A Pilot Study of Momelotinib in combination with Hypomethylating Agent for Chronic Phase Myelodysplastic Syndromes/ Myeloproliferative Overlap Neoplasms and Chronic Neutrophilic Leukemia (M-HArbOr)

IND Sponsor/Principal Investigator:	Tania Jain, MBBS The Sidney Kimmel Comprehensive Cancer Center (SKCCC) at Johns Hopkins 1650 Orleans St. CRB1 Rm 3M88 Baltimore, MD 21287 PH: 410-955-7035 Fax: 410-955-1969 Email: tjain2@jhmi.edu
Statistician:	Ravi Varadhan, PhD
Co-investigators:	Mark Levis, MD, PhD
IND Number"	177627
Investigational Agent:	Momelotinib provided by GlaxoSmithKline (GSK)
Protocol Version:	26SEP2025

NCT07071155

The study will be conducted according to the protocol and in compliance with Good Clinical Practice (GCP), with the Declaration of Helsinki, and with other applicable regulatory requirements.

Table of Contents

1.0 PROTOCOL SYNOPSIS

A Pilot Study of Momelotinib in combination with Hypomethylating Agent for Chronic Phase Myelodysplastic Syndromes/Myeloproliferative Overlap Neoplasms and Chronic Neutrophilic Leukemia (M-HArbOr)

Principal investigator: Tania Jain

Hypothesis: Momelotinib (MMB) in combination with hypomethylating agent (HMA) will be efficacious in clinical and erythroid responses in patients with myelodysplastic syndromes/ myeloproliferative overlap neoplasms (MDS/MPN) and chronic neutrophilic leukemia (CNL)

Study design: This is an open-label study of MMB-HMA in MDS/MPN and CNL. We will enroll a total of 18 evaluable patients using a modified 3+3 dose escalation design followed by expansion.

Dose Escalation Phase:

- The first 3 patients will receive MMB 150 mg daily in combination with azacitidine
- If 0/3 patients experience dose-limiting toxicities (DLTs) during the DLT evaluation period, we will escalate to MMB 200 mg daily
- If 1/3 patients experience a DLT at 150 mg, we will enroll 3 additional patients at 150 mg:
    - If 1/6 total patients experience DLTs, we will escalate to 200 mg
    - If 2/6 patients experience DLTs, 150 mg will be declared the maximum tolerated dose (MTD)
- If ≥2/3 (or >2/6) patients experience DLTs at 150 mg, then 150 mg will exceed the MTD and the study will be paused for safety analysis

Expansion Phase:

Once the MTD is determined (either 150 mg or 200 mg), all remaining patients up to the total of 18 evaluable patients will be treated at the MTD. If 200 mg is determined to be safe, approximately 12-15 patients will be treated at this dose level. DLTs will be assessed during the first 28 days of treatment. The definition of DLT is provided in **Section 8.2.7**. Continuous safety monitoring will occur throughout the study for all patients as detailed in **Section 12.3**.

Primary objective: The primary objective of this study is to obtain estimates of efficacy of MMB in combination with HMA (MMB-HMA) in MDS/MPN and CNL.

Key secondary objective: (1) To evaluate feasibility and safety of MMB-HMA in MDS/MPN and CNL. (2) To evaluate erythroid response with MMB-HMA (3) To evaluate spleen size reduction with MMB-HMA in MDS/MPN and CNL (4) To evaluate patient-reported outcomes with MMB-HMA in MDS/MPN and CNL (5) To evaluate the trough concentrations of MMB single agent and with HMA in MDS/MPN and CNL.

Accrual objective: The accrual goal is 18 evaluable patients with MDS/MPN or CNL.

Accrual period: We anticipate an accrual period of two years.

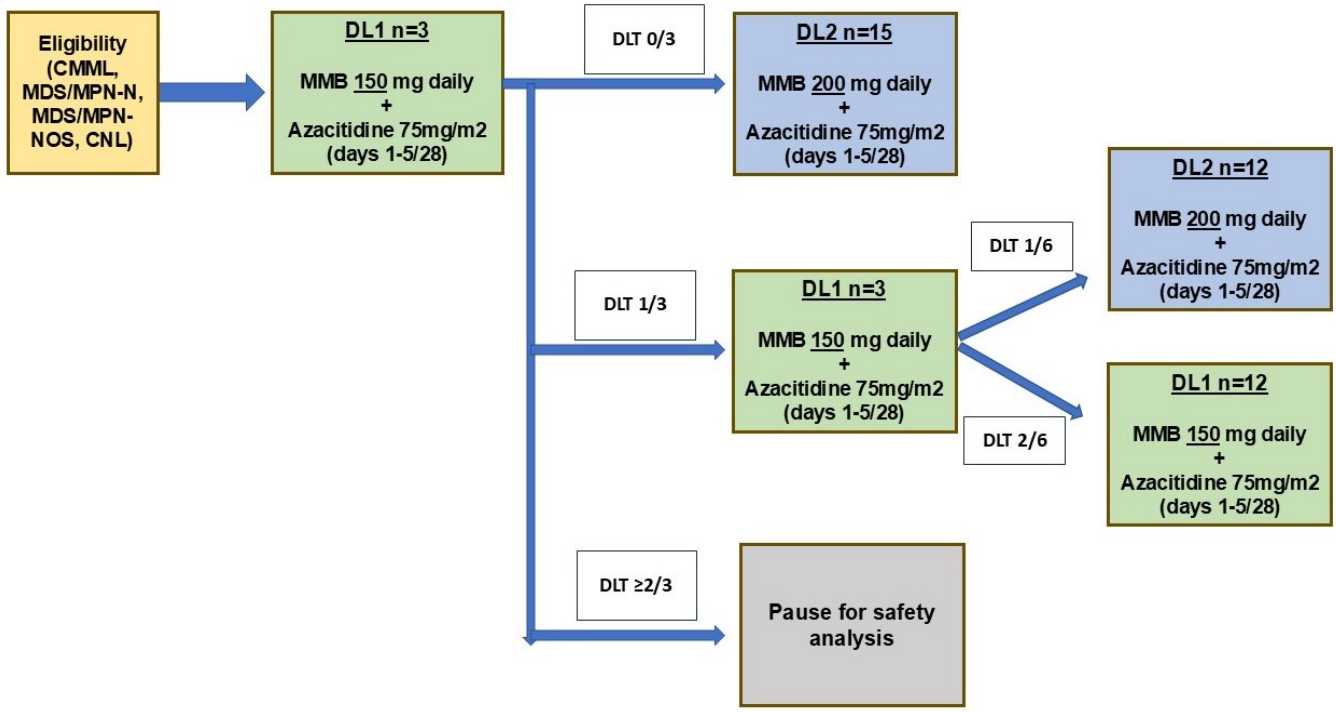
Key eligibility criteria:

(1) Patients with a WHO diagnosis of chronic myelomonocytic leukemia (CMML), MDS/MPN-not otherwise specified (MDS/MPN-NOS), MDS/MPN with neutrophilia (MDS/MPN-N), CNL[1,2].
(2) Age >=18 years
(3) Blood counts with platelets >25,000/microL, ANC >=0.75 x 10^9/L (without transfusion or growth factor support)
(4) Baseline splenomegaly with ≥5 cm below costal margin or ≥450 cm^3 on imaging (ultrasound, CT or MRI)

Treatment Description: All patients regardless of race or gender who fit the eligibility criteria will be considered for this study. MMB will be administered at a dose of 150mg daily for the first 3 patients and escalated to 200 mg daily for the remaining patients, unless DLT criteria are met[3]. Azacitidine will be administered at 75 mg/m^2 for days 1-5 in a 28-day cycle subcutaneously or intravenously.

2.0 TREATMENT SCHEMA

Figure 1: Treatment schema for MMB-HMA in MDS/MPN and CNL



3.0 STUDY OBJECTIVES

3.1 Primary objectives

The primary objective of this study is to obtain estimates of efficacy of MMB in combination with hypomethylating agent (MMB-HMA) in MDS/MPN and CNL.

Primary endpoints: Complete response, partial remission or clinical benefit per MDS/MPN IWG criteria[4] assessed at 24 weeks.

3.2 Secondary objectives

(1) To evaluate feasibility and safety of MMB-HMA in MDS/MPN and CNL
(2) To evaluate erythroid response with MMB-HMA
(3) To evaluate spleen size reduction with MMB-HMA in MDS/MPN and CNL
(4) To evaluate efficacy of MMB-HMA on patient-reported outcomes in MDS/MPN and CNL
(5) To evaluate the trough concentrations MMB with HMA in MDS/MPN and CNL.

Secondary endpoints:
(1) Feasibility will be defined as the proportion of patients who maintain 60% relative dose intensity for 24 weeks.
(2) Incidence, severity, and duration of adverse events will be assessed on an ongoing basis while patients are on treatment, using CTCAE version 5.0 and evaluated by predetermined physical exam, laboratory values for blood counts and chemistries.
(3) Erythroid response will be evaluated at 12 weeks and 24 weeks, and defined by hemoglobin increase by ≥2.0 g/Dl in patients with anemia at enrollment or transfusion independence for ≥8 weeks for patients requiring at least 4 packed red blood cell (PRBC) transfusions in the 8 weeks prior to initiation of treatment[4].
(4) Spleen response will be evaluated at 12 weeks and 24 weeks, as reduction in spleen volume of ≥ 35% from baseline and by spleen response by consensus response criteria[3,4].
(5) Patient reported outcomes (PRO) will be evaluated by 50% reduction in MPN-SAF TSS from baseline at week 12 and week 24 and patient's global impression of change (PGIC) at week 12 and week 24[5].
(6) Trough plasma concentration for MMB and metabolite M21 will be measured as a trough (approximately 20-26 hours after the previous dose of MMB an prior to the next dose on study intervention) at 12 weeks and 24 weeks in 10 patients.

3.3 Tertiary/exploratory objectives

Additional exploratory objectives will include estimates of survival, transplantation outcomes in those who undergo a blood or marrow transplantation (BMT) especially

with mutations in *EZH2, RUNX1*, or *SETBP1,* responses in specific somatic mutations especially combinations of *ASXL1/SRSF2/SETBP1*, single cell RNA sequencing, cell free DNA analysis for evaluation of clonal signatures, and CCRL2 evaluations to determine genomic aberrations and mechanism of resistance or relapse to MMB-HMA.

4.0 BACKGROUND AND RATIONALE

4.1 Unmet need in MDS/MPN

Myeloproliferative/ myelodysplastic neoplasms (MDS/MPN) are clonal myeloid malignancies including chronic myelomonocytic leukemia (CMML), MDS/MPN with neutrophilia (MDS/MPN-N, also known as *bcr-abl1* negative atypical chronic myeloid leukemia, aCML), MDS/MPN with SF3B1 and thrombocytosis (MDS/MPN-SF3B1-T, previously called as MDS/MPN with ringed sideroblasts and thrombocytosis) and MDS/MPN-not otherwise specified (MDS/MPN-NOS, also referred to as MDS/MPN-unclassified)[1,2]. Chronic neutrophilic leukemia is a rare clonal MPN. While rare and heterogenous, these diagnoses have common features of Philadelphia chromosome negativity, proliferative or hypercellular along with dysplastic marrow features, commonly seen extramedullary hematopoiesis, and blood count aberrations including leukocytosis, anemia and thrombocytosis or even thrombocytopenia.

The diagnosis in MDS/MPN is based on features of bone marrow morphology, blood counts and molecular findings. The genomic landscape in MDS/MPN is diverse, an aid to diagnosis of subtype of MDS/MPN, and bears prognostic value. While cytogenetics and copy number analysis are often normal, gene mutations are a common feature seen in over 90% patients with MDS/MPN. In CMML, co-expression of TET2 and SRSF2 mutations results in shift towards monocytosis, and subsequent acquisition of ASXL1 or growth signaling mutations such as *NRAS* or *CBL* result in high-risk disease[6,7]. Mutations in *SETBP1* and *CSF3R* occur commonly in MDS/MPN-N and CNL[8,9]. *ETNK1* mutations were recently reported in about 9% MDS/MPN-N but also seen in a smaller fraction of CMML[8,10]. MDS/MPN-NOS is the subtype is that is the least defined. Common mutations reported here include epigenetic regulators (*ASXL1, TET2*), spliceosome pathways (*SRSF2, ZRSR2, U2AF1*), signal transduction pathways (*JAK2, NRAS*), and *TP53* which invariably has a negative impact on survival[7].

Despite the heterogeneity, the diagnostic entities in MDS/MPN overlap have shared marrow features, and treatment options for all of these diagnoses remain limited while prognosis is dismal. In patients with high risk or advanced disease, survival is under 2 years[11]. Many patients are not candidates for potentially curative allogeneic

bone or marrow transplantation (BMT) due to lack of disease control or advanced age or comorbidities. Despite BMT, relapse as well as nonrelapse mortality remains a challenge[12-14].

4.2 Current treatment landscape in MDS/MPN

Current treatment options for MDS/MPN are limited and often include hypomethylating agents and in select eligible patients, BMT. However, responses with either are low. Our data and others' have shown that responses to HMA are minimal, short-lived, and never curative[15-17]. Even if clinical response is noted, there is no reduction in mutational burden or elimination of the mutant clone[16,17]. Prior studies have explored the role of other agents in MDS/MPN based on data from MDS or myelofibrosis. Hydroxyurea has resulted in responses but at the cost of anemia and pancytopenia[18,19]. Additionally, transformation to acute leukemia was notably higher with hydroxyurea compared to decitabine[18]. Use of interferon resulted in little clinically meaningful improvement[20].

While there is no established standard for treatment in chronic phase, HMAs are commonly used to control myeloproliferation, decrease splenomegaly, and alleviate other disease-related symptoms or cytopenias. The applicability of HMA in MDS/MPN overlaps is derived from its use in MDS and CMML. HMA are often used as a bridge to transplant, and in those with no targetable mutations in MDS/MPN overlap neoplasms, which is most commonly the case. Responses, however, have remained poor, highlighting the significant unmet need for MDS/MPN overlap which have a unique biology and often do not have targetable mutations (data from prior studies summarized below). More recently, JAK inhibitors have been used either as a single agent or in combination with HMA in this disease with the demonstration of activation of JAK-STAT pathway in CMML or by virtue of CSF3R mutations[21,22]. Data that exist to date on the use of HMA or JAK inhibitors or combination thereof is summarized below:

Reference	Agent	Diagnosis included	Response rates	Duration of response	Survival outcomes
Hypomethylating agent alone (Azacitidine or decitabine)					
Adès et al. 2013[23]	Azacitidine	CMML (n=76)	43% response by IWG 2006, 17% CR	Variable; patients who achieved a response had better OS (median 29.6 mo vs 19 mo)	Median survival 26 mo
Kongtim et al. 2016[24]	Azacitidine or decitabine in 37 (all patients	CMML (n=47 with CMML-1/2,	41% complete remission/ marrow complete		Post-transplant PFS was

	included were treated with HMA as bridge to BMT)	n=36 with post-CMML AML)	remission with Aza or Dec		superior with HMA (43%) vs other therapies (27%)
Coston et al. 2019[25]	Azacitidine (n=56) or decitabine (n=65)	CMML (n=121)	41% response by IWG MDS/ 56% by MDS/MPN IWG, CR <20%; no difference by Aza or Dec	Median duration of best response 4-6mo	Median survival HMA treated 31 mo (vs 18mo with conventional care)
Duchman et al. 2018[26]	Azacitidine (n=68) or decitabine (n=106)	CMML (n=174)	52% ORR, 17% CR by IWG 2006; responses not different by Aza or Dec	NR	Median survival 23 mo
Sun et al. 2023[27]	HMA (N=9)	aCML (N=31)	ORR 33.3% to HMA	NR	Median survival 20 mo
Jain et al. 2023[28]	Azacitidine or decitabine	aCML (N=13)	8/13 had improvement in leucocytosis	Variable	Variables
Kong et al. 2019[29]	Decitabine	aCML (N=7, overall cohort n=54)	NR	NR	Median survival 10 mo for the overall cohort
Triguero et al. 2022[30]	Azacitidine	CMML (n=91)	58% ORR by MDS/MPN IWG	14 mo	Median survival 24 mo
Tong et al. 2015[31]	Decitabine	aCML (n=4)	3/4 CR by MDS IWG	Hematological response 1-2.5mo	
Hausman et al. 2016[32]	Decitabine	aCML (n=1)	Hematological response and transfusion independence	NR	Underwent transplant
Jiang et al. 2016	Decitabine	aCML (n=2)	Marrow response and hematological response in both patients	NR	NR
JAK inhibitors alone					
Dao et al. 2014[33]	Ruxolitinib	aCML (n=1), *CSF3R T618I* mutated	Improvement in blood counts, reduction of spleen/symptoms	NR	NR

Padron et al. 2016[34]	Ruxolitinib	CMML (n=20)	Total response rate (combining IWG MDS2006 and spleen response) 35%	NR	
Padron et al. 2022 (abstract)[35]	Ruxolitinib	CMML (n=29)	MDS/MPN IWG ORR 17%, Clinical benefit 66%	NR	Median OS 24 mo
Kuykendall et al. 2024 (abstract)[36]	Fedratinib	aCML (n=6), CNL (n=5), MDS/MPN-U (n=7), MDS/MPN-RS-T (n=6)	53% at week 24	NR	Median OS 19.7mo
Hypomethylating agent plus JAK inhibitor					
Assi et al. 2017[11]	Ruxolitinib plus azacitidine	CMML (n=17), MDS/MPN-U (n=17), aCML (n=4)	57% objective response by MDS/MPN IWG 2015. 75% with pretreatment splenomegaly had >50% reduction in splenomegaly. 45% responders responded only after addition of azacitidine	Median 8 mo (range, 2.3-32 mo)	CMML: 15.1 mo, MDS/MPN-U: 26.5 mo, aCML: 8 mo
Montalban-Bravo et al. 2021[37]	HMA alone (n=19), HMA Rux (n=6), Ruxolitinib (n=5), HMA combination (N=4), Chemotherapy (n=3)	aCML (n=65)	ORR for HMA 26%, HMA Rux 0, Ruxolitinib 9%, HMA combination 50%, Chemotherapy 100%	Median 2.7 mo	Median survival 25 mo

aCML, atypical CML; CMML, chronic myelomonocytic leukemia; HMA, hypomethylating agent; IWG, international working group; MDS/MPN-U, MDS/MPN overlap unclassified; NR, not reported; ORR, overall response rate.

