg/kg Q3W) and ipilimumab (3 mg/kg Q3W) to evaluate safety and preliminary anti-tumor activity of the triplet regimen. Part 2 was a randomized, double-blind evaluation of BMS-986253 (3600 mg Q2W) in combination with nivolumab (1 mg/kg Q3W) and ipilimumab (3 mg/kg Q3W) (Cohort 2A) vs nivolumab and ipilimumab plus placebo (Cohort 2B) in participants with melanoma that have progressed on anti-PD-(L)1 therapy with the objectives of comparing anti-tumor activity and assessing the safety of the triplet combination of BMS-986253 with nivolumab and ipilimumab. As of 27 Jan 2023, 57 participants across 18 sites in eight countries have been treated in the blinded part 2. To date, 3 HLH cases have been reported in Part 2, 2 of which were fatal.

The sponsor's safety monitoring team determined that the rate of HLH reported is higher than anticipated and elected to unblind the treatment assignment for the 3 participants to evaluate a potential contribution of BMS-986253. The randomization of the 3 participants with HLH was divided between the two arms. Of the 2 HLH cases with a fatal outcome, 1 occurred in each arm (2A and 2B). Overall, the incidence rates of HLH reported in the 2 arms were not considered meaningfully different. There were no HLH cases reported in participants treated with BMS-986253 in the following cohorts:

BMS-986253 monotherapy in phase 1 Study CA027-001 (n=15), BMS-986253 + nivolumab inCA027-002 Part 1A/B (n=144), nivolumab + ipilimumab + BMS-986253 in CA027-002 Part

1C (n=15), nor in participants (n=122) in 8 investigator sponsored research studies evaluating BMS-986253 in combination with nivolumab and other drugs in oncology indications.

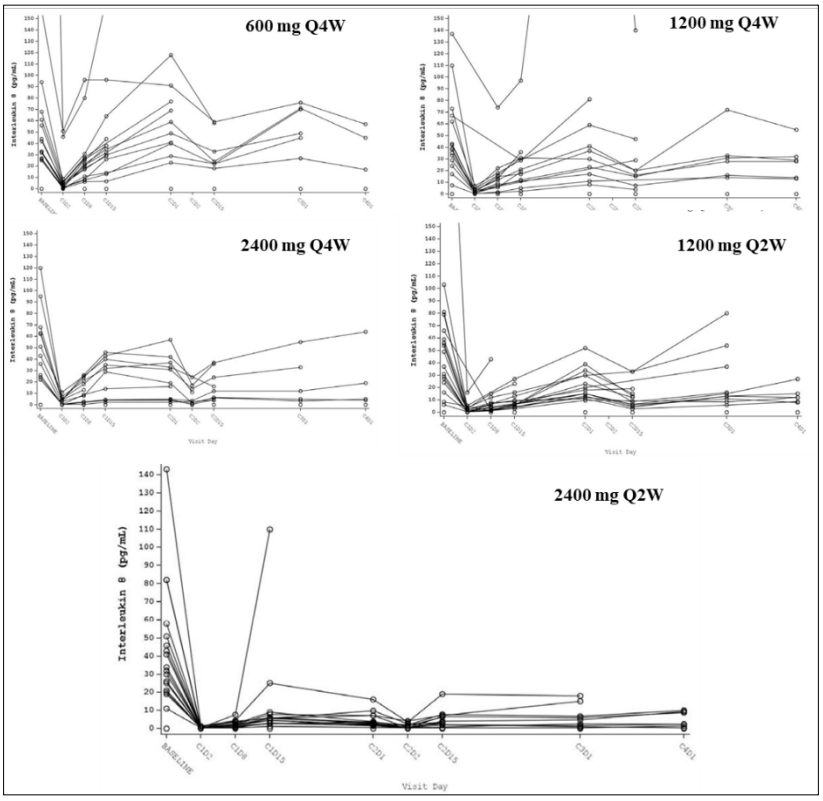
In summary, it was determined that a contributory factor of BMS-986253 for the reported cases of HLH cannot be ascertained. The basis for the higher-than-expected frequency of HLH in the study cannot yet be determined and the evaluation is further confounded by the presence of significant comorbidities in the affected participants, including sepsis, possible gastrointestinal perforation, and viral infection (i.e., a recent COVID-19 infection in one participant, and evidence of EBV in 2 participants), all of which can present with an overlapping symptom complex and/or may contribute to the development of HLH. In addition, HLH case reports are a well described complication of immune checkpoint inhibitor monotherapy (pembrolizumab or nivolumab alone) or nivolumab/ipilimumab combinations. [98]

Because BMS-986253 is scheduled for intravenous (IV) administration, extravasation at the site of infusion may induce reactions such as edema, redness, itching, and tenderness. To date, no injection-site reactions have been reported.

1.2.4.2 Dosing

In a previous trial that enrolled non-cancer subjects noted above,[96] BMS-986253 was given as a single IV dose first at escalating dose levels ranging from 0.15 to 8 mg/kg. Subsequently, the same participants were treated with 4 weekly doses of 0.15 to 4 mg/kg. In the trial with advanced solid cancers as monotherapy,[97] BMS-986253 was given as a single IV dose first at escalating dose levels ranging from 4 to 32 mg/kg. Subsequently, the same participants were treated with the antibody every 2 weeks until progression with the same dose. In a currently ongoing trial that enrolled advanced cancer participants in combination with nivolumab at a dose of 480 mg every 4 weeks,[95] BMS-986253 is given as a single IV flat dose escalating from 600 to 2400 mg every 4 weeks and as a single IV flat dose escalating from 1200 to 2400 mg every 2 weeks. The last dosing regimen of 2400 mg every 2 weeks showed the best profile in terms of the deepest and most durable reduction of serum IL-8 levels among dose groups (Figure 2). Based on this, exploratory PK/PD modeling on serum IL-8 suggested that higher dose of BMS-986253 may further improve serum IL-8 suppression. Ongoing studies are currently testing higher dosing of 3600 mg every 2 weeks [Personal communication with BMS].

Figure 2. Flat dosing regimens and serum IL-8 levels in subjects treated with BMS-986253 in combination with nivolumab.



1.2.4.3 Pharmacokinetic and pharmacodynamic data

After single dose administration, the peak BMS-986253 serum concentration occurs at around 1 hour. Maximum plasma concentrations are dose-dependent, but plasma clearance rates are dose-independent. The half-life of the antibody is approximately 11.3 days. The pharmacodynamics effect was evaluated by measuring the IL-8 levels in wound fluid. In the three highest dose levels tested, there appeared to be a dose-dependent reduction in the IL-8 concentration in the wound fluid (2, 4, and 8 mg/kg).[96] In the phase 1 dose escalation study as monotherapy,[97] a sustained reduction in serum IL-8 > 50% was detected in 6 of 15 participants by assessing changes in serum IL-8 measured in samples obtained pre- and post-dose. Of the 6 participants exhibiting a sustained reduction in serum IL-8, four were from the 6-participant cohort dosed at 32 mg/kg, and one of each was from the 4- and 16-mg/kg 3-participant cohorts. In the ongoing phase 1/2a trial in advanced cancers in combination with nivolumab,[95] Single Molecule Array (SIMOA) technology is being used to detect serum free IL-8 (IL-8 that is not bound to therapeutic antibody). The serum free IL-8 results (as of the data cut-off date 16-Jan-2020) for 76 participants who were treated with varying doses of BMS-986253 in combination with nivolumab 480 mg Q4W and all participants displayed a rapid decrease in free serum IL-8 (Cycle 1 Day 2). The data suggest that BMS-986253 decreases free serum IL-8 in a dose- and frequency-dependent manner and that the 2,400 mg Q2W dosing provides the deepest and most durable suppression of free serum IL-8, with modeling suggesting that higher dose of BMS-986253 may further improve serum IL-8 suppression.

1.2.5 Rationale for Myeloid Malignancy Program Investigation

In general, long term treatment outcomes for MDS participants are dismal. It is estimated that of every 100 MDS participants, four will be long-time survivors, with the rest of succumbing to either MDS- or treatment-related complications (67) or MDS-unrelated complications (29).[3] There has been no progress in populations based studies in survival of MDS participants during last 2 decades.[77] Novel approaches are needed which do not rely exclusively on cytotoxic therapy and/or intervene earlier in the course of the disease. Current clinical trials for participants with MDS enroll less than 5% of MDS participants.[76] With better understanding of complex MDS pathophysiology, trials using combination treatments are emerging, especially for those ineligible for the HSCT, therefore representing an unmet need.[11]

Since immune disturbance in MDS is common pathologic finding,[99] and MDSCs have be found to induce myelodysplasia,[60] with evidence of VEGF-independent neoangiogenesis and overexpression of EMT transcription factors as important processes in the evolution of MDS,[53] there is a reasonable evidence that by blocking IL-8-mediated processes with IL-8 neutralization, a positive, disease-modifying therapeutic effect could be achieved. Preclinical *in vitro* work has also shown that blockade of the IL-8 receptor, CXCR2, led to significant reduction in the proliferation of several leukemic cell lines and primary AML/MDS cells. [37]

In the preclinical experiments done in Laboratory of Receptor Biology and Gene Expression (NCI/CCR), a heterozygous U2AF1 mutation was found to lead to widespread changes in translation such that mutant cells showed a 'non-oncogene addiction' to the ribosome biogenesis machinery.[69] These data indicate an unanticipated functional connection between a splicing factor mutation and the ribosome biogenesis machinery. The preceding observations necessitate clinical correlates which specifically interrogate post-transcriptional regulation in MDS. Although there has been exhaustive DNA and RNA sequencing in MDS, there has been little if any quantitative measurements of translational regulation and this trial will allow a novel insight in the pathophysiology if MDS in synergy with the ongoing basic laboratory NCI/CCR research.

A new Clinical and Translational Correlates Facility was recently funded by the *FY20 Directors Challenge Innovation Award* and is physically housed initially within NHLBI space (PI Christopher Hourigan *et al*). This facility will create the ability to perform standardized research correlates proposed on this study and across the growing NIH Myeloid Malignancies Clinical Trials portfolio. Work from intramural investigators has recently demonstrated that high-sensitivity genomic measurements outperform conventional clinical assessments for myeloid malignancy participants in predicting relapse and survival following HSCT and suggest that additional intervention on high-risk subjects can improve clinical outcomes.[100] This sets the stage for a "precision medicine" approach where personalized assessments of clonal disease burden can be used not only to judge the success of therapy, but also as a target for intervention.

In this trial we hypothesize that the addition of BMS-986253 to treatment with DNMTi is safe in adult MDS participants. Based on the presented data on IL-8 in MDS, we also hypothesize that IL8 suppression with BMS-986253 will enhance efficacy of DNMTi therapy in adult HR-MDS participants and will be also effective for cytopenia-improvement as monotherapy in LR-MDS participants.

2 ELIGIBILITY ASSESSMENT AND ENROLLMENT

2.1 ELIGIBILITY CRITERIA

2.1.1 Inclusion Criteria

1. Participants must have histologically or cytologically confirmed MDS according to 2016 WHO criteria[1]
    a. And:
2. have HR-MDS (R-IPSS ≥ 3.5) and received a minimum of 2 and maximum of 8 prior cycles for phase I and 4 for phase II of DNMTi therapy, or
3. have LR-MDS (R-IPSS <3.5),
    a. and, at least one cytopenia:
        i. granulocytes < 1.0 x 10^9/L and/or
        ii. hemoglobin < 110 g/L with signs/symptoms of symptomatic anemia or transfusion-dependency
        iii. platelets < 100 x 10^9/L

2.1.1.1 Age ≥18 years

Because no dosing or adverse event data are currently available on the use of BMS-986253 as monotherapy or in combination with DNMTi in participants <18 years of age, children are excluded from this study, but will be eligible for future pediatric trials.

2.1.1.2 ECOG performance status ≤2 (Karnofsky ≥60%, see **Appendix A**).

2.1.1.3 Life expectancy greater than 6 months.

2.1.1.4 Participants must have adequate organ function as defined below:

– total bilirubin	≤1.5 X institutional upper limit of normal OR ≤3 X institutional upper limit of normal in participants with Gilbert's syndrome (*except for participants with increased bilirubin levels attributed to intramedullary hemolysis, which will be allowable)
– AST(SGOT)/ALT(SGPT)	≤3 X institutional upper limit of normal OR ≤5 X institutional upper limit of normal if related to disease specific cause
– creatinine clearance (by Cockcroft-Gault)	≥60 mL/min/1.73 m^2 for participants with creatinine levels above institutional normal.

2.1.1.5 The effects of BMS-986253 on the developing human fetus are unknown. For this reason and because DNMTi as well as other therapeutic agents used in this trial are known to be teratogenic, women of child-bearing potential (WOCBP) and men must agree to use adequate contraception (hormonal or barrier method of birth control;

abstinence) prior to study entry, for the duration of study participation, and up to 6 months after study completion and last dose of DNMTi.

2.1.1.6 Ability of subject to understand and the willingness to sign a written informed consent document.

2.1.2 Exclusion Criteria

2.1.2.1 For phase I: Participants with HR-MDS (R-IPSS ≥3.5) that have not yet received or received less than 2 cycles of DNMTi therapy.

2.1.2.2 Participants with LR-MDS (R-IPSS <3.5) with the following characteristics that have not yet received or are still deriving benefit from the following standard of care therapies:

- Hgb <10 g/dL, Epo level <500 mU/mL: Erythropoietin-stimulating agents (ESAs)
- MDS with del5q: Lenalidomide
- MDS with ringed sideroblasts (MDS-RS) with SF3B1 mutation: Luspatercept

2.1.2.3 Participants with platelet transfusion-refractory thrombocytopenia, with inability to keep platelet threshold above 10K/mcL with transfusions or those with ongoing or uncontrolled hemorrhagic complications.

2.1.2.4 Participants with clinically significant neutropenia, ANC<100, with frequent hospitalizations for infection (average >1 hospitalization per month in past 6 months)

2.1.2.5 Participants who are receiving or have received any other investigational agents within 28 days before start of study treatment.

2.1.2.6 History of allergic reactions attributed to compounds of similar chemical or biologic composition to DNMTi or other agents used in study.

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

2.1.2.8 Pregnant women or women presently breast-feeding their children are excluded due to unknown risks to a developing fetus or infant.

2.1.2.9 Any significant disease that, in the opinion of the investigator, may impair the participant's tolerance of study treatment.

2.1.2.10 Active or uncontrolled autoimmune diseases requiring treatment.

2.1.2.11 Chronic hepatitis B or C infection, because potential immune impairment caused by these disorders may diminish the effectiveness of this immunologic therapy.

2.1.2.12 HIV-positive participants are ineligible because of the potential for decreased immune response.

2.1.2.13 Presence of any other malignancy (except basal and squamous cell carcinoma of the skin, or stable chronic cancers on hormone or targeted therapy) for which participant received systemic anticancer treatment within 24 months prior to enrollment.

2.1.2.14 Prior history of allogeneic hematopoietic stem cell transplantation.

2.1.3 Recruitment Strategies

This protocol will be advertised on NIH websites (clinicaltrials.gov, future Myeloid Malignancy Program Web Site) and on NIH social media platforms.

2.2 SCREENING EVALUATION

2.2.1 Screening activities performed prior to obtaining informed consent

Minimal risk activities that may be performed before the subject has signed a consent include the following:

- Email, written, in person or telephone communications with prospective subjects
- Review of existing medical records to include H&P, laboratory studies, etc.
- Review of existing MRI, x-ray, or CT images
- Review of existing photographs or videos
- Review of existing pathology specimens/reports from a specimen obtained for diagnostic purposes

2.2.2 Screening activities performed after a consent for screening has been signed

The following activities will be performed only after the subject has signed the consent for this study for screening. Assessments performed at outside facilities or on another NIH protocol within the timeframes listed below may be abstracted and used to determine eligibility once a participant has signed the consent for this study. Note: Given the standard nature of the planned clinical laboratories, interlaboratory variability is not a concern and participants may have clinical labs drawn locally, with results sent to the NIH study team (e.g., via fax).

Screening tests are valid for 30 days prior to enrollment unless otherwise specified.

- Medical history
- Physical examination
- Laboratory evaluations
- ECG

If protocol therapy is started > 8 days of these eligibility screening evaluations, the medical history, physical examination, laboratory evaluations, and ECG must be repeated prior to starting protocol therapy (i.e., repeated at Baseline/prior to C1D1; see Section **2.4**).

2.2.2.1 Histologic confirmation: All participants are required to have histologically confirmed MDS. Pathology reports from outside institutions confirming the diagnosis will be acceptable for eligibility purposes with required secondary NIH pathology review.

2.2.2.2 History and physical examination: Complete history and physical examination (including height, weight, vital signs, and performance score).

2.2.2.3 Laboratory Evaluation: Laboratory data are to be obtained:

- Hematological Profile: CBC with differential
- Biochemical Profile: total bilirubin, BUN, albumin, calcium, creatinine, SGOT [AST], SGPT[ALT], phosphorous, magnesium, potassium, sodium,

LDH, uric acid, ferritin, endogenous erythropoietin, vitamin B12, folate, copper, zinc, ANA, thyroid function studies (TSH, Free T4)

- Infectious serologies including HIV, HBV, HCV
- SARS-CoV2 testing per clinical center guidelines
- Urine and/or serum pregnancy test for female participants of childbearing potential (within 24 hours prior to start of therapy)

2.2.2.4 Cardiac Evaluation: Electrocardiogram (ECG) will be obtained.

2.2.2.5 Bone Marrow aspirate and biopsy - (May be performed during baseline evaluation) must be done within 30 days prior to treatment initiation

2.3 PARTICIPANT REGISTRATION AND STATUS UPDATE PROCEDURES

Registration and status updates (e.g., when a participant is taken off protocol therapy and when a participant is taken off-study) will take place per CCR SOP ADCR-2, CCR Participant Registration & Status Updates found at: https://ccrod.cancer.gov/confluence/pages/viewpage.action?pageId=73203825.

2.3.1 Screen Failures

Screen failures are defined as participants who consent to participate in the clinical trial but are not subsequently assigned to the study intervention or entered in the study. A minimal set of screen failure information is required to ensure transparent reporting of screen failure participants, to meet the Consolidated Standards of Reporting Trials (CONSORT) publishing requirements and to respond to queries from regulatory authorities. Minimal information includes demography, screen failure reason, eligibility criteria, and any serious adverse event (SAE).

Individuals who do not meet the criteria for participation in this trial (screen failure) because of any specific inclusion/exclusion criteria by discretion of PI may be rescreened.

2.3.2 Treatment Assignment (for Phase I and II)

Cohorts in phase I:

Number	Name	Description
1	*"Lower-risk" MDS: eligible lower-risk phase I participants*	*Participants with confirmed MDS and R-IPSS score < 3.5 (low and lower intermediate-risk) that are eligible for phase I.*
2	*"Higher-risk" MDS: eligible higher-risk phase I participants*	*Participants with confirmed MDS and R-IPSS score ≥3.5 (high and higher intermediate-risk) that are eligible for phase I.*

Cohorts in Phase II:

Number	Name	Description

3	*"Lower-risk" MDS*	*Participants with confirmed MDS and R-IPSS score < 3.5 (low and lower intermediate-risk)*
4	*"Higher-risk" MDS*	*Participants with confirmed MDS and R-IPSS score ≥3.5 (high and higher intermediate-risk)*

Arms

Number	Name	Description
1	*escalating doses of treatment for LR-MDS*	*escalating doses of BMS-986253*
2	*escalating dose of treatment for HR-MDS*	*escalating doses of BMS-986253 + DNMTi (decitabine and cedazuridine)*
3	*phase II dose of BMS-986253 for LR-MDS**	*phase II dose of BMS-986253*
4	*phase II dose of BMS-986253 for HR-MD*	*phase II dose of BMS-986253 + DNMTi (decitabine and cedazuridine)*

*Poor-risk genomic features, such as bi-allelic TP53 mutation, can escalate a participant from LR-MDS cohort #3 to HR-MDS cohort #4 for phase II, per PI discretion.

Arm Assignment

Participants in cohort 1 are assigned to arm 1; Cohort 2 assigned to arm 2; Cohort 3 are assigned to arm 3, and cohort 4 are assigned to arm 4.

2.4 BASELINE EVALUATION

To be performed within 8 days prior to initiating study treatment.

