CONCERTO: A phase 2 trial of cobimetinib in newly diagnosed or HMA-treated CMML patients with RAS pathway mutations

IRB # 132394

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LIST OF ABBREVIATIONS

Abbreviation or Term[1]	Definition/Explanation
AE	Adverse event
ALT	Alanine aminotransferase
ANCOVA	Analysis of covariance
ANOVA	Analysis of variance
APTT	Activated partial thromboplastin time
AST	Aspartate aminotransferase
AV	Atrioventricular
β-HCG	Beta-human chorionic gonadotropin
BID	Twice daily
BLQ	Below limit of quantification
BMI	Body mass index
BP	Blood pressure
BUN	Blood urea nitrogen
Ca^{++}	Calcium
CBC	Complete blood count
CFR	Code of Federal Regulations
CHF	Congestive heart failure
CI	Confidence interval
Cl-	Chloride
CL_{cr}	Creatinine clearance
C_{max}	Maximum observed concentration
C_{min}	Trough observed concentration
CNS	Central nervous system
CR	Complete response
CRF	Case report form
CT	Computed tomography
CTCAE	Common Toxicity Criteria for Adverse Events
CV	Coefficient of variation
CYP	Cytochrome P450

Abbreviation or Term[1]	Definition/Explanation
D/C	Discontinue
ECOG	Eastern Cooperative Oncology Group
eCRF	Electronic case report form
DLT	Dose Limiting Toxicity
ECG	Electrocardiogram
Eg	Exempli Gratia (for example)
FACS	Fluorescence-Activated Cell Sorting
FDA	Food and Drug Administration
FDG-PET	Fluorodeoxyglucose (FDG)-positron emission tomography (PET)
GCP	Good Clinical Practice
GFR	Glomerular filtration rate
GGT	Gamma-glutamyltransferase
GLP	Good laboratory practice
HBsAg	Hepatitis B surface antigen
HBV	Hepatitis B virus
HCO_3^-	Bicarbonate
HCV	Hepatitis C virus
HIV	Human immunodeficiency virus
HR	Heart rate
hr	Hour or hours
IC_{50}	Half maximal inhibitory concentration
i.e.	Id est (that is)
IEC	Independent ethics committee
IND	Investigational New Drug
INR	International normalized ratio
IRB	Institutional review board
IU	International unit
IV	Intravenous, intravenously
LDH	Lactate dehydrogenase
LLQ	The lower limit of quantitation

Abbreviation or Term[1]	Definition/Explanation
MedDRA	Medical Dictionary for Drug Regulatory Activities
MRI	Magnetic resonance imaging
MRSD	The maximum recommended starting dose
MTD	Maximum tolerated dose
MUGA	Multigated acquisition scan
NOAEL	No-observed-adverse-effect level
NOEL	No-observed-effect-level
PD	Pharmacodynamic(s)
PFS	Progression-Free Survival
PK	Pharmacokinetic(s)
PO	Per os (administered by mouth)
PR	Partial response
PT	Prothrombin time
PTT	Partial thromboplastin time
QC	Quality control
RBC	Red blood cell
QD	Once-daily
QTc	QT interval corrected
QTcF	QT interval corrected using Fredericia equation
SAE	Serious adverse event
SD	Standard deviation or stable disease
$T_{1/2}$	Terminal elimination half-life
T_3	Triiodothyronine
T_4	Thyroxine
T_{max}	Time of maximum observed concentration
TID	Three times daily
TSH	Thyroid-stimulating hormone
ULN	The upper limit of normal
ULQ	The upper limit of quantitation
UV	Ultraviolet

Abbreviation or Term[1]	Definition/Explanation
WBC	White blood cell
WOCBP	Women of childbearing potential
WONCBP	Women of nonchildbearing potential

[1] All of these abbreviations may or may not be used in the protocol.

PROTOCOL SIGNATURE

I confirm that I have read this protocol, and I will conduct the study as outlined herein and according to the ethical principles stated in the latest version of the Declaration of Helsinki, the applicable ICH guidelines for good clinical practice, and the applicable laws and regulations of the federal government. I will promptly submit the protocol to the IRB for review and approval. Once the protocol has been approved by the IRB, I understand that any modifications made during the study must first be approved by the IRB prior to implementation except when such modification is made to remove an immediate hazard to the subject.

I will provide copies of the protocol and all pertinent information to all individuals responsible to me who assist in the conduct of this study. I will discuss this material with them to ensure that they are fully informed regarding the study treatment, the conduct of the study, and the obligations of confidentiality.

This document is signed electronically through submission and approval by the Principal Investigator at Huntsman Cancer Institute in the University of Utah IRB Electronic Research Integrity and Compliance Administration (ERICA) system. For this reason, the Principal Investigator at Huntsman Cancer Institute will not have a hand-written signature on this signature page.

Instructions to multi-site Principal Investigators at locations other than Huntsman Cancer Institute: SIGN and DATE this signature page and PRINT your name. Return the original, completed and signed, to the HCI Research Compliance Office. Retain a copy in the regulatory binder.

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Signature of Principal **Date**

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Principal Investigator Name (Print)

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Name of Institution

STUDY SUMMARY

Title	A phase 2 trial of cobimetinib in newly diagnosed or HMA-treated CMML patients with RAS pathway mutations
Short Title	CONCERTO
Protocol Identifiers (IRB – internal)	132394
IND number	150928
Phase	Phase 2
Design	Simon's two-stage
Study Duration	60 months
Study Center(s)	This study will be conducted at the Huntsman Cancer Institute and up to 2 additional U.S. cancer centers.
Objectives	**Primary Objective:** To assess the efficacy of cobimetinib in patients with newly diagnosed and HMA- refractory chronic myelomonocytic leukemia (CMML). **Secondary Objectives:** • To assess the safety of cobimetinib treatment in CMML. • To assess the complete response (CR) + partial reponse (PR) rate (as defined by the 2015 MDS/MPN-IWG criteria) with cobimetinib treatment in CMML. • To assess the long term efficacy of cobimetinib treatment in CMML.
Number of Subjects	29
Diagnosis and Main Eligibility Criteria	**Key Inclusion Criteria:** • Newly diagnosed or hypomethylating agent (HMA) refractory chronic myelomonocytic leukemia (CMML; 2022 WHO classification) with RAS pathway activation • ECOG Performance Status ≤ 3. • Left ventricular function ≥ 50% **Key Exclusion Criteria:** • Previous exposure to experimental MEK inhibitors for CMML. • Grade ≥ 2 QTcF prolongation on screening electrocardiogram (ECG) or clinically significant cardiovascular disease • Clinical or laboratory evidence of central nervous system (CNS) leukemia. • History of retinal detachment, central serous retinopathy (CSR), retinal vein occlusion (RVO), or at risk for CSR or RVO following screening ophthalmologic exam.

Study Product, Dose, Route, Regimen	Cobimetinib 60 mg by mouth once daily for three weeks followed by one week off.
Duration of administration	Until a treatment discontinuation criterion is met
Statistical Methodology	Simon's two-stage design (Simon, 1989) will be used for both cohorts. In the newly diagnosed patients, the null hypothesis that the true response rate is 0.35 will be tested against a one-sided alternative. In the first stage, 9 patients will be accrued. If there are 3 or fewer responses in these 9 patients, the study will be stopped. Otherwise, 5 additional patients will be accrued for a total of 14. The null hypothesis will be rejected if 7 or more responses are observed in 14 patients. This design yields a type I error rate of 0.1678 and power of 0.8028 when the true response rate is 0.59. In the HMA refractory patients, the null hypothesis that the true response rate is 0.10 will be tested against a one-sided alternative. In the first stage, 6 patients will be accrued. If there are 0 responses in these 6 patients, the study will be stopped. Otherwise, 9 additional patients will be accrued for a total of 15. The null hypothesis will be rejected if 3 or more responses are observed in 15 patients. This design yields a type I error rate of 0.1559 and power of 0.8100 when the true response rate is 0.30. The trial will be evaluated quarterly for excess toxicity. A rate of 20% grade 3 or higher non-hematological toxicity is acceptable, while a rate of 30% is unacceptable. The trial will be stopped if more than 2/5, 3/9, 4/13, 5/17, 6/22, 7/26, or 8/29 patients experience grade 3 or higher non-hematologic adverse events attributed to study therapy which are not improved or resolved with standard interventions such as dose hold, dose reduction or pharmacologic therapy (e.g. diuretic therapy) and continue to pose a significant clinical risk to the patient as determined by both the PI and medical monitor.

SCHEMA

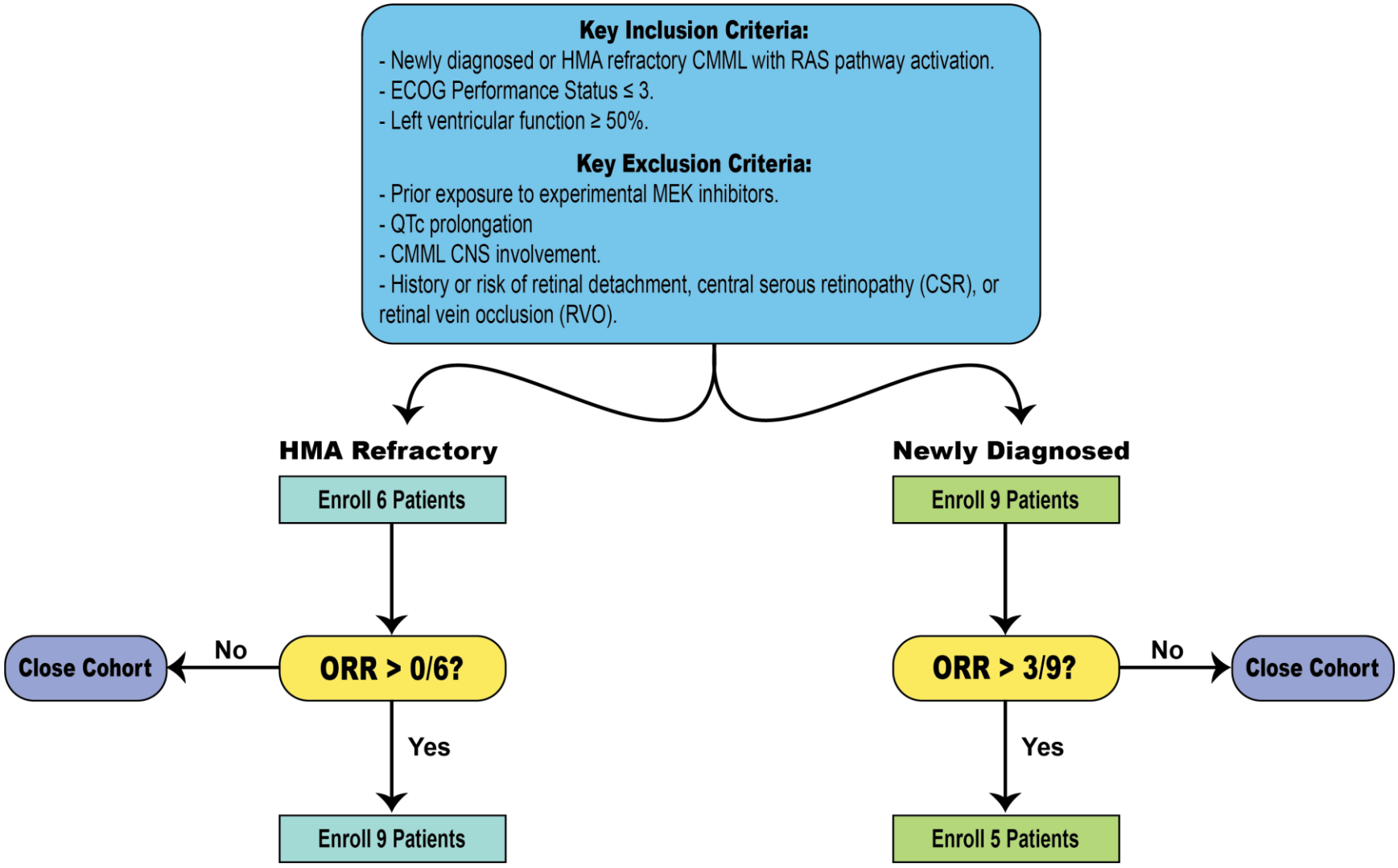


Figure 1: Study Schema

1 OBJECTIVES

1.1 Primary Objective

To assess the efficacy of cobimetinib in patients with newly diagnosed and HMA- refractory chronic myelomonocytic leukemia (CMML).

Primary Endpoints: Overall response rate defined as the proportion of patients achieving complete remission, complete cytogenetic remission, partial remission, marrow response, and clinical benefit according to the 2015 MDS/MPN-IWG criteria.

1.2 Secondary Objective(s)

1.2.1 To assess the safety of cobimetinib treatment in CMML.

Secondary Endpoint: Frequency of adverse events (AEs) characterized by seriousness, severity (as defined by CTCAE, version 5.0), duration, and relationship to study therapy.

1.2.2 To assess the complete response (CR) + partial response (PR) rate (as defined by the 2015 MDS/MPN-IWG criteria) with cobimetinib treatment in CMML.

Secondary Endpoint: Proportion of patients achieving CR+PR at any time point.

1.2.3 To assess the long term efficacy of cobimetinib treatment in CMML.

Secondary Endpoints:

- Progression-free survival (PFS) from the time of treatment initiation to 36 months after the start of therapy, the time of progression, initiation of alternative treatment, or death.
- Overall survival (OS) as defined as the time from the initiation of study therapy until death from any cause.

1.3 Exploratory Objective(s)

To assess the effect of cobimetinib treatment on molecular and phenotypic disease characteristics and characterize mechanisms of resistance.

Exploratory Endpoints:

- Evaluate changes in variant allele burden with cobimetinib treatment.
- Evaluate changes in circulating inflammatory cytokine concentrations with cobimetinib treatment
- Evaluate changes in symptom burden using the MPN SAF-TSS with cobimetinib treatment

- Evaluate cellular MAPK signaling in patients treated with cobimetinib and preliminarily assess causes for primary and secondary resistance
- Evaluate changes in cell surface immunophenotype of circulating monocytes with cobimetinib treatment.

2 BACKGROUND

2.1 Chronic Myelomonocytic Leukemia

Chronic myelomonocytic leukemia (CMML), with an estimated incidence of 4 cases per 100,000 persons per year, accounts for the vast majority of hematologic malignancies classified as myelodysplastic/myeloproliferative (MDS/MPN) neoplasms.[1,2] As a disease group, MDS/MPN is characterized by features consistent with ineffective hematopoiesis, such as cytopenias, but also exhibit signs characteristic of myeloid hyperplasia, such as splenomegaly, leukocytosis and debilitating constitutional symptoms. CMML is poor-risk leukemia of older adults, with an average age of diagnosis of 72 years.[3] Even with currently available therapies, the median overall survival is dismal, ranging from 12-29 months.[1] The inferior survival outcomes in CMML are primarily driven by a high risk of progression to acute myeloid leukemia (AML). Allogeneic stem cell transplant for CMML is potentially curative, but relapse rates and transplant-related mortality are high, and few patients are eligible due to advanced age and co-morbidities.

Table 1: WHO 2022 diagnostic criteria for CMML.

