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STUDY TITLE: A Phase II Study of CPX-351 as a Novel Therapeutic Approach for Patients with Myelodysplastic Syndromes (MDS) after Hypomethylating Agent Failure

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SUPPLIED AGENT***(S):*** CPX-351

IND #: 143227

SUMMARY OF CHANGES

Protocol Date	Section	Change
Protocol Version 5.0		
01/18/2020	All	Updated PI and contact information to Dr. Mukherjee throughout protocol
	6.4	Clarified adverse event reporting requirements during follow-up period.
Protocol Version 4.0		
06/01/2020	4.1	Updated inclusion criteria to include MDS/MPN
06/01/2020	4.1	Updated inclusion criteria for creatinine requirements
Protocol Version 3.0		
11/13/2019	1.2	Corrected dosing reconstitution from 5mg - 8.8mg/mL to 5mg - 2.2mg/mL
11/13/2019	9.1	Corrected dosing reconstitution from 5mg - 8.8mg/mL to 5mg - 2.2mg/mL
11/13/2019	11.1.1	Added language which will allow ECHO, EKG and Bone marrow biopsy and aspirate to be used for screening if completed within 28 days of C1D1 and prior to consent.
11/13/2019	11.2	Added footnote r, which will allow ECHO, EKG and Bone marrow biopsy and aspirate if completed prior to consent and within 28 days of C1D1 to be used for screening.
Protocol Version 2.0		
09/18/2019	11.2	Updated requirements of ECHO at C1D1.
09/18/2019	11.2	Removed serum chemistry from follow-up visits.
09/18/2019	11.2	Updated requirements of vitals at induction and during consolidation.
09/18/2019	All	Updated remission bone marrow biopsy from D28 +/- 7 days to D35 +/- 10 days.
09/18/2019	11.2	Removed windows from follow-up and survival follow-up visits.
09/30/2019	SOC	Updated summary of changes table.
Protocol Version 1.0		
03/27/2019	4.1	Changed inclusion criteria from serum creatinine to creatinine clearance, and changed bilirubin inclusion criteria
03/27/2019	4.2	Added criteria to exclude all patients with AML and Wilsons disease
03/27/2019	6.1	Added information regarding premedication
03/27/2019	6.3	Added new EOT criteria for toxicities
03/27/2019	6.3	Added new EOS criteria. Table 2.
03/27/2019	11.2	Changed frequency of ECHO to D1 of every cycle
03/27/2019	14.0	Added toxicity monitoring plan

Protocol Summary

Protocol Number/Title	CASE 2918: A Phase II Study of CPX-351 as a Novel Therapeutic Approach for Patients with Myelodysplastic Syndromes (MDS) after Hypomethylating Agent Failure
Study Phase	Phase II
Brief Background/Rationale	Epigenetic changes such as alterations in DNA methylation and histone modification play an important role in the pathophysiology of myelodysplastic syndromes (MDS). While hypomethylating agents (HMAs) such as azacitidine and decitabine have become the standard of care for patients with higher-risk MDS, they have limited efficacy. Response rates range from 20-40% and last a median of 9-10 months. Complete remissions are rare and the majority (50-70%) of patients remains resistant/refractory to these drugs. The poor success of HMAs is due, in part, to the limited understanding of mechanisms that underlie resistance. Given the poor survival of patients who fail HMAs, novel agents that overcome HMAs failure are desperately needed. Despite several novel compounds that have been investigated at the time of HMA failure, no therapy has proven to show overall survival (OS) compared to conventional care. This in part is due to the lack of our understanding into the mechanisms of resistance to HMA and the failure of accurately risk stratifying patients in this setting. We have previously shown that IPSS, IPSS-R and other commonly used MDS prognostic models, (e.g., the World Health Organization (WHO) classification-based Prognostic Scoring System (WPSS), and the MD Anderson Prognostic Scoring System (MDAPSS) have limited predictive power in the HMA failure setting[1-4]. We therefore developed and validated a new model to predict outcome of patients after hypomethylating agent failure (HMAF) that includes 6 clinical variables: age, performance status, complex cytogenetics ($\geq$4 abnormalities), marrow blast percentage >20%, platelet count, and red cell transfusion dependency[4]. This model separates patients into two risk categories: lower-risk, with a median OS of 11.0 months (95% CI 8.8-13.6); and higher-risk disease, with median OS of 4.5 months (95% CI 3.9-5.3)[4]. The model

	was subsequently validated in an independent cohort of 223 MDS patients derived from the Groupe Francophone des Myélodysplasies (GFM) database and in a phase III randomized clinical trial. Thus, risk stratifying MDS patients by the new model at the time of HMA failure may open new opportunity for drug approvals in this setting[5-6]. Identifying novel drugs that can improve the outcome of MDS patients after HMA failure remains an unmet need.
Primary Objective	Evaluate the efficacy of CPX-351 as measured by overall response rate (ORR), i.e. by IWG 2006 criteria for MDS patients after Hypomethylating agent failure. **Endpoint and time frame:** Overall response rate (ORR), i.e. by IWG 2006 criteria for MDS and patients at end of induction (C1D35 +/-10).
Secondary Objective(s)	• To determine the time to response (TTR) associated with CPX-351 in patients with MDS **Endpoint and time frame:** TTR associated with CPX-351 in patient with MDS at the end of induction (C1D35 +/-10). • To evaluate the duration of response (DOR) in patients achieving a response **Endpoint and time frame:** DOR in patients achieving a response at the time of response (C1D35 +/-10) and up to 1 year after the end of treatment. • To evaluate the event-free survival (EFS) and the overall survival (OS) probability of all patients enrolled in this trial. **Endpoint and time frame:** EFS and OS probability of all patients enrolled in this trial at end of induction (C1D35 +/-10) and up to 1 year after the end of treatment.
Estimated Study Duration	Estimated date first subject enrolled: March, 2019 Estimated date last subject enrolled: March, 2020
Duration of Participation	Patient participation is expected to average 6 to 12 months
Sample Size	25 patients

Disease sites/Conditions	Myelodysplastic Syndrome (MDS)
Interventions	• CPX-351 44mg/m^2 (daunorubicin 44 mg/m^2 and cytarabine 100 mg/m^2), IV days 1, 3, and 5 during the induction phase. • CPX-351 15.4mg/m^2 (daunorubicin 15.4 mg/m^2 and cytarabine 35 mg/m^2), IV every 28 days for up to 4 cycles during the consolidation phase for patients achieving a response.

Abbreviations

AE	Adverse Event
ALL	Acute Lymphoblastic Leukemia
ALT	Alanine Aminotransferase
AML	Acute Myeloid Leukemia
AML-MRC	Acute Myeloid Leukemia with Myelodysplasia Related Changes
ANC	Absolute Neutrophil Count
AST	Aspartate Aminotransferase
AZA	Azacitidine
BSA	Body Surface Area
BUN	Blood Urea Nitrogen
CCCC	Case Comprehensive Cancer Center
CCF	Cleveland Clinic Foundation
CI	Confidence Intervals
CTCAE	Common Terminology Criteria for Adverse Events
CR	Complete remission
CRi	Complete remission with incomplete count recovery
CRF	Case Report Form
DAC	Decitabine
DCRU	Dahm's Clinical Research Unit
DLT	Dose Limiting Toxicity
DOR	Duration of response
DSMP	Data Safety Monitoring Plan
DSTC	Data Safety and Toxicity Committee
ECOG	Eastern Cooperative Oncology Group
EFS	Event free survival
EOS	End of Study
EOT	End of Treatment
FDA	Food and Drug Administration
FU	Follow-up
GCP	Good Clinical Practice
G-CSF	Granulocyte-colony stimulating factor
GM-CSF	Granulocyte-macrophage colony-stimulating factor
GFM	Groupe Francophone des Myélodysplasies
Hgb	Hemoglobin
HI	Hematologic Improvement
HIPAA	Health Insurance Portability and Accountability Act of 1996
HMA	Hypomethylating agent
HMAF	Hypomethylating agent failure
HR	Hazard Ratio
HSCT	Hematopoietic stem cell transplant
HU	Hydrea