Medical Assessment:

- History and physical examination including vital signs (blood pressure, pulse, respiratory rate, oxygen saturation)
- Height and weight
- Performance status determination (see **Appendix A** for ECOG)
- ECG
- Concomitant medications assessment
- Questionnaires/assessments:
  Note: These apply to English speaking participants only.
  - Rockwood/CFS and MDS-CI Questionnaire
  - **European Organization for Research and Treatment of Cancer (EORTC) quality of life questionnaire = EORTC QLQC30 score**
  - Psychosocial Assessment

Laboratory Assessments:

- Complete blood count plus differential, platelet count, and reticulocyte count
- Serum chemistries (Na, K, Cl, CO_2, glucose, BUN, creatinine, albumin, calcium, magnesium, phosphorus, alkaline phosphatase, ALT, AST, total bilirubin, LDH, TSH, erythropoietin), CRP
- Blood type and screen (as clinically indicated)
- Urinalysis
- Research blood per section **5.1** Blood sample for T-cells, B-cells, and NK cells [TBNK] (CD3, CD4, CD8, CD19 clinical panel)
- Bone Marrow aspirate and biopsy - (May be performed during screening evaluation) must be done within 30 days prior to treatment initiation.
    - Morphology, flow cytometry, cytogenetics, and molecular tests, and research collection (See Section **5.1**)
- Next Generation Sequencing- panel of myeloid genes from the peripheral blood and/or marrow. (May be performed during screening evaluation) must be done within 30 days prior to treatment initiation.
- Peripheral blood flow cytometry (if peripheral blood blasts present, will trend at end of each treatment cycle until clearance)

To be performed within 24 hours prior to initiating study treatment:

- Serum beta-HCG for females of childbearing potential (FCBP): A female of childbearing potential is a sexually mature woman who:
    - Has not undergone a hysterectomy, tubal ligation, or bilateral oophorectomy
    - Has not been naturally postmenopausal for at least 24 consecutive months (i.e., has had menses at any time in the preceding 24 consecutive months).

In addition, male and female participants should be willing to practice effective birth control prior to study entry, during the study, and for six months following the last study treatment, unless they have had a prior vasectomy, hysterectomy, or bilateral oophorectomy.

An extension up to 72 hours prior to the start of study treatment is permissible in situations where results cannot be obtained within the standard 24-hour window.

3 STUDY IMPLEMENTATION

3.1 STUDY DESIGN

This study consists of two phases:

- Phase I: determination of OBD of BMS-986253 with and without DNMTi for HR- and LR-MDS cohorts, respectively, and
- Phase II: examining the efficacy of BMS-986253 with and without DNMTi for HR- and LR-MDS cohorts, respectively

In the Phase I, subjects will be enrolled to start treatment with BMS-986253 after a minimum of 2 cycles and up to initiation of an 8th cycle of DNMTi.

The safety endpoint will be DLT on D28. In addition, follow up for safety will be assessed 100 days after the last dose of treatment.

OBD will be the lowest tolerated dose level showing optimal biological activity, defined as maximal suppression of serum free IL-8 levels.

Participants enrolled on phase I will be treated at the corresponding BMS-986253 dose level until occurrence of disease progression, death, or unacceptable toxicity or until response assessment on C7D1 (maximum 6 cycles) if no evidence of clinical response. The participants will be followed up for overall, event- and progression-free survival until the study closure. The study will be closed when all enrolled participants have been followed up for at least 8 years or have died.

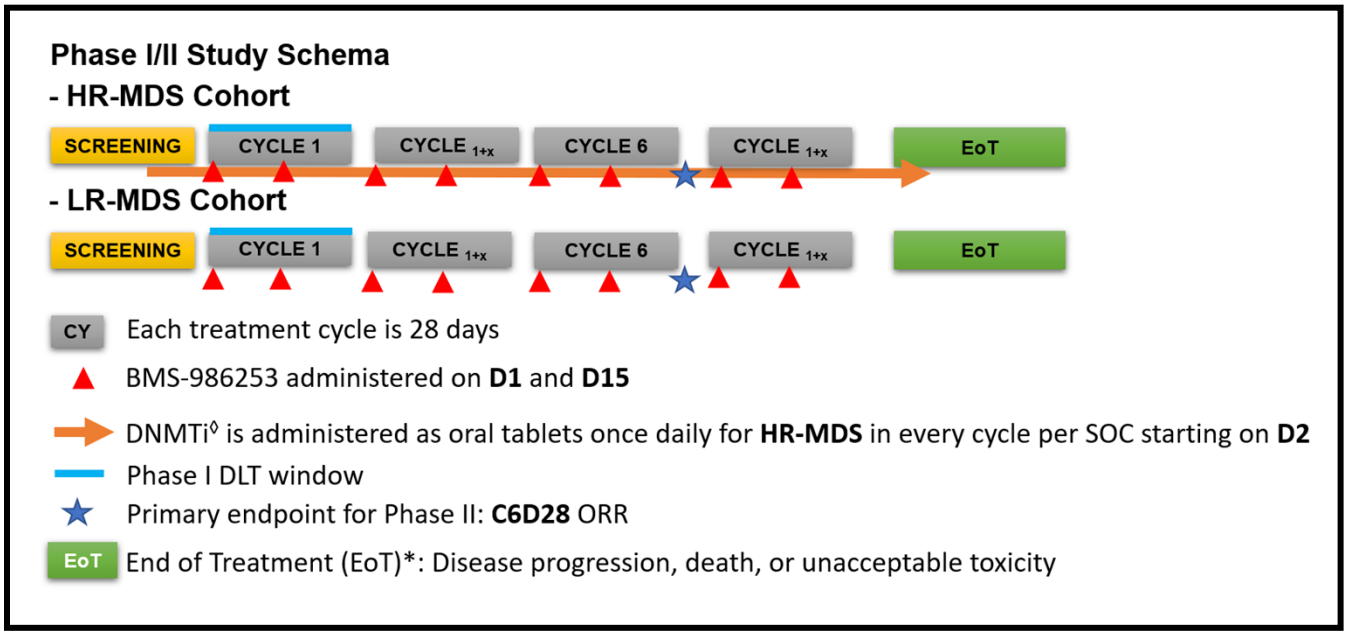
Both Phase I and II portions of study will enroll two cohorts:

A) HR-MDS: subjects with higher-risk MDS that will be treated with BMS-986253 in combination with DNMTi.

B) LR-MDS: subjects with lower-risk MDS that will be treated with BMS-986253 given as monotherapy.

In the Phase II portion, the treatment naïve subjects (or up to 4 cycles of prior DNMTi) will start treatment with BMS-986253 from the first cycle and the efficacy will be assessed until any off-treatment criteria are met (Section **3.8**). BMS-986253 will be administered on days 1 and 15 of each cycle, and participants will remain on therapy until disease progression, death, or unacceptable toxicity or taken off therapy if no evidence of clinical response after 6 cycles (C7D1). The participants will be followed up for overall, event- and progression-free survival until the study closure. The study will be closed when all enrolled participants have been followed up for at least 5 years or have died.

Study treatment schema



In the HR-MDS Cohort, DNMTi therapy (marked by the orange line) may start prior to study enrollment. As stated in the eligibility sections (see Section **2.1.1): For HR-MDS cohort, participants are eligible if they have received a minimum of 2 cycles of DNMTi therapy and up to a maximum of 8 prior cycles for phase I, and up to maximum 4 cycles of DNMTi therapy for phase II.

◊Once enrolled on study, DNMTi administration will be aligned to start on D2 of the on-protocol treatment cycles with oral decitabine and cedazuridine, to be taken once daily for 5 total days (D2-6).

*EOT will occur at disease progression, death, unacceptable toxicity OR if no clinical response is seen by completion of 6 cycles of therapy.

3.1.1 Dose Limiting Toxicity (DLT)

DLT is defined as any of the following:

- Any grade ≥ 3 non-hematologic toxicity that is possibly, probably, or definitely related to study drug, except transient (≤ 48 hour) grade 3 fatigue, nausea, local reactions, flu-like symptoms, fever, headache, infusion reactions, or laboratory abnormalities that are not associated with organ pathology.
- In the absence of active MDS, hematologic DLTs for each arm include:
    - LR-MDS arm: any grade ≥4 decrease in ANC or PLTs lasting more than 7 days.
    - HR-MDS arm: any grade ≥4 decrease ANC or PLTs lasting more than 28 days.
    - If the bone marrow at the end of cycle 1 of therapy is hypoplastic (< 5% cellularity), adjustments to treatment schedule will be allowed to delay next cycle for up to 2 weeks after count recovery or if toxicity resolves to Grade 2 or below.
- Liver Injury (DILI) as defined by a positive Hy's Law (https://www.fda.gov/media/116737/download):
    - AT (ALT or AST) elevation > 3 times upper limit of normal (ULN), AND
    - Total bilirubin > 2 times ULN, without initial findings of cholestasis (elevated serum alkaline phosphatase), AND
    - No other immediately apparent possible causes of AT 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.
- The following toxicities are not considered dose-limiting in MDS participants:
    - Grade 3 or 4 febrile neutropenia
    - Grade 3 or 4 infection only if a direct complication of cytopenias due to active underlying MDS
    - Grade 3 or 4 hypotension explained by sepsis
    - Grade 3 or 4 hemorrhage/bleeding
    - Other expected direct complication of cytopenia due to active myeloid malignancy
- Any adverse reaction that leads to dose reduction or withdrawal.

3.1.2 Dose Escalation

Participants will receive BMS-986253 A safety lead-in will be performed. The safety lead-in will be 28 days in length and consist of 2 doses of BMS-986253 (on days 1 and 15) with a safety evaluation through day 28. Dose escalation will proceed in cohorts of 3–6 participants. The MTD is the dose level at which no more than 1 of up to 6 participants experience DLT during one cycle (28 days) of treatment, and the dose below that at which at least 2 (of ≤6) participants have DLT as a result of the drug. If a participant did not experience DLT and did not finish treatment, he or she will not be evaluable for toxicity and will be replaced in the dose level. Participants will be taken off treatment if unacceptable toxicity occurs and is attributed to all therapeutic

agents (see section **3.8**). These patients will also be evaluated for safety and efficacy (see Section **7.4.1** and **8**).

Dose Escalation Schedule	
Dose Level	Dose of BMS-986253
Level -1	600 mg IV Q2W over 60 minutes
Level 1	1200 mg IV Q2W over 60 minutes[a]
Level 2	2400 mg IV Q2W over 120 minutes[b]
Level 3	3600 mg IV Q2W over 120 minutes [b]

[a] 60 minute duration will be used for pts weighing > 35 kg. For pts weighing < 35 kg the infusion duration should be 120 minutes.

[b] 120 minute duration will be used for pts weighing > 35 kg. For pts weighing < 35 kg the infusion duration should be 180 minutes.

Dose escalation will follow the rules outlined in the Table below.

Number of Participants with DLT at a Given Dose Level	**Escalation Decision Rule**
0 out of 3	Enter up to 3 participants at the next dose level
≥ 2	Dose escalation will be stopped. This dose level will be declared the maximally administered dose (highest dose administered). Up to 3 additional participants will be entered at the next lowest dose level if only 3 participants were treated previously at that dose.
1 out of 3	Enter up to 3 more participants at this dose level. • If 0 of these 3 participants experience DLT, proceed to the next dose level. • If 1 or more of this group develop DLT, then dose escalation is stopped, and this dose is declared the maximally administered dose. Up to 3 additional participants will be entered at the next lowest dose level if only 3 participants were treated previously at that dose.
≤1 out of 6 at highest dose level below the maximally administered dose that exhibits optimal biologic activity	This is the OBD and is generally the recommended phase 2 dose. At least 6 participants must be entered at the recommended phase 2 dose.

The report including the supporting safety data and delineation of each criteria met, with the dose-escalation decisions will be provided to the Sponsor (OSROSafety@nih.gov) before additional participants will be enrolled into the study. The Dose Escalation Determination form on the sponsor website: https://ccrod.cancer.gov/confluence/display/CCRCRO/Forms+and+Instructions may be used for this purpose.

Documentation of dose escalation determinations including the criteria met must be provided to the Sponsor prior to dose administration at the next dose level. An OSRO Dose Escalation Determination template form is available for recording of dose escalation related PI determinations or another format may be used but all equivalent information and PI signature is required.

The completed form or equivalent documentation should be kept in the site study files, sent to the Sponsor and available for review by the OSRO Clinical Site Monitors.

3.2 DRUG ADMINISTRATION

3.2.1 BMS-986253

Product Name	BMS-986253-01 Injection, 100mg/mL (1000 mg/vial OR 1200 mg/vial)
Product description and Packaging	*Packaging:* Vials are labeled with a one panel clinical label. Individual vials are packaged into a labeled carton. Vials should remain in the original carton until use. *Vials:* 20 cc Type I Glass Vial; with 20 mm seal *Appearance:* 1000 mg/vial and 1200 mg/vial – Colorless to slightly yellow liquid (NGT Y5); Clear to opalescent (NGT 18 NTU); Light (Few) particulates (consistent in appearance to proteinaceous particles) may be present.
Product Ingredients	Each vial contains 1000 mg or 1200 mg of BMS-986253

3.2.1.1 Drug Product Preparation

Handling: As with all injectable drugs, care should be taken when handling and preparing BMS-986253. BMS-986253 should be prepared using local regulation/guidelines regarding engineering (e.g., a biological safety cabinet, laminar or vertical flow hood) and the administrative controls required for the preparation and administration of hazardous compounds (if so determined), to include standard procedures for the safe handling of sterile products applying aseptic techniques. Gloves are required. If BMS-986253 solution comes in contact with the skin or mucosa, immediately and thoroughly wash with soap and water. For additional information, please refer to the Safety Data Sheet (SDS).

Preparation:

- Withdraw the required volume of BMS-986253 and transfer into an intravenous container.
- Dilute BMS-986253 (1000 mg/vial or 1200 mg/vial) with either 0.9% Sodium Chloride Injection, or 5% Dextrose Injection to prepare an infusion with a final concentration ranging from 10 mg/mL to 16mg/mL (see table 3.1.2-1 below). BMS-986253 is compatible in polyolefin, PVC/non-PVC, DEHP/non- DEHP containers.
- Mix diluted solution by gentle inversion. Do not shake.
- Discard partially used vials or empty vials of BMS-986253.
- If using Close System Transfer Device (CSTD) for preparation and/or administration of BMS-986253 please check below list of compatible CSTD devices. Please reach out to us at pharmacyservices@bms.com for compatibility information on any other CSTDs.

Drug Product	Compatible CSTDs
BMS-986253, 1000 mg/vial	BD (Phaseal), ICU Medical (Chemolock and Chemoclave), B.Braun (OnGuard/Tevadaptor) and Equashield, Carefusion (Texium/SmartSite)

3.2.1.2 Recommended Storage and Use Conditions

The product does not contain a preservative. After preparation, store the BMS-986253 infusion either:

- at room temperature for no more than 4 hours from the time of preparation. (This includes room temperature storage of the infusion in the IV container and time for administration of the infusion.)

or

- under refrigeration at 2°C to 8°C (36°F to 46°F) for no more than 24 hours from the time of infusion preparation (including the maximum 4 hour RT storage period).

Do not freeze.

3.2.1.3 Dosage and administration

Administration: Visually inspect drug product solution for particulate matter and discoloration prior to administration. Discard the vial if the solution is cloudy, discolored, or contains extraneous particulate matter other than a few translucent-to-white, proteinaceous particles. Do not shake the vial.

BMS 986253 is to be administered as an IV infusion and not by IV push or bolus injection.

BMS-986253 infusion should be administered over protocol specified administration time through an intravenous line containing a sterile, non-pyrogenic, low protein binding polyethersulfone (PES) or Nylon in-line filter (pore size of 0.2). Do not co-administer other

drugs (outside of the ones listed in this protocol) through the same intravenous line. Flush the intravenous line "above" the in-line filter at end of infusion with appropriate diluent.

Dose level	Infusion total volume	Concentration	Rate duration
600 mg	50 mL	12 mg/mL	60 min
1200 mg	100 mL	12 mg/mL	60 min[a]
2400 mg	200 mL	12 mg/mL	120 min[b]
3600 mg	250 mL	14.4 mg/mL	120 min[b]

[a] 60 minute duration will be used for pts weighing > 35 kg. For pts weighing < 35 kg the infusion duration should be 120 minutes.

[b] 120 minute duration will be used for pts weighing > 35 kg. For pts weighing < 35 kg the infusion duration should be 180 minutes.

BMS-986253 should be dosed per subject assignment and as outlined in the study drug dosing section of the clinical protocol (See section **3.1.2**).

See BMS-986253 guidance document for specific instructions on dosing solution preparation and infusion duration.

See section **3.2.1.4.1** for Safety monitoring guidelines during first infusion of BMS-986253.

3.2.1.4 Infusion reactions

While rare, infusion reactions can occur with infusion of BMS-986253. Most infusion reactions if they occur are mild with symptoms ranging from local skin erythema, skin rash, flushing, headache, nausea, fevers, chills or shaking, itching, they can present as more severe reactions including hypotension, wheezing, dyspnea or hypoxemia, angioedema, facial swelling, dizziness or presyncope, which can be fatal if untreated. The onset and timing for these reactions include during or after the infusion on the day of infusion or the day after infusion, with resolution commonly 48 hours after onset of symptoms.

Monitoring for these symptoms of infusion reaction and prompt recognition with appropriate interventions is imperative and will be required on this protocol.

Management should be according to best medical judgment and up-to-date guidelines (for example by NCCN, available at https://www.nccn.org/professionals/physician_gls/pdf/immunotherapy.pdf, ESMO[101]).

3.2.1.4.1 Safety Monitoring Guidelines for infusion of BMS-986253:

Vital signs, including blood pressure, heart rate, temperature, respiratory rate and SpO2 must be taken at the following intervals:

- For first hour of infusion: every 15 minutes.
- For second hour of infusion: every 30 minutes.
- Through one hour post-completion of infusion: every 30 minutes.

If participants experience any signs or symptoms of hypersensitivity, which include dyspnea, stridor, scratchy throat, throat or facial swelling, changes in vital signs including hypoxia hypotension, lethargy/confusion or change in mental status, immediate medical attention is needed with appropriate management per NIH Clinical Center Anaphylaxis Treatment Medication Guidelines (http://intranet.cc.nih.gov/pharm/pdf/ATM_GUIDELINES.pdf).

3.2.2 DNA methyltransferase inhibitors (DNMTi)

For HR-MDS cohort, the study drug of BMS-986253 will be given in combination with standard of care (SOC) FDA-approved DNMTi PO decitabine and cedazuridine according to guidelines outlined in FDA product label. SOC DNMTi will be administered via oral route once daily starting D2 of each treatment cycle through D6.

3.3 DOSE MODIFICATIONS

No dose modifications are allowed for BMS-986253. Dose modifications for toxicity related to the DNMTi used will be done according to standard of care per the FDA product label recommendations.

3.4 EVALUATIONS DURING THE TREATMENT

All evaluation days, for flexibility around participant schedules, can be performed up to +/-3 days. If a participant visit is delayed greater than 3 days due to weather, medical issues, or etc., the next evaluation will occur when possible and the 2 week cycle will reset from that point (the next dose will be 2 weeks +/-3 days from the previous dose).

Phase I and Phase II, C1, C($_{1+x}$) and beyond (until off treatment criteria are met):

- Day 1 – all lab checks and medical evaluation will be done **pre-dose:**
  - History and Physical Exam
  - Vital signs
  - CBC with differential, platelet count, and reticulocyte count
  - Serum chemistry panel (includes sodium, chloride, potassium, CO2, BUN, Creatinine, glucose, AST/ALT, Alkaline phosphatase, total bilirubin, direct bilirubin, albumin, total protein, magnesium, phosphorous, calcium, LDH, uric acid), CRP
  - Blood type and screen (as clinically indicated)
  - TBNK (CD3, CD4, CD8, CD19 clinical panel)
  - Urinalysis
  - Serum beta-HCG for females of childbearing potential (FCBP) (within 24 hours of Day 1)
  - Blood samples for pharmacokinetics (PK) and pharmacodynamics (PD) (see section **5.1**)
    - For Phase I participants only
  - Transfusion dependency assessment
  - Concomitant medications assessment
  - BMS-986253 administration

- Day 2:
  - Vital signs (only for Cycle 1)

- Clinician assessment (only for Cycle 1)
- Blood samples for 24-hour PK/PD timepoint (see Section **5.1**)
- Start oral decitabine and cedazuridine (Day 1 of 5 of DNMTi)

- Days 3-6:
  - DNMTi administration of oral decitabine and cedazuridine (HR-MDS cohorts).

