Study Title:	A Phase I/II, open-label, multi-center study evaluating the safety and efficacy of Ruxolitinib and CPX-351 in combination for the treatment of Advanced Phase Myeloproliferative Neoplasms.
Protocol Number:	OSU-20393
Investigational product:	Ruxolitinib (Jakafi®); CPX-351(Vxyeos™)
Version Number:	6.8
Version Date:	27 September 2023
Replaces:	Version 6.7
IND/IDE Status:	IND/IDE #141783
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Multi-Center Trial Program:	Clinical Trials Office The Ohio State University Comprehensive Cancer Center Fax: 614-366-6652 Email: OSUCCC-CTO-MCTP@osumc.edu
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SYNOPSIS

Study Title	A Phase I/II, open-label, multi-center study evaluating the safety and efficacy of Ruxolitinib and CPX-351 in combination for the treatment of Advanced Phase Myeloproliferative Neoplasms.
Protocol #	OSU-20393
Study Center	multicenter [U.S. only]
Clinical Phase	Phase I/II - Combination
Interventional Study Type	*Single-arm*
Précis	Patients with myeloproliferative neoplasms (MPNs) that progress to an accelerated phase (AP) or blast phase (BP) have poor clinical outcomes. Prior publications highlight the important role of the janus kinase inhibitor, ruxolitinib, in the treatment of MPNs and its preliminary efficacy in combination with hypomethylating agents for the treatment of secondary AML. In this phase I/II study, the safety and efficacy of the liposomal formulation of cytarabine and daunorubicin (CPX-351) will be investigated in combination with ruxolitinib to treat patients with MPN in accelerated phase (AP) or blast phase (BP). The phase I portion of the study will use an adaptive design to identify the maximum tolerated dose (MTD) of ruxolitinib when used in combination with CPX-351. The phase II portion of the study will open for enrollment using ruxolitinib at the MTD or recommended phase II dose (RP2D).
Primary Objectives	Phase I: To evaluate the MTD (or RP2D) of ruxolitinib in combination with CPX-351. Phase II: To evaluate the objective response rate by the end of induction or re-induction therapy in participants with MPN-AP/BP following treatment with the combination of ruxolitinib and CPX-351 (per 2012 MPN-BP criteria).
Secondary Objectives	1. To evaluate the safety and tolerability of ruxolitinib in combination with CPX-351. 2. Assess survival outcomes associated with ruxolitinib in combination with CPX-351.
Exploratory Objectives	1. To evaluate various response rates (i.e., ≥MLFS, ≥CRi) among participants with MPN-AP/BP using ELN criteria. 2. Assess the proportion of treated participants with minimal residual disease
Primary Endpoints	Phase I: Dose-level-specific DLT rates of ruxolitinib given in combination with a fixed CPX-351 regimen Phase II: Proportion of participants that achieve at least an Acute Leukemia Response-Partial (≥ALR-P), per 2012 MPN-BP
Secondary Endpoints	1. Incidence of adverse events as assessed by CTCAE v5.0 2. Overall survival 3. Event-free survival 2. Overall survival Event-free survival 4. Relapse-free survival 5. Remission Duration 6. Proportion of participants proceeding to transplant.

Exploratory Endpoints	1. Proportion of participants that achieve a CR or CRi [per ELN criteria] 2. Rate of composite complete remission defined as combined rate of CR, CRi, or MLFS [per ELN criteria]. 3. Minimal residual disease and molecular CR (mCR)
Number of Participants	Up to 47 participants will be enrolled to this study.
Duration of Therapy	Treatment period is anticipated to be ~12 months
Duration of Follow Up	Follow up will occur for 1 year post completion of last study dose.
Key Inclusion Criteria	1. Ability to understand and the willingness to sign a written informed consent document. 2. Age ≥18 years at time of informed consent. Both men and women and members of all races and ethnic groups will be included. 3. Eastern Cooperative Oncology Group (ECOG) performance status 0 to 2. (Refer to Appendix A). 4. Participants eligible for this study have either MPN in accelerated phase (AP) or blast phase (BP), defined as: a. MPN-AP is defined by 10% to 19% blasts in the peripheral blood or bone marrow b. MPN-BP is defined by ≥20% blasts in the blood or bone marrow, • Either MPN-AP or MPN-BP requires a previous diagnosis of polycythemia vera (PV), essential thrombocythemia (ET), primary or secondary myelofibrosis (MF), or MDS/MPN overlap with intermediate-2 or high risk disease according to IPSS as well as progression on or failure to respond to at least one line of therapy. • Participants with ET, PV, or MF that have received prior MPN-associated therapy (e.g., hydroxyurea, hypomethylating agents [azacitidine, decitabine], anti-platelet therapies [e.g., aspirin, anagrelide], as well as JAK2 inhibitor therapy [e.g., ruxolitinib or other investigational JAK2 inhibitor]) are eligible. They must discontinue prior to starting therapy; no wash-out is required. 5. Female participants of childbearing potential must agree to use adequate contraception (2 forms of contraception or abstinence) from the screening visit until 30 days following the last dose of study treatment. Should a woman become pregnant or suspect she is pregnant while she or her partner is participating in this study, she should inform her treating physician immediately. 6. Male participants of childbearing potential having intercourse with females of childbearing potential must agree to abstain from heterosexual intercourse or have their partner use 2 forms of contraception from the screening visit until 90 days after the last dose of study treatment. They must also refrain from sperm

	donation from the screening visit until 90 days following the last dose of study treatment. 7. Left ventricular ejection fraction at ≥ 50% as measured by echocardiogram (ECHO) or multigated acquisition (MUGA) scan (within 14 days prior to initiating study intervention). 8. Candidate for cytotoxic-intensive induction chemotherapy. 9. Willing to take oral medication. 10. Adequate organ function as defined by the following: a. Serum creatinine ≤2× the upper limit of normal (ULN), or glomerular filtration rate >20ml/min/1.73m^2 as calculated by Cockcroft-Gault formula. b. Serum potassium, magnesium, and calcium (corrected for albumin) within institutional normal limits or can be corrected with supplementation. c. Total serum bilirubin ≤2.5× ULN. d. Serum aspartate transaminase (AST) and/or alanine transaminase (ALT) ≤2.5× ULN.
Key Exclusion Criteria	1. Ongoing participation in another clinical trial. 2. Isolated myeloid sarcoma (i.e., participants must have blood or marrow involvement with AML to enter the study). 3. Acute promyelocytic leukemia (FAB M3 Classification). 4. Active central nervous system (CNS) involvement by AML 5. Current treatment or treatment within 2 weeks or 5 half-lives (whichever is longer) prior to the first dose of study medication with another investigational medication or current enrollment in another investigational drug protocol (unless there is evidence of rapidly progressive disease in which case a shorter interval from last therapy may be acceptable). 6. Any unresolved toxicity equal to or greater than Grade 2 from previous anticancer therapy, except for stable chronic toxicities not expected to resolve, such as peripheral neurotoxicity. 7. Incomplete recovery from any prior surgical procedures or had surgery within 4 weeks prior to study entry, excluding the placement of vascular access. 8. Disseminated intravascular coagulopathy with active bleeding or signs of thrombosis. 9. Participants with rapidly progressive disease (defined by blast count doubling within 48 hours) or organ dysfunction that would prevent them from receiving these agents. 10. Participants with uncontrolled infection will not be enrolled until infection is treated and symptoms controlled. a. Participants with an infection receiving treatment (antibiotic, antifungal or antiviral treatment) may be entered into the study but must be afebrile and hemodynamically stable for ≥72 hrs.

	11. Known hypersensitivity to ruxolitinib, cytarabine, daunorubicin, or liposomal products. 12. Known diagnosis of Wilson's disease or other copper metabolism disorder. 13. Uncontrolled intercurrent illness or any concurrent condition that, in the Investigator's opinion, would jeopardize the safety of the participant or compliance with the protocol per investigator's discretion. Including, but not limited to, symptomatic congestive heart failure, unstable angina pectoris, serious cardiac arrhythmia, myocardial infarction within 6 months prior to enrollment, New York Heart Association (NYHA) Class III or IV heart failure, severe uncontrolled ventricular arrhythmias. 14. Participants with prior cumulative anthracycline exposure of greater than 368 mg/m^2 daunorubicin (or equivalent). 15. All participants must discontinue anti-platelet agents or anticoagulants prior to initiation of study drug, including therapeutic doses of aspirin and clopidogrel.
Investigational Products	***CPX-351*** (induction and re-induction: 100 units/m^2, IV over 90 minutes; consolidation: 65 units/m^2, IV over 90 minutes) ***Ruxolitinib*** (MTD, PO, *b.i.d*; dose levels [DL] -2 – 5 mg QD; DL-1 – 5 mg *b.i.d*; DL1 – 10 mg; DL2 – 20 mg; DL3 – 30 mg; DL4 – 40 mg).
Statistical Considerations	<u>Phase I:</u> Phase I is dose-escalation trial using a Bayesian "keyboard" design. Ruxolitinib will be increased sequentially (10, 20, 30, 40 mg) from DL1 through DL4 in order to determine the MTD of ruxolitinib in combination with CPX-351; a cohort of 3 participants will be evaluated before an escalation decision is made. <u>Phase II:</u> A Simon's two-stage minimax design will be used to assess the efficacy of ruxolitinib in combination with CPX-351. In the first stage, 12 participants will be accrued. If there are 5 or fewer responses (defined as ≥ALR-P) by the end of induction or re-induction therapy in these 12 participants, the study will be stopped. Otherwise, 14 additional participants will be accrued for a total of 26 participants. The null hypothesis will be rejected if, by the end of induction or re-induction, 15 or more responses are observed in 26 participants. A sample size of 26 participants is required to detect 65% (desired) vs. 40% (historical) objective response rate based on the Simon's two-stage minimax design with a one-sided type I error rate of 0.05 and power of 0.81.

SCHEMATIC OF STUDY DESIGN

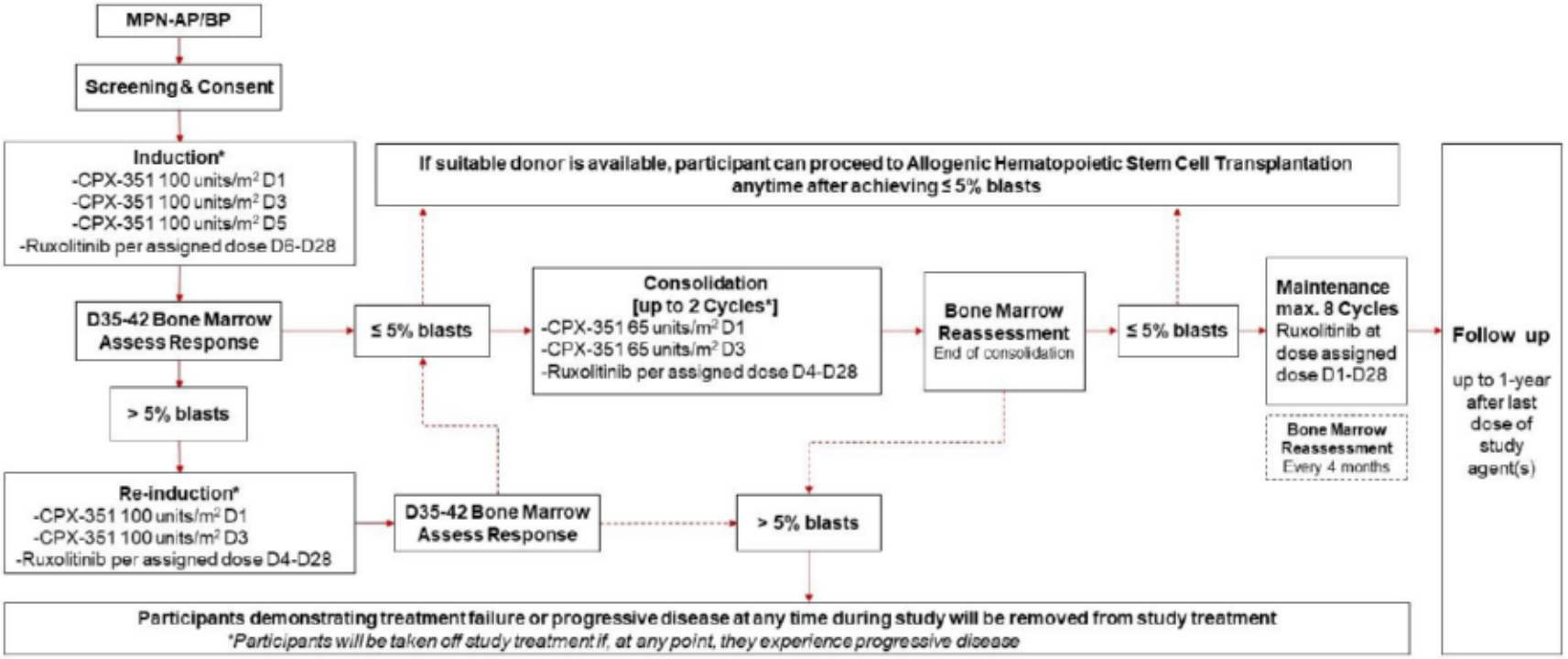

Figure 1. Overview of Trial Design.

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LIST OF ABBREVIATIONS

AE	Adverse event
ALP	Alkaline phosphatase
ALT	Alanine aminotransferase
AML	Acute myelogenous leukemia
ANC	Absolute neutrophil count
AST	Aspartate aminotransferase
ATC	Anatomical Therapeutic Chemical (Classification System)
AUC	Area under the curve
BMA, BMB	Bone marrow aspiration/biopsy
b.i.d	Twice daily
BUN	Blood urea nitrogen
CBC	Complete blood cell (count)
CCR	Composite complete remission
CFR	United States Code of Federal Regulations
CoC	National Institutes of Health (NIH) Certificate of Confidentiality
CR	Complete remission
CRi	Complete remission with incomplete marrow recovery
CRC	Clinical Research Coordinator
CRMS	Clinical research management system
CRQA	Clinical Research Quality & Administration
CRF	Case report form
CSRC	Clinical Scientific Review Committee (OSU)
CT	Computerized tomography
CTCAE	Common Terminology Criteria for Adverse Events
CTEP	Cancer Therapy Evaluation Program
CTMS	Clinical Trial Management System
DFS	Disease-free survival
DLT	Dose limiting toxicity
DSMB	Data and Safety Monitoring Board
DSMC	Data and Safety Monitoring Committee
DSMP	Data and Safety Monitoring Plan
ECG	Electrocardiogram
ECHO	Echocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	Electronic Case Report Form
eCRIS	Electronic Clinical Research Information System
EDC	Electronic data capture
ET	Essential thrombocythemia
FCBP	Female of childbearing potential
FDA	United States Food and Drug Administration
GCP	Good Clinical Practice
HBeAg	Hepatitis B "e" antigen
HBV	Hepatitis B virus
HCT	Hematocrit
HCV	Hepatitis C virus
HDL-C	High-density lipoprotein cholesterol
HGB	Hemoglobin
HIPPA	Health Insurance Portability and Accountability Act
HIV	Human immunodeficiency virus
IB	Investigator's brochure

IC_{50}	Inhibition concentration at 50%
ICF	Informed Consent Form
ICH	International Conference on Harmonization
IDE	Investigational device exemption
IND	Investigational new drug application
IRB	Institutional Review Board
IV	Intravenous
LDH	Lactate dehydrogenase
LDL-C	Low-density lipoprotein cholesterol
LFT	Liver function test
MedDRA	Medical Dictionary for Regulatory Activities
MF	Myelofibrosis
MFC	Multi-color flow cytometry
MPN	Myeloproliferative neoplasm
MRI	Magnetic resonance imaging
MTD	Maximum tolerated dose
mTPI	Modified toxicity probability interval
MUGA	Multiple Gated Acquisition
N/A	Not applicable
NCI	National Cancer Institute
OHRP	Office for Human Research Protections
ORR	Overall response rate
OSU	The Ohio State University
PD	Progressive Disease
PET	Positron emission tomography
PI	Principle Investigator
PK	Pharmacokinetics
PMF	Primary myelofibrosis
PO	*Per os* (by mouth, orally)
PR	Partial remission
PTT	Prothrombin time
PV	polycythemia vera
QOL	Quality of Life
RBC	Red blood cell (count)
RP2D	Recommended Phase II Dose
RNI	Reportable new information
SAE	Serious adverse event
SD	Stable disease
SGOT	Serum glutamic oxaloacetic transaminase
SGPT	Serum glutamic pyruvic transaminase
TSMP	Trial Specific Monitoring Plan
UA	Urinalysis
ULN	Upper limit of normal
UP	Unanticipated problem
WBC	White blood cell (count)

1. BACKGROUND INFORMATION AND SCIENTIFIC RATIONALE

1.1 OVERVIEW OF MYELOPROLIFERATIVE NEOPLASMS

Myeloproliferative neoplasms (MPN) consisting of polycythemia vera (PV), essential thrombocytosis (ET), and primary myelofibrosis (PMF) are a heterogenous group of BCR-ABL-negative hematopoietic stem cell disorders characterized by myeloproliferation without dysplasia, bone marrow hypercellularity, predisposition to thrombosis, hemorrhage, and bone marrow fibrosis.[1] MPNs share mutations that constitutively activate the several signal-transduction pathways responsible for hematopoiesis[1,2], which include: JAK2 (exon 145–8 and exon 12)[3], MPL (exon 10)[4,5], TET2[6], ASXL1[7], IDH1[8,9], IDH2[9,10], CBL[11], IKZF1[12], LNK[13], and EZH2[14] (**Table 1**).

Table 1. Mutations in Myeloproliferative Neoplasms

		Approximate Mutational Frequency, %		
Mutation	**Chromosome Location**	**PV**	**ET**	**PMF**
JAK2				
Exon 14 mutation, (JAK2V617F)	9p24	95	55	60
Exon 12 mutation	9p24	3	infrequent	infrequent
CALR exon 9 deletion/insertion	19p13.2	infrequent	25	25
MPL exon 10 mutation	1p34	infrequent	3	7
LNK exon 2 mutation	12q24.12	infrequent	infrequent	infrequent
TET2 mutations (several exons)	4q24	16	5	17
ASXL1 exon 12 mutation	20q11.1	7	4	20
IDH1/IDH2 exon 4 mutation	2q33.3 / 15q26.1	2	1	4
EZH2 mutations (several exons)	7q36.1	infrequent	infrequent	5
IKZF1 (mostly deletions)	7p12	infrequent	infrequent	infrequent

The estimated incidence of MPNs varies per subtype, but is greater for PV (0.4–2.8 per 100,000/year) and ET (0.4–3.4 per 100,000/year) as compared to PMF (0.8–2.1 per 100,000/year). The majority of MPN patients are diagnosed after 60 years of age, but disease may occur at any time. The median age of diagnosis for PV, ET and PMF is 61, 56, and 65 years, respectively.[2]

In contrast to myeloid neoplasms, MPNs have a natural history that, with supportive care alone is usually measured in decades. Reported median survivals, among those ≤60 years, is approximately 24 years for PV, 33 years for ET, and 15 for PMF.[15] Unfortunately, MPNs are also at a great risk of transforming to AML, which is associated with a poor prognosis.

1.1.1 MPN TO AML TRANSFORMATION

Also referred to as leukemic transformation (LT, or MPN-blast phase), MPN that progresses on to a blast phase (BP) is defined as a blast count of >20% in the bone marrow or peripheral blood, and has a median time to transformation of 10-12 years.[16-18] The risk of MPN-BP is greater among those with PMF (11%) and PV (7%) than ET (1.5%).[19,20] The median survival among patients with MPN-BP transformation is only 3-6 months.[16-18,20,21]

Of five studies from which supportive data was collected, all consisted of retrospective analyses of patients with MPN's transformed to secondary AML. Patients who received treatment were most often stratified into three treatment groups including intensive induction, low-intensity

induction and supportive/palliative care; the latter two defined as "non-curative treatment".[16-18,21] Candidates for allogeneic hematopoietic stem-cell transplant (allo-HSCT) were present in each study, and their median overall survival compared to those receiving treatment or palliative care measures.

Complex cytogenetics and/or abnormalities were present at transformation in 91% (N=91) of patients in the Mesa et al.[17] study, 64% (N=75) of patients in the Kennedy et al.[16] study, 52% (N=23) of patients in the Passamonti et al.[18] study, and 72% (N=74) of patients in the Tam et al.[21] cohort. Patients receiving standard induction typical of de novo AML were determined as fit based on comorbidity profile and per physician discretion, as current guidelines are not standard (**Table 2**).

Table 2. Summary of relevant clinical data from the above summarized studies

	Mesa et al[17] (N=91)	**Kennedy et al[16] (N=75)**	**Passamonti et al[18] (N=23)**	**Tam et al[21] (N=74)**
Intensive Induction (n)	n=24 (26% of N)	n=38 (51% of N)	n=8 (35% of N)	n=41 (55% of N)
Responders	0	18 (47% of n)	1 (13% of n)	18[€] (46% of n)
Median Survival (months)	3.9 months	9.4 months	5.6 months	7 months***
Non-Curative Treatment (y)	-	y=37 (49% of N)	y=15 (65% of N)	-
Responders	-	2 (5% of y)	0	-
Median Survival	-	2.3 months	2.5 months	-
Low Intensity Induction	19 (21% of N)	-	-	12 (16% of N)
Responders	0	-	-	0
Median Survival	2.9 months	-	-	7 months***
Supportive Care	48 (53% of N)	-	-	19 (26% of N)
Responders	0	-	-	0
Median Survival	2 months	-	-	6 weeks
Transplant	1*	17^ (23% of N)	1[Ø] (4% of N)	8[α] (11% of N)
Responders	-	5**	1	-
Median Survival	-	47 months	-	6-131 months[ρ]

Responders: Defined as achievement of a CR/CRi in response to treatment.
Median Survival: Calculated as the time of diagnosis of leukemic transformation to date of death or date of last follow-up.
Transplant: patients were eligible for transplant if they achieved CR/CRi after intensive induction, with the exception of Kennedy et al (refer to "^" below).