With BMT, potential cures are possible[12-14,38]. In a single center study from the Mayo Clinic, BMT resulted in overall survival was 55%, relapse 29% and nonrelapse mortality 25% at a median follow up of 21 months[14]. In our multi-institution study, haploidentical donor BMT resulted in overall survival of 56%, progression-free survival 48%, relapse 27% and NRM 25% at 3 years with graft failure in 6% patients[12]. These outcomes with

BMT are overall inferior to those expected with acute myeloid malignancies. We believe that this difference is at least in part due to limited bridging therapies for MDS/MPN and lack of disease control or remission prior to BMT in MDS/MPN. Furthermore, many patients cannot even get to BMT due to poor disease control. Our study demonstrated suboptimal disease control in the form of enlarged spleen or increased blasts at the time of BMT specifically increase risk of relapse[12]. Hence, better approaches for bridging to BMT need to be explored in MDS/MPN.

The advances in therapies for MDS/MPN are limited by the lack of understanding of the underlying biology, limitations in classification, and implications of molecular profile. Clinical trials often exclude these diagnoses aimed at MDS or MPN, due to presumed poor prognosis. This in turn limits further understanding of underlying biology and pathophysiology of MDS/MPN. In the presence of *RUNX1, EZH2*, and *SETBP1,* responses to HMA are almost non-existent[15]. Additionally, specific mutation combination of *ASXL1, SRSF2*, and *SETBP1* portends a significantly poor prognosis and is commonly accompanied with growth signaling mutations[28]. Hence, inclusion of molecular profiles in diagnosis as well as treatment responses is critical to further the field.

4.3 Rationale for momelotinib

Momelotinib (MMB) is a small molecular inhibitor of JAK1 and JAK2 and activin A receptor, type 1/activin-like kinase 2 (ACRV1/ALK2). Preclinical data demonstrate that MMB inhibits ACVR1-mediated expression of hepcidin in the liver, thereby increasing iron availability for erythropoiesis[39]. MMB inhibits ACVR1/ALK2, decreases hepcidin production, and ameliorates anemia of chronic disease in rodents.[40] The compound has demonstrated significant activity in vivo in JAK2-dependent nonclinical models. Momelotinib shows selectivity over other tyrosine and serine/threoninie kinases and potent in vitro inhibitory activity against JAK2 V617F mutant, which is seen in myelofibrosis and several MDS/MPN.

MMB has potent inhibitory in vitro activity against JAKV617F mutation, resulting in inhibition of JAK1 and JAK2 signaling events. Via inhibition of JAK2 signaling, it inhibits the formation of V617F mutant myeloid colonies suggesting a strong overall inhibition of JAK-STAT pathway. MMB has demonstrated activity in both in vitro JAK2-dependent cellular assays and in in vivo animal models. In addition to JAK-STAT pathway inhibition, MMB also has a unique mechanism of inhibition of ACVR1 which offers the possibility of anemia improvement.

The biology of MDS/MPN is complex and remained poorly understood until recently. A growing body of data now suggests that GM-CSF hypersensitivity that signals via JAK-STAT pathway plays a major role in CMML and other MPNs[22,34]. Not surprisingly, JAK inhibitors like ruxolitinib have demonstrated promising activity in CMML and other MDS/MPN[34,41], demonstrating the therapeutic potential of targeting JAK-STAT signaling in MDS/MPN. Anemia is commonly seen at presentation in MDS/MPN. The drivers of anemia in these diagnoses can be complex including clonal proliferation, progressive fibrosis, sequestration due to splenomegaly, and exacerbation of myelosuppression by commonly used JAK inhibitors, ruxolitinib or fedratinib. Furthermore, these patients also have anemia resulting from chronic inflammation due to hyperactivation of ACVR1/hepcidin axis and chronically elevate inflammatory cytokines as seen in MPNs[42]. High circulating hepcidin levels interfere with iron metabolism and decrease iron absorption from the gut, increasing iron retention within cellular stores and decreasing iron availability for effective erythropoiesis, despite iron overload from recurrent transfusions. Hepcidin production can also be stimulated through interleukin-6 induced JAK-STAT signaling, leading to significant elevation of hepcidin in anemia patients with MPNs[43]. Importantly, JAK-STAT-directed hepcidin production is dependent on basal level of ACVR1/SMAD1/5/8 signaling, and thus dysregulated hepcidin cannot be corrected by JAK-STAT inhibition alone[44-46]. Taken together, these data suggest that hyperactivation of ACVR1 and dysregulated JAK-STAT signaling result in loss of iron hemostasis and iron-restricted anemia in MPNs. Ruxolitinib and fedratinib are potent inhibitors of JAK-STAT signaling but lack activity against ACVR1. In contrast, MMB results in inhibition of ACVR1-mediated expression of hepcidin in the liver and consequently the anemia benefit that has been reported in myelofibrosis[3,39,40,47].

4.4 Rationale for momelotinib and hypomethylating agents

Pre-clinical work from the Karantanos lab at the Johns Hopkins School of Medicine has shown high C-C motif atypical chemokine receptor-like 2 (CCRL2) expression in CD34+ cells from MDS/MPN patients[48]. CCRL2 induces JAK2/STAT signaling[48] and CCRL2-expressing cells while refractory to azacitidine, show high sensitivity to the JAK2 inhibition[49]. HMAs remain the mainstay of treatment in MDS/MPN and CNL. We hypothesize that the combination of HMA and MMB will allow for improved efficacy of HMA by improving resistance conferred by high CCRL2 expression in MDS/MPN. Furthermore, HMA and JAK inhibitors have independent activity in MDS and MPN, respectively[50,51]. MMB specifically has demonstrated spleen size reduction in 26.5% patients as well as ≥50% reduction in total symptom score in 28.4% patients in patients who had not been treated with a JAK inhibitor in the past[51].

Furthermore, toxicity profiles of HMA and MMB are non-overlapping. Previously, the safety and efficacy of combination of HMA and JAK inhibitors has been reported with ruxolitinib in MPNs and MDS/MPN[11,52]. We have observed no unexpected side effects with combining HMA with momelotinib or fedratinib in the Johns Hopkins Leukemia Clinic in MPN patients. We have used MMB at 200 mg daily in at least 2 patients who have been on treatment for over 2 months at the time of this writing. Hence, in this study, we propose a treatment combination of HMA and MMB with a goal to improve disease features as well as to specifically improve anemia.

Given the availability of luspaterecept for MDS/MPN with SF3B1 mutation and overall lower risk of this entity, we will only include CMML, MDS/MPN-N, MDS/MPN-NOS, and CNL in this study. Additionally, mechanisms of anemia in MDS/MPN with SF3B1 mutation are likely not driven by ACVR1 overexpression. Hence the rationale for the role of MMB in this entity is unclear.

In summary, we propose a clinical trial of momelotinib in combination with hypomethylating agent (MMB-HMA) in patients with chronic (<10% blasts) phase MDS/MPN to evaluate efficacy and safety in this patient population.

5.0 DRUG INFORMATION

5.1 Pharmacology and clinical safety profile

MMB is a potent and selective small-molecule inhibitor of JAK1, JAK2, and ACRV1/ALK2. MMB shows selectivity over other tyrosine and serine/threonine kinases and potent in vitro inhibitory activity against the JAK2V617F mutant signaling. MMB has demonstrated significant activity in JAK2-dependent models[53]. Additionally, MMB inhibition of ACVR1 results in reduced SMAD1/5/8 signaling, reduction of hepatic hepcidin transcription, and consequently increased erythropoiesis in a rodent model of anemia of chronic disease[39,40].

MMB has been investigated in 22 studies including phase 1, 2 and 3 clinical trials. Of these, 21 studies have been completed, which includes 6 in healthy volunteers, 8 in patients with MPNs, 4 in solid tumor patients, 1 in patients with renal impairment, 1 in patients with hepatic impairment. Overall, 1423 subjects have been dosed with MMB so far. Molecular enzyme and receptor binding studies indicate that MMB demonstrated little propensity for common receptor- and enzyme-mediated drug-induced adverse events (AEs). In addition, in vitro studies with Caco-2 cells indicated that MMB and M21 do not

inhibit thiamine transport[54]. MMB was metabolized via multiple metabolic pathways and was eliminated as a combination of metabolites and unchanged parent drug. MMB metabolism involved oxidation and scission of the morpholine ring, amide hydrolysis, N-dealkylation, nitrile hydrolysis, nitrile oxidation, and taurine conjugation of the cyanomethylamide. Metabolite profiling identified 3 major metabolites: an amide hydrolysis product M19, a morpholino cleavage metabolite M20, and a morpholino lactam metabolite M21. M21 is the major and pharmacologically active circulating plasma metabolite in humans, and M19 is the major metabolite in mice, rats, and dogs. Cardiovascular safety pharmacology studies indicate that MMB does not significantly affect cardiovascular parameters at pharmacologically relevant doses. A dose of 100 mg/kg MMB decreased arterial blood pressure and concurrently increased heart rate. QTc intervals were not notably altered by MMB administration and exposure at this dose level was approximately 4-fold above the estimated free drug Cmax in patients with MF. MMB was presented for the phase 3 clinical trials as film-coated tablets containing 50 mg, 100 mg, 150 mg or 200 mg of MMB (free base equivalent) as its dihydrochloride monohydrate salt.

The pharmacokinetics of MMB were evaluated in various phase 1,2 and in 3 phase 3 studies, SIMPLIFY-1 (GS-US-352-0101), SIMPLIFY-2 (GS-US-352-1214), and MOMENTUM (SRA-MMB-301)[3,51,55]. In SIMPLIFY-1, and MOMENTUM (SRA-MMB-301), in addition to trough PK samples in multiple visits, frequent PK samples were collected at week 2 in a subgroup of myelofibrosis patients (approx. 20 patients in each study). The data from the PK subgroups of subjects with myelofibrosis from studies SIMPLIFY-1 and SIMPLIFY-2 were pooled together. The Cmax range was 104 to 1050 ng/mL (median 437 ng/mL) and the AUC range was 608.4 to 6748 ng h/mL (median 2918 ng h/mL)[56].

The effect of renal impairment on the PK and safety of MMB was evaluated in Study GS-US-352-1152 following a single dose of MMB 200 mg. No differences in exposure of MMB or its metabolites M21 (Cmax and AUC) were observed between subjects with moderate or severe renal impairment and matched healthy control subjects. Therefore, dose adjustments of MMB are not necessary in subjects with mild to severe renal impairment.

The effect of hepatic impairment on the PK and safety of MMB was evaluated in Study GS-US-352-1153 following a single dose of MMB 200 mg. The observed differences in plasma exposures of MMB and its M21 metabolite between subjects with moderate hepatic impairment and healthy control subjects were not considered to be clinically relevant.[57] Therefore, dose adjustments of MMB are not considered necessary in subjects with mild or moderate hepatic impairment. In patients with severe hepatic impairment, however, MMB AUC_{∞} was increased (GMR, 197%; 90%CI, 129%–301%), and M21 AUC_{∞}

was decreased (GMR, 52%; 90%CI, 34%–79%). Therefore, patients with severe hepatic impairment (Child-Pugh Class C), if enrolled, will be started at 150 mg momelotinib once daily.

5.2 Momelotinib data from clinical trials

5.2.1 SIMPLIFY-1 Study

SIMPLIFY-1 was an international, randomized, double-blind, active-controlled phase 3 study evaluating MMB versus ruxolitinib in 432 subjects with myelofibrosis, previously untreated with a JAK inhibitor[51]. MMB was non-inferior to ruxolitinib for spleen response rate at week 24 with 26.5% (57 subjects) in the MMB group and 29.5% (64 subjects) in the ruxolitinib group achieved this endpoint. A lower percentage of subjects in the MMB group (28.4%) achieved a TSS response compared with the ruxolitinib group (42.2%) at week 24 (statistically did not meet non-inferiority).

A greater proportion of subjects in the MMB group were TI at week 24 (66.5%) compared with the ruxolitinib group (49.3%, Figure 2), i.e., had no RBC transfusion and no hemoglobin level below 8 g/dL in the prior 12 weeks, excluding cases associated with clinically overt bleeding. This difference was nominally significant ($p < 0.001$). A smaller proportion of the MMB group was transfusion dependence at week 24 (30.2%) compared with the ruxolitinib group (40.1%), i.e., had ≥ 4 units of RBC transfusion or a hemoglobin level below 8 g/dL in the prior 8 weeks, excluding cases associated with clinically overt bleeding. This difference was nominally significant ($p = 0.001$).

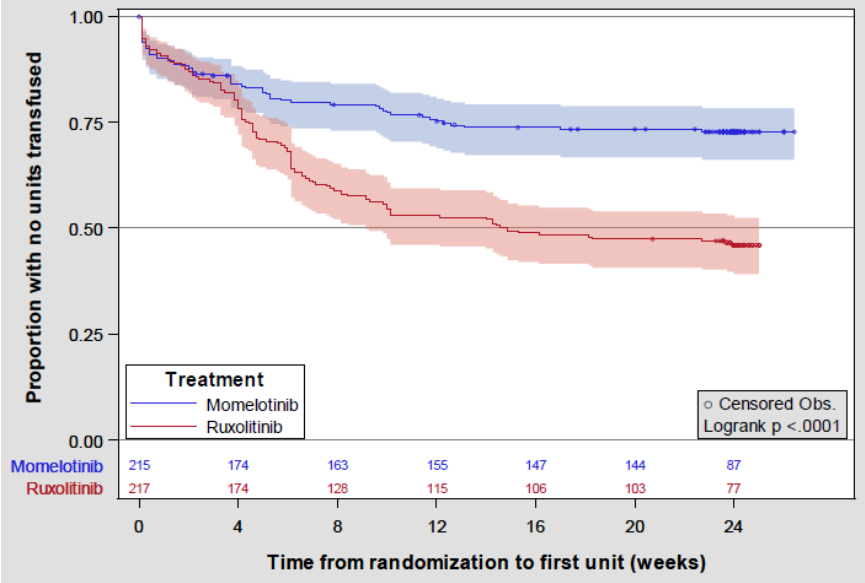


Figure 2: Kaplan Meier Estimates of proportion of Patients Not Requiring RBC Transfusion During 24 Weeks of Ruxolitinib or MMB Treatment (SIMPLIFY-1)

5.2.2 SIMPLIFY-2 Study

SIMPLIFY-2 was an international, randomized, open-label, phase 3 study evaluating MMB versus best available therapy (BAT) in 156 subjects with MF who were previously treated with ruxolitinib[55]. A similar proportion of subjects had a splenic response at week 24 in the MMB group (7 subjects, 6.7%) compared with the BAT group (3 subjects, 5.8%), which was treated with ruxolitinib in 89% of patients. A substantially higher, and nominally statistically superior TSS response rate at week 24 was observed in MMB-treated subjects compared to those in the BAT control group (26.2%) and (5.9%) respectively MMB (nominal $p < 0.001$), a 4-fold improvement. A greater proportion of subjects in the MMB group were transfusion independent at week 24 (43.3%) compared with the BAT group (21.2%), i.e, had no RBC transfusion and no hemoglobin level below 8 g/dL in the prior 12 weeks. The median rate of RBC transfusion (excluding cases associated with clinically overt bleeding) was lower in the MMB group (0.5 units/month) compared with the BAT group (1.2 units/month) at week 24. This was despite the imbalance in the baseline inclusion where all patients had required either an RBC transfusion or a dose reduction while on ruxolitinib (prior to MMB treatment on SIMPLIFY-2) and had grade 3 thrombocytopenia, anemia or bleeding. Additionally, 58% of patients in the MMB arm required a dose reduction of ruxolitinib and had these grade 3 adverse events, compared with 39% of patients in the BAT arm. Furthermore, 40% of patients in the MMB group did not need transfusions over the treatment period compared with 27% of patients in the

BAT group. Throughout the study, mean hemoglobin and mean platelet counts were higher in the MMB arm compared to the BAT arm.

5.2.3 MOMENTUM Study

MOMENTUM is an international, randomized, double-blind, active-controlled, phase 3 study intended to confirm the differentiated clinical benefit of MMB versus danazol in symptomatic, anemic subjects with myelofibrosis who have previously received approved JAK inhibitor therapy[3]. The study met its primary efficacy endpoint of statistically significant superiority of MMB [24.6% (95% CI: 17.49, 32.94)] over danazol [9.2% (95% CI: 3.5, 19.0)] in the proportion of subjects with ≥ 50% reduction in symptoms from baseline at week 24 in MFSAF TSS. Transfusion independence at week 24 was 30.8% (95% CI: 23.0, 39.5) for the MMB group and 20.0% (95% CI: 11.1, 31.8) for the danazol group. Lastly, spleen response rate was 40.0% (95% CI: 31.5, 49.0) for the MMB group and 6.2% (95% CI: 1.7, 15.0) for the danazol group (Figure 3). All patients on this study had received prior ruxolitinib and 5% had also been treated with fedratinib prior to enrollment on this trial.