- Day 8:
  - Weekly Labs (only for Cycle 1) CBC/diff, reticulocyte count, chemistries (as above and included CRP)

- Day 15 – all lab checks and medical evaluation will be done **pre-dose:**
  - History and Physical Exam
  - Vital signs
  - CBC with differential, platelet count, and reticulocyte count
  - Blood type and screen (as clinically indicated)
  - Serum chemistry panel (includes sodium, chloride, potassium, CO2, BUN, Creatinine, glucose, AST/ALT, Alkaline phosphatase, total bilirubin, direct bilirubin, albumin, total protein, magnesium, phosphorous, calcium, LDH, uric acid), CRP
  - TBNK (CD3, CD4, CD8, CD19 clinical panel)
  - Urinalysis
  - Serum beta-HCG for females of childbearing potential (FCBP) (within 24 hours of Day 1)
  - Blood samples for pharmacokinetics (PK) and pharmacodynamics (PD) (see section **5.1**)
    - For Phase I participants only
  - Concomitant medications assessment
  - BMS-986253 administration

- Days 16
  - Vital signs (only for Cycle 1)
  - Clinician assessment (only for Cycle 1)
  - Blood samples for 24-hour PK timepoint (see Section **5.1**)

- Day 22:
  - Weekly Labs (only for Cycle 1) CBC/diff, reticulocyte count, chemistries (as above including CRP)

- Day 28
  - Bone marrow evaluation (aspiration and biopsy) per protocol or per clinical necessity.
    - Morphology, flow cytometry, cytogenetics, molecular tests, and research - see section **5.1**)
    - Per protocol, bone marrow biopsy after initiation of therapy required:
      - Phase I post cycle 1(C1D28 +/- 3 days)

- Phase II post cycle 2 (C2D28 +/- 3 days)
- Phase II post cycle 6 (C6D28 +/- 3 days)
- With development of treatment-related aplasia or concern for disease progression

▪ All other BMB are optional and per PI or LAI discretion.

o Peripheral blood flow cytometry (if peripheral blood blasts present, will trend at end of each treatment cycle until clearance)
o Research blood per section **5.1**

AT DISEASE PROGRESSION

If participant has disease progression on treatment while being evaluated at the NIH the following tests will be done within 7 days after diagnosis of progression.

- Research Blood per section **5.1**
- TBNK (CD3, CD4, CD8, CD19 clinical panel)
- Adverse event and transfusion requirement assessment
- Mandatory Bone Marrow Biopsy and aspirate
- Peripheral blood flow cytometry (if evidence of peripheral blood blasts and NGS myeloid mutation panel)
- CBC with differential, platelet count, and reticulocyte count
- Blood type and screen (as clinically indicated)
- Serum chemistry panel (includes sodium, chloride, potassium, CO2, BUN, Creatinine, glucose, AST/ALT, Alkaline phosphatase, total bilirubin, direct bilirubin, albumin, total protein, magnesium, phosphorous, calcium; also need LDH, uric acid, CRP)
- PT/INR, PTT and fibrinogen

END OF TREATMENT VISIT

Will be done 30 ± 7 days from the end of the last cycle on therapy.

- History & Physical Exam
- Vital signs
- Serum beta-HCG for females of childbearing potential (FCBP) Urinalysis
- CBC with differential, platelet count, and reticulocyte count
- Fibrinogen
- Blood type and screen (as clinically indicated)
- Serum chemistry panel (includes sodium, chloride, potassium, CO2, BUN, Creatinine, glucose, AST/ALT, Alkaline phosphatase, total bilirubin, direct bilirubin, albumin, total protein, magnesium, phosphorous, calcium; also need LDH, uric acid, CRP)
- Concomitant medications assessment
- Adverse event and transfusion dependency assessment
- Research blood collection only if bone marrow performed (see section **5.1**)
- TBNK (CD3, CD4, CD8, CD19 clinical panel)
- EORTC (see section **3.5.3**)
- Psychosocial Assessment (see section **3.5.3**)

FOLLOW-UP

After the End of Treatment visit, follow up will occur via phone call every 3 months (+/- 1 month) for first 24 months, then every 6 months (+/- 3 months) at least 5 years post enrollment. . Outside medical records will be requested along with the phone call for the first follow-up visit only.

- Overall survival, event- and progression-free survival status

Adverse events assessment (only at first follow-up visit)

END OF STUDY

- Overall survival, event- and progression-free survival status will be assessed via phone call.

3.5 ON STUDY ASSESSMENTS/EVALUATIONS

The timepoints for assessments are listed in Section **0**, Study Calendar. Unless otherwise indicated, assessments on dosing days must be performed prior to the administration of study therapy. For screening procedure details, refer to section **2.2.** Baseline evaluations do not need to be repeated if already performed at screening within 8 days prior to initiation of study therapy.

3.5.1 Safety Assessments and Other Assessments

- Physical exam - review of organ systems, weight, and vital signs (i.e., temperature, pulse, respirations, blood pressure). Height will only be required prior to treatment no later than cycle 1 day 1. After initiation of study drug, symptom-directed physical examinations will be performed as clinically indicated in the investigator's judgment.
- Medical history – performed during long term follow up in order to assess safety and efficacy.
- Concomitant medications – a record of all medications including herbal supplements but not including study therapy that a participant has taken during the study will be recorded in order to assess confounding factors in safety and efficacy assessments
- Adverse events – participant reported adverse events will be collected throughout the study in order to assess safety.
- ECOG performance status: an assessment of activities of daily living
- Bone marrow biopsy and aspiration: required at screening/baseline, Phase I post cycle 1(C1D28 +/- 3 days) and Phase II post cycle 2 (C2D28 +/- 3 days) and post cycle 6 (C6D28 +/- 3days); and if needed clinically in the setting of aplasia or concern for disease progression
- Electrocardiogram 12-lead ECGs will be performed at baseline only for safety
- Blood chemistries - Sodium (Na), Potassium (K), Chloride (Cl), Total CO2 (bicarbonate), Creatinine, Glucose, Urea nitrogen (BUN), Albumin, Calcium total, Magnesium total (Mg), Inorganic Phosphorus, Alkaline Phosphatase, ALT/GPT, AST/GOT, Total Bilirubin, Direct Bilirubin, Total Protein will be performed to assess organ function

- CBC with differential includes Neutrophils, Lymphocytes, Monocytes, Eosinophils, Basophils, WBC, RBC, Hemoglobin, Hematocrit, RBC Indices, MCV, RDW, Platelet.
- TBNK for research
- Other blood test: amylase lipase, creatine kinase, ACTH, TSH, free T4, PT, PTT, INR, ESR and CRP will be performed per study calendar to assess organ function
- Urinalysis for safety
- Serum or urine pregnancy test – performed prior to administration of study therapy in women of childbearing potential and women < 12 months since the onset of menopause to ensure participant is not pregnant

3.5.2 Efficacy Assessments

- Cytogenetic response rate
- Time to best response (CR, PR, marrow CR+HI, HI)
- Disease free survival (definition: time to relapse for participants who achieve CR)
- Progression free survival (definition: disease progression or death from MDS)
- Leukemia free survival (definition: progression to AML or death from any cause)
- Overall survival (definition: death from any cause)
- Transfusion-dependence and independence, for RBC and platelets

3.5.3 Questionnaires

Participant questionnaires are only offered in English and are therefore not required in non-English speaking participants that may be enrolled on the protocol.

3.5.3.1 Rockwood Frailty Index

The Rockwood Clinical Frailty Score (CFS) was developed as a deployable tool to be used by clinicians to assess level of vulnerability. It uses clinical descriptors and pictographs to divide participants into 9 levels of vulnerability ranging from 1 (very fit) to 9 (terminally ill). [102] This 9-point scale uses a visual chart to assess frailty classifications; someone with a score of ≥5 is classified as frail. The CFS was validated in a sample of 2305 older Canadian participants who remained alive 5 years after the Canadian Study of Health and Aging (CSHA-2). [103] CFS will be completed at baseline only in a clinical setting. A member of the study team will observe the participants physical activity and ability and score them.

3.5.3.2 MDS-CI

MDS-specific comorbidity index (MDS-CI) is a scoring system for MDS participants to be used by clinicians using a time-dependent index to predict the effects of comorbidities on treatment outcomes. [104] Five comorbidities independently predictive for non-leukemic death (cardiac, hepatic, pulmonary, renal, solid tumor) were assigned a score proportional to the regression coefficient of the multivariable Cox's proportional hazards model, the MDS-CI score was calculated as the sum of these weighted scores, and grouped into three risk groups – low, intermediate, and high risk. The MDS-CI was validated in a sample of 840 MDS participants from Pavia, Italy and a validation cohort of 504 participants in Dusseldorf, Germany. [26] MDS-CI will be completed at baseline only. A member of the study team will assess clinical information and score by completing the standard form.

3.5.3.3 European Organization for Research and Treatment of Cancer (EORTC) quality of life questionnaire = EORTC QLQC30 score

The European Organization for Research and Treatment of Caner (EORTC) Quality of Life Questionnaire is a participant self-report questionnaire used to assess participants' health-related quality of life in the oncology field. [105] This questionnaire incorporates nine multi-item scales, three symptom scales, a global health scale, and a quality-of-life scale. This questionnaire was validated across three language-cultural groups as well as against different questionnaires. [106] EORTC QLQ-C30 has been the most frequently used participant-reported outcome (PRO)/quality of life questionnaire in published MDS studies to-date and has commonly been a contributory measure of PRO to drug-approval processes for MDS. [107] EORTC-QLQC will be completed using self-administered form by participant at baseline, C3D28 (+/- 1 day), C6D28 (+/- 1 day), C9D28 (+/- 1 day), C12D28 (+/- 1 day), C24 (+/-1 day), and end of treatment.

3.5.3.4 NIH MDS Adult Psychosocial Assessment

The psychosocial assessment is a self-report form that was originally developed for the NIH gastrointestinal stromal tumor (GIST) Clinic[108] in order to identify specific psychosocial areas of concern and symptoms not covered in the Patient-Reported Outcomes Measurement Information System (PROMIS) and other standardized measures. It contains items covering demographic factors, perceived general health, psychosocial concerns, psychiatric history, self-identified needs, and interest in a range of possible psychosocial services. It has now been adapted and is being used with patients at the NIH participating in the Medullary Thyroid Cancer (MTC) and RUNX1 natural history studies. Three versions of the interview were created; one for adult patients to complete on their own (age >18 years), another for parents of children to complete about their child, and a third, briefer interview for adolescent patients (ages 12-17 years). This questionnaire will be provided to patients for completion at baseline, C12D28 (+/- 1 day) , C24D28 (+/-1 day), and end of treatment

3.6 STUDY CALENDAR

Phase I and II

Procedure	Screening [a]	Baseline [c]	All Cycles					At Disease Progression [m]	End of treatment visit [k]	Post Therapy Follow-up [l]	End of Study
			Day 1 [f]	Day 2	Day 15 [f]	Day 16	Day 28				
History and PE	X	X	X	X[g]	X	X[g]			X		
Vital signs [t]	X	X	X	X	X	X			X		
Height and Weight	X	X[o]									
Performance Score	X	X									
Labs [n]	X	X	X		X			X	X		
Serum Pregnancy Test	X	X [e]	X [e]		X[e]				X		
Urinalysis		X	X		X				X		
ECG	X	X									
Bone Marrow bx and aspirate (see section 5.1)	X	X [d]					X[j]	X			
Histologic Confirmation [b]	X										
Correlative Research Studies (see section 5.1)		X					X	X	X		
PK/PD (see section 5.1)[i]			X	X	X	X					
NIH advanced Directive		X									
DNMTi Administration[h]				X							
BMS-986253 Administration[q]			X		X						
Response Evaluation[r]							X				
Follow-up by phone call										X	X
Transfusion Dependency Assessment			X					X	X		
Adverse Event Assessment			X	X	X	X	X	X	X	X[s]	
Concomitant Medications		X	X		X				X	X	
Questionnaires[p] Rockwood/CFS MDS-CI EORTC QLQC30 score Psychosocial assessment		X[p]							X[p]		

a. Screening tests are valid for 30 days prior to enrollment unless otherwise specified.
b. Any time prior to enrollment
c. Within 8 days prior to initiating study treatment unless otherwise noted
d. May be performed during screening evaluation; must be done within 30 days prior to treatment initiation.
e. To be performed within 24 hours prior to initiating study treatment:
f. Pre-dose unless otherwise noted.
g. Clinician Assessment only (only for Cycle 1)

h. Higher-Risk (HR) MDS Cohorts only, to initiate PO DNMTi on D2 (+/- 1 day per PI or LAI discretion), and continue daily dosing through D6 of each cycle
i. PK sampling Cycle 1(day 1 and day 15) and cycle 2 (day 1 only) for Phase I participants only-See section **5.1.3.1** for PK blood draw details. PD sampling for Phase I participants only - (baseline, C1D2, C1D15, C2D1, C2D2, C2D15, C3D1, C4D1 - see section **5.1.3.2** for blood draw details
j. See section **5.1**: bone marrow biopsy and aspiration required at screening/baseline, Phase I post cycle 1(C1D28 +/- 3 days) and Phase II post cycle 2 (C2D28 +/- 3 days) and post cycle 6 (C6D28 +/- 3days); and if needed clinically in the setting of aplasia or concern for disease progression. All other are optional and per PI discretion.
k. Will be done 30 ± 7days from the end of the last study cycle.
l. Follow up will occur via phone call every 3 months (+/- 1 month) for first 24 months, then every 6 months (+/- 3 months)up to 5 years post enrollment. . Outside medical records will be requested along with the phone call for the first follow-up visit only.
m. Within 7 days
n. See section **2.2.2**, **2.4**, and **3.4** for detailed lab collection instructions. For Cycle 1, patients will undergo weekly lab monitoring with CBC/diff, and chemistry (see section **3.4**) on days 8 and 22.
o. Weight only
p. Rockwood/CFS and MDS-CI to be completed at baseline only; EORTC-QLQC and Psychosocial assessment will be completed per section **3.5.3**. Questionnaires required only in English speaking participants.
q. See Safety monitoring guidelines during infusion (Section **3.2.1.4.1**)
r. Response assessment Phase I post cycle 1 and as clinically indicated and Phase 2 post cycle 2, post cycle 6, and as clinically indicated.
s. Only at first follow up time point; See section **6.1**
t. See Section **3.2.1.4.1** for details on frequency of vital sign monitoring during first infusion of BMS-986253. Vital signs required for D2 and D16 of Cycle 1 only.

* CFS: Clinical Frailty Scale; MDC-CI: MDS-Specific Comorbidity Index; EORTC-QLQC: European Organization for Research and Treatment of Cancer (EORTC) quality of life questionnaire (QLQ)

3.7 COST AND COMPENSATION

3.7.1 Costs

NIH does not bill health insurance companies or participants for any research or related clinical care that participants receive at the NIH Clinical Center. If some tests and procedures are performed outside the NIH Clinical Center, participants may have to pay for these costs.

3.7.2 Compensation

Participants will not be compensated on this study.

3.7.3 Reimbursement

The NCI will cover the costs of some expenses associated with protocol participation. Some of these costs may be paid directly by the NIH and some may be reimbursed to the participant/guardian as appropriate. The amount and form of these payments are determined by the NCI Travel and Lodging Reimbursement Policy.

3.8 CRITERIA FOR REMOVAL FROM PROTOCOL THERAPY AND OFF STUDY CRITERIA

Prior to removal from protocol therapy, effort must be made to have all subjects complete a safety visit approximately 100 days after the last dose of study therapy.

3.8.1 Criteria for removal from protocol therapy

- Progressive disease
- Participant requests to be withdrawn from active therapy
- Unacceptable toxicity as (section **3.3**)
- Lack of clinical response seen after 6 cycles of therapy (C7D1)
- Completion of safety visit
- Investigator discretion
- Positive pregnancy test

3.8.2 Off-Study Criteria

- Participant requests to be withdrawn from study
- Death
- Screen failure
- Permanent loss of capacity to consent

3.8.3 Completion of protocol-driven follow-up. Lost to Follow-up

A participant will be considered lost to follow-up if he or she fails to return for 3 scheduled visits and is unable to be contacted by the study site staff.

The following actions must be taken if a participant fails to return to the clinic for a required study visit:

- The site will attempt to contact the participant and reschedule the missed visit within 30 days and counsel the participant on the importance of maintaining the assigned visit schedule and ascertain if the participant wishes to and/or should continue in the study.

- Before a participant is deemed lost to follow-up, the investigator or designee will make every effort to regain contact with the participant (where possible, 3 telephone calls and, if necessary, an IRB approved certified letter to the participant's last known mailing address or local equivalent methods). These contact attempts should be documented in the participant's medical record or study file.
- Should the participant continue to be unreachable, he or she will be considered to have withdrawn from the study with a primary reason of lost to follow-up.

4 CONCOMITANT MEDICATIONS/MEASURES

4.1 ALLOWED CONCOMITANT MEDICATIONS/SUPPORTIVE MEASURES:

4.1.1 Antimicrobial Prophylaxis

- Per standard of care supportive measures for participants with MDS, standard antimicrobial prophylaxis will be considered for neutropenic participants who exhibit ANC <1000 for ≥7 days prior to study enrollment, either initiation of continuation of prior supportive therapy, including but not limited to:
  - antibacterial prophylaxis with levofloxacin 750 mg daily
  - antiviral prophylaxis with acyclovir 800 mg twice daily
- For participants with clinical indication administration of anti-*Pneumocystis jiroveci* pneumonia prophylactic therapy is allowed.
- For participants with history of fungal infection, or other clinical indication, continuation of antifungal prophylaxis will be allowed.

4.1.2 Hematologic support

- Due to the hematologic abnormalities associated with MDS, management of hematologic toxicity in MDS participants will be at the discretion of the PI.
- Transfusions of red blood cells and platelets will be allowed per the appropriate participant-specific hematologic parameters.
- Growth factor support with G-CSF, erythropoietin agonists, and/or thrombopoietin agonists will not be allowed while on trial.

4.1.3 Management of HLH:

Patients with HLH who have deteriorating organ function (eg, cardiovascular, pulmonary, renal, hepatic, or neurologic) should be managed immediately with stoppage of BMS-986253. Evidence of end-organ damage should prompt consideration of initiation of HLH-specific treatment.

Treatment options include:

1) Steroids:

   Dexamethasone is given intravenously or orally and tapered over the eight-week induction:

   - Weeks 1 and 2 – 10 mg/m2 daily
   - Weeks 3 and 4 – 5 mg/m2 daily

- Weeks 5 and 6 – 2.5 mg/m2 daily
- Week 7 – 1.25 mg/m2 daily
- Week 8 – Taper dose to zero

2) HLH-94 Protocol: consists of eight weeks of induction therapy with etoposide (VP-16) and dexamethasone, with intrathecal therapy for those with CNS involvement.

- Etoposide (VP-16) is given at a dose of 150 mg/m2 twice weekly for the first two weeks, and once weekly for weeks three through eight. [109]

4.2 DRUG INTERACTIONS:

- There are no special warnings or precautions in term of drug interaction with BMS-986253. [95]

4.3 CONTRAINDICATED AGENTS:

- No other antineoplastic, immunomodulatory, or immunosuppressive therapies, including corticosteroids (barring adrenal insufficiency supplementation dosing), should be given concomitantly while on trial.
- Growth factor support will not be allowed (see Section **4.1.2**).