ICF	Informed Consent Form
ICH	International Conference on Harmonization
IEC	Institutional Ethics Committee
IRB	Institutional Review Board
IWG	International Working Group
LLN	Lower Limit of Normal
MDAPSS	MD Anderson Prognostic Scoring System
MDS	Myelodysplastic Syndrome
MPN	Myeloproliferative Neoplasm
ORR	Overall Response Rate
OS	Overall survival
PD	Progressive Disease
PI	Principle Investigator
PR	Partial remission
PRMC	Protocol Review and Monitoring Committee
SAE	Serious Adverse Event
SD	Stable Disease
SOC	Standard of Care
tAML	Therapy Related Acute Myeloid Leukemia
TLS	Tumor lysis syndrome
TTR	Time to response
UH	University Hospitals
ULN	Upper Limit of Normal
WHO	World Health Organization
WPSS	World Health Organization Classification-Based Prognosis Scoring System

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1.0 Introduction

1.1 Background of Study Disease

Epigenetic changes such as alterations in DNA methylation and histone modification play an important role in the pathophysiology of myelodysplastic syndromes (MDS). While hypomethylating agents (HMAs) such as azacitidine and decitabine have become the standard of care for patients with higher-risk MDS, they have limited efficacy. Response rates range from 20-40% and last a median of 9-10 months. Complete remissions are rare and the majority (50-70%) of patients remains resistant/refractory to these drugs. The poor success of HMAs is due, in part, to the limited understanding of mechanisms that underlie resistance. Given the poor survival of patients who fail HMAs, novel agents that overcome HMAs failure are desperately needed. Despite several novel compounds that have been investigated at the time of HMA failure, no therapy has proven to show overall survival (OS) compared to conventional care. This in part is due to the lack of our understanding into the mechanisms of resistance to HMA and the failure of accurately risk stratifying patients in this setting.

We have previously shown that IPSS, IPSS-R and other commonly used MDS prognostic models, (e.g., the World Health Organization (WHO) classification-based Prognostic Scoring System (WPSS), and the MD Anderson Prognostic Scoring System (MDAPSS) have limited predictive power in the HMA failure setting[1-4]. We therefore developed and validated a new model to predict outcome of patients after hypomethylating agent failure (HMAF) that includes 6 clinical variables: age, performance status, complex cytogenetics (≥4 abnormalities), marrow blast percentage >20%, platelet count, and red cell transfusion dependency[4]. This model separates patients into two risk categories: lower-risk, with a median OS of 11.0 months (95% CI 8.8-13.6); and higher-risk disease, with median OS of 4.5 months (95% CI 3.9-5.3)[4]. The model was subsequently validated in an independent cohort of 223 MDS patients derived from the Groupe Francophone des Myélodysplasies (GFM) database and in a phase III randomized clinical trial. Thus, risk stratifying MDS patients by the new model at the time of HMA failure may open new opportunity for drug approvals in this setting[5, 6].

Identifying novel drugs that can improve the outcome of MDS after HMA failure remains an unmet need.

1.2 Name and Description of Investigational Agent CPX-351

1.2.1 Preclinical Data

CPX-351 is a liposomal formulation of a fixed combination of the antineoplastic drugs cytarabine and daunorubicin. These two drugs are present inside the liposome in a 5:1 molar ratio. The liposome membrane is composed of distearoylphosphatidylcholine, distearoylphosphatidylglycerol and cholesterol in a 7:2:1 molar ratio. These liposomes have a nominal diameter of approximately 100nm and are suspended in sucrose. Sterilization is achieved by filtration through a 0.22 μm filter.

CPX-351 is provided as a sterile, pyrogen-free lyophilized formulation in 50 mL glass, single-use vials. Each vial contains 100mg/m^2 of CPX-351 where each vial contains 100 mg cytarabine and 44 mg daunorubicin base in liposomes. The lyophilized cake is reconstituted with sterile water for injection to obtain a homogeneous dispersion at 5 mg-2.2mg/mL (cytarabine-daunorubicin).

The pre-clinical pharmacology and toxicology are summarized in the Investigator's Brochure for CPX-351.

1.2.2 Clinical Data

Phase I study of CPX-351

In a phase 1 dose-escalation trial, CPX-351 induction was administered on days 1, 3, and 5 by 90-minute infusion to 48 relapsed or refractory patients with acute myeloid leukemia (AML) or high-risk myelodysplasia. Doses started at 3 mg/m^2 with dose doublings in single-patient cohorts until a pharmacodynamic effect (treatment-related adverse events or reduction in bone marrow cellularity or blast count) was observed, followed by 33% escalations in three patient cohorts until dose-limiting toxicity (DLT) occurred. The maximum-tolerated dose was 101 mg/m^2. DLTs consisted of hypertensive crisis, congestive heart failure, and prolonged cytopenias. Identified adverse events were similar with cytarabine and daunorubicin treatment. Response occurred at doses as low as 32 mg/m^2. Of 43 patients with AML, nine had complete response (CR) and one had CR

with incomplete platelet recovery; of patients with acute lymphoblastic leukemia (ALL), one of three had CR. Eight CRs were achieved among the 31 patients with prior cytarabine and daunorubicin treatment. CR in AML occurred in 5 of 26 patient's age ≥ 60 years and in 5 of 17 patients younger than 60 years of age. Median half-life was 31.1 hours (cytarabine) and 21.9 hours (daunorubicin), with both drugs and their metabolites detectable > 7 days after the last dose. The targeted 5:1 molar ratio was maintained at all dose levels for up to 24 hours[7].

Phase II study of CPX-351

A randomized, multicenter, open-label, phase 2 trial was conducted to evaluate the efficacy and safety of CPX-351 compared with investigators' choice of first salvage treatment in adult patients with first relapse AML. The primary endpoint of the study was 1-year overall survival (OS), and Kaplan-Meier analysis did not show a significant difference between the two treatment groups (HR, 0.75; $P = 0.33$). Survival at 1-year was 36% and 27% ($P = 0.33$) for CPX-351 and salvage treatment arms, respectively. Patients were stratified at baseline according to the European Prognostic Index (EPI), and results showed that CPX-351-treated patients with the EPI-defined poor-risk strata demonstrated higher response rates (39.3% CPX-351 versus 27.6% salvage arm) and improvements in event-free survival (EFS) (HR, 0.63; $P = 08$) and OS (HR, 0.55; $P = 0.22$). The overall rates of grade 5 AEs were similar between the CPX-351 (23.5%) and salvage treatment arms (20.5%)[8].

Phase III study of CPX-351

A phase 3, randomized, multicenter, open-label study evaluated the efficacy and safety of CPX-351 compared with conventional 7 + 3 (cytarabine for 7 days plus daunorubicin for 3 days) regimen in adult patients (60 to 75 years) with newly-diagnosed therapy-related Acute Myeloid Leukemia (tAML) or Acute Myeloid Leukemia with Myelodysplasia related changes (AML-MRC). The primary efficacy endpoint was overall survival (OS). The results showed OS was significantly greater in the CPX-351 group compared with the 7 + 3 group. The median OS was 9.56 months with CPX-351 and 5.95 months with 7 + 3 (Hazard Ratio [HR] 0.69; $P = 0.005$). Grade 3-5 non-hematologic

adverse events (AEs) occurring ≥ 5% were similar between the two groups, except pneumonia (20% vs 15%) and bacteremia (10% vs 2%) were numerically higher in the CPX-351 compared with 7 + 3 groups, respectively. Also, median time to recovery of absolute neutrophil count (ANC) ≥ 500/μL and platelets ≥ 50,000/μL were longer in the CPX-351 group than 7 + 3 group[9].

1.4 Rationale

Treatment options are limited for patients diagnosed with MDS at the time of HMA failure. Although the outcome remains poor, hematopoietic stem cell transplant (HSCT) may prolong survival for a subset of patients[10]. However, achievement of CR prior to transplant is important for improved outcomes[10]. Treatment with 7+3 chemotherapy regimen has been used, resulting in a response rate of approximately 30% in this patient population. Especially, in patients who progress to AML[11]. Transplant remains an important option for these patients who can tolerate chemotherapy.