* In Mesa et al only 1 patient proceeded to transplant, but outcome was not analyzed in the study.
^ In Kennedy et al, patients were eligible for transplant if they achieved CR/CRi/chronic MPN after induction therapy. This total includes 1 patient who achieved CR after treatment with hydroxyurea, included in the non-curative treatment cohort.
** Represents the number of patients alive and in remission at the time of last follow-up prior to study publication.
[Ø]The single patient who underwent transplant is also the only patient to achieve CR after intensive induction. Still alive at time of publication (+70 days post-**transplant**), no median survival calculated.
[€]Of the 41 receiving intensive induction therapy, 2 patients were not evaluable. Percentage of n is out of 39 patients.

*** 7 months median survival reflects those patients who received treatment.
[α]Tam et al transplant cohort was for patients undergoing transplant early in disease course (transplant as first line of therapy (2) or achieving CR/CRi after first treatment (6)). 11 total underwent transplant at some point during treatment.
[β]Median survival is represented as a range. Actuarial survival was 73% at 31 month follow-up; one patient had continued remission at 133 months[5].

Of the 91 patients enrolled in the Mesa et al[17] study, 24 underwent intensive induction, 19 low-intensity induction, and 48 received supportive care. Median survival in the cohort receiving supportive care was 2 months (0-20.1 months) from leukemic transformation, and those receiving low-intensity induction had a median survival of 2.9 months (0.4-22.5 months). Among those receiving intensive induction, 33% died from treatment-related complications, and none achieved a complete remission (CR/CRi). In total, average overall survival (OS) in those undergoing treatment with intensive AML induction was 3.9 months (1.6-57 months); only one patient underwent allo-HSCT and was not included in analysis. Of all treatment groups, 98% died and median survival was 3 months.[17]

The remaining studies included an analysis of transplant efficacy, and found a higher proportion of patients achieving CR/CRi after intensive induction.[16,18,21] In the 75 patient, retrospective analysis by Kennedy et al[16], 38 were treated with intensive induction, of which 18 achieved CR/CRi after the first cycle of therapy. Patients receiving intensive induction versus non-intensive/supportive care had a median overall survival of 9.4 versus 2.3 months. Of those achieving a CR/CRi or chronic MPN after treatment, 17 proceeded to transplant; 44% of those receiving intensive induction, one patient achieved CR after hydroxyurea. Two year OS in transplant versus non-transplant cohorts was 47% versus 15%.

Both the Passamonti et al[18] and the Kennedy et al[16] studies found no significant difference between those receiving intensive induction and palliative/low-intensity induction in terms of OS. Only 1 of 8 patients treated with intensive induction in the Passamonti et al[18] study cohort achieved a CR, with a median survival of 5.6 months. A single patient underwent allo-HSCT, and was alive at the time of study publication.

Tam et al[21] reported on 74 patients that developed AML from MPN. Among these, 41 patients underwent intensive induction with only 46% achieving CR/CRi. Median progression-free survival was 5 months in this group. Eleven patients underwent allo-HSCT, of which those undergoing transplant as either first therapy or after responding to initial therapy fared the best, as 73% of these patients were alive at 31 month follow-up.

Of those studies including transplanted patients, median survival unanimously surpassed that of those in other treatment or supportive care categories.[16,18,21] Each of the aforementioned studies suggests further investigation into treatment regimens that can lift the dismal prognosis of MPN leukemic transformation.

1.2 OVERVIEW OF RUXOLITINIB

Ruxolitinib (Jakafi®) is a potent, and selective inhibitor of Janus kinase 1 (JAK1) (inhibition concentration 50% [IC_{50}]=3.3 ± 1.2 nM) and JAK2 (IC50=2.8 ± 1.2 nM) with modest to marked selectivity against TYK2 (tyrosine kinase 2) (IC_{50}=19 ± 3.2 nM) and JAK3 (IC_{50}=428 ± 243 nM), respectively. Ruxolitinib interferes with the signaling of a number of cytokines and growth factors that are important for hematopoiesis and immune function. Ruxolitinib has received FDA-approval for treatment of patients with myeloproliferative disorders, PV, PMF, and ET.

The JAK/STAT signaling pathway is important when considering cellular response to growth factors and cytokines, with JAK enzymes being of further importance in both myeloid and

lymphoid cellular proliferation and differentiation.[22] This pathway plays key roles in myeloproliferative neoplasms (MPNs) and myeloid leukemias, with constitutive activation of the STAT5 protein contributing to the transformation of MPNs to secondary acute myeloid leukemia (AML).[22] While the JAK2 mutation is often present in MPNs, this mutation is not always seen after transformation to AML, suggesting the presence of mutant clone(s) or of leukemia arising from a JAK2 wild-type cell.[22,23] Additionally, while a JAK2 mutation is not always evident in AML, this myeloid malignancy can exhibit activated STAT3/STAT5 proteins.[22,24]

In a study conducted at MD Anderson from 2008-2010, 38 patients with relapsed/refractory AML (de novo or secondary to MPN), ALL, MDS, or CML were enrolled in a single-agent study of ruxolitinib.[22] Of the 3 patients showing complete response (2 CR, 1 CRi), all had AML secondary to an MPN (2 MF, 1 ET).[22] Two of these patients had JAK2 V617F mutations present both before and after therapy.[22] Ultimately this study found no correlation between response and presence of the JAK2 V617F mutation, suggestive of the fact that additional pathways or clones may play a role in progression to secondary AML.[22]

There has also been research discussing "ruxolitinib withdrawal syndrome" and/or "ruxolitinib discontinuation syndrome" in individuals who abruptly stop therapy, including relapse of disease symptoms as early as 1-week post-discontinuation, worsened splenomegaly and cytopenias, and some hemodynamic decompensation.[25,26] This coincides with the idea that JAK inhibitors primarily act to down-regulate pro-inflammatory cytokines compared to clonal suppression, with these syndromes exhibiting quick changes in inflammatory cytokine activity.[25,26]

1.2.1 MECHANISM OF ACTION

Members of the JAK family (JAK1, JAK2, JAK3, and TYK2) function by transducing signals from cytokines, interleukins and growth factors that act through a number of transmembrane receptor families.[27] Canonical JAK signaling involves active JAKs phosphorylating tyrosine residues in the cytoplasmic region of receptor complexes that in turn recruits signal transducers and activators of transcriptions (STATs). The STATs form dimers that translocate to the nucleus when phosphorylated on highly conserved tyrosine residues by JAKs or other tyrosine kinases, and bind specific promoter sequences to modulate transcription of genes controlling cellular proliferation, differentiation and apoptosis.[27]

Aberrant activation of JAK family members in hematological malignancies is associated with promoting increased proliferation and survival of cancer cells.[28,29] For example, activating mutation in JAK2 (a valine to phenylalanine change, V617F) is observed in 50–95% of patients with PV, ET and PMF. Specifically, $JAK2^{V617F}$ caused a PV phenotype in a mouse model by eliciting downstream Stat5a/b signaling. As such, inhibition of JAK signaling through use of inhibitors like ruxolitinib has been investigated as a viable approach to treating patients with PV, ET, and MF.[28,29]

1.2.2 PRE CLINICAL EXPERIENCE

Preclinical findings revealed that Ruxolitinib was efficacious in mouse models of Philadelphia chromosome negative MPNs and in additional preclinical tumor models representing both hematological and solid tumors expressing wild-type JAKs or a clinically relevant constitutively active mutant JAK2. Efficacy was also observed in rodent models of cytokine-dependent inflammation. In cell-based assays, ruxolitinib increased inflammatory cytokine levels observed in MPNs that contribute to MPN-related systemic symptoms. Specifically, ruxolitinib was found to potently inhibit interleukin (IL)-23, stimulated IL-22 production in human T cells (IC_{50}=50 nM), as well as IL-6, granulocyte-macrophage colony-stimulating factor (GM-CSF) and

thrombopoietin (TPO) induced STAT3 phosphorylation in human peripheral blood mononuclear cells with IC_{50} < 100 nM.[30] Ruxolitinib inhibited G-CSF-stimulated STAT3 phosphorylation in human neutrophils (IC50=28 ± 9 nM), as well as TPO induced STAT3 phosphorylation in human whole blood (IC50=281 ± 62 nM). Finally, ruxolitinib inhibited the production of IL-17 in response to IL-23 in T cells, and the production of monocyte chemotactic protein-1 in response to IL-6 in peripheral blood mononuclear cells with IC50 values of ≤120 nM (Fridman et al 2011).

1.2.3 CLINICAL STUDIES OF RUXOLITINIB

As of 22 February 2017, more than 8326 patients have received ruxolitinib in Novartis and Incyte sponsored interventional clinical trials. Please refer to investigator brochure (IB) for additional details.

1.2.3.1 *Pharmacokinetics*

Ruxolitinib capsule was developed for oral administration and has an elimination half-life of approximately 3 hours, and is metabolized for excretion in urine (74%) and feces (22%). Ruxolitinib is primarily eliminated by oxidative metabolism catalyzed via CYP3A4 and CYP2C9, but is not a substrate for transporters including P-glycoprotein (Pgp). As such, co-medications inhibiting CYP3A4 and CYP2C9 enzymes may increase the exposure to ruxolitinib.

1.2.3.2 *Efficacy*

The results of two randomized Phase III studies in MF (COMFORT -I, COMFORT-II) demonstrate that ruxolitinib has a favorable risk-benefit profile in patients with MPN. COMFORT-I was a randomized, double-blind, placebo-controlled, multicenter study comparing the efficacy and safety of ruxolitinib tablets given b.i.d. to a matched placebo in 309 patients with PMF, PPV-MF, or PET-MF. COMFORT-II was an open-label, randomized, active-comparator, multicenter study comparing the efficacy and safety of ruxolitinib tablets versus BAT as selected by the investigators in 219 adult patients with PMF, PPV-MF or PET-MF.

A significantly larger proportion of patients randomized to receive ruxolitinib achieved a ≥35% reduction from baseline in spleen volume compared to patients randomized to control. This effect was observed at both Week 24 (primary endpoint in COMFORT-I) and Week 48 (primary endpoint in COMFORT-II). Notably, among the 93 patients in COMFORT-I and the 75 patients in COMFORT-II who had a ≥35% reduction at any time point during the study, the probability that a patient would maintain a response on ruxolitinib for at least 24 weeks was 89% and 87% in COMFORT-I and COMFORT-II respectively. Likewise, the probability of maintaining a response for at least 48 weeks was 76% and 72% in COMFORT-I and COMFORT-II respectively; and the probability of maintaining a response for at least 96 weeks was 67% and 61% in COMFORT- I and COMFORT-II, respectively. Result from the COMFORT-II study at 5-year follow-up reveal that among patients treated with ruxolitinib, the estimated probability (Kaplan-Meier) of maintaining spleen volume reduction at the 3.0 year time point was 0.51 (95% CI: 0.38, 0.62) and was 0.48 (95% CI: 0.35, 0.60) for later time points up to 5.0 years.

In COMFORT-I, 42 patients (27.1%) randomized to ruxolitinib and 54 (35.1%) patients randomized to placebo died through the 144 week follow-up. This includes 43 patients who died during randomized treatment after crossover, and up to 28 days after study withdrawal, and 53 patients who died more than 28 days after withdrawal from the study, which represents a hazard ratio of 0.687 (95% CI; 0.459, 1.029; p = 0.0668).

Results from the COMFORT-II study show that the risk of death was reduced by 33% in the ruxolitinib arm compared to the best available treatment (BAT) arm (HR=0.67; 95% CI: 0.44,

1.02). Moreover, the estimated survival probability at 5.0 years was 56% (95% CI: 0.47, 0.64) in the ruxolitinib arm and 44% (95% CI: 0.31, 0.56) in the BAT arm.

Progression-free survival (PFS) was only assessed in the COMFORT-II study, and was defined as the interval between randomization and the earliest of either increase in spleen volume ≥ 25% from on-study nadir, splenic irradiation, splenectomy, leukemic transformation or death. Of 89 PFS events in the ruxolitinib arm and 35 events in the BAT arm, 78 events (53.4%) and 27 events (37.0%), respectively, were due to spleen volume increase. The risk of progression or death was reduced by ruxolitinib by 22% (HR=0.78; 95% CI: 0.53, 1.16). The Kaplan-Meier estimate of PFS at the 5.0-year time point was 0.24 for the ruxolitinib treatment arm (95% CI: 0.16, 0.32), and was 0.18 for the BAT arm (95% CI: 0.07, 0.33).

1.2.3.3 *Safety*

Please refer to Section 8.4 for details of adverse events associated with ruxolitinib.

The most frequently reported adverse event (AE) was thrombocytopenia, which was reported by 40.9% of ruxolitinib-treated patients compared with 9.3% of patients receiving placebo and 12.3% of patients receiving BAT. Anemia was the second most frequently reported AE and occurred in 36.5% of ruxolitinib-treated patients as compared with 14.6% in placebo recipients and 13.7% in BAT-treated patients. The most frequently reported serious AEs (SAE) in ruxolitinib-treated patients were anemia (4.0%) and pneumonia (3.7%). Pneumonia was the only SAE that was reported in more than 5% in any treatment group (COMFORT-I ruxolitinib group with 6.5% and COMFORT-II BAT group with 5.5%).

1.3 OVERVIEW OF CPX-351

CPX-351 (Vxyeos™) is a liposomal combination of daunorubicin and cytarabine. CPX-351 was given FDA approval in August 2017 for the treatment of adults with newly-diagnosed therapy-related acute myeloid leukemia (t-AML) or AML with myelodysplasia-related changes (AML-MRC). Please refer to manufacturer IB for additional details.

1.3.1 MECHANISM OF ACTION

The liposomal formulation of daunorubicin and cytarabine at a fixed 1:5 molar ratio shows synergistic effects in targeting tumor cells. Daunorubicin is an anthracycline topoisomerase inhibitor and has antimitotic and cytotoxic activity, which is achieved by forming complexes with DNA, inhibiting topoisomerase II activity, inhibiting DNA polymerase activity, affecting regulation of gene expression, and producing DNA-damaging free radicals.

Cytarabine is a nucleoside metabolic inhibitor, which functions as a cell cycle phase-specific antineoplastic agent, affecting cells only during the S-phase of cell division. Cytarabine acts primarily through inhibition of DNA polymerase.

1.3.2 PRE-CLINICAL EXPERIENCE

Mayer et al[31] reported that treatment of murine leukemic cells in vivo with CPX-351 achieved a 90% cure rate, which was superior to the activity of daunorubicin and cytarabine combined in saline. Notably, CPX-351 given at 50% of its maximum tolerated dose (MTD) resulted in a net median survival approximately 20 days, and reflected anti-tumor activity that was >2,000 times greater than what would be expected if each encapsulated drug had contributed in only an additive fashion to its activity.

1.3.3 CLINICAL STUDIES OF CPX-351

1.3.3.1 *Pharmacokinetics*

CPX-351 exhibits a plasma half-life of 31.5 hours for daunorubicin and 40.4 hours for cytarabine, with greater than 99% of the daunorubicin and cytarabine in the plasma remaining encapsulated within the liposomes. The clearance (%CV) is 0.16 L/h (53.3%) for daunorubicin and 0.13 L/h (60.2%) for cytarabine. CPX-351 is characterized by daunorubicin being metabolized by aldoketo reductase to the active metabolite daunorubicinol, and cytarabine metabolized by cytidine deaminase to the inactive metabolite 1-β-arabinofuronosyluracil (AraU). Urinary excretion of daunorubicin and daunorubicinol accounts for 9% of the administered dose of daunorubicin, and urinary excretion of cytarabine and AraU accounts for 70% of the administered dose of cytarabine.

1.3.3.2 *Efficacy*

Lancet et al[32] reported on the multicenter, randomized, open-label, parallel arm study (NCT00788892) comparing CPX-351 to first-line conventional cytarabine plus daunorubicin (7+3). Of the 126 patients enrolled, 85 were treated with CPX-351 and 41 were assigned 7+3. Patients receiving CPX-351 had a higher CR rate than those given 7+3 (41 CR + 15 CRi/84 [66.7%] vs 20 CR + 1 CRi/41 [51.2%]; p = 0.07). Patients achieved 48.8% CR in both treatment, but CRi responses were higher among those given CPX-351 than control arm (17.9% vs. 2.4%). The median time to response was 6 days longer for CPX-351 (48 vs 42 days), but the median duration of response was similar (8.9 vs 8.6 months). At 24-month follow-up the authors reported a median OS of 14.7 vs 12.9 months and median event-free survival (EFS) of 6.5 vs 2.0 months for the CPX-351 and control arms, respectively.

Cortes et al[33] reported on a phase II in which 125 patients with first-relapse AML were randomized to receive either CPX-351 or physician's choice chemotherapy. In this study, CPX-351 at a dose of 65 units/m^2 (where 1 unit = 1.0 mg cytarabine + 0.44 mg daunorubicin) was administered by 90-minute infusion on days 1, 3, and 5 (first induction) and days 1 and 3 (second induction and consolidation). Treatment regimens in the control arm consisted primarily of cytarabine (97.7%) and anthracycline (77.3%), usually with additional agents (79.4%), such as etoposide (54.5%) or gemtuzumab ozogamicin (18.2%). Though overall improvements in efficacy outcomes were not observed in this study, the authors noted that patients in the CPX-351 treatment arm have more CR and CRi responses than those receiving control treatment (30 CR [37%] + 10 CRi [12.3%] vs. 14 CR [31.8%] + 4 CRi [9.1%], respectively). When patients were stratified per the European Prognostic Index (EPI) into favorable, intermediate, and poor-risk groups based on duration of first CR, cytogenetics, age, and transplant history, EPI-defined poor-risk strata had higher response rates (39.3% vs 27.6%) and improvements in event-free survival (HR, 0.63; P = .08) and overall survival (HR, 0.55; P = .02). Additionally, the risk of 60-day mortality was lower among those given CPX-351 than control therapy (16.1% vs 24.1%).

In another randomized, phase III, multicenter, open-label study (NCT01696084; CLTR0310-301) CPX-351 (daunorubicin 44 mg/m^2 and cytarabine 100 mg/m^2) was given intravenously on days 1, 3, and 5 for the first induction and on days 1 and 3 for the second induction (if needed). For consolidation, the CPX-351 dose (daunorubicin 29 mg/m^2 and cytarabine 65 mg/m^2) was given on days 1 and 3. In the 7+3 control arm, the first induction consisted of cytarabine (100 mg/m^2/day) on days 1 through 7 by continuous infusion and daunorubicin (60 mg/m^2/day) on days 1, 2, and 3. For second induction and consolidation cycles, cytarabine (100 mg/m^2/day)

was given on days 1 through 5 and daunorubicin (60 mg/m^2/day) on days 1 and 2. A total of 153 patients were randomized to receive CPX-351 and 156 patients were assigned to the control arm. The median overall survival was nearly double among patients receiving CPX-351 than those separately administered cytarabine and daunorubicin (9.56 months vs. 5.95 months, respectively). Notably, the rate of allo-HSCT in first CR was 20% in the CPX-351 arm and 12% in the control arm. Likewise, the overall rate of HSCT (i.e., induction failure, first CR, or as salvage after relapse) was 34% (52/153) in the CPX-351 arm and 25% (39/156) in the control arm.

1.3.3.3 *Safety*

Please refer to Section 8.4 for details of adverse events associated with CPX-351.

The most common serious adverse reactions (incidence > 3%) on the CPX-351 arm were blood and lymphatic system disorders, infections, general disorders (e.g., fatigue), and gastrointestinal disorders,. Adverse reactions led to discontinuation of CPX-351 in 18% (28/153) of patients, and 13% (20/151) in the control arm.

1.4 RATIONALE

Patients with MPN that progresses to an accelerated phase or blast phase have an especially poor response to treatment designed for AML, including initial therapy.[17] Retrospective analyses of patients who undergo leukemic transformation shows that reversion to a chronic myeloproliferative state occurs in only 41% of those that receive induction chemotherapy. [17] Even so, this remission is short-lived as median survival is only 3.9 months. Rather, the best outcomes appear to be among those patients that undergo allo-HSCT following induction chemotherapy.[34]

The exact mechanism as to why only a subset of patients with MPN progress to blast phase remains unclear, but it is recognized that the ability to salvage these individuals is possible with successful allo-HSCT following cytoreductive therapy. The positive clinical trial results associated with the use of ruxolitinib to treat patients with MPN has opened the door for subsequent investigations into assessing whether JAK inhibition can be used to treat MPN blast phase.[35] Use of ruxolitinib as a salvage therapy in MPN blast phase patients achieved modest clinical benefit with only 3 of 18 patients showing a significant response (2 CR and 1 CRi).[36] These findings have offered some encouragement towards further examining ruxolitinib in combination with other chemotherapies to treat MPN-AP/BP, but results thus far have been largely anecdotal.[37-40] Preliminary results from a phase I/II study suggest that ruxolitinib in combination with decitabine had a 42% overall response rate among patients with post-MPN AML.[41] The findings from this study suggested that a recommended phase II dose (RP2D) of 50 mg (*b.i.d*) ruxolitinib was tolerable.

Bolstered by the recent FDA-approval of CPX-351 as a treatment for patients with newly diagnosed t-AML and AML-MRC, the present study seeks to capitalize on the potential efficacy of combining CPX-351 with ruxolitinib to treat patients with MPN-AP/BP. As such, this phase I/II study will evaluate the safety and efficacy of this drug combination. The phase I portion of the study will assess the maximum tolerated dose (MTD) as well as the safety and tolerability of ruxolitinib in combination with CPX-351. The phase II portion of the study will evaluate the treatment efficacy of CPX-351 in combination with ruxolitinib at the RP2D.