Prerequisite criteria
1. Persistent absolute (≥0.5 × 10^9/L) and relative (≥10%) peripheral blood monocytosis.
2. Blasts constitute <20% of the cells in the peripheral blood and bone marrow.
3. Not meeting diagnostic criteria of chronic myeloid leukaemia or other myeloproliferative neoplasms.
4. Not meeting diagnostic criteria of myeloid/lymphoid neoplasms with tyrosine kinase fusions.
Supporting criteria
1. Dysplasia involving ≥1 myeloid lineages.
2. Acquired clonal cytogenetic or molecular abnormality.
3. Abnormal partitioning of peripheral blood monocyte subsets.
Requirements for diagnosis
- Pre-requisite criteria must be present in all cases.
- If monocytosis is ≥ 1 × 10^9/L: one or more supporting criteria must be met.
- If monocytosis is ≥0.5 and <1 × 10^9/L: supporting criteria 1 and 2 must be met.
Subtyping criteria
- Myelodysplastic CMML (MD-CMML): WBC < 13 × 10^9/L
- Myeloproliferative CMML (MP-CMML): WBC ≥ 13 × 10^9/L
Subgrouping criteria (based on percentage of blasts and promonocytes)
CMML-1: <5% in peripheral blood and <10% in bone marrow
CMML-2: 5–19% in peripheral blood and 10-19% in bone marrow

Diagnostic criteria for CMML according

to the 2022 World Health Organization (WHO) revision of myeloid neoplasms includes both the presence of absolute peripheral blood (PB) monocytosis ≥ 0.5 x 10^9/L and relative monocytes ≥ 10% of the white blood cell (WBC) differential[4]. Although it is a chronic leukemia characterized by <20% blasts in the PB or bone marrow (BM), the blast percentage is prognostic in CMML and further stratifies patients into the categories described in **Table 1**.

Prior to 2001, CMML was classified as a subtype of MDS as per the reigning yet now largely-defunct French-American-British cooperative group designation. In 2001, WHO first separated CMML from MDS to include in the newly created MDS/MPN overlap category, but the decades-long perception of CMML as an MDS variant continued to affect clinical trial design and treatment approaches for the next 10-15 years. As such, treatment options currently available for CMML patients are extrapolated from randomized trials in MDS that included only a small number of actual CMML cases. Consistent with standard-of-care treatment for MDS, hypomethylating agents (HMAs) such as 5-azacitidine and decitabine are typically used for frontline therapy in CMML. Most CMML-specific phase 2 studies with HMAs have demonstrated an overall response rate of 30-40% and complete remission (CR) rates of <20%[1]. Moreover, responses tend to be transient, rarely lasting more than 18 months[5]. Although HMAs have been associated with improved survival in CMML compared to conventional care, they do not alter mutational frequencies and are not thought to prevent the transformation to AML that occurs 20-30% of CMML patients. The favorable impact of HMAs on overall survival in CMML may be related to epigenetic restoration of normal hematopoiesis, thereby circumventing transfusion dependence and infectious complications. However, it is increasingly apparent that HMAs do not constitute disease-modifying therapy in CMML. Better, more targeted agents are needed.

2.1.1 RAS Mutations in CMML

It has been recognized that CMML bifurcates into two phenotypic variants, the so-called "dysplastic" (MDS-CMML; WBC <13 x 10^9) and "proliferative" (MPN-CMML; WBC ≥ 13 x 10^9) subtypes.[6] These categories are clinically, morphologically, and molecularly distinct from one another, with MPN-CMML cases frequently demonstrating hyperactivation of the RAS/MAPK signaling pathway.[7] Distinct RAS pathway activating mutations may be found in up to 50% of patients with CMML. These include somatic gain-of-function mutations in positive regulators of RAS signaling, (i.e. *KRAS*, *NRAS*, *PTPN11*, *FLT3*, *BRAF, JAK2*) as well as loss-of-function mutations in negative regulators (i.e. *NF1, CBL*).[7,8] Although CMML otherwise exhibits a daunting level of genetic heterogeneity - with multiple mutations in epigenetic regulators, transcription factors, and spliceosome components - RAS pathway activation represents a unifying feature amongst disparate individual mutational landscapes.[9] The high prevalence of RAS activating mutations in CMML suggests a critical dependency on this growth signaling pathway.

In a disease already characterized by limited treatment options and sub-optimal outcomes, MPN-CMML patients appear to have a decreased survival compared to MDS-CMML patients.[10,11] Although more studies are needed, there is evidence that RAS-mutant CMML patients have had an especially poor prognosis in CMML.[7] This suggests that the myeloproliferative features conferred by RAS pathway activation portend a more aggressive disease course. Growth factor mutations in genes such as RAS and FLT3 have been observed to be late events in AML pathogenesis, and the occurrence of these events at the time of CMML diagnosis is likely to be representative of advanced disease. Moreover, higher WBC count has been associated with decreased CR rates to HMA therapy in CMML, demonstrating that MPN-CMML patients may demonstrate relative HMA resistance compared to their MDS-CMML counterparts.[11] The predictive impact of RAS pathway mutations on HMA therapy in CMML is not well-studied, but given the association of these mutations with MPN-CMML, one would expect these patients to demonstrate increased HMA refractoriness. In fact, this assertion is supported by our institutional data (**Figure 1**).

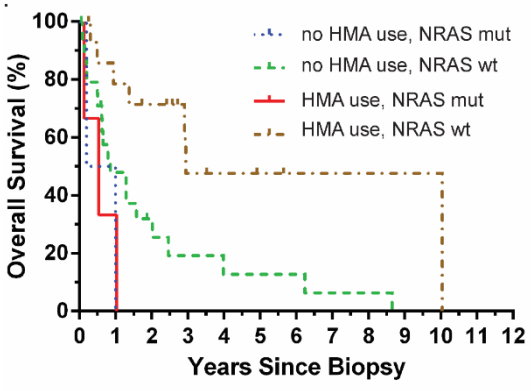


Fig 1. Overall survival of CMML patients with or without *NRAS* mutations stratified by HMA treatment.

Bone marrow transplant is a curative option for CMML patients, but candidacy is limited by age and competing co-morbidities. Importantly, long-term survival following transplant remains suboptimal, with only 20-40% of patients alive after 5 years[12]. Improved treatment options for this patient population are urgently needed. To-date, strategies to treat CMML have focused largely on addressing the dysplastic component of the disease with HMA therapy. Although HMA therapy can transiently ameliorate cytopenias, it fails to significantly modulate disease biology and meaningful responses (i.e. CRs) are lacking. Targeting the molecular features driving aberrant myeloproliferation in CMML represents a potentially disease-modifying treatment avenue.

2.1.2 Study Population

Patients with CMML-1 and CMML-2 will be enrolled and are eligible for the trial. Contemporary CMML prognostic scoring systems incorporating molecular information have superseded the CMML-1/-2 (blast-based) staging for accurate risk prediction in CMML and are consistently preferred and recommended by experts in the field[13]. The Europenia LeukemiaNet (ELN) panel recommends that all CMML patients should undergo risk assessment by these current models[2]. These models, including the Mayo Molecular Model (MMM)[14], the Groupe Francophone des Myelodysplasies (GFM) model[15] and the CMML Prognostic Scoring System (CPSS-mol) model[16], exhibit superiority over traditional blast-based prognostic scoring in predicting overall survival

and leukemia-free survival. With these models, patients who fall into the CMML-0 category based on blast percentage can be deemed high-risk due to the presence of adverse molecular and cytogenetic features, severe cytopenias necessitating frequent transfusion of blood products, high absolute monocyte counts and leukocytosis with presence of circulating immature myeloid precursors that not limited to blasts. It is notable that two of the three models (the MMM and the GFM model) did not find blast percentage to be an independent risk factor on multivariable analysis and as such, blast percentage is not included as a parameter in their respective scoring algorithms.

Although hypomethylating agents (HMAs) are routinely used to treat CMML and are FDA-approved for MDS, no tried and true standard-of-care therapy actually exists given the lack of randomized trial data in this disease space.[5] Most of the data supporting the use of HMAs in CMML has been extrapolated from MDS literature[1,5], and as such, HMA therapy was never designed to address the myeloproliferative variant of CMML, which is highly associated with RAS-pathway activating mutations.[7] Phase 2 studies of HMAs in CMML have demonstrated consistently poor overall survival of 12-30 months and complete remission rates of <20%.[1,5] Moreover, HMA therapy fails to alter mutant allele burden in CMML patients and is not believe to be is not disease-modifying.[17] Several reviews on CMML have reported commonly accepted ORR for HMAs in newly diagnosed CMML patients of 30-40%[5,18,19] but ORR to HMAs for CMML patients with myeloproliferative features (our study population) is reported to be even lower[5,20,21].

The absence of strong data supporting HMA use in CMML, specifically in MPN-CMML, justifies the use of cobimetinib in newly diagnosed CMML patients with RAS-pathway mutations as a frontline experimental therapy.

2.2 MEK Inhibition in CMML

2.2.1 Preclinical data

TET2 is the most commonly mutated gene in CMML, with loss-of-function mutations leading to impaired DNA methylation and epigenetic dysregulation of transcription.[22] Murine studies have demonstrated that *TET2* loss and *NRAS*^{G12D} cooperate to induce a lethal CMML-like disease in vivo with leukocytosis, monocytosis, and thrombocytopenia.[23] Epigenetic reprogramming by *TET2* loss results in loss of negative regulation of the MAPK pathway, thereby augmenting baseline RAS pathway activation in the *NRAS*^{G12D} mutant cells and GM-CSF hypersensitivity. The MEK inhibitor, binimetinib, decreased ERK activation in double-mutant cells and reduced leukocytosis, splenomegaly, and BM leukemia burden in diseased mice while significantly extending survival. Improved survival was also noted in secondary recipients engrafted with binimetinib treated *TET2*$^{-/-}$ *NRAS*^{G12D} cells, suggesting that single-agent MEK inhibition targets leukemia-initiating cells and modifies disease. Two other MEK inhibitors, selumetinib and PD-032 also demonstrated efficacy as single agents in the same mouse model of CMML.

2.2.2 Clinical data

A phase 1/2 study of the oral MEK inhibitor trametinib was performed in relapsed/refractory or *NRAS* mutant AML, MDS, and CMML. The CMML patients (n=11) were heavily pretreated, with 82% having received previous chemotherapy and 36% having received ≥ 3 or more prior lines of treatment. The response rate in the CMML cohort was 27% (n=3), including one CR, one partial CR, and one marrow CR. The median duration of response in these patients was 8 weeks, with one patient experiencing a response for 25 weeks. The achievement of CRs in this small, heavily pretreated, treatment-refractory group is encouraging. Additionally, 36% of CMML patients experienced ≥ 50% reduction in bone marrow blasts and 45% experienced ≥ 50% reduction in PB blasts. It is possible that observed response rates to MEK inhibition may be higher in a treatment-naïve CMML cohort with RAS activation and could even be used as a bridge to stem cell transplant. Notably, the use of single-agent trametinib was found to be tolerable, with the most common toxicities being diarrhea (30%), rash (25%), nausea (13%), and elevated ALT (11%).

2.3 Cobimetinib

The inhibition of MEK is a promising strategy to control the growth of tumors that are dependent on aberrant signaling in the RAS /MAPK pathway. Cobimetinib is a novel and highly selective inhibitor of MEK, and consequently of the intracellular components of the MAPK pathway affecting tumor cell proliferation and survival. The inhibition of MEK is a promising strategy to control the growth of tumors that are dependent on aberrant signaling in the RAS/RAF pathway.

Cobimetinib demonstrates biochemical selectivity for MEK, with an IC_{50} of 4.2nM against MEK1 compared with an IC_{50} against a panel of more than 100 serine-threonine and tyrosine kinases. As of July 2018, cobimetinib has been approved in approximately 64 countries, including the United States, Switzerland and the European Union for use in combination with vemurafenib for the treatment of patients with unresectable or metastatic melanoma with BRAFV600 mutations

2.3.1 Dose Rationale

The dose of cobimetinib will be 60 mg (3 tablets of 20 mg) once daily. This dose is based on a 28-day cycle. Each dose should be taken once daily for 21 consecutive days (Days 1 to 21-treatment period); followed by a 7-day break (Days 22 to 28-treatment break). Each subsequent cobimetinib treatment cycle should start after the 7-day treatment break has elapsed. This cobimetinib dose and schedule are based on a previous phase 1 non-randomized, open-label, safety, PK, and dose-escalation study (MEK4592g). This study was conducted in patients with metastatic or unresectable solid tumors. In this trial, the maximum tolerated dose for the 21/7 schedule was found to be 60mg daily[24].

2.4 Design Rationale

This is a phase 2, non-randomized, single-arm study. The rationale behind the phase 2 design is two-fold. First, a phase 1 dose-escalation study of cobimetinib as monotherapy in cancer patients was previously completed and established the MTD and optimal dosing schedule

(60mg daily; 21/7) as described above[24]. This cobimetinib dosing schedule was demonstrated to be safe and very efficacious (89% ORR) in a phase 2 study of 18 patients with histiocytic neoplasms, 83% of whom exhibited RAS-pathway activating mutations[25]. Second, a previous phase 1/2 dose-escalation, nonrandomized trial of the MEK inhibitor trametinib in RAS-mutated AML patients, and a small cohort of CMML patients (n=11) established that single-agent MEK inhibition is safe in patients with leukemia, including CMML[26]. A subsequent study has confirmed the safety of MEK inhibitors as monotherapy in AML[27].

The primary endpoint is objective response rate as per the 2015 MDS/MPN-IWG criteria. The null hypothesis is a response rate of 10% in HMA-treated patients and 35% in newly diagnosed patients. The response rate of 35% in newly diagnosed patients is based on historical response rates with frontline HMA therapy in CMML patients[1]. As second-line therapies for CMML do not exist, we would regard a response rate of 10% as standard-of-care for patients who have failed HMA therapies. Simon's two-stage design (Simon, 1989) will be used for both cohorts.

CMML patients comprise an elderly population and often have additional medical comorbidities that limit their activity. CMML patients with an ECOG performance status ≤ 3 are eligible to enroll in this trial. The decision was made to include patients with an ECOG PS of 3 to increase external validity and mimic real-world treatment conditions.

3 DRUG INFORMATION

3.1 Cobimetinib

Cobimetinib is a reversible inhibitor of mitogen-activated protein kinase (MAPK)/extracellular signal-regulated kinase 1 (MEK1) and MEK2. MEK proteins are upstream regulators of the extracellular signalrelated kinase (ERK) pathway, which promotes cellular proliferation.

3.1.1 Pharmacology

The pharmacokinetics of cobimetinib was studied in healthy subjects and cancer patients. Cobimetinib exhibits linear pharmacokinetics in the dose range of 3.5 to 100 mg (i.e., 0.06 to 1.7 times the recommended dosage). Following oral administration of 60 mg once daily, steady-state was reached by 9 days with a mean accumulation ratio of 2.4-fold (44% CV).

Absorption: Following oral dosing of 60 mg once daily in cancer patients, the median time to achieve peak plasma levels (T_{max}) was 2.4 (range:1–24) hours, geometric mean steady-state $AUC_{0\text{-}24h}$ was 4340 ng·h/mL (61% CV) and C_{max} was 273 ng/mL (60% CV). The absolute bioavailability of cobimetinib was 46% (90% CI: 40%, 53%) in healthy subjects. A high-fat meal (comprised of approximately 150 calories from protein, 250 calories from carbohydrate, and 500–600 calories from fat) had no effect on cobimetinib AUC and C_{max} after a single 20 mg cobimetinib was administered to healthy subjects.