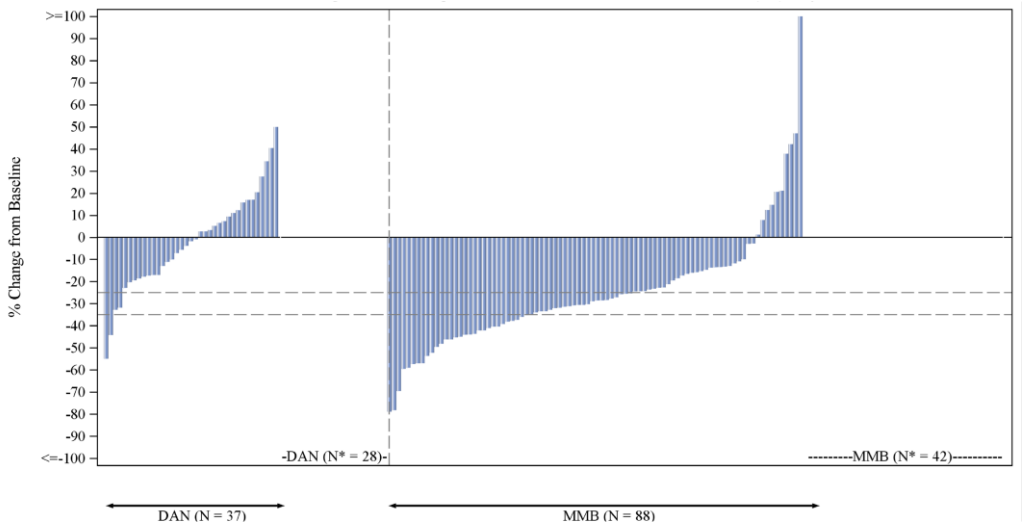


Figure 3: Percent Change from Baseline in Spleen Volume at Week 24 for Each Subject in MOMENTUM study

5.3 Known potential risks

In prior studies, cytopenias and gastrointestinal side effects have been reported with MMB. In SIMPLIFY-1, most common adverse events included thrombocytopenia

(18.7%), diarrhea (18.2%), and headache (17.8%). In the group of patients exposed to MMB, the most commonly reported Grade 3 or 4 adverse events were thrombocytopenia (13.4%), anemia (11.7%), pneumonia (7.3%) and hypertension (4.9%). In SIMPLIFY-2, the most commonly reported adverse events in the MMB group were diarrhea (32.7%), asthenia and nausea (19.2%), and cough and thrombocytopenia (17.3%); and the most common Grade 3 or 4 adverse events were anemia (22.9%), thrombocytopenia (15.3%), asthenia (7.6%) and neutropenia and pneumonia (6.3%). The 2 most commonly reported adverse events in MOMENTUM study were thrombocytopenia and diarrhea (22.3% each). Safety data from the above phase 3 randomized studies in the momelotinib clinical development program were pooled and analyzed. The most commonly reported adverse events include infections (39.7%), diarrhea (22.8%), thrombocytopenia (21.0%), nausea (16.7%), anemia (13.8%) and headache (13.4%). The most common Grade 3 or 4 events, occurring in at least 5% of subjects during randomized treatment with momelotinib, were thrombocytopenia (10.7%) and anemia (8.3%). As of March 14, 2025, based on a review of the GSK global safety database – including ongoing interventional and completed studies across all phases (n=1424) and post-marketing reports (1600 patient-years)---using the broad SMQ definition of severe cutaneous adverse reactions (SCARs), there were 3 cases of cutaneous adverse reactions that were severe and considered related to momelotinib (data available with GSK). There is no data on effects of MMB on human male or female fertility; however, in animal studies, MMB impaired fertility in rats. There are no data on the presence of MMB in human milk. MMB was present in rat pups following nursing from treated dams, with adverse effects in the offspring. A risk to the breastfed child cannot be excluded. Hence, patients must not breastfeed during treatment with MMB and for at least 1week after completing therapy.

6.0 STUDY DESIGN AND ENDPOINTS

6.1 Study design description

This is an open-label, phase 1 study of MMB-HMA in MDS/MPN and CNL.
Approximately 18 evaluable patients will be included in this study using a modified 3+3 dose escalation design followed by expansion.

Dose Escalation Phase:

- The first 3 patients will receive MMB 150 mg daily in combination with azacitidine
- If 0/3 patients experience dose-limiting toxicities (DLTs) during the DLT evaluation period, we will escalate to MMB 200 mg daily
- If 1/3 patients experience a DLT at 150 mg, we will enroll 3 additional patients at

150 mg:
    - If 1/6 total patients experience DLTs, we will escalate to 200 mg
    - If 2/6 patients experience DLTs, 150 mg will be declared the maximum tolerated dose (MTD)
- If ≥2/3 (or >2/6) patients experience DLTs at 150 mg, then 150 mg will exceed the MTD and the study will be paused for safety assessment

Expansion Phase:
Once the MTD is determined (either 150 mg or 200 mg), all remaining patients up to the total of 18 evaluable patients will be treated at the MTD. If 200 mg is determined to be safe, approximately 12-15 patients will be treated at this dose level. DLTs will be assessed during the first 28 days of treatment. The definition of DLT is provided in Section 8.2.7. Continuous safety monitoring will occur for the entirety of the study for all patients as detailed in Section 12.3.

6.2 Study endpoints

6.2.1 Primary endpoints

To evaluate efficacy with MMB-HMA in MDS/MPN and CNL, we will measure the proportion of patients who achieve a clinical response at week 24 (compared to baseline) defined as complete response, partial remission or clinical benefit by international consortium response criteria for MDS/MPN in adults[4].

6.2.2 Secondary endpoints

(1) To evaluate **feasibility and safety** of MMB-HMA in MDS/MPN and CNL, we will:
(i) Determine the proportion of patients who maintain 60% relative dose intensity for 24 weeks.
(ii) Measure the incidence, duration, and severity of adverse events per CTCAE v.5.0 as reported from physical exams, changes in vital signs, laboratory data including hematology parameters and serum chemistry.
(iii) Determine the proportion of patients experiencing grade ≥ 3 adverse events or severe adverse events as defined by CTCAE v.5.0

(2) To evaluate **erythroid response** with MMB-HMA in MDS/MPN and CNL (in patients with anemia at enrollment), we will:
(i) Determine the proportion of patients who achieve erythroid response at week 12 per international consortium criteria

(ii) Determine the proportion of patients who achieve erythroid response at week 24 per international consortium criteria

(3) To evaluate **spleen size reduction** with MMB-HMA in MDS/MPN and CNL, we will:
(i) Determine the proportion of patients who achieve a spleen response at week 12 per international consortium criteria
(ii) Determine the proportion of patients who achieve a spleen response at week 24 per international consortium criteria
(iii) Determine the proportion of patients who achieve a spleen volume reduction of ≥ 35% from baseline at week 12
(iv) Determine the proportion of patients who achieve a spleen volume reduction of ≥ 35% from baseline at week 24

(4) To evaluate efficacy of MMB-HMA on **patient-reported outcomes** in MDS/MPN and CNL, we will:
(i) Evaluate the proportion of patients who have a 50% reduction in MPN-SAF TSS from baseline to week 12 in patients with baseline TSS ≥ 10
(ii) Evaluate the proportion of patients who have a 50% reduction in MPN-SAF TSS from baseline to week 24 in patients with baseline TSS ≥ 10
(iii) Evaluate the overall change in MPN-SAF TSS compared to baseline at week 12
(iv) Evaluate the overall change in MPN-SAF TSS compared to baseline at week 24
(v) Evaluate the patient's global impression of change (PGIC) at week 12 (**Appendix 4**)
(vi) Evaluate the PGIC at week 24

(5) To evaluate the trough concentrations of MMB single agent and with HMA in MDS/MPN and CNL:
(i) Evaluate trough concentrations of MMB at week 12 and at week 24 in 10 patients
(ii) Evaluate trough concentrations of metabolite M21 at week 12 and 24 in 10 patients

6.2.3 Exploratory endpoints

(1) To evaluate survival, we will estimate overall survival defined as time from first treatment to death from any cause. For reference, the median overall survival in the diagnoses included in around 2 years.

(2) To estimate outcomes of BMT in the subset of patients undergoing BMT following treatment with MMB-HMA, especially in patients with *EZH2, SETBP1* or *RUNX1* mutations.

(3) To estimate responses in specific mutation combinations, we will correlate responses with somatic mutations specifically a combination of *ASXL1, SRSF2*, and *SETBP1*.

(4) To evaluate reduction in somatic mutation burden, we will use highly sensitive cell-free DNA from peripheral blood

(5) To evaluate the role of CCRL2 expression in MDS/MPN patient samples and MMB-HMA response, we will correlate response with CCRL2 expression in patient CD34+ cells.

(6) To evaluate additional mechanisms of resistance to MMB-HMA, we will obtain single cell analysis at week 12. To identify resistant clones and mechanism of resistance, we will evaluate single cell RNA sequencing in 3 responders and 2 non-responders.

7.0 PATIENT SELECTION

7.1 Inclusion criteria

1. Patients of age 18 or older with a diagnosis of MDS/MPN or CNL as specified below

2. Eligible diagnoses by WHO or ICC diagnostic criteria:

    - a. Chronic myelomonocytic leukemia
    - b. MDS/MPN with neutrophilia, previously known as atypical chronic myeloid leukemia
    - c. Chronic neutrophilic leukemia
    - d. MDS/MPN-not otherwise specified

3. Chronic phase disease with <10% blasts in peripheral blood and marrow within 1 month from planned start of treatment

4. Eastern Cooperative Oncology Group (ECOG) Performance Score[58] of 0-2 (**Appendix 5**)

5. Patients can be treatment naïve or could have undergone prior treatments for MDS/MPN as below:

a. Prior treatment with non-JAK inhibitors or hypomethylating agents are allowed (e.g., hydroxyurea, immunomodulatory agents, steroids). Hydroxyurea can be continued until or even beyond initiation of treatment for 2 months if needed for cytoreduction
b. If non-MMB JAK inhibitors were used for treatment and stopped due to side effects (e.g., anemia from ruxolitinib, gastrointestinal toxicity from fedratinib, etcetera), these patients will be allowed to enroll on this study as long as JAK inhibitor was stopped at least 2 weeks prior to anticipated start date of treatment
c. If prior hypomethylating agent was used and stopped longer than 3 months prior to anticipated start date of treatment due to side effects, these patients will be eligible. However, if hypomethylating agents were stopped due to lack of clinical benefit, these patients will not be deemed eligible
d. Prior treatment with erythropoietic stimulating agents is allowed if last treatment was more than 4 weeks prior to anticipated start date of treatment
e. Splenic radiation should have been performed more than 2 months before anticipated start date of treatment
f. Any prior or ongoing investigation therapy or agents should be stopped longer than 4 weeks of anticipated start date of treatment

6. Blood counts with platelets >=25,000/microL, ANC >=0.75 x 10^9/L (without transfusion or growth factor support)

7. Baseline splenomegaly with ≥5 cm below costal margin or ≥450 cm^3 on imaging (ultrasound, CT or MRI)

8. Adequate organ function with creatinine clearance measured by Cockcroft-Gault calculation ≥30 mL/min, total bilirubin ≤1.5×ULN (isolated bilirubin >1.5 x ULN is acceptable if bilirubin is fractionated and direct bilirubin <35%), INR ≤1.5 × ULN unless participant is receiving anticoagulant therapy as long as PT or aPTT is within the therapeutic range of intended use of anticoagulants, albumin ≥2.5 g/dL.

9. Patients who have previously undergone an allogeneic stem cell transplantation will be allowed to enroll as long as: BMT was > 6 months ago from screening, and there is no evidence of grade >1 acute GVHD, and there is no acute/chronic GVHD requiring systemic immunosuppression.

10. Willing and able to sign the informed consent form

11. Life expectancy > 24 weeks

12. Willing and able to complete patient-reported outcome assessments using an ePRO device according to protocol

13. Patients of child-bearing potential, or those with partners of child-bearing potential or pregnant or lactating partners, who are willing to follow highly effective contraceptive requirements. List of contraceptives allowed during the study is provided in Appendix 7. Females of reproductive potential should use effective contraception during study treatment and for 6 months following the last dose for HMA-MMB and 1 week following the last dose for MMB. Males with female partners of reproductive potential should use effective contraception during study treatment and for 3 months following the last dose for HMA-MMB and 1 week following the last dose for MMB. Patients should not breastfeed during treatment and for 1 week after the last dose.

14. Patients of child-bearing potential with a negative highly sensitive serum pregnancy test within 24 hours before the first dose of momelotinib.

7.2 Exclusion criteria

1. Diagnosis of MDS/MPN with SF3B1 mutation and thrombocytosis (excluded due to unclear role of ACRV1 in the pathogenesis of anemia)

2. Peripheral blood or marrow (by immunohistochemistry) blast percentage ≥10%

3. Prior lack of response to MMB or hypomethylating agents.

4. Known history of allergic reaction to momelotinib

5. AST or ALT above 2.5 x ULN (above 5 x ULN if liver is involved by extramedullary hematopoiesis as judged by the investigator or if related to iron chelator therapy that was started within the prior 60 days)

6. The following treatments within the time periods as specified:
   a. Momelotinib at any time prior to screening
   b. Erythropoietic stimulating agents within 4 weeks of treatment
   c. Investigational agent within 4 weeks of the first dose of study treatment
   d. Immunosuppressive agents within 28 days (low dose steroids ≤10 mg daily prednisone or equivalent is allowed)
   e. Potent cytochrome P450 3A4 (CYP3A4) inducers, except for rifampin and rifampicin, within 14 days prior to the first dose of momelotinib. Strong CYP3A4 inducers can lead to decreased MMB exposure and risk a lack of efficacy. Therefore, alternative medicinal product to strong CYP3A4 inducer should be considered.

   *Momelotinib is a BCRP inhibitor. Coadministration of momelotinib has the potential to increase the plasma concentration of BCRP substrates, such as rosuvastatin and sulfasalazine. While this is not an exclusion, participants should be monitored for adverse reactions with coadministration.

*Momelotinib is an organic anion transporting polypeptide (OATP) 1B1/1B3 substrate. Concomitant use with an OATP1B1/1B3 inhibitor may increase momelotinib exposure. While this is not an exclusion patients should be monitored for adverse reactions with coadministration with OATP1B1/1B3 inhibitors, including ciclosporin.

7. Unsuitable for spleen volume measurements due to prior splenectomy or unwilling or unable to undergo any imaging (ultrasound, CT without contrast or MRI without contrast) for spleen volume measurement per requirements

8. Patients with an active invasive concurrent malignancy, whose natural history or treatment has a significant potential to interfere with the safety or efficacy assessment of the investigational regimen. Localized prostate cancer that has been treated surgically or by radiotherapy with curative intent and presumed cured is allowed. History of non-melanoma skin cancers such as basal cell carcinoma or squamous cell carcinoma are also allowed. Completely resected intraepithelial carcinoma of cervix or papillary thyroid or follicular thyroid cancers are also allowed at the investigator's discretion.

9. Untreated or active infections are excluded as below:
   a. Chronic active or acute viral hepatitis A, B, or C infection. Participants with positive hepatitis C antibody due to prior resolved disease can be enrolled, only if a confirmatory negative hepatitis C RNA test is obtained. If HBsAg and/or anti-HBc antibody is positive, we recommend consultation with a hepatologist regarding monitoring for reactivation versus prophylactic hepatitis B therapy.
   b. HIV with CD4+ cell count under 400 cells/ μL or on treatment with anti-retroviral therapy that is specifically excluded per the criteria above. HIV patients on established anti-retroviral therapy allowed per protocol for at least 4 weeks and CD4+ count above or equal to 400 cells/ μL
   c. Infections requiring intravenous antibiotics

10. Nonhematologic toxicities from prior therapies that are unresolved and are of grade >1

11. Documented myocardial infarction or unstable/uncontrolled cardiac disease (e.g, unstable angina, congestive heart failure [New York Heart Association > Class III]) within 6 months of start of treatment.

12. Presence of peripheral neuropathy of grade ≥2

13. Pregnant women are excluded from this study because the effects of momelotinib on embryotoxicity, survival, and teratogenicity remain unclear. In animal models, reduced pup survival was reported in reproductive and developmental toxicity studies

14. Patients unable to swallow medications

15. Patient has any medical condition that puts the patient at an acceptable high risk with participation in the study per physician assessment or has any condition that confounds the ability to interpret data from the study.
16. Any major surgery or radiation or intervention that interferes with safety or feasibility of enrollment per investigator assessment

7.3 Registration procedure

The research nurse or data manager should be contacted to confirm a treatment slot is available before approaching a subject. All subjects must be registered with the Clinical Research Office at Johns Hopkins SKCCC before enrollment to study.

To register a patient, the following documents should be completed by the research nurse or Study Coordinator:

- Signed patient consent form
- Registration form
- Source documents

Subjects will be assigned a screening number (ID) at screening. The screening ID will be used on all correlative samples. Treatment may not begin until eligibility has been confirmed. The screening ID number will become the study ID. Instructions concerning correlative/special studies will be conveyed.

7.4 Early withdrawal or termination

The duration of each cycle is 28 days, and treatment is be planned until disease progression or unacceptable side effects. However, treatment on the clinical trial may be discontinued for any of the following reasons:

1. As mentioned above, disease progression by international consensus criteria[4] or lack of response (response to be considered as clinical benefit, partial response or complete response by international consensus criteria for MDS/MPN).
2. Any unacceptable adverse events
3. The patient (or legal guardian) may withdraw consent at any time for any reason. Consent withdrawn means that the participant has explicitly indicated that they

do not want to be followed any longer; in this case no further data, except data in the public domain, may be solicited from or collected on the participant. Consent may also be partial; participants may choose to discontinue study treatment and remain in the study to be followed for safety/disease assessments.

4. Further participation would be injurious to participant's health in investigator's medical assessment
5. Dosing delays lasting >12 consecutive weeks (discontinuation due to adverse events will be managed per Section 8.2.8)
6. Patient has a documented positive serum pregnancy test
7. Patient is lost to follow-up
8. Study termination by sponsor or by local authority or IRB
9. If during the course of the study, a participant is found not meeting eligibility criteria, study PI in collaboration with local investigator will determine whether the patient should be withdrawn from study treatment
10. If a patient is not able to comply with study treatment or study procedures in investigator's opinion, study PI in collaboration with local investigator will determine whether the patient should be withdrawn from study treatment

For these patients, end of treatment and follow-up procedures will be conducted as listed in **Section 8.3.1**. Every patient will be followed for 30 days following end of treatment for adverse events monitoring. If the participant discontinues study treatment and actively withdraws consent for collection of follow-up data (safety follow-up and/or disease assessment), then no additional data collection should occur; however, participants will have the option of withdrawing consent for study treatment but continuing in the follow-up period of the study for safety/efficacy assessments. Patients who discontinue for reasons other than progressive disease will have post-treatment follow-up for disease status and toxicity up to 30 days. After documented disease progression, each patient will be followed for overall survival until death, withdrawal of consent, or the end of the study, whichever occurs first.

7.5 Handling withdrawals or termination

Reasonable efforts should be made to maintain contact with a patient who withdraws early. If the patient remains at participant institution for further care, clinic visits may be tracked, and the condition of the patient followed. If the patient is not continuing care at SKCCC or another treating site, contact information will be updated at the end of treatment visit, including accurate phone numbers, and email address. The importance of the follow-up period for adverse events and serious adverse events will be stressed to the patient.

