A Phase 2 Study of CPX-351 for treatment of AML or higher risk MDS relapsed or refractory to prior therapy with Hypomethylating (HMA) Agent

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Study IRB-28524 NCT02019069

Prior Date: 25 August 2015
Revision Date: 28 February 2017
SRC Approval Date: 14 October 2013

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PROTOCOL SYNOPSIS .....

TITLE	A Phase 2 Study of CPX-351 for treatment of AML and higher risk MDS relapsed or refractory to prior therapy with Hypomethylating (HMA) agent
STUDY PHASE	Phase 2 Study
INDICATION	Treatment of older patients with AML or Higher Risk MDS, relapsed or refractory to HMA therapy
INVESTIGATIONAL PRODUCT	CPX-351
PRIMARY OBJECTIVE(S)	1) Determine the efficacy of CPX-351 in study population. Outcome measure: response rate (CR + CRi) 2) Determine the safety of CPX-351 in study population. Outcome measure: Safety Data (30 and 60 day mortality, SAEs, Grade 3-5 AE frequency) Study Population: Subjects age 60 and older with: 1) higher risk MDS who are refractory or relapsed after prior HMA therapy 2) Subjects with MDS who are HMA relapsed or refractory who have progressed to AML 3) AML with refractory/relapsed disease after prior HMA therapy
SECONDARY OBJECTIVE(S)	1) Determine the duration of remission 2) Determine overall survival at 12 months 3) Determine the early induction mortality at Day 60 after 1st induction
TREATMENT SUMMARY	Up to 2 courses of induction therapy are allowed. First Induction: CPX-351 at a dose of 65 units/m2/day, on Days 1, 3, and 5; Second Induction: CPX-351 at a dose of 65 units/m2/day on Days 1 and 3; Up to 2 courses of post-remission therapy are allowed: CPX-351 at a dose of 65 units/m2/day, on Days 1 and 3.
SAMPLE SIZE	33
STATISTICAL CONSIDERATIONS	Simon 2-stage minimax design being used to determine the sample size and optimizing identification of early effect.

DOSING SCHEME

COURSE	CPX-351 DOSE
INDUCTION 1	65 units/m2/day on Day 1, 3, and 5
INDUCTION 2	
- Full Dose	65 units/m2/day on Day 1 and 3
- Reduced Dose*	43 units/m2/day on Day 1 and 3
CONSOLIDATION 1	
- Full Dose	65 units/m2/day on Day 1 and 3
- Reduced Dose*	43 units/m2/day on Day 1 and 3
CONSOLIDATION 2	
- Full Dose	65 units/m2/day on Day 1 and 3
- Reduced Dose*	Either 30 or 43 units/m2/day on Day 1 and 3

***Reduced doses may be given based on toxicities experienced during prior cycles**

LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

ADL	Activities of daily living
AE	Adverse event
AML	Acute Myeloid Leukemia
BID	Twice daily
BSA	Body surface area
CBC	Complete blood count
CI	Confidence interval
CMAX	Maximum concentration of drug
CNS	Central nervous system
CRF	Case report/Record form
CR	Complete response
CTCAE	Common Terminology Criteria for Adverse Events
DLT	Dose Limiting Toxicity
DSMB	Data Safety Monitoring Board
ECG	Electrocardiogram
GI	Gastrointestinal
Hgb	Hemoglobin
HIV	Human Immunodeficiency Virus
HMA	Hypomethylation therapy
HPF	High-power field
HTN	Hypertension
IRB	Institutional Review Board
IV	Intravenous
LLN	Lower limit of normal
MDS	Myelodysplastic syndrome
OS	Overall survival
PLT	Platelet
PD	Progressive diseased
PFS	Progression free survival
PR	Partial response
QD	Once daily
RR	Response rate
SAE	Serious adverse event
SD	Stable disease
TTP	Time to progression
ULN	Upper limit of normal
UNK	Unknown
WBC	White blood cell
WHO	World Health Organization