5 CORRELATIVE STUDIES FOR RESEARCH

5.1 BIOSPECIMEN COLLECTION

5.1.1 Summary Table of Planned Correlative Tests/assays and Biospecimens Collection:

Test/assay	Volume (approx.)	Type of tube[a]	Collection Site/ Type of Specimen	Collection point	Location of specimen analysis
Pharmacokinetics: Antibody PK	5 mL	SST vacutainer tubes -Serum samples should then be transferred to micronic tubes for shipping to bioanalytical lab.	- Peripheral blood	See section **5.1.3** for PK and PD sampling schedules.	BPC
Serum Free Simoa IL-8 assay	5 mL				BPC
Leukocyte Subsets: CD3, CD4, CD8, CD19, CD4:CD8 ratio, NK markers	3mL per tube	EDTA tube	- PBMC	Baseline and D1 of each treatment cycle	Fresh peripheral blood will be drawn, and lympho-phenotyping will be performed using Clinical

(TBNK panel)					Center's CLIA certified Immunophenotyping (TBNK) panel and reported in the CRIS.
Next generation sequencing/ Myeloid molecular mutation panel: TSO-500 Panel	2 mL per tube	EDTA (lavender top) or ACD (yellow top)	- Bone marrow aspirate	(1) Baseline bone marrow (2) Bone marrow C1D28 for Phase I (3) Bone marrow C2D28 for Phase II (3) Bone marrow C6D28 for Phase II	NCI Laboratory of Pathology
Flow Cytometry	3-5mL per tube	Sodium Heparin green top	- Bone marrow aspirate	Baseline and with every bone marrow evaluation per protocol	NCI, DLM
Clinical MDS FISH* *only needed if cytogenetic analysis not possible	3 mL per tube if bone marrow 5 mL per tube if whole blood	Sodium Heparin green top	- Bone marrow aspirate	Baseline and with every bone marrow evaluation per protocol	Mayo send out test
Clinical Cytogenetics	6 mL	Sodium Heparin green top	- Bone Marrow	Baseline and with every bone marrow evaluation per protocol	Mayo send out test
Pathologic evaluation - Bone Marrow Biopsy	Core biopsy	Per standard practice/slide preparation	- Bone Marrow Biopsy	Baseline and with every bone marrow	DLM

		and inclusion of core biopsy		evaluation per protocol	
Peripheral Blood flow cytometry	2 mL	EDTA tube	- Peripheral Blood	Baseline If peripheral blood blasts present, will trend at end of each treatment cycle until clearance	NCI, DLM
Research Sample	10 mL	EDTA tube	- Marrow aspirate	Baseline and with every bone marrow evaluation	BPC
Research: S100A8, S100A9	3 mL	EDTA tube	Bone marrow aspirate	Baseline and with every bone marrow evaluation	1W-3888 Dr. Rosandra Kaplan laboratory
Research: Ribosome footprinting; Quantitative mass spectrometry	10 mL	EDTA tube	- Marrow aspirate	Baseline and with every bone marrow evaluation	Dr. Daniel Larson laboratory
Research: - Deep NGS Sequencing - Singe cell sequencing -Somalogic - Whole Genome Sequencing	12.5mL 2.5ml	2.5ml Paxgene, 10ml EDTA tube 2.5ml Paxgene tube	Blood - Bone marrow aspirate	Blood (Baseline and with every bone marrow evaluation) Bone Marrow (Screening/baseline (Phase I and Phase II), C1D28 Phase I, C2D28 and C6D28 for Phase II)	BPC
a. Please note that tubes and media may be substituted based on availability with the permission of the PI or laboratory investigator.					

5.1.2 Immune Monitoring

- Cytokines analysis
  - Evaluation of serum levels of and changes in (pre- versus post-treatment) cytokines (IL-8, IFN-γ, IL-10, IL-12, IL-2, IL-4, TGF-ß, IL-6, CXCL1, IL-1α).

- Cytokines will be measured in peripheral blood samples as well as bone marrow.

- Cell subset analysis
  - Flow cytometry
    - Monitoring of cellular subsets including lymphocyte subsets, MDSCs, NK cells, and Tregs
    - Flow cytometry will be conducted on both peripheral blood and bone marrow aspirate samples.
  - TBNK peripheral blood panel

5.1.3 PK/PD Sampling Schedule (Phase I)

5.1.3.1 PK Sampling Schedule

5.1.3.1.1 Cycle 1 Day 1 (C1D1) and Day 15 (C1D15)

Time	Administration of BMS-986253	PK
Before infusion, within 30 minutes		X
Start of infusion	X	
1 hour after end of infusion (+30 minutes/-5 minutes)		X
4 hours after end of infusion (+/- 45 minutes)		X
12 hours after end of infusion (+/- 2 hours)		X
24 hours after infusion (+/- 4 hours)		X

5.1.3.1.2 Cycle 2 Day 1 (C2D1)

Time	Administration of BMS-986253	PK
Before infusion, within 30 minutes		X
Start of infusion	X	
At least 1 hour after end of Infusion (between 1-2 hours after end of infusion)		X

5.1.3.2 PD Sampling Schedule:

Free serum IL-8 levels will be assessed by ultrasensitive immunoassay based on Quanterix Simoa technology (lower limit of quantification = 0.86 pg/mL) by Myriad-RBM.

- Baseline (pre-administration of BMS-986253,- 60 minutes)
- C1D2 (24 hours after infusion, +/- 4 hours)

- C1D15 (pre-administration of BMS-986253,- 60 minutes)
- C2D1(pre-administration of BMS-986253,- 60 minutes)
- C2D2(24 hours after infusion, +/- 4 hours)

- C2D15(pre-administration of BMS-986253,- 60 minutes)
- C3D1 (pre-administration of BMS-986253, - 60 minutes)
- C4D1 (pre-administration of BMS-986253, - 60 minutes)

5.1.4 Disease Monitoring

- Bone marrow evaluation for correlative studies will be done at each study time point when performed for clinical purposes including biopsy and aspirate: prior to initiation of treatment (baseline) and for interim assessment per the outlined study calendar (See **Section 0**).
    - Pathology review of aspirate and core biopsy with immunohistochemistry-defined immunophenotyping
    - Flow cytometric evaluation of cell subsets and immunophenotyping of myeloblasts, if present.
    - Cytogenetics
    - Fluorescence in situ hybridization (FISH)
    - Next generation sequencing/ molecular mutation analysis
- None of the resulting information from correlative studies will be returned to the participant or used in clinical decision making unless performed in a CLIA-certified laboratory and ordered for a clinical indication.
- Research samples of the bone marrow will also be collected and stored for further analyses, which may include (but not limited to):
    - Cytokine evaluation
    - Whole genome sequencing
    - Single cell sequencing
    - Ultra-deep NGS measurable residual disease mutational analysis
    - Quantitative mass spectrometry
    - Ribosome footprinting
    - *Ex vivo* culture and phenotypic analysis
- All participants will receive a careful medical and clinical evaluation with particular focus on indicators of possible germline predisposition. Where appropriate, germline testing for mutations in genes predisposing to myeloid malignancy will be obtained. For positive cases, referral to clinical protocols at NIH and elsewhere will be made after discussion with individual participants about available treatment options.

5.2 SAMPLE STORAGE, TRACKING AND DISPOSITION

Samples will be ordered in CRIS and tracked through a Clinical Trial Data Management System. Should a CRIS screen not be available, the CRIS downtime procedures will be followed. Samples will not be sent outside NIH without appropriate approvals and/or agreements, if required.

5.2.1 Samples Managed by Dr. Larson Laboratory

Sample Data Collection

All samples sent to the Larson Laboratory will be barcoded, with data entered and stored in Labmatrix utilized by the BPC. This is a secure program, with access to Labmatrix limited to defined Larson lab personnel, who are issued individual user accounts. Installation of Labmatrix is limited to computers specified by Dr. Larson. These computers all have a password restricted login screen.

Labmatrix creates a unique barcode ID for every sample and sample box, which cannot be traced back to participants without Labmatrix access. The data recorded for each sample includes the participant ID, name, trial name/protocol number, time drawn, cycle time point, dose, material type, as well as box and freezer location. Participant demographics associated with the clinical center participant number are provided in the system. For each sample, there are notes associated with the processing method (delay in sample processing, storage conditions on the ward, etc.).

Sample Storage and Destruction

Barcoded samples are stored in barcoded boxes in a locked freezer at either -20 or -80°C according to stability requirements. These freezers are located onsite in the Larson Lab in the Bethesda campus. Visitors to the laboratory are required to be accompanied by laboratory staff at all times.

Access to stored clinical samples is restricted. Samples will be stored until requested by a researcher named on the protocol. All requests are monitored and tracked in Labmatrix. All researchers are required to sign a form stating that the samples are only to be used for research purposes associated with this trial (as per the IRB approved protocol) and that any unused samples must be returned to the BPC. It is the responsibility of the NCI Principal Investigator to ensure that the samples requested are being used in a manner consistent with IRB approval.

Following completion of this study, samples will remain in storage as detailed above. Access to these samples will only be granted following IRB approval of an additional protocol, granting the rights to use the material.

If, at any time, a participant withdraws from the study and does not wish for their existing samples to be utilized, the individual must provide a written request. Following receipt of this request, the samples will be destroyed (or returned to the participant, if so requested). The PI will record any loss or unanticipated destruction of samples as a deviation. Reporting will be per the requirements of section **7.2**.

Sample barcodes are linked to participant demographics and limited clinical information. This information will only be provided to investigators listed on this protocol, via registered use of the Labmatrix. It is critical that the sample remains linked to participant information such as race, age, dates of diagnosis and death, and histological information about the tumor, in order to correlate genotype with these variables.

5.2.2 Samples Managed by Dr. Figg's Blood Processing Core (BPC)

Blood and Bone Marrow Collection

Please e-mail NCIBloodcore@mail.nih.gov at least 24 hours before transporting samples (the Friday before is preferred).

For sample pickup, page 102-11964.

For immediate help, call 240-760-6180 (main blood processing core number) or, if no answer, 240-760-6190 (main clinical pharmacology lab number).

For questions regarding sample processing, contact NCIBloodcore@mail.nih.gov

The samples will be processed, barcoded, and stored in Dr. Figg's lab until requested by the investigator.

See **Appendix E** for processing instructions.

Sample Data Collection

All samples sent to the Blood Processing Core (BPC) will be barcoded, with data entered and stored in Labmatrix utilized by the BPC. This is a secure program, with access to Labmatrix limited to defined Figg lab personnel, who are issued individual user accounts. Installation of Labmatrix is limited to computers specified by Dr. Figg. These computers all have a password restricted login screen.

Labmatrix creates a unique barcode ID for every sample and sample box, which cannot be traced back to participants without Labmatrix access. The data recorded for each sample includes the participant ID, name, trial name/protocol number, time drawn, cycle time point, dose, material type, as well as box and freezer location. Participant demographics associated with the clinical center participant number are provided in the system. For each sample, there are notes associated with the processing method (delay in sample processing, storage conditions on the ward, etc.).

Sample Storage and Destruction

Barcoded samples are stored in barcoded boxes in a locked freezer at either -20 or -80°C according to stability requirements. These freezers are located onsite in the BPC and offsite at NCI Frederick Central Repository Services in Frederick, MD. Visitors to the laboratory are required to be accompanied by laboratory staff at all times.

Access to stored clinical samples is restricted. Samples will be stored until requested by a researcher named on the protocol. All requests are monitored and tracked in Labmatrix. All researchers are required to sign a form stating that the samples are only to be used for research purposes associated with this trial (as per the IRB approved protocol) and that any unused samples must be returned to the BPC. It is the responsibility of the NCI Principal Investigator to ensure that the samples requested are being used in a manner consistent with IRB approval.

Following completion of this study, samples will remain in storage as detailed above. Access to these samples will only be granted following IRB approval of an additional protocol, granting the rights to use the material.

If, at any time, a participant withdraws from the study and does not wish for their existing samples to be utilized, the individual must provide a written request. Following receipt of this request, the samples will be destroyed (or returned to the participant, if so requested).. The PI will record any loss or unanticipated destruction of samples as a deviation. Reporting will be per the requirements of section **7.2**.

Sample barcodes are linked to participant demographics and limited clinical information. This information will only be provided to investigators listed on this protocol, via registered use of the Labmatrix. It is critical that the sample remains linked to participant information such as race,

age, dates of diagnosis and death, and histological information about the tumor, in order to correlate genotype with these variables.

5.3 SAMPLES FOR GENETIC/GENOMIC ANALYSIS

5.3.1 Description of the scope of genetic/genomic analysis

- Myeloid mutation molecular analysis – Next Generation Sequencing (NGS):
    - Bone marrow aspirate and peripheral blood samples will be sent for NGS as discussed in clinical monitoring section above.
        - These will detect mutations and report respective variable allele frequency which will help support whether the mutations are somatic versus germline. With any concern for germline mutation, further testing will be supported for confirmation.
        - As NGS analysis is for clinical purposes and is being performed by a CLIA-certified clinical laboratory, NGS results may be added to the medical record and returned to the participant to help inform future therapy.
- Research whole genome sequencing, Single cell sequencing, Ultra-deep NGS measurable residual disease mutational analysis.
- Genetic Biomarkers:
    - IL-8 is a stimulator of angiogenesis, which acts through the receptors CXCR1 and CXCR2, the latter being the endothelial receptor. The IL-8 -251T > A polymorphism increases plasma IL-8 levels by increasing IL-8 production[110] [96] Single nucleotide polymorphisms (SNPs) the IL-8/CXCR1/CXCR2 genes could alter treatment response or outcome by affecting the IL-8 signaling pathway.
    - This will be assessed via WGS studies, and correlation between these genetic variants and toxicity and clinical endpoints will be explored.
- Germline-predisposition to MDS evaluation:
    - All participants will receive a careful medical and clinical evaluation with particular focus on indicators of possible germline predisposition. Where appropriate, especially for participants diagnosed with MDS under the age of 40 years or with a strong family history, germline testing for mutations in genes predisposing to myeloid malignancy will be obtained via skin biopsy and culturing of fibroblasts.
    - For positive cases, referral to clinical protocols at NIH and elsewhere will be made after discussion with individual participants about available treatment options.

5.3.2 Description of how privacy and confidentiality of medical information/biological specimens will be maximized

NGS analysis will be both for clinical and research purposes. Results of NGS testing performed by a CLIA-certified clinical laboratory will be added to the medical record and returned to the

participant to help inform future therapy. Research sequencing results will not be returned to participants, unless a potentially actionable clinically actionable gene variant is identified (see 5.3.3). If a germline mutation is found upon further testing, participant will be referred to genetic counseling. PHI will be linked to the sample as this is an important part of disease management and prognostication and is standard. PHI will not be released to third parties. Research sequencing will be uploaded to public databases in compliance with NIH genomic data sharing policies.

5.3.3 Management of Results

Subjects will be contacted if a clinically actionable gene variant is discovered. Clinically actionable findings for the purpose of this study are defined as disorders appearing in the American College of Medical Genetics and Genomics recommendations for the return of incidental findings that is current at the time of primary analysis. (A list of current guidelines is maintained on the CCR intranet: https://ccrod.cancer.gov/confluence/display/CCRCRO/Incidental+Findings+Lists). Subjects will be contacted at this time with a request to provide a sample to be sent to a CLIA certified laboratory. If the research findings are verified in the CLIA certified lab, the subject will be offered the opportunity to come to NIH (at our expense) to have genetic education and counseling to explain this result. If the subject does not want to come to NIH, a referral to a local genetic healthcare provider will be provided (at their expense).

This is the only time during the course of the study that incidental findings will be returned. No interrogations regarding clinically actionable findings will be made after the primary analysis.

6 DATA COLLECTION AND EVALUATION

6.1 DATA COLLECTION

The PI will be responsible for overseeing entry of data into a 21 CFR Part 11-compliant data capture system provided by the NCI CCR and ensuring data accuracy, consistency and timeliness. The principal investigator, associate investigators/research nurses and/or a contracted data manager will assist with the data management efforts. Primary and final analyzed data will have identifiers so that research data can be attributed to an individual human subject participant.

All adverse events, including clinically significant abnormal findings on laboratory evaluations, regardless of severity, will be followed until return to baseline or stabilization of event.

Document AEs from the first study intervention, study day 1, through study day 100 after the subject received the last product administration, except for Grade 1 AEs, which will be collected and recorded for first 30 days on study only. After 100 days, only adverse events which are serious and related to the study investigational agent need to be recorded.

An abnormal laboratory value will be recorded in the database as an AE **only** if the laboratory abnormality is characterized by any of the following:

- Results in discontinuation from the study
- Is associated with clinical signs or symptoms
- Requires treatment or any other therapeutic intervention

- Is associated with death or another serious adverse event, including hospitalization.
- Is judged by the Investigator to be of significant clinical impact
- If any abnormal laboratory result is considered clinically significant, the investigator will provide details about the action taken with respect to the test drug and about the participant's outcome.

The PI evaluation of each AE not captured in the clinical database determining that it meets the criteria above will be documented in the source documents.

End of study procedures: Data will be stored according to HHS, FDA regulations, and NIH Intramural Records Retention Schedule as applicable.

Loss or destruction of data: Should we become aware that a major breach in our plan to protect subject confidentiality and trial data has occurred, this will be reported expeditiously per requirements in section **7.2.1**.

6.2 DATA SHARING PLANS

6.2.1 Human Data Sharing Plan

What data will be shared?

I will share human data generated in this research for future research as follows*:*

_x__ Coded, linked data in an NIH-funded or approved public repository.

_x__ Coded, linked data in BTRIS (automatic for activities in the Clinical Center)

_x__ Identified or coded, linked data with approved outside collaborators under appropriate agreements.

How and where will the data be shared?

Data will be shared through:

__x_ An NIH-funded or approved public repository. Insert name or names: CCR BPC Figg lab.

__x_ BTRIS (automatic for activities in the Clinical Center)

__x_ Approved outside collaborators under appropriate individual agreements.

__x_ Publication and/or public presentations.

When will the data be shared?

_x__ Before publication.

_x__ At the time of publication or shortly thereafter.

6.2.2 Genomic Data Sharing Plan

Unlinked genomic data will be deposited in public genomic databases in compliance with the NIH Genomic Data Sharing Policy.

6.3 RESPONSE CRITERIA

In addition to a baseline bone marrow biopsy, bone marrow biopsy samples from the participant's previous biopsy procedures will be requested from outside institutions: a formalin-fixed paraffin-embedded (FFPE) block or 10 unstained slides from initial MDS diagnosis, and an FFPE block from the most recent MDS biopsy prior to the participant arriving at NCI. These archival samples will be used to reconfirm the MDS diagnosis by NIH pathology department.

Participants will be assessed for response by standard response criteria for MDS.[85] For the purposes of this study, participants will be re-evaluated for response after each cycle by CBC with differential to assess for improvement in cytopenias and by protocol-defined time points for bone marrow evaluation. If results from interim bone marrow assessment demonstrate progression of disease (as defined by an increase in the number of malignant cells or blasts when compared to pre-treatment bone marrow examination or worsening cytopenias by amounts as defined below in section **6.3.1**), the subject will be taken off study.

Participants with ECOG performance status if 0-2 who fail to achieve a CR but have achieved a PR, SD, or hematologic improvement will be eligible for receive additional therapy if no other contraindications to further treatment.

6.3.1 Response Criteria

The table below shows the 2006 International Working Group response criteria for altering the natural history of MDS,[111] with modified definitions for HI-E, HI-P, and HI-N in the suggested 2018 International Working Group response criteria.[85]

Category	**Response criteria** (responses must last at least 4 weeks)

Complete remission	• Bone marrow: ≤5% myeloblasts with normal maturation of all cell lines*
	• Persistent dysplasia will be noted*
	• Peripheral blood†
	  ◦ Hgb ≥11 g/dL
	  ◦ Platelets ≥100 X 10^9/L
	  ◦ Neutrophils ≥1.0 X 10^9/L
	  ◦ Blasts 0%

Partial remission	All CR criteria if abnormal before treatment except: • Bone marrow blasts decreased by ≥50% over pretreatment but still >5% • Cellularity and morphology not relevant
Marrow CR	• Bone marrow: ≤5% myeloblasts and decrease by ≥50% over pretreatment • Peripheral blood: if HI responses, they will be noted in addition to marrow CR

Stable disease	Failure to achieve at least PR, but no evidence of progression for >8 wks
Failure	Death during treatment or disease progression characterized by worsening of cytopenias, increase in percentage of bone marrow blasts, or progression to more advanced MDS FAB subtype than pre-treatment
Relapse after CR or PR	At least 1 of the following: • Return to pre-treatment bone marrow blast percentage • Decrement of ≥50% from maximum remission/response levels in granulocytes or platelets • Reduction in Hgb concentration by ≥1.5 g/dL or transfusion dependence
Cytogenetic response	Complete • Disappearance of the chromosomal abnormality without appearance of new ones Partial • At least 50% reduction of the chromosomal abnormality
Disease progression	For participants with: • Less than 5% blasts: ≥50% increase in blasts to >5% blasts • 5%-10% blasts: ≥50% increase to 10% blasts • 10%-20% blasts: ≥50% increase to >20% blasts • 20%-30% blasts: ≥50% increase to >30% blasts Any of the following: • At least 50% decrement from maximum remission/response in granulocytes or platelets • Reduction in Hgb by ≥2 g/dL • Transfusion dependence
Survival	Endpoints: • Overall: death from any cause • Event free: failure or death from any cause • PFS: disease progression or death from MDS • DFS: time to relapse • Cause-specific death: death related to MDS

MDS, myelodysplastic syndromes; Hgb, hemoglobin; CR, complete remission; HI, hematologic improvement; PR, partial remission; FAB, French-American-British; AML, acute myeloid leukemia; PFS, progression-free survival; DFS, disease-free survival.
To convert hemoglobin from grams per deciliter to grams per liter, multiply grams per deciliter by 10.
*Dysplastic changes should consider the normal range of dysplastic changes.
†In some circumstances, protocol therapy may require the initiation of further treatment (eg, consolidation, maintenance) before the 4-week period. Such participants can be included in the response category into which they fit at the time the therapy is started. Transient cytopenias during repeated chemotherapy courses should not be considered as interrupting durability of response, as long as they recover to the improved counts of the previous course.