8.0 TREATMENT PLAN AND STUDY SCHEDULE

8.1 Study procedures and evaluations

8.1.1 Standard of care study procedures

Several procedures, laboratory and diagnostics will be conducted per standard of care for MDS/MPN and CNL. These will include physical examination, vital signs, complete blood count with differential, comprehensive metabolic profile, amylase, lipase, serum pregnancy test, bone marrow biopsy and aspirate including cytogenetics, FISH, heme malignancy fusion panel, and NGS from blood or marrow. During follow up, monitoring of physical examination, vital signs, complete blood count with differential, and comprehensive metabolic profile will occur following stand of care monitoring for any patient with MDS/MPN or CNL.

8.1.2 Study-specific procedures

Section 8.3.1 summarizes study events and evaluations to be performed at each visit and schedule of these visits. Individual procedures are described below. Additional procedures or evaluations may be deemed necessary at unscheduled times if deemed clinically necessary by treating investigator. Additional evaluations may be deemed necessary by study team for reasons of patient safety. In some cases, such evaluation/testing may be potentially sensitive in nature (e.g., HIV, Hepatitis B/C, etc.), and thus local regulations may require that additional consent be obtained from the patient. In these cases, such evaluations/testing will be performed in accordance with those regulations.

8.1.3 Pre-treatment evaluation and study procedures/evaluation

8.1.3.1 Informed consent

Prior to any study procedure or study-related evaluation, informed consent must be obtained and documented by the patient's dated signature or by the patient's legally acceptable representative's dated signature on a consent form. The dated signature of the person conducting the consent discussion must also appear on the consent form.

8.1.3.2 Assessment of inclusion/ exclusion criteria

All inclusion and exclusion criteria will be reviewed by the study team prior to initiation of treatment per the study. PI (or site PI at collaborating institutions) or sub-investigator will sign the inclusion/exclusion criteria and ensure that the patient qualifies for the clinical trial.

8.1.3.3 Demographics

Demographical information will be collected at clinic visit and will include birth date, age, sex, race, and ethnicity.

8.1.3.4 Medical history and concurrent medications

A detailed medical history will be obtained by the investigator or qualified designee. All active and prior medical conditions and any condition diagnosed that is considered to be clinically significant by the investigator, will be recorded. Details regarding the disease for which the patient has enrolled in this study will be recorded separately and not listed as medical history.

The investigator or qualified designee from study team will review patient medications at the start of screening visit and throughout the study period until the last dose of study treatment. Any medications that may be associated with SAEs should be recorded as defined in the SAE section of the protocol.

8.1.3.5 History and physical examination

Complete medical history should include particular attention to the following details:

a) Presentation for the current diagnosis
b) Previous treatment and response
c) Previous transfusions and transfusion reactions
d) Previous serious infections
e) Allergies
f) Current medications
g) Assessment of performance status

Patient's baseline symptoms that are present at the closest time before the start of the study drug will be evaluated and recorded. This will also include MPN-SAF TSS score (**see Appendix 3**). Detailed physical exam including spleen size by palpation

(craniocaudal dimension of spleen as palpable below costal margin) will be recorded by investigator. Clinically significant abnormal findings at baseline will be recorded.

8.1.3.6 Vital signs

The investigator or qualified designee from study team will record vital signs at screening visit and at each visit prior to administration of drug. Vital signs will include blood pressure, pulse rate, respiratory rate, temperature, height and weight.

8.1.3.7 Performance status

The investigator or qualified designee from study team will record performance status by Eastern Cooperative Oncology Group (ECOG) performance status scale (see **Appendix 5**).

8.1.3.8 Laboratory procedures and data

Laboratory data at baseline will include CBC with differential, comprehensive metabolic panel including potassium and creatinine and liver enzymes, LDH, beta-HCG for women of child-bearing age, magnesium, phosphorus, uric acid, C-reactive protein, amylase, lipase, and coagulation profile. At follow up visits as shown in **Section 8.3.1.14**, CBC with differential, comprehensive metabolic panel, LDH, tumor lysis labs (phosphorus, magnesium and uric acid in addition to potassium and creatinine in CMP), and beta-HCG for women of child-bearing age, will be performed.

Patients of child-bearing potential must have a negative highly sensitive serum pregnancy test within 24 hours before the first dose of momelotinib. In addition, regular pregnancy testing will be conducted as noted below while on treatment and up to at least 1 month after the last dose of MMB. Additional serum or urine pregnancy tests may be performed, as determined necessary by the treating physician or required by local regulation to establish the absence of pregnancy at any time during the patient's participation in the program. In the event of a positive pregnancy test, the participant must stop momelotinib treatment immediately.

8.1.3.9 Bone marrow biopsy

Bone marrow biopsy and aspirate will be conducted at baseline within 4 weeks of anticipated start day of treatment. Flow cytometry, cytogenetics, hematological malignancy fusion panel, next generation sequencing will be sent from the bone marrow.

Additional bone marrow biopsy will be performed after cycle 6 completion (day 168) +/- 14 days.

8.1.3.10 Spleen size assessment

Spleen imaging will be performed at baseline (within 28 days of cycle 1 day 1), on the day of week 12 assessment (+/- 5 days), at the day of week 24 assessment (+/- 10 days), and every 12 weeks thereafter (+/- 15 days), and at end of treatment or relapse/progression. Ultrasound will be the preferred modality of spleen imaging and spleen size dimensions (length, height, width) as well as spleen volume will be reported. In situations where ultrasound is not feasible, CT or MRI without contrast is allowed. It is strongly encouraged to keep the modality of spleen imaging consistent throughout the study.

8.1.3.11 Correlative studies

Correlatives studies will include evaluation for NGS, targeted-deep sequencing using cell free DNA, single cell analysis and CCRL2 expression on CD34+ cells. NGS will be performed on the marrow aspirate (or PB if dry tap) at baseline using standard myeloid panel with a sensitivity of at least 5%. Mutations panel should include at least the following genes of known relevance in these diagnoses: *JAK2, MPL, CALR, ASXL1, SRSF2, SETBP1, EZH2, RUNX1, TET2, DNMT3A, U2AF1, ZRSR2, SF3B1, CSF3R, KRAS, NRAS, CBL, PTPN11, TP53, PHF6, IDH1, IDH2, ETV6*. NGS performed within 6 months from start of treatment can be used as baseline if approved by study PI. PB sample for cell free DNA will be obtained at baseline, week 12 and week 24 assessment. Samples for single cell analysis and CCRL2 expression (CD34+ cells from the bone marrow) will be collected at baseline and with the bone marrow at week 24 assessment. Additional sample will be collected from PB at week 12 for the first 10 patients. These samples will be shipped to Hopkins as described in Appendix 6.

8.2 Study treatment and dose adjustments

8.2.1 Momelotinib

MMB will be administered using modified 3+3 dose escalation design followed by expansion. The first three patients will be treated at 150mg daily and if DLT criteria are not met, the remaining patients will be treated at 200mg daily to a total of 18 evaluable patients[3] (all in combination with azacitidine). If DLTs are met with in the dose escalation phase (first three patients), then the patients will be treated at 150mg or 200mg daily (in combination with azacitidine) as elaborated in Section 6.1. MMB can be administered at

any time of the day but is encouraged to be taken around the same time every day. A dose is considered "missed" if not given within 10 hours or the typical time of administration. If a dose is missed, the next scheduled dose should be taken the following day. No additional doses are to be taken to make up for the missed dose.
Dose interruptions, reductions, or modifications for toxicity are described in **Section 8.2.8**. The lowest dose of MMB allowed will be 100 mg daily.

8.2.2 Hypomethylating agent

5-Azacytidine will be used as HMA In the study. Azacitidine will be added at standard dose of 75 mg/m2 intravenously or subcutaneously on days day 1-5 of each 28-day cycle. Azacitidine can be started at a lower dose of 50 mg/m2 or 25 mg/m2 if deemed appropriate due to pre-existing cytopenias (absolute neutrophil count < 1000/mm^3 or platelet count < 50000/mm^3).

8.2.3 Infection prophylaxis and therapy

All patients are expected to pursue prophylactic antiviral therapy for shingles prevention using acyclovir or valacyclovir during treatment. Standard interventions as appropriate for any infections occurring during study period should be adopted.

8.2.4 Prophylaxis and management of expected toxicity

Prophylactic anti-emetics (e.g., ondansetron) will be available to patients for use as needed for management of nausea. Similar anti-diarrheas such as loperamide will be available for diarrhea as needed. If diarrhea is considered to be related to an infection, appropriate investigations and management will be followed.

8.2.5 Transfusions and growth factor support

Standard parameters for transfusions for hemoglobin (at least for hemoglobin < 7g/dL) and platelets (at least for platelets < 10,000 per microliter). Higher thresholds for transfusions can be applied in cases of clinical need including but not limited to bleeding, cardiac disease, symptomatic anemia etcetera. Growth factors will be avoided during the course of the study with exceptions such as sepsis in a setting of neutropenia if deemed appropriate by treating team.

8.2.6 Hydroxyurea for leukocytosis

For patients with leukocytosis > 50,000/microliter or worsening leukocytosis during screening and baseline, hydroxyurea can be used up to a dose of 2000 mg daily per discretion of treatment physician and discussion with study PI. Hydroxyurea can be continued for up to 2 months following study initiation. If hydroxyurea is being considered for use outside of above parameters, it will need to be discussed with study PI.

8.2.7 Dose-limiting toxicities

Dose limiting toxicity (DLT) will be defined as the occurrence of any toxicities as listed in the table below, except those with a clear alternative explanation occurring during the course of the study. All DLTs will be assessed for severity by the investigator with CTCAE version 5.0. DLT observation period is defined as the first treatment cycle (cycle 1) which will be 4 weeks (28 days) in duration from the start of treatment for all patients.

• **Toxicity**	• **Definition**
• Non-hematologic	Any Grade ≥ 3 non-hematologic toxicity EXCEPT: • Grade 3 fatigue, asthenia, fever, anorexia, or constipation • Grade 3 nausea, vomiting, or diarrhea not requiring tube feeding, total parenteral nutrition, or hospitalization and resolves to grade < 2 within 72 hours • Grade 3 AST or ALT elevation that resolves to Grade ≤1 within 72 hours) • Grade 3 or 4 isolated electrolyte abnormalities that resolve, with or without intervention, to < Grade 2 levels in < 72 hours
• Hematologic	Any of the following: • Grade 3 thrombocytopenia with bleeding • Any grade 4 thrombocytopenia* • Grade 4 decrease in neutrophil count lasting > 14 days • Grade 3 or 4 febrile neutropenia of any duration *Grade 4 thrombocytopenia in patients enrolled with platelets <50,000/microL will be confirmed with a second read which can be done the same day.

8.2.8 Dosing delays and modification for toxicity

Adverse events of cytopenias, especially thrombocytopenia or neutropenia can result in dose interruptions or modifications, or both as described in the table below. Dose reductions will occur in 50 mg daily decrements and the lowest dose allowed for MMB is 100 mg daily.

Dose adjustments for MMB for adverse events

• **Adverse event**	• **Action**
Thrombocytopenia	
• ***Baseline platelet count: ≥100,000/mm3***	
• Platelet count: 20,000 to <50,000/mm3	• Reduce the daily dose by 50 mg from the last administered dose[a]
• Platelet count: <20,000/mm3	• Interrupt treatment until platelets ≥50,000/mm3; restart momelotinib at a daily dose reduced by 50 mg below the last administered dose[a]
• ***Baseline platelet count: ≥50,000 to <100,000/mm3***	
• Platelet count: <20,000/mm3	• Interrupt treatment; Resume when/ if platelet count recovers to ≥50% of baseline value in the absence of platelet transfusion for ≥5 days, at a reduced daily dose of MMB reduced by 50 mg below the last administered dose[a]
• **Baseline platelet count: <50,000/mm3**	
• Platelet counts: <20,000/mm3	• Interrupt treatment; Resume when/ if platelet count recover to >25,000/mm3, at a reduced daily dose of MMB reduced by 50 mg below the last administered dose[a]
Neutropenia	
• ANC <500/mm3	• Interrupt treatment as appropriate • Resume treatment when ANC >750/mm3, at a reduced daily dose of MMB reduced by 50 mg below the last administered dose[a] • Re-escalation can be allowed upon resolution of toxicity and return of ANC to baseline level

Non-hematological or other toxicities	
• Grade 3 or 4 non-hematologic toxicity	• Interrupt treatment for grade 3 or 4 non-hematologic toxicity that the investigator considers related to the study treatment • Resume treatment at dose reduced by 50 mg daily upon resolution of toxicity to grade ≤1 or baseline grade[a]
• Grade 3 or 4 Severe Cutaneous Adverse Reactions (SCARs)	• Permanently discontinue and do not reintroduce
• Grade ≥2 bleeding event	• Interrupt treatment for grade ≥2 bleeding event that the investigator considers related to the study treatment • Resume treatment at dose reduced by 50 mg daily upon resolution of toxicity to grade ≤1 or baseline grade[a]

a. In situations where grade 4 neutropenia or thrombocytopenia occurs on 100mg daily of MMB, rechallenge with 100mg MMB will be allowed upon resolution of the toxicity to grade 2 or better or once at pre-treatment levels. This reintroduction will be done upon discussion with IND sponsor,

b. If the previous dose was 100mg daily, then reinitiate treatment at same dose of 100 mg

Dose adjustments for azacitidine for adverse events

Standard dose for azacitidine is 75 mg/m^2 intravenously or subcutaneously on days day 1-5 of each 28-day cycle, and is the recommended dose for this study. Azacitidine can be started at a lower dose of 50 mg/m^2 or 25 mg/m^2 if deemed appropriate due to pre-existing cytopenias in the form of neutrophil count < 1000/mm^3 or platelets <50000/mm^3.

While on treatment, for cytopenias that do not improve despite lowering the dose of MMB to 100mg daily, we then recommend decreasing the dose of azacitidine from 75mg/m^2 to 50mg/m^2 or from 50mg/m^2 to 25mg/m^2.

8.3 Study schema and sample collection

8.3.1 Scheduled study visits

Study visits and associated evaluations are described and tabulated below.

8.3.1.1 Screening visit will be conducted when considering the patient for this study and can be used for consent. Demographics, medical history, concurrent medications will be collected at this visit. Laboratory data will be collected as outlined in the table***.*** These assessments and investigations will be conducted within 28 days of start of study treatment on cycle 1 day 1. These will include:

a) Evaluation of history and physical examination including spleen size on palpation
b) Review of prior and current medications
c) Vital signs
d) ECOG performance status
e) Recording of patient height and weight
f) CBC with differential
g) Comprehensive metabolic panel (sodium, potassium, chloride, bicarbonate, BUN, creatinine, total protein, albumin, AST, ALT, alkaline phosphatase total bilirubin, calcium), direct bilirubin, magnesium, phosphorus, uric acid, LDH, amylase, lipase, C-RP, coagulation profile, HIV, Hepatitis B/C testing
h) Serum pregnancy test
i) Peripheral blood smear evaluation for blasts
j) Bone marrow biopsy and aspirate if not dry tap, including flow cytometry, cytogenetics, hematological malignancy fusion panel, next generation sequencing (NGS), single cell sequencing, and CCRL2 correlatives
k) Spleen size assessment preferably by ultrasound (CT or MRI without contrast are alternatives)
l) pH, glucose, protein, blood, ketones [bilirubin, urobilinogen, nitrite, leukocyte esterase] by dipstick. Urine protein: creatinine ratio (uPCR) if urine dipstick shows > 2+ protein.

8.3.1.2 Cycle 1 day 1 (cycle length = 28 days)

a) Confirmation of patient eligibility prior to initiation of study treatment
b) Record baseline MPN SAF TSS score
c) Evaluation of history and physical examination including spleen size on palpation
d) Review of current medications
e) Vital signs
f) ECOG performance status
g) Record patient height and weight
h) CBC with differential
i) Comprehensive metabolic panel as above, direct bilirubin, magnesium, phosphorus, uric acid, LDH, amylase, lipase, C-RP, serum pregnancy test

j) Administer study treatment and provide medication supply sufficient to last until the next study-defined next visit
k) Provide the patient with adverse event diary

8.3.1.3 Cycle 1 days 8, 15, 22 (+/- 5 days)

a) History and physical examination
b) Review of medications
c) Vital signs
d) ECOG performance status
e) CBC with differential
f) Comprehensive metabolic panel as above, direct bilirubin, magnesium, phosphorus, uric acid

8.3.1.4 Cycle 2 day 1 (+/- 5 days)

a) History and physical examination including spleen size on palpation
b) Review of medications
c) Vital signs
d) ECOG performance status
e) Record patient height and weight
f) CBC with differential
g) Comprehensive metabolic panel, direct bilirubin, magnesium, phosphorus, uric acid, LDH, amylase, lipase, C-RP, serum pregnancy test
h) Record MPN SAF TSS score
i) Record PGIC
j) Administer study treatment and provide medication supply sufficient to last until next cycle
k) Ensure the patient has adverse event diary

8.3.1.5 Cycle 2 day 15 (+/- 5 days)

a) History and physical examination
b) Review of medications
c) Vital signs
d) ECOG performance status
e) CBC with differential
f) Comprehensive metabolic panel, direct bilirubin, magnesium, phosphorus, uric acid

8.3.1.6 Cycle 3 day 1 (+/- 5 days)

a) History and physical examination including spleen size on palpation
b) Review of medications
c) Vital signs
d) ECOG performance status
e) Record patient height and weight
f) CBC with differential
g) Comprehensive metabolic panel, direct bilirubin, magnesium, phosphorus, uric acid, LDH, amylase, lipase, C-RP, serum pregnancy test
h) Record MPN SAF TSS score
i) Record PGIC
j) Administer study treatment and provide medication supply sufficient to last until next cycle
k) Ensure the patient has adverse event diary

8.3.1.7 Cycle 4 day 1 (+/- 5 days) [Assessment here will be counted towards week 12 assessment]

a) History and physical examination including spleen size on palpation
b) Review of medications
c) Vital signs
d) ECOG performance status
e) Record patient height and weight
f) CBC with differential
g) Comprehensive metabolic panel, direct bilirubin, magnesium, phosphorus, uric acid, LDH, amylase, lipase, C-RP, serum pregnancy test
h) Record MPN SAF TSS score
i) Record PGIC
j) Administer study treatment and provide medication supply sufficient to last until next cycle
k) Ensure the patient has adverse event diary
l) Peripheral blood samples for cytogenetics, NGS, and cell free DNA correlatives. Blood samples for MMB/M21 trough concentrations (for the first 10 patients)
m) Spleen size assessment preferably by ultrasound (CT or MRI without contrast are alternatives)
n) MDS/MPN response assessment by international consensus criteria (will contribute to interim futility analysis for first 6 patients)