1. OBJECTIVES

1.1 Primary Objectives

The primary objective of this study will be to determine the efficacy and safety profile of the use of CPX-351 in older patients (age 60 and older) with:
- Higher risk MDS who are refractory/relapsed after prior HMA therapy
- Subjects with MDS who are HMA relapsed/refractory who have progressed to AML
- AML with refractory/relapsed disease after prior HMA therapy for AML

1.2 Primary Outcome Measures:

- Determine safety in this patient population
- Determine the response rate (CR + CRi for AML + CR for MDS) following induction with CPX-351

1.3 Secondary Objectives

- Determine the duration of remission following induction therapy with CPX-351
- Determine overall survival at 12 months
- Determine the early induction mortality (at 60 days) following CPX-351 in this cohort following induction therapy

2. BACKGROUND

2.1 Study Disease: AML and MDS

2.1.1 Acute Myeloid Leukemia

Acute myeloid leukemia is predominantly a disease of the older adults with a median age of diagnosis of 67 years [1]. Standard induction chemotherapy for acute myeloid leukemia consists of cytarabine plus an anthracycline. Predictors of adverse prognosis with this treatment include age > 60 years, poor risk karyotype abnormalities, poor performance status, and secondary AML [2]. Treatment with a supportive care strategy alone results in median survival on the order of several weeks [3]. Standard induction chemotherapy in older adults results in suboptimal outcomes, with complete response (CR) rates of 40% and a median survival of 1 year [4]. For older patients with poor risk cytogenetics and AML secondary to an antecedent hematologic malignancy, complete response (CR) rates are in the 20-30% range, and most patients relapse within 3-6 months. Similarly patients who relapse or do not achieve complete remission with traditional induction chemotherapy have a poor prognosis with reinduction therapy [5]. For these reasons, there is currently no standard of care for treatment in this patient population, and the National Comprehensive Cancer Network (NCCN) guidelines list clinical trials as a first-line option for almost all AML patients over the age of 60 (NCCN guidelines for AML). Therapy options include traditional induction chemotherapy, supportive care with transfusions and growth factor support as tolerated, low dose cytarabine, hypomethylating agents (HMA) with the azanucleosides (azacitadine or decitabine), and use of lenalidomide.

2.1.2 Symptomatic Myelodysplastic syndrome (MDS)

The risk of MDS increases with increasing age. The median age in most series is >/= 65 years. Risks of progressive MDS include bone marrow failure and progression to AML. Current treatment strategies include transfusion and growth factor support, as well as treatment with hypomethylation therapy (HMA) and lenalidomide in select patients.

2.1.3 Outcomes of HMA treatment in MDS

The CALGB 9221 (comparing azacitidine versus best supportive care) and AZA-001 (comparing azacitidine to several different types of conventional care) studies helped establish HMA therapy as the first line standard of care for most patients with higher risk MDS [6-8]. In the CALGB 9221 study, 191 patients with a median age of 68 with MDS were randomized to azacitidine (AZA) versus best supportive care. The response rate was 60% in the azacitidine group (CR 7%, PR 16%, improvement 37%) vs 5% in the best supportive care group; there was a trend towards improved median overall survival in the AZA arm, however it was non-significant (20 months vs 14 months, p=0.10; including significant 53% cross-over; [6]). In the AZA-001 trial, randomizing 358 patients with higher risk MDS to azacitidine vs conventional care arm (either best supportive care or low dose cytarabine or intensive treatment; no cross-over allowed), median overall survival was prolonged in the azacitidine group (24.5 mo vs 15 mo, p=0.0001) [7]. Of note, in patients who are not transplant eligible, it is uncertain whether HMAs are superior to intensive chemotherapy (in the AZA-001 trial, the cohorts comparing intensive chemotherapy vs AZA were small) [7, 9]. Patients with higher risk MDS who have failed hypomethylation therapy or have progression to AML on HMA therapy, have limited therapeutic options (see below for further discussion).