Distribution: Cobimetinib is 95% bound to human plasma proteins in vitro, independent of drug concentration. No preferential binding to human red blood cells was observed (blood to plasma ratio of 0.93). The estimated apparent volume of distribution was 806 L in cancer patients based on a population PK analysis.

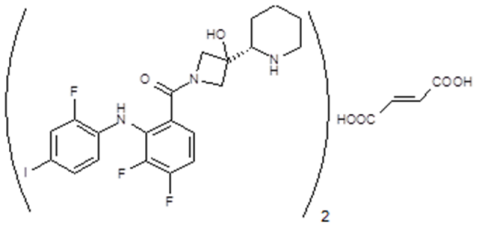
Elimination: Following oral administration of cobimetinib 60 mg once daily in cancer patients, the mean elimination half-life ($t_{1/2}$) was 44 (range: 23–70) hours and the mean apparent clearance (CL/F) was 13.8 L/h (61% CV).

Metabolism: CYP3A oxidation and UGT2B7 glucuronidation were the major pathways of cobimetinib metabolism in vitro. Following oral administration of a single 20 mg radiolabeled cobimetinib dose, no oxidative metabolites >10% of total circulating radioactivity were observed.

Excretion: Following oral administration of a single 20 mg radiolabeled cobimetinib dose, 76% of the dose was recovered in the feces (with 6.6% as unchanged drug) and 17.8% of the dose was recovered in the urine (with 1.6% as unchanged drug).

3.1.2 Physical and Chemical Properties

Cobimetinib fumarate is a kinase inhibitor. The chemical name is (*S*)-[3,4-difluoro-2-(2-fluoro-4iodophenylamino)phenyl] [3-hydroxy-3-(piperidin-2-yl)azetidin-1-yl]methanone hemifumarate. It has a molecular formula $C_{46}H_{46}F_6I_2N_6O_8$ (2 $C_{21}H_{21}F_3IN_3O_2$ $C_4H_4O_4$) with a molecular mass of 1178.71 as a fumarate salt. Cobimetinib fumarate has the following chemical structure:



3.1.3 Pharmaceutical Properties and Formulation

Cobimetinib is a fumarate salt appearing as white to off-white solid and exhibits a pH-dependent solubility. The inactive ingredients are **Tablet Core:** microcrystalline cellulose, lactose monohydrate, croscarmellose sodium, magnesium stearate. **Coating:** polyvinyl alcohol, titanium dioxide, polyethylene glycol 3350, talc.

3.1.4 Clinical Safety:

The safety and efficacy of cobimetinib were established in a multicenter, randomized (1:1), double-blinded, placebo-controlled trials conducted in 495 patients with previously untreated, BRAF V600 mutation-positive, unresectable or metastatic, melanoma. The presence of BRAF V600 mutation was detected using the cobas® 4800 BRAF V600 mutation test. All patients received vemurafenib 960 mg orally twice daily on days 1–28 and were randomized to receive cobimetinib 60 mg or matching placebo orally once daily on days 1–21 of an every 28-day cycle. Randomization was stratified by geographic region (North America vs. Europe vs. Australia/New Zealand/others) and disease stage (unresectable Stage IIIc, M1a, or M1b vs. Stage M1c). Treatment continued until disease progression or unacceptable toxicity. Patients randomized to receive placebo were not offered cobimetinib at the time of disease progression. The major efficacy outcome was investigator-assessed progression-free survival (PFS) per RECIST v1.1. Additional efficacy outcomes were investigator-assessed confirmed objective response rate, overall

survival, PFS as assessed by blinded independent central review, and duration of response. The median age of the study population was 55 years (range 23 to 88 years), 58% of patients were male, 93% were White and 5% had no race reported, 60% had stage M1c disease, 72% had a baseline ECOG performance status of 0, 45% had an elevated baseline serum lactate dehydrogenase (LDH), 10% had received prior adjuvant therapy, and <1% had previously treated brain metastases. Patients with available tumor samples were retrospectively tested using next-generation sequencing to further classify mutations as V600E or V600K; test results were obtained on 81% of randomized patients. Of these, 86% were identified as having a V600E mutation and 14% as having a V600K mutation.

Use in specific populations:

Pregnancy: Based on findings from animal reproduction studies and its mechanism of action, cobimetinib can cause fetal harm when administered to a pregnant woman. There are no available data on the use of cobimetinib during pregnancy. In animal reproduction studies, oral administration of cobimetinib in pregnant rats during organogenesis was teratogenic and embryotoxic at exposures (AUC) that were 0.9 to 1.4-times those observed in humans at the recommended human dose of 60 mg. Advise pregnant women of the potential risk to a fetus. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2–4% and 15–20%, respectively.

Animal Data: Administration of cobimetinib to pregnant rats during the period of organogenesis resulted in increased post-implantation loss, including total litter loss, at exposures (AUC) of 0.9–1.4 times those in humans at the recommended dose of 60 mg. The post-implantation loss was primarily due to early resorptions. Fetal malformations of the great vessels and skull (eye sockets) occurred at the same exposures.

Lactation: There is no information regarding the presence of cobimetinib in human milk, effects on the breastfed infant, or effects on milk production. Because of the potential for serious adverse reactions in a breastfed infant, advise a nursing woman not to breastfeed during treatment with cobimetinib and for 2 weeks after the final dose.

Hepatic Impairment: Pharmacokinetics of cobimetinib has not been studied in patients with moderate or severe hepatic impairment. Dose adjustment is not recommended for patients with mild hepatic impairment (total bilirubin less than or equal to ULN and AST greater than ULN **or** total bilirubin >ULN but ≤ 1.5 times ULN and any AST) based on results of the population pharmacokinetic analysis.

Renal Impairment: No dedicated pharmacokinetic trial in patients with renal impairment has been conducted. Dose adjustment is not recommended for mild to moderate renal impairment (CLcr 30 to 89 mL/min) based on the results of the population pharmacokinetic analysis. A recommended dose has not been established for patients with severe renal impairment.

4 STUDY DESIGN

4.1 Description

This is an open-label, nonrandomized phase 2 trial to assess the efficacy of cobimetinib in RAS pathway activated CMML. Two cohorts of patients will be accrued using Simon's two-stage design (Simon, 1989) for both cohorts. Cohort 1 will enroll nine newly diagnosed patients in the first stage and if four or more responses are observed five additional patients will be enrolled in the second stage. Cohort 2 will enroll six HMA refractory patients in the first stage and if one or more responses are observed then nine additional patients will be enrolled in the second stage. Study treatment safety will be periodically monitored for excessive toxicity as described in Section 11.3.

Table 2: Cohort Enrollment

Cohort	Stage 1 (n)	Stage 2 (n)
Cohort 1: Newly Diagnosed	9	5
Cohort 2: HMA Refractory	6	9

All eligible patients will be treated daily with cobimetinib in 28-day cycles. Cobimetinib will be administered consecutively for three weeks followed by a one week break prior to the start of the following cycle. Patients will remain on study therapy until treatment discontinuation criteria is met.

Due to discontinuation of cobimetinib supply from the benefactor, study participants who are currently on treatment will discontinue study cobimetinib early under Amendment 6 (v.09DEC2025). These subjects will discontinue treatment and proceed to EOT and Follow-Up.

4.2 Number of Patients

Cohort 1 (newly diagnosed) will enroll N=14 patients. Cohort 2 (HMA refractory) will enroll N=15 patients. The total number of patients on study will be N=29.

4.3 Number of Study Centers

This is a multisite study to be conducted at the Huntsman Cancer Institute at the University of Utah, Salt Lake City, Utah. Up to 2 additional sites may be included.

4.4 Study Duration

From the first patient on trial to completion of the last patient’s final follow-up, the trial duration is expected to be 60 months.

5 ELIGIBILITY CRITERIA

This eligibility checklist is used to determine patient eligibility and filed with the enrolling investigator's signature in the patient research chart.

Patient No. _____

Patient's Initials: (L,F,M) _____

5.1 Inclusion Criteria

Yes/No (Response of "no" = patient ineligible)

5.1.1 _____ Male or female subject aged ≥ 18 years.

5.1.2 _____Untreated or hypomethylating agent (HMA) refractory chronic myelomonocytic leukemia (CMML-1/-2; 2022 WHO classification) with RAS pathway activation as determined by standard-of-care hematopoietic cell sequencing results on peripheral blood or bone marrow demonstrating NRAS, KRAS, PTPN11, FLT3, CBL, JAK2, BRAF or NF1 mutations at a variant allele frequency ≥ 5%. BMBx, NGS, FISH or BCR-ABL1 PCR, and cytogenetics should be done at the primary trial site within 21 days prior to C1D1. Results from a previous NGS panel completed within 60 days of registration may be used for the purpose of confirming eligibility.

If the patient is FLT3-ITD positive, the FLT3-ITD PCR allelic ratio must be ≥ 0.05 on testing done on screening biopsy (NOTE: cannot quantitate FLT3-ITD VAF by NGS, must be a separate PCR test).

5.1.3 _____ ECOG Performance Status ≤ 3.

5.1.4 _____ Adequate organ function as defined as:

- Hepatic:
  - Total Bilirubin ≤ 1.5x institutional upper limit of normal (ULN)
    - Unless elevation is related to Gilbert's syndrome, hemolysis, or thought to be due to leukemic hepatic involvement.
  - AST(SGOT)/ALT(SGPT) ≤ 3 × institutional ULN
    - Unless elevation is related to leukemic hepatic involvement.
- Renal:
  - Serum creatinine ≤ 2x ULN

OR

- Estimated creatinine clearance ≥ 30 mL/min by Cockcroft-Gault formula:
  - Males: $\frac{(140-age)\times weight[kg]}{serum\ creatinine\left[\frac{mg}{dL}\right]\times 72}$
  - Females: $\left(\frac{(140-age)\times weight[kg]}{serum\ creatinine\left[\frac{mg}{dL}\right]\times 72}\right)\times 0.85$

5.1.5 _____ Left ventricular function ≥ 50% as assessed by echocardiogram or multigated acquisition scan (MUGA)

5.1.6 _____ Negative pregnancy test for women of childbearing potential or evidence of post-menopausal status. Women will be considered post-menopausal if they have been amenorrheic for 12 months without an alternative medical cause. The following age-specific requirements apply:

- Women <50 years of age would be considered post-menopausal if they have been amenorrheic for 12 months or more following cessation of exogenous hormonal treatments and if they have luteinizing hormone and follicle-stimulating hormone levels in the post-menopausal range for the institution or underwent surgical sterilization (bilateral oophorectomy or hysterectomy).
- Women ≥50 years of age would be considered post-menopausal if they have been amenorrheic for 12 months or more following cessation of all exogenous hormonal treatments, had radiation-induced menopause with last menses >1 year ago, had chemotherapy-induced menopause with last menses >1 year ago, or underwent surgical sterilization (bilateral oophorectomy, bilateral salpingectomy or hysterectomy).

5.1.7 _____ Highly effective contraception for both male and female subjects throughout the study and at least 3months after the last dose of study therapy as described in Section 7.4.

5.1.8 _____ Recovery to baseline or Grade ≤ 1 CTCAE v5.0 from toxicities related to any prior treatments, unless AE(s) are clinically nonsignificant and/or stable on supportive therapy.

5.1.9 _____ Able to provide informed consent and willing to sign an approved consent form that conforms to federal and institutional guidelines.

5.2 Exclusion Criteria

Yes/No (Response of "yes" = patient ineligible)

5.2.1 _____Previous exposure to experimental MEK inhibitors for CMML.

5.2.2 _____Grade 2 or greater QTcF prolongation on screening electrocardiogram (ECG) or clinically significant cardiovascular disease (uncontrolled or symptomatic atrial arrhythmias, congestive heart failure, myocardial infarction/CABG/PCI within 6 months of screening, uncontrolled arterial hypertension or history of ventricular arrhythmia)

5.2.3 _____Clinical or laboratory evidence of central nervous system (CNS) leukemia.

5.2.4 _____Major surgery within 4 weeks prior to study drug initiation.

5.2.5 _____History of interstitial lung disease or pneumonitis.

5.2.6 _____ History of retinal detachment, central serous retinopathy (CSR), retinal vein occlusion (RVO), or at high risk for CSR or RVO following screening ophthalmologic exam at discretion of PI/Sub-I following review of exam findings, and, if necessary, consultation with ophthalmology provider.

5.2.7 _____ Patients with muscular and/or neuromuscular disorders associated with elevated CPK (e.g. inflammatory myopathies, muscular dystrophy, amyotrophic lateral sclerosis, or spinal muscular atrophy).

5.2.8 _____Any active significant gastrointestinal dysfunction as determined by the clinical investigator to interfere with the patient's ability to swallow or absorb the study treatment, (i.e refractory nausea and vomiting, malabsorption and external biliary shunt)

5.2.9 _____Pregnant or nursing (lactating) women.

5.2.10 _____On chronic treatment with strong CYP3A inhibitors or patients taking St. John's Wort, carbamazepine, efavirenz, phenytoin, rifampin, and other strong and moderate CYP3A inducers.

5.2.11 ____ Treatment for any other malignancy within 2 years of study enrollment, except for adequately treated basal cell or squamous cell skin cancer, carcinoma in situ of the breast, bladder or cervix, low-grade (Gleason 6 or below) prostate cancer on surveillance with no plans for treatment intervention (eg, surgery, radiation, or castration), prostate cancer that has been adequately treated with prostatectomy or radiotherapy and currently with no evidence of disease or symptoms, or any solid tumor malignancy that has been adequately treated for which there is no evidence of active disease within the last 2 years. Patients with monoclonal gammopathy of undetermined significance (MGUS) are permitted to enroll.

5.2.12 _____ Known HIV infection with a detectable viral load at the time of screening.

Note: Patients on effective antiretroviral therapy with an undetectable viral load at the time of screening are eligible for this trial.

5.2.13 _____ Active infection including tuberculosis (clinical evaluation that includes clinical history, physical examination, and radiographic findings, and TB testing in line with local practice), hepatitis B (known positive HBV surface antigen (HBsAg) result), or hepatitis C. Active, controlled infections that, in the opinion of the PI, do not increase risk or interfere with study participation are allowed with prior medical monitor approval.

Note: Patients with a past or resolved HBV infection (defined as the presence of hepatitis B core antibody [anti-HBc] and absence of HBsAg) are eligible. Patients positive for hepatitis C (HCV) antibody are eligible only if polymerase chain reaction is negative for HCV RNA.

5.2.14 _____ Subjects taking prohibited medications as described in Section 6.3.2. A washout period of prohibited medications for a period of at least 5 half-lives or as clinically indicated should occur before the start of treatment.

5.2.15 _____ Known prior severe hypersensitivity to cobimetinib or any component in its formulations (NCI CTCAE v5.0 Grade ≥ 3).

5.2.16 _____ Medical, psychiatric, cognitive, or other conditions that may compromise the subject's ability to understand the subject information, give informed consent, comply with the study protocol or complete the study.

I certify that this patient meets all inclusion and exclusion criteria for enrollment onto this study.

_____ _____ _____

Investigator Signature **Date** **Time**

5.3 Recruitment Strategies

Potential patients will be identified by Investigators in the setting of their outpatient clinics.

6 TREATMENT PLAN

6.1 Administration Schedule

Cobimetinib is taken on a 28-day cycle. Each dose consists of three 20 mg tablets (60 mg) and should be taken once daily for 21 consecutive days (Days 1 to 21-treatment period); followed by a 7-day break (Days 22 to 28-treatment break). Each subsequent cobimetinib treatment cycle should start after a 7-day treatment break has elapsed.