Hematologic Improvement

Category	Participant pre-trial baseline	Response criteria

<table>
<tr><td rowspan="4">Erythroid response (HI-E)</td><td>No Transfusion Dependence at baseline (0 RBC transfusions in 16 weeks)</td><td colspan="2">At least 2 consecutive Hgb measurements ≥1.5 g/dL for a period of minimum 8 weeks in an observation period of 16 to 24 weeks compared with the lowest mean of 2 Hgb measurements (apart from any transfusion) within 16 weeks before treatment onset; only a response duration of at least 16 weeks, however, is considered clinically meaningful</td></tr>
<tr><td>Low Transfusion Dependence at baseline (3-7 RBC transfusions in 16 weeks in at least 2 transfusion episodes, maximum 3 in 8 weeks)</td><td colspan="2">Transfusion independence, defined by the absence of any transfusions for at least 8 weeks in an observation period of 16-24 weeks with the same transfusion policy compared with 16 weeks prior to treatment; only a response duration of at least 16 weeks, however, is considered clinically meaningful</td></tr>
<tr><td rowspan="2">High Transfusion Dependence at baseline (≥8 RBC transfusions in 16 weeks, ≥ 4 transfusion episodes in 8 weeks)</td><td>Major response</td><td>Transfusion independence, defined by the absence of any transfusions over a period of minimum 8 weeks in an observation period of 16-24 weeks with the same transfusion policy compared with 16 weeks prior to treatment; only a response duration of at least 16 weeks, however, is considered clinically meaningful</td></tr>
<tr><td>Minor response</td><td>Transfusion independence, defined by the absence of any transfusions over a period of minimum 8 weeks in an observation period of 16-24 weeks with the same transfusion policy compared with 16 weeks prior to treatment; only a response duration of at least 16 weeks, however, is considered clinically meaningful</td></tr>
<tr><td>Platelet response (HI-P)</td><td>Pre-treatment PLT <100 x 10^9/L</td><td colspan="2">• Absolute increase of 30 x 10^9/L for participants starting with >20 x 10^9/L PLTs
or
• Increase from <20 x 10^9/L to >20 x 10^9/L and by at least 100%
In addition:</td></tr>
</table>

		• In addition, evolution of bleeding symptoms is to be taken into account • Increments of platelets also for participants with a pre-treatment PLT count of ≥100 x 10^9 are to be reported
Neutrophil response (HI-N)	Pre-treatment ANC <1.0 x 10^9/L	• At least 100% increase and an absolute increase >0.5 x 10^9/L • Increments of neutrophils also for participants with a pre-treatment ANC of ≥1.0 x 10^9/L are to be reported

6.4 TOXICITY CRITERIA

The following adverse event management guidelines are intended to ensure the safety of each participant while on the study. 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).

7 NIH REPORTING REQUIREMENTS / DATA AND SAFETY MONITORING PLAN

7.1 DEFINITIONS

Please refer to definitions provided in Policy 801: Reporting Research Events found at: https://irbo.nih.gov/confluence/pages/viewpage.action?pageId=36241835#Policies&Guidance-800Series-ComplianceandResearchEventReportingRequirements.

7.2 OHSRP OFFICE OF COMPLIANCE AND TRAINING / IRB REPORTING

7.2.1 Expedited Reporting

Please refer to the reporting requirements in Policy 801: Reporting Research Events and Policy 802 Non-Compliance Human Subjects Research found at: https://irbo.nih.gov/confluence/pages/viewpage.action?pageId=36241835#Policies&Guidance-800Series-ComplianceandResearchEventReportingRequirements. Note: Only IND Safety Reports that meet the definition of an unanticipated problem will need to be reported per these policies.

7.2.2 IRB Requirements for PI Reporting at Continuing Review

Please refer to the reporting requirements in Policy 801: Reporting Research Events found at: https://irbo.nih.gov/confluence/pages/viewpage.action?pageId=36241835#Policies&Guidance-800Series-ComplianceandResearchEventReportingRequirements.

7.3 NCI CLINICAL DIRECTOR REPORTING

Problems expeditiously reviewed by the OHSRP in the NIH eIRB system will also be reported to the NCI Clinical Director/designee; therefore, a separate submission for these reports is not necessary.

In addition to those reports, all deaths that occur within 30 days after receiving a research intervention should be reported via email unless they are due to progressive disease.

To report these deaths, please send an email describing the circumstances of the death to NCICCRQA@mail.nih.gov within one business day of learning of the death.

7.4 NIH Required Data and Safety Monitoring Plan

7.4.1 Principal Investigator/Research Team

The clinical research team will meet on a regular weekly basis when participants are being actively treated on the trial to discuss each participant. Decisions about dose level enrollment and dose escalation if applicable will be made based on the toxicity data from prior participants.

All data will be collected in a timely manner and reviewed by the principal investigator or a lead associate investigator. Events meeting requirements for expedited reporting as described in section **7.2.1** will be submitted within the appropriate timelines.

The principal investigator will review adverse event and response data on each participant to ensure safety and data accuracy. The principal investigator will personally conduct or supervise the investigation and provide appropriate delegation of responsibilities to other members of the research staff.

8 SPONSOR PROTOCOL/SAFETY REPORTING

8.1 Definitions

8.1.1 Adverse Event

Any untoward medical occurrence in a participant or clinical investigation subject administered a pharmaceutical product and which does not necessarily have a causal relationship with this treatment. An adverse event (AE) can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal (investigational) product, whether or not related to the medicinal (investigational) product. (ICH E6 (R2))

8.1.2 Serious Adverse Event (SAE)

An adverse event or suspected adverse reaction is considered serious if in the view of the investigator or the sponsor, it results in any of the following:

- Death
- A life-threatening adverse event (see section **8.1.3**)
- Inpatient hospitalization or prolongation of existing hospitalization
    - A hospitalization/admission that is pre-planned (i.e., elective or scheduled surgery arranged prior to the start of the study), a planned hospitalization for pre-existing condition, or a procedure required by the protocol, without a serious deterioration in health, is not considered a serious adverse event.

  - A hospitalization/admission that is solely driven by non-medical reasons (e.g., hospitalization for participant or subject convenience) is not considered a serious adverse event.
  - Emergency room visits or stays in observation units that do not result in admission to the hospital would not be considered a serious adverse event. The reason for seeking medical care should be evaluated for meeting one of the other serious criteria.
- Persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions
- A congenital anomaly/birth defect
- Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered a serious adverse drug experience when, based upon appropriate medical judgment, they may jeopardize the participant or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition.

8.1.3 Life-threatening

An adverse event or suspected adverse reaction is considered "life-threatening" if, in the view of either the investigator or sponsor, its occurrence places the participant or subject at immediate risk of death. It does not include an adverse event or suspected adverse reaction that, had it occurred in a more severe form, might have caused death. (21CFR312.32)

8.1.4 Severity

The severity of each Adverse Event will be assessed utilizing the CTCAE version 5.0.

8.1.5 Relationship to Study Product

All AEs will have their relationship to study product assessed using the terms: related or not related.

- Related – There is a reasonable possibility that the study product caused the adverse event. Reasonable possibility means that there is evidence to suggest a causal relationship between the study product and the adverse event.

- Not Related – There is not a reasonable possibility that the administration of the study product caused the event.

8.1.6 Adverse Events of Special Interest (AESI)

- Potential Drug Induced Liver Injury (DILI), positive Hy's Law, defined as:
  - AT (ALT or AST) elevation > 3 times upper limit of normal (ULN), AND
  - Total bilirubin > 2 times ULN, without initial findings of cholestasis (elevated serum alkaline phosphatase), AND
  - No other immediately apparent possible causes of AT 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.

8.2 ASSESSMENT OF SAFETY EVENTS

AE information collected will include event description, date of onset, assessment of severity and relationship to study product and alternate etiology (if not related to study product), date of resolution of the event, seriousness and outcome. The assessment of severity and relationship to the study product will be done only by those with the training and authority to make a diagnosis and listed on the Form FDA 1572 as the site principal investigator or sub-investigator. AEs occurring during the collection and reporting period will be documented appropriately regardless of relationship. AEs will be followed through resolution.

SAEs will be:

- Assessed for severity and relationship to study product and alternate etiology (if not related to study product) by a licensed study physician listed on the Form FDA 1572 as the site principal investigator or sub-investigator.
- Recorded on the appropriate SAE report form, the medical record and captured in the clinical database.
- Followed through resolution by a licensed study physician listed on the Form FDA 1572 as the site principal investigator or sub-investigator.

For timeframe of recording adverse events, please refer to section **6.1**. All serious adverse events recorded from the time of first investigational product administration must be reported to the sponsor with the exception of any listed in section **8.4**.

8.3 REPORTING OF SERIOUS ADVERSE EVENTS

Any AE that meets protocol-defined serious criteria or meets the definition of Adverse Event of Special Interest that require expedited reporting must be submitted immediately (within 24 hours of awareness) to OSRO Safety using the CCR SAE report form. Any exceptions to the expedited reporting requirements are found in section **8.4**.

All SAE reporting must include the elements described in section **8.2**.

SAE reports will be submitted to the Center for Cancer Research (CCR) at: OSROSafety@mail.nih.gov and to the CCR PI and study coordinator. CCR SAE report form and instructions can be found at: https://ccrod.cancer.gov/confluence/display/CCRCRO/Forms+and+Instructions

Following the assessment of the SAE by OSRO, other supporting documentation of the event may be requested by the OSRO Safety and should be provided as soon as possible.

8.4 WAIVER OF EXPEDITED REPORTING TO CCR

As death/hospitalization due to disease progression are part of the study objectives in the phase 2 portion of the study (PFS, OS, ORR), and captured as an endpoint in this study, they will not be reported in expedited manner to the sponsor during the phase II portion of the study. However, if there is evidence suggesting a causal relationship between the study drug and the event, report the event in an expedited manner according to section **8.3**.

8.5 SAFETY REPORTING CRITERIA TO THE PHARMACEUTICAL COLLABORATOR

Note: The PI/study team designee will be required to handle all reporting noted below to the pharmaceutical collaborator.

- For Non-Serious AEs:
  - Adverse Events that are routinely collected according to GCP shall be submitted to BMS every three (3) months by the last working day of the third month.
  - The collection of non-serious AE information should begin following the subject's study drug administration. 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 100 days following the last dose of study treatment, except for Grade 1 AEs, which will be collected and recorded for first 30 days on study only.
  - 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.

- For Serious Adverse Events (SAEs):
  - All SAEs that occur following the subject's study drug administration through (100) days of discontinuation of dosing must be reported to BMS Worldwide Safety, whether related or not related to study drug.
  - An SAE report should be completed for any event where doubt exists regarding its seriousness
  - If the investigator believes that an SAE is not related to study drug, but is potentially related to the conditions of the study (such as withdrawal of previous therapy or a complication of a study procedure), the relationship should be specified in the narrative section of the SAE Report Form.
  - An appropriate SAE form (e.g. ex-US = CIOMS form or USA = Medwatch form) should be used to report SAEs to BMS. Note: Please include the BMS Protocol number on the SAE form or on the cover sheet with the SAE form transmission.
  - For studies with long-term follow-up periods in which safety data are being reported, include the timing of SAE collection.
  - The Sponsor will reconcile the clinical database AE cases (case level only) transmitted to BMS Global Pharmacovigilance (Worldwide.Safety@bms.com).
  - The Investigator will request from BMS GPV&E, aepbusinessprocess@bms.com the SAE reconciliation report and include the BMS protocol number every 3 months and prior to data base lock or final data summary
  - GPV&E will send the investigator the report to verify and confirm all SAEs have been transmitted to BMS GPV&E.
    - The data elements listed on the GPV&E reconciliation report will be used for case identification purposes. If the Investigator determines a case was not transmitted to BMS GPV&E, the case should be sent immediately to BMS (Worldwide.Safety@bms.com).

- In addition to the Sponsor Investigator's responsibility to report events to their local HA, suspected serious adverse reactions (whether expected or unexpected) shall be reported by BMS to the relevant competent health authorities in all concerned countries according to local regulations (either as expedited and/or in aggregate reports).
- In accordance with local regulations, BMS will notify sponsor investigators of all reported SAEs that are suspected (related to the investigational product) and unexpected (ie, 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.
- Other important findings which may be reported by BMS as an Expedited Safety Report (ESR) include: increased frequency of a clinically significant expected SAE, an SAE considered associated with study procedures that could modify the conduct of the study, lack of efficacy that poses significant hazard to study subjects, clinically significant safety finding from a nonclinical study, , or sponsor or BMS decision to end or temporarily halt a clinical study for safety reasons.
    - Upon receiving an ESR from BMS, the investigator must review and retain the ESR with the IB. Where required by local regulations or when there is a central IRB/IEC for the study, the sponsor will submit the ESR to the appropriate IRB/IEC. The investigator and IRB/IEC will determine if the informed consent requires revision. The investigator should also comply with the IRB/IEC procedures for reporting any other safety information.

SAEs, whether related or not related to study drug, and pregnancies must be reported to BMS within 24 hours \ 1 Business Day of becoming aware of the event. SAEs must be recorded on either CIOMS, MedWatch, or approved site SAE form.

- Pregnancies must be reported and submitted to BMS. BMS will perform due diligence follow-up using the BMS Pregnancy Form which the investigator must complete.
    - SAE Email Address: Worldwide.Safety@BMS.com
    - SAE Facsimile Number: +1 609-818-3804
- If only limited information is initially available, follow-up reports are required. (Note: Follow-up SAE reports should include the same investigator term(s) initially reported.)
- If an ongoing SAE changes in its intensity or relationship to study drug or if new information becomes available, a follow-up SAE report should be sent within 24 hours \ 1 Business Day to BMS using the same procedure used for transmitting the initial SAE report.

BMS Safety Reporting. Study Team shall report to BMS all Serious Adverse Events. Reports shall be provided in accordance with applicable federal laws. Study Team shall comply with BMS's reasonable follow-up requests.

- Case-level Reconciliation.
    - Study Team shall perform case-level reconciliation as instructed by BMS to confirm BMS's receipt of all reports from Study Team. Study Team shall initiate

reconciliation activity by e-mailing AEPBUSINESSPROCESS@BMS.com to request a reconciliation report.
    - Such reconciliation shall be performed quarterly, unless otherwise agreed by BMS in writing.
- Study Team shall comply with all applicable federal laws, including those related to data privacy, when undertaking these safety reporting-related obligations.
- Study Team shall promptly report to BMS all Product Quality Complaints (as defined at http://www.globalbmsmedinfo.com) associated with a BMS product no later than one (1) business day or three (3) calendar days, whichever is earlier after becoming aware of the event. Study Team shall report the information to IMPQualityComplaints@bms.com.

8.6 REPORTING PREGNANCY

All required pregnancy reports/follow-up to OSRO will be submitted to: OSROSafety@mail.nih.gov and to the CCR PI and study coordinator. Forms and instructions can be found here: https://ccrod.cancer.gov/confluence/display/CCRCRO/Forms+and+Instructions

8.6.1 Maternal exposure

If a participant becomes pregnant during the course of the study, the study treatment should be discontinued immediately, and the pregnancy reported to the Sponsor no later than 24 hours of when the Investigator becomes aware of it. The Investigator should notify the Sponsor no later than 24 hours of when the outcome of the Pregnancy becomes known,

Pregnancy itself is not regarded as an SAE. However, congenital abnormalities or birth defects and spontaneous miscarriages that meet serious criteria (section **8.1.2**) should be reported as SAEs.

The outcome of all pregnancies should be followed up and documented.

If, following initiation of the investigational product, it is subsequently discovered that a study participant is pregnant or may have been pregnant at the time of investigational product exposure, including during at least 5 half-lives after product administration, the investigational product will be permanently discontinued in an appropriate manner (eg, dose tapering if necessary for participant).

The investigator must immediately notify Worldwide.Safety@bms.com of this event and complete one of the following forms within 24 hours of awareness of the event via either the CIOMS, MedWatch or appropriate Pregnancy Surveillance Form in accordance with SAE reporting procedures.

Protocol-required procedures for study discontinuation and follow-up must be performed on the participant.

8.6.2 Paternal exposure

Male participants should refrain from fathering a child or donating sperm during the study and for 6 months after the last dose of BMS-986253 or DNMTi.

Pregnancy of the participant's partner is not considered to be an AE. However, the outcome of all pregnancies occurring from the date of the first dose until 6 months after the last dose should,

if possible, be followed up and documented. Pregnant partners may be offered the opportunity to participate in an institutional pregnancy registry protocol (e.g., the NIH IRP pregnancy registry study) to provide data about the outcome of the pregnancy for safety reporting purposes.

8.7 REGULATORY REPORTING FOR STUDIES CONDUCTED UNDER CCR-SPONSORED IND

Following notification from the investigator, CCR, the IND sponsor, will report any suspected adverse reaction that is both serious and unexpected. CCR will report an AE as a suspected adverse reaction only if there is evidence to suggest a causal relationship between the study product and the adverse event. CCR will notify FDA and all participating investigators (i.e., all investigators to whom the sponsor is providing drug under its INDs or under any investigator's IND) in an IND safety report of potential serious risks from clinical trials or any other source, as soon as possible, in accordance to 21 CFR Part 312.32.

All serious events will be reported to the FDA at least annually in a summary format.

8.8 SPONSOR PROTOCOL DEVIATION REPORTING

A Protocol Deviation is defined as any non-compliance with the clinical trial Protocol, Manual of Operational Procedures (MOP) and other Sponsor approved study related documents, GCP, or protocol-specific procedural requirements on the part of the participant, the Investigator, or the study site staff inclusive of site personnel performing procedures or providing services in support of the clinical trial.

It is the responsibility of the study Staff to document any protocol deviation identified by the Staff or the site Monitor in the CCR Protocol Deviation Tracking System (PDTS) online application. The entries into the PDTS online application should be timely, complete, and maintained per CCR PDTS user requirements.

In addition, any deviation to the protocol should be documented in the participant's source records and reported to the reviewing IRB per their guidelines. OSRO required protocol deviation reporting is consistent with E6(R2) GCP: Integrated Addendum to ICH E6(R1): 4.5 Compliance with Protocol; 5.18.3 (a), and 5.20 Noncompliance; and ICH E3 16.2.2 Protocol deviations.

9 CLINICAL MONITORING

Clinical site monitoring is conducted to ensure:

- that the rights of the participants are protected;
- that the study is implemented per the approved protocol, Good Clinical Practice and standard operating procedures; and
- the quality and integrity of study data and data collection methods are maintained.

Monitoring for this study will be performed by NCI CCR Office of Sponsor and Regulatory Oversight (OSRO) Sponsor and Regulatory Oversight Support (SROS) Services contractor. Clinical site monitoring activities will be based on OSRO standards, FDA Guidance E6(R2) Good Clinical Practice: Integrated Addendum to ICH E6(R1) March 2018, and applicable regulatory requirements.