8.3.1.8 Cycle 5 day 1 and Cycle 6 day 1 (+/- 5 days)

a) History and physical examination including spleen size on palpation
b) Review of medications
c) Vital signs
d) ECOG performance status
e) Record patient height and weight
f) CBC with differential
g) Comprehensive metabolic panel, direct bilirubin, magnesium, phosphorus, uric acid, LDH, amylase, lipase, C-RP, serum pregnancy test
h) Record MPN SAF TSS score
i) Record PGIC
j) Administer study treatment and provide medication supply sufficient to last until next cycle
k) Ensure the patient has adverse event diary

8.3.1.9 Cycle 7 day 1 (+/- 10 days) [Assessment here will be counted towards week 24 assessment]

a) History and physical examination including spleen size on palpation
b) Review of medications
c) Vital signs
d) ECOG performance status
e) Record patient height and weight
f) CBC with differential
g) Comprehensive metabolic panel, direct bilirubin, magnesium, phosphorus, uric acid, LDH, amylase, lipase, C-RP, serum pregnancy test
h) Blood samples for MMB/M21 trough concentrations (for the first 10 patients)
i) Record MPN SAF TSS score
j) Record PGIC
k) Administer study treatment and provide medication supply sufficient to last until next cycle
l) Ensure patient has adverse event diary
m) Bone marrow biopsy and aspirate if not dry tap, including flow cytometry, cytogenetics, NGS and CD34+cells for single cell analysis and CCRL2 studies
n) Spleen size assessment preferably by ultrasound (CT or MRI without contrast are alternatives)
o) MDS/MPN response assessment by international consensus criteria

8.3.1.10 Cycle 8 onwards day 1 (+/- 15 days)

a) History and physical examination including spleen size on palpation
b) Review of medications
c) Vital signs
d) ECOG performance status
e) Record patient height and weight
f) CBC with differential
g) Comprehensive metabolic panel, direct bilirubin, magnesium, phosphorus, uric acid, LDH, amylase, lipase, C-RP, serum pregnancy test
h) Record MPN SAF TSS score
i) Record PGIC
j) Administer study treatment and provide medication supply sufficient to last until next cycle
k) Ensure the patient has adverse event diary
l) Spleen size assessment preferably by ultrasound (CT or MRI without contrast are alternatives) every 3 months
m) MDS/MPN response assessment by international consensus criteria every 3 months

8.3.1.11 At progression or relapse

a) History and physical examination including spleen size on palpation
b) Review of medications
c) Vital signs
d) ECOG performance status
e) Record patient height and weight
f) CBC with differential
g) Comprehensive metabolic panel, direct bilirubin, magnesium, phosphorus, uric acid, LDH, amylase, lipase, C-RP
h) Spleen size assessment preferably by ultrasound (CT or MRI without contrast are alternatives)
i) Bone marrow biopsy and aspirate if not dry tap, including flow cytometry, cytogenetics, NGS and CD34+cells for single cell analysis and CCRL2 studies

8.3.1.12 End of treatment visit

a) History and physical examination
b) Review of medications
c) Vital signs
d) ECOG performance status

e) CBC with differential
f) Comprehensive metabolic panel, direct bilirubin, magnesium, phosphorus, uric acid, LDH, amylase, lipase, C-RP, serum pregnancy test
g) Record MPN SAF TSS score
h) Record PGIC

8.3.1.13 End of study visit

a) History and physical examination
b) AE assessment

8.3.1.15 Study Schedule table

	Screening 4 weeks prior to cycle 1 day 1	Cycle 1 day1	Cycle 1 days 8,15,22 (+/-5 days)	Cycle 2 day 1 (+/-5 days)	Cycle 2 day 15 (+/-5 days)	Cycle 3 day 1 (+/-5 days)	Cycle 4 day 1 (+/-5 days) [Day of week 12 assessment]	Cycle 5 day 1 (+/-5 days)	Cycle 6 day 1(+/-5 days)	Cycle 7 day 1) (+/-10 days) [Day of week 124 assessment	Cycle x day 1 (+/-15 days)	At relapse/ progression	End of treatment visit	End of Study Visit*
Momelotinib		x	x	x	x	x	x	x	x	x	x			
Azacitidine		D1-5	D1-5	D1-5	D1-5	D1-5	D1-5	D1-5	D1-5	D1-5	D1-5			
Consent	x													
Demographics	x													
Medical history	x													x
Concurrent meds	x	x	x	x	x	x	x	x	x	x	x	x	x	
History/ Physical exam	x	x	x	x	x	x	x	x	x	x	x	x	x	x
MPN-SAF TSS	x	x	x	x	x	x	x	x	x	x	x	x	x	
Vitals signs	x	x	x	x	x	x	x	x	x				x	
Height	x	x		x		x	x	x	x	x	x			
Weight	x	x		x		x	x	x	x	x	x			
Performance status	x	x		x		x	x	x	x	x	x			
CBC with differential	x	x	x	x	x	x	x	x	x	x	x	x	x	
Comprehensive metabolic panel	x	x	x	x	x	x	x	x	x	x	x	x	x	
Coagulation profile	x													

Direct bilirubin	x	x	x	x	x	x	x	x	x	x	x	x	x	
HIV, Hepatitis B/C serologies	x													
LDH		x		x		x	x	x	x	x	x			
Amylase/Lipase		x		x		x	x	x	x	x	x			
C-reactive protein		x		x		x	x	x	x	x	x	x	x	
Tumor lysis labs		x	x	x	x	x	x	x	x	x	x			
Beta-HCG (women)*		x		x		x	x	x	x	x	x		x	
Peripheral blood sample for PKs							X (n=10)			X (n=10)				
Bone marrow biopsy	x									x		x		
Cytogenetics/ FISH BM	x									x		x		
Heme malignancy fusion panel BM	x													
Cytogenetics from PB							x							
Flow cytometry BM	x									x		x		
Next generation sequencing	BM									BM		BM		
Ultrasound for spleen size assessment	x						x			x	q3 months	x		
MDS/MPN response assessment										x				
Peripheral blood smear	x													
Adverse event evaluation		x	x	x	x	x	x	x	x	x	x		x	x
Samples for correlative studies from PB	x						x			x				
Samples for correlative studies from BM	x									x		x		

	Screening	Cycle 1 day1	Cycle 1 days 8,15,22 (+/-5 days)	Cycle 2 day 1 (+/-5 days)	Cycle 2 day 15 (+/-5 days)	Cycle 3 day 1 (+/-5 days)	Cycle 4 day 1 (+/-5 days) [Day of week 12 assessment]	Cycle 5 day 1 (+/-5 days)	Cycle 6 day 1(+/-5 days)	Cycle 7 day 1) (+/-10 days) [Day of week 124 assessment	Cycle x day 1 (+/-15 days)	At relapse/ progression	End of treatment visit	End of Study Visit

*A repeat pregnancy test will also be performed at 1 month following the last dose of MMB or at end of study visit.

8.3.2 Early termination visit

If a patient withdraws participation for any reason prior to completion of study treatment plan, any subsequent procedures or evaluations will be per investigator discretion in accordance with standard of care management. Evaluations of adverse events and serious adverse events will continue as described in **Section 7.4.**

8.3.3 Unscheduled study visits

Unscheduled visits are those that occur outside of the Scheduled study visits table including but not limited to history/physical examination, inpatient hospitalization or unexpected extended hospitalization or management of adverse events. These will be documented in the patient's medical record by investigator or appropriate study designee and included on the adverse event log. Adverse event or serious adverse event data will be logged appropriately.

8.4 Duration of treatment

Study treatment is planned to continue until clinical benefit is observed or until criteria for withdrawal or termination are met as outlined in **Section 7.4**.

8.5 Duration of follow-up

Patients will be followed for at least 30 days from end of study for toxicity monitoring. Overall survival data will be continued to be collected as allowed by participant.

9.0 DATA MONITORING AND MANAGEMENT

The SMC Subcommittee will review the study based on DSMP (version 6.0; 2/21/19). In addition to Compliance Reviews, all trial monitoring and reporting will be reviewed annually by the SKCCC Safety Monitoring Committee. The PI is responsible for internally monitoring the study. Data must be reviewed to assure the validity of data, as well as the safety of the subjects. The PI will also monitor the progress of the trial, review safety reports, and clinical trial efficacy endpoints and to confirm that the safety outcomes favor continuation of the study.

The SKCCC Compliance Monitoring Program will provide external monitoring for JHU-affiliated sites in accordance with SKCCC DSMP (Version 6.0, 02/21/2019). The SMC Subcommittee provides thorough and ongoing review of patient risks, study progress, safety, data accuracy and integrity, and overall protocol compliance, and a full SMC study review will occur at least annually.

9.1 Data Reporting and Monitoring plan

Data will be maintained on case report forms in a RedCap database house by Johns Hopkins School of Medicine. The PI will be responsible for evaluation of data, disease response, and weekly overall toxicities.

The investigators will review data to assure the validity of data, as well as, the safety of the subjects through internal data review. They will also monitor the progress of the trial. The investigators will be responsible for maintaining the clinical protocol.

The principal investigator will be responsible for reporting adverse events, assuring that consent is obtained and documented, reporting of unexpected outcomes, and reporting the status of the trial in the annual report submitted to the IRB and to the trial monitoring review group.

Content of the annual report at a minimum should include year-to-date and full trial data on accrual and eligibility, protocol compliance, treatment administration, toxicity and ADR

reports, response, survival, regulatory compliance, compliance with prearranged statistical goals. The report should be submitted in a timely manner according to the schedule defined by the SKCCC Clinical Research Office. The trial should be placed on hold or closed if there is non-compliance with this reporting. This report serves as the annual report for the IRB.

The Protocol Chair and SMC will periodically review safety data. Enrollment of participants in the trial will be suspended at any time if any of these reviews concludes that there are significant safety concerns.

9.2 Adverse Event Reporting

9.2.1 Overview

The Principal Investigator is responsible for the detection and documentation of events meeting the criteria and definition of an AE (adverse event) or SAE (serious adverse event) as described in sections 9.3, 9.4 and 9.5 in this protocol. All AEs and SAEs will be recorded in the source documents and on the appropriate electronic CRF(s).

Adverse events that are classified as serious according to the definition of health authorities must be reported promptly and appropriately to the Principal Investigator, the IRB and health authorities. This section defines the types of AEs and outlines the procedures for appropriately collecting, grading, recording and reporting them. Information in this section complies with 21CFR 312; ICH Guideline E2A: Clinical Safety Data Management: Definitions and Standards for Expedited Reporting; and ICH Guideline E-6: Guidelines for Good Clinical Practice; and applies the standards set forth in the National Cancer Institute (NCI), Common Terminology Criteria for Adverse Events, Version 5.0 (November 27, 2017).

All adverse events will be reported to JHU Institutional Review Board.

9.2.2 Definitions

An Adverse Event (AE) is defined as any untoward medical occurrence associated with the use of a drug in humans, whether or not considered drug related.

An AE can therefore be any adverse change or exacerbation from a baseline condition or any unfavorable and unintended sign (including abnormal laboratory finding, for example), symptom, or disease temporally associated with the use of investigational product which occurs following the initial administration of an investigational product

whether or not the event is considered to be related to the investigational product. Examples of this include but are not limited to the following:

- Adverse changes including new signs and symptoms, intercurrent illness modifying the clinical course, or the worsening of a baseline condition including the increased frequency of an event or an increased intensity of a condition
- Concomitant disease with onset or increased severity after the start of study product administration
- A new pattern in a pre-existing condition, occurring after the receipt of investigational product that may signal a clinically meaningful change
- Clinically significant changes in laboratory values

9.2.2.1 Adverse reaction and suspected adverse reaction

An adverse reaction means any adverse event caused by a drug. Adverse reactions are a subset of all suspected adverse reactions for which there is reason to conclude that the drug caused the event.

Suspected adverse reaction (SAR) means any adverse event for which there is a reasonable possibility that the drug caused the adverse event. For the purposes of safety reporting, ‘reasonable possibility’ means there is evidence to suggest a causal relationship between the drug and the adverse event. A suspected adverse reaction implies a lesser degree of certainty about causality than adverse reaction, which means any adverse event caused by a drug (21 CFR 312.32(a)).

9.2.2.2 Unexpected adverse events

A SAR is considered “unexpected” if it is not identified in the package insert and/or drug label, or protocol, or is not listed at the specificity, or severity that has been observed (21 CFR 312.32(a)):

“An adverse event or suspected adverse reaction is considered "unexpected" if it is not listed in the investigator brochure or is not listed at the specificity or severity that has been observed; is not consistent with the risk information described in the general investigational plan or elsewhere in the current application. For example, under this definition, hepatic necrosis would be unexpected (by virtue of greater severity) if the investigator brochure referred only to elevated hepatic enzymes or hepatitis. "Unexpected," as used in this definition, also refers to adverse events or suspected

adverse reactions that are mentioned in the investigator brochure as occurring with a class of drugs or as anticipated from the pharmacological properties of the drug, but are not specifically mentioned as occurring with the particular drug under investigation."

9.2.2.3 Other Adverse Events and Adverse Events of Special Interest (AESIs)

Adverse events of special interest are events that are being actively monitored as a result of a previously identified signal (even if non-serious). Adverse events of special interest of Momelotinib will be reported to the PI as defined in this protocol. The PI will ensure that if there are any changes to the AESI list, these changes will be updated in the protocol as soon as practical.

Adverse events of special interest (even if non-serious):

- Cytopenias: ≥ grade 4
- Severe cutaneous adverse reactions (SCARs) ≥ grade 3

Other adverse events will be identified by the PI during the evaluation of safety data. Significant adverse events of particular clinical importance, other than SAEs and those AEs leading to discontinuation of the subject from the study, will be classified as other adverse events. For each, a narrative may be written and included in the clinical study report.

9.3 Collecting and recording adverse events

Methods of Collection

The process of review of all AEs by the PI will be documented on AE collection forms. Source documentation, including all available clinic notes, will be reviewed from the time a subject signs consent until the participant comes off study or through the End of Study visit, whichever comes first.

The methods for collecting AEs will include:

- Observing the participant.
- Questioning the participant in an objective manner.
- Receiving an unsolicited complaint from the participant.

All toxicities, abnormal laboratory results and/or potential adverse events experienced by accrued subjects during this time will be assessed by the PI who will do the initial determination of the relation, or attribution, of an AE to study participation and will record the initial determination on the appropriate AE collection form. The relation of an

AE to study participation will be determined using definitions in section 9.5.1. These assessments are to occur regularly for the time period specified and confirmed by the PI based on attribution to study intervention(s).

An abnormal value or result from a clinical or laboratory evaluation (e.g., a radiograph, an ultrasound, or an electrocardiogram) can also indicate an AE if it is determined by the Investigator to be clinically significant. If this is the case, it must be recorded in the source document and as an AE on the appropriate AE form(s). The evaluation that produced the value or result should be repeated until that value or result returns to normal or can be explained and the participant's safety is not at risk.

Adverse Events

All AE grades will be defined per NCI-CTCAE version 5.0 criteria unless otherwise specified.

9.4 Recording method

9.4.1 Adverse events

Throughout the study, the Investigator will record AEs on the appropriate eCRF regardless of their relation to study participation. The Investigator will treat participants experiencing AEs appropriately and observe them at suitable intervals until their symptoms resolve or their status stabilizes.

9.4.2 Serious adverse events

An AE or SAR is considered "serious" if, in the view of the Investigator, it results in any of the following outcomes:

- Death: A death that occurs during the study or that comes to the attention of the Principal Investigator receives the first dose of study medication until 30 days following cessation of treatment must be reported whether it is considered treatment- related or not.
- A life-threatening event: An AE or SAR is considered "life-threatening" if, in the view of the Investigator, its occurrence places the subject at immediate risk of death. It does not include an AE or SAR that, had it occurred in a more severe form, might have caused death.
- An event that requires intervention to prevent permanent impairment or damage. An important medical event that may not result in death, be life threatening, or

require hospitalization may be considered serious when, based upon appropriate medical judgment, it may jeopardize the participant and may require medical or surgical intervention to prevent one of the outcomes listed above.

Serious AEs will be recorded and health authorities will be notified as outlined in section 9.5.2.

9.5 Grading and attribution of adverse events

9.5.1 Grading criteria

The study site will grade the severity of AEs experienced by study participants according to the criteria set forth in the National Cancer Institute's Common Terminology Criteria for Adverse Events Version 5.0 (published November 27, 2017). This document (referred to herein as the "NCI-CTCAE v. 5.0 manual") provides a common language to describe levels of severity, to analyze and interpret data, and to articulate the clinical significance of all AEs.

Severity of adverse events will be graded on a scale from 1 to 5 according to the following standards in the NCI-CTCAE v. 5.0 manual:

- Grade 1 = mild - Does not interfere with routine activities and minimal level of discomfort.
- Grade 2 = moderate- - Interferes with routine activities or moderate level of discomfort
- Grade 3 = severe- Unable to perform routine activities or significant level of discomfort
- Grade 4 = life-threatening or disabling - Hospitalization or ER visit for potentially life-threatening event
- Grade 5 = death.

For additional information and a printable version of the NCI-CTCAE v. 5.0 manual, go to https://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm#ctc_50

FDA guidelines for toxicity will be followed; however, if a subject is evaluated in an emergency room for nonlife threatening illness or symptoms (i.e., visits emergency department on weekend for mild problems because the physician's office is closed), the information from that visit will be reviewed and severity of the adverse event will be assessed according to the subject's clinical signs and symptoms.

The term “severe” is often used to describe intensity (severity) of a specific event (as in mild, moderate, or severe myocardial infarction); the event itself however, may be of relatively minor medical significance (such as severe headache). This is not the same as “serious”, which is based on subject/event outcome or action criteria usually associated with events that pose a threat to a subject’s life or functioning. Seriousness (not severity) serves as a guide for defining regulatory reporting obligations.