2.1.4 Outcomes of HMA treatment in AML

In the original AZA-001 trial [7] 113 study patients originally classified as MDS were reclassified as AML based on the WHO classification from 2008. In a second analysis of these patients, there was no significant difference in the CR rate between the AZA versus conventional care arm; however there was a significant difference in the median overall survival of 24.5 months versus 16 months (HR=0.47, p=0.005;[10]). However it is important to remember this analysis involves only patients with a low blast count AML. In a phase II study of decitabine in older patients with untreated AML (who were not candidates for or refused intensive chemotherapy), the response rate was 64% (CR+CRi) with a median overall survival of 55 weeks [11]. For newly diagnosed AML, the decision to proceed with either intensive chemotherapy or HMA therapy first line is often at physician-patient discretion after discussion of the two options.

2.1.5 Outcomes of HMA treatment failure in MDS and secondary AML

Unfortunately most responders to HMA therapy progress within 2 years (secondary HMA treatment failure) and a significant portion of patients have no response with initial HMA therapy (primary HMA treatment failure). There are no consistent markers at this time to prospectively predict who will fail primary HMA therapy. Several recent retrospective reviews have evaluated the outcome of patients who fail HMA therapy. In a retrospective review of the outcome of 74 patients with secondary AML (arising from MDS) after azacitidine failure, the median overall survival was found to be only 3.4 months with a one year survival of 8% [12]. In another retrospective review [13] the outcome of 435 patients with high risk MDS/RAEB-T post azacitidine failure was evaluated. Median overall survival was only 5.6 months and 2 year survival probability was 15%. In another retrospective review [14], evaluating the outcome of 87 patients with MDS and CMML with failure

to decitabine (defined as primary failure, loss of response, or progression to AML), a similarly poor outcome was identified with a median survival of 4.3 months after decitabine failure with a 12 month survival rate of 28%. Of the 87 patients, 22 patients had evolved to AML at the time of decitabine failure and 65 patients remained with MDS. Of the patients with AML, 10 received chemotherapy with Idarubicin and Cytarabine (IA), with 2 achieving CR and one patient achieving a bone marrow CR. Of the 65 patients with MDS, 10 received IA chemotherapy with 2 patients obtaining a bone marrow CR; 30 patients received investigational agents; 2 patients of 4 undergoing an allogeneic stem cell transplant achieved a sustained CR >/= 24 months. Thus these results reveal the following:

1) patients with higher risk MDS and AML who fail HMA therapy have very poor outcomes, after both primary and secondary failure;
2) new treatment strategies are needed in patients with higher risk MDS and AML who have failed HMA therapy; there are no standard treatment options in this patient population;
3) patients who have failed prior HMA therapy can still respond to intensive chemotherapy, though with sub-optimal outcomes with current intensive chemotherapy.

2.2. Study Agent Summary

CPX-351 is a liposomal formulation of a fixed molar ratio of 5:1 of cytarabine:daunorubicin. The 2 drugs are present inside each liposome. The liposome membrane is composed of distearoylphosphatidylcholine, distearoylphosphatidylglycerol, and cholesterol in a 7:2:1 molar ratio. These liposomes have a diameter of approximately 100 nm and are suspended in sucrose. CPX-351 will be provided from Celator pharmaceuticals as a sterile, pyrogen free, purple, lyophilized product in 50 mL glass, single-use vials. Sterilization is done via filtration through a 0.22 um filter. Vials are stored at 5 degrees +/- 3 degrees Celsius. Each vial after initial reconstitution with 20 ml sterile water contains 100 units of CPX-351 (5 units per mL; 100 units per vial). Each unit contains 1.0 mg cytarabine and 0.44 mg daunorubicin base in liposomes. After dilution in either normal saline or dextrose injection to a final concentration of 0.10 units/ml to 1.32 units/ml, CPX-351 is infused over 90 minutes intravenously through either a peripheral or central venous access.

Cytarabine is a traditional anti-metabolite chemotherapy agent thought to work by interfering with DNA synthesis in its active triphosphate form (cytosine arabinoside triphosphate). It may also inhibit alpha-DNA polymerase and inhibit DNA repair through effects on beta-DNA polymerase. Daunorubicin is a traditional chemotherapy agent of the anthracycline family thought to cause DNA damage via affecting topoisomerase II, leading to changes in DNA coiling/uncoiling and ligation/religation, ultimately affecting DNA and RNA synthesis. Anthracyclines may also cause reactive oxygen species generation.