6.2 Cobimetinib

Cobimetinib is a reversible inhibitor of mitogen-activated protein kinase (MAPK)/extracellular signal-regulated kinase 1 (MEK1) and MEK2. MEK proteins are upstream regulators of the extracellular signal related kinase (ERK) pathway, which promotes cellular proliferation.

6.2.1 How Supplied, Stored, Packaged and Labeled

Cobimetinib will be supplied by Genentech as white, round, film-coated 20 mg tablets for oral administration, debossed on one side with “COB”. Each 20 mg tablet contains 22 mg of cobimetinib fumarate, which corresponds to 20 mg of the cobimetinib free base.

Store at room temperature below 30°C (86°F).

6.2.2 Preparation and Administration

Cobimetinib will be prepared and dispensed by appropriately trained and delegated personnel. Subjects will be provided enough investigational product for a full cycle to self-administer at home. Cobimetinib will be administered orally once daily (every 24 hours ± 4 hours) without regard for food, proton pump inhibitors, or other acid-reducing agents. Subjects should not take extra medication for any reason nor should they re-administer in the case of vomiting after administration. If a dose is missed outside of the dosing window, the dose should not be made up. If a dose is vomited, treatment should be continued as prescribed the following day and the dose should not be made up.

6.2.3 Accountability and Compliance

Cobimetinib must be requested by submitting an order form directly to the drug depot and will be shipped directly to the investigational site.

The investigator, or a responsible party designated by the investigator, must maintain an adequate record of receipt, distribution, and return of all study drugs in the form of a Drug Accountability Form. Such records must be provided to the drug supplier upon request.

Drug compliance will be recorded by patients on the drug diary (see Appendix 5). A member of the study team will review patient drug compliance at the end of treatment for

each cycle and provide patient re-education as required. At the discretion of the principal investigator, a subject may be discontinued from the trial for non-compliance with study visits or study drug.

Excess or unused study drug should be returned to the investigative site, for accounting and destroyed in accordance with GCP after drug accountability has been performed.

6.3 Concomitant Medications and Therapies

Concomitant medications include any prescription or over-the-counter preparation, including vitamins, dietary supplements, over-the-counter medications, and oral herbal preparations taken during the study. Patients may continue their baseline medication(s) providing that the medications are not prohibited on study. Any diagnostic, therapeutic, or surgical procedure performed during the study period should be recorded, including the dates, description of the procedure(s), and any clinical findings, if applicable.

6.3.1 Allowed Therapy

Any medication which is considered necessary for a subject's welfare is permitted and may be given at the discretion of the investigator. Medications for the treatment of underlying disease and symptomatic treatment of adverse events are permitted. Exceptions are listed in the section below.

Use of Blood Products

During treatment, patients may receive red blood cell (RBC) or platelet transfusions, if clinically indicated, per institutional guidelines. Patients who require repeated transfusion support should be discussed with the Sponsor-Investigator.

Appropriate anti-coagulation is allowed during the study (e.g., low molecular weight heparin, direct factor Xa inhibitors, etc.). Warfarin is allowed during the study provided patients are monitored for INR twice a week during the first two cycles of therapy, then weekly to biweekly thereafter.

Patients may receive supportive care with erythropoietin, darbepoetin, granulocyte-colony stimulating factor or granulocyte macrophage-colony stimulating factor, pegylated growth factors, and platelet stimulatory factors, in accordance with clinical practice or institutional guidelines before entry and throughout the study.

Hydroxyurea use is allowed during screening through C2D28 for cytoreduction in cases of highly proliferative CMML. Patients with WBC $\geq$ 25K/uL must be placed on hydroxyurea (at a minimum dose of 500mg twice daily) and allopurinol 3 days prior to C1D1 as leukemoid reaction and tumor lysis syndrome-like reactions to cobimetinib have been observed in the first week of therapy.

6.3.2 Prohibited Therapy

Medications or vaccinations specifically prohibited in the exclusion criteria are not allowed during the active treatment period. Patients are prohibited from receiving the following therapies during the treatment phase of this trial:

- Any other investigational drug is prohibited.
- Strong CYP3A4 inducers and inhibitors are prohibited.
- Moderate CYP3A4 inducers.
- Herbal preparations or over-the-counter supplements containing herbal ingredients (St. John's Wort, Estroven, Blue Cohosh, THC) are prohibited.
- Any live-attenuated vaccine therapies for the prevention of infectious disease (e.g. MMR, or rotavirus).

6.3.3 Cautionary Therapy

Caution should be exercised when administering cobimetinib with a moderate CYP3A4 inhibitor. Patients on the study who require treatment with moderate CYP3A4 inhibitors should be closely monitored for signs of cobimetinib toxicity with specific attention to known class toxicities at regularly scheduled clinic visits. Additionally, the dose of cobimetinib must be reduced to 20mg daily for the duration of concurrent administration. Patients who have previously undergone cobimetinib dose reduction who require treatment with moderate CYP3A4 inhibitors must hold cobimetinib until therapy with the moderate CYP3A4 inhibitor is complete. Previously dose-reduced patients who require ongoing treatment with CYP3A4 inhibitor >28 days will be evaluated for permanent study therapy discontinuation at the discretion of the PI. Once the moderate CYP3A4 inducer is discontinued, the initial dose of cobimetinib may be resumed.

Medications with a known risk for QTc prolongation should be administered with caution and additional ECG monitoring should be performed with the addition of QTc prolonging agents to ensure that the QTcF interval does not exceed >500ms with a change from baseline in QTcF of $\geq$ 60 ms. Should the QTcF interval >500msec, follow instructions for triplicate ECG in Section 10.5 and if necessary, consider alternative agent or dose-reduce cobimetinib as per dose modification guidelines in Section 7.2.

6.3.4 Diet

Patients on cobimetinib should maintain adequate caloric and fluid intake. Due to CYP3A4 interactions, subjects will be advised to avoid grapefruit, Seville oranges, pomelos, and star fruit including products containing these fruits (e.g. juices, jams, marmalades, etc.).

6.4 Duration of Therapy

Study subjects may remain on treatment until treatment discontinuation criteria is met or until 12 cycles of cobimetinib treatment have been completed, or the study drug supply is no longer available. Any patient determined to be deriving clinical benefit after 12 months of therapy in the opinion of the investigator may continue treatment after discussion and approval from the Sponsor and Principal Investigator.

6.4.1 Criteria for discontinuation of treatment ("off-treatment")

Patients may withdraw from treatment or the study overall at any time at their own request, or they may be withdrawn at the discretion of the Investigator for safety, behavioral reasons, or the inability of the patient to comply with the protocol-required schedule of study visits or procedures. In addition to the drug-specific discontinuation criteria listed in Dose Modification Section (Section 7.2), the following will result in treatment discontinuation:

- Disease progression per MDS/MPN-IWG.
- Loss of clinical benefit in the opinion of the investigator.
- No significant clinical benefit after 3 cycles of treatment as determined by the Principal Investigator.
- Unacceptable Toxicity. If a treatment-related dose delay for toxicity lasts for > 28 days, treatment will be discontinued permanently.
- Completed 12 months of cobimetinib treatment unless the patient is deriving clinical benefit after 12 months of therapy and will continue treatment after discussion and approval from the Sponsor and Principal Investigator.
- Subject withdraws consent from the study treatment and/or study procedures.
- Non-compliance as defined as missing > 20% of required study drug treatment without the necessity for AE management.
- Pregnancy
- Significant protocol violation
- The patient refused further treatment
- Study treatment terminated by investigator sponsor
- Lost to follow-up
- Death

6.4.2 Criteria for discontinuation of study ("off study")

Subjects will be taken off study for the following:

- Completed study follow-up period
- Screen failure
- The subject is lost to follow-up
- Continuation of the trial would be harmful to the subject's well-being in the investigator's opinion.
- Development of intercurrent illness or situation which would, in the judgment of the investigator, significantly affect assessments of clinical status and trial endpoints.

- Participant requests to be withdrawn from the study
- Death
- Study terminated by investigator sponsor.

7 TOXICITIES AND DOSE MODIFICATION

Every effort should be made to administer the investigational product at the planned dose and schedule. In the event of study treatment toxicity, dosing may be interrupted, delayed and/or reduced as described in the below sections or at the discretion of the treating physician following consultation with the study PI . In the event of multiple toxicities, dose modifications should be based on the worst toxicity observed (CTCAE v5.0) and/or the most conservative recommendation for any given toxicity. Patients are to be instructed to notify Investigators at the first occurrence of any adverse symptom.

All dose modifications must be clearly documented in the patient's medical chart and in the electronic case report form (eCRF). Appropriate follow-up assessments should be done until adequate recovery occurs as assessed by the Investigator.

7.1 Dose Interruptions

Dose interruptions for study treatment-related AEs are allowed as per the dose modification recommendations. Doses of any investigational product that were not administered due to toxicity will not be replaced within the same cycle. In addition to dose interruption, the need for a dose reduction at the time of treatment resumption should also be considered based on the dose modification recommendations. If a toxicity-related dose delay lasts for > 28 days, treatment will be discontinued permanently.

7.1 Dose Reductions

Following dosing interruption due to treatment-related toxicity, the study drug may need to be resumed at a reduced dose as per the dose modification recommendations. Dose reduction should proceed by decreasing the administered dose by one dose level per Table 3. If a patient requires a dose reduction beyond dose level -2, study therapy should be discontinued and that patient should continue on study follow-up.

Once the study treatment has been reduced for a given patient, all subsequent cycles should be administered at that dose level. Intra-patient dose re-escalation is not allowed.

Table 3: Cobimetinib dose levels

Dose Level	Cobimetinib
Dose Level 0	60 mg orally once daily
Dose Level -1	40 mg orally once daily
Dose Level -2	20 mg orally once daily

7.2 Dose Modifications and Guidelines for Adverse Event Management

Patients experiencing adverse events attributed to study drug may undergo dose modifications for toxicity management. **Dose modification guidelines are provided below for adverse events considered to be related (definitely, probably, or possibly related) to the study medication.** When considering hematologic adverse events, baseline (C1D1) values should be taken into consideration where noted below before initiating dose modifications.

Table 4: Guidelines for Adverse Event Management

Toxicity and Severity	Supportive care and dose adjustment guidelines
Thrombocytopenia	
Grade 1 or 2	Maintain dose. Rule out other causes including drug effects.
Grade 3 without bleeding	Maintain dose. Rule out other causes including drug effects.
Grade 4 without bleeding and baseline platelet count ≥ 25,000/uL	Rule out other causes including drug effects. Platelet transfusion is allowed if clinically indicated. For the first occurrence: hold cobimetinib until ≤ Grade 3 or baseline and reduce by 1 dose level. If recurrent, the investigator may decide to continue cobimetinib dosing without dose reductions and/or interruptions \, provided that platelet counts and bleeding symptoms/signs are closely monitored. Additional dose holds/reductions for thrombocytopenia are allowed if felt to be significantly impacting patient quality of life (e.g. patient is transfusion-dependent).
Grade 4 without bleeding and baseline platelet count < 25,000/uL	Rule out other causes.. If persistent, the investigator may decide to continue cobimetinib dosing without dose reductions and/or interruptions, provided that platelet counts and bleeding symptoms/signs are closely monitored. Platelet transfusion is allowed if clinically indicated... Dose holds/reductions for severe thrombocytopenia are allowed if felt to be significantly impacting patient quality of life (e.g. patient is transfusion-dependent).
Grade ≥3 with bleeding	Interrupt cobimetinib dosing and check platelet counts weekly until the bleeding has stopped, the patient is clinically stable, and the platelets have recovered to Grade ≤ 3 or baseline. Platelet transfusion is allowed if clinically indicated.When resuming cobimetinib, reduce by 1 dose level.
Neutropenia	
Grade 4 neutropenia (afebrile) and baseline neutrophil count ≥ 500 OR Febrile neutropenia	Institute and prophylactic antibiotics as clinically indicated per institutional guidelines. Hold cobimetinib and check neutrophil count at least weekly until recovery to Grade ≤ 3 and/or the patient is afebrile and clinically stable. For the first occurrence: reduce by 1 dose level upon resolution. If the second occurrence: follow the above procedure and hold cobimetinib. Continue to dose reduce by 1 dose level upon resolution.

Grade 4 neutropenia (afebrile) and baseline neutrophil count < 500	Maintain dose. Institute prophylactic antibiotics as clinically indicated per institutional guidelines.
Anemia	
Treat per institutional guidelines including blood transfusions and/or erythropoietin. Consider transfusing for symptoms with hemoglobin >8 g/dL (Grade < 3) or for any Grade 3 (hemoglobin <8 g/dL). If possible, maintain cobimetinib dose as long as the patient is clinically stable, but if a dose reduction or interruption is desired, this is allowable following discussion with the PI.	
Edema	
Grade 1 or 2	Maintain dose. Rule out other causes. Institute diuretic therapy and/or measures such as salt or fluid restriction or use of compression hose as necessary.
Grade 3	Hold cobimetinib until ≤ Grade 1 and resume at the next lower dose level
Nausea, acute	
Grade 1 or 2	Maintain dose. Rule out other causes. Use standard additional anti-nausea medications. If persistent, use additional anti-nausea medications, if needed . Olanzapine 2.5 to 5 mg PO every morning, per NCCN guidelines, can mitigate nausea and anorexia.
Grade 3	Rule out other causes. Use additional anti-nausea medications, if needed. Olanzapine 2.5 to 5 mg PO every morning, per NCCN guidelines, can mitigate nausea and anorexia. Interrupt cobimetinib dosing until resolved to Grade ≤2 or baseline and reduce by 1 dose level.
Diarrhea	
Grade 1 or 2	Maintain dose. Rule out other causes including other drug effects and infection. Treat per institutional guidelines with antidiarrheals, such as loperamide.
Grade 3	Hold cobimetinib until ≤ Grade 1 and resume at the next lower dose level
Abdominal pain	
Grade 1 or 2	Maintain dose. Rule out other causes such as heartburn/GERD or constipation and consider pain control measures with laxatives/stool softeners, antacids, antispasmodics, or mild analgesics such as acetaminophen.
Grade 3	Hold cobimetinib ≤ Grade 1 and resume at the next lower dose level
Cardiomyopathy	

Asymptomatic absolute decrease in LVEF from baseline of > 10% and less than institutional LLN	Hold cobimetinib for 2 weeks and repeat LVEF. Resume at next lower dose if all of the following are present: -LVEF is at or above LLN -Absolute decrease from baseline LVEF is 10% or less Permanently discontinue cobimetinib if any of the folllwing are present: -LVEF is less than LLN or -Absolute decrease from baseline is >10%
Symptomatic LVEF decrease from baseline	Hold cobimetinib for 2 weeks and repeat LVEF. Resume at next lower dose level if all of the following are present: -Symptoms resolved -LVEF is at or above LLN - Absolute decrease from baseline LVEF is 10% or less Permanently discontinue cobimetinib if any of the following are present: -LVEF is less than LLN or -Absolute decrease from baseline is >10% -Symptoms are persistent
QTcF prolongation	
Grade 3	Repeat ECG in triplicate as per Section 10.5. If Grade 3 prolongation is confirmed, hold cobimetinib until improved to ≤ Grade 2, review concomitant medications and minimize other QTc-prolonging medications. Resume cobimeteinib at the same dose level and repeat ECG within 7 days of restarting. If Grade 3 QTcF prolongation recurs (2nd occurrence), hold cobimetinib until improved ≤ Grade 2 and resume at next lower dose level.
Hemorrhage	
Grade 3	Hold cobimetinib for 2 weeks: If improved to Grade 0 or 1, resume at next lower dose level If not improved to Grade 0 or 1, permanently discontinue
Grade 4	Permanently discontinue
Uveitis	
Grade 3	Hold cobimetinib until improved to ≤ Grade 1 and resume at the same dose or consider dose reduction to the next lower dose level
Grade 4	Permanently discontinue
Serous retinopathy	