CPX-351 has shown better overall response rate and improved overall survival in patients with AML with underlying MDS changes compared to 7+3 suggesting that CPX-351 can be used in this patient population. Thus, we hypothesize that treating MDS patients, who failed or are intolerant to their initial treatment with HMA's, with CPX-351 will overcome HMA resistance and sensitize the MDS cells to this treatment.

2.0 Study Objectives

2.1 Primary Objective

- Evaluate the efficacy of CPX-351 as measured by overall response rate (ORR), i.e. by IWG 2006 criteria for MDS patients after Hypomethylating agent failure.

2.2 Secondary Objective(s)

- To determine the time to response (TTR) associated with CPX-351 in patients with MDS.
- To evaluate the duration of response (DOR)

- To evaluate the event-free survival (EFS) and the overall survival (OS) probability of all patients enrolled in this trial.

3.0 Study Design

3.1 Overview of Study Design

This is a phase II study of single agent CPX-351 administered at the standard FDA approved dose of 44 mg/m^2 (daunorubicin 44 mg/m^2 and cytarabine 100 mg/m^2) intravenously on days 1, 3, 5 of the induction cycle. If patients achieve complete remission (CR), complete remission with incomplete count recovery (CRi) or partial remission (PR) (section 12.0, Table 2) they will be eligible to continue on to consolidation therapy, which will consist of CPX-351 at a dose of 15.4 mg/m^2 (daunorubicin 15.4 mg/m^2 and cytarabine 35 mg/m^2) every 28 days Patients can receive up to 4 cycles of consolidation therapy.

3.2 Number of Subjects

Approximately 25 patients will be enrolled in this trial.

3.3 Replacement of Subjects

Patients who receive any doses of CPX-531 will be not be replaced. Patient's slots will only be replaced if they are discontinued from the study prior to dosing with CPX-351. Missed doses of CPX-351 will be re-administered at the discretion of the treating physician.

3.4 Expected Duration of Treatment and Subject Participation

Enrollment to this study is estimated to occur over three years. Upon signing consent, patients will undergo screening to determine if the patient meets all inclusion and exclusion criteria, as outlined in section 4.1 and 4.2. Following screening, all eligible patients will be enrolled and begin induction therapy which will occur over a 35 day cycle and/or at count recovery with CPX-351 dosing on days 1, 3 and 5.

Patients who achieve a response (section 12.0, Table 2) may proceed with the consolidation phase of the trial with CPX-351 dosing on days 1 and 3 of every 28 days. Patients can receive up to 4 cycles of consolidation. Treatment will continue during the duration of the study unless patients exhibit evidence of treatment failure, disease progression, experience an unacceptable toxicity, or the investigator determines that discontinuation of treatment is in the best interest of the patient. Patients will be treated with CPX-351 based on a calculation determined from the patient's body surface area (BSA). BSA will be calculated before each day of dosing and will be based on the patient's height (measured at baseline) and weight (measured each visit).

4.0 Subject Selection

4.1 Inclusion Criteria

Each patient must meet all of the following inclusion criteria to be eligible for enrollment:

1. Patients must be $\geq$ 18 years of age
2. Patients must give voluntary written consent before performance of any study related procedures not part of standard medical care
3. Diagnosis of MDS or MDS/MPN according to 2016 WHO criteria[12]
4. Primary therapy failure with either hypomethylating agents (decitabine or azacitidine) defined as:
    - Progression (according to 2006 IWG criteria)[13] after initiation of azacitidine or decitabine treatment; or
    - Failure to achieve complete or partial response or hematological improvement (according to 2006 IWG)[13] after at least 4-6 cycles (4-weeks cycle) of azacitidine or decitabine; or
    - Relapse after initial complete or partial response or hematological improvement (according to 2006 IWG criteria)[13] observed after at least 4 cycles of azacitidine or decitabine.
5. Eastern Cooperative Oncology Group (ECOG) Performance Status $\leq$ 2
6. Subjects must have normal organ and marrow function defined as:
    - If total bilirubin $\leq$ 2x upper limit of normal ($\leq$ 3 x ULN if considered to be due to leukemic involvement or Gilbert's syndrome) at the discretion of the treating physician following discussion with PI) Patients with a bilirubin level of >3 mg/dL will be excluded

- Calculated creatinine clearance value of $\geq$ 30ml/min AND a serum creatinine $\leq$ 1.5mg/dL
- LVEF $\geq$ 50%

7. Female patients who:
    - Are postmenopausal for at least 1 year before the screening visit, OR
    - Are surgically sterile, OR
    - Agree to practice true abstinence from heterosexual contact or agree to use effective contraception without interruption during the study therapy and 90 days after the last dose
8. Male patients who:
    - Are surgically sterile, OR
    - Agree to practice true abstinence from heterosexual contact or agree to use effective contraception without interruption during the study therapy and 90 days after the last dose

4.2 Exclusion Criteria

The presence of any of the following will exclude a subject from study enrollment.

1. Prior treatment with CPX-351, or known hypersensitivity to CPX-351 or its components.
2. Prior treatment with intensive chemotherapy.
3. Patients with confirmed Wilson's disease will be excluded.
4. Diagnosis of acute myeloid leukemia (AML)
5. Any serious medical condition, laboratory abnormality, or psychiatric illness that, in the view of the treating physician, would place the participant at an unacceptable risk if he or she were to participate in the study or would prevent that person from giving informed consent.
6. Any active malignancy (unrelated, non-hematological malignancy) diagnosed within the past 6 months of starting the study drug (other than curatively treated carcinoma-in-situ of the cervix or non-melanoma skin cancer).
7. Patients with uncontrolled intercurrent illness including, but not limited to ongoing or active infection, symptomatic congestive heart failure, unstable angina pectoris, cardiac arrhythmia, or psychiatric illness/social situations that would limit compliance with study requirements.
8. Known history of HIV or active hepatitis B or C.
9. Active Wilsons disease
10. Major surgery within 2 weeks prior to study enrollment.

11. Pregnant or lactating females
12. Male and female patients who are fertile who do not agree to use an effective barrier methods of birth control (i.e. abstinence or 2 forms of contraception) to avoid pregnancy while receiving study treatment.

4.3 Inclusion of Women and Minorities

Men, women and members of all races and ethnic groups are eligible for this trial.

5.0 Registration

All subjects who have been consented are to be registered in the OnCore™ Database. For those subjects who are consented, but not enrolled, the reason for exclusion must be recorded.

All subjects will be registered through Cleveland Clinic and will be provided a study number by contacting the study coordinator listed on the cover page.

6.0 Treatment Plan

6.1 Treatment Regimen Overview

Consent and Screening

Upon signing consent, patients will begin the screening phase. The screening period begins the day the patient signs consent and can take place over a 28 day period leading up to dosing on day 1 (D1). During the screening period patients will be assessed to determine if they meet eligibility for this study per the inclusion and exclusion criteria as outlined in sections 4.1 and 4.2. Once the patient is deemed eligible they will be stratified into two arms based on the post-HMA failure model (Appendix V).

Stratification

Prior to beginning treatment, all eligible patients will be stratified into low vs. high risk based on the post-HMA failure model (Appendix V)[4]. Seven patients will be enrolled into the low risk arm and seven patients will be enrolled into the high risk arm. Once 14 patients, across both arms, have been enrolled and evaluated for a response (D35 +/- 10 days bone marrow), an interim analysis will be conducted to determine benefit in

each arm. The arm with the greatest response will then enroll an additional 11 patients, for a total of 18 patients in that arm. Overall, this study will enroll 25 patients.

Induction

The induction phase is defined as the time between the first day (D1) of study drug to day 35 and/or count recovery. During the induction phase of the study, all patients will be treated with the FDA approved standard dose of CPX-351 at 44mg/m^2 (daunorubicin 44 mg/m^2 and cytarabine 100 mg/m^2) on days 1, 3, and 5. Study drug will be administered per the study calendar (section 11.2) unless patient exhibits any EOT criteria. Premedication with anti-emetics is recommended prior to treatment with CPX-351. No re-induction will be allowed and no day 14 bone marrow biopsy is required. A bone marrow biopsy and aspirate will be obtained on day 35 +/-10 days to confirm response. If no evidence of blasts > 5%, G-CSF will be allowed to improve counts at the discretion of the treating physician. Following the bone marrow, patients who meet the response criteria per section 12.0 can then continue onto the consolidation phase of this study.