1.5 POTENTIAL RISKS AND BENEFITS

1.5.1 KNOWN POTENTIAL RISKS

The potential risks associated with treatment are detailed in Section 8.4. Additional details regarding specific risks for those participating in this clinical trial may be found in the informed consent documents

The combination of ruxolitinib along with CPX-351, or the individual components of CPX-351 (daunorubicin and cytarabine) have not been investigated. Devillier et al[40] reported on 6 patients (age range: 46 to 60 years) with post-MPN AML that were treated with the combination of ruxolitinib and 3 + 7 type of induction chemotherapy (cytarabine, 200 mg/ m^2/day x 7 days) with either idarubicin (12 mg/m^2/day x 3 days) or daunorubicin (60 mg/m^2/day x 3 days). Overall, the authors did not observe any severe toxicity during induction treatment and all patients maintained a good performance status after induction therapy. Two patients died in aplasia, with one showing an acute intestinal occlusive syndrome complicated by septic shock from gram-negative bacteria, and the other patient died by fatal inhalation pneumonia. In both cases, the authors noted that none of the therapeutic agents used were known to cause such side effects.

1.5.2 KNOWN POTENTIAL BENEFITS

Given the lack of treatment options for patients with MPN-AP/BP, the current study may provide access to a new treatment approach not previously available. It cannot, however, be guaranteed that participants in this study will directly benefit from treatment during participation, as the clinical trial is designed to provide information about the safety and effectiveness of the investigational approach.

2. STUDY DESIGN, OBJECTIVES AND ENDPOINTS

2.1 DESCRIPTION OF THE STUDY DESIGN

Refer to Section 9, Statistical Considerations for additional information regarding statistical methods used in this study.

This is a phase I/II, multicenter, open-label study to assess the safety and efficacy of ruxolitinib in combination with CPX-351 for treatment of MPN-AP/BP. Participants must meet the inclusion criteria, have none of the exclusion criteria, and have provided written informed consent before the conduct of any screening tests not performed routinely in their treatment.

The phase I portion of the study will establish the MTD for ruxolitinib in combination with a fixed dose of CPX-351. The Bayesian "keyboard" design will be used to determine the MTD of ruxolitinib in combination with CPX-351.[42] Participants will continue at their assigned dose level of ruxolitinib throughout re-induction (if delivered), consolidation, and maintenance therapy. The timing of dose administration for ruxolitinib will remain the same for all dose levels. Regardless of assigned dose level and separate from the study design, the treating physician may exercise clinical judgment and decrease the dose for any participant if there is unacceptable toxicity.

Eligible participants will receive induction therapy consisting of intravenous CPX-351 (100 units/m^2) on days (D) 1, 3, and 5 followed by a 23-day course of ruxolitinib (D6-D28). The first 3 participants will receive ruxolitinib at a dose of 10 mg *b.i.d.* The ruxolitinib dose for subsequent participants may differ (ranging from 5 mg *QD* to 40 mg *b.i.d.*) according to the "keyboard" design dose escalation/de-escalation rules (refer to Section 5.2.3). CPX-351 dosing is based on a 2018 study by Lancet and others in older newly diagnosed secondary AML participants.[43] To assess disease status, a bone marrow aspirate/biopsy will be performed between D35-D42 (or earlier if counts recover to ANC > 500/µL and platelet count > 50,000/µL).

If a bone marrow assessment is indeterminate (e.g., due to poor sample quality or low cellularity), a bone marrow aspirate may, at investigator's discretion, be repeated 7 days later. If there is residual disease (i.e., > 5% blasts and adequate cellularity) at the time of assessing the D35-D42 bone marrow biopsy (or earlier if counts recover to ANC > 500/µL and platelet count > 50,000/µL), then participants may undergo a single cycle of re-induction therapy with CPX-351 (100 units/m^2) administered on D1 and D3 followed by ruxolitinib at the participant's assigned dose level from D4-D28. If after re-induction, the D35-D42 bone marrow assessment shows a response of ≤5% blasts in marrow , then participants will receive up to 2 cycles of consolidation therapy (see Section 5.1.1.2). Following the final course of consolidation therapy, participants will undergo a bone marrow biopsy to assess disease status. Participants that successfully complete consolidation therapy with a continued response (≤ 5% blasts in marrow), but have not undergone allo-HSCT, will complete up to 8 cycles of maintenance therapy with ruxolitinib, administered at the participant's assigned dose level from D1-D28. However, dose adjustments may be allowed according to a participant's clinical course and blood cell counts. An enrollment of up to 24 participants is planned for the phase I portion of this study.

Once the MTD or recommended phase 2 dose (RP2D) is established and phase I objectives completed, the phase II portion of the trial will open for enrollment. The phase II portion of the trial will assess the efficacy of the ruxolitinib and CPX-351 combination by evaluating the rate of composite complete remission in participants using a Simon's two-stage minimax design as described in Section 9. Enrollment in phase II will include either 12 or 26 participants and phase

I participants treated at the MTD or RP2D can be included in this phase II population. The phase II combination treatment regimen will be the same as described for phase I except that the ruxolitinib dose will be fixed per the established MTD or RP2D that is determined following a formal toxicity assessment of all phase I participants through 6 cycles of study intervention.

Participants are eligible to proceed to allo-HSCT at any time after achieving ≥ALR-P if they have a suitable donor. In this case, participants will come off treatment and be followed for disease status and survival outcomes, including peri-transplant data.

2.2 STUDY OBJECTIVES AND ENDPOINTS

Refer to Section 7 regarding definitions for efficacy measures assessed in this study.

2.2.1 PRIMARY ENDPOINTS

	Objective	**Endpoint**	**Start**	**End**
Phase I	To identify the MTD of ruxolitinib in combination with CPX-351.	DLT (refer to section 5.2.1 for DLT definitions and evaluation period).	Day 1	Day 42
Phase II	To evaluate the objective response rate in participants with MPN-AP/BP following treatment with the combination of ruxolitinib and CPX-351 (per 2012 MPN-BP criteria).	Proportion of participants that achieve at least an Acute Leukemia Response-Partial response (≥ ALR-P, per 2012 MPN-BP criteria).	Day 1	End of induction or re-induction cycle (or upon assessment of the bone marrow biopsy performed near the end of these cycles if this occurs later)

2.2.2 SECONDARY ENDPOINTS

Objective	**Endpoint**	**Start**	**End**
1. To evaluate the safety and tolerability of ruxolitinib in combination with CPX-351	1. Incidence of adverse events as assessed by CTCAE v5.0	Day 1	End of 6 cycles with study intervention
		Day 1	Up to 30 days after last on-study dose
2. Assess survival outcomes associated with ruxolitinib in combination with CPX-351	2. Overall survival (OS)	Day 1	End of follow-up (1 year after last dose of study treatment) or death
	3. Event-free survival (EFS)	Day 1	Treatment failure, progressive disease, relapse, last exam date, or death (whichever is first)

Objective	Endpoint	Start	End
	4. Relapse-free survival (RFS)	Date of first documented response (ALR-C)	Date of relapse or death from any cause
	5. Remission Duration	Date of first documented response (ALR-C)	Date of documented relapse
	6. Proportion of participants proceeding to transplant.	Day 1	Time of transplant or end of follow-up (if no transplant)

2.2.3 EXPLORATORY ENDPOINTS

Objective	Endpoint	Start	End
1. To evaluate the rate of response among participants with MPN-AP/BP using ELN criteria.	1. Proportion of participants that achieve at least a CRi [per ELN criteria]	Day 1	End of induction or re-induction cycle (up to 8 weeks after start of study treatment)
	2. Rate of CCR; which is the proportion of participants that achieve at least a MLFS [per ELN criteria]		
2. Assess the proportion of treated participants with minimal residual disease	3. MRD negativity	Day 1	At end of induction or re-induction (approximately 1-2 months on-study)
			At end of consolidation (approximately 3-4 months on-study)
			At end of maintenance (approximately 12 months on-study].
	4. Frequency of each mutation (SNP)	Day 1	At end of induction or re-induction (approximately 1-2 months on-study)

3. STUDY ENROLLMENT AND WITHDRAWAL

3.1 PARTICIPANT INCLUSION CRITERIA

To be eligible to participate in this study, an individual must meet all of the following criteria:

1. Ability to understand and the willingness to sign a written informed consent document.
2. Age ≥18 years at time of informed consent. Both men and women and members of all races and ethnic groups will be included.
3. Eastern Cooperative Oncology Group (ECOG) performance status 0 to 2. (Refer to Appendix A).
4. Participants eligible for this study have either MPN in accelerated phase (AP) or blast phase (BP), defined as:
    a. MPN-AP is defined by 10% to 19% blasts in the peripheral blood or bone marrow
    b. MPN-BP is defined by ≥20% blasts in the blood or bone marrow
        - Either MPN-AP or MPN-BP requires a previous diagnosis of polycythemia vera (PV), essential thrombocythemia (ET), primary or secondary myelofibrosis (MF), or MDS/MPN overlap with intermediate-2 or high risk disease according to IPSS as well as progression on or failure to respond to at least one line of therapy.
        - Participants with ET, PV, or MF that have received prior MPN-associated therapy (e.g., hydroxyurea, hypomethylating agents [azacitidine, decitabine], anti-platelet therapies [e.g., aspirin, anagrelide], as well as JAK2 inhibitor therapy [e.g., ruxolitinib or other investigational JAK2 inhibitor]) are eligible. They must discontinue prior to starting therapy; no wash-out is required.
5. Female participants of childbearing potential must agree to use adequate contraception (2 forms of contraception or abstinence) from the screening visit until 30 days following the last dose of study treatment. Should a woman become pregnant or suspect she is pregnant while she or her partner is participating in this study, she should inform her treating physician immediately.
6. Male participants of childbearing potential having intercourse with females of childbearing potential must agree to abstain from heterosexual intercourse or have their partner use 2 forms of contraception from the screening visit until 90 days until the last dose of study treatment. They must also refrain from sperm donation from the screening visit until 90 days following the last dose of study treatment.
7. Left ventricular ejection fraction at ≥ 50% as measured by echocardiogram (ECHO) or multigated acquisition (MUGA) scan (14 days prior to initiating study treatment).
8. Candidate for cytotoxic-intensive induction chemotherapy.
9. Willing to take oral medication.
10. Adequate organ function as defined by the following:
    a. Serum creatinine ≤2× the upper limit of normal (ULN), or glomerular filtration rate >20ml/min/1.73m^2 as calculated by Cockcroft-Gault formula.
    b. Serum potassium, magnesium, and calcium (corrected for albumin) within institutional normal limits or can be corrected with supplementation.

c. Total serum bilirubin ≤2.5× ULN.

d. Serum aspartate transaminase (AST) and/or alanine transaminase (ALT) ≤2.5× ULN.

3.2 PARTICIPANT EXCLUSION CRITERIA

An individual who meets any of the following criteria will be excluded from participation in this study:

1. Ongoing participation in another clinical trial.
2. Isolated myeloid sarcoma (i.e., participants must have blood or marrow involvement with AML to enter the study).
3. Acute promyelocytic leukemia (FAB M3 Classification).
4. Active central nervous system (CNS) involvement by AML.
5. Current treatment or treatment within 2 weeks or 5 half-lives (whichever is longer) prior to the first dose of study medication with another investigational medication or current enrollment in another investigational drug protocol (unless there is evidence of rapidly progressive disease in which case a shorter interval from last therapy may be acceptable).
6. Any unresolved toxicity equal to or greater than Grade 2 from previous anticancer therapy, except for stable chronic toxicities not expected to resolve, such as peripheral neurotoxicity.
7. Incomplete recovery from any prior surgical procedures or had surgery within 4 weeks prior to study entry, excluding the placement of vascular access.
8. Disseminated intravascular coagulopathy with active bleeding or signs of thrombosis.
9. Participants with rapidly progressive disease (defined by blast count doubling within 48 hours) or organ dysfunction that would prevent them from receiving these agents.
10. Participants with uncontrolled infection will not be enrolled until infection is treated and symptoms controlled.
    a. Participants with an infection receiving treatment (antibiotic, antifungal or antiviral treatment) may be entered into the study but must be afebrile and hemodynamically stable for ≥72 hrs.
11. Known hypersensitivity to ruxolitinib, cytarabine, daunorubicin, or liposomal products.
12. History of Wilson's disease or other copper metabolism disorder.
13. Uncontrolled intercurrent illness or any concurrent condition that, in the Investigator's opinion, would jeopardize the safety of the participant or compliance with the protocol per investigator's discretion. Including, but not limited to, symptomatic congestive heart failure, unstable angina pectoris, serious cardiac arrhythmia, myocardial infarction within 6 months prior to enrollment, New York Heart Association (NYHA) Class III or IV heart failure, severe uncontrolled ventricular arrhythmias.
14. Participants with prior cumulative anthracycline exposure of greater than 368 mg/m^2 daunorubicin (or equivalent).
15. All participants must discontinue anti-platelet agents or anticoagulants prior to initiation of study drug, including therapeutic doses of aspirin and clopidogrel.

3.3 STRATEGIES FOR RECRUITMENT AND RETENTION

Participants for this study will be recruited from within the hematology and oncology practices at each participating site. Participants may be identified and referred to this study by their primary treating physician from the outside community. Participants may also initiate contact with the investigator through information of this study posted on the clinicaltrials.gov website.

3.3.1 ACCRUAL ESTIMATES

This study will not focus on any particular gender, racial or ethnic subset. No participant will be excluded from the study on the basis of gender, racial or ethnic origin. Male, female and minority volunteers will be recruited for this study from the general population and approximately 50% men and 50% women will be studied. Gender-nonconforming and gender-fluid individuals as members of the general population will also be recruited.

The projected gender, racial, and ethnic composition of the study will represent that of the state demographics for each participating site. This study plans to enroll approximately 50 participants across OSU and 4 other participating research sites (approximately 12 participants at each site). Time from first to last participant enrollment is expected to take 18 months.

3.3.2 INCLUSION OF CHILDREN

Children are excluded from this study as there is no dosing or adverse event data currently available for individuals <18 years of age that delineates the use of the study agents as described herein.

3.4 REGISTRATION PROCEDURES

This is a phase I/II trial, and there is no randomization for treatment.

3.4.1 OSU REGISTRATION

OSU patients will be registered by the OSU research coordinator, as per CTO standard practice.

3.4.2 MULTICENTER REGISTRATION

For subsite patients, sites must send the signed consent form, documentation of the consent process, and the Screening Form (refer to Supplemental Forms Document) within 2 business days of initial consent.

Patients will be registered after meeting all entry requirements and signing of the informed consent document.

OSU patients will be registered by the OSU research coordinator, as per CTO standard practice. Subsite patients will have eligibility verified and will be entered on study centrally at The Ohio State University by the Multi-Center Trial Program (MCTP). All subsites must email the MCTP to verify slot availabilities prior to consenting patients. Once a patient signs consent, the signed consent document and documentation of the consenting process must be faxed or securely emailed to the MCTP. The required forms, including Eligibility Criteria Checklist and Registration Form, can be found in the Supplemental Forms Document.

To register a subsite patient, the following documents must be completed by the subsite research team and faxed or securely e-mailed to the MCTP:

- Copy of all baseline tests required per the protocol calendar. Tests must be within the specified window.
- Signed Patient Consent Form, if not previously sent
- Signed Patient HIPAA Authorization Form (if separate), if not previously sent
- Consent Documentation Note, if not previously sent
- Completed & Signed Eligibility Checklist (refer to Supplemental Forms Document)
- Registration Form (refer to Supplemental Forms Document)
- Source documents verifying every inclusion & exclusion criteria

Upon receipt of registration documents, the MCTP will send an email confirming receipt. If confirmation of receipt is not received within 1 hour of submission, please contact the MCTP by phone and/or pager to confirm receipt.

Upon receipt of all required registration documents and upon verification the subsite patient meets all eligibility criteria, the MCTP will:

- Assign the patient a study sequence ID, if not already provided at time of consent
- Register the patient on the study
- Fax and/or e-mail the subsite the completed Registration Form with the assigned study sequence ID and registration date as confirmation of patient registration

Following registration, patients should begin protocol treatment within 4 weeks. Issues that would cause treatment delays should be discussed with the Principal Investigator and MCTP as soon as possible. If a patient does not receive protocol therapy following registration, the PI and MCTP must be notified immediately within 1 business day.

Each participating institution will order study agents directly. Agents may be ordered by a participating site only after the required regulatory documents, including the initial IRB approval for the site, have been forwarded to the MCTP and all other study-specific requirements have been met (as outlined during site activation).

3.5 PARTICIPANT SCREENING AND ENROLLMENT

In order to participate in this study, signed informed consent must be obtained from the participant or the participant's legally acceptable representative. The current, local Institutional Review Board (IRB) approved informed consent must be signed and dated by each participant prior to undergoing any study procedures or before any prohibited medications are withheld from the participant in order to participate in this study.

Screening will begin once the participant has provided written informed consent to participate in the study and ends on Day 1 of the study. All screening and baseline evaluations will be performed during the screening phase (i.e., up to 1 day before treatment when the study medication is initiated). Once eligibility has been confirmed, the participant can be officially enrolled in the study. The enrollment date will be the date that the OSU coordinating center confirms enrollment. Day 1 of the clinical trial will be when participants are started on CPX-351.

3.6 PARTICIPANT WITHDRAWAL OR DISCONTINUATION

Participants are free to withdraw consent and discontinue participation in the study at any time and without prejudice to further treatment. For subjects who withdraw consent, there must be

clear documentation of whether the subject withdraws consents to treatment only (i.e. agrees to follow-up) or withdraws consent to treatment and follow-up. If a participant no longer wants to receive investigational products, but is willing to come for follow-up appointments, the participant's request should be honored, if possible. The following are examples demonstrating why a participant's treatment might be discontinued:

- Toxicity precludes further study treatment.
- There is a need for any treatment not allowed by the protocol.
- The participant fails to meet the criteria for study treatment.
- Disease recurrence or progression.
- Investigator's discretion.

No further participant contact should be made if the participant withdraws consent for participation in the study. Information about the reason(s) for discontinuation and collection of any new or ongoing AEs should be collected at the time the participant withdraws consent.

For all other reasons for discontinuation from the study treatment phase, the participant should return to the clinic for the end of treatment (EOT) visit according to Section 6.10, Schedule of Events.

3.6.1 HANDLING PARTICIPANT WITHDRAWAL AND DISCONTINUATION

Participants that discontinue the first cycle without experiencing a DLT, and either: i) do not complete all 3 planned infusions of CPX-351, or ii) received ruxolitinib on less than 11 days during the first induction cycle, may be replaced. Participants may also be replaced if they voluntarily withdraw from the protocol, or if the participant is taken off study per the PI's discretion for reasons such as continued noncompliance. The reasons for withdrawal, if known, will be recorded.

3.7 OFF-STUDY CRITERIA

Criteria that can take a participant off-study include:

- Completed study follow-up period.
- Participant requests to be withdrawn from study without further follow-up.
- Death.

4.6.1 SCREEN FAILURE

Any participant that has signed the consent form (for either screening or study participation) but does not meet the study eligibility criteria, or meets study eligibility criteria but terminates the participation prior to receiving study treatment, will be considered a screen failure. The reason for screen failure should be captured in the database for each participant failing to meet the eligibility criteria.

3.8 STUDY DISCONTINUATION

This study may be temporarily suspended or prematurely terminated if there is sufficient reasonable cause. Written notification, documenting the reason for study suspension or termination, will be provided by the suspending or terminating party to OSU coordinating site, local IRB, and other regulatory authority (if required). If the study is prematurely terminated or suspended, the Investigator will promptly inform the IRB and will provide the reason(s) for the termination or suspension.

Reasons for terminating the study may include the following:

- Incidence or severity of adverse events, in this or other studies, indicates a potential health hazard to participants.
- Demonstration of efficacy that would warrant stopping.
- Data that are not sufficiently complete and/or evaluable.
- Investigator(s) do not adhere to the study protocol or applicable regulatory guidelines in conducting the study.
- Participant enrollment is unsatisfactory.
- Submission of knowingly false information from the study site to Sponsor or regulatory authorities.
- Upon instruction by local or other regulatory or oversight authority.

This study may resume once concerns about safety, protocol compliance, and/or data quality are addressed and satisfy the Sponsor, IRB, and/or other regulatory authority.

4. INVESTIGATIONAL PRODUCT

A list of the adverse events and potential risks associated with the investigational or other agents administered in this study can be found in Section 8.4, Adverse Event List(s).

4.1 CPX-351

CPX-351 (Vyxeos®) is a liposomal formulation of daunorubicin and cytarabine in a 1:5 molar ratio. Please refer to manufacturer IB for additional details.

4.1.1 ACQUISITION

CPX-351 will be supplied by the manufacturer, Jazz Pharmaceuticals, and prepared by local institution pharmacy per manufacturer instructions. Following submission and approval of the required regulatory documents, a supply of CPX-351 may be ordered from Jazz Pharmaceuticals by completing a Drug Request Form.

Allow 4 business days for shipment of drug from receipt of the Drug Request Form. Drug is protocol specific, but not participant specific. There will be no weekend or holiday delivery of drugs.

4.1.2 FORMULATION, APPEARANCE, PACKAGING AND LABELING

CPX-351 liposome for injection is supplied as a sterile, preservative-free, purple, lyophilized cake, in a single-dose vial. Each vial containing CPX-351 (NDC 68727-745-01) contains 44 mg daunorubicin and 100 mg cytarabine.

The daunorubicin is complexed with copper gluconate inside the liposome. The aqueous entrapped volume inside the liposome is kept at neutral pH using a triethanolamine buffer. These liposomes are prepared by a water-in-oil emulsion method and are suspended in phosphate-buffered sucrose at pH 7.4. The nominal size of these liposomes is approximately 100 nm and sterilization is achieved by filtration though a 0.22 µm filter.

4.1.3 PRODUCT STORAGE AND STABILITY

Store unreconstituted CPX-351 vials in a refrigerator at 2°C to 8°C (36°F to 46°F) in an upright position. The vial should be stored in its original carton to protect from light. The reconstituted or diluted infusion solution may be stored in a refrigerator at 2°C to 8°C (36°F to 46°F) for up to 4 hours, if necessary. Discard unused portion of reconstituted solution in vial per institutional guidelines.