≥ Grade 2 or symptomatic	Hold cobimetinib until improved to ≤ Grade 1 and resume at the next lower dose level if the first occurrence. Permanently discontinue if recurrent following dose reduction.
Retinal vein occlusion	Permanently discontinue cobimetinib
Photosensitivity	
Grade 1 or 2	Maintain dose. Patients taking cobimetinib are encouraged to wear clothing that protects the skin, lip balm and a broad-spectrum sunscreen with SPF 30 or higher when outside.
Intolerable grade 2	Hold cobimetinib until improved to ≤ Grade 1 and resume at the next lower dose level
Grade 3	Hold cobimetinib until ≤ Grade 1 and resume at the next lower dose level
Grade 4	Permanently discontinue cobimetinib
Rash	
Intolerable grade 2	Hold cobimetinib until improved to ≤ Grade 1 and resume at the same dose if the first occurrence or resume at the next lower dose level if recurrent
Grade 3	Hold cobimetinib until improved to ≤ Grade 1 and resume at the same dose if the first occurrence or resume at the next lower dose level if recurrent
Grade 4	Hold cobimetinib until improved to ≤ Grade 1 and resume at the next lower dose level if the first occurrence
Liver Laboratory abnormalities and hepatotoxicity	
AST/ALT Increase Grade 4	Hold cobimetinnib for up to weeks. If improved to Grade 0 or 1, then resume at the next lower dose level. If not improved to Grade 0 or 1 within 4 weeks, permanently discontinue. If recurrent, permanently discontinue.
≥ Grade 3 Bilirubin Increase	Hold cobimetinib until improved to ≤ Grade 1 and resume at the same dose if the first occurrence or resume at the next lower dose level if recurrent Permanently discontinue if recurrent at lowest dose level (-2)
AST/ALT > 5x ULN in combination with Bilirubin >2x ULN (or patient's baseline if baseline is elevated)	Permanently discontinue study therapy
Rhabdomyolysis and CPK elevation	

Grade 4 CPK elevation or any CPK elevation with new myalgias	Hold cobimetinib until ≤ Grade 3 and until the patient is not symptomatic then resume at the next lower dose level
Pneumonitis	
Grade 2	Hold cobimetinib until ≤ Grade 1 and resume at same dose level or consider dose reduction at the next lower dose level
Grade 3	Hold cobimetinib until ≤ Grade 1 and resume at the next lower dose level
Grade 4	Permanently discontinue cobimetinib
Other Grade 3 treatment-related adverse reaction (excluding conditions in 7.2.1)	Hold cobimetinib until ≤ Grade 1 and resume at the next lower dose level
First occurrence other Grade 4 treatment-related adverse reaction	Hold cobimetinib until ≤ Grade 1 and resume at the next lower dose level
Recurrent Grade 4 treatment-related adverse reaction	Permanently discontinue cobimetinib

7.2.1 Conditions Not Requiring Cobimetinib Dose Reduction

The following conditions are exceptions to the dose-modification guidelines and do not require a dose reduction or delay:

- Alopecia of any grade
- Electrolyte or serum analyte (e.g., urate) abnormalities that are reversible with standard interventions
- Isolated values of Grade ≥ 3 alkaline phosphatase. Determination of liver versus bone etiology should be made, and evaluation of gamma-glutamyl transferase, 5'-nucleotidase, or other liver enzymes should be performed.

In addition, cobimetinib dosing may be maintained in case of grade ≥ 3 hematological or non-hematological AEs not listed above (in Section 7.2) at the discretion of the enrolling physician and after consultation with the Sponsor-Investigator and the DSMC medical monitor.

7.3 Supportive Care

All supportive measures consistent with optimal patient care may be given throughout the study.

7.4 Contraception

Based on findings from animal reproduction studies and its mechanism of action, cobimetinib can cause fetal harm when administered to a pregnant woman. However, there are no

available data on the use of cobimetinib during pregnancy. In animal reproduction studies, oral administration of cobimetinib in pregnant rats during organogenesis was teratogenic and embryotoxic. For this reason, women of childbearing potential should be advised to use a method of highly effective contraception to eliminate the potential risk to a fetus. Male with partners of childbearing potential must practice a reliable method of contraception approved by the investigator. Contraception should start at the time of first dosing and continue until 3 monthsafter the last dose of cobimetinib

Acceptable highly effective contraceptive methods include:

- Bilateral tubal occlusion
- Vasectomized partner
- Intra-uterine devise (IUD) or hormone-releasing system (IUS)
- Any hormonal (estrogen combined with progesterone or progesterone alone) contraception associated with inhibition of ovulation: implanted, oral, intravaginal, transdermal, or injectable.
- The combination of a barrier method with spermicide (e.g., diaphragm, sponge, or male or female condoms).
- Abstinence from heterosexual intercourse.

8 SCHEDULE OF EVENTS

The Schedule of Events table provides an overview of the protocol visits and procedures. Refer to the Study Procedures section of the protocol for detailed information on each assessment required for compliance with the protocol. The Investigator may schedule visits (unplanned visits) in addition to those listed in the Schedule of Events table to conduct evaluations or assessments required to protect the wellbeing of the patient. This Schedule of Events will be followed for the entire study.

Table 5: Schedule of Events

Protocol Activities	**Screening**	**On-Treatment Period: One Cycle = 28 days**												**Post Treatment Period**	
		Cycle 1				**Cycle 2**		**Cycle 3**			**Cycle 4+**			**EOT[12]**	**Follow-up**
Day of Cycle		1	8	15	22	1	15	1	15	21	1	15	21		
Visit Window (days)	(-21 days)	± 3	± 3	± 3	± 3	± 3	± 3	± 3	± 3	± 3	± 3	± 3	± 3	± 3	± 14
Informed Consent[3]	X														
Demographics	X														
Medical History	X														
Eligibility Criteria	X														
Laboratory Studies															
Hematology[4, 5]	X	X	X	X	X	X	X	X	X		X	X		X	
Chemistry[4, 6]	X	X	X	X	X	X	X	X	X		X	X		X	
Creatine Kinase[4]		X		X		X	X	X	X		X	X		X	
Pregnancy Test[7]	X														
Coagulation Labs[8]	X														
Hepatitis and HIV Screening[9]	X														
Clinical Assessments															
Vital Signs[10]	X	X				X		X			X			X	
Physical Exam	X	X				X		X			X			X	
ECOG Score	X	X				X		X			X			X	
CCI & HCT-CI Score[11]	X														
Echocardiogram or MUGA[12]	X					X					X			X	
ECG[13]	X					X					X			X	
Ophthalmologic exam[14]	X					X					X			X[15]	
Adverse event collection[16]		X													
Concomitant Medications Collection	X	X													
Survival Follow-up[17]															X
Disease Assessments															

Bone marrow biopsy[18]	X									X			X	X	
MPN-SAF TSS[19]	X									X			X	X	
Treatment Compliance															
Cobimetinib		Oral Continuous Daily Dosing[20]													
Dosing diary and compliance check[21]		X				X		X			X				
Correlative Studies															
Correlative blood collection[22]	X									X			X	X	
Correlative marrow collection[23]	X									X			X	X	
Skin punch biopsy[24]	X														

[1] The end of treatment visit should occur when the decision to discontinue treatment is made or ± 3 days of C12D21 in patients who are not receiving considerable clinical benefit as per Section 6.4.. If this visit overlaps with a regularly scheduled visit, only the procedures listed in the calendar for the EOT visit will be performed. The EOT biopsy and echocardiogram will be completed ≤ 3 days of the decision to discontinue study treatment. An echocardiogram does not need to be repeated if the last echocardiogram was completed ≤ 35 days prior to the EOT visit.

[2] Subjects who are still on treatment as of as of Amendment 6 (v.09DEC2025) will proceed to EOT and Follow-Up as soon as logistically feasible.

[3] Must be obtained prior to undergoing any study procedure and may occur within ≤ 60 days prior to cycle one day one.

[4] Hematology includes CBC with differential and platelets.

[5] Labs on D8, D15 and D22 may be done locally.

[6] Chemistry includes LDH, phosphorus, magnesium, uric acid and a Complete Metabolic Panel (CMP): Albumin, Alkaline Phosphatase, Aspartate Aminotransferase, Alanine Aminotransferase, Total Bilirubin, Calcium, Carbon Dioxide, Creatinine, Chloride, Glucose, Total Potassium, Protein, Sodium, and Urea Nitrogen.

[7] Pregnancy test (serum or urine; if urine is positive it must be confirmed with serum test) must be obtained at ≤ 7 days prior to C1D1 for all women of childbearing potential and as clinically indicated while on treatment.

[8] Coagulation panel to include PT/INR and PTT and is to be completed at screening.

[9] Hepatitis panel to include Hepatitis B Virus Core antibodies, hepatitis B surface AG w/reflex, and Hepatitis C Virus Antibody at screening. HIV testing includes HIV-1 and HIV-2 antibody testing.

[10] Vital signs include systolic/diastolic blood pressure, heart rate, respiration rate, pulse oximetry, weight, and body temperature. Height will be captured at screening only.

[11] Baseline Charlson Comorbidity Index and Hematopoietic Cell Transplantation-specific comorbidity index (HCT-CI) scores will be assessed and recorded at screening. See appendices 7-8.

[12] Echocardiogram or MUGA is required at baseline, prior to C2D1, and then after every three cycles of treatment thereafter (i.e. C5D1, C8D1, ect.) to assess LEVF. Echocardiograms/MUGAshould be conducted ≤ 7 days prior to initiation of the next cycle of therapy.

[13] ECGs should be conducted at screening, C2D1, every three months while on study therapy (i.e. C5D1, C8D1, C11D1), and at the EOT visit. QTc will be calculated using the Fridericia calculation.

[14] Ophthalmologic exams will be performed at screening, C2D1 , every three cycles until cycle 11 (i.e., C5D1, C8D1, and C11D1), every four cycles from cycle 11 through cycle 23 (i.e., C15D1, C19D1, and C23D1), and then every six cycles until treatment discontinuation (i.e.,C29D1, C35D1, C41D1, etc.). Ophthalmologic exams should be conducted ≤ 7 days prior to initiation of the next cycle of therapy.

[15] Ophthalmologic exam does not need to be performed at the end of treatment visit if an evaluation has been performed within the last 12 weeks and there are no clinically significant findings and/or changes from baseline.

[16] Adverse event collection should begin with the first dose of study drug and end 30 days after the last dose of study drug.

[17] Patients will be contacted every three months (±14 days) from the EOT visit until 36 months has elapsed from the initiation of study therapy. For subjects who went off study treatment per Amendment 6, cobintinib dosing information should be collected.

[18] Patients on study therapy will undergo a bone marrow biopsy at screening, C3D21, C6D21, and C12D21. Patients who discontinue treatment early or continue treatment beyond 12 cycles will have an additional biopsy at EOT . Bone marrow biopsies may be conducted ± 3 days of Day 21; however, days 19-21 are preferred. Screening and end of treatment bone marrow studies include pathology, flow cytometry, NGS, FLT3-ITD PCR, FISH and cytogenetics. On-treatment bone marrow studies include pathology, flow cytometry, NGS, FLT3-ITD PCR, and cytogenetics. FLT3-ITD PCR will not be required for on-treatment bone marrow studies if negative at screening. If clinically indicated, unscheduled samples may be collected following a discussion between the treating physician and the Principal Investigator.

[19] Patients on study treatment will have MPN-SAF-TSS performed at screening, C3D21, C6D21, and C12D21. Patients who discontinue treatment early or continue treatment beyond 12 cycles as per Section 6.4 will have testing also performed at EOT. See Appendix 4.

[20] Cobimetinib is taken on a 28-day cycle. It should be taken once daily for 21 consecutive days (Days 1 to 21-treatment period); followed by a 7-day break (Days 22 to 28-treatment break). Each subsequent cobimetinib treatment cycle should start after a 7-day treatment break has elapsed.

[21] On day one of every cycle, patients will be issued a dosing diary to return on the day one of the following cycle to track regimen compliance. See Appendix 5.

[22] Correlative blood samples should be drawn at screening, C3D21, C6D21, and C12D21. Patients who discontinue treatment early or continue treatment beyond 12 cycles as per Section 6.4 will also have testing performed at EOT

[23] Correlative bone marrow aspirate samples should be drawn at screening, C3D21, C6D21, and C12D21. Patients who discontinue treatment early or continue treatment beyond 12 cycles as per Section 6.4 will also have testing performed at EOT. If clinically indicated, unscheduled samples may be collected following a discussion between the treating physician and the Principal Investigator.

[24] To be performed at the time of screening bone marrow biopsy.

9 STUDY PROCEDURES

9.1 Screening

For screening procedures see the Schedule of Events and the Assessments Section. Screening activities may only begin after a subject has signed consent. All screening activities must take place within 21 days prior to cycle one day one unless otherwise noted.

9.2 Treatment Period

Once a subject has completed screening, has been found to be eligible, and has been registered, treatment procedures may begin. The start of a new cycle of therapy may be delayed up to 7 days to allow for holidays or patient preference. See the Schedule of Events and the Assessments Section for treatment period procedures.

9.3 End of Treatment

Upon discontinuation of study treatment, an End of Treatment visit will occur. The end of treatment visit should occur when the decision to discontinue treatment is made. If this visit overlaps with a regularly scheduled visit, only the procedures listed in the calendar for the EOT visit will be performed. For End of Treatment procedures see the Schedule of Events and the Assessments Section.

9.4 Long Term Follow-Up

Upon disease progression or initiation of a new anticancer therapy, patients will be followed for survival in long-term follow-up for a total of 36 months from the start of therapy. Patients will be contacted every three months (±14 days) until the end of the study, patient withdrawal of consent, or death of any cause. Survival status may be collected by public records, medical records, or by contacting the patient by phone. All efforts should be made to contact the patient for these time points. Subjects who ended treatment per Amendment 6 (v.09DEC2025) should be followed for SOC dosing of cobimetinib. Community sourced cobimetinib will not be considered a new line of therapy if given at the same dose and frequency as outlined in the protocol.

9.4.1 Lost to follow-up

Patients will be considered lost to follow-up only if no contact has been established by the time the study is completed, such that there is insufficient information to determine the patient's status at that time. Patients who refuse to continue participation in the study, including telephone contact, should be documented as "withdrawal of consent" rather than "lost to follow-up." Investigators should document attempts to re-establish contact with missing patients throughout the study period. If contact with a missing patient is re-established, the patient should not be considered lost to follow-up and evaluations should resume according to the protocol.

To support key endpoints of OS analysis, the survival status of all patients in the full analysis and the safety analysis sets should be re-checked, this includes those patients who withdrew consent or are classified as "lost to follow up."