Consolidation

The consolidation phase is defined as C2D1 to C5D28 or once the patients meet EOT criteria (section 6.3, Table 1). Only patients with a documented response (CR, CRi, or PR) from the D35 (+/-10 days) bone marrow are eligible for consolidation therapy. Prior to the first cycle of consolidation therapy the patients must have a PS of 0-2. During the consolidation phase, CPX-351 must be given no earlier than 35 days after the start of induction and no later than 75 days after the start of induction. For all subsequent cycles, there must be at least 35 days between the start of each cycle. Patients must have recovered to ANC >500/ μL and platelets >50,000/μL to be eligible for any consolidation therapy.

During the consolidation phase, CPX-351 will be given at 15.4 mg/m^2 (daunorubicin 15.4 mg/m^2 and cytarabine 35 mg/m^2) on days 1 and 3 of each 28 day cycle. Consolidation therapy can be continued up to 4 cycles in the absences of toxicities or reasons that require discontinuation and/or any EOT criteria (section 6.3, Table 1).

Premedication with anti-emetics is recommended prior to treatment with CPX-351. No other chemotherapy consolidation treatment is permitted. Only HSCT (hematopoietic stem cell transplant) is permitted in place of, or following, chemotherapy consolidation. Delays in administrating consolidation cycles will be allowed at the discretion of the treating physician and after discussion with the PI.

End of Treatment and Follow-up

At the point in which the patient completes therapy per protocol or meets any EOT criteria (section 6.3, Table 1), the patient will enter into the follow-up period. The patient will be followed for survival for 1 year and/or until death, whichever occurs first. During the first 6 months of follow-up the patient will be seen in clinic as standard of care (SOC) every 30 days, per the study calendar (section 11.2). End of study (EOS) is defined as the time the patient completes 1 year of follow, withdraws consent and/or patient's death, whichever occurs first.

6.1.1 Name of **Investigational Agent**

CPX-351

6.2 General Concomitant Medications and Supportive Care Guidelines

Patients should be off any prior treatment or line of therapy at least 2 weeks prior to D1 of induction therapy with the exception of hydrea. Hydrea will be allowed at the discretion of the treating physician but must be stopped prior to starting CPX-351.

Necessary supportive measures for optimal medical care will be given throughout the treatment as determined by the treating physician and the patient's medical needs. No concomitant chemotherapy, immunotherapy, or therapy with monoclonal antibodies will be allowed during the study.

Prophylactic antibiotics and antiviral agents (e.g. levofloxacin, valacyclovir, etc.) are recommended while on study; however, the use of these or other drugs will be left to the treating physician's discretion. Use of colony-stimulating factors or combinations

thereof (e.g. G-CSF, GM-CSF, or erythropoietin) are at the discretion of the treating physician and are permitted if judged in the patient's best medical interest. At the D35 (+/- 10 days) bone marrow, if there is no evidence of blasts > 5%, G-CSF will be allowed to improve counts at the discretion of the treating physician.

6.3 Criteria for Removal from Study

In the absence of treatment delays due to adverse events, treatment may continue for one cycle of induction therapy and up to four cycles of consolidation therapy if patients achieve response criteria per section 12.0 or until one of the following criteria applies:

End of Treatment Criteria:

• Disease progression (section 12.0),
• Intercurrent illness that prevents further administration of treatment,
• The investigator and/or treating physician considers it, for safety reasons, to be in the best interest of the subject. Unacceptable adverse events defined as following:
  • Any unacceptable treatment related grade 3 or 4 toxicities that fail to recover to baseline or < Grade 3 in the absence of treatment within 4 weeks
  • Impaired cardiac function
  • Severe OR life-threatening hypersensitivity reactions
  • Grade 4 non-hematological organ toxicities regardless of time to recovery, excluding:
  • Grade 4 fatigue, asthenia fever, anorexia or constipation
  • Grade 4 nausea, vomiting or diarrhea not requiring tube feeding, total parenteral nutrition, or requiring or prolonging hospitalization
  • Infection, bleeding, or other expected direct complication of cytopenias due to active underlying leukemia
  • Grade 4 infusion reaction including cytokine release syndrome (CRS), if successfully managed and which resolves within 72 hours
  • Grade 4 tumor lysis syndrome (TLS) if it is successfully managed clinically and resolves within 7 days without end-organ damage
  • Grade 4 isolated electrolyte abnormalities that last <72 hours
• Patient decision to withdraw from treatment (partial consent) or from the study (full consent),
• Pregnancy during the course of the study for a child-bearing participant
• Death while patient is on the study

Table 1: End of Treatment Criteria

End of Study Criteria:

- Patient decision to withdraw from the study (full consent),
- Non-compliance with the study protocol,
- Death while patient is in the follow-up phase,
- Patient completed treatment and follow-up phase per protocol.

Table 2: End of Study Criteria

6.4 Duration of Follow Up

Following completion of active treatment (EOT) and while still on study (Follow up), patients will be followed for survival as for 1 year. During the first 6 months of follow-up, the patient will be seen in clinic as standard of care every 30 days, per the study calendar (section 11.2). The clinical course of all grade 3 or 4 events will be followed until resolution, stabilization, or until it has been determined study treatment or study participation is not the cause. New onset adverse events will not be recorded during follow-up.

Serious adverse events that are ongoing at the end of active treatment (EOT), will necessitate follow-up to determine the final outcome. Any serious adverse events that occur after the study period (EOT) and are considered related or possibly related to study treatment or study participation will be recorded and reported immediately, per institutional review board (IRB) requirement.

7.0 Dose Delays/Dose Modifications

No dose reductions of CPX-351 will be allowed during the study. Dose delays will be at the discretion of the treating physician after discussion with the PI. Missed doses of CPX-351 can be made up on subsequent days if felt to be in the best interest of the patient. CPX-351 doses must be given at least 24 hours apart. This will be determined by the treating physician following discussion with the PI.

If at any time during an infusion the patient experiences moderate hypersensitivity reactions, discontinuation of that infusion is mandatory. Premedicate with antihistamines and/or corticosteroids prior to all subsequent infusions. If a patient experiences a mild hypersensitivity reaction, regardless or premedication, infusion must be interrupted and can be re-initiated at half the prior rate.

8.0 Adverse Events and Potential Risks

8.1 Definitions

8.1.1 Adverse Event

An **adverse event** (AE) is any unfavorable or unintended event, physical or psychological, associated with a research study, which causes harm or injury to a research participant as a result of the participant's involvement in a research study. The event can include abnormal laboratory findings, symptoms, or disease associated with the research study. The event does not necessarily have to have a causal relationship with the research, any risk associated with the research, the research intervention, or the research assessments.

Adverse events may be the result of the interventions and interactions used in the research; the collection of identifiable private information in the research; an underlying disease, disorder, or condition of the subject; and/or other circumstances unrelated to the research or any underlying disease, disorder, or condition of the subject.

8.1.2 Serious Adverse Events

A **serious adverse event** (SAE) is any adverse experience occurring at any dose that results in any of the following outcomes:

- Results in **death.**
- Is a **life-threatening** adverse experience. The term life-threatening in the definition of serious refers to an adverse event in which the subject was at risk of death at the time of the event. It does not refer to an adverse event which hypothetically might have caused death if it were more severe.
- Requires **inpatient hospitalization or prolongation of existing hospitalization**. Any adverse event leading to hospitalization or prolongation of hospitalization will be considered as Serious, UNLESS at least one of the following expectations is met:
    - The admission results in a hospital stay of less than 24 hours OR

- The admission is pre-planned (e.g., elective or scheduled surgery arranged prior to the start of the study) OR
- The admission is not associated with an adverse event (e.g., social hospitalization for purposes of respite care.

However, it should be noted that invasive treatment during any hospitalization may fulfill the criteria of "medically important" and as such may be reportable as a serious adverse event dependent on clinical judgment. In addition, where local regulatory authorities specifically require a more stringent definition, the local regulation takes precedent.

- Results in **persistent or significant disability/incapacity**. The definition of disability is a substantial disruption of a person's ability to conduct normal life's functions.
- Is a **congenital anomaly/birth defect**.
- Is an **important medical event**. Important medical events that may not result death, be life-threatening, or require hospitalization may be considered a serious adverse experience when, based upon appropriate medical judgment, they may jeopardize the subject and 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 disease or disorders, or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse. The development of a new cancer is always considered an important medical event.