Details of clinical site monitoring will be documented in a Clinical Monitoring Plan (CMP) developed by OSRO. CMPs will be protocol-specific, risk-based and tailored to address human

subject protections and integrity of the study data. OSRO will determine the intensity and frequency of monitoring based on several factors, including study type, phase, risk, complexity, expected enrollment rate, and any unique attributes of the study and the site. The Sponsor will conduct a periodic review of the CMP to confirm the plan's continued appropriateness. A change to the protocol, significant or pervasive non-compliance with GCP, or the protocol may trigger CMP updates.

OSRO SROS Monitoring visits and related activities will be conducted throughout the life cycle of each protocol. The first activity is before the study starts to conduct a Site Assessment Visit (SAV) (as warranted), followed by a Site Initiation Visit (SIV), Interim Monitoring Visit(s) (IMVs), and a study Close-Out Visit (COV).

Some monitoring activities may be performed remotely, while others will occur at the study site(s). Monitoring visit reports will describe visit activities, observations, and associated action items or follow-up required for resolution of any issues, discrepancies, or deviations. Monitoring reports will be distributed to the study PI, NCI CCR QA, CCR Protocol Support Office, coordinating center (if applicable), and the Sponsor regulatory file.

The site Monitor will inform the study team of any deviations observed during monitoring visits. If unresolved, the Monitor will request that the site Staff enter the deviations in the CCR Protocol Deviation Tracking System (PDTS) for deviation reporting to the Sponsor and as applicable per institutional and IRB guidance.

10 STATISTICAL CONSIDERATIONS

10.1 OBJECTIVES AND ENDPOINTS

OBJECTIVES	ENDPOINTS	JUSTIFICATION FOR ENDPOINTS
Primary		
Phase I: To determine OBD for BMS-986253 and RP2D, separately by cohort.	-Incidence of AEs, SAEs -AEs meeting protocol defined DLT criteria -AEs leading to discontinuation, death, and laboratory abnormalities. - OBD (RP2D) assessed during the first 30 days of treatment: - OBD will be the safest and lowest dose level showing optimal biological activity, defined as maximal suppression of serum free IL-8 levels.* *Maximal suppression of serum free IL-8 levels will be monitored for a	standard endpoint for phase I protocol, see Section 3.1.1 Due to this being a targeted therapy, will pursue OBD instead of MTD as primary endpoint.

OBJECTIVES	ENDPOINTS	JUSTIFICATION FOR ENDPOINTS
	goal of achieving IL-8 levels below the lower limit of detection of the assay in real time as outlined in Section **5.1.3.2** [ultrasensitive immunoassay based on Quanterix Simoa technology (lower limit of quantification = 0.86 pg/mL) by Myriad-RBM]	
Phase II: To determine efficacy as measured by overall response rate, separately by cohort.	-ORR per each cohort -assessed from first cycle until time of disease relapse, disease progression, or death, whichever occurs first, assessed every 3-6 months until 8 years.	Efficacy evaluation, standard for phase II protocol
Secondary		
Phase 1: To describe pharmacokinetic properties of BMS-986253 in MDS participants by cohort.	AUC, half-life, and steady state concentration Assessed during the first 30 days of treatment	Pharmacokinetic studies to evaluates for adequate absorption of therapy and define half-life/AUC and other properties of the study drug
Phase II: To evaluate safety and secondary clinical outcomes of BMS-986253 in MDS participants by cohort.	-Safety, as measured by: Incidence of AEs, SAEs; and AEs leading to discontinuation, death, and laboratory abnormalities, assessed from first cycle until time of disease relapse, disease progression, or death, whichever occurs first, assessed every 3-6 months - Clinical outcomes including: overall improvement rate (OIR), cytogenetic response rate, time to best response (CR, PR, marrow CR, or HI) , disease free survival (DFS: definition: time to relapse for participants who achieve CR), progression free survival (PFS; definition: disease progression or	Confirm safety and evaluate efficacy through long-term clinical outcomes

OBJECTIVES	ENDPOINTS	JUSTIFICATION FOR ENDPOINTS
	death from MDS), leukemia free survival (LFS; definition: progression to AML or death from any cause), and overall survival (OS: definition: death from any cause); assessed every 3-6 months	
Exploratory		
To evaluate changes in serum cytokine levels pre- and post-treatment with BMS-986253.	Each of these will be evaluated using descriptive methods and reported as exploratory results. If any statistical tests are performed in these analyses, the results will be presented without adjustment for multiple comparisons but reported in the context of the number of tests performed. See section **5** for collection timepoints.	Evaluate mechanistic and immunologic effects of the study drug
To evaluate the cell composition in the peripheral blood and bone marrow microenvironment before and after treatment with BMS-986253.		
To evaluate changes in the transcriptome and proteome in response to treatment with BMS-986253.		
To determine the degree of bone marrow myeloid-derived suppressor cell (MDSC) infiltration.		
To describe changes in genetic clonal diversity during treatment with BMS-986253 in combination with DNMTi.		
To assess cell-autonomous effects on the MDS clone by measuring biomarkers in the Akt pathway (i.e. pS743) in MDS blasts.		
To evaluate cell-autonomous and microenvironment dependent		

OBJECTIVES	ENDPOINTS	JUSTIFICATION FOR ENDPOINTS
activity of BMS-986253 using ex vivo culture of participant-derived hematopoietic stem and progenitor cells.		
To assess quality of life improvement by participant reported outcomes using the EORTC QLQC30 score.		

10.2 SAMPLE SIZE DETERMINATION

The trial will begin with a phase I dose escalation phase using a standard 3+3 design to determine OBD, separately for each cohort. With 3 dose levels per cohort (and dose level -1), and no more than 6 participants per dose level, up to 18 participants may be enrolled in phase I per cohort, total 36 maximum.

In phase I/II, there will be two cohorts:

1. "Higher-risk" MDS (HR-MDS) Cohort with R-IPSS ≥3.5: Intermediate and high-risk participants receiving combination treatment
2. "Lower-risk" MDS (LR-MDS) Cohort with R-IPSS <3.5: Lower intermediate and low-risk participants receiving single agent anti-IL8 treatment.

Based on the literature, DNMTi previously untreated participants with intermediate and high-risk disease have clinical response rates of approximately 20-50%; thus, in view of heterogeneity of prior results a response rate of at least 40% in participants treated with combination therapy would be desirable. [75, 112] In participants with low-risk disease, response rates are likely to be lower, and expected to be less than 30% from monotherapy;[84, 91, 92] thus, also attaining a response rate of at least 30% with monotherapy would be considered desirable.

Participants enrolled during phase I who are treated at the OBD may be included in the first stage portion of the trial if they meet the same eligibility as the participants in the phase II portion.

The two phase II cohorts will each have their own sample size determination:

- In participants in the higher-risk HR-MDS cohort (with either intermediate or high-risk MDS), the trial will be conducted using a Simon optimal two-stage phase II trial design to rule out an unacceptably low response rate (CR+PR+mCR with HI) of 30% (p0=0.30) in favor of an improved response rate of 50% (p1=0.50) in order to determine if the combination will be able to potentially improve upon heterogeneous 20-50% response rates in participants who have received other agents. [75, 112] With alpha=0.10 (probability of accepting a poor treatment=0.10) and beta=0.20 (probability of rejecting a good treatment=0.20), the first stage will enroll 15 evaluable participants, including the 6 participants from the phase I dose escalation that reached OBD, and if 0 to 5 of the 15 has

a response, then no further participants will be accrued. If 6 or more of the first 15 participants has a response, then accrual would continue until a total of 32 evaluable participants have been treated in that cohort. As it may take up to several months to determine if a participant has experienced a response, a temporary pause in the accrual may be necessary to ensure that enrollment to the second stage is warranted. If there are only 6-12 participants with a response out of 32 participants, this would be an uninterestingly low response rate. If there were 13 or more of 32 (40.6%) who experienced a response, treatment in this cohort would be sufficiently interesting to warrant further study in later trials. Under the null hypothesis (30% response rate), the probability of early termination is 72.2%.

- In participants with low-risk MDS, the trial will be conducted using a Simon optimal two-stage phase II trial design to rule out an unacceptably low response rate (CR+PR+mCR with HI) of 20% (p0=0.20) in favor of an improved response rate of 40% (p1=0.40) in order to determine if monotherapy with BMS-986253 will be able to improve upon an expected response rate below 30% in participants who have received other agents. [76, 83, 84] With alpha=0.10 (probability of accepting a poor treatment=0.10) and beta=0.20 (probability of rejecting a good treatment=0.20), the first stage will enroll 12 evaluable participants, including the 6 participants from the phase I dose escalation, that reached MTD, and if 0 to 2 of the 12 has a response, then no further participants will be accrued. If 3 or more of the first 12 participants has a response, then accrual would continue until a total of 25 evaluable participants have been treated in that cohort. As it may take up to several months to determine if a participant has experienced a response, a temporary pause in the accrual may be necessary to ensure that enrollment to the second stage is warranted. If there are only 3-7 participants with a response out of 25 participants, this would be an uninterestingly low response rate. If there were 8 or more of 25 (32.0%) who experienced a response, treatment in the appropriate cohort would be sufficiently interesting to warrant further study in later trials. Under the null hypothesis (20% response rate), the probability of early termination is 55.8%.

Secondary endpoints include progression free survival, overall survival, median survival, duration of response, and leukemia free survival. These will be determined separately in each of the phase II cohorts. Overall survival is considered an important endpoint in these participants and will be considered the most important secondary endpoint.

It is expected that up to 12-15 participants with MDS may be accrued per year. Thus, in order to accrue up to 18+18+32+25 = 93 participants, it is expected that 4-5 years may be required to accrue the total number of required evaluable participants. In order to allow for a small number of inevaluable participants and potentially large number of screen failures, the accrual ceiling will be set at 200 participants.

10.3 POPULATIONS FOR ANALYSES

10.3.1 Evaluable for toxicity

All participants will be evaluable for toxicity from the time of their first treatment with BMS-986253.

10.3.2 Evaluable for objective response

Only those participants who have measurable disease present at baseline, have received at least one cycle of therapy with study drug, and have had their disease re-evaluated will be considered evaluable for response. These participants will have their response classified according to the definitions stated below. (Note: Participants who exhibit objective disease progression prior to the end of cycle 1 will also be considered evaluable.)

10.4 STATISTICAL ANALYSES

10.4.1 General Approach

- Participants in phase I will be evaluated for safety, reporting the toxicities noted per dose level.
- Participants in phase II will have their response rate reported along with a confidence interval.

10.4.2 Analysis of the Primary Endpoints

- Participants enrolled in phase I will have the grades and types of toxicity reported at each dose level separately by cohort. The overall estimate of the fraction of participants who have a DLT at the OBD will be reported by cohort.
- Participants evaluated in phase II will have the fraction with clinical responses reported separately by cohort, with a separate 95% confidence interval for each cohort.

10.4.3 Analysis of the Secondary Endpoint(s)

- The secondary objectives for phase I are to describe pharmacokinetic properties of BMS-986253 in MDS participants and to evaluate safety and tolerability of BMS-986253 in MDS participants. The AUC, half-life, and Css of BMS-986253 will be evaluated in participants, separately by dose level and cohort using descriptive statistics.
- The secondary objectives for phase II are:
- (a) to evaluate the safety and tolerability of the agent as measured by the grades and types of toxicity noted for the agent at each dose level, separately by cohort; and,
- (b) to evaluate efficacy, as measured by clinical outcomes, including OIR (CR + PR + HI + marrow CR + SD), cytogenetic response rate, time to best response, disease free survival (DFS; definition: time to relapse for participants who achieve CR), progression free survival (PFS; definition: disease progression or death from MDS), leukemia free survival (LFS; definition: progression to AML or death from any cause), and overall survival (OS; definition: death from any cause).
    - OIR and cytogenic response rate will each be reported as a fraction, separately by cohort, along with a 95% confidence interval. Time to best response, DFS, PFS, LFS, and OS will be evaluated separately for each phase II cohort using the Kaplan-Meier method. In each case, the median time to event will be reported along with a 95% confidence interval for the median.

10.4.4 Safety Analyses

The safety and tolerability of the agent will be evaluated by reporting the grades and types of toxicity noted for the agent at each dose level.

Our goal toxicity rate is less than 20% and toxicity assessment will use Bayesian toxicity monitoring with maximum probability of DLT of 0.2, prior distribution (1,1), maximum patients 32, minimum number of patients before stopping 6, cohort size 1, and posterior probability > 80%. Using this approach, the study would be paused for review for toxicities in 2/6, 3/7, or 4/11, 5/15, 6/20, 7/24, 8/28, or 9/32 patients. The same boundaries would apply to both the LR-MDS and HR-MDS cohorts up to their respective enrollment goals.

10.4.5 Baseline Descriptive Statistics

Standard sample statistics will be provided for each cohort and overall.

10.4.6 Planned Interim Analyses

As indicated above in section **10.2**, Participants in phase II will be evaluated after 15 or 12 participants have been treated per cohort, an evaluation will be performed of the responses at that point to determine suitability to enroll the remaining participants. Specifically, the trial will proceed to the second stage if there is at least 1 of 6 responses in patients with MDS. With a safety evaluation through day 28 required for the interim analysis in each cohort, enrollment to the cohort will be halted to allow for an analysis by the study statistician. A brief memo will be created by the study statistician to document the number of responses in the first stage for each cohort and will be reviewed by the PI and study team. The memo will be provided to study sponsor prior to continuation of accrual. Also, if the required number of responses is observed before that time, the memo will be generated, reviewed and provided to the study sponsor at that point without a pause in accrual. Response rates will be calculated using the revised International Working Group (IWG) 2018 response criteria as described in the protocol.

10.4.7 Sub-Group Analyses

Results from phase II will be presented according to MDS-subgroup, disease risk category and genomic features.

10.4.8 Tabulation of individual Participant Data

None will be provided.

10.4.9 Exploratory Analyses

The exploratory objectives and methods of analysis include:

- To evaluate changes in serum cytokine levels pre- and post-treatment with BMS-986253; this will be a descriptive analysis and may be accompanied by Wilcoxon signed rank tests for phase II data, by cohort.
- To evaluate the cell composition in the peripheral blood and bone marrow microenvironment before and after treatment with BMS-986253; this will be a descriptive analysis.
- To determine the degree of myeloid-derived suppressor cell (MDSC) infiltration; this will be a descriptive analysis.

- To describe changes in genetic clonal diversity during treatment with BMS-986253 in combination with DNMTi; this will be descriptive.
- To assess cell-autonomous effects on the MDS clone by measuring biomarkers in the Akt pathway (i.e. pS743) in MDS blasts; this will be descriptive.
- To assess quality of life improvement by participant reported outcomes using the EORTC QLQC30 score; this will be analyzed using standard methods for evaluating these outcomes.

All exploratory analyses will be performed with descriptive intent, largely done separately by cohort. In the cases in which a statistical test is performed, the tests will be done without formal adjustment for multiple comparisons, but in the context of the number of tests performed.

11 COLLABORATIVE AGREEMENTS

11.1 COOPERATIVE RESEARCH AND DEVELOPMENT AGREEMENT (CRADA)

This study will be conducted under a Collaborative Research and Development Agreement (CRADA) with Bristol Myers Squibb (pending).

12 HUMAN SUBJECTS PROTECTIONS

12.1 RATIONALE FOR SUBJECT SELECTION

No subjects will be excluded from participation based on gender, race or ethnicity. The study will be open to all subjects who satisfy the inclusion criteria and provide an informed consent to the protocol.

12.2 PARTICIPATION OF CHILDREN

Children will not be eligible for participation in this study due to lack of adequate safety data in children. Biologic rationale and preclinical work were validated in adult population and would need reanalysis in children, where MDS may arise more so from inherited bone marrow failure syndromes than in adults and have a different pathophysiology.

12.3 RISK/BENEFIT ASSESSMENT

12.3.1 Known Potential Risks

- All known potential risks associated with BMS-986253 from prior experience in humans has been discussed in Section **14**. No prior history of infusion reactions have been reported in prior studies of this product. SAEs in prior trials (See Section **14** for toxicity data) have mostly been deemed not-treatment related, but of course there is an unknown element here which is why this is a phase I safety study and participants will be closely monitored for all AEs.
- Other risks involved in the study include that of standard MDS procedures, including regular blood draws and bone marrow evaluations. These are invasive procedures that carry with them the risk of infection, bleeding and damage to surrounding tissues/organs. Phlebotomy and bone marrow evaluations will be conducted by well-trained personnel who follow sterile techniques to minimize complications.

Due to the unknown effects of BMS-986253 on the fetus and infants, women of reproductive age will only be allowed to enroll if they commit to following a strict manner of contraception; Women who are breast-feeding will not be eligible for the trial. Men who are sexually active with women of childbearing age will also have to commit to strict contraceptive practices while on study.

12.3.1.1 Procedure risks

12.3.1.1.1 Blood samples

Side effects of repeated blood sampling depend in part on how the blood is drawn. If through an intravenous catheter, risks include contamination of the catheter which would result in a serious blood stream infection, requiring admission to the hospital and giving participants antibiotics through the vein; if blood is drawn through a needle into the skin, side-effects could include pain and bruising in the area where the blood was drawn. Other side-effects can include bruising, redness, discomfort or bleeding at the site of the needle stick, and possible lightheadedness, or rarely, fainting. If too much blood is taken over a prolonged period, red blood cell count may drop (this is called "anemia"). As a precaution, red blood cell level will be checked, and iron treatments or a blood transfusion will be given if needed. Up to 50mL of blood may be collected at one time, no more than 300mL will be collected over an 8-week period.

12.3.1.1.2 Bone marrow aspiration/biopsy

The bone marrow aspiration and biopsy may cause pain, bruising, bleeding and infection. Soreness near the site may last for a couple of days after the procedure. Participants may have more pain, risk of bleeding and bruising if they complete both aspiration and biopsy rather than just the aspiration.

12.3.1.1.3 Electrocardiogram

Other than possibly experiencing some minor skin irritation from the electrodes there are no anticipated risks related to complete the electrocardiogram and/or the echocardiogram.

12.3.1.1.4 Intravenous catheter

The risks of IV insertion include temporary pain and bleeding or bruising at the site where the IV enters the skin. In placing the IV, there is a small chance of fluid leaking into the tissue surrounding the IV and infection, which may cause some swelling and discomfort. Rarely, the IV site may become infected, which might require treatment with antibiotics.

12.3.1.1.5 Questionnaires

Some of the questions in the questionnaire may be upsetting or make participants feel uncomfortable. Participants can skip any of the questions they do not want to answer or can stop at any time.

12.3.1.1.6 Risk of losing data

This includes the risk that data obtained during this study, including data related to genotype, DNA sequencing, or risk for disease tendency or trait can be released to members of the public, insurers, employers, or law enforcement agencies. Although there are no plans to release results to the participants, family members, or health care providers, this risk will be included in the informed consent document.

12.3.1.1.7 Risk of receiving unwanted information

Anxiety and stress may arise as a result of the anticipation that unwanted information regarding disease-related DNA sequencing or disease tendencies, or misattributed paternity. Participants will be clearly informed that the data related to DNA sequencing and genetic analysis is coded, investigational and will not be shared with participants, family members, or health care providers.

12.3.2 Known Potential Benefits

Due to the significant preclinical and prior clinical experience with BMS-986253, this study hypothesis has strong evidence that BMS-986253 may have disease-modifying beneficial therapeutic activity in MDS. If this is confirmed via this trial, participants have the potential for immediate-benefits that include, improved cytopenias, less transfusion- and growth factor-dependence, less complications of cytopenias such as infections and hemorrhagic complications. Transfusion independence also leads to improved quality of life. Long-range potential benefits, should our investigational agent confirm efficacy, include stability of MDS disease with improved quality of life and potential for less progression into AML, which is associated with significant morbidity and mortality.

12.3.3 Assessment of Potential Risks and Benefits

Risks to participants were minimized in the study and involve no more than that expected from standard of care monitoring of MDS, which includes regular peripheral blood draws, transfusions and bone marrow evaluations. The potential disease modifying/therapeutic benefit of BMS-986253 as an investigative agent outweighs the risks discussed, which are otherwise mostly standard procedures for participants with MDS. In terms of the rare risk of infusion-site reactions with BMS-986253 administrations, administering personnel will be trained to monitor for signs and symptoms of such reactions and act upon the earliest sign of its development. Should participants develop AEs at any point on trial or simply do not want to continue on study, they will be allowed to withdraw their consent and discontinue study at any time.