- Lost to Follow up – site personnel should check hospital records, the patients' current physician, and a publicly available death registry (if available) to obtain a current survival status.
- If the patient has actively withdrawn consent to the processing of their personal data, the survival status of the patient can be obtained by site personnel from publicly available death registries (if available) where it is possible to do so under applicable local laws to obtain a current survival status.

10 STUDY ASSESSMENTS

Every effort should be made to ensure that the protocol-required tests and procedures are completed as described. However, it is anticipated that from time to time there may be circumstances, outside of the control of the Investigator that may make it unfeasible to perform the test. In these cases, the Investigator will take all steps necessary to ensure the safety and well-being of the patient. When a protocol-required test cannot be performed, the Investigator will document the reason for this and any corrective and preventive actions that he or she has taken to ensure that normal processes are adhered to as soon as possible.

10.1 Demographics and Medical History

Demographics and medical history will be collected at the time of screening for each eligible patient. The following information will be collected: age, gender, co-morbidities, prior cancers, prior cancer therapy, transfusion-dependence, smoking status, previous hypomethylating agent (HMA) therapy, and best response achieved on prior HMA therapy.

10.2 Physical Examinations and Vital Signs

Patients will have physical examinations to include major body systems, vital signs, assessment of ECOG performance status (see Appendix 1), weight and height (height will be measured at screening only) at the time points described in the Schedule of Events. If necessary to facilitate scheduling, physical exams may occur one day prior to study treatment.

Vital signs, including blood pressure, pulse rate, and temperature will be also recorded at the time points described in the Schedule of Events. Vital signs should be taken prior to the administration of any investigational product at the visit.

10.3 Adverse Events

Adverse events experienced during trial participation will be collected per the Schedule of Events and Adverse Events Section. Each study participant will be questioned about the occurrence of adverse events in a non-leading manner. Should the treating investigator feel that the adverse event is attributed to study therapy, then dose modification guidelines in Section 7.2 will be followed.

10.4 Mutation Testing

It is required that all patients have confirmation and documentation of the necessary RAS pathway activating mutation through local laboratory next-generation sequencing. The

mutational status must be confirmed by a local Clinical Laboratory Improvement Amendments (CLIA) certified laboratory.

Consistent with standard-of-care for patients with CMML, the institutional hematology sequencing will be used for the detection of single nucleotide variants and small insertions/deletions of diagnostic, prognostic, or other clinical significance in myeloid malignancies:

- University of Utah: ARUP Laboratories Myeloid Malignancies Mutation Panel by Next Generation Sequencing

  https://ltd.aruplab.com/Tests/Pub/2011117

- Oregon Health & Science University: Knight Diagnostic Laboratories GeneTrails Hematologic Malignancies 220 Gene Panel

  https://knightdxlabs.ohsu.edu/home/test-details?id=GeneTrails+Hematologic+Malignancies+220+Gene+Panel

- University of Washington/Fred Hutchinson Cancer Research Center: Myeloid Gene Panel by NGS (HCAPA)

  https://testguide.labmed.uw.edu/public/view/HCAPMY

Genomic variants will be interpreted per 2017 guideline recommendations by AMP/ASCO/CAP using COSMIC, peer-reviewed literature, and AMP/CAP/ASCO variant classification guidelines. Variants detected on institutional sequencing panels will be considered "RAS pathway activating" if they are reported to be of known significance in myeloid malignancies on institutional sequencing panels and the variant interpretation (as reported by laboratory clinical variant scientists) is known or predicted to result in gain-of-function for positive regulators of RAS/MAPK signaling (i.e. *NRAS*, *KRAS*, *PTPN11*, *JAK2, BRAF*) or loss-of-function in negative regulators (i.e. *CBL*, *NF1*) of RAS/MAPK signaling.

10.5 12-Lead Electrocardiograms

All patients require a single 12-lead ECG measurement according to the Schedule of Events. The parameters to be recorded are QT, QTcF, PR, and QRS. A standard 12-lead (with a 10-second rhythm strip) tracing will be used for all ECGs. If the QTcF is prolonged (>500 msec) then a **triplicate** ECG should be conducted with two minutes between readings. Mean QTc will be calculated using the Fridericia calculation. If the mean QTcF is >500 msec (≥ Grade 3 QTcF prolongation), follow dose modification guidelines in Section 7.2.

10.6 Echocardiogram/MUGA

LVEF will be assessed by transthoracic echocardiogram or MUGA performed at the time points indicated on the Schedule of Events. LVEF assessed by transesophageal echocardiogram will also be acceptable if deemed necessary by the treating investigator.

10.7 Laboratory Assessments

Samples for all laboratory assessments will be drawn at the time points indicated in the Schedule of Events and when clinically indicated. Laboratory tests may be performed up to 3

days prior to the scheduled clinic visit. All safety laboratory analyses will be performed by the local laboratory for each study center or the subject's local laboratory per the schedule of events. All safety laboratory assessments must be reviewed by the treating investigator prior to study drug administration. When applicable, results from the pregnancy test must also be available for review prior to dosing.

Table 6: Laboratory Assessments

Laboratory Assessments	
CBC with Platelet Count and Differential (Hematology)	• White Blood Cell Count • Hemoglobin • Hematocrit • Red Blood Cell Count • Mean Corpuscular Volume • Red Cell DistributionWidth • Platelets • Absolute Neutrophil Count and % • Absolute Lymphocyte Count and % • Absolute Monocyte Count and % • Absolute Basophil Count and % • Absolute Eosinophil Count and %

Chemistry	• Creatine Kinase
	• LDH
	• Magnesium
	• Phosphorus
	• Uric Acid
	• Complete Metabolic Panel (CMP)
	  ○ Sodium
	  ○ Potassium
	  ○ Chloride
	  ○ Carbon Dioxide
	  ○ Alkaline Phosphatase
	  ○ Aspartate Aminotransferase
	  ○ Alanine Aminotransferase
	  ○ Urea Nitrogen
	  ○ Glucose
	  ○ Creatinine
	  ○ Calcium
	  ○ Protein
	  ○ Albumin
	  ○ Bilirubin
	  ○ Anion Gap

Coagulation	• PT • INR

	• PTT
Hepatitis	• Hepatitis B Virus Core Antibodies • Hepatitis B Surface AG w/ reflex to confirm • Hepatitis C Virus Antibody • HIV 1,2 Antibodies
Pregnancy	Beta-hCG Qualitative Urine or Serum

10.8 Disease Assessment

Disease assessments will be conducted per the 2015 MDS/MPN-IWG criteria. Disease assessments will require bone marrow biopsy, aspirate, and the Myeloproliferative Neoplasm Symptom Assessment Form Total Symptom Score (MPN-SAF-TSS) as indicated in the Schedule of Events.

10.8.1 Bone Marrow Biopsy

Disease assessments will include bone marrow biopsy and aspirate at the time points indicated on the Schedule of Events. To facilitate timely review of results, bone marrow biopsies may be performed ± 3 days from D21 of cycles as indicated in the Schedule of Events. At minimum, marrow and aspirate testing should include leukocyte and lymphocyte flow cytometry, chromosome analysis, mutational next-generation sequencing (NGS) panel, FLT3-ITD PCR and fluorescence in situ hybridization (FISH) for myeloproliferative disease (MPD). The following data points should be recorded in the corresponding eCRF.

- Blast, monoblast, and promonocyte count
- Any NGS and/or PCR identified mutations with corresponding allele freqency
- Percent cellularity
- Bone marrow fibrosis grade
- Cytogenetics
- FISH. For sites that do not have a MPD FISH panel, a BCR-ABL1 PCR may be completed.

10.8.2 Myeloproliferative Neoplasm Symptom Assessment Form Total Symptom Score (MPN-SAF-TSS)

The MPN-SAF-TSS will be administered at the time points indicated on the Schedule of Events. The MPN-SAF-TSS should be completed prior to meeting with the treating investigator.

10.9 Ophthalmologic Exam

A full ophthalmic examination with pupil dilation will be performed at the time points described in the Schedule of Events and will include best-corrected distance visual acuity

(BCVA), an automated threshold visual field (VF) of the central 10 degrees (with retesting if an abnormality is noted), and spectral-domain ocular coherence tomography (SD-OCT).

All ophthalmology assessments may be conducted ≤ 7 days prior to the clinic visit to enable results to be available for review.

11 CRITERIA FOR EVALUATION AND ENDPOINT

11.1 Safety

Routine safety and tolerability will be evaluated from the results of reported signs and symptoms, scheduled physical examinations, vital sign measurements, and clinical laboratory test results. More frequent safety evaluations may be performed if clinically indicated or at the discretion of the investigator.

11.2 Efficacy

Overall response criteria are based on the Myelodysplastic/Myeloproliferative (MDS/MPN) International Working Group 2015 consortium proposal for response criteria for myelodysplastic/myeloproliferative neoplasms in adults (Appendix 3).

11.3 Stopping Rules

The trial will be evaluated quarterly for excess toxicity. A rate of 20% grade 3 or higher non-hematological toxicity is acceptable, while a rate of 30% is unacceptable. The trial will be stopped if more than 2/5, 3/9, 4/13, 5/17, 6/22, 7/26, or 8/29 patients experience grade 3 or higher non-hematologic adverse events **attributed to study therapy** which are not improved or resolved with standard interventions such as dose hold, dose reduction or pharmacologic therapy (e.g. diuretic therapy) and continue to pose a significant clinical risk to the patient as determined by both the PI and medical monitor. The operating characteristics presented below were calculated using the R function "toxbdry" in the package "clinfun". The output in the table below is from toxbdry(0.15, 0.4, c(5,9,13,17,22,26,29), cP0=0.1, cP1=0.9, ngrid=6).

Table 7: Operating characteristics of Stopping Rule (N = 29)

Operating characteristics of Stopping Rule			
Probability of DLT	Probability of Crossing Boundary	Probability of Stopping Before Last Patient	Expected Sample Size
0.15	0.089	0.087	27.5
0.20	0.238	0.230	25.4
0.25	0.449	0.431	22.3
0.30	0.664	0.641	18.8
0.35	0.829	0.808	15.4

0.40	0.929	0.914	12.6

11.4 Statistical hypothesis

We hypothesize that treatment with MEK inhibitor will produce a superior overall response rate in newly diagnosed and HMA-refractory CMML patients with RAS pathway activation compared to HMAs.

11.5 Sample size determination

Simon's two-stage design[28] will be used for both cohorts. In the newly diagnosed patients, the null hypothesis that the true response rate is 0.35 will be tested against a one-sided alternative. In the first stage, 9 patients will be accrued. If there are 3 or fewer responses in these 9 patients, the study will be stopped. Otherwise, 5 additional patients will be accrued for a total of 14. The null hypothesis will be rejected if 7 or more responses are observed in 14 patients. This design yields a type I error rate of 0.1678 and power of 0.8028 when the true response rate is 0.59.

In the HMA refractory patients, the null hypothesis that the true response rate is 0.10 will be tested against a one-sided alternative. In the first stage, 6 patients will be accrued. If there are 0 responses in these 6 patients, the study will be stopped. Otherwise, 9 additional patients will be accrued for a total of 15. The null hypothesis will be rejected if 3 or more responses are observed in 15 patients. This design yields a type I error rate of 0.1559 and power of 0.8100 when the true response rate is 0.30.

At the time of interim analysis per the two-stage design re-evaluation of the starting dose of cobimetinib will be considered should the rates of treatment-related Grade 3/4 non-hematologic AEs be higher than what was reported in the Diamond et al study[25].

11.5.1 Population for analyses

A modified intent-to-treat data set will be employed to analyze all toxicity and efficacy endpoints. All patients who have received one dose of cobimetinib will be considered evaluable for primary and secondary endpoints.

11.6 Statistical Analyses

11.6.1 Primary endpoint

The primary endpoint is overall response rate according to the 2015 MDS/MPN-IWG criteria. Overall response rate (ORR) will encompass patients achieving a complete remission, complete cytogenetic remission, partial remission, marrow response and clinical benefit as per these criteria.

Simon's two-stage design (Simon, 1989) will be used for both cohorts. In the newly diagnosed patients, the null hypothesis that the true response rate is 0.35 will be tested against a one-sided alternative. In the first stage, 9 patients will be accrued. If there are 3 or fewer responses in these 9 patients, the study will be stopped. Otherwise, 5 additional patients will be accrued for a total of 14. The null hypothesis will be rejected if 7 or more

responses are observed in 14 patients. This design yields a type I error rate of 0.1678 and power of 0.8028 when the true response rate is 0.59.

In the HMA refractory patients, the null hypothesis that the true response rate is 0.10 will be tested against a one-sided alternative. In the first stage, 6 patients will be accrued. If there are 0 responses in these 6 patients, the study will be stopped. Otherwise, 9 additional patients will be accrued for a total of 15. The null hypothesis will be rejected if 3 or more responses are observed in 15 patients. This design yields a type I error rate of 0.1559 and power of 0.8100 when the true response rate is 0.30. Two-sided 90% and 95% exact binomial confidence intervals will be reported separately for the newly diagnosed and HMA refractory patients.

11.6.2 Secondary endpoint

Secondary endpoints will be analyzed descriptively. Each secondary endpoint will be analyzed for all patients together as well as stratified into newly diagnosed and HMA refractory subgroups.

- The frequency of adverse events (AEs) characterized by seriousness, severity (as defined by CTCAE, version 5.0), duration, and relationship to study therapy. The frequency of AEs will be tabulated. The proportion of patients with AEs will be tabulated.
- The proportion of patients achieving CR + PR at any time point. The proportion of patients achieving CR will be reported along with 90% and 95% exact binomial confidence intervals.
- Progression-free survival (PFS) from the time of treatment initiation to 36 months after the start of therapy, the time of progression, initiation of alternative treatment, or death. Kaplan-Meier methods and associated confidence intervals will be used to analyze PFS. Subjects who move to follow-up after Amendment 6 (v.09DEC2025) and are able to obtain cobimetinib at the same dose and frequency per SOC will continue to be included in the analysis of PFS.
- Overall survival (OS) as defined as the time from the initiation of study therapy until death from any cause. Kaplan-Meier methods and associated confidence intervals will be used to analyze OS.

11.6.3 Exploratory Endpoints

- The statistical analysis of the exploratory objectives will be descriptive.

12 REGISTRATION GUIDELINES

Study-related screening procedures can only begin once the patient has signed a consent form.

Patients must meet all of the eligibility requirements listed in Section 5 prior to registration.

Patients must be registered before receiving any study treatment and must begin treatment within five working days after registration.

To register an eligible patient at HCI, complete a Clinical Trials Office Patient Registration Form, and submit to CTORegistrations@hci.utah.edu. To register a patient at a site outside of HCI, complete a Clinical Trials Office Patient Registration Form, and submit to MultisiteRegistrations@hci.utah.edu.

13 DATA SUBMISSION SCHEDULE

The Case Report Forms (CRFs) are a set of (electronic or paper) forms for each patient that provides a record of the data generated according to the protocol. CRF's should be created prior to the study being initiated and updated (if applicable) when amendments to the protocol are IRB approved. These forms will be completed on an on-going basis during the study. The medical records will be a source of verification of the data. During the study, the CRFs will be monitored for completeness, accuracy, legibility, and attention to detail by a member of the Research Compliance Office. The CRFs will be completed by the Investigator or a member of the study team as listed on the Delegation of Duties Log. The data will be reviewed no less than annually by the Data and Safety Monitoring Committee. The Investigator will allow the Data and Safety Monitoring Committee or Research Compliance Office personnel access to the patient source documents, clinical supplies dispensing and storage area, and study documentation for the above-mentioned purpose. The Investigator further agrees to assist the site visitors in their activities.