There are two categories of reportable adverse events: 1) adverse events that are attributable to the use of momelotinib; and 2) adverse events that are not attributable to the use of the momelotinib. All reporting of adverse events will be carried out according to current IRB and FDA guidelines.

Attribution Definitions

Adverse events will be categorized for their relation to the investigational treatment. The Principal Investigator will do the initial determination of the relation, or attribution, of an AE to study participation and will record the initial determination on the appropriate eCRF and/or SAE reporting form. The relation of an AE to study participation will be determined using definitions in the Attribution of Adverse Events Table below.

Attribution of Adverse Events Table

Table 9.5.1 (1)

Code	Descriptor	Relationship (to primary investigational product and/or other concurrent mandated study therapy)
Unrelated Categories		
1	Unrelated	The adverse event is clearly not related.
2	Unlikely	The adverse event is unlikely related.
Related Categories		
3	Possible	The adverse event has a reasonable possibility to be related; there is evidence to suggest a causal relationship.
4	Probable	The adverse event is likely related.
5	Definite	The adverse event is clearly related.

9.5.2 Sponsor Responsibilities for Reporting serious adverse events

9.5.2.1 Health Authority

The sponsor shall be responsible for complying, within the required timelines, with any safety reporting obligation towards the competent health authorities, the Ethics Committees (EC) or Independent Review Board (IRB) and the participating (co- or sub-) investigators.

9.5.2.2 General

The Sponsor/Investigator is obligated to report to the FDA suspected adverse reaction that is both serious and unexpected. (see 21 CRF, part 312.32):

- Serious Adverse Event - any adverse experience which is fatal or life-threatening, permanently disabling, requires inpatient hospitalization, or is a congenital anomaly, cancer, or overdose;
- Unexpected Adverse Event - any adverse experience that is not identified in nature, severity or frequency in the current Investigator Brochure.

ALL serious adverse events, regardless of causality must be reported to the following entities:

- IND Sponsor-Investigator – Dr. Jain;
- IRB (per the IRB's reporting requirements)

Investigator Reporting Responsibilities

The conduct of the study will comply with all FDA safety reporting requirements. An investigator must immediately report to the sponsor-Investigator, Dr. Jain, any serious adverse event, whether or not considered drug related, including those listed in this protocol or investigator brochure. This report must include an assessment of whether there is a reasonable possibility that the drug caused the event. Study endpoints that are serious adverse events (e.g., all-cause mortality or dose limiting toxicities [DLTs]) and show evidence suggesting a causal relationship between the drug and the event (e.g., death from anaphylaxis) must also be immediately reported to the IND sponsor-investigator, who will in turn report these events to GSK, the sponsor of the drug, the JHU IRB and the FDA as required.

The sponsor-investigator, Dr. Jain, is responsible for evaluating all adverse events to determine whether criteria for "serious" and "unexpected" as defined above are present. This SKCCC clinical trial requires maintenance of a study-specific master adverse event log to document all nonserious and serious adverse events as well as a protocol deviation log. These logs will be reviewed by Dr. Jain throughout the duration of the study, and reported to the JHU IRB annually.

The IND sponsor- investigator is required to furnish all reports to GSK, who in turn is

responsible for collecting and evaluating the results obtained. The IND sponsor-Investigator is also required to submit annual reports to both the FDA and the JHU IRB on the progress of the clinical investigations.

Sponsor SAE Reporting to the FDA

All SAEs are reported to the FDA via the IND annual report per 21 CFR 312.33. SAEs deemed unexpected and related to the investigational product qualify for expedited reporting and must be submitted by the IND Sponsor, Dr. Jain, to the FDA on a FDA Form 3500A as per 21 CFR 312.32 as shown immediately below.

7 Calendar-Day Telephone or Fax IND Safety Report to FDA

The Sponsor is required to notify the FDA of any fatal or life-threatening adverse event that is unexpected and assessed by the Sponsor Investigator to be possibly related to the use Momelotinib within 7 calendar-days of first learning of the event. An unexpected adverse event deemed possibly related to the use of an investigational study drug is defined as any adverse drug experience of which the specificity or severity is not consistent with the current investigator brochure, the general investigational plan, or elsewhere in the current application, as amended.

Such reports are to be telephoned, faxed or emailed to the FDA within 7 calendar-days of first learning of the event. Each transmission should be directed to the FDA new drug review division in the Center for Drug Evaluation and Research or in the product review division for the Center for Biologics Evaluation and Research, whichever department is responsible for the review of the IND and to the Regulatory Project Manager and the Chief, Project Management Staff in the FDA review division that has responsibility for review of the IND.

15 Calendar-Day Written IND Safety Report to FDA

The IND Sponsor is required to notify the FDA, and all participating investigators, in a written IND Safety Report, of any serious, unexpected adverse event considered by the IND Sponsor to be possibly related to the use of momelotinib within 15 calendar-days of first learning of the event. If applicable, the IND Sponsor must also notify the FDA, and all participating investigators of any finding from tests in laboratory animals that suggests a significant risk for human subjects including reports of mutagenicity, teratogenicity, or carcinogenicity within 15 calendar-days of first learning of the event.

A serious, unexpected adverse event deemed possibly related to the use of an investigational study drug is any adverse drug experience of which the specificity or severity is not consistent with the current investigator brochure, the general investigational plan, or elsewhere in the current application, as amended, and results in any of the following outcomes:

- Death (reported first as a 7-day telephone/fax report);
- Life-threatening adverse drug experience (reported first as a 7-day phone/fax

report);
- Inpatient hospitalization or prolongation of existing hospitalization;
- A persistent or significant disability/incapacity, or a congenital anomaly/birth defect;

Or is an important medical event that may not result in death, be life-threatening, or require hospitalization but is considered a serious adverse drug experience when, based upon appropriate medical judgment, it may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition.

The Principal Investigator is required to notify the Institutional Review Board (IRB) of a serious adverse event according to institutional policy. The requirements for IRB Protocol Problem Reporting at Johns Hopkins are can be found at this website: https://www.hopkinsmedicine.org/institutional-review-board/guidelines-policies

From the time of consent through 30 days following cessation of treatment, all adverse events must be reported by the investigator. Such events will be recorded at each examination on the Adverse Event case report forms/worksheets. The reporting timeframe for adverse events meeting any serious criteria is described below. The investigator will make every attempt to follow all subjects with non-serious adverse events for outcome.
Adverse events will not be collected for subjects during the pre-screening period as long as that subject has not undergone any protocol-specified procedure or intervention. If the subject requires a blood draw, fresh biopsy etc., the subject is first required to provide consent to the main study and AEs will be captured according to guidelines for standard AE reporting. All adverse events regardless of CTCAE grade must also be evaluated for seriousness. Expected adverse events will be reported using NCI's Common Terminology Criteria for Adverse Events (CTCAE) Version 5.0 at regular intervals as defined in the patient monitoring section (section 9.0).

Sponsor-Investigator Notification Requirements to GSK

All adverse events will be recorded from the time the consent form is signed through 30 days following cessation of treatment and at each examination on the Adverse Event case report forms/worksheets. The reporting timeframe for adverse events meeting any serious criteria is described below. All SAEs (regardless of causality), pregnancies, and follow up information must be reported to GSK on an GSK specific SAE or Pregnancy Report Form within 24 hours of becoming aware of the initial event or follow-up information. The Sponsor Institution must provide a causality assessment and must sign and date all SAE Report Forms.

If supporting documentation is included in the submission to GSK (e.g., hospital reports, consultant reports, death certificates, autopsy reports, etc.), please redact any patient identifiers (including Medical Record number).

GSK SAE and Pregnancy Reporting Information:

Email: OAX37649@gsk.com or Fax: +44(0) 2081814780

Unexpected, grade 3-5 adverse events will be reported via an Adverse Event Report form to the investigators. Unexpected Grade 3 adverse events must be reported within 3 business days of knowledge of the event. Unexpected, grade 4-5 adverse events or serious adverse events must be reported via an adverse event report form to the study PI within one working day of discovery or notification of the event.

Any unexpected, either life threatening or fatal adverse event must be reported within 7 working days to the Johns Hopkins Institutional Review Board (IRB). Otherwise, unexpected serious adverse events must be reported within 15 days. The study staff will assume responsibility for reporting to the CRO and IRB, and to other investigators.

9.5.3 Protocol-specific expedited adverse event reporting exclusions

Grades 3 and 4 adverse events (including hospitalization/prolonged hospitalization) do not require expedited reporting in the following scenarios:

- Progression of the disease should NOT be reported as an AE/SAE unless it is considered to be drug related by the investigator.
- Hospitalization due to signs and symptoms of disease progression does NOT require reporting as an SAE.

9.5.4 Reporting protocol deviation

The term “protocol deviation” is not defined by either the HHS human subjects regulations (45 CFR or the FDA human subjects regulations (21 CFR 50). For JHM purposes, a protocol deviation is a minor or administrative departure (see definitions below) from the protocol procedures approved by the IRB that was made by the PI without prior IRB approval. Please note: Eligibility exceptions for enrollment of a specific individual who does not meet the inclusion/exclusion criteria in the IRB approved protocol are not deviations. Eligibility exceptions are considered changes in research that require IRB review and approval before a subject who does not meet the approved protocol inclusion/exclusion criteria may be enrolled.

Reporting Protocol Deviations to the JHM IRB

There are several types of deviations from protocol procedures recognized by the JHM IRB, and each type has a different IRB reporting requirement:

A. Protocol deviations that constitute unanticipated problems involving risks require prompt reporting to the JHM IRB: A protocol deviation that constitutes an "unanticipated problem involving risks to subjects or to others" (see Policy No. 103.6(b) for the definition of an unanticipated problem) must be reported promptly to the IRB, as follows:

1. *Emergency deviations*: When a deviation occurs in an emergency situation, such as when a departure from the protocol is required to protect the life or physical well-being of a participant. The Principal Investigator and the reviewing IRB must be notified as soon as possible, but not later than 5 days after the emergency situation occurred (21 CFR 812.150(a)(4)).

2. *Major, non-emergent deviations without prior approval*: A planned deviation that is non- emergent and represents a major change in the protocol as approved by the IRB. The JHU Principal Investigator and the IRB must approve the request before the proposed change is implemented. If a major, non-emergent deviation occurs without prior IRB approval the event is considered non-compliance. Non-compliance must be reported to the IRB promptly.

B. Protocol deviations that are only minor or administrative: At JHM, minor or administrative protocol deviations are defined as those which do not "affect the scientific soundness of the research plan or the rights, safety, or welfare of human subjects." If a protocol deviation occurs which meets this definition, the deviation should be reported to the JHM IRB at the time the continuing review application is submitted. Examples of minor or administrative deviations could include: follow up visits that occurred outside the protocol required time frame because of the participant's schedule, or blood samples obtained at times close to but not precisely at the time points specified in the protocol.

9.6 Toxicity monitoring

We will employ a Bayesian toxicity monitoring strategy to monitor dose-limiting toxicity rate, as outlined in **section 12.3**.

9.7 Data management

Data will be maintained on case report forms in REDCap and on appropriate spreadsheets. The investigators will be responsible for evaluation of overall toxicities.

10.0 MEASUREMENT OF EFFECT AND ENDPOINTS

This is a non-blinded pilot study. Analysis of response and safety are planned. Exploratory analyses of overall survival, feasibility of transplantation, and BMT outcomes are planned.

10.1 Analysis population

All patients who receive at least three cycles will be considered evaluable for efficacy analysis, with the exception of patients who discontinue treatment early due to toxicity or disease progression, who will be considered as non-responders. Those who receive at least 1 one dose of MMB will be considered for safety analysis.

10.2 Sample size

This study includes relatively rare diagnoses of MDS/MPN (CMML, MDS/MPN-N, MDS/MPN-NOS) and CNL. Treatment options in these diagnostic entities are limited. Johns Hopkins is a tertiary center and a referral center for this rare diagnosis. Approximately 100 new patients with these diagnoses are seen at JHU every year. Our total sample size is N=18 evaluable patients. The MDS/MPN disease group is relatively uncommon, hence this is essentially a pilot study aimed at gathering information for a larger definitive study.

10.3 Response rate

Response rate will be evaluated by the international consortium criteria for MDS/MPN and will include complete response, partial remission or clinical benefit per the criteria[4]. This will include assessment of marrow blasts, marrow cellularity, marrow fibrosis, WBC, hemoglobin, platelets, neutrophil count, blast %, neutrophilic precursors, monocyte count, extramedullary disease including palpable hepatosplenomegaly, and spleen size reduction.

10.4 Safety and feasibility

Safety and feasibility will be measured by assessment of toxicity using CTCAE version 5.0. All grade toxicities will be collected and reported.

10.5 Erythroid response

Erythroid response will be measured by improvement in hemoglobin by ≥2 g/dL (relative to baseline) in patients who have anemia at the time of enrollment and/or transfusion independence for patients requiring at least 4 packed red cells transfusion in the previous 8 weeks[4]. (see **Appendix 1**)

10.6 Spleen response

Spleen response will be measured by physical exam which will measure the craniocaudal dimension of spleen by cm below costal margin in the mid-clavicular line[4](see **Appendix 1**). Spleen imaging will be done in addition to physical exam for evaluation of reduction in spleen volume.

10.7 Patient reported outcomes

Patient reported outcomes (PRO) will be evaluated using MPN-SAF TSS and by PGIC. MPN-SAF TSS has been extensively used in MPNs and in MDS/MPN[5]. PGIC is an established metric for oncology patients.

10.8 Overall survival

Interval from Day 0 to date of death from any cause or last patient contact.

10.9 Transplantation

Patients who are able to proceed with transplantation after therapy without increase in blasts, splenomegaly or fibrosis will be considered transplant eligible post-MMB-HMA. Outcomes following BMT will be evaluated in comparison with a retrospective cohort especially focusing on patients with mutations in *EZH2, SETBP1,* or *RUNX1*[12].

10.10 Pharmacokinetics

Trough concentrations of MMB and M21 will be listed for each participant at weeks 12 and 24 for the first 10 patients. Additionally, we will use descriptive statistics to summarize trough concentrations of MMB and M21 at the two study visits. Trough concentrations of MMB and M21 from this study might be combined with PK from other studies for Population PK and Exposure-Response further modeling purposes.

11.0 CORRELATIVE STUDIES

Correlative studies will be exploratory aimed at:

(i) Evaluation of the role of NGS mutations at baseline in response with MMB-HMA especially on those with combination of *ASXL1, SRSF2*, and *SETBP1*.

(ii) Evaluation of reduction in somatic mutation burden or clonal reduction with treatment using cell free DNA

(iii) Determining the role of CCRL2 in treatment response and impact of treatment on CCRL2 mediated signaling of JAK-STAT pathway

(iv) Identifying mechanisms of resistance and relapse using single cell analysis in responders and non-responders.

11.1 NGS mutations

While cytogenetics are often normal, somatic mutations are commonly seen in MDS/MPN. Our prior work has demonstrated that MDS/MPN with mutations in *EZH2, RUNX1* or *SETBP1* has a very low likelihood of response to commonly HMA monotherapy[15]. We have also recently demonstrated that the co-occurrence of mutations in *ASXL1, SRSF2,* and *SETBP1* have a particularly poor prognosis and survival without BMT is often under 1 year[28]. Growing evidence suggests that NGS mutations are likely a better in defining individual diagnostic entities of MDS/MPN due to their prognostic value. Hence, we hypothesize that responses to therapies such as combination of MMB and HMA will be correlated with the driving NGS mutations. In this study, we will correlate responses to therapy with underlying mutations at baseline.

11.2 Targeted sequencing using cell free DNA

NGS from the marrow can be difficult to obtain frequently due to invasive nature of the procedure. While NGS can be performed from peripheral blood mononuclear cells, these do not capture the extramedullary hematopoiesis which is common in patients with MPNs and MDS/MPNs. Hence, we hypothesize that using cell free DNA from peripheral blood can provide both a minimally invasive and comprehensive approach to evaluate clonal evolution in MDS/MPN. We will serially monitor for persistent clones using minimally invasive cell free DNA assessments in the peripheral blood. For cell free DNA isolation, peripheral blood will be spun down in swing-rotor centrifuge at 2000 rpm for 10 min at room temperature. Six to 10 mL of plasma will be removed and spun down at 4000 rpm for 30 minutes. Supernatant will be aliquoted and stored at -80C. DNA will be isolated from fresh plasma using QIAmp MinElute cfDNA kit (Qiagen) per manufacturer protocol. This will yield 50-500ng of circulating cell-free DNA obtained from 6-10mL plasma, respectively. The targeted deep NGS panel will interrogate for the presence of 50 genes most frequently mutated in myeloid malignancies. For somatic variant analysis, the library will be prepared using xGen Dual Index UMI Adapters and KAPA Hyper Prep Kit and libraries will be sequenced using Illumina novaSeq system (Illumina) using a 2x150 bp protocol. We will barcode DNA molecules with unique 8-nucleotide sequence pre-PCR amplification to allow recognition of PCR duplicates. We will use a minimum 200ng DNA and sequence libraries at a minimum post-PCR deduplication depth of 10000x to achieve a sensitivity of 10^{-2} to 10^{-3}. This will distinguish clonal somatic mutations from background variants. Finally, we will analyze this data using Dr. Lukasz Gondek's (co-investigator) custom variant detection pipeline as published[59].

11.3 CCRL2 expression on CD34+ cells

Our preliminary data suggest that CCRL2 regulates both JAK1 and JAK2 leading to STAT1/3/5 activation in JAK2 mutated and wild-type AML cell lines[48,49]. Moreover, CCRL2 expression promotes the development of resistance to JAK2 selective inhibition with fedratinib but is associated with higher sensitivity to the dual JAK1/JAK2 inhibitor momelotinib. Our hypothesis is that MDS/MPN patients with high expression of CCRL2 will demonstrate better response to momelotinib therapy. Bone marrow aspirates will be collected before the initiation of treatment and at 6 months following the initiation of treatment. The expression of CCRL2 will be measured in CD34+, CD34+CD38-, CD34- and blasts populations by flow cytometry. The CCRL2 mean fluorescent intensity (MFI) in CD34+ cells and blasts before the initiation of treatment will be correlated with response by linear regression analysis. The patients will be stratified as "low CCRL2 expressers" and "high CCRL2 expressers" based on the median CCRL2 MFI in CD34+ cells and

blasts before the initiation of treatment. Logistic regression analysis will be also used to correlate response and CCRL2 expression in CD34+ cells.