8.1.3 Adverse Event Evaluation

The investigator or designee is responsible for ensuring that all adverse events (both serious and non-serious) observed by the clinical team or reported by the subject which occur after the subject has signed the informed consent are fully recorded in the

subject's medical records. Source documentation must be available to support all adverse events.

A laboratory test abnormality considered clinically relevant as deemed by the treating physician should be reported as an adverse event.

The investigator or sub-investigator (treating physician if applicable) will provide the following for all adverse events (both serious and non-serious):

- Event term (as per CTCAE)
- Description of the event
- Date of onset and resolution
- **Expectedness of the toxicity**
- **Grade of toxicity**
- **Attribution of relatedness to the investigational agent- (this must be assigned by an investigator, sub-investigator, or treating physician)**
- Action taken as a result of the event, including but not limited to; no changes, dose interrupted, reduced, discontinued, etc. or action taken with regard to the event, i.e. no action, received conmed or other intervention, etc.
- Outcome of event

Descriptions and **grading scales** found in the NCI Common Terminology Criteria for Adverse Events (CTCAE) version **5.0** will be utilized for AE reporting.

An expected adverse event is an event previously known or anticipated to result from participation in the research study or any underlying disease, disorder, or condition of the subject. The event is usually listed in the Investigator Brochure, consent form or research protocol.

An unexpected adverse event is an adverse event not previously known or anticipated to result from the research study or any underlying disease, disorder, or condition of the subject.

Attribution is the relationship between an adverse event or serious adverse event and the study drug. Attribution will be assigned as follows:

- Definite – The AE is clearly related to the study drug.
- Probable – The AE is likely related to the study drug.
- Possible – The AE may be related to the study drug.
- Unlikely – The AE is doubtfully related to the study drug.
- Unrelated – The AE is clearly NOT related to the study drug.

Protocol must specify if attribution is required for individual components of the treatment regimen or the treatment regimen as a whole.

8.2 Potential Risks of **CPX-351**

COMMON, SOME MAY BE SERIOUS In 100 people receiving CPX-351 more than 10 and up to 100 may have:
▪ Abdominal pain ▪ Anemia ▪ Anxiety ▪ Arrhythmia ▪ Chest pain ▪ Chills ▪ Constipation ▪ Cough ▪ Decreased appetite ▪ Delirium ▪ Diarrhea ▪ Dizziness ▪ Dyspnea ▪ Edema ▪ Fatigue ▪ Febrile neutropenia ▪ Fungal infection ▪ Headache ▪ Hemorrhage ▪ Hypertension ▪ Hypotension ▪ Hypoxia ▪ Rash ▪ Mucositis ▪ Musculoskeletal pain

- Nausea
- Neutropenia
- Non-conduction cardio toxicity
- Pleural effusion
- Pneumonia
- Pruritus
- Pyrexia
- Rash
- Sleep disorders
- Vomiting

OCCASIONAL, SOME MAY BE SERIOUS

In 100 people receiving CPX-351 from 4 to 20 may have:

- Acute renal failure
- Cellulitis
- Catheter/injection site reaction
- Ejection fraction decreased
- Fatigue
- Hemorrhoids
- Hypokalemia
- Malignant neoplasm progressive
- Petechiae
- Pneumonia
- Pyrexia
- Rash
- Sepsis
- Urinary tract infection
- Renal insufficiency
- Respiratory failure
- Transfusion reactions
- Upper respiratory induction (excluding fungal)
- Visual impairments (except bleeding)

8.3 SAE Report Form

SAEs will be recorded on the FDA Form 3500A (MedWatch) but should only be reported as instructed below. The electronic FDA SAE reporting forms should not be used.

8.4 Reporting Procedures for Serious Adverse Events

For the purposes of safety reporting, all adverse events will be reported that occur through 30 days after the final dose of study drug. Adverse events, both serious and non-

serious, and deaths that occur during this period will be recorded in the source documents. All SAEs should be monitored until they are resolved or are clearly determined to be due to a subject's stable or chronic condition or intercurrent illness(es). Related AEs will be followed until resolution to baseline or grade 1 or stabilization.

8.4.1 SAE Reporting Requirements

- Participating investigators (all sites) must report all serious adverse events to the Lead Site Principal Investigator (e.g. Sponsor-Investigator) within **24 hours** of discovery or notification of the event. The participating investigator must also provide follow-up information on the SAE until final resolution.
- The Lead Site Principal Investigator will review the SAE and report the event to the FDA, external collaborator(s), and IRB as applicable.
- The Principal Investigator must send all SAEs (initial and follow-up) that require collection and reporting per protocol, and which occur in a subject who received CPX-351 as study drug, to Jazz Pharmaceuticals within 1 business day of their awareness of the SAE to AEreporting@jazzpharma.com.
- It is the Sponsor-Investigator's responsibility (e.g. lead site PI) to ensure that ALL serious adverse events that occur on the study (e.g. ALL SAEs that occur at each enrolling institution) are reported to all participating sites.

Institutional Review Board Reporting Requirements:

- Investigative sites will report adverse events to their respective IRB according to the local IRB's policies and procedures in reporting adverse events.

8.5 SAEs and OnCore

- All SAEs will be entered into OnCore.
- A copy of the SAE form(s) submitted to the sponsor-investigator is also uploaded into Oncore.

8.6 Data Safety and Toxicity Committee

It is the responsibility of each site PI to ensure that ALL SAEs occurring on this trial (internal or external) are reported to the Case Comprehensive Cancer Center's Data

and Safety Toxicity Committee. This submission is simultaneous with their submission to the sponsor and/or other regulatory bodies.

The sponsor-investigator is responsible for submitting an annual report to the DSTC as per CCCC Data and Safety Monitoring Plan.

8.7 Data and Safety Monitoring Plan (DSMP)

This protocol will adhere to the policies of the Case Comprehensive Cancer Center Data and Safety Monitoring Plan in accordance with NCI guidelines.

9.0 PHARMACEUTICAL INFORMATION

A list of the adverse events and potential risks associated with the investigational or commercial agents administered in this study can be found in Section 8.

9.1 Investigational Agents

9.1.1 Name of Agent CPX-351

Other Names: CPX-351

Product description: CPX-351 (daunorubicin and cytarabine) liposome for injection is a combination of daunorubicin and cytarabine in a 1:5 molar ratio encapsulated in liposomes for intravenous administration. The liposome membrane is composed of distearoylphosphatidylcholine (DSPC), distearoylphosphatidylglycerol (DSPG), and cholesterol in a 7:2:1 molar ratio.

Solution preparation: The appropriate number of vials of CPX-351 (cytarabine:daunorubicin) Liposome Injection should be removed from the refrigerator prior to reconstitution. Reconstitute with 19 mL of sterile water for injection using a 20 mL syringe. Do not heat CPX-351 (cytarabine:daunorubicin) Liposome Injection. After reconstitution, invert vials gently 3- 4 times and let rest for 15 minutes and repeat vial inversion prior to withdrawing drug for dilution. The concentration of the reconstituted dispersion is 5 mg-2.2mg/mL (cytarabine-daunorubicin). CPX-351 should be diluted in approximately 500 mL of sodium chloride injection or dextrose injection.

The IV bags and infusion sets must be non-DEHP. Aseptic technique must be strictly observed throughout the handling of CPX-351 (cytarabine:daunorubicin) Liposome

Injection since no bacteriostatic agent or preservative is present. The infusion of CPX-351 (cytarabine:daunorubicin) Liposome Injection must be started within 4 hours of dilution. Vials are for single use. Unused material should be recorded as such and discarded according to institutional policies. Procedures for proper handling and disposal of anticancer drugs should be implemented.

Storage requirements: Store un-reconstituted 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.

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

Route of administration: The infusion of CPX-351 (cytarabine:daunorubicin) Liposome Injection will be performed through a central venous catheter, using an infusion pump to ensure that the drug is infused over the specified time period. Non-DEHP containing administration sets should be used. **Do not use an in-line filter.** CPX-351 should never be given by the intramuscular or subcutaneous route. Administer CPX-351 over approximately 90 minutes via an infusion pump. Flush the line to ensure administration of the full dose. The dosage (total mg/m^2), start/stop time of the infusion, total volume infused, must be documented in the patient's chart.