Data capture should be restricted to endpoints and relevant patient information required for planned manuscripts.

14 CORRELATIVE STUDIES

To support exploratory objectives and correlative studies, blood and tissue samples will be collected at the time points indicated on the Schedule of Events. After completion of the described correlative studies, any remaining blood or tissue will be stored for future unspecified cancer research. With the participant's approval and as approved by the Institutional Review Board (IRB), de-identified biological samples will be stored at Huntsman Cancer Institute's Biorepository.

At the time of consent, subjects will be given the opportunity to authorize the biobanking of their remaining samples for use in future undisclosed cancer research. During the conduct of the study, an individual participant can choose to withdraw consent to have biological specimens stored for future research. However, the withdrawal of consent with regard to biosample storage may not be possible after the study is completed.

14.1 Bone marrow aspirate samples

Up to 20 mLs of bone marrow aspirate will be collected at the time points noted on the Schedule of Events. These samples will be used to explore the changes in allele burden, mechanisms of resistance, and cellular changes. Testing may include, but is not limited to:

- Whole exome sequencing
- RNA sequencing
- Flow cytometry

- Immunohistochemistry
- Immune cell enumeration and characterization
- Immunoblot

Specimen collection and processing instructions can be found in the lab manual.

14.2 Skin punch biopsy

A skin punch biopsy will be collected at screening for DNA extraction to establish a germline control for whole-exome sequencing.

Testing may include, but is not limited to:

- Whole exome sequencing

Specimen collection and processing instructions can be found in the lab manual.

14.3 Blood correlative studies

Up to 60 mL will be collected for required samples at the time-points noted on the Schedule of Events.

These samples will be used to assess the effect cobimetinib treatment has on molecular and phenotypic disease characteristics. They will also be used to evaluate and characterize mechanisms of therapy resistance and to identify potential biomarkers of response.

Testing may include, but is not limited to:

- Flow cytometry
- Cytokine/chemokine/interferon assays
- Immunohistochemistry
- Immune cell enumeration and characterization
- Colony assays
- Single-cell sequencing to evaluate clonal dynamics
- Next-Gen Sequencing

Specimen collection and processing instructions can be found in the lab manual.

15 ETHICAL AND REGULATORY CONSIDERATIONS

15.1 Human Subject Protections

The study will be conducted in accordance with the appropriate FDA, IRB, ICH GCP, and other federal and local regulatory requirements, as applicable. Informed consent will be obtained from all research participants before performing any study procedures using the most recent IRB-approved version. All patients must be at least 18 years of age to participate.

15.2 Institutional Review

Before study initiation, the investigator must have written and dated approval/favorable opinion from the IRB/IEC for the protocol, consent form, subject recruitment materials (eg, advertisements), and any other applicable patient-facing documents. The investigator should also provide the IRB/IEC with a copy of the Investigator Brochure or product labeling information.

The investigator or designee should provide the IRB/IEC with reports, updates, and other information (eg, expedited safety reports, amendments, and administrative letters) according to regulatory requirements or institution procedures.

15.3 Data and Safety Monitoring Plan

A Data and Safety Monitoring Committee (DSMC) is established at Huntsman Cancer Institute (HCI) to ensure the well-being of patients enrolled on Investigator Initiated Trials that do not have an outside monitoring review. The roles and responsibilities of the DSMC are outlined in the NCI-approved Data and Safety Monitoring (DSM) plan. The activities of the committee include reviewing adverse events (including SAEs), deviations, important medical events, significant revisions or amendments to the protocol, and approving cohort/dose escalations. If the DSMC and/or the PI have concerns about unexpected safety issues, the study will be stopped and will not be resumed until the issues are resolved. The DSMC also reviews and approves audit reports generated by the Research Compliance Office.

This study is classified as high risk per the NCI-approved DSM plan.

Each high-risk study will be assigned a physician member of the DSMC as a medical monitor, or in rare cases, an external medical monitor. The medical monitor will be notified of all serious adverse events (SAEs). Specific notifications will also be issued when dose-limiting toxicity is encountered and when the MTD dose is defined. Approval of the medical monitor is required for all dose escalations. All serious adverse events (SAEs) occurring in patients treated at HCI or its affiliates will also be reviewed by the full DSMC monthly. The full committee will also review all toxicities for patients on treatment.

Each high-risk study will also be assigned a dedicated research compliance officer who will monitor the trial. High-risk studies will be monitored by RCO personnel after the first patient is enrolled and every three months thereafter during active enrollment. The RCO monitor will review the study status and summarize enrollment, toxicities, SAEs, dose-escalation, statistical endpoints (e.g., stopping rules), deviations, etc. for the full DSMC membership at the regularly scheduled meetings. Amendments that increase risk, change dosing, or impact study objectives will be reviewed by the DSMC and approved by the PRMC and IRB. High-risk trials will be formally reviewed by the DSMC after the first patient is enrolled and then quarterly thereafter.

An initial audit of high-risk studies will be conducted by the RCO approximately one year after enrollment begins and annually thereafter. Audits of high-risk studies may be conducted more frequently as requested by the DSMC, IRB, PRMC, RCO management, or the PI.

15.4 Adverse Events (AEs)

An AE is any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of an investigational medicinal product (IMP) or other protocol-imposed intervention, regardless of attribution.

This includes the following:

- AEs not previously observed in the subject that emerged during the protocol-specified AE reporting period, including signs or symptoms associated with CMML that were not present prior to the AE reporting period.
- Complications that occur as a result of protocol-mandated interventions (e.g., invasive procedures such as bone marrow biopsies).
- Preexisting medical conditions (other than the condition being studied) judged by the investigator to have worsened in severity or frequency or changed in character during the protocol-specified AE reporting period.

Collection of adverse events will begin with the first dose of study medication and end 30 after the last dose of study drug (or until new cancer treatment is initiated).

Information about all adverse events, whether volunteered by the subject, discovered by investigator questioning, or detected through physical examination, laboratory test, or other means, will be collected, recorded, and followed as appropriate.

The adverse event should be evaluated to determine:

1. The severity grade based on CTCAE v5.0 (grade 1-5)
2. Its relationship to the study drug (definite, probable, possible, unlikely, not related)
3. Its duration (start and end dates or if continuing at the final exam)
4. Action taken (no action taken; study drug dosage adjusted/temporarily interrupted; study drug permanently discontinued due to this adverse event; concomitant medication taken; non-drug therapy given; hospitalization/prolonged hospitalization)
5. Whether it constitutes an SAE

All adverse events will be treated appropriately. Such treatment may include changes in study drug treatment as listed in the dose modification section of this protocol (see section 7.2 for guidance). Once an adverse event is detected, it should be followed until its resolution, and assessment should be made at each visit (or more frequently, if necessary) of any changes in severity, the suspected relationship to the study drug, the interventions required to treat it, and the outcome.

Information about common side effects already known about cobimetinib is described in the Drug Information (section 3), the investigator brochure, and the current product insert. This information will be included in the patient informed consent and will be discussed with the patient during the study as needed.

All adverse events will be immediately recorded in the patient research chart.

15.4.1 Instructions for Recording Adverse Events

Investigators should use correct medical terminology/concepts when reporting AEs or SAEs. Avoid colloquialisms and abbreviations.

Eliciting Adverse Events

A consistent methodology for eliciting AEs at all subject evaluation time points should be adopted. Examples of non-directive questions include:

- "How have you felt since your last clinical visit?"
- "Have you had any new or changed health problems since you were last here?"

Diagnosis vs. Signs and Symptoms

If known at the time of reporting, a diagnosis should be reported rather than individual signs and symptoms (e.g., record only liver failure or hepatitis rather than jaundice, asterixis, and elevated transaminases). However, if a constellation of signs and/or symptoms cannot be medically characterized as a single diagnosis or syndrome at the time of reporting, it is acceptable to report the information that is currently available. If a diagnosis is subsequently established, it should be reported as follow-up information.

Preexisting Medical Conditions

A preexisting medical condition is one that is present at the start of the study. Such conditions should be reported as medical and surgical history. A preexisting medical condition should be re-assessed throughout the trial and reported as an AE or SAE only if the frequency, severity, or character of the condition worsens during the study. When reporting such events, it is important to convey the concept that the preexisting condition has changed by including applicable descriptors (e.g., "more frequent headaches").

Abnormal Test Findings

Abnormal test finding, such as incidental image findings, should only be listed as an adverse event if it meets the following criteria:

- Is associated with accompanying symptoms; and/or
- Requires additional testing or intervention; and/or
- Leads to changes in study therapy dosing; and/or
- Leads to the addition or change of a concomitant medication or therapy; and/or
- Is considered an adverse event by the treating investigator.

An abnormal test considered to be an error should not be listed as an adverse event. Repeating a test due to an abnormal result in the absence of any of the criteria above does not require listing as an adverse event.

Hospitalizations for Medical or Surgical Procedures

Any AE that results in hospitalization or prolonged hospitalization should be documented and reported as an SAE. If a subject is hospitalized to undergo a medical or surgical procedure as a result of an AE, the event responsible for the procedure, not the procedure itself, should be reported as the SAE. For example, if a subject is hospitalized to undergo coronary bypass surgery, record the heart condition that necessitated the bypass as the SAE.

For hospitalizations that do not require reporting see section 15.5

Deaths

All deaths that occur during the protocol-specified AE reporting period (15.4.1), regardless of attribution, will be reported to the appropriate parties. When recording a death, the event or condition that caused or contributed to the fatal outcome should be reported as the single medical concept. All deaths that occur during the protocol-specified AE reporting period must be reported as follows:

- Death should be reported as an SAE within one working day of first knowledge and documented in the patient's research chart and eCRF, regardless of cause.
- The cause of death should be reported as an SAE, whether it was the result of an AE, was due to disease progression, or the cause is unknown.
- If an autopsy is performed, a copy of the results should be included in the patient's research chart to confirm the cause of death.

Deaths occurring after the protocol defined safety follow up period after the administration of the last dose of study drug should be documented in the eCRF. If the death occurred as a result of an event that started after the defined safety follow up period and the event is considered to be due to late-onset toxicity to study drug, then it should also be reported as an SAE. (See Section 15.4.1 AE Reporting Period)

Assessment of Severity of Adverse Events

The adverse event severity grading scale for the NCI CTCAE (v5.0) will be used for assessing adverse event severity. The below table should be used for assessing severity for adverse events that are not specifically listed in the NCI CTCAE.

Table 8: Adverse event grading scale for events not specifically listed in the NCI CTCAE

Grade	Severity
1	Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; or intervention not indicated
2	Moderate; minimal, local, or non-invasive intervention indicated; or limiting age-appropriate instrumental activities of daily living [a]
3	Severe or medically significant, but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; or limiting self-care activities of daily living [b,c]

4	Life-threatening consequences or urgent intervention indicated [d]
5	Death related to adverse event [d]

NCI CTCAE National Cancer Institute Common Terminology Criteria for Adverse Events.

Note: Based on the most recent version of NCI CTCAE (v5.0), which can be found at: http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm

a. Instrumental activities of daily living refer to preparing meals, shopping for groceries or clothes, using the telephone, managing money, etc.

b. Examples of self-care activities of daily living include bathing, dressing, and undressing, feeding oneself, using the toilet, and taking medications, as performed by patients who are not bedridden.

c. If an event is assessed as a "significant medical event," it must be reported as a serious adverse event

d. Grade 4 and 5 events must be reported as serious adverse events

15.4.2 Adverse Events of Special Interest (AESI)

AESIs are a subset of Events to Monitor (EtMs) of scientific and medical concern specific to the product, for which ongoing monitoring and rapid communication by the Investigator to the Sponsor is required. Such an event might require further investigation in order to characterize and understand it. Depending on the nature of the event, rapid communication by the trial Sponsor-Investigator to other parties (e.g., Regulatory Authorities) may also be warranted.

Adverse events of special interest for this study are:

- Any grade Serous retinopathy, including events of retinal detachment, retinal pigment epithelium detachment, neurosensory retinal detachment or central serous chorioretinopathy
- Symptomatic heart failure / Grade ≥ 2 left ventricular dysfunction
- Grade ≥ 3 CPK or Rhabdomyolysis
- Grade ≥ 3 Diarrhea
- Grade ≥ 3 rash
- Significant liver toxicity: AST and/or ALT > 10 X upper limit of normal
- Cases of potential drug-induced liver injury that include an elevated ALT or AST in combination with either elevated bilirubin or clinical jaundice, as defined by Hy's law:
    - Treatment-emergent ALT or AST > 3 x ULN in combination with total bilirubin > 2 x ULN
    - Treatment-emergent ALT or AST > 3 x ULN in combination with clinical jaundice
- Suspected transmission of an infectious agent by the study drug, as defined below:

- Any organism, virus, or infectious particle (e.g., prion protein transmitting transmissible spongiform encephalopathy), pathogenic or non-pathogenic, is considered an infectious agent. Transmission of an infectious agent may be suspected from clinical symptoms or laboratory findings that indicate an infection in a patient exposed to a medicinal product. This term applies only when contamination of the study drug is suspected

15.4.3 Reporting of Pregnancy

Although pregnancy is not considered an adverse event, it is the responsibility of investigators or their designees to report any pregnancy or lactation in a subject, including the pregnancy of a male subjects' female partner as an SAE. Pregnancies or lactation that occurs during the course of the trial or within 90 days of the last dose of study drug in a female patient or female partner of the male patient must be reported to the DSMC, IRB, FDA, Genentech and the sponsor as applicable. All subjects and subjects with partners of childbearing potential who become pregnant must be followed to the completion/termination of the pregnancy. Pregnancy outcomes including spontaneous or therapeutic abortion, intrauterine death, and miscarriage must be reported as serious events. Similarly, any congenital anomaly/birth defect in a child born to a female subject exposed to the study drug should be reported as an SAE.

15.5 Serious Adverse Event (SAE)

Information about all serious adverse events will be collected and recorded. A serious adverse event is an undesirable sign, symptom or medical condition which:

- Results in death (i.e., the AE causes or leads to death).
- It is life-threatening (i.e., the AE, in the view of the investigator, places the subject at immediate risk of death. It does not include an AE that, had it occurred in a more severe form, might have caused death.).
- Results in persistent or significant disability/incapacity (i.e., the AE results in substantial disruption of the subject's ability to conduct normal life functions).
- Is medically significant (e.g., defined as an event that jeopardizes the patient or may require medical or surgical intervention to prevent one of the outcomes listed above).
- Causes congenital anomaly or birth defect in a neonate/infant born to a mother exposed to the investigational product.
- Requires inpatient hospitalization or prolongation of existing hospitalization, unless hospitalization is for:
  - Routine treatment or monitoring of the studied indication, not associated with any deterioration in condition (procedures such as central line placements, paracentesis, pain control)
  - Elective or pre-planned treatment for a pre-existing condition that is unrelated to the indication under study and has not worsened since the start of study drug

- Treatment on an emergency outpatient basis for an event not fulfilling any of the definitions of an SAE given above and not resulting in hospital admission
- Social reasons and respite care in the absence of any deterioration in the patient's general condition

Collection of serious adverse events will begin after the first dose of study drug and end 90 days after the last dose of study treatment or until new cancer treatment is initiated, whichever happens first.