4.1.4 COMPATIBILITY

CPX-351 should be reconstituted in 0.9% sodium chloride, USP or 5% dextrose, USP. CPX-351 is not to be mixed or infused with other drug agents.

4.1.5 HANDLING

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

4.1.6 PREPARATION

Calculate the CPX-351 dose based on daunorubicin and individual participant's body surface area (BSA) using the participant's baseline height and weight measurements. Calculate the number of vials of CPX-351 based on the daunorubicin dose. If weight changes more than 10% from the cycle 1 Day 1 measurements, than dose will be adjusted. The oncology pharmacist will be consulted.

Remove the appropriate number of vials of CPX-351 from the refrigerator and equilibrate to the room temperature for 30 minutes. Then, reconstitute each vial with 19 mL of Sterile Water for Injection using a sterile syringe and immediately thereafter start a 5-minute timer. Carefully swirl the contents of the vial for 5 minutes while gently inverting the vial every 30 seconds. Do not heat, vortex, or shake vigorously. After reconstitution, let rest for 15 minutes. The reconstituted product should be an opaque, purple, homogeneous dispersion, essentially free from visible particulates. After reconstitution (but before final dilution), each mL will contain 2.2 mg of daunorubicin and 5 mg of cytarabine. Gently invert each vial 5 times prior to withdrawing the reconstituted product for further dilution. If the reconstituted product is not diluted into an infusion bag immediately, store in refrigerator at 2ºC to 8ºC for up to 4 hours.

Calculate the volume of reconstituted CPX-351 required using the following formula:

Volume required (mL) = [dose of daunorubicin (mg/m^2) x participant's BSA (m^2)] ÷ 2.2 (mg/mL)]

Aseptically withdraw the calculated volume of the reconstituted product from the vial(s) with a sterile syringe and transfer it to an infusion bag containing 500 mL of 0.9% Sodium Chloride Injection, USP or 5% Dextrose Injection, USP. There may be residual product remaining in the vial. Discard unused portion. Gently invert the bag to mix the solution. The dilution of the reconstituted product results in a deep purple, translucent, homogeneous dispersion, free from visible particulates.

One unit of CPX-351 contains 1.0 mg cytarabine plus 0.44 mg daunorubicin (base) with 5 units /mL..

If the diluted infusion solution is not used immediately, store in refrigerator at 2ºC to 8ºC for up to 4 hours.

4.1.7 ADMINISTRATION

CPX-351 should be administered through a central venous catheter or peripherally inserted central catheter by constant IV infusion over 90 minutes using an infusion pump. Do not use an in-line filter. CPX-351 should never be given by the intramuscular or subcutaneous route. After administration, flush line with 0.9% sodium chloride, USP or dextrose 5% injection, USP.

4.1.8 SPECIAL CONSIDERATIONS FOR ADMINISTRATION

4.1.8.1 *Organ function*

Prior to initiating induction, the participant should be assessed for cardiac function and obtain liver and renal function studies. Likewise, assess cardiac function, complete blood counts, liver and renal function before each consolidation cycle. Do not start CPX-351 consolidation until the ANC recovers to greater than 500/µL and the platelet count recovers to greater 50,000/µL in the absence of unacceptable toxicity.

4.1.8.2 *Tissue Necrosis*

Daunorubicin has been associated with local tissue necrosis at the site of drug extravasation. In clinical trials with CPX-351, one event of extravasation occurred, but no necrosis was observed. Care should be taken to ensure that there is no extravasation of drug when CPX-351 is administered.

4.2 RUXOLITINIB

Ruxolitinib (Jakafi®) is a potent selective inhibitor of JAK1 (IC_{50}=3.3 ± 1.2 nM) and JAK2 (IC_{50}=2.8 ± 1.2 nM) with modest to marked selectivity against TYK2 (IC_{50}=19 ± 3.2 nM) and JAK3 (IC_{50}=428 ± 243 nM), respectively. Please refer to package insert for additional details.

4.2.1 ACQUISITION

Ruxolitinib will be supplied by the manufacturer, Incyte Corporation, and prepared by local institution pharmacy per manufacturer instructions. Following submission and approval of the required regulatory documents, a supply of ruxolitinib may be ordered from Incyte Corporation by completing a Drug Request Form.

4.2.2 FORMULATION, APPEARANCE, PACKAGING AND LABELING

Ruxolitinib 5 mg tablets are round and white to off-white in color and is soluble in aqueous buffers across a pH range of 1 to 8. Ruxolitinib tablets are for oral administration. Ruxolitinib will be supplied as 5 mg tablets packaged in 60-count high-density polyethylene bottles. All tablet excipients comply with the requirements of the applicable compendial monographs.

All Incyte investigational product labels will be in the local language and will comply with the legal requirements of each country and will state "Caution: New Drug--Limited by Federal (or United States) law to investigational use."

4.2.3 PRODUCT STORAGE AND STABILITY

Store at a controlled room temperature between 20°C and 25°C (68°F and 77°F); excursions permitted between 15°C to 30°C (59°F and 86°F).

Based on available stability data, ruxolitinib should be stored in high density polyethylene (HDPE) bottles with induction sealing and child-resistant closure under the storage condition of “Do not store above 30°C”. Additionally, an in-use period is assigned to all dosage strengths.

4.2.4 COMPATIBILITY

Ruxolitinib can be taken with or without food.

4.2.5 HANDLING

Ruxolitinib must be dispensed only by the investigator or assigned designee, (e.g., study pharmacist, research nursing staff) to ensure the proper number of capsules are made available to the participants to satisfy dosing requirements for the study. The containers provided to the

participant should be labeled with proper instructions for use. The lot numbers, dosing start dates and the number of capsules for each dosage strength must be recorded on the drug accountability pages of record.

4.2.6 PREPARATION

Ruxolitinib is packaged as film-coated tablets. No additional preparation is required

4.2.7 ADMINISTRATION

Ruxolitinib is dosed orally and can be administered with or without food. If a dose is missed, the participant should not take an additional dose, but should take the next usual prescribed dose.

4.2.8 SPECIAL CONSIDERATION FOR ADMINISTRATION

4.2.8.1 *Lipid elevations*

Ruxolitinib is associated with increases in lipid parameters including total cholesterol, low-density lipoprotein (LDL) cholesterol, and triglycerides. Assess lipid parameters approximately 8-12 weeks following initiation of Ruxolitinib therapy. Monitor and treat according to clinical guidelines for the management of hyperlipidemia.

4.2.8.2 *Non-Melanoma Skin Cancer*

Non-melanoma skin cancers including basal cell, squamous cell, and Merkel cell carcinoma have occurred in patients treated with ruxolitinib. For participants on maintenance therapy, perform periodic skin examinations during their scheduled physical exams.

4.3 **ACCOUNTABILITY**

The Investigator, or a responsible designee, must maintain a careful record of the inventory and disposition of the study agents. (See the NCI Investigator's Handbook for Procedures for Drug Accountability and Storage).

Responsibility for drug accountability at the study site rests with the Investigator; however, the Investigator may assign some of the drug accountability duties to an appropriate pharmacist or designee. Inventory and accountability records must be maintained and readily available for inspection by the study monitor and are open to inspection at any time by any applicable regulatory authorities or other oversight bodies.

The Investigator or designee will collect and retain all used, unused, and partially used containers of study medication until full accounting has been completed. The Investigator or designee must maintain records that document:

- Investigational product delivery to the study site.
- The inventory at the site.
- Use by each participant including pill/unit counts from each supply dispensed.
- Return of investigational product to the Investigator or designee.
- Destruction or return of investigational product for final disposal.

These records should include dates, quantities, batch/serial numbers (if available), and the unique code numbers (if available) assigned to the investigational product and study participants.

The investigational product must be used only in accordance with the protocol. The Investigator will also maintain records adequately documenting that the participants were provided the correct study medication specified.

Completed accountability records will be archived by the site. At the completion of the study, the Investigator or designee will oversee shipment of any remaining study drug back to the manufacturer for destruction according to institutional standard operating procedures. If local procedures mandate site destruction of investigational supply, prior written approval must be obtained from manufacturer.

4.4 DESTRUCTION AND RETURN

At the end of the study unused supplies of CPX-351 or ruxolitinib should be destroyed according to institutional policies. Drug supplies will be counted and reconciled in full at the site with all monitoring procedures complete before destruction. Destruction will be documented in the Drug Accountability Record Form.

5. TREATMENT PLAN

5.1 DOSAGE AND ADMINISTRATION

Treatment with CPX-351 during induction will be administered in an inpatient setting. Thereafter, CPX-351 may, per institutional standards, be administered in an outpatient setting. Ruxolitinib is an oral medication and will be self-administered by the study participant. In general, a treatment cycle is defined as 28 consecutive days. Reported adverse events and potential risks are described in Section 8.4, Adverse Event List(s). Appropriate dose modifications are described in Section 5.2, Dosing Delays and Modifications. No investigational or commercial agents or therapies other than those described below may be administered with the intent to treat the participant's MPN-AP/BP.

Regimen Description					
Agent	*Premedication; Precautions*	*Dose*	*Route*	*Schedule*	*Cycle Length*
CPX-351 induction*	Prophylactic anti-emetic	100 units/m^2	IV *	Day 1,3, 5	Up to 28 days†
CPX-351 re-induction*	Prophylactic anti-emetic	100 units/m^2	IV*	Day 1 & 3	Up to 28 days†
CPX-351 consolidation*	Prophylactic anti-emetic	65 units/m^2	IV*	Day 1 & 3	28 days
Ruxolitinib induction	-	Assigned	PO	Day 6 – 28	Up to 28 days†
Ruxolitinib re-induction	-	Assigned	PO	Day 4 – 28	Up to 28 days†
Ruxolitinib consolidation	-	Assigned	PO	Day 4 – 28	28 days

**Administer through a central venous catheter or peripherally inserted central catheter by constant IV infusion per institutional standard using an infusion pump. Do not use an in-line filter*
† *Cycle length during induction and re-induction may be shorter if a participant fails to achieve < 5% blasts in the marrow or has partial count recovery. Refer to Section 5.1.1.1*

5.1.1 PHASE I

5.1.1.1 *Induction Therapy*

CPX-351 will be IV administered on Day 1, 3, and 5 of the first induction cycle. From Day 6 to 28, participants will orally receive ruxolitinib at the assigned dose level outlined in Section 5.2. A bone marrow aspirate/biopsy will be performed between D35-D42 (or earlier if counts partially recover to ANC > 500/µL and platelets > 50,000/µL]) to assess disease status and possible need for re-induction. Note that if disease response and residual disease are not clearly delineated, per principal investigator, then a repeat bone marrow aspirate/biopsy may be performed on D56. Conversely, a bone marrow aspirate/biopsy may be performed earlier than D35 if disease progression is suspected or upon count recovery (ANC and platelet count noted above). The results of this earlier marrow may, per investigator discretion, be used to support re-induction.

If there is residual disease (i.e., >5% blasts in bone marrow) at the D35-D42 bone marrow assessment (or earlier if counts partially recover to ANC > 500/µL and platelets > 50,000/µL), then participants may, per the discretion of the treating physicians, undergo a single cycle of re-induction therapy with CPX-351 (100 units/m^2) administered on Day 1 and 3 of the re-induction

cycle followed by ruxolitinib (PO) at the assigned dose level from Day 4 through 28. If the initial D35-D42 marrow results in a blast count recovery of >5 to ≤10% then participants may undergo a repeat bone marrow exam 1 week later to confirm residual disease. If a participant is re-induced, a bone marrow aspirate/biopsy will be performed 35-42 days after commencing this cycle (or earlier if counts recover to ANC > 500/µL and platelets > 50,000/µL]) to assess disease response.

For induction or re-induction, if at time of bone marrow assessment there is ≤ 5% blasts then participants will proceed to receive up to 2 cycles of consolidation therapy provided that counts have partially recovered to ANC > 500/µL and platelets > 50,000/µL (see Section 5.1.1.2). Participants that have primary refractory disease following courses of both induction and re-induction therapy will be considered induction failures and come off study treatment but may still be followed for assessment of disease status and survival outcomes. These participants will be offered salvage chemotherapy regimens per institutional guidelines and/or advised on other possible clinical trials.

5.1.1.2 *Consolidation Therapy*

Following induction (or re-induction), participants that have ≤ 5% blasts in bone marrow after counts have partially recovered (i.e., ANC > 500/µL and platelets > 50,000/µL) will receive up to 2 cycles of consolidation therapy. Each consolidation cycle is approximately 28 days in length and subsequent cycles will begin within 2 weeks following partial hematological recovery (ANC > 500/µL and platelets > 50,000/µL) but not earlier than 4 weeks from the beginning of the previous cycle. Each cycle of consolidation may be delayed based on investigator's clinical judgement. Any delay in treatment should be recorded in appropriate CRF.

1st Consolidation Cycle: CPX-351 (65 unit/m^2/day) will be administered IV over 90 minutes on Days 1 and 3. Ruxolitinib (PO) will be given at the assigned dose level on Days 4-28.

2nd Consolidation Cycle: CPX-351 (65 unit/m^2/day) will be administered IV over 90 minutes on Days 1 and 3. Ruxolitinib (PO) will be given at the assigned dose level on Days 4-28.

5.1.1.3 *Maintenance Therapy*

Participants who have successfully completed consolidation therapy with a continued ≤5% blasts in bone marrow and have not undergone allo-HSCT will complete up to 8 cycles of maintenance therapy with ruxolitinib at the assigned dose level. Adjustments to the dose level, , will be allowed *based on the package insert for ruxolitinib use in MF as per FDA approval. Please see table below for dose adjustment guidance.*

Platelet Count	Dose at Time of Platelet Decline				
	25 mg twice daily	20 mg twice daily	15 mg twice daily	10 mg twice daily	5 mg twice daily
	New Dose	New Dose	New Dose	New Dose	New Dose
100 to less than 125×10^9/L	20 mg twice daily	15 mg twice daily	No Change	No Change	No Change
75 to less than 100×10^9/L	10 mg twice daily	10 mg twice daily	10 mg twice daily	No Change	No Change
50 to less than 75×10^9/L	5 mg twice daily	5 mg twice daily	5 mg twice daily	5 mg twice daily	No Change
Less than 50×10^9/L	Hold	Hold	Hold	Hold	Hold

5.1.2 PHASE II

The phase II portion of the trial will open once the MTD or RP2D has been established. For the purposes of this study, the RP2D for ruxolitinib will be the same as the MTD unless the formal toxicity assessment of all phase I participants through 6 cycles of treatment concludes that a safer dose should be used (refer to Section 5.2.2). The treatment plan, including drug regimen, schedule, and assessments will remain the same as phase I except that ruxolitinib will be administered at the MTD or RP2D (rather than at the dose determined by the Keyboard design).

5.1.3 ALLOGENEIC STEM CELL TRANSPLANTATION (ALLO-HSCT)

Participants can proceed to allo-HSCT at any time after achieving ≤ 5% blasts in bone marrow if they have a suitable donor. In this case, participants will come off study treatment and be followed for disease status and survival outcomes.

5.2 **DOSING DELAYS AND MODIFICATIONS**

5.2.1 DEFINITION OF DOSE-LIMITING TOXICITY (DLT)

Toxicities will be assessed using the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE v5.0). Participants who experience DLTs may continue on trial provided that the toxicity has resolved to ≤Grade 2 within 2 weeks of onset.

It is recognized that drug-related toxicity in this population may be difficult to ascertain, given the aggressive hematologic disease and intensive chemotherapy that is standard. Site investigators will attempt to assign attribution of toxicities to each drug if possible. Toxicities with a reasonable possibility of being attributable to any of the study agents (i.e., ruxolitinib or CPX-351 [i.e., daunorubicin and/or cytarabine]) will be eligible for DLT consideration. Toxicities that result directly from active leukemia will not be eligible for DLT consideration. Specific definitions for non-hematological and hematological DLTs are as follows:

5.2.1.1 *Non-hematologic Toxicity*

Study drug-related non-hematologic toxicities of grade ≥ 3 will be considered a DLT, with the following exceptions:

- **(i)** grade 3 nausea and vomiting that resolves to grade < 3 within 72 hours,
- **(ii)** grade 3-4 infections that have not resulted from unexpectedly complicated (in terms of degree or duration) myelosuppression,
- **(iii)** infection-related toxicities (e.g., fever/sepsis) as determined by the provider,
- **(iv)** transient grade ≥ 3 electrolyte abnormalities that are not clinically significant and are correctable within 24 hours, and
- **(v)** grade 3 transient liver function test abnormalities (AST, ALT, or alkaline phosphatase) that resolve to grade < 2 within 5 days.
    - Any grade 3 elevations (regardless of duration) in AST or ALT accompanied by a Grade 2 bilirubin increase will be a DLT (Hy's law).

5.2.1.2 *Hematologic Toxicity*

A hematologic DLT will be defined as an ANC < 500/μL by Day 42 from start of on-study induction in the setting of ≤ 5% blasts according to the D35-42 bone marrow exam and no evidence of persistent cytogenetic abnormalities. If persistent cytogenetic abnormalities or immunophenotypic evidence of leukemia is present, myelosuppression would be considered secondary to leukemia even if morphology shows ≤ 5% blasts.

Beyond Day 42, participants who are disease-free (i.e., ≤ 5% blasts on prior bone marrow exam and no cytogenetic abnormalities) yet have ANC < 500/μL or platelets < 20,000/μL will have a bone marrow biopsy by day 56 to determine if the cause of low counts is marrow aplasia or residual disease. If this Day 56 bone marrow biopsy shows marrow aplasia, participants will be taken off study treatment.

For participants with >5% blasts, myelodysplastic changes, or evidence of disease by flow cytometry or cytogenetics, failure to recover neutrophil or platelet count may not be considered DLT as this could be the result of persistent disease. These participants will be treated per protocol or with alternative therapies at investigator's discretion.

5.2.1.3 *Duration of DLT assessment*

The DLT evaluation period for the purposes of establishing a MTD/RP2D will occur between start of the first CPX-351 dose (i.e., Day 1) up to 28 days from start of on-study induction for non-hematological DLTs, and up to 42 days from start of on-study induction for hematological DLTs. Patients that receive at least 75% of Ruxolitinib and 75% of CPX-351 doses or patients discontinued prior due to a DLT will be considered DLT evaluable.

5.2.2 DEFINITION OF MAXIMUM TOLERATED DOSE (MTD)

The MTD of ruxolitinib in combination with CPX-351 100 unit/m^2 is the dose closest to a target DLT probability of 0.25 (Refer to Section 9.2.1). The MTD will be estimated based on a Bayesian "Keyboard" design and isotonic regression applied to observed dose-level-specific DLT rates.[42] The RP2D is the same as the MTD unless the MTD is not found in the trial (e.g., no observed DLTs at the highest dose level) or if the pre-phase II formal toxicity assessment of all phase I subjects (evaluated up to 6 treatment cycles with ruxolitinib) identifies a safer dose.

Identification of the RP2D by formal toxicity assessment will include joint review of data by the PI and OSU Data and Safety Monitoring Committee (DSMC).

5.2.3 DOSE ESCALATION

Table 3. Ruxolitinib dose levels

Dose Level	***Ruxolitinib***	***CPX-351 (Induction dose)***
-2	5 mg, *QD*	100 unit/m^2
-1	5 mg, *b.i.d*	100 unit/m^2
1(starting dose)	10 mg, *b.i.d*	100 unit/m^2
2	20 mg, *b.i.d*	100 unit/m^2
3	30 mg, *b.i.d*	100 unit/m^2
4	40 mg, *b.i.d*	100 unit/m^2

The ruxolitinib dose levels are shown in Table 3. The study will start at dose level 1 and the dose will be continued, escalated, or de-escalated (according to the rules in Table 4) after evaluating each subsequent set of 3 DLT-evaluable participants. A total of 24 participants will be evaluated in Phase I of this trial. Per the Table 4 "keyboard" design rules (generated by specifying a target DLT probability of 0.25 and an acceptable DLT interval of 0.20 and 0.30 at www.trialdesign.org), each new cohort will be treated at the same, higher, or lower dose level depending on the cumulative number of dose-level-specific DLTs and the positional relationship between the "strongest key" (i.e., the toxicity interval with the highest likelihood of including the true DLT rate of the current dose level) and the acceptable DLT interval.

Table 4. Keyboard design decision rule for dose escalation/de-escalation

Number of patients treated:	**3**	**6**	**9**	**12**	**15**	**18**	**21**	**24**
Escalate if # of DLT ≤	0	1	1	2	2	3	4	4
De-escalate if # of DLT ≥	1	2	3	4	5	6	7	8
Eliminate if # of DLT ≥[a]	3	4	5	6	7	8	9	10

[a] When the current dose is eliminated from the trial, the higher doses should also be eliminated and the dose is automatically de-escalated to the next lower level for treating the next new patient. A minimum of three patients must be treated before a dose can be eliminated.

5.2.4 DOSE DELAYS

Treatment may be delayed for up to 5 days from the end of a previous treatment cycle. In case of a treatment delay, subsequent study assessment days will be adjusted accordingly.

5.2.5 GENERAL DOSE MODIFICATION GUIDELINES

Dose delays and modifications will be made as indicated in the following table(s). The descriptions and grading scales found in the revised CTCAE v5.0 will be utilized for dose delays and dose modifications.

5.2.5.1 *CPX-351*

Table 5. CPX-351 – Recommended Dose Modifications – Hypersensitivity	
Hypersensitivity	**Management/Next Dose**

Grade 1	For hypersensitivity reactions of any grade/severity, infusion reactions will be treated according to institutional standards.	Once symptoms resolve, reinitiate infusion at half the prior rate of infusion. Consider premedication with antihistamines and/or corticosteroids for subsequent doses.
Grade 2		Do not reinitiate infusion. For subsequent doses, pre-medicate with antihistamines and/or corticosteroids prior to initiating infusion at the same rate
Grade 3		Permanently discontinue CPX-351
Grade 4		Permanently discontinue CPX-351

Table 6. CPX-351 – Recommended Dose Modifications – Cardiotoxicity	
Cardiotoxicity	**Management/Next Dose**
Discontinue CPX-351 in participants exhibiting impaired cardiac function.	