CPX-351 was developed as a more efficacious drug compared to the free drug combination of cytarabine and daunorubicin. The proposed mechanism for increased efficacy compared to free drug treatment includes the following:

1. The 5:1 molar ratio of the cytarabine:daunorubicin is synergistic; this combination was found to be synergistic in leukemia cell lines and murine models;
2. The 5:1 ratio was found to be maintained for >24 hours after infusion;
3. The liposomal formulation provides drug stability compared to free drug cocktail with CPX-351 found to be in circulation for >7 days after infusion;

4. CPX-351 accumulates in the bone marrow;
5. Preferential uptake of CPX-351 has been observed within the cytoplasm of leukemic cells. The combined effect of the mechanisms above have been the proposed mechanism overall by which CPX-351 has an increased rate of leukemic cell clearance compared to traditional induction therapy given as free drug.

In the preclinical studies by [15] various fixed ratio liposomal formulations of combined cytarabine and daunorubicin were tested in leukemia cell lines and murine models; the 5:1 cytarabine:daunorubicin drug ratio (CPX-351) was the most synergistic. *In vivo* pharmacokinetics in a mouse model were significant for findings of a longer elimination half-life with CPX-351, with the maintenance of a ratio of cytarabine:daunorubicin of 5:1-9:1 for over 24 hours whereas free drug was noted to be rapidly removed from the circulation. The absolute plasma concentrations of both drugs were significantly higher with CPX-351 compared to administration of free drug cocktail. Fixed drug ratio liposomal formulations ranging from 1:1 to 12:1 were evaluated in a P388 leukemia mouse model, with findings of the 5:1 drug ratio being most therapeutically active with findings of increased survival. In the CCRF-CEM human leukemia xenograft model, CPX-351 was found to accumulate in the bone marrow, and in particular, the concentration of cytarabine and daunorubicin was found to be higher in leukemic cells compared to normal bone marrow cells.

Cytarabine is normally metabolized to its active form, cytosine arabinoside triphosphate by deoxycytidine kinase. It is inactivated by pyrimidine nucleoside deaminase, which converts it to a non-toxic uracil derivative (ara-U). Daunorubicin is extensively metabolized in the liver and other tissues to daunorubicinol, which is the major metabolite with antineoplastic activity. Daunorubicin is eliminated by both urinary and biliary excretion. In pharmacokinetic analysis of preclinical mouse, rat, and dog models, following CPX-351 administration, cytarabine: daunorubicin ratios were noted to be maintained between 3:1-10:1 (depending on the model) for 24 hours, whereas free drug cocktails had more rapid changes in ratio and exposure time. CPX-351 was found to have linear pharmacokinetics with low volume of distribution. In pharmacokinetic evaluation of CPX-351 in humans, parent drugs and their major metabolites were detected in plasma, reflecting bioavailability, with increased half-life in comparison to predicted values of clearance of free drug cytarabine and daunorubicin.

There have been three clinical studies of CPX-351 that have finished accrual. In the first in man initial phase I/II study [16] patients with relapsed and refractory acute myeloid leukemia, acute lymphoblastic leukemia, or high risk MDS, with a median age of 60.5 (range 25-78), were treated with CPX-351. The identified maximum tolerated dose was 101 units/m2 and responses were seen in patients with previously treated, relapsed AML. Of the total 48 patients in the study (36 in the Phase I; 12 in phase II added), 43 (89.6%) had AML (5 primary refractory, 18 first salvage, 10 second salvage, 10 >2nd salvage); 10 of these 43 patients obtained a remission (9 CR, 1 CR with incomplete platelet recovery). 5 of the remissions were seen in patients >60 years of age. The median duration of remission was 6.9 months. In terms of pharmacokinetic results, the 5:1 molar ratio of cytarabine: daunorubicin was maintained for up to 24 hours on days 1 and 5 at all dose levels; the mean elimination half-lives of daunorubicin and cytarabine were markedly prolonged with CPX-351, compared to expected values with traditional use of these drugs.