Toxicities that fall within the definitions listed above must be reported as an SAE regardless if they are felt to be treatment-related or not. Toxicities unrelated to treatment that do NOT fall within the definitions above must simply be documented as AEs in the patient research chart.

15.6 SAE Reporting Requirements

SAEs must be reported to the DSMC, the FDA, the IRB, and Genentech. A MedWatch 3500A form must be completed and submitted to HCI-RCO@utah.edu as soon as possible, but no later than 1 working day of first knowledge or notification of the event. SAE reports should include the following:

- Narrative of the event.
- Investigator causality assessment (i.e., definite, probable, possible, unlikely, not related to study drug).
- Expectedness of the event (i.e., expected or unexpected event).
  - Expected adverse events are those adverse events that are listed or characterized in the Package Insert (PI) or current Investigator Brochure (IB).
  - Unexpected adverse events are those not listed in the PI or current IB or not identified. This includes adverse events for which the specificity or severity is not consistent with the description in the PI or IB. For example, under this definition, hepatic necrosis would be unexpected if the PI or IB only referred to elevated hepatic enzymes or hepatitis.

15.6.1 DSMC Notifications:

A member of the HCI Research Compliance Office (RCO) will process and submit the MedWatch form to the proper DSMC member as necessary for each individual study. The RCO will summarize and present all reported SAEs according to the Data and Safety Monitoring Plan at the monthly DSMC meeting.

15.6.2 FDA Notifications

For Investigator-Initiated IND Studies, some additional reporting requirements for the FDA apply in accordance with the guidance set forth in 21 CFR 600.80.

- Events meeting the following criteria need to be submitted to the Food and Drug Administration (FDA) as expedited IND Safety Reports according to the following guidance and timelines:7 Calendar Day Telephone or Fax Report:

The RCO is required to notify the FDA of any fatal or life-threatening adverse event that is unexpected and assessed by the Investigator to be possibly related to the use of cobimetinib. An unexpected adverse event is one that is not already described in cobimetinib Investigator Brochure. Such reports are to be telephoned or faxed to the FDA, DSMC, and Genentech within 7 calendar days of first learning of the event.

- 15 Calendar Day Written Report:

The RCO is also required to notify the FDA and all participating investigators, in a written IND Safety Report, of any serious, unexpected AE that is considered reasonably or possibly related to the use of cobimetinib. An unexpected adverse event is one that is not already described in the cobimetinib investigator brochure.

Written IND Safety reports should include an Analysis of Similar Events in accordance with regulation 21 CFR 312.32. All safety reports previously filed by the investigator with the IND concerning similar events should be analyzed and the significance of the new report in light of the previous, similar reports commented on.

Written IND safety reports with Analysis of Similar Events are to be submitted to the FDA, Genentech, and all participating investigators within 15 calendar days of first learning of the event. The FDA prefers these reports on a MedWatch 3500 form, but alternative formats are acceptable (e.g., summary letter).

FDA fax number for IND Safety Reports:

Fax: 1 (800) FDA 0178

All written IND Safety Reports submitted to the FDA by the Investigator must also be faxed to Genentech Drug Safety: Fax: (650) 225-4682 or (650) 225-4630Email: usds_aereporting-d@gene.com**For questions related to safety reporting, please contact Genentech Drug Safety:**Tel: (888) 835-2555Fax: (650) 225-4682 or (650) 225-4630The Sponsor of the Study will be responsible for the distribution of safety information to Site IRB as discussed in section 15.6.3.

15.6.3 IRB Notification

Events meeting the University of Utah IRB or local IRB reporting requirements will be submitted per local guidelines.

15.6.4 MedWatch 3500A Reporting Guidelines

In addition to completing appropriate patient demographic (Section A) and suspect medication information (Section C & D), the report should include the following information within the Event Description (Section B.5) of the MedWatch 3500A form:

- Protocol number and title description
- Description of event, severity, treatment, and outcome if known

- Supportive laboratory results and diagnostics (Section B.6)
- Investigator's assessment of the relationship of the adverse event to each investigational product and suspect medication

Follow-Up Information

Additional information may be added to a previously submitted report by any of the following methods:

- Adding to the original MedWatch 3500A report and submitting it as follow-up
- Adding supplemental summary information and submitting it as follow-up with the original MedWatch 3500A form
- Summarizing new information and faxing it with a cover letter including patient identifiers (i.e. D.O.B. initial, patient number), protocol description and number, if assigned, brief adverse event description, and notation that additional or follow-up information is being submitted (The patient identifiers are important so that the new information is added to the correct initial report)

MedWatch 3500A (Mandatory Reporting) form is available at https://www.fda.gov/media/69876/download

15.7 Genentech Notifications

Serious adverse events (SAEs), pregnancy reports (including pregnancy occurring in the partner of a male study subject) AEs of special interest (AESIs) and Special Situation Reports, and Product Complaints (with or without an AE) originating from the Study for the Product where the patient has been exposed to the Genentech Product, will be sent on a MedWatch form with the Fax Cover Sheet (Appendix 6). Transmission of these reports must be completed within the timelines specified below:

- Serious AE reports that are related to the Product shall be transmitted to Genentech within thirty (30) calendar days of the awareness date.
- Other Serious AE reports that are unrelated to the Product shall be transmitted to Genentech within thirty (30) calendar days of the awareness date.
- AESIs shall be forwarded to Genentech within thirty (30) calendar days of the awareness date.
- Pregnancy reports shall be transmitted to Genentech within thirty (30) calendar days of the awareness date. Pregnancies will be followed up until the outcome of the pregnancy is known, whenever possible, based upon due diligence taken to obtain the follow-up information.
- Pregnancies in Female Partners of Male Patients should be submitted to Genentech within thirty (30) calendar days of the awareness date by the Clinical Trial Pregnancy Reporting Form.

- Other Special Situation Reports should be collected even in the absence of an Adverse Event and transmitted to Genentech within thirty (30) calendar days for the following situations:
    - Data related to the Product usage during breastfeeding
    - Data related to overdose, abuse, misuse or medication error (including potentially exposed or intercepted medication errors)
    - In addition, reasonable attempts should be made to obtain and submit the age or age group of the patient, in order to be able to identify potential safety signals specific to a particular population
- A Product Complaint is defined as any written or oral information received from a complainant that alleges deficiencies related to identity, quality, safety, strength, purity, reliability, durability, effectiveness, or performance of a product after it has been released and distributed to the commercial market or clinical trial. All Product Complaints (with or without an AE) shall be forwarded to Genentech within thirty (30) calendar days of the awareness date.
    - All protocol-defined AEs, SAEs, AESIs, Special Situation Reports (including pregnancy reports) and Product Complaints ***with*** an AE (initial and follow-up) will be submitted to Genentech either electronically or by fax to:
        - Fax: 650-238-6067
        - Email: usds_aereporting-d@gene.com
    - All Product Complaints ***without*** an AE should call via:
        - PC Hotline: (800) 334-0290 (M-F: 5am to 5pm PST)

It is understood and agreed that the sponsor-investigator will be responsible for the evaluation of AEs/SAEs, AESIs, Special Situation Reports (including pregnancy reports) and Product Complaints (with or without an AE) originating from the study.

These single case reports will be exchanged between the parties as outlined above so that regulatory obligations are met.

15.7.1 Post-Study Adverse Events

15.7.2 The investigator should expeditiously report any SAE occurring after a subject has completed or discontinued study participation if attributed to prior cobimetinib exposure. If the investigator should become aware of the development of cancer or a congenital anomaly in a subsequently conceived offspring of a female subject-including pregnancy occurring in the partner of a male study subject who participated in the study, this should be reported as an SAE adequately to Genentech drug Safety during follow up periodStudy Close-Out

Any study report submitted to the FDA by the Sponsor-Investigator should be copied to Genentech. This includes all IND annual reports and the Clinical Study Report (final study report). Additionally, any literature articles that are a result of the study should be sent to Genentech/Roche. Copies of such reports should be mailed to the assigned Clinical Operations contact for the study and Genentech Drug Safety CTV oversight mailbox at: ctvistsa@gene.com

15.8 Protocol Amendments

Any amendments or administrative changes to an IRB approved protocol will not be initiated without submission of an amendment for IRB review and approval.

These requirements for approval will in no way prevent any immediate action from being taken by the investigator in the interests of preserving the safety of all subjects included in the trial.

Any amendments to the protocol that significantly affect the safety of subjects, scope of the investigation, or the scientific quality of the study are required to submit the amendment for review by Genentech.

Any amendments to the protocol that significantly affect the safety of subjects, the scope of the investigation, or the scientific quality of the study will be submitted to the FDA for review.

15.9 Protocol Deviations

A protocol deviation (or violation) is any departure from the defined procedures and treatment plans as outlined in the protocol version submitted and previously approved by the IRB. Protocol deviations have the potential to place participants at risk and can also undermine the scientific integrity of the study thus jeopardizing the justification for the research. Protocol deviations are unplanned and unintentional events.

Because some protocol deviations pose no conceivable threat to participant safety or scientific integrity, reporting is left to the discretion of the PI within the context of the guidelines below. The sponsor requires the **prompt reporting** to HCI RCO of protocol deviations which are:

- Exceptions to eligibility criteria.
- Intended to eliminate an apparent immediate hazard to a research participant or

- Harmful (caused harm to participants or others, or place them at increased risk of harm - including physical, psychological, economic, or social harm), or
- Possible serious or continued noncompliance

15.10 FDA Annual Reporting

An annual progress report will be submitted to the FDA within 60 days of the anniversary of the date that the IND went into effect. (21 CFR 312.33).

15.11 Clinical Trials Data Bank

The study will be registered on **http://clinicaltrials.gov** and the NCI CTRP (Clinical Trials Reporting Program) by the Clinical Trials Office.

15.12 Record Keeping

Per 21 CFR 312.57, the Investigator records shall be maintained for a period of 2 years following the date a marketing application is approved; or, if no application is filed or the application is not approved, until 2 years after the investigation is discontinued and the FDA is notified.

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Appendix 1 - Eastern Cooperative Oncology Group Performance Status Criteria (ECOG) & Karnofsky Performance Scale Index (KPS) equivalency

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

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Appendix 2: Inducers and Inhibitors of CYP3A4

Strong CYP3A4 Inhibitors	Strong CYP3A4 Inducers	Moderate CYP3A4 Inducers
Atazanavir	Apalutamide	Efavirenz
Boceprevir	Carbamazepine	Modafinil
Clarithromycin	Dexamethasone	Etravirine
Cobicistat	Enzalutamide	Nafcillin
Conivaptan	Fosphenytoin	Dabrafenib
Curcumin	Lumacaftor	Bexarotene
Danazol	Midostaurin	Avasimibe
Danoprevir	Mitotane	Echinacea
Darunavir	Pentobarbital	
Delavirdine	Phenobarbital	
Diltiazem	Primidone	
Ditiocarb	Rifampicin	
Econazole	Rifamycin	
Efavirenz	Rifaximin	
Elvitegravir	Rimexolone	
Ergotamine	St. John's Wort	
Idelalisib		
Indinavir		
Ketoconazole		
Loperamide		
Lopinavir		
Methimazole		
Midostaurin		
Naloxone		
Nefazodone		
Nelfinavir		
Nilotinib		
Posaconazole		
Ribociclib		
Ritonavir		
Saquinavir		
Stiripentol		
Telaprevir		
Telithromycin		
Terfenadine		
Tipranavir		
Troleandomycin		
Voriconazole		

Appendix 3: 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[a]**
- **Osteomyelofibrosis absent or equal to "mild reticulin fibrosis" (≤grade 1 fibrosis)[b]**
- **Peripheral blood[c]**
  - **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[d]**

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[e]**
- **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.**

Disease Progression
(Combination of 2 major criteria, 1 major and 2 minor criteria, or 3 minor criteria from the lists below)

Major criteria

- **Increase in blast count[f]**
  - **<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[g]**
  - **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[h]**
- **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)[i]**

[a] 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.

[b] 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.

[c] 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.

[d] 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.

[e] 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 × 109/L) and resolution of leukocytosis to WBC ≤10 × 109 cells/L but ≥1.5 × 109/L. Hgb should be maintained >11 g/dL and platelets ≥100 × 109/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 × 109/L monocytosis in the absence of infection, cytokine treatment, or other reactive causes.

[f] Blasts as measured from the bone marrow.

[g] 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.

[h] 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.

[i] 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.

Savona M, Malcovati, L, Komrokji R, et al. An international consortium proposal of uniform response criteria for myelodysplastic/myeloproliferative neoplasms. *Blood.*2015;**125**:1857-65.

1. Savona M, Malcovati, L, Komrokji R, et al. An international consortium proposal of uniform response criteria for myelodysplastic/myeloproliferative neoplasms. *Blood.*2015;**125**:1857-65.

Appendix 4: Myeloproliferative Neoplasms Symptom Assessment Form- Total Symptom Score (MPN-SAF TSS) Form

Patient initials: _____ ***Patient Study ID:***_____

Study Time Point (cycle/day): _____ ***Date:*** _____

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)
Numbness/ Tingling (in my hands and feet)	(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)

What is your Overall Quality of Life?	(As good as it can be) 0 1 2 3 4 5 6 7 8 9 10 (As bad as it can be)

Patient signature: _____ ***Date:***_____

Appendix 5: Patient Dosing Diary

Subject Number: _____ Date: _____

Cobimetinib should be taken once daily (every 24 hours ± 4 hours) for 21 consecutive days (Days 1 to 21-treatment period); followed by a 7-day break (Days 22 to 28-treatment break). If a dose is missed outside of the dosing window, the dose should not be made up. If a dose is vomited, treatment should be continued as prescribed the following day and the dose should not be made up.

Day	Date	Time	Number of tablets taken	Comments
1		**:**		
2		**:**		
3		**:**		
4		**:**		
5		**:**		
6		**:**		
7		**:**		
8		**:**		
9		**:**		
10		**:**		
11		**:**		
12		**:**		
13		**:**		
14		**:**		
15		**:**		
16		**:**		

17		**:**		
18		**:**		
19		**:**		
20		**:**		
21		**:**		
22		**---:---**	**0**	
23		**---:---**	**0**	
24		**---:---**	**0**	
25		**---:---**	**0**	
26		**---:---**	**0**	
27		**---:---**	**0**	
28		**---:---**	**0**	
29		**:**		
30		**:**		
31		**:**		

Patient Signature Date

Appendix 6: Safety Reporting Fax Cover Sheet

Genentech
A Member of the Roche Group

SAFETY REPORTING FAX COVER SHEET
Genentech Supported Research

AE/SAE FAX No: (650) 238-6067

Genentech Study Number	
Principal Investigator	
Site Name	
Reporter Name	
Reporter Telephone #	
Reporter Fax #	

Initial Report Date	
Follow-up Report Date	

Subject Initials (Enter a dash if patient has no middle name)	

SAE or Safety Reporting questions, contact Genentech Drug Safety: (888) 835-2555

PLEASE PLACE MEDWATCH REPORT or SAFETY REPORT BEHIND THIS COVER SHEET

Appendix 7: Hematopoietic Cell Transplantation - specific comorbidity index (HCT-CI)

Use MDCalc calculator to determine score
https://www.mdcalc.com/hematopoietic-cell-transplantation-specific-comorbidity-index-hct-ci

Appendix 8: Charlson Comorbidity Index

Use MDCalc calculator to determine score

https://www.mdcalc.com/charlson-comorbidity-index-cci#evidence