Drug Procurement: CPX-351 will be supplied for this study by Jazz Pharmaceutical.

Drug Accountability: The study pharmacist or designee must maintain records of the delivery of CPX-351 to the study site, the inventory at the site, the use by each patient, and the disposition of unused product. These records should include dates, quantities, lot numbers, expiration dates and patient identifications. Institutions should maintain records that document adequately that the patients were provided the doses specified by the protocol and reconcile all investigational product received from the Sponsor. Records of storage conditions (temperature logs) must be kept for the entire period that CPX-351 is maintained at the institution.

Drug Destruction: At the completion of the study, there will be a final reconciliation of drug shipped, drug consumed, and drug remaining. This reconciliation will be logged on

the drug reconciliation form, signed and dated. Any discrepancies noted will be investigated, resolved, and documented prior to return or destruction of unused study drug. Drug destroyed on site will be documented in the study files.

10.0 EXPLORATORY or CORRELATIVE STUDIES

Bio specimens (whole blood, 10 mL) will be collected as outlined in section 11.2 at screening, C1D35 (+/- 10 days) and EOT for general research purposes, potentially including genetic analysis research. All subjects must consent to provide archived sample for future research.

All samples obtained will be stored at the Cleveland Clinic Translational Hematology and Oncology Research laboratory. Samples will remain at the Cleveland Clinic to be used for research purposes for this study as well as for future research projects approved by the IRB.

10.1 Collection of Samples

10mL of whole blood will be collected in an extra lab tube at screening, C1D35 (+/- 10 days) and EOT (section 11.2). Details and instructions about the collection, processing and shipping can be found in the Lab Manual. All samples will be housed at and should be delivered and/or shipped to:

Principle Research Technologists
Translational Hematology and Oncology Laboratory
Cleveland Clinic, LC – NE6 – 250
9620 Carnegie, Avenue
Cleveland, OH 44195
Phone: (216) 444-0256

11.0 STUDY PARAMETERS AND CALENDAR

11.1 Study Parameters

11.1.1 Screening Evaluations (Consent to D-1)

1. History and physical examination.
2. ECOG performance status (Appendix I).

3. Vitals.
4. Hematology exam (Appendix IV).
5. Serum chemistry exam (Appendix IV).
6. Echocardiogram and electrocardiogram (If completed prior to consent and within 28 days of C1D1, may count towards screening procedures).
7. Bone marrow aspirate and biopsy, including cytogenetics, within 28 days of therapy start to confirm diagnosis (If completed prior to consent and within 28 days of C1D1, may count towards screening procedures).
8. Serum pregnancy test for women of childbearing potential within Child bearing potential is defined as not post-menopausal for 12 months or no previous surgical sterilization.
9. Documentation in the medical record (consisting of start date, dose, frequency, route, and if applicable stop date) of all medications including vitamins and other over the counter medications.
10. Documentation in the medical record (consisting of start and stop date, dose, frequency and route) of any prior administration of cancer agent therapy.
11. Documentation in the medical record of all adverse events (graded per CTCAE V. 5.0) present at baseline. Documentation must include start and stop dates (if resolved), relationship to CPX-351 and grade.

11.1.2 Induction Therapy (C1D1 to C1D35 and/or count recovery).

1. Physical examination will occur daily while inpatient (Appendix IV).
2. ECOG performance status will be collected daily while in-patient (Appendix I).
3. Vitals will be collected daily while in-patient (Appendix IV).
4. Echocardiogram will be completed on day 1 prior to dosing.
5. Hematology exam on days 1-5, and twice weekly during days 6-27 (Appendix IV).
6. Serum chemistry exam on days 1-5, and twice weekly days 6-27 (Appendix IV).
7. Administration of CPX-351 at 44mg/m^2 on days 1, 3 and 5.
8. Bone marrow aspirate and biopsy, including cytogenetics, on D35 (+/- 10 days)

9. Disease response assessment will be assessed by the treating physician on D35 (+/- 10 days) (Table 2).
10. Serum pregnancy test on C1D1 only for women of childbearing potential. Child bearing potential is defined as not post-menopausal for 12 months or no previous surgical sterilization.
11. Documentation in the medical record (consisting of start date, dose, frequency, route, and if applicable stop date) of all medications including vitamins and other over the counter medications.
12. Documentation in the medical record (consisting of start and stop date, dose, frequency and route) of any prior administration of cancer agent therapy.
13. Documentation in the medical record of all adverse events (graded per CTCAE V. 5.0). Documentation must include start and stop dates (if resolved), relationship to CPX-351 and grade.

Consolidation Therapy (C2D1 to C5D28)

1. Physical examination on day 1 of each 28 day cycle (Appendix IV).
2. ECOG performance status will be collected on day 1 of each 28 day cycle (Appendix I).
3. Vitals will be collected prior to dosing on days 1 and 3 (Appendix IV).
4. Echocardiogram will be completed prior to dosing on day 1 of every cycle
5. Hematology exam on dosing days 1 and 3 of and twice weekly during each 28 day cycle (Appendix IV).
6. Serum chemistry exam on dosing days 1 and 3 and twice weekly during each 28 day cycle (Appendix IV).
7. Administration of CPX-351 at 15.4mg/m^2 (daunorubicin 15.4 mg/m^2 and cytarabine 35 mg/m^2) on days 1 and 3 of every 28 day cycle
8. Serum pregnancy test will be collected on day 1 of every 28 day cycle, only for women of childbearing potential. Child bearing potential is defined as not post-menopausal for 12 months or no previous surgical sterilization.

9. Documentation in the medical record (consisting of start date, dose, frequency, route, and if applicable stop date) of all medications including vitamins and other over the counter medications will be collected on day one of every 28 day cycle.
10. Documentation in the medical record (consisting of start and stop date, dose, frequency and route) of any prior administration of cancer agent therapy will be collected on day one of every 28 day cycle.
11. Documentation in the medical record of all adverse events (graded per CTCAE V. 5.0). Documentation must include start and stop dates (if resolved), relationship to CPX-351 and grade will be collected on day one of every 28 day cycle.

End of Treatment (EOT)

1. Physical examination (Appendix IV).
2. ECOG performance status (Appendix I).
3. Vitals (Appendix IV).
4. Hematology exam (Appendix IV).
5. Serum chemistry exam (Appendix IV).
6. Bone marrow aspirate and biopsy, including cytogenetics.
7. Disease assessment (Table 2).
8. Documentation in the medical record (consisting of start date, dose, frequency, route, and if applicable stop date) of all medications including vitamins and other over the counter medications will be collected.
9. Documentation in the medical record (consisting of start and stop date, dose, frequency and route) of any prior administration of cancer agent therapy will be collected.
10. Documentation in the medical record of all adverse events (graded per CTCAE V. 5.0). Documentation must include start and stop dates (if resolved), relationship to CPX-351 and grade will be collected.