In Study 204, a phase II study in newly diagnosed, older patients with AML age 60-75, CPX-351 was randomized to traditional induction 7+3 therapy in a 2:1 randomization. Patients with both standard risk and high risk AML were included. High risk AML was defined as having either older

age (age 70-75), complex cytogenetics (>/= 3 cytogenetic abnormalities) or secondary AML. The response rate was 66.7% in the CPX-351 group compared to 51.2% in the 7+3 treatment group (p=0.0712), with increased responses seen in the CRi group of patients receiving CPX-351 compared to standard 7+3 treatment. Kaplan-Meier analysis after a minimum followup of 1 year was notable for non-significant improvement in event free survival and overall survival in the CPX-351 group. Early induction mortality (at Day 30 and 60) trended towards being lower for CPX-351 (4.7% vs 14.6%, p=0.053) compared to 7+3. In patients with secondary AML, treatment with CPX-351 resulted in reduced 60-day early mortality (6.1% vs 31.6%) and a statistically significant survival advantage (median OS 12.1 mo vs 6.1 mo; HR = 0.41, p=0.02) in comparison to 7+3.

In Study 205, a phase II trial in patients with AML in first relapse age 18-65, CPX-351 was randomized to induction therapy of investigator choice. The response rate was 49.4% in the CPX-351 arm versus 40.9% in the salvage control arm, with median OS of 8.5 months versus 6.3 months respectively. CPX-351 was found to have a significant difference in median OS in the unfavorable EPI risk group (6.6 months vs 4.2 months, HR 0.55, p=0.02).

Based on the clinical trials above, the safety profile for CPX-351 appears to be similar to traditional 7+3 therapy. The most common grade 3-5 adverse events (>10%) included febrile neutropenia, bacteremia, pneumonia, sepsis, fatigue, and hypokalemia. CPX-351 therapy did results in higher rates of bone marrow aplasia, and concomitantly, longer periods of neutropenia and thrombocytopenia were seen, with higher rates of infection and bleeding events. However the 60-day mortality in Study 204 with direct comparison of CPX-351 vs 7+3 was notable for lower mortality in the CPX-351 arm (Study 204: 4.7% vs 14.6%). This suggests that increased clearance of disease in this particular study was an important factor contributing to reduction in early mortality risk.

In terms of drug interactions with CPX-351, there are no drug interaction studies of CPX-351 specifically. Drug interactions are expected to be similar to those expected with cytarabine and daunorubicin.

The current proposed trial will be to evaluate the safety and efficacy of CPX-351 for patients with higher risk MDS and AML refractory or relapsed to hypomethylation therapy, a population with an un-met need for treatment options. The dosing regimen will be CPX-351: 65 units/m2/day on Days 1, 3, 5 during induction therapy #1. A second course of induction therapy with CPX-351 at 65 units/m2/day on Days 1 and 3 will be allowed depending on response during induction #1. Patients achieving a complete remission or complete remission with incomplete count recovery (CR or CRi) after induction therapy will be eligible to proceed with 2 courses of consolidation therapy with CPX-351 at doses of 65 units/m2/day on Days 1 and 3 during each course of consolidation therapy. Patients achieving a CR/CRi will be allowed to proceed with a hematopoietic stem cell transplant (HSCT) should they have a donor and wish to proceed for post remission therapy.

The maximum tolerated dose for induction therapy from the initial phase I/II trial was found to be CPX-351 101 units/m2 on Days 1, 3, and 5. In the initial phase I/II trial, 3 of the total 11 remissions (CR/CRi) were noted in lower dose levels: 43 units/m2 (2 patients: 1 with AML and 1 with ALL) and 76 units/m2 (1 patient with AML). Our patient population will include patients older than 75 (whereas the phase II study 204 was limited to age 60-75) with a combined population of higher risk MDS and AML with age > 60 without preset upper age limit. Given underlying hematologic dysplasia expected in patients with MDS, as well as the older age group in our patient population,

we have chosen a lower dose of CPX-351 for induction and consolidation therapy, since it will be important to identify whether a dose between 43-75 units/m2 confers benefit without additional risk. Additionally given the poor outcome of patients with HMA failure in both AML and MDS, there may be inherently different biological features of patients with HMA responsive and HMA refractory disease that may predispose them to have different outcomes to drug therapies.