11.4 RNA sequencing analysis

We propose bulk RNA sequencing on PBMCs derived at week 12 . For this analysis, we sort neutrophils for bulk sequencing. We will also conduct single cell analysis for comparison in frequencies and differential expression between cells in responders versus non-responders. Bulk RNA sequencing is advantageous because it will provide sufficient sequence depth for detailed pathway analysis and prior data show expression in PBMCs in MPNs. We will also assess transcriptomes at the single cell level in 3 responders and 2 non-responders (or at relapse), for the following reasons: 1) First, single cell RNA sequencing will allow us to precisely determine differences in frequency of cell identity in responders and non-responders, on the transcriptome, 2) single cell RNA sequencing will also allow us to identify pathways within distinct cells that persistent after treatment in responders and non-responders, and, 3) single cell RNA sequencing provides precision that is lost when gene expression from transcriptomes of diverse cells are averaged. To this end, we will conduct single cell RNA sequencing on bone marrow CD34+ samples from 3 responders and 3 non-responders using our Johns Hopkins transcriptomics core. These will be done using matched samples for these patients at baseline and at week 24. We will compare transcriptomic profiles of cells derived from responders and non-responders to identify which genes are dysregulated within single cells. Transcriptomes will be clustered and cell identity assigned to each cluster based on published markers.

12.0 STATISTICAL DESIGN

12.1 Analysis of primary endpoint

The primary objective of this study is to obtain an estimate of efficacy of MMB in combination with hypomethylating agents (MMB-HMA) in MDS/MPN and CNL. The primary endpoint is complete response, partial remission or clinical benefit per MDS/MPN IWG criteria[4] assessed at 24 weeks. We will combine patients treated at momelotinib 150mg and 200mg daily for efficacy evaluation. We will have a sample size of N=18 to estimate the efficacy. Assuming response rates of 28-50%, the 90% exact binomial confidence intervals would be:

# Responding (out of 18)	Est (two-sided 90% exact CI)
5	0.28 (0.12, 0.50)

6	0.30 (0.16, 0.55)
7	0.39 (0.20, 0.61)
8	0.44 (0.24, 0.66)
9	0.50 (0.29, 0.71)

12.2 Analysis of secondary endpoints

Secondary objectives are (1) to evaluate feasibility and safety of MMB-HMA in MDS/MPN and CNL, (2) to evaluate erythroid response with MMB-HMA, (3) to evaluate spleen size reduction with MMB-HMA in MDS/MPN and CNL (4) to evaluate improvement of MMB-HMA on patient-reported outcomes in MDS/MPN and CNL.

Feasibility will be defined as the proportion of patients who maintain 60% dose intensity for 24 weeks.

Incidence, severity and duration of adverse events will be assessed on an ongoing basis while patients are on treatment, using CTCAE version 5.0 and evaluated by predetermined physical exam, laboratory values for blood counts and chemistries.

Erythroid response will be evaluated at 12 weeks and 24 weeks. Response would be counted as positive if hemoglobin increases by ≥2.0 g/dL at either 12 or 24 weeks or if the patient achieves transfusion independence for ≥8 weeks in those requiring at least 4 PRBC transfusions in the 8 weeks prior to initiation of treatment[4]. Erythroid response will be estimated as a simple proportion along with two-sided 90% exact binomial confidence interval. We will also estimate the change in hemoglobin as a continuous variable along with its 90% confidence interval.

Spleen response will be evaluated at 12 weeks and 24 weeks, as reduction in spleen volume of ≥ 35% from baseline (we will take the largest of the two reductions) and by spleen response by consensus response criteria[3,4]. Spleen response will be estimated as a simple proportion along with two-sided 90% exact binomial confidence interval. We will also estimate the change in spleen volume as a continuous variable along with its 90% confidence interval.

Patient reported outcomes (PRO) will be evaluated by 50% reduction in MPN-SAF TSS from baseline at week 12 and week 24 (the best outcome of the two) and PGIC at week 12 and week 24[5]. PRO improvement will be estimated as a simple proportion along with two-sided 90% exact binomial confidence interval. We will also estimate the change in PRO scores as continuous variables along with their 90% confidence intervals.

12.3 Continuous Toxicity monitoring

We will employ a Bayesian toxicity monitoring strategy to monitor dose-limiting toxicity rate during the expansion phase with 12 patients. The DLTs were defined in **Section 8.2.7** occurring within the first cycle of treatment (28 days). If the posterior probability of observed toxicity rate being greater than 30% is greater than 0.7, we will pause the study. Assuming a Beta (0.5, 0.5) prior distribution for the toxicity response, the Table below shows the Bayesian monitoring strategy for N=12 patients (for the MMB 200mg daily dose).

Stop if # DLTs	≥ 2	≥ 3	≥ 4	≥ 5
# patients	5	7	10	12

The above monitoring strategy has the following operating characteristics:

True Toxicity rate	Avg samples size (% early stop)
0.1	11.3 (8.7%)
0.2	9.8 (30.4%)
0.3	7.9 (55.8%)
0.4	6.1 (77.7%)
0.5	4.8 (91.5%)

13.0 ETHICAL CONSIDERATIONS AND COMPLIANCE WITH GOOD CLINICAL PRACTICE

13.1 Statement of compliance

This trial will be conducted in compliance with the protocol, current Good Clinical Practice (GCP) guidelines—adopting the principles of the Declaration of Helsinki—and all applicable regulatory requirements. Prior to study initiation, the protocol and the informed consent documents will be reviewed and approved by the sponsor and an appropriate ethics review committee or institutional review board (IRB). Any amendments to the protocol or consent materials must also be approved by the Sponsor,

the IRB and submitted to FDA before they are implemented.

13.2 Informed consent

The informed consent form is a means of providing information about the trial to a prospective participant and allows for an informed decision about participation in the study. All participants (or their legally acceptable representative) must read, sign, and date a consent form before participating in the study, taking any study drugs, and/or undergoing any study-specific procedures. If a participant does not speak and read English, the consent materials must be translated into the appropriate language. The informed consent form must be updated or revised whenever important new safety information is available, whenever the protocol is amended, and/or whenever any new information becomes available that may affect participation in the trial.

A copy of the informed consent will be given to a prospective participant for review. The attending physician, in the presence of a witness, will review the consent and answer questions. The participant will be informed that participation is voluntary and that he/she may withdraw from the study at any time, for any reason.

13.3 On-study date

A participant will be considered on study upon the date of signed consent.

13.4 Privacy and confidentiality

A participant's privacy and confidentiality will be respected throughout the study. Each participant will be assigned a sequential identification number. This number, rather than the participant's name, will be used to collect, store, and report participant information.

14.0 REFERENCES

1. Arber DA, Orazi A, Hasserjian RP, et al: International Consensus Classification of Myeloid Neoplasms and Acute Leukemia: Integrating Morphological, Clinical, and Genomic Data. Blood, 2022
2. Khoury JD, Solary E, Abla O, et al: The 5th edition of the World Health Organization Classification of Haematolymphoid Tumours: Myeloid and Histiocytic/Dendritic Neoplasms. Leukemia, 2022
3. Verstovsek S, Gerds AT, Vannucchi AM, et al: Momelotinib versus danazol in symptomatic patients with anaemia and myelofibrosis (MOMENTUM): results from an international, double-blind, randomised, controlled, phase 3 study. Lancet 401:269-280, 2023
4. Savona MR, Malcovati L, Komrokji R, et al: An international consortium proposal of uniform response criteria for myelodysplastic/myeloproliferative neoplasms (MDS/MPN) in adults. Blood 125:1857-65, 2015
5. Emanuel RM, Dueck AC, Geyer HL, et al: Myeloproliferative neoplasm (MPN) symptom assessment form total symptom score: prospective international assessment of an abbreviated symptom burden scoring system among patients with MPNs. J Clin Oncol 30:4098-103, 2012
6. Palomo L, Meggendorfer M, Hutter S, et al: Molecular landscape and clonal architecture of adult myelodysplastic/myeloproliferative neoplasms. Blood 136:1851-1862, 2020
7. Patnaik MM, Lasho TL: Genomics of myelodysplastic syndrome/myeloproliferative neoplasm overlap syndromes. Hematology Am Soc Hematol Educ Program 2020:450-459, 2020
8. Gambacorti-Passerini CB, Donadoni C, Parmiani A, et al: Recurrent ETNK1 mutations in atypical chronic myeloid leukemia. Blood 125:499-503, 2015
9. Meggendorfer M, Bacher U, Alpermann T, et al: SETBP1 mutations occur in 9% of MDS/MPN and in 4% of MPN cases and are strongly associated with atypical CML, monosomy 7, isochromosome i(17)(q10), ASXL1 and CBL mutations. Leukemia 27:1852-60, 2013
10. Lasho TL, Finke CM, Zblewski D, et al: Novel recurrent mutations in ethanolamine kinase 1 (ETNK1) gene in systemic mastocytosis with eosinophilia and chronic myelomonocytic leukemia. Blood Cancer J 5:e275, 2015
11. Assi R, Kantarjian HM, Garcia-Manero G, et al: A phase II trial of ruxolitinib in combination with azacytidine in myelodysplastic syndrome/myeloproliferative neoplasms. Am J Hematol 93:277-285, 2018
12. Jain T, Tsai HL, Elmariah H, et al: Haploidentical donor hematopoietic cell transplantation for myelodysplastic/myeloproliferative overlap neoplasms: results from a North American collaboration. Haematologica 108:3321-3332, 2023
13. Onida F, de Wreede LC, van Biezen A, et al: Allogeneic stem cell transplantation in patients with atypical chronic myeloid leukaemia: a retrospective study from the Chronic Malignancies Working Party of the European Society for Blood and Marrow Transplantation. Br J Haematol 177:759-765, 2017
14. Sharma P, Shinde SS, Damlaj M, et al: Allogeneic hematopoietic stem cell transplant in adult patients with myelodysplastic syndrome/myeloproliferative neoplasm (MDS/MPN) overlap syndromes. Leuk Lymphoma 58:872-881, 2017
15. Karantanos T, Tsai HL, Gondek LP, et al: Genomic landscape of myelodysplastic/myeloproliferative neoplasm can predict response to hypomethylating agent therapy. Leuk Lymphoma:1-7, 2022
16. Merlevede J, Droin N, Qin T, et al: Mutation allele burden remains unchanged in chronic myelomonocytic leukaemia responding to hypomethylating agents. Nat Commun 7:10767, 2016

17. Unnikrishnan A, Papaemmanuil E, Beck D, et al: Integrative Genomics Identifies the Molecular Basis of Resistance to Azacitidine Therapy in Myelodysplastic Syndromes. Cell Rep 20:572-585, 2017

18. Itzykson R, Santini V, Thepot S, et al: Decitabine Versus Hydroxyurea for Advanced Proliferative Chronic Myelomonocytic Leukemia: Results of a Randomized Phase III Trial Within the EMSCO Network. J Clin Oncol 41:1888-1897, 2023

19. Martinez-Trillos A, Gaya A, Maffioli M, et al: Efficacy and tolerability of hydroxyurea in the treatment of the hyperproliferative manifestations of myelofibrosis: results in 40 patients. Ann Hematol 89:1233-7, 2010

20. Tefferi A, Elliot MA, Yoon SY, et al: Clinical and bone marrow effects of interferon alfa therapy in myelofibrosis with myeloid metaplasia. Blood 97:1896, 2001

21. Maxson JE, Gotlib J, Pollyea DA, et al: Oncogenic CSF3R mutations in chronic neutrophilic leukemia and atypical CML. N Engl J Med 368:1781-90, 2013

22. Padron E, Painter JS, Kunigal S, et al: GM-CSF-dependent pSTAT5 sensitivity is a feature with therapeutic potential in chronic myelomonocytic leukemia. Blood 121:5068-77, 2013

23. Ades L, Sekeres MA, Wolfromm A, et al: Predictive factors of response and survival among chronic myelomonocytic leukemia patients treated with azacitidine. Leuk Res 37:609-13, 2013

24. Kongtim P, Popat U, Jimenez A, et al: Treatment with Hypomethylating Agents before Allogeneic Stem Cell Transplant Improves Progression-Free Survival for Patients with Chronic Myelomonocytic Leukemia. Biol Blood Marrow Transplant 22:47-53, 2016

25. Coston T, Pophali P, Vallapureddy R, et al: Suboptimal response rates to hypomethylating agent therapy in chronic myelomonocytic leukemia; a single institutional study of 121 patients. Am J Hematol 94:767-779, 2019

26. Duchmann M, Yalniz FF, Sanna A, et al: Prognostic Role of Gene Mutations in Chronic Myelomonocytic Leukemia Patients Treated With Hypomethylating Agents. EBioMedicine 31:174-181, 2018

27. Sun Y, Wang Q, Zhang X, et al: Molecular genetics and management of world health organization defined atypical chronic myeloid leukemia. Ann Hematol 102:777-785, 2023

28. Jain T, Ware AD, Dalton WB, et al: Co-occurring mutations in ASXL1, SRSF2, and SETBP1 define a subset of myelodysplastic/ myeloproliferative neoplasm with neutrophilia. Leuk Res 131:107345, 2023

29. Kong JH, Nam H, Go TH, et al: Characteristics and survival of patients with atypical chronic myeloid leukemia. Blood Res 54:233-236, 2019

30. Triguero A, Xicoy B, Zamora L, et al: Response to azacitidine in patients with chronic myelomonocytic leukemia according to overlap myelodysplastic/myeloproliferative neoplasms criteria. Leuk Res 116:106836, 2022

31. Tong X, Li J, Zhou Z, et al: Efficacy and side-effects of decitabine in treatment of atypical chronic myeloid leukemia. Leuk Lymphoma 56:1911-3, 2015

32. Hausmann H, Bhatt VR, Yuan J, et al: Activity of single-agent decitabine in atypical chronic myeloid leukemia. J Oncol Pharm Pract 22:790-794, 2016

33. Dao KH, Solti MB, Maxson JE, et al: Significant clinical response to JAK1/2 inhibition in a patient with CSF3R-T618I-positive atypical chronic myeloid leukemia. Leuk Res Rep 3:67-9, 2014

34. Padron E, Dezern A, Andrade-Campos M, et al: A Multi-Institution Phase I Trial of Ruxolitinib in Patients with Chronic Myelomonocytic Leukemia (CMML). Clin Cancer Res 22:3746-54, 2016

35. Padron E, Tinsley-Vance SM, DeZern AE, et al: Efficacy and Safety of Ruxolitinib for Treatment of Symptomatic Chronic Myelomonocytic Leukemia (CMML): Results of a Multicenter Phase II Clinical Trial. Blood 140:1101-1103, 2022

36. Kuykendall AT, Jain T, Singh A, et al: A Phase 2 Study of Fedratinib in Patients with MDS/MPN and Chronic Neutrophilic Leukemia. Blood 144:481-481, 2024
37. Montalban-Bravo G, Kanagal-Shamanna R, Sasaki K, et al: Clinicopathologic correlates and natural history of atypical chronic myeloid leukemia. Cancer 127:3113-3124, 2021
38. Dholaria B, Radujkovic A, Estrada-Merly N, et al: Outcomes of allogeneic haematopoietic cell transplantation for chronic neutrophilic leukaemia: A combined CIBMTR/CMWP of EBMT analysis. Br J Haematol 198:785-789, 2022
39. Oh ST, Talpaz M, Gerds AT, et al: ACVR1/JAK1/JAK2 inhibitor momelotinib reverses transfusion dependency and suppresses hepcidin in myelofibrosis phase 2 trial. Blood Adv 4:4282-4291, 2020
40. Asshoff M, Petzer V, Warr MR, et al: Momelotinib inhibits ACVR1/ALK2, decreases hepcidin production, and ameliorates anemia of chronic disease in rodents. Blood 129:1823-1830, 2017
41. Kuykendall AT, Pettit KM, Singh A, et al: A Phase 2 Study of Fedratinib in Patients with MDS/MPN and Chronic Neutrophilic Leukemia. Blood 142:73-73, 2023
42. Naymagon L, Mascarenhas J: Myelofibrosis-Related Anemia: Current and Emerging Therapeutic Strategies. Hemasphere 1:e1, 2017
43. Birgegard G, Samuelsson J, Ahlstrand E, et al: Inflammatory functional iron deficiency common in myelofibrosis, contributes to anaemia and impairs quality of life. From the Nordic MPN study Group. Eur J Haematol 102:235-240, 2019
44. Steinbicker AU, Sachidanandan C, Vonner AJ, et al: Inhibition of bone morphogenetic protein signaling attenuates anemia associated with inflammation. Blood 117:4915-23, 2011
45. Theurl I, Schroll A, Nairz M, et al: Pathways for the regulation of hepcidin expression in anemia of chronic disease and iron deficiency anemia in vivo. Haematologica 96:1761-9, 2011
46. Wang RH, Li C, Xu X, et al: A role of SMAD4 in iron metabolism through the positive regulation of hepcidin expression. Cell Metab 2:399-409, 2005
47. Fabian MA, Biggs WH, 3rd, Treiber DK, et al: A small molecule-kinase interaction map for clinical kinase inhibitors. Nat Biotechnol 23:329-36, 2005
48. Karantanos T, Teodorescu P, Perkins B, et al: The role of the atypical chemokine receptor CCRL2 in myelodysplastic syndrome and secondary acute myeloid leukemia. Sci Adv 8:eabl8952, 2022
49. Karantanos T, Teodorescu P, Arvanitis M, et al: CCRL2 affects the sensitivity of myelodysplastic syndrome and secondary acute myeloid leukemia cells to azacitidine. Haematologica, 2022
50. Fenaux P, Mufti GJ, Hellstrom-Lindberg E, et al: Efficacy of azacitidine compared with that of conventional care regimens in the treatment of higher-risk myelodysplastic syndromes: a randomised, open-label, phase III study. Lancet Oncol 10:223-32, 2009
51. Mesa RA, Kiladjian JJ, Catalano JV, et al: SIMPLIFY-1: A Phase III Randomized Trial of Momelotinib Versus Ruxolitinib in Janus Kinase Inhibitor-Naive Patients With Myelofibrosis. J Clin Oncol 35:3844-3850, 2017
52. Masarova L, Verstovsek S, Hidalgo-Lopez JE, et al: A phase 2 study of ruxolitinib in combination with azacitidine in patients with myelofibrosis. Blood 132:1664-1674, 2018
53. Tyner JW, Bumm TG, Deininger J, et al: CYT387, a novel JAK2 inhibitor, induces hematologic responses and normalizes inflammatory cytokines in murine myeloproliferative neoplasms. Blood 115:5232-40, 2010
54. Giacomini MM, Hao J, Liang X, et al: Interaction of 2,4-Diaminopyrimidine-Containing Drugs Including Fedratinib and Trimethoprim with Thiamine Transporters. Drug Metab Dispos 45:76-85, 2017