11.2 Calendar

Period	Screening Period		Induction Phase						Consolidation Phase				End of Treatment (EOT)	Follow-up[g]
			1 cycle						Up to 4 cycles					
Day	28 Days	1	2	3	4	5	6-27	35[l]	1[dij]	2	3	4 - 28		
CPX-351 Administration[a]		X		X		X			X		X			
Informed Consent Form (ICF)	X													
Disease history and prior therapies	X													
History and physical exam[b]	X								X				X	
Vital signs[b]	X	X[op]		X[op]				X	X[op]		X[op]			
Concomitant medications	X	X							X				X	
ECOG performance status[c]	X								X				X	
Hematology[b]	X	X	X	X	X	X	X[n]	X	X[e]			X[n]	X	X[g]
Serum chemistry[b]	X	X	X	X	X	X	X[n]	X	X[e]			X[n]	X	
Pregnancy test	X	X[k]							X[k]					
Echocardiogram	X[r]	X[q]							X					
Electrocardiogram	X[r]													
Bone marrow biopsy and aspiration[b]	X[r]							X					X	
Disease response assessment[f]	X							X					X	
Correlative analysis blood draw[m]	X							X					X	
Survival follow-up														X[h]
Adverse event assessment	← X →													

a: During the induction phase all patients will receive 44mg/m^2. Following the induction phase if patients achieve a response (per section 12.0) they may continue onto the consolidation phase. During the consolidation phase patients will receive 15.4mg/m^2 (daunorubicin 15.4 mg/m^2 and cytarabine 35 mg/m^2) for up to 4 cycles.

b: See Appendix IV for required tests.

c: See Appendix I for performance status grading.

d: Indicates at +/-3 day window.

e: Required twice weekly to monitor counts, can be completed at a local laboratory.

f: See Section 12.0 for MDS response assessment criteria.

g: Follow up will occur monthly as SOC for the first 6 months of follow-up. See section 6.4 for adverse event reporting requirements.

h: Survival Follow up will occur bimonthly (60 days) for a duration of 1 year from patient's EOT visit.

i: During only the first cycle in consolidation phase, CPX-351 must be given no earlier than 35 days after the start of induction and no later than 75 days after the start of induction. There should be 35 days between the start of each subsequent consolidation cycles Patients must have recovered to ANC >500/µL and platelets >50,000/µL to be eligible for any consolidation therapy.

j: Prior to the first cycle of consolidation therapy, patient must have an ECOG PS of 0-2.

k: Must be negative prior to dosing.

l: Indicates a +/-10 day window.

m: 10mL of whole blood will be collected in an extra lab tube for these tests.

n: Hematology and serum chemistry will be assessed 1-3x weekly at the discretion of the treating physician to monitor counts. These can be completed at a local laboratory.

o: On dosing days, for induction phase only, vitals must be collected prior to infusion, 5, 10, 30 and 60 minutes post the start of infusion and at the end of infusion. On dosing days, for consolidation phase, vitals must be collected prior to infusion and at the end of infusion.

p: Indicates a (+/-) 5 minute window.

q: Required if patient has not had an ECHO within 28 days of C1D1.

r: If completed prior to consent and within 28 days of C1D1, may count towards screening procedures.

12.0 MEASUREMENT OF EFFECT

Response criteria will be defined by the IWG criteria ET 2006. Patients will be assessed for response at the end of induction cycle.

Response criteria will be defined as follow:

Response	**Definition** **Responses must be for at least 4 weeks)**
Complete remission (CR)	**Marrow**: < 5% myeloblasts with normal maturation of all cell lines. Persistent dysplasia will be noted (dysplastic changes should consider the normal range of dysplastic changes.) **Blood:** - Hemoglobin (Hgb) ≥ 11 g/dL (un transfused, patient not on EPO) - Neutrophils ≥ 1x109/L (not on myeloid growth factor) - Platelets ≥ 100 x 109/L (not on thrombopoietic agent) - No blasts
Partial remission (PR)	All CR criteria (if abnormal prior to treatment), except: Marrow blasts decreased by ≥50% compared with pretreatment but still > 5%. Cellularity and morphology not relevant
Marrow CR	Marrow: ≤ 5% myeloblasts and decrease by ≥ 50% over pretreatment Blood: if hematologic improvement (HI) responses, they will be noted in addition to the marrow CR
Stable disease (SD)	Failure to achieve at least PR, but no evidence of progression for > 8 weeks
Failure	Death during treatment or disease progression characterized by worsening of cytopenias, increase in percentage of marrow blasts, or progression to an MDS FAB subtype more advanced than pretreatment.

Relapse after CR or PR (PD)	At least one of the following: - Return to pretreatment bone marrow blast percentage - Decrement of ≥ 50% from maximum remission/response levels in granulocytes or platelets - Reduction in Hgb concentration by ≥ 1.5 g/dL or transfusion dependence (in the absence of another explanation, such as acute infection, GI bleeding, hemolysis, etc.)
Cytogenetic response	Complete: Disappearance of the chromosomal abnormality without appearance of new ones Partial: At least 50% reduction of the chromosomal abnormality
Hematologic Improvement	**Response Criteria (responses must last at least 8 weeks)**
Erythroid response (pretreatment, < 11 g/dL)	Hgb increase by ≥ 1.g/dL Relevant reduction of units of RBC transfusions by an absolute number of at least 4 RBC transfusions/8wk compared with the pretreatment transfusion number in the previous 8 wk. Only RBC transfusions given for a Hgb of ≤ 9 g/dL pretreatment will count in the RBC transfusion response evaluation
Platelet response (pretreatment, < 100x109/L)	Absolute increase of ≥ 30 x 109/L for patients starting with > 20 x 109/L Increase from < 20 x 109/L to > 20 x 109/L and by at least 100%
Neutrophil response (pretreatment, < 1 x 109/L)	At least 100% increase an absolute increase > 0.5 x 109/L
Progression or relapse after HI	At least 1 of the following: At least 50% decrement from maximum response levels in granulocyte or platelets Reduction in Hgb by ≥1.5 g/dL Transfusion dependence (in the absence of another explanation, such as acute infection, GI bleeding, hemolysis, etc.)

Table 3: Response Criteria for MDS Patients

13.0 DATA REPORTING / REGULATORY CONSIDERATIONS

Adverse event lists, guidelines, and instructions for AE reporting can be found in Section 8.0 (Adverse Events: List and Reporting Requirements).

13.1 Data Reporting

The OnCore® Database will be utilized, as required by the Case Comprehensive Cancer Center, to provide data collection for both accrual entry and trial data management. OnCore® is a Clinical Trials Management System housed on secure servers maintained at Case Western Reserve University. OnCore® Access to data through OnCore® is restricted by user accounts and assigned roles. Once logged into the OnCore® system with a user ID and password, OnCore® defines roles for each user which limits access to appropriate data. User information and password can be obtained by contacting the OnCore® Administrator at OnCore-registration@case.edu.

OnCore® is designed with the capability for study setup, activation, tracking, reporting, data monitoring and review, and eligibility verification. This study will utilize electronic Case Report Form completion in the OnCore® database. A calendar of events and required forms are available in OnCore®.

13.2 Regulatory Considerations

The study will be conducted in compliance with ICH guidelines and with all applicable federal (including 21 CFR parts 56 & 50), state or local laws.

13.2.1 Written Informed consent

Provision of written informed consent must be obtained prior to any study-related procedures. The Principal Investigator will ensure that the subject is given full and adequate oral and written information about the nature, purpose, possible risks and benefits of the study as well as the subject's financial responsibility. Subjects must also be notified that they are free to discontinue from the study at any time. The subject

should be given the opportunity to ask questions and be allowed time to consider the information provided.

The original, signed written Informed Consent Form must be kept with the Research Chart in conformance with the institution's standard operating procedures. A copy of the signed written Informed Consent Form must be given to the subject. Additionally, documentation of the consenting process should be located in the research chart.

13.2.2 Subject Data Protection

In accordance with the Health Information Portability and Accountability Act (HIPAA), a subject must sign an authorization to release medical information to the sponsor and/or allow the sponsor, a regulatory authority, or Institutional Review Board access to subject's medical information that includes all hospital records relevant to the study, including subjects' medical history.

13.2.3 Retention of records

The Principal Investigator of The Case Comprehensive Cancer Center supervises the retention of all documentation of adverse events, records of study drug receipt and dispensation, and all IRB correspondence for as long as needed to comply with local, national and international regulations. No records will be destroyed until the Principal Investigator confirms destruction is permitted.

13.2.4 Audits and inspections

Authorized representatives of the sponsor, a regulatory authority, an Independent Ethics Committee (IEC) or an Institutional Review Board (IRB) may visit the site to perform audits or inspections, including source data verification. The purpose of an audit or inspection is to systematically and independently examine all study-related activities and documents to determine whether these activities were conducted, and data were recorded, analysed, and accurately reported according to the protocol, Good Clinical Practice (GCP), guidelines of the International Conference on Harmonization (ICH), and

any applicable regulatory requirements. For multi-center studies, participating sites must inform the sponsor-investigator of pending audits.