Renal Impairment: Dosage adjustment is not required for participants with mild (creatinine clearance (CLCR) 60 mL/min to 89 mL/min by Cockcroft Gault equation (C-G)) or moderate (CLCR 30 mL/min to 59 mL/min) renal impairment. CPX-351 has not been studied in participants with severe renal impairment (CLCR 15 mL/min to 29 mL/min) or end-stage renal disease.

Hepatic Impairment: Dosage adjustment is not required for participants with a bilirubin level less than or equal to 3 mg/dL. CPX-351 has not been studied in participants with bilirubin level greater than 3 mg/dL

5.2.5.2 *Ruxolitinib*

Based on the known thrombocytopenia with CPX-351 treatment, this study will increase the platelet threshold to 20,000 per µL with transfusion support during induction/consolidation therapy. Dose modifications for participants that do not recover platelets >10,000/µL for 48 hours despite adequate platelet transfusion support include the following:

Ruxolitinib will be held until platelet count is >10,000/µL with transfusion support. Once participants have achieved ≤ 5%-blasts in bone marrow, if platelet count continues to be ≤10,000/µL, ruxolitinib will be held until platelet count recovers to 20,000/µL. If platelets are >20,000/µL and ≤50,000/µL, the dose of ruxolitinib will be reduced by 50%; once platelets recover to >50,000/µL, the ruxolitinib dose can be escalated back to the original dose. For bleeding events that are grade ≥ 3, ruxolitinib will be held, and only restarted once the bleeding event resolves to grade < 3. In such cases, the restarting dose of ruxolitinib will be reduced by 50%.

No dose ruxolitinib adjustment is necessary when a mild or moderate CYP3A4 inhibitor is used as concomitant medication, although participants should be monitored closely for cytopenias when starting a mild or moderate CYP3A4 inhibitor during ruxolitinib treatment

For administration of strong CYP3A4 inhibitors, refer to appendix B for IB required dose reduction and monitor platelet counts.

Additional guidelines for managing ruxolitinib-associated toxicities are shown in Table 7.

Table 7. Ruxolitinib – Recommended Dose Modifications by Toxicity Grade		
Renal Impairment	**Management/Next Dose**	
Moderate (CrCl 30–59 mL/min) or Severe (CrCl 15–29 mL/min)	10 mg twice daily	
	Discontinue	
Hepatic Impairment	**Management/Next Dose**	
	Platelet Count	**Recommended Starting Dose**
AST/SGOT, ALT/SGPT categories A, B, C)	>3-10 x ULN	Interrupt study treatment dosing until resolved to ≤ grade 1 or baseline, then if resolved within 7 days: • Restart study treatment at unchanged dose level • If resolved in more than 7 days, then restart study treatment at reduced level
	>10 x ULN	Interrupt study treatment dosing until resolved to ≤ grade 1, or baseline, then: • restart study treatment at reduced level

In the event that ruxolitinib needs to be discontinued, please do not abruptly discontinue to avoid discontinuation syndrome. The discontinuation should be done over 7-10 days with a 50% dose reduction for 3-4 days followed by a 75% dose reduction or stoppage of the drug. If the patient is on less than 10 mg of ruxolitinib daily, only one dose reduction to 5 mg is required before stopping the drug altogether.

5.3 TREATMENT PERIOD AND MAINTENANCE

A treatment cycle is defined as the first day of study drug administration (Day 1) through and including Day 28.

Induction therapy: Participants will receive CPX-351 (100 units/m^2) as induction therapy on Days 1, 3, and 5 of Cycle 1. Ruxolitinib will be administered *b.i.d.* starting on Day 6 of Cycle 1 and will continue up to Day 28 of Cycle 1. Participants may receive an additional re-induction cycle if clinically indicated, which will repeat the treatment regimen. For re-induction, participants will receive CPX-351 (100 units/m^2) on Days 1 and 3 along with ruxolitinib to be administered *b.i.d.* starting on Day 4 of the re-induction cycle and continue through to Day 28.

Consolidation therapy: Participants may receive CPX-351 (65 units/m^2) as consolidation therapy on days 1 and 3 for up to 2 cycles. Ruxolitinib will be administered *b.i.d* starting on Day 4 and will continue up to Day 28 for up to 2 cycles.

Maintenance therapy: Following completion of consolidation therapy, participants will continue to receive ruxolitinib starting on Day 1 and continuing up to Day 28 of each subsequent cycle for a total period of 8 months (i.e., up to 8 cycles of ruxolitinib monotherapy at assigned dose).

Provided participants have not met any criteria for discontinuation of therapy (including allo-HSCT) the estimated on-study treatment time is as follows:

Treatment	Duration of Treatment Period	Duration of entire study
Induction	~28 days	2 years
Re-induction	~28 days	
Consolidation (2 cycles)	~56 days	
Maintenance (up to 8 cycles)	~224 days	

5.4 CONCOMITANT MEDICATION AND SUPPORTIVE CARE GUIDELINES

Supportive measures for optimal medical care are to be given throughout the study as indicated by the treating physician's assessment of the participant's medical need and institutional and general medical guidelines for the care of participants undergoing treatment of MPN-AP/BP.

Medications required to treat AEs, manage cancer symptoms, concurrent diseases and supportive care agents, such as pain medications, anti-emetics and anti-diarrheals are allowed in general. The participant must be told to notify the investigational site about any new medications begun after the start of the study treatment. All medications (other than investigational products) and significant non-drug therapies (including vitamins, herbal medications, physical therapy and blood transfusions) administered during the study must be listed on the case report form (CRF).

5.4.1 NAUSEA AND VOMITING

Participants may be premedicated for nausea and vomiting according to institutional standards.

5.4.2 HYPERSENSITIVITY/INFUSION-RELATED REACTIONS

For CPX-351, participants will not be routinely premedicated for hypersensitivity or infusion-related reactions initially during the first infusion of the first treatment course. If the participant develops a hypersensitivity reaction then individual should be premedicated at all subsequent infusions. Refer to Table 5 for treatment guidelines.

5.4.3 INFECTION PROPHYLAXIS

The use, and choice, of prophylactic antibacterial, antifungal, and antiviral agents is recommended according to institutional guidelines. Use of anti-infective agents as prophylaxis and treatment must be documented on the case report forms.

For CPX-351 treatment course, prophylactic use of anti-infectives is highly recommended during the period of profound neutropenia until ANC returns to 500/µL or greater.

Ruxolitinib is associated with herpes zoster (HSV), and possible prophylaxis for HSV infection includes use of acyclovir or valacyclovir. Levofloxacin may be used for bacterial prophylaxis, as long as participant is not febrile.

For ruxolitinib, azoles such as posaconazole, fluconazole,voriconazole, will need to be used cautiously as prophylaxis and may require measurement of drug levels to monitor dose. Potential interaction of antifungals should be reviewed with an oncology pharmacist and the study investigator.

5.4.4 GROWTH FACTOR SUPPORT

The use of growth factors will be according to institutional protocol and ASCO criteria.[44] Use of growth factors must be documented on the case report forms.

5.4.5 BLOOD PRODUCTS

All blood products are to be irradiated and leukocyte-reduced according to institution guidelines. Additionally, cytomegalovirus (CMV)-negative participants should receive CMV-negative blood products according to institutional guidelines. Use of transfusion support must be documented on the case report forms.

5.4.6 ANTICOAGULATION / ANTIPLATELET MEDICATIONS

Medications that are anticoagulants (e.g., warfarin, heparin/low molecular weight heparin [e.g., danaparoid, dalteparin, tinzaparin, enoxaparin] or inhibit platelet function are generally not permitted beginning with the Baseline Visit (Day -14) through the final dose of ruxolitinib with the exception of a maximal dose of 81 mg a day of aspirin given per physician discretion per standard of care and over-the-counter doses of NSAIDs and acetaminophen. Participants receiving over-the-counter NSAIDs should not exceed the recommended dose and should be encouraged to use gastroprotective agents (antacids, H2 antagonists or proton pump inhibitors). Anticoagulation is allowed provided that platelet counts are maintained above 50,000 per µL.

5.4.7 GASTROINTESTINAL

Anti-emetics, anti-diarrheal agents and acid suppressive therapies (e.g., antacids, H2 blockers, proton pump inhibitors) are allowed and should be administered per institutional guidelines. Participants with uncomplicated mild to moderate diarrhea (Grade 1 or 2) without signs of infection, treat with loperamide 2 mg every 4 hours for 24 hours. Participants presenting with progressive and uncontrolled diarrhea treat with octreotide, IV fluids, and antibiotics.

5.4.8 CARDIOTOXIC DRUGS

CPX-351 contains the anthracycline daunorubicin, which has a known risk of cardiotoxicity. Concomitant use of cardiotoxic drugs may increase the risk of daunorubicin-induced cardiac toxicity. Cardiotoxic drugs (e.g., tricyclic antidepressants, antipsychotics, antihistamines, anticonvulsants, dextropropoxyphene, calcium channel blockers, beta blockers [e.g., propranolol, sotalol, digoxin, antiarrhythmic drugs) are allowable at the discretion of the study investigator. Participant use of concomitant cardiotoxic drug agents must be recorded in the CRF.

5.4.9 CONTRACEPTION

CPX-351 can cause embryo-fetal harm, and ruxolitinib may have adverse effects on a fetus in utero. Furthermore, it is not known if either drug agent has transient adverse effects on the composition of sperm. Men and non-pregnant, non-breast-feeding women may be enrolled if

they are willing to use 2 methods of birth control or are considered highly unlikely to conceive. Highly unlikely to conceive women are defined as: 1) surgically sterilized, or 2) postmenopausal (a woman who is ≥ 45 years of age and has not had menses for more than 1 year), or 3) not heterosexually active for the duration of the study. The two birth control methods can either be two barrier methods or a barrier method plus a hormonal method to prevent pregnancy. Participants should start using birth control from study visit 1 throughout the study period up to 6 months after the last dose of study therapy.

The following are considered adequate barrier methods of contraception: diaphragm, condom, copper intrauterine device, sponge, or spermicide. Appropriate hormonal contraceptives will include any registered and marketed contraceptive agent that contains an estrogen and/or a progestational agent (including subcutaneous, intrauterine, or intramuscular agents).

Participants should be informed that taking the study medication may involve unknown risks to the fetus (unborn baby) if pregnancy were to occur during the study. In order to participate in the study they must adhere to the contraception requirement (described above) for the duration of the study and during the follow-up period defined in Section 3.1. If there is any question that a participant will not reliably comply with the requirements for contraception, that participant should not be entered into the study.

5.4.10 USE IN PREGNANCY

If a participant inadvertently becomes pregnant while on treatment with CPX-351 or ruxolitinib, the participant will immediately be removed from the study. The site will contact the participant at least monthly and document the participant's status until the pregnancy has been completed or terminated. The site will report the outcome of the pregnancy to Sponsor without delay and within 24 hours if the outcome is a serious adverse experience (e.g., death, abortion, congenital anomaly, or other disabling or life-threatening complication to the mother or newborn).The pregnancy will be recorded on the CRF and reported by the Investigator to the IRB. If a male participant impregnates his female partner the pregnancy will be recorded on the CRF and reported by the Investigator to the IRB. Refer to Section 8.6.3.

5.4.11 USE IN NURSING WOMEN

It is unknown whether ruxolitinib, daunorubicin, cytarabine, or their metabolites are excreted in human milk. Since many drugs are excreted in human milk, and because of the potential for serious adverse reactions in the nursing infant, participants who are breast-feeding are not eligible for enrollment.

5.5 PRECAUTIONARY AND PROHIBITED MEDICATIONS, TREATMENTS, AND PROCEDURES

5.5.1 DRUG INTERACTIONS

No concomitant therapy or investigational therapy is allowed during the study. Unless at the discretion of the investigator, the use of herbal or botanicals for anticancer purposes is not permitted during the study.

To the extent possible, use of nephrotoxic (e.g., vancomycin, amphotericin B) and hepatotoxic (e.g., cyclosporine) agents should be avoided during treatment period. The use of NSAIDs should be limited.

5.5.2 CPX-351

5.5.2.1 *Cardiotoxicity*

Prior therapy with anthracyclines, pre-existing cardiac disease, previous radiotherapy to the mediastinum, or concomitant use of cardiotoxic drugs may increase the risk of daunorubicin-induced cardiac toxicity. CPX-351 is not recommended in those with left ventricular ejection fraction (LVEF) that is ≥ 50%. Discontinue CPX-351 in participants exhibiting impaired cardiac function.

5.5.2.2 *Copper toxicity*

CPX-351 contains 5mg/ml copper gluconate, of which 14% is copper. Individuals with Wilson's disease or other copper-related metabolic disorders are excluded from this study; however, participants showing acute copper toxicity should be managed according to institutional guidelines, which includes monitoring total serum copper, serum nonceruloplasmin bound copper, 24-hour urine copper levels and serial neuropsychological examinations in these participants. On-study treatment will be halted in participants with clinical evidence of copper toxicity, and they will be removed from study.

5.5.2.3 *Hemorrhage*

Serious or fatal hemorrhage events, including fatal central nervous system (CNS) hemorrhages, associated with prolonged severe thrombocytopenia, have occurred in patients treated with CPX-351. Grade 3 or greater events occurred in 12% of those treated with CPX-351. Monitor blood counts regularly until recovery and administer platelet transfusion support as required (per institutional guidelines).

5.5.2.4 *Hyperuricemia*

As a cytotoxic agent, CPX-351 may induce hyperuricemia secondary to rapid lysis of leukemic cells. Consideration should be given to initiating anti-hyperuricemic therapy (e.g., allopurinol) prior to administering CPX-351. Monitor blood uric acid levels and initiate appropriate therapy in the event that hyperuricemia develops.

5.5.2.5 *Severe Myelosuppression*

Severe myelosuppression occurs after administration of therapeutic doses of CPX-351. Obtain baseline assessment of blood counts and carefully monitor for possible clinical complications due to myelosuppression, including serious infection or hemorrhage. Due to the long plasma half-life of CPX-351, time to recovery of ANC and platelets may be prolonged and require additional monitoring. Use appropriate supportive measures (e.g., anti-infectives, colony-stimulating factors, transfusions).

5.5.2.6 *Hypersensitivity Reactions*

Serious hypersensitivity reactions, including anaphylactic reactions, have been reported with daunorubicin and cytarabine. Monitor participants for hypersensitivity reactions. Refer to Table 5 for treatment guidelines. If a severe or life-threatening hypersensitivity reaction occurs,

permanently discontinue CPX-351, treat symptoms according to the standard of care, and monitor until symptoms resolve.

5.5.2.7 *Evaluation of Hepatic and Renal Function*

Significant hepatic or renal impairment may increase the risk of toxicity associated with cytarabine and daunorubicin. Evaluation of hepatic and renal function using conventional clinical laboratory tests is recommended prior to administration of CPX-351 and periodically during treatment.

5.5.3 RUXOLITINIB

5.5.3.1 *Concomitant CYP3A4 inhibitors/inducers/substrates*

The principal investigator should be alerted if the subject is taking any agent categorized as a moderate or potent CYP3A4 inhibitor (please see Appendix B). Dose adjustment is not required when ruxolitinib is co-administered with rifampin or other CYP3A4 inducers, but these agents should be used with caution in combination with ruxolitinib and alternative therapy used if available. No dose adjustment is necessary when a mild or moderate CYP3A4 inhibitor is used as concomitant medication, although participants should be monitored closely for cytopenias when starting a mild or moderate CYP3A4 inhibitor during ruxolitinib treatment

There is no dose reduction when mild or moderate CYP3A4 inhibitors are used as concomitant medication, although participants will be monitored closely for cytopenias during ruxolitinib treatment. For administration of strong CYP3A4 inhibitors, refer to appendix B for IB required dose reduction and monitor platelet counts.

5.5.3.2 *Decrease in blood cell count*

Ruxolitinib can cause hematologic adverse reactions, including thrombocytopenia, anemia and neutropenia. A complete blood count must be performed before initiating therapy with ruxolitinib. Complete blood counts should be monitored every 2-4 weeks until doses are stabilized, and then as clinically indicated and dose adjusted. Thrombocytopenia was generally reversible and was usually managed by reducing the dose or temporarily withholding ruxolitinib. However, platelet transfusions may be required as clinically indicated. Participants developing anemia may require blood transfusions. Dose modifications or interruption for individuals developing anemia may also be considered. Neutropenia (ANC <500/μL) is generally reversible and was managed by temporarily withholding ruxolitinib.

5.5.3.3 *Infections*

Serious bacterial, mycobacterial, fungal, viral and other opportunistic infections have occurred in patients treated with ruxolitinib. Ruxolitinib therapy should not be started until active serious infections have resolved.

Hepatitis B viral load (HBV-DNA titer) increases, with and without associated elevations in alanine aminotransferase and aspartate aminotransferase, have been reported in participants with chronic HBV infections taking ruxolitinib. Those with chronic HBV infection should be treated and monitored according to institutional guidelines.

5.5.3.4 *Tuberculosis*

Tuberculosis has been reported in patients receiving ruxolitinib for myelofibrosis. Before starting ruxolitinib therapy, participants should be evaluated for latent or active tuberculosis as per institutional guidelines.

5.5.3.5 *Progressive Multifocal leukoencephalopathy (PML)*

PML has been reported with ruxolitinib treatment. Monitor for neuropsychiatric symptoms suggestive of PML. If PML is suspected, ruxolitinib should be stopped and the participant evaluated.

7.2.2.6 *Non-melanoma skin cancers (NMSCs)*

NMSC, including basal cell, squamous cell, and Merkel cell carcinoma have been reported in patients treated with ruxolitinib. Most of these patients had histories of extended treatment with hydroxyurea and prior histories of NMSC or pre-malignant skin lesions. Periodic skin examination is recommended for those who are at increased risk for skin cancer.

6. STUDY PROCEDURES/EVALUATIONS AND SCHEDULE

6.1 STUDY SPECIFIC PROCEDURES

6.1.1 MEDICAL HISTORY

A medical history will be obtained by the investigator or qualified designee. In addition to collecting information on demographics, the medical history will include all active conditions, and any prior conditions that are considered to be clinically significant by the PI. Details regarding the participant's AML will be recorded separately and not listed as medical history.

6.1.2 DISEASE ASSESSMENT

The investigator or qualified designee will obtain prior and current details regarding the participant's MPN–BP/AP(refer to Section 7.2.1).

6.1.3 MEDICATION HISTORY

All concomitant medications and treatments must be recorded in the CRF. Any prior medication received up to 30 days prior to the Baseline visit will be recorded in the CRF. Concomitant treatments that are required to manage a subject's medical condition during the study will also be recorded in the CRF. Prior and/or ongoing medications will be reviewed during screening to determine subject eligibility. The medication record will be maintained following enrollment including any changes to the dose or regimen. Prior and concomitant medication including any prescription, over the counter or natural/herbal preparations taken will be recorded.

6.1.4 PHYSICAL EXAMINATION

Physical exams must be performed by a medically qualified individual such as a licensed physician, physician's assistant or advanced registered nurse practitioner as local law permits. The physical exam at baseline should include a complete physical exam per institutional standards. All other physical exams after baseline will include an evaluation of any AEs, or any previously reported symptoms, or prior physical examination findings. Dermatological exams will be included as part of the physical exam.

As part of baseline visit, physical examination is to be conducted within 14 days prior to start of treatment. When possible, screening and baseline visit can be represented as the same visit. All physical examinations will also include:

6.1.4.1 *Vital signs*

Vitals to be collected include BP, HR, and temperature. As part of baseline visit, vitals should be obtained within 14 days prior to first dose of study agent. Vitals will also be obtained during treatment.

Significant findings that were present prior to the signature of the informed consent must be included in the Medical History eCRF page. Significant new findings that begin or worsen after eligibility confirmation must be recorded on the Adverse Event eCRF page.

6.1.4.2 *Height and weight*

Height and weight is required as part of screening. Thereafter, only weight will be collected on days of physical exam.

6.1.4.3 *Performance status*

Performance status will be determined for all participants at screening and at select times during treatment as per assessment schedule in Section 6.10. Refer to Appendix A for performance criteria.

6.1.5 ELECTROCARDIOGRAM

Electrocardiogram (ECG) will be performed according to institutional guidelines within 28 days prior to initiating treatment, as well as at on-study times indicated in Section 6.10.

6.1.6 DIAGNOSTIC IMAGING

Cardiac function will also be assessed by multi-gated radionuclide angiography (MUGA) scan or echocardiography (ECHO). ECHO is to be performed at screening (i.e., 14 days prior to initiating study intervention) and thereafter only as clinically indicated.

Chest X-ray or Chest computed tomography (CT) per institutional guidelines.

All procedures will be performed according to institutional guidelines within 28 days prior to initiating treatment, as well as at on-study times indicated Section 6.10.

6.1.7 MEDICAL DIARY

Participants that self-administer ruxolitinib are required to maintain a medication diary to assess compliance. Participants will receive instruction on how to administer ruxolitinib from a physician, clinical research nurse, or other designated, qualified healthcare provider. Participants will be provided with a medical diary and are required to record the date, dose, and the time of the ingestion. A medication diary is not necessary if electronic medical record captures dosing times while participants are inpatient.

6.1.8 ADVERSE EVENT EVALUATION

Toxicities and adverse events will be assessed at each visit using the CTCAE v5.0. Safety will be monitored by assessing physical examination, vital signs, body height and weight, performance status, ECG, hematology and chemistry as indicated in Section 6.10.