55. Harrison CN, Vannucchi AM, Platzbecker U, et al: Momelotinib versus best available therapy in patients with myelofibrosis previously treated with ruxolitinib (SIMPLIFY 2): a randomised, open-label, phase 3 trial. Lancet Haematol 5:e73-e81, 2018

56. Vlasakakis G, McCabe MT, Ho YL, et al: Momelotinib: Mechanism of action, clinical, and translational science. Clin Transl Sci 17:e70018, 2024

57. Xin Y, Kawashima J, Weng W, et al: Pharmacokinetics and Safety of Momelotinib in Subjects With Hepatic or Renal Impairment. J Clin Pharmacol 58:522-532, 2018

58. Oken MM, Creech RH, Tormey DC, et al: Toxicity and response criteria of the Eastern Cooperative Oncology Group. Am J Clin Oncol 5:649-55, 1982

59. Gondek LP, Zheng G, Ghiaur G, et al: Donor cell leukemia arising from clonal hematopoiesis after bone marrow transplantation. Leukemia 30:1916-1920, 2016

15.0 APPENDICES

Appendix 1. International consortium response criteria in MDS/MPN
Appendix 2: International consortium criteria for progression in MDS/MPN
Appendix 3: MPN-SAF TSS score
Appendix 4: Patient Global Impression of Change (PGIC)
Appendix 5: ECOG Performance status
Appendix 6: Sample shipping details
Appendix 7: Contraceptives guidance on the study

Appendix 1. International consortium response criteria in MDS/MPN

Table 2. Proposed criteria for measurement of treatment response in adult MDS/MPN

CR (presence of all of the following improvements)*
Bone marrow: ≤5% myeloblasts (including monocytic blast equivalent in case of CMML) with normal maturation of all cell lines and return to normal cellularity*
Osteomyelofibrosis absent or equal to "mild reticulin fibrosis" (≤grade 1 fibrosis)†
Peripheral blood‡
WBC ≤10 × 10^9 cells/L
Hgb ≥11 g/dL
Platelets ≥100 × 10^9/L; ≤450 × 10^9/L
Neutrophils ≥1.0 × 10^9/L
Blasts 0%
Neutrophil precursors reduced to ≤ 2%
Monocytes ≤1 × 10^9/L
Extramedullary disease: Complete resolution of extramedullary disease present before therapy (eg, cutaneous disease, disease-related serous effusions), including palpable hepatosplenomegaly
Provisional category of CR with resolution of symptoms:‡ CR as described above, and complete resolution of disease-related symptoms as noted by the MPN-SAF TSS
Persistent low-level dysplasia is permitted given subjectivity of assignment of dysplasia*
Complete cytogenetic remission
Resolution of previously present chromosomal abnormality (known to be associated with myelodysplastic, syndrome myeloproliferative neoplasms, or MDS/MPN), as seen on classic karyotyping with minimal of 20 metaphases or FISH§
Partial remission
Normalization of peripheral counts and hepatosplenomegaly with bone marrow blasts (and blast equivalents) reduced by 50%, but remaining >5% of cellularity *except* in cases of MDS/MPN with ≤5% bone marrow blasts at baseline
Marrow response
Optimal marrow response: Presence of all marrow criteria necessary for CR without normalization of peripheral blood indices as presented above.
Partial marrow response: Bone marrow blasts (and blast equivalents) reduced by 50%, but remaining >5% of cellularity, or reduction in grading of reticulin fibrosis from baseline on at least 2 bone marrow evaluations spaced at least 2 mo apart
Clinical benefit
Requires 1 of the following in the absence of progression or CR/partial response and independent of marrow response (cord blood response must be verified at ≥8 wk) to be considered a clinical benefit
Erythroid response
Hgb increase by ≥2.0 g/dL
TI for ≥ 8 wk for patients requiring at least 4 packed red blood cell transfusions in the previous 8 wk
Only red blood cell transfusions given based on physician's judgment for a pretreatment Hgb of ≤8.5 g/dL will count in the red blood cell TI response evaluation‖
Platelet response
Transfusion independence when previously requiring platelet transfusions of at least a rate of 4 platelet transfusions in the previous 8 wk
Pretreatment ≤20 × 10^9/L: increase from <20 × 10^9/L to >20 × 10^9/L and by at least 100%
Pretreatment >20 × 10^9/L but ≤ 100 × 10^9/L: absolute increase of ≥30 × 10^9/L‖
Neutrophil response
Pretreatment ≤0.5 × 10^9/L at least 100% increase and an absolute increase ≥0.5 × 10^9/L
Pretreatment, >0.5 × 10^9/L and ≤1.0 × 10^9/L At least 50% increase and an absolute increase ≥0.5 × 10^9/L‖
Spleen response
Either a minimum 50% reduction in palpable splenomegaly of a spleen that is at least 10 cm at baseline or a spleen that is palpable at more than 5 cm at baseline becomes not palpable
Symptom response
Improvement in symptoms as noted by decrease of ≥50% as per the MPN-SAF TSS scoring <20 were not considered eligible for measuring clinical benefit.¶

*Presence of dysplastic changes, which may be interpreted within the scope of normal range of dysplastic changes, may still exist in the presence of CR as allowed in MDS IWG. Marrow should exhibit age-adjusted normocellularity in CR.

†If there is no significant fibrosis present on the initial bone marrow biopsy, a second biopsy is not required to prove resolution of fibrosis. Grading of fibrosis in measurement of treatment response should be according to the European Consensus System.[67]

‡Given the current lack of a validated tool to assess complete resolution of symptoms in MDS/MPN, "CR with resolution of symptoms" (a complete resolution of disease-related symptoms as noted by the MPN-SAF TSS in presence of CR) will be a provisional category of disease response.

§Loss of cytogenetic burden of disease by (via FISH or classic karyotyping) known to adversely affect prognosis is required to reach complete cytogenetic remission. Decrease in the cytogenetic burden of disease must be by ≥50% (via FISH or classic karyotyping) to be indicative of a partial cytogenetic response. Given variability of fluorescent probes used in FISH, cytogenetic normalization via FISH will depend on the performance characteristics of the specific probes used.

‖Resolution of abnormal peripheral blood counts must persist for at least 2 separate analyses over at least 8 wk. In the case of proliferative MDS/MPN, CR will include resolution of thrombocytosis to a normal platelet count (150-450 × 10^9/L) and resolution of leukocytosis to WBC ≤10 × 10^9 cells/L but ≥1.5 × 10^9/L. Hgb should be maintained >11 g/dL and platelets ≥100 × 10^9/L without the support of transfusions. Clinical benefit may occur when these changes occur in absence of other changes required for CR or marrow response. Platelet and packed red blood cell TI would be considered for clinical benefit, and duration of TI should be monitored. Reduction in myeloid precursors (promyelocytes, myelocytes, metamyelocytes, nucleated red blood cells) to less than appreciable levels (≤2-3%) and/or 1 × 10^9/L monocytosis in the absence of infection, cytokine treatment, or other reactive causes.

Appendix 2: International consortium criteria for progression in MDS/MPN

Table 3. Proposed criteria for measurement of disease progression in adult MDS/MPN

Combination of 2 major criteria, 1 major and 2 minor criteria, or 3 minor criteria from list
Major criteria
Increase in blast count*
<5% blasts: ≥50% increase and to >5% blasts
5-10% blasts: ≥50% increase and to >10% blasts
10-20% blasts: ≥50% increase and to >20% blasts
20-30% blasts: ≥50% increase and to >30% blasts†
Evidence of cytogenetic evolution‡
Appearance of a previously present or new cytogenetic abnormality in complete cytogenetic remission via FISH or classic karyotyping
Increase in cytogenetic burden of disease by ≥50% in partial cytogenetic remission via FISH or classic karyotyping
New extramedullary disease
Worsening splenomegaly
Progressive splenomegaly that is defined by IWG-MRT: the appearance of a previously absent splenomegaly that is palpable at >5 cm below the left costal margin or a minimum 100% increase in palpable distance for baseline splenomegaly of 5-10 cm or a minimum 50% increase in palpable distance for baseline splenomegaly of >10 cm
Extramedullary disease outside of the spleen
To include new/worsening hepatomegaly, granulocytic sarcoma, skin lesions, etc.
Minor criteria
Transfusion dependence§
Significant loss of maximal response on cytopenias ≥50% decrement from maximum remission/response in granulocytes or platelets
Reduction in Hgb by ≥1.5g/dL from best response or from baseline as noted on complete blood count
Increasing symptoms as noted by increase in ≥50% as per the MPN-SAF TSS‖
Evidence of clonal evolution (molecular)¶

*Blasts as measured from the bone marrow.

†Patients with development of acute myeloid leukemia from MDS/MPN; 20-30% blasts may be allowed on some clinical trials for patients with MDS/MPN.

‡Increase in cytogenetic burden of disease by ≥50% (via FISH or classic karyotyping). Given variability of fluorescent probes used in FISH, cytogenetic normalization via FISH will depend on specific probes used.

§Transfusion dependency is defined by a history of at least 2 U of red blood cell transfusions in the past month for a hemoglobin level <8.5 g/dL that was not associated with clinically overt bleeding. Cytopenias resulting from therapy should not be considered in assessment of progression.

‖MPN-SAF TSS validation among patients with MDS/MPN is currently under way (R.A. Mesa, personal communication, 2014).

¶The identification of new abnormalities using single nucleotide polymorphism arrays or sequencing or a clearly significant increase in mutational burden of a previously detected abnormality. Precise criteria for defining new abnormalities and what exactly constitutes a significant increase in mutational burden are open to interpretation; we suggest that this criterion should be used conservatively based on current evidence.

Appendix 3: MPN-SAF TSS score

Symptom	1 to 10 (0 if absent) ranking 1 is most favorable and 10 least favorable
Please rate your fatigue (weariness, tiredness) by circling the one number that best describes your WORST level of fatigue during past 24 hours*	(No Fatigue) 0 1 2 3 4 5 6 7 8 9 10 (Worst Imaginable)
Circle the one number that describes how, during the past week how much difficulty you have had with each of the following symptoms	
Filling up quickly when you eat (Early satiety)	(Absent) 0 1 2 3 4 5 6 7 8 9 10 (Worst Imaginable)
Abdominal discomfort	(Absent) 0 1 2 3 4 5 6 7 8 9 10 (Worst Imaginable)
Inactivity	(Absent) 0 1 2 3 4 5 6 7 8 9 10 (Worst Imaginable)
Problems with concentration - Compared to prior to my MPD	(Absent) 0 1 2 3 4 5 6 7 8 9 10 (Worst Imaginable)
Night sweats	(Absent) 0 1 2 3 4 5 6 7 8 9 10 (Worst Imaginable)
Itching (pruritus)	(Absent) 0 1 2 3 4 5 6 7 8 9 10 (Worst Imaginable)
Bone pain (diffuse not joint pain or arthritis)	(Absent) 0 1 2 3 4 5 6 7 8 9 10 (Worst Imaginable)
Fever (>100 F)	(Absent) 0 1 2 3 4 5 6 7 8 9 10 (Daily)
Unintentional weight loss last 6 months	(Absent) 0 1 2 3 4 5 6 7 8 9 10 (Worst Imaginable)

Appendix 4: Patient Global Impression of Change (PGIC)

Instructions: Circle the answer that is most appropriate.

Since the start of the treatment you've received in this study, your myelofibrosis symptoms are:

- Very much improved
- Much improved
- Minimally improved
- No change
- Minimally worse
- Much worse
- Very much worse

Appendix 5: ECOG Performance status

GRADE	ECOG PERFORMANCE STATUS
0	Fully active, able to carry on all pre-disease performance without restriction
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light house work, office work
2	Ambulatory and capable of all selfcare but unable to carry out any work activities; up and about more than 50% of waking hours
3	Capable of only limited selfcare; confined to bed or chair more than 50% of waking hours
4	Completely disabled; cannot carry on any selfcare; totally confined to bed or chair
5	Dead

Oken MM, Creech RH, Tormey DC, Horton J, Davis TE, McFadden ET, Carbone PP. Toxicity and response criteria of the Eastern Cooperative Oncology Group. *Am J Clin Oncol.* 1982 Dec;5(6):649-655. PMID: 7165009.

Appendix 6: Specimen collection details

Pharmacokinetics (10.11)	Sample collection: 2 mL-3 mL human blood is collected to harvest plasma samples, K2 EDTA blood collection tube. Sample processing: whole blood samples will be collected in K2 EDTA blood collection tube, and placed on ice-water bath for up to 120 min to harvest plasma samples. Within 120 min of blood drawing, centrifuge at 2000 g at 2-8C to harvest plasma samples, plasma samples are split into primary polypropylene tube and backup tube. Plasma samples are stored at -70C cryo freezer for storage before shipping. Shipping address: Primary samples can be shipped to the following address with an electronic manifest. Attention: Stephanie Crutchfield 700 Pennsylvania Drive, Exton, PA 19341 Phone: 1-484-878-9739 Email: sample_management@frontagelab.com
NGS (11.1):	Sample collection: 10 mL EDTA tube (lavender) Sample processing: DNA will be extracted from total blood and NGS sequencing libraries will be prepared using UMI-UDI library preparation. DNA will be fragmented, and end-repaired. Unique Molecular Identifiers (UMIs) and Unique Dual Indexes (UDIs) will be added during adapter ligation to track individual DNA molecules and minimize index hopping. Libraries will be amplified, purified, and quality-checked before sequencing on an Illumina platform. We will use DNA hybridization probes to enrich for 50 genes most commonly mutated in myeloid malignancies. Sequencing data will be processed to remove duplicates using UMIs, ensuring accurate variant detection and analysis. Shipping address: Primary samples can be shipped to the following address: Gondek Lab, CRB1-216, 1650 Orleans Street, Baltimore, MD 21287 T: (410) 502-5847

Targeted sequencing using cell free DNA (11.2)	Sample collection: 2x 10mL Streck tubes Sample processing: described below (in RNA sequencing), sequencing as described above but without DNA fragmentation. Shipping address: Primary samples can be shipped to the following address: Gondek Lab, CRB1-216, 1650 Orleans Street, Baltimore, MD 21287 T: (410) 502-5847
CCRL2 expression on CD34+ cells (11.3)	Sample collection: total 15 ml of peripheral blood, 2 green top tubes. Sample processing: If possible, sites can ficoll the cells, pellet the MNCs and freeze them and ship them to us as frozen MNCs. Cell separation will be performed using Ficoll-Paque products and subsequently peripheral blood mononuclear cells will be separated to CD34+ and CD34- cells using magnetic bead cell separation. Then cells will stained for CD34 (FITC), CD38 (BV-605) and CCRL2 (PE) and analyzed by flow cytometry. Shipping address: Please ship the cells using FedEx (Account: 2361-4022-9) to: 1650 Orleans Street, Baltimore, MD, 21287 CRB1, Room 238 Attn: Theodoros Karantanos
RNA sequencing analysis (11.4)	Sample collection: we will use cells from NGS samples (no additional blood required) Sample processing: Peripheral blood mononuclear cells (PBMCs) will be isolated via density-gradient centrifugation and lymphocytes will be depleted using CD3 and CD19 antibodies. The remaining myeloid cells will be resuspended and loaded onto the 10x Chromium system to generate Gel Bead-In-Emulsions (GEMs) containing single cells and barcoded primers. After cell lysis and reverse transcription, cDNA is amplified, and libraries are prepared for sequencing. Libraries are sequenced on an Illumina platform, and data are processed with the 10x Genomics Cell Ranger pipeline for downstream analysis. Shipping address: Primary samples can be shipped to the following address:

	Gondek Lab, CRB1-216, 1650 Orleans Street, Baltimore, MD 21287 T: (410) 502-5847

Appendix 7: Contraceptives guidance on the study

• **Highly Effective Methods[b] That Have Low User Dependency** *Failure rate of <1% per year when used consistently and correctly.*
Implantable progestogen-only hormone contraception associated with inhibition of ovulation[c]
Intrauterine device (IUD)
Intrauterine hormone-releasing system (IUS)[c]
Bilateral tubal occlusion/ligation
Azoospermic partner (vasectomized or due to a to medical cause) • *Azoospermia is a highly effective contraceptive method provided that the partner is the sole sexual partner of the woman of childbearing potential and the absence of sperm has been confirmed. If not, an additional highly effective method of contraception should be used. Spermatogenesis cycle is approximately 90 days.* Note: documentation of azoospermia for a male participant can come from the site personnel's review of the participant's medical records, medical examination, or medical history interview.
• **Highly Effective Methods[b] That Are User Dependent** *Failure rate of <1% per year when used consistently and correctly.*
Combined (estrogen- and progestogen-containing) hormonal contraception associated with inhibition of ovulation[c] • oral • intravaginal • transdermal • injectable
Progestogen-only hormone contraception associated with inhibition of ovulation[c] • oral • injectable
Sexual abstinence • *Sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the study intervention. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the study and the preferred and usual lifestyle of the participant.*

a. Contraceptive use by men or women should be consistent with local regulations regarding the use of contraceptive methods for those participating in clinical studies.
b. Failure rate of <1% per year when used consistently and correctly. Typical use failure rates differ from those when used consistently and correctly.
c. If locally required, in accordance with Clinical Trial Facilitation Group (CTFG) guidelines, acceptable contraceptive methods are limited to those that inhibit ovulation as the primary mode of action.

Note: Periodic abstinence (calendar, sympto-thermal, post-ovulation methods), withdrawal (coitus interruptus), spermicides only, and lactational amenorrhea method (LAM) are not acceptable methods of contraception. Male condom and female condom should not be used together (due to risk of failure from friction).