2.3 Rationale

We hypothesize that CPX-351 will be effective in clearance of leukemic or dysplastic clones in patients who have failed prior HMA given: 1) its increased total plasma concentration and maintenance of a synergistic ratio for 24 hours, 2) accumulation in bone marrow and proposed preferential uptake in leukemic cells compared to normal bone marrow cells.

Interestingly, in the subset analysis of patients in the phase II trial of CPX-351 (study 204), the response rate (CR/CRi) in secondary AML was an impressive 57.5% in the CPX-351 arm vs 31.6% in the 7+3 arm. The 60-day mortality was also reduced in the CPX-351 arm (6.1% versus 31.6%). Additionally there was a significant difference in the median overall survival between the two groups (12.1 months versus 6.1 months; p=0.02; HR 0.41). Thus Celator pharmaceuticals is in the process of developing CPX-351 further in a phase III randomized trial of 7+3 versus CPX-351 in patients with previously untreated secondary AML.

However there are no trials of CPX-351 in patients with relapsed/refractory higher risk MDS and AML after prior HMA therapy. HMA therapy is the standard of care for patients with higher risk MDS. However if they have primary refractory disease or relapse after prior HMA therapy or progress to AML on HMA therapy, there is currently no standard of care for this group of patients. HMA therapy is also now actively being investigated in patients with AML. For patients with AML who fail HMA therapy (primary refractory) or have progressive disease on HMA therapy after initial response, there is similarly no current standard of care. Therefore we believe it will be important to identify the safety and efficacy of CPX-351 in this patient population, which has a very poor outcome at present.

Thus, given the encouraging response rate of CPX-351 seen in older patients with AML, including secondary AML, and the reasonable 60 day mortality seen in the prior phase II trial in older patients, we propose an open label phase II study of CPX-351 in older patients (age 60 and older) with higher risk MDS and AML with HMA relapsed or refractory disease.

2.4 Study Design

This will be an open label, fixed dose intervention phase II trial of CPX-351 in patients with higher risk MDS with HMA refractory/relapse disease, and patients with AML with failure to prior HMA therapy for either AML or MDS. The primary outcome is designed to evaluate safety and efficacy of CPX-351 in this patient population.

2.4.1 Study treatment

In this study patients will receive CPX-351 for induction course #1 at a dose of 65 units/m2/day on days 1, 3 and 5 intravenously, over approximately 90-minute infusions. The doses of CPX-351 are calculated using the patient's actual weight.

- Patients who have evidence of morphological leukemia free state with < 5% blast count on Day 14 marrow (+/-3 days) will be monitored for count recovery, followed by consolidation therapy for those patients achieving a CR/CRi. Each consolidation therapy course will consist of CPX-351

given at a dose of 65 units/m2/day on days 1 and 3, given over approximately 90 min infusions. A second course of consolidation will be given after appropriate count recovery after the first consolidation course.

- For patients who have a reduced blast count on the Day 14 marrow (+/- 3 days) compared to baseline but have not yet achieved a morphological leukemia free state (< 5% blasts), a second course of induction with CPX-351 will be given, at a dose of 65 units/m2/day on Days 1 and 3.
- Patients who have absolutely no change in the blast count on the Day 14 marrow (+/- 3 days) compared to baseline will be discontinued from study treatment and followed for survival
- Patients whose assessment of a morphological leukemia free state on the Day 14 (+/-3 days) marrow is equivocal by pathology, will have a repeat bone marrow biopsy done 7+/-3 days later. If repeat marrow shows morphological leukemia free state with < 5% blasts, patients will be monitored for count recovery followed by consolidation therapy for patients achieving a CR/CRi. If repeat marrow shows ≥ 5% blasts, patients will undergo a second induction course with CPX-351 at a dose of 65 units/m2/day on days 1 and 3.
- For patients who achieve an initial morphologic leukemia free state after first induction but have disease relapse within (≤) 15 days (defined by > 5% blasts on bone marrow biopsy or peripheral circulating blasts) will be eligible for a second course of induction therapy at PI discretion, if safe to administer.
- Patients who achieve a CR/CRi after a second course of induction, will receive consolidation therapy. Patients who are unable to achieve a CR/CRi after a second course of induction, will be discontinued from the study and followed for survival.