14.0 STATISTICAL CONSIDERATIONS

In determining the sample size for the patient cohort, Minimax Simon's two-stage design (Simon, 1989) will be used. The null hypothesis that the true response rate is 0.1 will be tested against a one sided alternative. In the first stage, 7 patients will be accrued in each arm. If there are two or less responses in these 7 patients, the arm will be stopped. Interim analysis will conducted to determine the benefit of applying the drug in each arm. In the winning arm, 11 additional patients will be accrued for a total of 18. The null hypothesis will be rejected if 4 or more responses are observed in 18 patients. This design yields a type I error rate of 0.1 and power of 0.8 when the true response rate is 0.3.

Descriptive statistical analysis will be calculated, including histograms or box-plots, proportions, range, means and standard deviations. Fisher's exact test and Wilcoxon rank test will be used in univariate analyses of categorical and continuous variables, respectively. Overall response (CR + CRi +) rate and its 95% CI. Given there is no adjustment for multiple comparisons, need to note the p-values from the univariate analyses will be nominal and not used to infer significance.

Toxicity Monitoring Rules

The following toxicity monitoring plan will terminate the trial early given evidence for excessive rates of toxicity with CPX-351based on the method of Thall et al.[14] Early termination will be applied to evaluate patients experiencing toxicity defined as any grade $\geq$3 non-hematologic AE that is determined to be at least possibility related to CPX-351. A total of 25 patients will be enrolled. The monitoring rules target a toxicity rate of 20% and assume a non-informative Beta (0.2, 0.8) prior distribution. The trial will stop early for toxicity if Pr(Toxicity Rate > 0.20 | data) > 0.85, i.e. stop early if the evidence for excessive toxicity (higher than 20%) for the target population given observed data is sufficiently high (probability > 0.85). Monitoring will be carried out

from the 3rd patient. Table 5 summarizes the resultant stopping boundaries and Table 6 summarizes the trial's operating characteristics.

Table 5. Summary of early stopping boundaries from the 3rd patient. Target toxicity rate is 20%. Using prior of Beta (0.2, 0.8) and posterior probability threshold of 0.85. E.g. If 3 or more patients experience grade ≥3 non-hematologic AEs out of the first 6 patients, the trial will stop early. Whenever a grade ≥3 non-hematologic AE is observed, check this table to see if the boundary has been crossed. E.g. if a total of 4 grade ≥3 non-hematologic AEs has been observed on trial, and the total number of patients treated is 9 or less, then stop the trial for excessive toxicity.

Stop Early if #Patients Experienced grade ≥3 non-hematologic AE	2	3	4	5	5	6	7	8
Total #Patients Treated	3	6	9	12	15	18	21	24

Table 6. Summary of operating characteristics based on 10,000 simulations using boundaries in Table 5 for early stopping. For example, if the true toxicity rate is 20%, the probability of early stopping is 0.27, and if the true toxicity rate is 40%, the probability of early stopping is 0.88.

Scenario	True Toxicity Rate	Pr(Early Stop)	Average #Patients Treated	Average #Toxicities
1	- 0.10	0.05	23.2	2.3
2	0.20	0.27	19.8	4.0
3	0.30	0.62	14.6	4.4
4	0.40	0.88	9.8	3.9

Summary statistics of toxicity will be provided in frequencies and percentages. Toxicity rate will be estimated along with 95% CIs. Other statistical analyses will be carried out as appropriate.

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APPENDIX I

PERFORMANCE STATUS CRITERIA

ECOG Performance Status Scale		Karnofsky Performance Scale	
Grade	Description	Percent	Description
0	Normal activity. Full 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% if 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

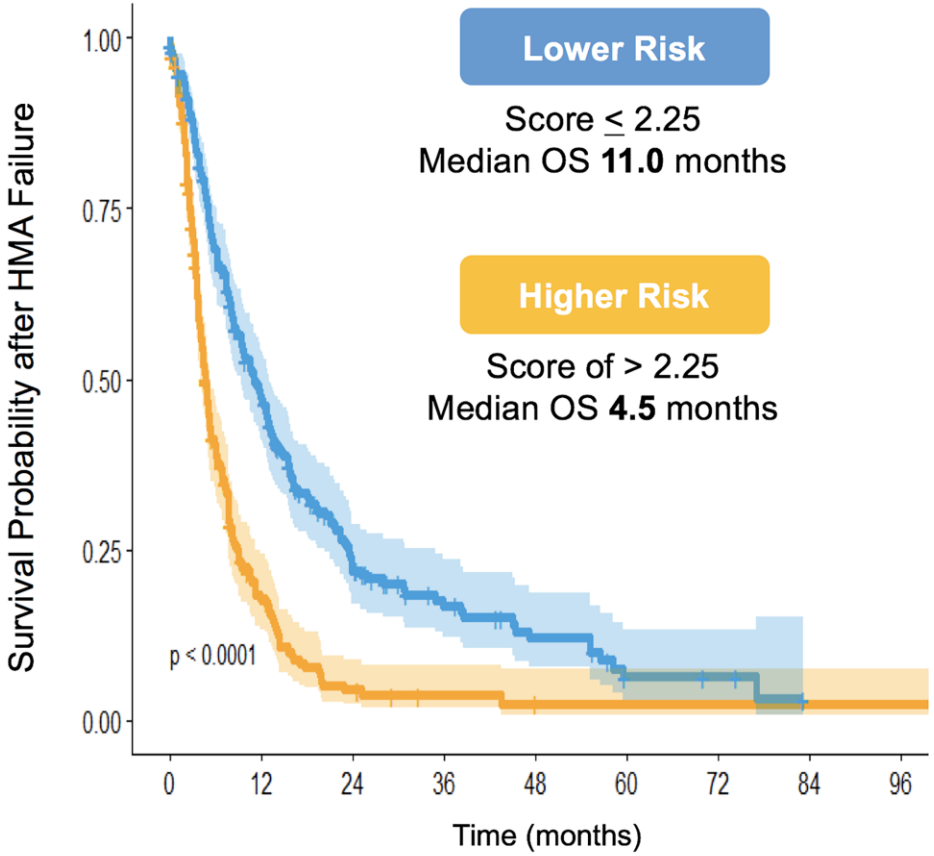
APPENDIX II: STUDY DESIGN TIME POINT DEFINITIONS

Study Time Points	Definitions
Screening	The screening period will occur over 28 days from the time of consent to day -1.
Induction Period	Day 1[a] to D35 and/or count recovery
Disease Response	The D35 (+/-10 days) bone marrow.
Consolidation Period	The consolidation period is defined as C2D1 through C5D28. Patients who meet disease response criteria will be eligible to receive up to 4 cycles of consolidation therapy.
End of Treatment (EOT)	The day patients meets the defined EOT criteria (Table 1) and discontinues study treatment.
Follow up	Patient will be followed monthly as SOC every 30 days for the duration of 6 months after EOT.
End of Study (EOS)	The time the patient completes 1 year of follow up and/or patient's death, whichever were to occur first.
a: Day 1 is defined as the first dose of CPX-351	

APPENDIX IV: STUDY DESIGN TIME POINT DEFINITIONS

Hematology	Serum Chemistry	Vitals	Physical Exam	Bone Marrow Biopsy & Aspirate
RBC count	Total protein	Temperature	Height[a]	Marrow blast percent
WBC count	Albumin	Respirations	Weight[b]	Marrow cellularity
Hematocrit	Sodium	Blood Pressure		Auer Rods
Hemoglobin	Potassium	Pulse		Dysplasia
MCV	Chloride			Cytogenetics
MCHC	Bicarbonate			
Platelet count	Glucose			
Neutrophils	AST			
Eosinophils	ALT			
Basophils	Creatinine			
Monocytes	Calcium			
Lymphocytes	Bilirubin			
Blast percent	Alkaline phosphate			
	Phosphorus			
	Uric acid			
	Magnesium			
a: Height will only be collected at screening b: On dosing days, weight will be collected prior to dosing				

APPENDIX V: Post-HMA Failure Model



Parameter at HMA failure	Score
ECOG Performance status > 1	1.0
Complex Karyotype (≥ 4 abnormalities)	1.0
Age, years	
> 75 - ≤ 84	1.0
> 84	2.0
Bone Marrow Blast > 20 %	.75
Transfusion dependent (yes)	.75
Platelets × 10^9/L	
< 30	1.0

Post-HMA Failure Model