Adverse events will be monitored from the time of informed consent. Participants will be instructed to report all AEs during the study and will be assessed for the occurrence of AEs throughout the study. All AEs (serious and non-serious) must be recorded on the source documents and CRFs regardless of the assumption of a causal relationship with the study drug.

6.2 LABORATORY PROCEDURES AND EVALUATIONS

6.2.1 HEMATOLOGY

Hematologic profiling will be collected per institutional standards, and will include evaluation of hematocrit, hemoglobin, platelets, white blood cells with differential (basophils, eosinophils, lymphocytes, monocytes, neutrophils), and absolute lymphocyte count.

Must be collected per institutional guidelines at the visits outlined in the Section 6.10, Schedule of Events.

6.2.2 BLOOD CHEMISTRY

Blood chemistry will be collected per institutional standards and will include the following: Creatinine, BUN, total bilirubin, Alkaline Phosphatase, AST or ALT, serum electrolytes, magnesium, calcium, and potassium, uric acid, as well as lactate dehydrogenase.

Lipid panel will be collected per institutional standards and will include the following: total cholesterol, high-density lipoprotein cholesterol (HDL-C), low-density lipoprotein cholesterol (LDL-C), and triglycerides.

Total serum copper, serum non ceruloplasmin bound copper if clinically indicated.

Must be collected per institutional guidelines at the visits outlined in the Section 6.10, Schedule of Events.

6.2.3 URINALYSIS

Urinalysis (dipstick measurement [pH, specific gravity, protein, glucose, ketones, nitrite, leukocyte esterase] with microscopic analysis, if results of the dipstick indicate additional testing required).

24-hour urine copper levels if clinically indicated.

Must be collected per institutional guidelines at the visits outlined in the Section 6.10, Schedule of Events.

6.2.4 COAGULATION PANEL

INR, prothrombin time (PTT). Must be collected per institutional guidelines at the visits outlined in the Section 6.10, Schedule of Events.

6.2.5 PREGNANCY TEST

A serum or urine pregnancy test is required during screening for all persons of childbearing potential. The pregnancy test is required within 7 days prior to study intervention and results must be available prior to administration of study agent. If the urine pregnancy test is positive, a serum pregnancy test must be performed per institutional standards.

6.2.6 BONE MARROW EXAM

Bone marrow biopsy/aspirate must be collected per institutional guidelines at the visits outlined in the Section 6.10, Schedule of Events. Additional bone marrow evaluations may occur if clinically indicated at the discretion of the investigator (e.g., at the time of suspected disease progression or disease remission.)

Bone Marrow Aspirate (5-8 ml in sodium heparin-coated tubes) will be collected to assess (per institutional guidelines):

- Hematopathology review
- myeloid:erythroid ratio per standard of care
- Cellularity (%)
- Blast quantification per standard of care.
- Cytogenetics will be performed as standard of care.
- Minimum residual disease assessment

6.3 EXPLORATORY STUDIES

6.3.1 MOLECULAR RESPONSE

For those with suspected response (CMR or CCR [per 2012 MPN-criteria]), detection of molecular response may be assessed by either multi-color flow cytometry (MFC) or next-generation sequencing (NGS) technology. Known mutations in Jak-2 (Exon 14 mutation [JAK2V617F], Exon 12 mutation), CALR and other post-MPN AML mutations (e.g., MPL, LNK, and TET2) will be assessed.

Bone marrow samples for MRD are to be sent at the time of suspected response at the end of induction or re-induction, at the end of consolidation, and end of maintenance if response is sustained.

6.3.1.1 *Collection of Specimen(s) for MRD gene profiling*

Bone Marrow: 5-8 mL will be collected in green-top (Na-Hep) tubes.

i) Handling of Specimen(s)

Contact Leukemia Tissue Bank (see below) for additional information regarding sample handling and preparation. Label all tubes containing samples with the following information:

- Study00020393
- Participant Study ID#
- Sample type (i.e., blood, bone marrow aspirate, bone marrow core)
- Date of collection

ii) Shipping of Specimen(s)

Deliver to laboratory at shipping address below within 24 hours of collection. If sample cannot arrive within 24 hours, refrigerate until sample can be transported, then transport on ice packs; do not freeze.

iii) Site(s) Performing Correlative Study

OSUCCC Leukemia Tissue Bank
300 W. 10th Ave., Lobby
Columbus, OH 43210
Phone: 614-688-4754

Subsites should e-mail the following address to let the lab know the sample is coming:

CCC-LTB@osumc.edu, and should include tracking information. Samples should be sent using FIRST OVERNIGHT delivery at ROOM TEMPERATURE.

All samples will be shipped, within 24 hours of collection, to OSU for processing. On Monday through Thursday samples should be sent to the address above. When Friday draws are unavoidable, subsites must notify the Lab [contact info above] as far in advance as possible, so they can plan to have a technician present on the weekend to receive the sample.

6.4 SCREENING ASSESSMENTS

There will be a screening (consultation) visit as part of standard of care. If a participant is eligible for the study after review of key inclusion/exclusion criteria, a baseline visit (within 4 weeks of screening visit) will be scheduled while staff members are requesting insurance authorization to participate in a clinical trial.
The following will be reviewed at screening visit:

- Clinical history and physical exam (per standard of care)
- Informed consent obtained and documented

6.4.1 INFORMATION TO BE COLLECTED ON SCREENING FAILURES

A participant who signed an informed consent form but failed to be started on treatment for any reason will be considered a screen failure. Those found not to be eligible after signing the main study consent will be considered screening failures, and data will be handled in the same manner. The demographic information, informed consent, and inclusion/exclusion pages must also be completed for screen failures. No other data will be entered into the clinical database for individuals who are screen failures.

6.5 BASELINE ASSESSMENTS

Toxicities which occur prior to the start of treatment will not be subject to analysis. Consent must be obtained before initiation of any clinical screening procedure that is performed solely for the purpose of determining eligibility for this research study. Evaluations performed as part of routine care before informed consent can be utilized as screening evaluations if done within the defined time period.

Baseline assessments will occur over a 14-day period prior to start of treatment with study agent. Participants will be evaluated for medical history, physical examination, vital signs, performance status, concomitant medications, blood sampling for laboratory tests, ECG, MUGA or ECHO evaluation, bone marrow aspiration/biopsy.

Participants receiving any other anti-cancer treatment should be stopped within 2 weeks prior to starting first dose of on-study treatment.

6.6 ASSESSMENTS DURING TREATMENT

Specific on-study assessments are listed in the Section 6.10, Schedule of Events.

Visits will occur on Day 1 of every cycle, with additional visits listed in Table 8. (for induction) and Table 9 (for consolidation cycles). Scheduled on-study treatment visits occurring during maintenance with ruxolitinib is shown in Table 10.

Under certain circumstances (e.g., clinic holiday, inclement weather) scheduled visits may be delayed by no more than 3 days, or may occur earlier than scheduled by no more than 3 days during each treatment cycle.

6.7 EARLY TERMINATION OR END OF TREATMENT VISIT

Any participant that completes or discontinues treatment must be evaluated within 30 days after termination and prior to allo-HSCT or the initiation of any salvage therapy, if not performed within the last 30 days. End of treatment assessments are listed in Table 11 of the Section 6.10, Schedule of Events. If participants do not reach the end of treatment due to transition to hospice or death, an end of treatment visit will not be conducted.

At the discretion of the Sponsor-investigator, participants may have the option to continue on study drug; particularly if there is a documented clinical benefit.

6.8 FOLLOW-UP

Participants will be followed every 2 months after removal from protocol therapy until the earliest of the following occurrences: 1 year after end of treatment, death, or start of new treatment. Participants removed from protocol therapy for unacceptable AE(s) will be followed until resolution or stabilization of the AE. Follow-up assessments are listed in Table 11 of Section 6.10.

6.9 UNSCHEDULED VISITS

Unscheduled study visits may occur at any time if medically warranted. Any assessments performed (e.g., laboratory or clinical assessments) at those visits should be recorded in the eCRF.

6.10 SCHEDULE OF EVENTS

Table 8. Schedule of Procedures and Evaluations for Induction Therapy with CPX-351 and ruxolitinib

Visit Days (± 3 Days)		Screen†	Baseline‡	Treatment Period* Induction 1 and 2 (Days)																											
				1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26	27	28	29-42
Treatment Administration[A]	CPX-351			X		X		X[B]																							
	Ruxolitinib								X[C]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Informed consent		X																													
Inclusion/exclusion criteria		X																													
Medical history		X																													
Medication history[D]		X		X																										X	
Physical Examination[E]		X	X	X													X													X	
Spleen assessment[F]			X																												
Chest X-ray/CT			X																												
ECG			X																												
ECHO/MUGA			X																												
Hematology[G]			X	X		X		X		X		X		X		X		X		X		X		X		X		X		X	
Blood chemistry[H]			X	X		X		X									X													X	
Urinalysis			X	X																											
Coagulation			X	X																											
Pregnancy test[I]			X																											X	
Bone Marrow Exam			X																												X[K]
Response Assessments[K]																															X
AE assessment[L]			X	X----------X																											

† To be performed within 4 weeks of baseline.
‡To be performed within 14 days of cycle 1, Day 1.
*Treatment cycles are 28 days; however the treatment cycle interval may be increased due to toxicity according to the dose modification guidelines provided in Section 5.2.5. If the interval is increased, all procedures should be performed based on the new dosing schedule.
[A] For induction, CPX-351 is administered at a dose of 100 units/m^2 (IV over 90 minutes). If re-induction is clinically indicated, CPX-351 is administered at a dose of 100 units/m^2. Ruxolitinib will be self-administered orally at the assigned dose level for the phase I portion of the trial. The phase II portion of the study will open for enrollment once the MTD/RP2D for ruxolitinib is identified, in which case ruxolitinib will be self-administered at the fixed MTD/RP2D.

[B] CPX-351 is given on day 5 for initial induction only. If re-induction is clinically indicated, then CPX-351 administration will occur only on days 1 and 3.
[C] Ruxolitinib is started on day 6 of initial induction only. If re-induction is clinically indicated, then ruxolitinib will be administered starting on day 4.
[D] For concomitant medications – enter new medications started during the trial through the end of study visit. Record all medications taken for grade 3 and 4 SAEs as defined in Section 8.6.
[E] All physical exams will include assessing weight, vital signs, and ECOG performance status. Height will be measured at screening visit only.
[F] Spleen assessment will be performed at baseline and then as clinically indicated. Spleen assessment should be performed using an abdomen ultrasound (CT/MRI imaging is acceptable if done in lieu of ultrasound for clinical care). It is preferred that the same imaging modality used at baseline be used throughout the study for the same participant. All palpitations should be measured with a soft-centimeter ruler – not finger breadths.
[G] Hematology should be collected pre-dose on Day 1, and three times weekly every 28 day cycle. Hematology will include the following: hematocrit, hemoglobin, platelets, white blood cells with differential (basophils, eosinophils, lymphocytes, monocytes, neutrophils), and absolute lymphocyte count.
[H] Blood chemistry tests will include the following: creatinine, BUN, total bilirubin, Alkaline Phosphatase, AST or ALT, serum electrolytes, magnesium, calcium, and potassium, uric acid, as well as lactate dehydrogenase. Lipid panel will be collected per institutional standards at baseline or Day 1 and 8-12 weeks after the start of ruxolitinib. The lipid panel will include the following: total cholesterol, high-density lipoprotein cholesterol (HDL-C), low-density lipoprotein cholesterol (LDL-C), and triglycerides. Testing for HIV, HBV or HCV will only take place during screening.
[I] For women of reproductive potential, a urine pregnancy test should be performed within 7 days prior to first dose of trial treatment. If urine pregnancy results cannot be confirmed as negative, a serum pregnancy test performed by the local study site laboratory will be required. Pregnancy tests (serum and/or urine tests) should be repeated, if required, per institutional guidelines.
[J] A D35-D42 bone marrow is required for all study participants; however earlier bone marrow evaluation is permitted those whose counts partially recover (defined as ANC ≥ 500/μL and platelets ≥ 50,000/μL). For these exceptions, the earlier bone marrow will be used as the post-initial induction cycle marrow to assess response and eligibility for allo-HSCT and consolidation. A bone marrow biopsy by day 56 may be required for disease-free participants with an ANC < 500/μL or platelets < 20,000/μL beyond Day 42.
[K] Response to induction therapy is made on D35-D42 (or earlier if counts recover to ANC ≥ 500/μL and platelets ≥ 50,000/μL) or when treatment failure is suspected. The bone marrow assessment and the peripheral counts are not required to be performed on the same day but evaluation of blood cell counts (including peripheral blasts) must be performed within 14 days of the bone marrow assessment (D35-D42 exam)
[L] AEs and laboratory safety measurements will be graded per NCI CTCAE v5.0. All AEs, whether gradable by CTCAE or not, will also be evaluated for seriousness.

Table 9. Schedule of Procedures and Evaluations for Consolidation Therapy with CPX-351 and ruxolitinib

		Treatment Period Consolidation 1 and 2 (Days)																									
Visit Days (± 3 Days)		**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**	**15**	**16**	**17**	**18**	**19**	**20**	**21**	**22**	**23**	**24**	**25**	**26**	**27**	**28**
Treatment Administration[A]	CPX-351	X		X																									
	Ruxolitinib				X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Medication history[B]																													X
Physical examination[C]															X														X
Hematology[D]		X		X		X									X														
Blood chemistry[E]		X		X		X									X														
ECHO/MUGA[F]		X																											
Pregnancy test[G]		X													X														
Bone marrow exam																													X
Response assessments[H]																													X
AE assessment[I]		X----------																											----------X

[A] CPX-351 is administered at a fixed dose of 65 units/m^2 (IV over 90 minutes). Ruxolitinib will be self-administered orally at the assigned dose level for the phase I portion of the trial. The phase II portion of the study will open for enrollment once the MTD/RP2D for ruxolitinib is identified, in which case ruxolitinib will be self-administered at the fixed MTD/RP2D.
[B] enter new medications started during the trial through the end of trial visit. Record all medications taken for grade 3 and 4 SAEs as defined in Section 8.6
[C] All physical exams will include assessing weight, vital signs, and ECOG performance status.
[D] Hematology should be collected pre-dose on Day 1 and 3 of each consolidation cycle. Hematology will include the following: hematocrit, hemoglobin, platelets, white blood cells with differential (basophils, eosinophils, lymphocytes, monocytes, neutrophils), and absolute lymphocyte count.
[E] Blood chemistry will include the following: creatinine, BUN, total bilirubin, Alkaline Phosphatase, AST or ALT, serum electrolytes, magnesium, calcium, and potassium, uric acid, as well as lactate dehydrogenase. Lipid panel will be collected per institutional standards at baseline or Day 1 and 8-12 weeks after the start of ruxolitinib. The lipid panel will include the following: total cholesterol, high-density lipoprotein cholesterol (HDL-C), low-density lipoprotein cholesterol (LDL-C), and triglycerides.
[F] Assess LVEF by ECHO or MUGA within 7 days prior to starting each cycle of consolidation therapy if clinically indicated.
[G] For women of reproductive potential, a urine pregnancy test should be performed within 7 days prior to first dose of trial treatment. If urine pregnancy results cannot be confirmed as negative, a serum pregnancy test performed by the local study site laboratory will be required. Pregnancy tests (serum and/or urine tests) should be repeated, if required, per institutional guidelines.
[H] Response to consolidation therapy is made on the first day when all criteria for ≥ALR-P or treatment failure are met. Peripheral blood counts used for a response evaluation must be performed within 14 days of the bone marrow assessment.
[I] AEs and laboratory safety measurements will be graded per NCI CTCAE v5.0. All AEs, whether gradable by CTCAE or not, will also be evaluated for seriousness.

Table 10. Schedule of Procedures and Evaluations for Maintenance Therapy with Ruxolitinib

	Maintenance Treatment Period Up to 8 Cycles (Days)																										
Visit Days (± 3 Days)	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**	**15**	**16**	**17**	**18**	**19**	**20**	**21**	**22**	**23**	**24**	**25**	**26**	**27**	**28**
Treatment Administration[A] Ruxolitinib	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Medication history[B]																												X
Physical Examination[C]	X													X														X
Hematology[D]	X													X														X
Blood chemistry[E]	X													X														X
Bone Marrow Exam																												X[F]
Response Assessments																												X
AE assessment[G]	X----------																											----------X

[A] Ruxolitinib will be administered orally, twice a day (PO, b.i.d) at the assigned dose level starting for the phase I portion of the trial. The phase II portion of the study will open for enrollment once the MTD/RP2D for ruxolitinib is identified, in which case ruxolitinib will be administered at a fixed dose per the MTD/RP2D.
[B] Enter new medications started during the trial through the end of trial visit. Record all medications taken for grade 3 and 4 SAEs as defined in Section 8.6
[C] All physical exams will include assessing weight, vital signs, and ECOG performance status.
[D] Hematology will include the following: hematocrit, hemoglobin, platelets, white blood cells with differential (basophils, eosinophils, lymphocytes, monocytes, neutrophils), and absolute lymphocyte count.
[E] Blood chemistry will include the following: creatinine, BUN, total bilirubin, Alkaline Phosphatase, AST or ALT, serum electrolytes, magnesium, calcium, and potassium, uric acid, as well as lactate dehydrogenase.
[F] Participants will undergo bone marrow biopsy/aspirate every 4 months while on maintenance therapy. Provider discretion will allow for additional marrows if clinically indicated.
[G] AEs and laboratory safety measurements will be graded per NCI CTCAE v5.0. All AEs, whether gradable by CTCAE or not, will also be evaluated for seriousness.

	Table 11. Schedule of Procedures and Evaluations for End of Treatment and Follow-up (does not apply to transplant participants*)							
Visit Days (± 10 Days)	**EOT†**	**Follow-up (months)**						
		1	**3**	**5**	**6**	**7**	**9**	**12**
Participant status report[A]	X	X	X	X		X	X	X
CBC with differential[B]	X	X	X	X		X	X	X
Blood chemistry[C]	X		X[D]----------X					
Bone Marrow Exam[E]	X		X----------X					
AE assessment[F]	X	X			X			
	† Perform EOT assessment for any participant that completes or discontinues treatment early. Evaluations must be completed within 30 days after termination and prior to allo-HSCT or the initiation of any salvage therapy, if not performed within the last 30 days. [A] Participants may be contacted by phone, and survival status will be collected and documented. Hematology and biochemistry labs and bone marrow are not required if participants are called by phone for status. [B] Hematology will include the following: hematocrit, hemoglobin, platelets, white blood cells with differential (basophils, eosinophils, lymphocytes, monocytes, neutrophils), and absolute lymphocyte count. [C] Blood chemistry will include the following: creatinine, BUN, total bilirubin, Alkaline Phosphatase, AST or ALT, serum electrolytes, magnesium, calcium, and potassium, uric acid, as well as lactate dehydrogenase. [D] Perform monthly only if abnormality(ies) persists at the end of the Treatment Period. Perform until abnormality(ies) returns to baseline, or the initiation of new therapy and/or relapse (whichever is earliest). [E] An end of treatment bone marrow exam is not required; however, tissue may be collected from any procedure performed if clinically indicated. For participants in CR or CRi a bone marrow exam may be performed at any time that there is a suspicion of relapse. For participants in CR, perform if peripheral blood counts fall below 1000/µL for ANC or 100,000/µL for platelets for >1 month. For participants in CRi perform if counts fall significantly below peak recovery levels. If the peripheral blood counts in a participant with a CRi recover to CR levels (≥1000/µL for ANC and ≥100,000/µL for platelets), perform a bone marrow evaluation within 14 days to confirm CR. For CRi, if increased blasts are noted, a bone marrow biopsy should be performed at time of count recovery or 7 to 10 days later if this has not occurred to differentiate between residual disease versus marrow regeneration before a treatment decision is made. Following the first year of follow up, record relapse information, including any bone marrow evaluations. Not required following the initiation of new therapy and/or relapse. [F] Assess AEs that were ongoing at the time of discontinuation. Do not record any new AEs. AEs that persist without evidence of recovery for >30 days are considered permanent sequelae and do not require further follow-up. * Transplant patients should be followed for survival and disease status.							

7. EFFICACY MEASURES

7.1 DEFINITION OF EFFICACY MEASURES

Assessment of clinical response will be made according to the Post-Myeloproliferative Neoplasm Acute Myeloid Leukemia Consortium (2012 MPN-BP criteria)[45] or European LeukemiaNet (ELN) recommendations as indicated.[46] The major criteria for judging response will include physical examination and examination of blood and bone marrow. Relevant laboratory studies that are abnormal prior to study will be repeated according to the study schedule to document the degree of maximal response.