2.4.2 Patient population

We plan on evaluating CPX-351 in 3 primary populations: (A) patients with higher risk MDS age 60 and older who are refractory/relapsed after prior HMA therapy, (B) patients with AML age 60 and older who are refractory/relapsed after prior HMA therapy, (C) Subjects age 60 and older with higher risk MDS who are HMA relapsed/refractory who have progressed to AML.

2.5 Correlative Studies Background

Traditionally cytogenetics have been used to stratify patients with AML into three main risk-categories: favorable, intermediate, and poor risk [2, 17] with risk categorization being relevant to both prognosis as well as treatment guidance in relation to traditional induction and consolidation therapy. More recently, molecular characterization of AML has identified significant genotypic and epigenetic heterogeneity. Mutations in FLT3, NPM1, and CEBPA have been shown to have prognostic and treatment relevance [18]. Current institutional standard of care includes assessment of cytogenetics and molecular analysis. Cytogenetic analysis is also an important component of the IPSS prognostic evaluation in patients with MDS [19]. A cancer somatic mutation panel (also called snapshot panel) is also routinely obtained at Stanford for patients with neoplasms. Thus as part of routine evaluation of patients with AML and MDS, we will review cytogenetic and molecular mutational data as available. We will then compare whether cytogenetic or certain molecular mutations are associated with response to CPX-351. The sample size from a genetic perspective, may be a limitation of noting an association; however if possible associations noted, this can be pursued further in the future by evaluating a larger group of patients who have received CPX-351 and comparing responders to non-responders in prior or future studies of CPX-351. Given that the response rate was higher in Study 204 of CPX-351 in comparison to 7+3 in older patients,

particularly with additional patients achieving CRi, we hypothesize that the pharmacokinetic properties of CPX-351 result in deeper clearance of leukemic cells and may even overcome some fraction of chemotherapy resistance seen with traditional induction therapy. Given that secondary AML appeared to have a particularly significant benefit with CPX-351 in Study 204 and is often associated with certain adverse risk cytogenetics, we hypothesize that CPX-351 is associated with increased response to chemotherapy even in poor risk cytogenetic risk groups.

We are planning to perform the following correlative studies:

a. Whether molecular mutations are associated with response to CPX-351 using molecular mutational data as available.

b. Whether cytogenetic abnormalities (obtained by standard karyotype and FISH analysis) are associated with response to CPX-351, using cytogenetic data as available

3. PARTICIPANT SELECTION AND ENROLLMENT PROCEDURES

Refer to the Participant Eligibility Checklist in Appendix A.

3.1 Study Eligibility/Inclusion Criteria:

To be eligible to participate in this study, a patient must meet following criteria:

- Ability to understand and voluntarily give informed consent
- Age ≥ 60
- Pathological diagnosis of AML (by WHO criteria) or higher risk MDS (includes int-2 and high risk MDS by IPSS) along with one of the following:
    - Patients with de novo or secondary MDS with progression/refractoriness after HMA treatment who have not transformed to AML
    - Patients with MDS and prior HMA treatment for MDS who transform to AML
    - Patients with AML who are refractory/relapsed after HMA therapy for their AML are eligible
- Life expectancy > 1 month
- Eastern Cooperative Oncology Group (ECOG) performance status 0-2
- Able to adhere to the study visit schedule and other protocol requirements
- Laboratory values fulfilling the following:
    - Serum creatinine < 2.0 mg/dL
    - Serum total bilirubin ≤ 2.5 mg/dL. Note, patients with Gilbert's syndrome may have elevated bilirubin at baseline prior to diagnosis with AML or MDS. Patients with Gilbert's syndrome are included if their total bilirubin is ≤ 2 times their baseline total bilirubin.
    - Serum alanine aminotransferase or aspartate aminotransferase < 3 times ULN
- Cardiac ejection fraction ≥ 45% by echocardiography (transthoracic echocardiography) or MUGA scan
- Patients with second malignancies may be eligible at discretion of PI given acute life threatening nature of untreated AML or higher risk MDS. Patients maintained on long-term non-chemotherapy treatment, eg, hormonal therapy, are also eligible.