12.4 CONSENT PROCESS AND DOCUMENTATION

The informed consent document will be provided as a physical or electronic document to the participant for review prior to consenting. A designated study investigator will carefully explain the procedures and tests involved in this study, and the associated risks, discomforts and benefits. In order to minimize potential coercion, as much time as is needed to review the document will be given, including an opportunity to discuss it with friends, family members and/or other advisors, and to ask questions of any designated study investigator. A signed informed consent document will be obtained prior to entry onto the study.

The initial consent process as well as re-consent, when required, may take place in person or remotely (e.g., via telephone or other NIH approved remote platforms used in compliance with local policy, including HRPP Policy 303) per discretion of the designated study investigator and with the agreement of the participant. Whether in person or remote, the privacy of the subject will be maintained. Consenting investigators (and participant, when in person) will be located in a private area (e.g., clinic consult room). When consent is conducted remotely, the participant will be informed of the private nature of the discussion and will be encouraged to relocate to a more private setting if needed.

Consent will be documented with required signatures on the physical document (which includes the printout of an electronic document sent to participant) or as described below, with a manual (non-electronic) signature on the electronic document. When required, witness signature will be obtained similarly as described for the investigator and participant.

Manual (non-electronic) signature on electronic document:

When a manual signature on an electronic document is used for the documentation of consent at the NIH Clinical Center, this study will use the following to obtain the required signatures:

- Adobe platform (which is not 21 CFR Part 11 compliant); or,
- iMedConsent platform (which is 21 CFR Part 11 compliant)

During the consent process, participants and investigators will view individual copies of the approved consent document on screens at their respective locations (if remote consent); the same screen may be used when in the same location, but is not required.

Both the investigator and the participant will sign the document using a finger, stylus or mouse.

Note: Refer to the CCR SOP PM-2, Obtaining and Documenting the Informed Consent Process for additional information (e.g., verification of participant identity when obtaining consent remotely) found at: https://ccrod.cancer.gov/confluence/pages/viewpage.action?pageId=73203825.

13 REGULATORY AND OPERATIONAL CONSIDERATIONS

13.1 STUDY DISCONTINUATION AND CLOSURE

This study may be temporarily suspended or prematurely terminated if there is sufficient reasonable cause. Written notification, documenting the reason for study suspension or termination, will be provided by the suspending or terminating party to study participants, investigators, funding agency, the Investigational New Drug (IND) sponsor and regulatory authorities. If the study is prematurely terminated or suspended, the Principal Investigator (PI) will promptly inform study participants, the Institutional Review Board (IRB), and sponsor and will provide the reason(s) for the termination or suspension. Study participants will be contacted, as applicable, and be informed of changes to study visit schedule.

Circumstances that may warrant termination or suspension include, but are not limited to:

- Determination of unexpected, significant, or unacceptable risk to participants
- Demonstration of efficacy that would warrant stopping
- Insufficient compliance to protocol requirements
- Data that are not sufficiently complete and/or evaluable
- Determination that the primary endpoint has been met
- Determination of futility

Study may resume once concerns about safety, protocol compliance, and data quality are addressed, and satisfy the sponsor, IRB and as applicable, Food and Drug Administration (FDA).

13.2 Quality Assurance and Quality Control

Investigational site will perform internal quality management of study conduct, data and biological specimen collection, documentation and completion. An individualized quality management plan will be developed to describe a site's quality management.

Quality control (QC) procedures will be implemented beginning with the data entry system and data QC checks that will be run on the database will be generated. Any missing data or data anomalies will be communicated to the site(s) for clarification/resolution.

Following written Standard Operating Procedures (SOPs), the monitors will verify that the clinical trial is conducted and data are generated and biological specimens are collected, documented (recorded), and reported in compliance with the protocol, International Conference on Harmonisation Good Clinical Practice (ICH GCP), and applicable regulatory requirements (e.g., Good Laboratory Practices (GLP), Good Manufacturing Practices (GMP)).

The investigational site will provide direct access to all trial related sites, source data/documents, and reports for the purpose of monitoring and auditing by the sponsor, and inspection by local and regulatory authorities.

13.3 Conflict of Interest Policy

The independence of this study from any actual or perceived influence, such as by the pharmaceutical industry, is critical. Therefore, any actual conflict of interest of persons who have a role in the design, conduct, analysis, publication, or any aspect of this trial will be disclosed and managed. Furthermore, persons who have a perceived conflict of interest will be required to have such conflicts managed in a way that is appropriate to their participation in the design and conduct of this trial. The study leadership in conjunction with the National Cancer Institute has established policies and procedures for all study group members to disclose all conflicts of interest and will establish a mechanism for the management of all reported dualities of interest.

13.4 Confidentiality and Privacy

Participant confidentiality and privacy is strictly held in trust by the participating investigators, their staff, and the sponsor(s). This confidentiality is extended to cover testing of biological samples and genetic tests in addition to the clinical information relating to participants. Therefore, the study protocol, documentation, data, and all other information generated will be held in strict confidence. No information concerning the study or the data will be released to any unauthorized third party without prior written approval of the sponsor.

All research activities will be conducted in as private a setting as possible.

The study monitor, other authorized representatives of the sponsor, representatives of the Institutional Review Board (IRB), and/or regulatory agencies may inspect all documents and records required to be maintained by the investigator, including but not limited to, medical records (office, clinic, or hospital) and pharmacy records for the participants in this study. The clinical study site will permit access to such records.

The study participant's contact information will be securely stored at the/each clinical site for internal use during the study. At the end of the study, all records will continue to be kept in a secure location for as long a period as dictated by the reviewing IRB, Institutional policies, or sponsor requirements.

Study participant research data, which is for purposes of statistical analysis and scientific reporting, will be stored at the National Cancer Institute. This will not include the participant's contact or identifying information. Rather, individual participants and their research data will be identified by a unique study identification number. The study data entry and study management systems used by the clinical site(s) and by National Cancer Institute research staff will be secured and password protected. At the end of the study, all study databases will be archived at the National Cancer Institute.

To further protect the privacy of study participants, a Certificate of Confidentiality has been issued by the National Institutes of Health (NIH). This certificate protects identifiable research information from forced disclosure. It allows the investigator and others who have access to research records to refuse to disclose identifying information on research participation in any civil, criminal, administrative, legislative, or other proceeding, whether at the federal, state, or local level. By protecting researchers and institutions from being compelled to disclose information that would identify research participants, Certificates of Confidentiality help achieve the research objectives and promote participation in studies by helping assure confidentiality and privacy to participants.

14 PHARMACEUTICAL AND INVESTIGATIONAL INFORMATION

14.1 BMS-986253 (IND # 157591)

14.1.1 Source/Acquisition and Accountability

BMS-986253 is manufactured and supplied for the trial by Bristol-Myers Squibb (BMS).

BMS-986253 will be provided to the clinical trial site by the manufacturer. The investigator or designee (e.g., pharmacist) will maintain an ongoing inventory of the investigational product supply according to standard site procedures. The investigational product will be dispensed at the direction of an investigator for administration to a study participant enrolled on the clinical trial. Disposal of expired or unused product will be returned to the manufacturer or disposed of according to standard site procedures based on agreement between the manufacturer and the site.

14.1.2 Toxicity

A phase I/II clinical trial[96] designed to evaluate safety and efficacy in palmoplantar pustulosis (PPP), a rare chronic inflammatory skin disorder, enrolled 31 participants. For PPP, BMS-986253 showed efficacy in reducing disease activity. The antibody was well-tolerated, with no serious adverse events (SAE) attributed to treatment. The most frequently reported mild or moderate adverse events included nausea, nasopharyngitis, and headache. Moreover, no antihuman antibodies developed after administration of BMS-986253.[96] In the phase I trial of BMS-986253 in advanced solid tumors as monotherapy,[97] 11/15 subjects achieved the best response of stable disease (4 subjects had progressive disease). Reduction of serum IL-8 levels were observed across all dose levels (4, 8, 16 and 32 mg/kg every 2 weeks) without reaching a dose-limited toxicity (DLT) or defining maximum tolerated dose (MTD). Treatment with BMS-986253 reversed EMT process measured by the EMT markers and inhibited IL-8 induced peripheral blood cells migration isolated from the subjects post-treatment. The most common adverse events (AE), regardless of causality, were constipation (n=5), nausea (n=4) and anemia (n=4). Six subjects (40%) had grade 3 AEs with increased ALP (n=2) and anemia (n=2) being

the most common. Treatment-related AEs occurred in one-third of the subjects and were all grade 1 and 2 (anemia and fatigue as the most common). Four subjects experienced SAE non-related to the treatment (grade 3 pain, abdominal infection, fall, decreased ALP, hyponatremia [n=5]; grade 2 pulmonary embolism [n=1]). The pharmacokinetic (PK) analysis showed an approximate linear correlation between increasing dose and exposure for the dose range of 4 mg/kg to 32 mg/kg.[97]

In the currently ongoing clinical trial phase I/IIa (CA027-002, ClinicalTrials.gov NCT03400332), testing various flat doses of BMS-986253 in combination with nivolumab, treatment-related AEs were observed in 30/92 participants with solid cancer at the time of the preliminary analysis (data cut-off date of 16-Jan-2020). The most common treatment-related AEs in combination with nivolumab were fatigue (n=9), nausea (n=7), rash (n=3), and decreased appetite (n=3). Based on preliminary clinical data from that trial BMS-986253 does not appear to significantly increase the rate of nivolumab-induced AEs.[95]

Based on currently available clinical data from prior trials,[95-97] only 3 participants had infusion reactions. One participant received 8 mg/kg BMS-986253 monotherapy and experienced a grade 1 infusion reaction on Cycle 1 Day 1, which did not recur with subsequent infusions. Two participants treated with 2,400 mg BMS-986253 Q2W + 480 mg nivolumab Q4W experienced infusion reactions: one grade 2 infusion reaction on Cycle 1, Day 15 and continued to receive subsequent infusion of study therapy and tolerated well, and one experienced a grade 4 infusion reaction on Cycle 2, Day 15 that led to drug discontinuation. Of note, there has been a higher-than-expected incidence of hemophagocytic lymphohistiocytosis (HLH) in participants receiving ipilimumab + nivolumab + blinded study drug (BMS-986253 or placebo) in Part 2 of Study CA027-002. As of 31 Jan 2023, 144 participants were treated in Part 1 with the nivolumab + BMS-986253 doublet, across different dose levels and/or schedules of BMS-986253. No dose-dependent toxicities were identified. In Part 1C, 15 participants were treated with BMS-986253 (3600 mg Q2W) in combination with nivolumab (1 mg/kg Q3W) and ipilimumab (3 mg/kg Q3W) to evaluate safety and preliminary anti-tumor activity of the triplet regimen. Part 2 was a randomized, double-blind evaluation of BMS-986253 (3600 mg Q2W) in combination with nivolumab (1 mg/kg Q3W) and ipilimumab (3 mg/kg Q3W) (Cohort 2A) vs nivolumab and ipilimumab plus placebo (Cohort 2B) in participants with melanoma that has progressed on anti-PD-(L)1 therapy with the objectives of comparing anti-tumor activity and assess safety of the triplet combination of BMS-986253 with nivolumab and ipilimumab. As of 27 Jan 2023, 57 participants across 18 sites in eight countries have been treated in the blinded part 2. To date, 3 HLH cases have been reported in Part 2, 2 of which were fatal.

The sponsor's safety monitoring team determined that the rate of HLH reported is higher than anticipated and elected to unblind the treatment assignment for the 3 participants to evaluate a potential contribution of BMS-986253. The randomization of the 3 participants with HLH was divided between the two arms. Of the 2 HLH cases with fatal outcome, 1 occurred in each arm (2A and 2B). Overall, the incidence rates of HLH reported in the 2 arms were not considered meaningfully different. There were no HLH cases reported in participants treated with BMS-986253 in the following cohorts:

BMS-986253 monotherapy in phase 1 Study CA027-001 (n=15), BMS-986253 plus nivolumab in

CA027-002 Part 1A/B (n=144), nivolumab + ipilimumab + BMS-986253 in CA027-002 Part 1C (n=15), nor in participants (n=122) in 8 investigator sponsored research studies evaluating BMS-986253 in combination with nivolumab and other drugs in oncology indications.

In summary, it was determined that a contributory factor of BMS-986253 for the reported cases of HLH cannot be ascertained. The basis for the higher-than-expected frequency of HLH in the study cannot yet be determined and the evaluation is further confounded by the presence of significant comorbidities in the affected participants, including sepsis, possible gastrointestinal perforation, and viral infection (i.e. recent COVID-19 infection in one participant, and evidence of EBV in 2 participants), all of which can present with an overlapping symptom complex and/or may contribute to the development of HLH. In addition, HLH case reports are a well described complication of immune checkpoint inhibitor monotherapy (pembrolizumab or nivolumab alone) or nivolumab/ipilimumab combinations. [98]

Because BMS-986253 is scheduled for intravenous (IV) administration, extravasation at the site of infusion may induce reactions such as edema, redness, itching, and tenderness. To date, no injection-site reactions have been reported.

14.1.3 Formulation and preparation

- BMS-986253 injection is a sterile, non-pyrogenic, single use, preservative-free, ready-to-use IV injectable drug product supplied in a 20-cc (20R) Type I flint glass vial, stoppered with a 20-mm fluoropolymer film-laminated rubber stopper, and sealed with a 20-mm aluminum flip-off seal.
- BMS-986253 injection is formulated at a protein concentration of 100 mg/mL in 20 mM histidine buffer (pH of 6.0), which is composed of histidine, histidine hydrochloride monohydrate, sucrose, polysorbate 80, pentetic acid, and water for injection.
- Each vial of drug product contains the labeled amount of BMS-986253 with a nominal fill of 10 mL and 12 mL for the 1,000-mg/vial and 1,200-mg/vial presentations, respectively, and sufficient overfill (0.8 mL) to account for vial, needle, and syringe hold-up.
- The drug product must be diluted prior to dosing.

14.1.4 Stability and Storage

1. BMS-986253-01 Injection, 1000 mg/Vial (100 mg/mL) and BMS-986253-01 Injection, 1,200 mg/Vial (100 mg/mL)
   - BMS-986253 injection should be stored refrigerated at 2°C to 8°C (36°F to 46°F) and protected from light and freezing.

2. Diluted Solution of BMS-986253 Injection, 1000 mg/Vial (100 mg/mL) and 1,200 mg/Vial (100/mL) in an IV bag:
   - Administration of diluted BMS-986253 injection must be completed within 24 hours of preparation. If not used immediately, the infusion solution may be stored for up to 24 hours refrigerated at 2°C to 8°C (36°F to 46°F) protected from light; a maximum of 4 hours of the total 24 hours can be at room temperature (15°C to 25°C, 59°F to 77°F), ambient light.

- The diluted solution in an IV bag should not be shaken or frozen. Equilibration to room temperature is recommended for the infusion bag, drug product, or their combination prior to administration.

14.1.5 Administration procedures

Dilution of BMS-986253-01 Injection, 1,000 mg/Vial (100 mg/mL) and 200 mg/Vial (20 mg/mL):

- BMS-986253 injection is to be administered as an IV infusion, following dilution with normal saline or 5% dextrose injection to concentrations outlined in section **3.2.1.3**
- The infusion is to be administered through a sterile, non-pyrogenic, and low protein binding polyethersulfone or nylon 0.2 micrometer in line filter.
- No incompatibilities have been observed between constituted BMS-986253 and the recommended IV infusion bags or syringe.
- Dilution of BMS-986253 injection must be performed using sterile disposable syringes. Care must be taken to ensure sterility of the prepared solution as the drug product does not contain any antimicrobial preservative or bacteriostatic agent.

14.1.6 Incompatibilities

- There are no special warnings or precautions in term of drug interactions with BMS-986253.
- Chemical structure: consists of 1,322 amino acids with 1 nitrogen-linked glycosylation site on the heavy chain and is produced from a CHO cell line.
- Molecular weight: 145 kDa
- Mechanism of action: Fully human mAb against IL-8.

A copy of the drug brochure will be provided to the Pharmacy department; however, NCI pharmacy has had experience with this investigational product from a prior study in solid tumors (Bilusic et al).[97]

14.2 DNMTi (DECITABINE AND CEDAZURIDINE)

DNMTi is a combination of decitabine, a nucleoside metabolic inhibitor, and cedazuridine, a cytidine deaminase inhibitor, indicated for treatment of adult patients with myelodysplastic syndromes (MDS).

14.2.1 Source/Acquisition and Accountability

For subject administration, decitabine and cedazuridine will be purchased by the NIH Clinical Center Pharmacy Department from commercial sources.

14.2.2 Toxicity

Fatal and serious myelosuppression and infectious complications can occur. Can cause fetal harm. Most common adverse reactions (incidence ≥ 20%) are fatigue, constipation, hemorrhage, myalgia, mucositis, arthralgia, nausea, dyspnea, diarrhea, rash, dizziness, febrile neutropenia, edema, headache, cough, decreased appetite, upper respiratory tract infection, pneumonia, and transaminase increased. The most common Grade 3 or 4 laboratory abnormalities (≥ 50%) were leukocytes decreased, platelet count decreased, neutrophil count decreased, and hemoglobin decreased. [113-115]

14.2.3 Formulation and preparation

DNMTi (decitabine and cedazuridine) tablets, for oral use contain 35 mg decitabine and 100 mg cedazuridine. The tablets are biconvex, oval-shaped, film-coated, red and debossed with “H35” on one side. Each film-coated tablet contains the following inactive ingredients: lactose monohydrate, hypromellose, croscarmellose sodium, colloidal silicon dioxide, and magnesium stearate. The film coating material contains polyvinyl alcohol, titanium dioxide, polyethylene glycol, talc, and iron oxide red.

14.2.4 Stability and Storage

The tablet should be stored at 20°C to 25°C. Excursions of the tablet are permitted to 15°C to 30°C. Any unused portion of the tablet should be discarded using special handling and disposal procedures.

14.2.5 Administration procedures

The tablet should be taken on an empty stomach, 2 hours before or 2 hours after meals, and at the same time each day.

Tablet should be swallowed whole, and may not be crushed, cut, or chewed.

If a dose is missed within 12 hours of the time it is usually administered, administer the missed dose as soon as possible and then resume the normal daily dosing schedule. Extend the dosing period by 1 day for every missed dose to complete 5 daily doses for each cycle. If a dose is vomited, do not administer an additional dose (continue with the next scheduled dose).

14.2.6 Incompatibilities

Avoid coadministration of DNMTi with drugs that are metabolized by cytidine deaminase (CDA) enzymes.