7.2 EFFICACY CRITERIA FOR DISEASE RESPONSE

During the Treatment Phase participants will be assessed for response according to the following response criteria definitions:

7.2.1 MPN-AP/BP RESPONSE CRITERIA (PER 2012 MPN-BP CRITERIA[45])

Complete Molecular Response (CMR)	
Description:	Complete remission of both leukemia and MPN without detectable molecular markers associated with either leukemia or MPN
Hematologic profile:	ANC > 1000/µL Hemoglobin > 10 g/dL Platelets > 100,00/µL Absence of leukoerythroblastosis[1]
Spleen†:	Non-palpable
Bone Marrow:	Cellularity appropriate for age Resolution of abnormal morphology Blasts ≤ 5%[2] ≤ grade 1 marrow fibrosis
Cytogenetics	Normal karyotype[3]
Molecular markers	Loss of any previously documented markers associated with either the leukemic or MPN clone[4]
Complete Cytogenetic Response (CCR)	
Description:	Complete remission of both leukemia and MPN with detectable molecular markers associated with either leukemia or MPN
Hematologic profile:	ANC > 1000/µL Hemoglobin > 10 g/dL Platelets > 100,00/µL Absence of leukoerythroblastosis[1]
Spleen†:	Non-palpable
Bone Marrow:	Cellularity appropriate for age Resolution of abnormal morphology Blasts ≤ 5%[2] ≤ grade 1 marrow fibrosis
Cytogenetics:	Normal karyotype[3]
Molecular markers:	Residual expression of MPN/leukemia-associated gene mutations (e.g. JAK2V617F, MPL515L/K)[4]
Acute Leukemia Response-Complete (ALR-C)	
Description:	Complete remission of leukemia with residual MPN features

Hematologic profile:	Absence of blasts[1]
Spleen†:	< 25% increase in spleen size by palpation or imaging if baseline spleen < 10 cm or < 50% increase if baseline spleen ≥ 10 cm
Bone Marrow:	Blasts ≤ 5%[2]
Cytogenetics:	Loss of cytogenetic abnormality associated with leukemic clone, may have persistent abnormality associated with MPN
Molecular markers:	Loss of any previously identified markers in leukemic clone, may have persistent molecular markers associated with MPN[4]
Acute Leukemia Response-Partial (ALR-P)	
Description:	Decrease in leukemic burden but without resolution of peripheral blood or bone marrow blasts and residual MPN features
Hematologic profile:	> 50% reduction in blasts
Spleen†:	< 25% increase in spleen size by palpation or imaging if baseline spleen < 10 cm or < 50% increase if baseline spleen ≥ 10 cm
Bone Marrow:	> 50% reduction in blasts
Cytogenetics:	No new abnormalities
Molecular markers:	No new abnormalities
Stable Disease (SD)	
Description:	Failure to achieve at least ALR-P, but no evidence of progression for at least 8 weeks.
Progressive Disease (PD)	
Description:	Progression of leukemia and/or background MPN
Hematologic profile:	For patients with 10–20% blasts: ≥ 50% increase to > 20% blasts
Spleen†:	> 25% increase in spleen size by palpation or imaging if baseline spleen < 10 cm or > 50% increase if baseline spleen ≥ 10 cm
Bone Marrow:	For patients with 5–10% blasts: ≥ 50% increase to > 10% blasts
Cytogenetics:	Does not apply
Molecular markers:	Does not apply

*Adapted from Mascarenhas et al (2012)[45]
[1] absence of peripheral blood blasts by morphologic review of the peripheral smear on two occasions separated by at least 2 weeks
[2] blast percentage can be assessed by morphologic review of aspirate and, in cases of inaspirate marrows, immunohistochemical staining of the marrow for CD34+, CD117+ is acceptable
[3] normal karyotype by conventional cytogenetics in peripheral blood or bone marrow aspirate; if a cytogenetic abnormality is detected prior to treatment it must not be identified at time of assessment; if an abnormality is detected at baseline by FISH it must be absent by FISH at time of assessment
[4] absence or loss of evidence of mRNA transcript by quantitative PCR assay performed in a validated laboratory, this will also include any exploratory biomarkers determined to be positive prior to therapy.
† Evaluation of the spleen should be performed on physical exam. If palpable, measurements should be recorded using a soft-center ruler and not finger breadths. Imaging of the spleen should be performed according to institutional standards (e.g., ultrasound, MRI, CT); however, the same imaging modality used at baseline should be used throughout the study for the same participant.

7.2.2 AML RESPONSE CRITERIA DEFINITIONS (PER ELN CRITERIA)

CR without minimal residual disease (CR_{MRD-}):	• CR with negativity for a genetic marker, or CR with negativity by MFC or NGS

Morphologic Complete Remission (CR):	• Absolute neutrophil count ≥1 x 10^9/L (1000/µL); • Platelet count ≥ 100 x 10^9/L (100,000/µL); • Independence of red cell transfusions • Bone marrow blasts < 5%; • Absence of circulating blasts • Absence of blasts with Auer rods; • Absence of extramedullary disease;
CR with incomplete recovery (CRi):	• All CR criteria except for residual neutropenia (< 1 x 10^9/L [1000/µL) or thrombocytopenia (< 100 X 10^9/L [100,000/µL).
Morphologic leukemia-free state:	• Bone marrow blasts < 5%; • absence of blasts with Auer rods • absence of extramedullary disease • Count of at least 200 nucleated cells or at least 10% cellularity
Partial Remission (PR):	• All hematologic criteria of CR; bone marrow blast percentage of 5% to 25%; at least 50% decrease from pretreatment bone marrow blast percentage
Stable Disease (SD):	• Absence of CR_{MRD}-, CR, CRi, and PR; and criteria for PD not met. Period of stable disease should last at least 3 months.
Progressive Disease (PD):	Evidence for an increase in bone marrow blast percentage and/or increase of absolute blast counts in the blood: • >50% increase in marrow blasts over baseline (a minimum 15% point increase is required in cases with <30% blasts at baseline; or persistent marrow blast percentage of >70% over at least 3 mo; without at least a 100% improvement in ANC to an absolute level (>0.5 × 10^9/L [500/µL], and/or platelet count to >50 × 10^9/L [50 000/µL] nontransfused); or, in general, at least 2 cycles of a novel agent should be administered • >50% increase in peripheral blasts (WBC × % blasts) over baseline to >25 × 10^9/L (>25 000/µL) (in the absence of differentiation syndrome); or • New extramedullary disease

7.2.2.1 *Treatment Failure Definitions*

Primary refractory disease: No CR or CRi after 2 courses of intensive induction treatment; excluding participants with death in aplasia or death due to indeterminate cause

Death in aplasia:	Deaths occurring ≥7 d following completion of initial treatment while cytopenic; with an aplastic or hypoplastic bone marrow obtained within 7 d of death, without evidence of persistent leukemia
Death from indeterminate cause:	Deaths occurring before completion of therapy, or <7 d following its completion; or deaths occurring ≥7 d following completion of initial therapy with no blasts in the blood, but no bone marrow examination available

7.2.2.2 *Relapse Definition*

Hematological relapse (after CR_{MRD}-, CR, CRi):	Bone marrow blasts ≥5%; or reappearance of blasts in the blood; or development of extramedullary disease
Molecular relapse (after CR_{MRD}-):	If studied pretreatment, reoccurrence of MRD as assessed by RT-qPCR or by multiparametric flow cytometry

7.3 OBJECTIVE RESPONSE RATE

For the primary endpoint, ORR is defined as the proportion of efficacy-evaluable participants who achieve a response of ALR-P or greater (i.e., best response of ALR-P, ALR-C, CCR, or CMR, according to the 2012 MPN-BP response criteria) during the induction or re-induction cycles.

7.4 COMPOSITE COMPLETE REMISSION (CCR)

Composite complete remission (CCR) rate is the proportion of efficacy-evaluable participants who achieve a response of CRi or greater (based on the 2017 ELN recommendations for AML) during the induction or re-induction cycles.

7.5 OVERALL SURVIVAL

Defined for all participants who have at least one exposure to both study agents and measured from Cycle 1 Day 1 to the date of death from any cause or the date the participant was last known to be alive. Participants not known to have died at last follow-up (i.e., 1 year after the last dose of study drug) are censored on the date they were last known to be alive.

7.6 EVENT-FREE SURVIVAL (EFS)

Defined for all participants who have at least one exposure to both study agents. EFS will be measured from start of induction therapy (i.e., Cycle 1 Day 1) to the date of primary refractory disease, disease progression, hematologic relapse, or death from any cause, whichever of these events occurs first. Participants not known to have any of these events will be censored on the date they were last examined. [47,48]

7.7 RELAPSE-FREE SURVIVAL (RFS)

For participants who achieve ≥CRi, RFS will be measured from the date of first documented response (i.e., first occurrence of a CRi or better) to the date of hematologic relapse or death from any cause. Participants not known to have relapsed or died at time of last follow-up will be

censored on the date they were last examined (i.e., 1 year following completion of on-study therapy).

7.8 REMISSION DURATION

Only participants who achieve ≥CRi will be assessed for remission duration, which will be measured from the date of first documented response (i.e., first occurrence of a CRi or better) to the date of hematologic relapse. Participants not known to have relapsed at time of last follow-up will be censored on the date they were last examined and deaths before relapse will be considered a competing risk.

7.9 STEM CELL TRANSPLANT

The number and percentage of participants who undergo allo-HSCT will be computed among all participants who have at least one exposure to both study agents.

7.10 MRD NEGATIVITY

Only participants with a reported MRD assessment (negative or positive) from the local laboratory at the investigator site will be used in the calculation of MRD response rate, defined as the proportion of participants who have an MRD negative status (based on prior mutational status before initiating study treatment). MRD assessments (MFC or NGS) will occur at the end of induction or re-induction, end of consolidation, and end of maintenance.

8. SAFETY

8.1 SPECIFICATION OF SAFETY PARAMETERS

The site investigator is responsible for monitoring the safety of participants who have enrolled in the study. Safety assessments will be based on medical review of adverse events and the results of safety evaluations at specified time points as described in Section 6.10, Schedule of Events. Any clinically significant adverse events persisting at the end of treatment visit will be followed by the Investigator until resolution/stabilization or death, whichever comes first. Any patient that receives at least one dose of the study drug will be evaluated for safety.

8.2 DEFINITIONS

8.2.1 ADVERSE EVENT (AE)

An adverse event is defined as any undesirable physical, psychological or behavioral effect experienced by a participant during their participation in an investigational study, in conjunction with the use of the investigational product, whether or not considered intervention-related (21 CFR 312.32 (a)). In general, this includes signs or symptoms experienced by the participant from the time of eligibility confirmation to completion of the study.

AEs may include, but are not limited to:

- Subjective or objective symptoms spontaneously offered by the participant and/or observed by the Investigator or medical staff.
- Clinically significant laboratory abnormalities.
- A significant worsening of the participant's condition from study entry.
- Disease signs and symptoms and/or laboratory abnormalities existing prior to the use of the study treatment that resolve but then recur after treatment.
- Disease signs and symptoms and/or laboratory abnormalities existing prior to the use of the study treatment which increase in frequency, intensity, or a change in quality after treatment.

8.2.2 SERIOUS ADVERSE EVENT (SAE)

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

- Death,
- A life-threatening adverse event,
- In-patient hospitalization or prolongation of existing hospitalization,
- A persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions, or
- A congenital anomaly/birth defect.

Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered serious when, based upon appropriate medical judgment, they may jeopardize the participant and/or participant may require medical or surgical intervention to prevent one of the outcomes listed in this definition. Examples of such medical events include:

- Allergic bronchospasm requiring intensive treatment in an emergency room or at home,
- Blood dyscrasias or convulsions that do not result in in-patient hospitalization, or

- The development of drug dependency or drug abuse.

Given the nature of myeloid malignancies and use of therapeutics that can produce cytopenias, transfusion support and transfusion-related activities are standard of care supportive measures. Outpatient transfusion support may not be routinely available at local or smaller community centers or in the instance of blood bank restraints/ product availability. Therefore, admissions for routine transfusion support, transfusion-related activities or transfusion reactions will not be considered a serious adverse event and will not be reported as such. Cytopenias per CTCAE criteria will continue to be assessed and reported as adverse events with the relations and clinical significance assessed by the PI/treating physician as appropriate per the protocol guidance and Clinical Trials Office Standard Operating Procedures.

8.2.3 UNANTICIPATED PROBLEMS (UP)

The Office for Human Research Protections (OHRP) considers UPs involving risks to participants or others to include, in general, any incident, experience, or outcome that meets all of the following criteria:

1. Unexpected in terms of nature, severity, or frequency given (a) the research procedures that are described in the protocol-related documents, such as the IRB-approved research protocol and informed consent document; and (b) the characteristics of the participant population being studied;
2. Related or possibly related to participation in the research ("possibly related" means there is a reasonable possibility that the incident, experience, or outcome may have been caused by the procedures involved in the research); and
3. Suggests that the research places participants or others at a greater risk of harm (including physical, psychological, economic, or social harm) than previously known or recognized.

This study will use the OHRP definition of UP.

8.2.4 SEVERITY OF EVENT

The site investigator will grade the severity of each AE using, when applicable, the current version of the CTCAE v5.0. In the event of an AE for which no grading scale exists, the Investigator will classify the AE as defined below:

Grade 1:	Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated.
Grade 2:	Moderate; minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental ADL
Grade 3:	Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care ADL.
Grade 4:	Life-threatening consequences; urgent intervention indicated.
Grade 5:	Death related to AE.

Note: a semi-colon indicates 'or' within the description of the grade.

8.2.5 ASSESSMENT OF CAUSALITY RELATIONSHIP TO STUDY AGENT

For all collected AEs, the clinician who examines and evaluates the participant will determine the AE's causality based on temporal relationship and his/her clinical judgment. The degree of certainty about causality will be graded using the categories below.

Definitely Related:	There is clear evidence to suggest a causal relationship, and other possible contributing factors can be ruled out.
Potentially Related:	The event follows a reasonable temporal sequence from administration of the study drug, the event follows a known response pattern to the study drug based on the known pharmacology of the study drug, the event is reasonably related to the effect of the study drug
Unrelated	The event has no temporal relationship to study drug administration (too early or late or study drug not taken), or there is a reasonable causal relationship between the AE and another drug, concurrent disease, or circumstance.

8.3 EXPECTEDNESS

Site investigators will be responsible for determining whether an AE is expected or unexpected. An AE will be considered unexpected if the nature, severity, or frequency of the event is not consistent with the risk information previously described for the study agent.

8.4 ADVERSE EVENT LIST(S)

8.4.1 ADVERSE EVENT LIST FOR CPX-351

Detailed information about the risks and expected AEs of CPX-351 may be found in the manufacturer's IB.

In brief, the most frequent (incidence ≥ 2%) SAEs were infections and infestations, blood and lymphatic system disorders (e.g., febrile neutropenia, pancytopenia), respiratory, thoracic and mediastinal disorders (e.g., respiratory failure), cardiac disorders (i.e., cardiac failure), and nervous system disorders (e.g., syncopy). Results of a pooled safety analysis revealed that among 375 patients receiving CPX-351, the most common AEs (incidence ≥ 10%) observed were febrile neutropenia, nausea, diarrhea, constipation, edema (peripheral), rash, fatigue, edema, nausea, mucositis, diarrhea, constipation, musculoskeletal pain, fatigue, abdominal pain, dyspnea, , decreased appetite, headache, cough, and chills..

AEs leading to discontinuation on the CPX-351 in clinical trials included: prolonged cytopenias, infection, cardiotoxicity, respiratory failure, hemorrhage (GI and CNS), renal insufficiency, colitis, and generalized medical deterioration.

8.4.2 ADVERSE EVENT LIST FOR RUXOLITINIB

Detailed information about the risks and expected AEs of ruxolitinib may be found in the manufacturer's package insert. The safety of ruxolitinib was assessed across six clinical studies in which 617 patients with PMF or PV were treated with ruxolitinib. The most frequent AEs experienced include bruising, dizziness, headache, fatigue, and pruritus. Other AEs include thrombocytopenia, anemia, and neutropenia.

Ruxolitinib has not been well characterized in patients with post-MPN AML. In a phase 2 study of ruxolitinib to treat 38 patients with relapsed/refractory AML, ruxolitinib was well tolerated.[36] Of these 38 patients, only 4 developed grade 3 or greater toxicities. One had severe

thrombocytopenia at the time of study enrollment, and died of an intracranial hemorrhage while on study. Three patients had grade 1 or 2 toxicity, and the remaining patients did not have any side effects that were judged to be related to the study drug.

8.5 ADVERSE EVENT ASSESSMENT AND FOLLOW-UP

The occurrence of an UP, AE or SAE may come to the attention of study personnel during study visits and interviews of a study participant presenting for medical care, or upon review by a study monitor. All AEs including local and systemic reactions not meeting the criteria for SAEs will be captured on the appropriate CRF, except for grade 3 nausea and vomiting that resolves within 72 hours, and infection.

Information to be collected includes event description, time of onset, clinician's assessment of severity, seriousness, expectedness, relationship to study product (assessed only by those with the training and authority to make a diagnosis), and date of resolution/stabilization of the event. All AEs occurring while on study must be documented appropriately regardless of relationship. All AEs will be followed to adequate resolution.

Any medical condition that is present at the time that the participant is screened will be considered as baseline and not reported as an AE. However, if the study participant's condition deteriorates at any time during the study, it will be recorded as an AE.

Changes in the severity of an AE will be documented to allow an assessment of the duration of the event at each level of severity to be performed. AEs characterized as intermittent require documentation of onset and duration of each episode.

At each study visit, the Investigator will inquire about the occurrence of AE/SAEs since the last visit. Events will be followed for outcome information until resolution or stabilization.

The Investigator will record all reportable events with start dates occurring any time after informed consent is obtained until 7 (for AEs) or 90 days (for SAEs) after the last day of study participation or until the participant receives alternative therapy for their AML, whichever occurs first. Any SAE that occurs after treatment with alternative therapy will be reported only if the Investigator or current treating physician has assessed the SAE as related to the study treatment. Adverse events will be evaluated using the current version of the CTCAE v5.0.

8.6 REPORTING PROCEDURES

8.6.1 OSU IRB REPORTING OF UNANTICIPATED PROBLEMS AND ADVERSE EVENTS

The OSU principal investigator is required to submit all unexpected and serious adverse events to the OSU IRB within the institutional required timeframe. All AE/SAEs will be reported to the Data and Safety Monitoring Committee (DSMC) at the quarterly DSMC review meetings; however, the investigator determines corrective action is necessary, and "ad hoc" DSMC meeting will be called.

Fatal adverse events related to treatment which are unexpected must be reported to the OSU IRB and the DSMC within the required time frame per institutional, IRB, and DSMC policies. Fatalities not related to the study must also be reported within the institutional required timeframe.

8.6.2 CENTRAL REPORTING OF ADVERSE EVENTS FOR MULTICENTER STUDIES

NOTE: External participating sites are not permitted to report directly to the OSU IRB or FDA. All external site SAEs are to be reported to the OSU Principal Investigator and Multi-Center Trial Program (MCTP). The MCTP will facilitate submission of external site SAEs to the OSU IRB and FDA.

All serious adverse events (SAEs) and other adverse events must be recorded on case report forms. In addition, all SAEs must be reported to the OSU Principal Investigator and MCTP within 24 hours of knowledge of the event using the FDA MedWatch 3500A mandatory reporting form. External participating sites must also submit the "SAE Submission Form" cover sheet (refer to the Supplemental Forms Document).

Copies of de-identified source documentation pertaining to the SAE must be submitted to OSU. If a patient is permanently withdrawn from the study because of a SAE, this information must be included in the initial or follow-up SAE report form.

All SAEs must be submitted to the local IRB per local IRB and institutional policy.

Upon request of additional data or information that is deemed necessary must be reported to OSU as soon as possible but no later than 5 calendar days.

8.6.3 MEDWATCH REPORTING

The Sponsor-investigator is required to report AEs to the FDA through the MedWatch reporting program, even if the trial involves a commercially available agent. Adverse events to be reported include any UPs (i.e., not listed in the package insert) and any SAEs with a suspected association to the investigational product.

Adverse events that occur during clinical studies are to be reported to FDA as specified in the investigational new drug/biologic regulations using Form FDA 3500A, the Mandatory Reporting form (available here). A copy of Form FDA 3500 and supporting materials will be kept on file in the study regulatory binder.

8.6.4 SPONSOR OR ADDITIONAL REPORTING REQUIREMENTS

SAEs treatment-emergent for CPX-351 must be reported to Jazz Pharmaceuticals at AEReporting@jazzpharma.com.

Unexpected fatal or life-threatening experiences associated with the use of the study treatment will be reported to FDA as soon as possible, but in no event later than 7 calendar days after initial receipt of the information. All other serious unexpected experiences associated with the use of the study treatment will be reported to FDA as soon as possible, but in no event later than 15 calendar days after initial receipt of the information. All events reported to the FDA will also be reported to Jazz Pharmaceuticals at AEReporting@jazzpharma.com and SafetyReporting@Incyte.com as provided in the Research Agreement within 24 hours of reporting.

8.6.5 REPORTING OF PREGNANCY

To ensure participant safety, each pregnancy in a participant on study treatment must be reported within 24 hours of learning of its occurrence. The pregnancy should be followed to determine outcome, including spontaneous or voluntary termination, details of the birth, and the presence or absence of any birth defects, congenital abnormalities, or any pregnancy- or childbirth-related and/or newborn complications.

The pregnancy should be recorded on a CRF and reported by the site investigator to the Sponsor-investigator. Sponsor-investigator will report any on-study pregnancies to the drug manufacturer. Pregnancy follow-up should be reported using the same CRF. Any SAE(s) experienced during pregnancy must be reported.

If while on study treatment a participant's sexual partner becomes pregnant, the pregnancy and pregnancy outcomes must also be reported as described above. Consent to report information regarding the pregnancy should be obtained from the pregnant individual.

9. STATISTICAL CONSIDERATIONS

Refer to Section 2.1, Description of the Study Design for a detailed description of the study design and endpoints.

9.1 ANALYSIS POPULATIONS

A safety analysis set includes all participants who have at least one exposure to both study agents, regardless of how long they stay on study drug. Reason(s) for going off study treatment will be collected (and recorded in an eCRF) for every participant.

The phase I dose-determining set (DDS) consists of a subset of participants in the safety analysis set who have received all 3 planned infusions of CPX-351 and received ruxolitinib (at any dose) for at least 17 days during induction (~75% of the 23 days that ruxolitinib is scheduled for) or discontinue earlier due to DLT.

The phase II efficacy-evaluable population will include all subjects who have at least one exposure to both study agents and at least one response assessment (necessary to determine the response category, as documented for general adult AML[46] or for MPN-BP[45]).

The eligible population for analysis of overall survival, event-free survival, and the proportion of participants proceeding to transplant will consist of participants who have at least one exposure to both study agents (which is the same criteria as the safety analysis set).

9.2 DESCRIPTION OF STATISTICAL METHODS

9.2.1 PHASE I

The Maximum Tolerated Dose (MTD) of ruxolitinib in combination with CPX-351 is selected as the dose whose DLT probability is closest to the target DLT rate of 25% after applying isotonic regression to the observed dose-level-specific DLT rates. According to the "keyboard" design's decision rules (www.trialdesign.org), a cohort of 3 DLT-evaluable participants will be assessed before a decision is made on whether to escalate, de-escalate, or maintain the current dose level when treating the next cohort. The study will start at ruxolitinib dose level 1 (10 mg PO, *b.i.d.*) and a total of 24 participants will be evaluated for DLT status.

9.2.2 PHASE II

A Simon's two-stage minimax design achieving 80% power at a 5% false positive rate will be implemented. For a historical control estimate of ORR, we considered the 53% observed in the efficacy-evaluable population of a Phase I study of decitabine and ruxolitinib in MPN-AP/–BP patients and decided on 40% to account for our study's (i) more stringent definition of PR (and thus ORR) that requires >50% reduction in blast percentage in the bone marrow and peripheral blood (rather than just the peripheral blood) and (ii) shorter ORR evaluation time of 2 months.[39]

To formally evaluate the efficacy of the combination of CPX-351 and ruxolitinib, a null hypothesis that ORR ≤ 0.40 will be tested against a one-sided alternative hypothesis that ORR ≥ 0.65. In the first stage, 12 participants will be accrued. If there are 5 or fewer responses in these 12 participants by the end of induction or re-induction therapy, the study will be stopped. Otherwise, 14 additional participants will be accrued for a total of 26 participants. The null hypothesis will be rejected and the combination therapy deemed promising if 15 or more

responses are observed during induction or re-induction cycles among the 26 participants. Note that Phase I participants treated at the MTD/RP2D of ruxolitinib (when combined with CPX-351) can be included in the Phase II portion of this study.

9.2.3 ANALYSIS OF PRIMARY ENDPOINTS

The primary objective of the phase I portion of the study is to determine the MTD of ruxolitinib in combination with CPX-351 in participants with MPN-AP/BP as measured by the incidence of dose limiting toxicities for each dose level (see Section 5.2.1).

The primary endpoint of the phase II portion of the study is ORR, as defined in Section 7.4. We will compute the proportion of efficacy-evaluable participants achieving ORR and the exact binominal 95% confidence interval.

9.2.4 ANALYSIS OF THE SECONDARY ENDPOINTS

For the secondary endpoints, we will estimate the incidence of each treatment-related toxicity and provide exact 95% confidence intervals. Each toxicity event will be tabulated and summarized by severity and major organ site according to the CTCAE v5.0.

Time-to-event analyses (e.g., Kaplan-Meier curves or cumulative incidence curves) will be used to evaluate event-free survival, relapse-free survival, overall survival, and remission duration. A point estimate and exact 95% confidence interval will be computed for the proportion of participants who undergo an allo-HSCT.

We will assess all AEs and SAEs per CTCAE v5.0 as noted on the enrolled subjects at the end of 30 days and 6 months. These events will be assessed by the study team to determine overall safety of this study population.

9.2.5 ANALYSIS OF THE EXPLORATORY ENDPOINT

The relationships between MRD status, assessed by either MFC or NGS, and participant characteristics, response to study treatment, and clinical outcomes will be examined using Fisher's exact test and regression-based analyses (e.g., logistic regression or Cox regression).

Among the efficacy-evaluable population, the evaluation of exploratory responses, ≥CRi and CCR (per ELN criteria [defined in Sections 7.2.2 and 7.4]), will be computed with exact binominal 95% confidence interval.

9.2.6 PLANNED INTERIM ANALYSES

In the phase II part of the study, an interim analysis for futility will be conducted according to Simon's 2-stage minimax design after 12 participants are enrolled and their clinical outcomes are available for the induction and re-induction cycles. The accrual will be temporarily suspended after 12 participants until the interim analysis is complete. Note that phase I participants with MPN-AP/BP treated at the MTD/RP2D for ruxolitinib will be counted as part of this phase II stage-one group. If more than 12 of the 24 phase I participants are treated at the MTD/RP2D, the clinical responses of the first 12 participants (according to enrollment order) will be evaluated for Simon's stage-one analysis.

9.2.6.1 *Stopping Rules*

The overall study will be paused, and appropriate authorities (e.g., IRB, OSU DSMC) notified if the following events occur:

- Life-threatening grade 4 toxicity attributable to protocol therapy that is unmanageable or unexpected.
- Death suspected to be related to study drugs.

To insure long-term safety of the MTD/RP2D established in phase I, the phase II part of the study will have continuous toxicity monitoring and a stopping rule for study drug-related Grade 4 or higher toxicity per the CTCAE v5.0. The boundary was derived using the method of Ivanova et al[49] with the incidence ≤ 10% being acceptable and ≥ 30% unacceptable. If the true study drug-related Grade ≥4 toxicity rate is 10%, the probability of early stopping is 30%. If the true study drug-related Grade ≥4 toxicity rate is 30%, the probability of early stopping is 96%.

Table 12 shows the sequential boundaries for Phase II early stopping to be used in this study. Specifically, the trial will be stopped if the number of study drug-related Grade ≥4 toxicities is equal to or exceeds b_n out of n participants with completed follow-up.

Table 12. Sequential boundaries for toxicity monitoring

Number of Patients, n	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20
Boundary, b_n	-	2	2	2	2	2	2	3	3	3	3	3	3	4	4	4	4	4	4	4
Number of Patients, n	21	22	23	24	25	26														
Boundary, b_n	5	5	5	5	5	5														

The incidence of study drug-related Grade 4 or higher toxicity will be estimated and each toxicity event will be tabulated and summarized by severity and major organ site according to the CTCAE v5.0. In real time, we will conduct a comprehensive toxicity evaluation and consult with the OSU DSMC for guidance on possible modifications of the protocol, including dose modification and/or changes in eligibility criteria.

9.3 SAMPLE SIZE, POWER, ACCRUAL RATE AND STUDY DURATION

9.3.1 SAMPLE SIZE AND POWER

9.3.1.1 *Phase I*

A total of 24 participants will be enrolled at OSU and other collaborating study sites. Since this is a phase I trial using the "Keyboard" design, a traditional sample size and power analysis was not performed. A simulation was conducted to evaluate operating characteristics of the "Keyboard" design with the target DLT rate of 25%, acceptable toxicity probability interval of 0.20-0.30, and the sample size of 24 participants. The following table shows four hypothetical toxicity scenarios (i.e., true DLT rates per dose level) and corresponding operating characteristics such as the percentage of simulated trials where the MTD is correctly identified and percentage of participants that are over-dosed. Across these four scenarios, the design appropriately selects the MTD in the majority (≥ 49%) of the cases (Table 13).

Table 13. Operating characteristics of the proposed keyboard design with the target DLT probability of 25% and the sample size of 24.

	Dose Level -2	Dose Level -1	Dose Level 1 (starting dose)	Dose Level 2	Dose Level 3	Dose Level 4	Number of Patients	% Early Stopping
Scenario1								
True DLT rate	0.1	0.25	0.41	0.45	0.49	0.53		
Selection %	18.4	60.8	17.5	2.4	0.5	0.2		0.2
# Pts treated	5	9.77	7.42	1.49	0.25	0.05	24	
Scenario2								
True DLT rate	0.04	0.08	0.12	0.25	0.42	0.55		
Selection %	0	3.2	26.9	53.6	14.4	1.9		0
# Pts treated	0.33	1.99	8.81	8.73	3.44	0.7	24	
Scenario3								
True DLT rate	0.04	0.07	0.09	0.12	0.25	0.43		
Selection %	0	1.3	7.4	27.3	49.2	14.8		0
# Pts treated	0.2	1.3	5.82	7.28	6.43	2.96	24	
Scenario4								
True DLT rate	0.02	0.04	0.06	0.08	0.1	0.25		
Selection %	0	0.1	2.1	6.8	29.1	61.9		0
# Pts treated	0.07	0.68	4.61	4.98	6.36	7.3	24	

9.3.1.2 *Phase II*

A sample size of 26 participants is required to detect 65% (desired) vs. 40% (historical) response rate by the end of induction or re-induction therapy based on the Simon's two-stage minimax design with a one-sided type I error rate of 0.047 and power of 0.809. All participants treated at MTD/RP2D in the phase I portion of the trial will be included in the phase II analysis. Up to 47 participants will be enrolled with 24 participants in phase I, 26 participants in phase II, and at least 3 participants treated at the MTD/RP2D during phase I who will be carried over to the phase II portion. According to our simulation findings, at least 6 participants will likely be treated at the MTD/RP2D during phase I and thus will also be considered as a phase II participants.

9.4 HANDLING OF MISSING DATA

Every attempt will be made to obtain data at the defined time points as described in the primary and secondary endpoints. For time points that have no data, we will evaluate whether or not the other time points can be used to fulfill the primary and secondary data. If the data are not

sufficient to analyze specific endpoints, the participant's data may be excluded entirely or partially, depending on the specific endpoints in question and in consultation with the biostatistician. No missing data will be imputed. Whenever possible, all available data will be included in the analysis. A sample size for each analysis will be clearly stated along with the reason for exclusion, if any participant is excluded from the analysis due to missing data.

10. CLINICAL MONITORING

10.1 OSU DATA & SAFETY MONITORING PLAN

The data and safety monitoring plan will involve the continuous evaluation of safety, data quality and data timeliness. Investigators will conduct continuous review of data and patient safety at their regular Disease Group meetings (at least monthly) and the discussion will be documented in minutes. For each dose level, the Principal Investigator, study coordinator, and statistician, in consultation with treating physicians as appropriate will review all toxicities at a given dose level to inform the model for dose level adjustments. The Principal Investigator of the trial will review toxicities and responses of the trial where applicable at these disease center meetings and determine if the risk/benefit ratio of the trial changes. Frequency and severity of adverse events will be reviewed by the Principal Investigator and compared to what is known about the agent/device from other sources; including published literature, scientific meetings and discussions with sponsors, to determine if the trial should be terminated before completion. Serious adverse events will be reviewed by the OSUCCC Data and Safety Monitoring Committee (DSMC). The Principal Investigator will also submit progress reports that will be reviewed by the committee per the DSMC plan. All reportable SAEs will be reported to the IRB of record as per the policies of the IRB.

Mandatory safety and trial review teleconferences will be scheduled and moderated by the Multi-Center Trial Program (MCTP). All sites involved in the study are expected to have a representative present for every call to review and discuss patients on study and other applicable agenda items. Meeting minutes will be used to document each teleconference. The minutes will be stored in the MCTP protocol files. Teleconferences must minimally be held monthly and may be held more frequently, as needed. For studies closed to accrual with patients expected to remain on long-term treatment and/or follow-up, teleconferences may be extended to occur every two months or quarterly. Decreasing frequency of teleconferences requires OSU PI and MCTP approval.

10.2 CLINICAL DATA & SAFETY MONITORING

The OSU Investigator is ultimately, singularly responsible for overseeing every aspect of the investigation, including design, governing conduct at all participating sites, and final analysis of study data.

If monitoring is required, then monitoring visits will be performed during the study to ensure that the rights and well-being of human participants are protected, that the reported trial data are accurate, and that the conduct of the trial is in compliance with the protocol, GCP, and applicable regulatory requirements. In this cases, details of monitoring activities, including designation of assigned monitoring entities, scope of monitoring visits, timing, frequency, duration of visits, and visit reporting, will be included in a separate TSMP.

If monitoring is required, then the Investigator agrees that the monitor will be permitted to conduct monitoring visits at appropriate intervals. The Investigator agrees to provide all relevant information and documentation as requested by the monitor, including access to all original study documents and source data, including access to electronic medical records and/or source documents if necessary. The monitor will conduct source data review and verification as outlined in the TSMP, and following each visit will generate a report summarizing the visit findings.

In the absence of a formal monitoring plan, the Investigator may work with his/her study team to conduct and document internal monitoring of the study to verify protection of human participants, quality of data, and/or ongoing compliance with the protocol and applicable regulatory requirements.

If at any time Investigator noncompliance is discovered at OSU or any participating site, the Sponsor-investigator shall promptly either secure compliance or end the Investigator's participation in the study.

Independent audits will be conducted by the OSU DSMC to verify that the rights and well-being of human participants are protected, that the reported trial data are accurate, that the conduct of the trial is in compliance with the protocol and applicable regulatory requirements, and that evidence of ongoing investigator oversight is present.

10.3 QUALITY ASSURANCE & QUALITY CONTROL

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

The Sponsor-investigator, or study monitor, will verify that the clinical trial is conducted and data are generated, documented (recorded), and reported in compliance with the protocol, GCP, and the applicable regulatory requirements (e.g., Good Laboratory Practices (GLP), Good Manufacturing Practices (GMP)).

11. DATA HANDLING AND MANAGEMENT RESPONSIBILITIES

11.1 SOURCE DATA/DOCUMENTS

The Investigator is responsible for ensuring the accuracy, completeness, legibility, and timeliness of the data reported. All source documents should be completed in a neat, legible manner to ensure accurate interpretation of data. The Investigator will maintain adequate case histories of study participants, including accurate CRFs and source documentation.

11.2 PARTICIPANT & DATA CONFIDENTIALITY

The information obtained during the conduct of this clinical study is confidential, and unless otherwise noted, disclosure to third parties is prohibited. Information contained within this study will be maintained in accordance with applicable laws protecting participant privacy, including the provisions of the Health Insurance Portability and Accountability Act (HIPAA).

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

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

The study participant's contact information will be securely stored at each clinical site for internal use during the study. At the end of the study, all records will continue to be kept in a secure location for as long a period as dictated by local IRB and institutional regulations. Individual participants and their research data will be identified by a unique study identification number.

11.3 DATA COLLECTION & STORAGE: PRIVACY, CONFIDENTIALITY & SECURITY

Data collection is the responsibility of the clinical trial staff at the site under the supervision of the site Investigator. The Investigator is responsible for ensuring the accuracy, completeness, legibility, and timeliness of the data reported. Study staff will be trained with regard to these procedures.

Loss of participant confidentiality is a risk of participation. Efforts will be made to keep study participant identities confidential except as required by law. Participants' samples will be identified by code only. Specifically, each consenting participant will be assigned a unique coded identifier consisting of numbers. This identifier will be associated with the participant throughout the duration of their participation in the trial. The coded identifier will also be used to identify any participant specific samples.

Basic accrual tracking information (demographic, consent, visit information) will be captured in OSU's electronic database, OnCore. Any additional printed documents containing participant

identifiers, such as those from the medical record to confirm eligibility, will be filed in binders and kept in a locked, secure location.

Data from correlative studies will be entered into the EDC system by study personnel at OSU. All other electronic data extracts will be stored only on OSU computers and restricted drives, limited only to study investigators and staff with authorization to access the data. Quality assurance will be conducted as outlined in Section 10.3, Quality Assurance & Quality Control.

11.3.1 FUTURE USE OF STORED SPECIMENS

Each participant who signs consent will be assigned a unique coded identifier consisting of numbers. This identifier will be associated with the participant throughout the duration of their participation in the trial. The coded identifier will be used to identify any participant specific samples. Blood and bone marrow collected for the purposes of this protocol will be stored until they can be analyzed. Any remaining sample may be stored indefinitely and used for future research to address scientific questions and/or development of biological tests related to cancer.

11.4 MAINTENANCE OF RECORDS

Records and documents pertaining to the conduct of this study, source documents, consent forms, laboratory test results and medication inventory records, must be retained by the Investigator for a period of 2 years following the date a marketing application is approved for the drug for the indication for which it is being investigated; or, if no application is to be filed or if the application is not approved for such indicate, until 2 years after the investigation is discontinued and FDA is notified. No records will be destroyed without the written consent of the Sponsor-investigator. It is the responsibility of the Sponsor to inform the site investigators when these documents no longer need to be retained.

If the Investigator relocates or for any reason withdraws from the study, the study records must be transferred to an agreed upon designee, such as another institution or another investigator at OSU. Records must be maintained according to institutional or FDA requirements.

11.5 MULTICENTER GUIDELINES

The study will be managed per the Multi-Center Trial Program (MCTP) policies. Subsite data must be submitted to the MCTP as outlined in the protocol-specific monitoring plan. The protocol-specific monitoring plan will be provided by the MCTP to external participating sites prior to site activation. Data will be submitted using case report forms and the Data Submission Form cover sheet (refer to Supplemental Forms Document) supplied by the MCTP. Access to the OSU OnCore database may be provided to external participating sites for direct electronic data entry. All data submitted must be accompanied by supporting source documents, where applicable and as outlined in the protocol-specific monitoring plan.

As the study sponsor, The Ohio State University Comprehensive Cancer Center (OSUCCC) will audit each site as per OSU policies. Audits will be performed by the OSUCCC Clinical Research Audit Team. For sites with an auditing mechanism in place that are able to share documentation of their auditing standards and processes followed, an agreement may be requested for the site to perform local auditing and provide formal audit reports to the OSUCCC Multi-Center Trial Program (MCTP) and the Quality Assurance Oversight Committee.

11.6 PUBLICATION AND DATA SHARING POLICY

This study will comply with the NIH Public Access Policy, which ensures that the public has access to the published results of NIH funded research. It requires scientists to submit final peer-reviewed journal manuscripts that arise from NIH funds to the digital archive PubMed Central upon acceptance for publication.

This study will adhere to the requirements set forth by the ICMJE and FDAAA that requires all clinical trials to be registered in a public trials registry (e.g., ClinicalTrials.gov) prior to participant enrollment.

11.7 DELIVERY OF PROGRESS REPORTS TO STUDY FUNDER

Upon the request of Jazz Pharmaceuticals plc, the Institution will submit oral or written reports on the progress of the Study as provided by this protocol. Within one hundred twenty (120) days following the completion or termination of the study, Institution will furnish Jazz Pharmaceuticals with a final report detailing the results of the Study.

12. ETHICS/PROTECTION OF HUMAN PARTICIPANTS

12.1 ETHICAL STANDARD

The Investigator will ensure that this study is conducted in full conformity with Regulations for the Protection of Human Participants of Research codified in 45 CFR Part 46, 21 CFR Part 50, 21 CFR Part 56, 21 CFR 312 (for IND studies), and/or the ICH E6.

12.2 INSTITUTIONAL REVIEW BOARD

The protocol, informed consent form(s), recruitment materials, and all participant materials will be submitted to the local IRB for review and approval. Approval of both the protocol and the consent form must be obtained before any participant is enrolled. Any amendment to the protocol will require review and approval by the local IRB before the changes are implemented to the study. All changes to the consent form will be local IRB approved; a determination will be made regarding whether previously consented participants need to be re-consented.

12.3 INFORMED CONSENT

All participating study sites must have approval of informed consent form by the local IRB of record before consenting any participants. Written informed consent will be obtained from all participants, or the legally authorized representative of the participant, participating in this trial, as stated in the Informed Consent section of 21 CFR Part 50. Documentation of the consent process and a copy of the signed consent shall be maintained in the participant's medical record.

12.3.1 CONSENT PROCEDURES AND DOCUMENTATION

Informed consent is a process that is initiated prior to the individual's agreement to participate in the study and continues throughout the individual's study participation. Extensive discussion of risks and possible benefits of participation will be provided to the participants and their families as appropriate. Consent forms will be IRB-approved and the participant will be asked to read and review the document. The Investigator will explain the research study to the participant and answer any questions that may arise. All participants will receive a verbal explanation in terms suited to their comprehension of the purposes, procedures, and potential risks/benefits of the study, alternatives to participation, and of their rights as research participants. Participants will have the opportunity to carefully review the written consent form and ask questions prior to signing. The participants should have the opportunity to discuss the study with their surrogates or think about it prior to agreeing to participate. The participant will sign the informed consent document prior to any procedures being done specifically for the study. The participants may withdraw consent at any time throughout the course of the trial. A copy of the informed consent document will be given to the participants for their records. The rights and welfare of the participants will be protected by emphasizing to them that the quality of their medical care will not be adversely affected if they decline to participate in this study.

12.4 PROTOCOL REVIEW

The protocol and informed consent form for this study must be reviewed and approved in writing by The Ohio State University's Clinical Scientific Review Committee (CSRC) and the appropriate local IRB for each participating site prior to any participant being consented on this study.

12.5 CHANGES TO PROTOCOL

Each participating site must submit proposed protocol changes to the OSU Coordinating Center for review and endorsement before participating site may implement changes. Any modification of this protocol must be documented in the form of a protocol revision or amendment submitted by the Investigator and approved by the CSRC and IRB, before the revision or amendment may be implemented. The only circumstance in which the amendment may be initiated without regulatory approval is for a change necessary to eliminate an apparent and immediate hazard to the participant. In that event, the Investigator must notify the IRB and other regulatory authority (as required) within 5 business days after the implementation.

An Investigator who holds an IND application must also notify the FDA of changes to the protocol per 21 CFR 312.

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APPENDIX A: PERFORMANCE CRITERIA

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

APPENDIX B: SUMMARY OF CAUTIONARY MEDICATIONS

Strong Inhibitors	Moderate Inhibitors	Weak Inhibitors	All other inhibitors
indinavir nelfinavir ritonavir saquinavir clarithromycin* itraconazole ketoconazole* nefazodone* posaconazole* voriconazole* telithromycin*	Aprepitant* Erythromycin* Fluconazole* grapefruit juice* verapamil* diltiazem*	cimetidine	amiodarone chloramphenicol delaviridine diethyl-dithiocarbamate fluvoxamine gestodene imatinib mibefradil mifepristone norfloxacin norfluoxetine starfruit

*Close monitoring of platelet counts and dose reductions are required with the addition of moderate to potent CYP 3A4 inhibitors.

Cautionary at the Cohort Designated Dose:
Strong and Moderate CYP3A inhibitors If subject requires use of these medications at the cohort designated dose, use with caution. The total daily dose should be reduced by approximately 50% for Strong CYP3A inhibitors, and no reduction necessary for moderate inhibitors. **Strong and Moderate CYP3A inducers** If subject requires use of these medications at the cohort designated dose, use with caution and contact Sponsor-Investigator/coordinating center for guidance.