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16 LIST OF ABBREVIATIONS

Abbreviation	Term
ACAT	Ability to Consent Assessment Team
AE	Adverse Event/Adverse Experience
AESI	Adverse Event/Experience of Special Interest
ANC	Absolute neutrophil count
BTRIS	Biomedical Translational Research Information System
CCR	Center for Cancer Research
CDA	Confidential Disclosure Agreement
CFR	Code of Federal Regulations
CNS	Central nervous system
CONSORT	Consolidated Standards of Reporting Trials
COV	Close-out Visit
CR	Complete Response
CSR	Clinical Study Report
CRADA	Cooperative Research and Development Agreement
CT	Computed Tomography
CTA	Clinical Trials Agreement
CTCAE	Common Terminology Criteria for Adverse Events
DLT	Dose-limiting toxicity
DSMB	Data Safety Monitoring Board (DSMB)
DTA	Data Transfer Agreement
EC	Ethics Committee
eCRF	Electronic Case Report Form
ECOG	Eastern Cooperative Oncology Group
EFS	Event-free survival
EKG	Electrocardiogram
FDA	Food and Drug Administration
FWA	Federal-Wide Assurance
GCP	Good Clinical Practice
GDS	Genomic Data Sharing
GLP	Good Laboratory Practices
GMP	Good Manufacturing Practices
HBV	Hepatitis B virus
HCV	Hepatitis C virus
HHS	Health and Human Services
HIV	Human immunodeficiency virus
IB	Investigator's Brochure
IBC	Institutional Biosafety Committee
ICD/ICF	Informed Consent Document/Form
ICH	International Conference on Harmonisation
IMV	Interim Monitoring Visit

Abbreviation	**Term**
IND	Investigational New Drug
IRB	Institutional Review Board
IRBO	Institutional Review Board Office
IV	Intravenous
LAR	Legally Authorized Representative
MRI	Magnetic Resonance Imaging
MTA	Material Transfer Agreement
MTD	Maximal tolerated dose
N	Number (typically refers to subjects)
NCT	National Clinical Trial (number)
NDA	New Drug Application
NIH	National Institutes of Health
NOS	Not otherwise specified
OHSRP	Office for Human Subjects Research Protections
OHRP	Office for Human Research Protections
OS	Overall survival
OSRO	Office of Sponsor and Regulatory Oversight
PD	Progressive Disease
PET	Positron Emission Tomography
PFS	Progression-free survival
PI	Principal Investigator
PR	Partial Response
PS	Performance Status
QA	Quality Assurance
QC	Quality Control
rCR	Revised Common Rule
RECIST	Response Evaluation Criteria in Solid Tumors
RP2D	Recommended Phase II dose
SAE	Serious Adverse Event/Serious Adverse Experience
SAV	Site Assessment Visit
SIV	Site Initiation Visit
SD	Stable Disease
SMC	Safety Monitoring Committee
SOP	Standard Operating Procedure
ULN	Upper limit of normal
US	United States
WHO	World Health Organization

17 APPENDICES

17.1 APPENDIX A: PERFORMANCE STATUS CRITERIA

ECOG Performance Status Scale		**Karnofsky Performance Scale**	
Grade	Descriptions	Percent	Description
0	Normal activity. Fully active, able to carry on all pre-disease performance without restriction.	100	Normal, no complaints, no evidence of disease.
		90	Able to carry on normal activity; minor signs or symptoms of disease.
1	Symptoms, but ambulatory. 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).	80	Normal activity with effort; some signs or symptoms of disease.
		70	Cares for self, unable to carry on normal activity or to do active work.
2	In bed <50% of the time. Ambulatory and capable of all self-care, but unable to carry out any work activities. Up and about more than 50% of waking hours.	60	Requires occasional assistance, but is able to care for most of his/her needs.
		50	Requires considerable assistance and frequent medical care.
3	In bed >50% of the time. Capable of only limited self-care, confined to bed or chair more than 50% of waking hours.	40	Disabled, requires special care and assistance.
		30	Severely disabled, hospitalization indicated. Death not imminent.
4	100% bedridden. Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair.	20	Very sick, hospitalization indicated. Death not imminent.
		10	Moribund, fatal processes progressing rapidly.
5	Dead.	0	Dead.

17.2 APPENDIX B: 2016 WHO CLASSIFICATION FOR MYELODYSPLASTIC SYNDROME

Myelodysplastic syndromes (MDS)

- **MDS with single lineage dysplasia (MDS-SLD)**
- **MDS with ring sideroblasts (MDS-RS)**
  - **MDS-RS and single lineage dysplasia**
  - **MDS-RS and multilineage dysplasia**
- **MDS with multilineage dysplasia (MDS-MLD)**
- **MDS with excess blasts**
- **MDS with isolated del(5q)**
- **MDS, unclassifiable**
- ***Provisional entity: Refractory cytopenia of childhood***

17.3 APPENDIX C: REVISED INTERNATIONAL PROGNOSTIC SCORING SYSTEM (IPSS-R) FOR MYELODYSPLASTIC SYNDROMES

Prognostic variable	Score						
	0	0.5	1.0	1.5	2.0	3.0	4.0
Cytogenetics*	Very good		Good		Intermediate	Poor	Very poor
Bone marrow blast (percent)	≤2		>2 to <5		5 to 10	>10	
Hemoglobin (g/dL)	≥10		8 to <10	<8			
Platelets (cells/microL)	≥100	50 to 100	<50				
Absolute neutrophil count (cells/microL)	≥0.8	<0.8					

Risk group	IPSS-R score	Median overall survival (years)	Median time to 25 percent AML evolution (years)
Very low	≤1.5	8.8	>14.5
Low	>1.5 to 3.0	5.3	10.8
Intermediate	>3 to 4.5	3.0	3.2
High	>4.5 to 6	1.6	1.4
Very high	>6	0.8	0.7

AML: acute myeloid leukemia; MDS: myelodysplastic syndromes.
* Cytogenetic definitions:
Very good: –Y, del(11q)
Good: Normal, del(5q), del(12p), del(20q), double including del(5q)
Intermediate: del(7q), +8, +19, i(17q), any other single, double not including del(5q) or –7/del(7q), or independent clones
Poor: –7, inv(3)/t(3q)/del(3q), double including –7/del(7q), complex: 3 abnormalities.
Very poor: Complex: >3 abnormalities
This research was originally published in Blood. Greenberg PL, Tuechler H, Schanz J, et al. Revised International Prognostic Scoring System (IPSS-R) for myelodysplastic syndromes. Blood 2012. Copyright © 2012 the American Society of Hematology.

17.4 APPENDIX D: THE 2006 INTERNATIONAL WORKING GROUP RESPONSE CRITERIA WITH MODIFIED DEFINITIONS FOR HEMATOLOGIC IMPROVEMENT BY THE 2018 INTERNATIONAL WORKING GROUP RESPONSE CRITERIA.[85]

Category	**Response criteria** (responses must last at least 4 weeks)

Complete remission	• Bone marrow: ≤5% myeloblasts with normal maturation of all cell lines*
	• Persistent dysplasia will be noted*
	• Peripheral blood†
	  ◦ Hgb ≥11 g/dL
	  ◦ Platelets ≥100 X 10^9/L
	  ◦ Neutrophils ≥1.0 X 10^9/L
	  ◦ Blasts 0%

Partial remission	All CR criteria if abnormal before treatment except: • Bone marrow blasts decreased by ≥50% over pretreatment but still >5% • Cellularity and morphology not relevant
Marrow CR	• Bone marrow: ≤5% myeloblasts and decrease by ≥50% over pretreatment • Peripheral blood: if HI responses, they will be noted in addition to marrow CR
Stable disease	Failure to achieve at least PR, but no evidence of progression for >8 weeks
Failure	Death during treatment or disease progression characterized by worsening of cytopenias, increase in percentage of bone marrow blasts, or progression to more advanced MDS FAB subtype than pre-treatment
Relapse after CR or PR	At least 1 of the following: • Return to pre-treatment bone marrow blast percentage • Decrement of ≥50% from maximum remission/response levels in granulocytes or platelets • Reduction in Hgb concentration by ≥1.5 g/dL or transfusion dependence
Cytogenetic response	Complete • Disappearance of the chromosomal abnormality without appearance of new ones Partial • At least 50% reduction of the chromosomal abnormality
Disease progression	For patients with: • Less than 5% blasts: ≥50% increase in blasts to >5% blasts • 5%-10% blasts: ≥50% increase to 10% blasts

	• 10%-20% blasts: ≥50% increase to >20% blasts • 20%-30% blasts: ≥50% increase to >30% blasts Any of the following: • At least 50% decrement from maximum remission/response in granulocytes or platelets • Reduction in Hgb by ≥2 g/dL • Transfusion dependence
Survival	Endpoints: • Overall: death from any cause • Event free: failure or death from any cause • PFS: disease progression or death from MDS • DFS: time to relapse • Cause-specific death: death related to MDS

MDS, myelodysplastic syndromes; Hgb, hemoglobin; CR, complete remission; HI, hematologic improvement; PR, partial remission; FAB, French-American-British; AML, acute myeloid leukemia; PFS, progression-free survival; DFS, disease-free survival.
To convert hemoglobin from grams per deciliter to grams per liter, multiply grams per deciliter by 10.
*Dysplastic changes should consider the normal range of dysplastic changes.
†In some circumstances, protocol therapy may require the initiation of further treatment (eg, consolidation, maintenance) before the 4-week period. Such patients can be included in the response category into which they fit at the time the therapy is started. Transient cytopenias during repeated chemotherapy courses should not be considered as interrupting durability of response, as long as they recover to the improved counts of the previous course.

Hematologic Improvement

Category	**Patient pre-trial baseline**	**Response criteria**	
Erythroid response (HI-E)	No Transfusion Dependence at baseline (0 RBC transfusions in 16 weeks)	At least 2 consecutive Hgb measurements ≥1.5 g/dL for a period of minimum 8 weeks in an observation period of 16 to 24 weeks compared with the lowest mean of 2 Hgb measurements (apart from any transfusion) within 16 weeks before treatment onset; only a response duration of at least 16 weeks, however, is considered clinically meaningful	
	Low Transfusion Dependence at baseline (3-7 RBC transfusions in 16 weeks in at least 2 transfusion episodes, maximum 3 in 8 weeks)	Transfusion independence, defined by the absence of any transfusions for at least 8 weeks in an observation period of 16-24 weeks with the same transfusion policy compared with 16 weeks prior to treatment; only a response duration of at least 16 weeks, however, is considered clinically meaningful	
	High Transfusion Dependence at baseline (≥8 RBC transfusions in 16	Major response	Transfusion independence, defined by the absence of any transfusions over a period of minimum 8 weeks in an

	weeks, ≥ 4 transfusion episodes in 8 weeks)		observation period of 16-24 weeks with the same transfusion policy compared with 16 weeks prior to treatment; only a response duration of at least 16 weeks, however, is considered clinically meaningful
		Minor response	Transfusion independence, defined by the absence of any transfusions over a period of minimum 8 weeks in an observation period of 16-24 weeks with the same transfusion policy compared with 16 weeks prior to treatment; only a response duration of at least 16 weeks, however, is considered clinically meaningful
Platelet response (HI-P)	Pre-treatment PLT <100 x 10^9/L	• Absolute increase of 30 x 10^9/L for patients starting with >20 x 10^9/L PLTs or • Increase from <20 x 10^9/L to >20 x 10^9/L and by at least 100% In addition: • In addition, evolution of bleeding symptoms is to be taken into account • Increments of platelets also for patients with a pre-treatment PLT count of ≥100 x 10^9 are to be reported	
Neutrophil response (HI-N)	Pre-treatment ANC <1.0 x 10^9/L	• At least 100% increase and an absolute increase >0.5 x 10^9/L • Increments of neutrophils also for patients with a pre-treatment ANC of ≥1.0 x 10^9/L are to be reported	

17.5 APPENDIX E: BLOOD AND MARROW PROCESSING CORE PROTOCOLS

Anti-IL8 in MDS (IRB 000356):

1. Peripheral Blood: 2 x 5 mL SST tubes (1 tube for Antibody PK, 1 tube for free IL8 assay, protocols below)
2. Peripheral Blood: 1 x 10mL EDTA tube (for separation and storage of MNC and plasma, protocol below)
3. Peripheral Blood: 1 x 2.5mL Paxgene Tube (for storage, see protocol below)
4. Bone Marrow: 1 x 10mL EDTA tube (for separation and storage of MNC and plasma, protocol below)
5. Bone Marrow: 1 x 2.5mL Paxgene Tube (for storage, see protocol below)

Processing Protocols:

Bone Marrow and Peripheral Blood Processing from EDTA tubes

1. Spin the bone marrow (BM) aspirate or peripheral blood (PB) at 2500 rpm (1500 rcf) for 5 minutes to isolate neat plasma prior to adding the PBS/Ficoll.
2. Store 5 x 300uL aliquots of plasma at -80deg C.
3. Add 2 volumes of PBS to the PB/BM and be sure to mix well to ensure a good underlay of the Ficoll.
4. Add a 1:1 volume of Ficoll to the diluted BM/PB by carefully dispensing at the bottom of the conical tube. The BM/PB should lay on top of the Ficoll layer. Try not to mix the Ficoll and BM/PB.
5. Spin the tubes at 3000 rpm (2000 rcf) for 15 minutes.
6. The mononuclear layer interface will lay between the Ficoll and plasma/PBS layers and will often appear whitish if there is a larger number of cells. Carefully remove this interface taking as little Ficoll as possible. If you cannot see the layer, just remove several mL from on top of the Ficoll layer, this will contain all the cell. Dilute the interface containing the cells, with 4 volumes of RPMI (supplemented with 10%FBS, and 1% Pen/Strep). The remaining Ficoll and RBCs at the bottom of the tube can be discarded.
7. Spin the mononuclear cells at 1000rpm for 5 min.
8. Resuspend the cell pellet in 10 to 40ml of RBC Lysis Buffer (ie; Qiagen RBC Lysis Buffer). The volume of lysis buffer depends on the cell pellet. For very small pellets use 10mL, for very large pellets, use 40mL RBC lysis .
9. Resuspend the cells in RPMI (supplemented with 10%FBS, and 1% Pen/Strep) and count the cells using a hemacytometer.
10. Freeze the cells in 10% DMSO, 20% FBS, and 70% RPMI with no more than 10million cells per mL and 1 mL per cryotube. Freeze samples either using a cell freezer container in a -80deg C freezer (i.e.; Mr Frosty container) or a controlled rate freezer. Once cells have reached -80deg C, transfer cryotubes to a liquid nitrogen cryounit.

Antibody PK Studies (IL8 study), Peripheral Blood Processing from SST Tube:

1. Blood samples will be collected by direct venipuncture or through an indwelling catheter. If a catheter is used for blood collection, then approximately 1mL of blood should be

withdrawn initially then discarded. Only saline is permitted to keep catheters patent, unless discussed and agreed upon by the Sponsor. If samples are obtained through a heparin lock, sufficient blood (~1mL) must be withdrawn to remove the heparin solution.
2. Immediately after collection, gently invert each tube 5 times and allow blood to clot for 30-45m at room temperature (tube standing upright).
3. Centrifuge samples at 4deg C for 10min (singing buckets) or 15 minutes (fixed buckets) at 100-1300g until clot and serum are well separated. Note: If refrigerated centrifuge is not available, prechill centrifuge tube holders at -20deg C for 20m prior to centrifugation.
4. Transfer 1mL aliquots of serum into 4 appropriately labeled screw cap polypropylene tubes.
5. Keep samples at -80deg C until requested for shipment.

Free IL8 Studies (IL8 study), Peripheral Blood Processing from SST Tube:

1. Blood samples will be collected by direct venipuncture or through an indwelling catheter. If a catheter is used for blood collection, then approximately 1mL of blood should be withdrawn initially then discarded. Only saline is permitted to keep catheters patent, unless discussed and agreed upon by the Sponsor. If samples are obtained through a heparin lock, sufficient blood (~1mL) must be withdrawn to remove the heparin solution.
2. Immediately after collection, gently invert each tube 5 times and allow blood to clot for 30-45m at room temperature (tube standing upright).
3. Centrifuge samples at 4deg C for 10min (singing buckets) or 15 minutes (fixed buckets) at 100-1300g until clot and serum are well separated. Note: If refrigerated centrifuge is not available, prechill centrifuge tube holders at -20deg C for 20m prior to centrifugation.
4. Transfer 1mL aliquots of serum into 4 appropriately labeled screw cap polypropylene tubes.
5. Keep samples at -80deg C until requested for shipment.

PAXgene Tube Storage for BM/PB:

1. Tubes should remain upright. Incubate tubes at room temp for 2-72hrs after collection, then place at -20deg C for 24hr, then place in a -80deg C freezer.

17.6 APPENDIX F: CLINICAL DATA ELEMENTS FOR CRF ENTRY IN CLINICAL DATABASE

Patient (recipient) characteristics at protocol entry

- Sex (male, female)
- Age at enrollment (number)
- Ethnicity (white, black, American Indian/Alaskan native, Asian/Pacific islander, Hispanic, other)
- ECOG and Karnofsky performance status
- Diagnosis - MDS (high risk or low risk)
- 2016 WHO classification of MDS (MDS with single lineage dysplasia [MDS-SLD], MDS with ring sideroblasts and single lineage dysplasia [MDS-RS-SLD], MDS with ring sideroblasts and multilineage dysplasia [MDS-RS-MLD], MDS with multilineage dysplasia [MDS-MLD], MDS with excess blasts [MDS-EB], MDS with isolated del(5q), MDS unclassifiable [MDS-U],
- Date of MDS diagnosis (month, year)
- Age at MDS diagnosis
- Revised International Prognostic Scoring System (IPSS-R) score at MDS diagnosis
- Cytogenetic profile at diagnosis and enrollment, if available (see Appendix C)- only need overall score (very good, good, intermediate, poor, very poor)
- Bone marrow blasts %, if available
- Hemoglobin, if available
- Platelet count, if available
- Absolute neutrophil count (ANC), if available
- RBC transfusion dependance (transfusion dependent or independent)
- Platelet transfusion dependance (transfusion dependent or independent)
- Average # of transfusions per month (RBCs units and instances of platelets transfusions) in the 3 months leading up to baseline on study
- Laboratory values will be collected from time of screening for duration of trial
- TP53 mutation status at enrollment, if available (TP53 mutation positive or negative)
- Names and # of cycles of prior Lines of therapy for MDS.
- Response to most recent line of therapy: CR (complete response), PR (partial response), HI (hematologic improvement), mCR with HI (marrow CR with hematologic improvement), mCR without HI (marrow CR without hematologic improvement), SD (stable disease), PD (disease progression)
- MDS-CI (low risk, intermediate risk, high risk)
- Rockwood frailty index (see Clinical Frailty Scale)
- Disease status at time of enrollment: CR (complete response), PR (partial response), HI (hematologic improvement), mCR with HI (marrow CR with hematologic improvement), mCR without HI (marrow CR without hematologic improvement), SD (stable disease), PD (disease progression)
- Patient Reported Outcome Questionnaires (per section **3.5.3**)
    - Subjects > 18 years of age:
        1. EORTC QLQC30 score (patient reported)- see questionnaire
        2. NIH developed psychosocial assessment scale – see questionnaire

Data collection during study/treatment

- Cycle number & day of treatment
- Study Drug Administration
- Disease response at assessment timepoints: CR (complete response), PR (partial response), HI (hematologic improvement), mCR with HI (marrow CR with hematologic improvement), mCR without HI (marrow CR without hematologic improvement), SD (stable disease), PD (disease progression)
- Best overall response to study treatment: CR (complete response), PR (partial response), HI (hematologic improvement), mCR with HI (marrow CR with hematologic improvement), mCR without HI (marrow CR without hematologic improvement), SD (stable disease), PD (disease progression)
- Bone marrow percent blasts
- RBC transfusion dependence (transfusion dependent or transfusion independent)
- Platelet transfusion dependence (transfusion dependent or transfusion independent)
- # of transfusions per month (RBCs units and instances of platelets transfusions)
- Adverse events
- Patient Reported Outcome Questionnaires: (per section **3.5.3**)
    - EORTC QLQC30 score (patient reported) – see questionnaire
    - NIH developed psychosocial assessment scale – see questionnaire

Data collection at post-therapy follow-up visits

- Alive (yes/no)
- Adverse events
- Progression of MDS (if yes, to what and when)
- Diagnosed with sAML (yes/no)
    - If diagnosed with sAML, date of sAML diagnosis (month, year)
    - subsequent MDS/AML specific treatments including BMT until off study if information available.

Data collection at time of death

- Date of death
- Disease status at time of death: CR or not CR
- Cause of death: disease progression/relapse vs non-relapse mortality (definition of non-relapse mortality: subject in clinical remission at time of death)
- If non-relapse mortality, primary cause of death (e.g., infection, organ failure, other – per CTCAE)

17.7 APPENDIX G: DIAGNOSIS AND MANAGEMENT OF HLH

The following clinical and laboratory parameters can be indicative of a diagnosis of HLH:

- Fever ≥38.5°C, not explained by infection
- Peripheral blood cytopenia, with at least two of the following: hemoglobin <9 g/dL; platelets <100,000/microL; absolute neutrophil count <1000/microL, not explained by malignancy or treatment
- Hypertriglyceridemia (fasting triglycerides >265 mg/dL) and/or hypofibrinogenemia (fibrinogen <150 mg/dL)
- Hemophagocytosis in bone marrow, spleen, lymph node, or liver
- Ferritin >500 ng/mL
- Elevated soluble CD25 (soluble IL-2 receptor alpha [sIL-2R]) two standard deviations above age-adjusted laboratory-specific norms
- Elevated CXCL9
- Hemophagocytosis on bone marrow examination

If patient is not severely ill (eg, does not have deteriorating cardiovascular, pulmonary, renal, hepatic, or neurologic function), it may be possible to manage with stoppage of indefinite anti-IL8 therapy and close monitoring. In patients who are acutely ill or deteriorating, particularly those displaying end-organ damage, HLH-specific therapy would be initiated per institution specific protocols.