All patients must meet one of the qualifications as outlined below after prior HMA therapy:

1. **Relapse after CR/CRi or PR—1 or more of the following:**
    a. Return to pretreatment bone marrow blast percentage (for initial PR)

b. Reappearance of bone marrow blasts (> 5%) following initial CR/CRi.

2. **Disease progression**

a. For patients with 10% to 20% blasts: a 50% or more increase to more than 20% blasts.

b. For patients with > 20% blasts: a 50% or more increase to more than 40% blasts.

3. **Refractory disease**

No evidence of a response (CR, CRi, PR) following, at least, 6 cycles of hypomethylating agent.

3.2 Study Exclusion Criteria

- Patients who have previously undergone allogeneic hematopoietic stem cell transplant will be excluded from this study
- Patients who have previously had > 368 mg/m^2 cumulative dose of daunorubicin or > 368 mg/m^2 daunorubicin-equivalent anthracycline therapy (for example, from prior treatment of solid tumors). See appendix for anthracycline equivalence table.
- Acute promyelocytic leukemia [t(15;17)]
- Any serious medical condition, laboratory abnormality or psychiatric illness that would prevent obtaining informed consent
- Patients who have had conventional intensive cytotoxic induction chemotherapy for treatment of specifically MDS or AML are excluded.
- Patients who have not previously been treated with HMA therapy will be excluded
- Clinical evidence of active CNS leukemia
- Patients with evidence of uncontrolled current myocardial impairment (e.g. unstable ischemic heart disease, uncontrolled arrhythmia, symptomatic valvular dysfunction not controlled on medical therapy, uncontrolled hypertensive heart disease, and uncontrolled congestive heart failure)
- Active and uncontrolled infection. Patients with an active infection receiving treatment and hemodynamically stable for 48 hours may be entered into the study
- Known active uncontrolled HIV or hepatitis C infection
- Known hypersensitivity to cytarabine, daunorubicin or liposomal products
- Known history of Wilson's disease or other copper-related disorders
- Other medical or psychiatric illness or organ dysfunction or laboratory abnormality which in the opinion of the investigator would compromise the patient's safety or interfere with data interpretation
- Laboratory abnormalities:
    - Serum creatinine ≥ 2.0 mg/dL
    - Serum total bilirubin > 2.5 mg/dL. Note, patients with Gilbert's syndrome may have elevated bilirubin at baseline prior to diagnosis with AML or MDS. Patients with Gilbert's syndrome are excluded if their total bilirubin is > 2 times their baseline total bilirubin.
    - Serum alanine aminotransferase or aspartate aminotransferase > 3 times ULN

3.3 Informed Consent Process

All participants will have a verbal discussion regarding the study and be provided a consent form describing the study with sufficient information for participants to make an informed decision regarding their participation. Participants must sign the IRB approved informed consent prior to participation in any study treatment. The participant will receive a copy of the signed and dated

consent document. The original signed copy of the consent document will be retained in the medical record or research file.

3.4 Randomization Procedures

Not Applicable. This is a single intervention, open label phase II study of CPX-351.

3.5 Study Timeline

Primary Completion:

The study is anticipated to reach primary completion 24 months from the time the study opens to accrual.

Study Completion:

The study is anticipated to reach study completion 36 months from the time the study opens to accrual.

4. TREATMENT PLAN

This will be an open label, fixed dose intervention phase II trial of CPX-351 in patients with HMA refractory/relapsed higher risk MDS (age ≥ 60), AML with HMA refractory/relapse disease (age ≥ 60), and MDS that is refractory/relapsed after HMA treatment for MDS that has transformed to AML (age ≥ 60). The primary outcome is designed to evaluate safety and efficacy of CPX-351 in this patient population. Study enrollment duration is expected to be approximately 24 months. During the treatment phase of this study, patients will receive up to two courses of induction followed by two courses of consolidation therapy, with monitoring for safety (early deaths, adverse events) and efficacy measures.

4.1 Study and Treatment Plan Review

Study Enrollment

An explanation of the study, treatments, expected risks and benefits, and alternatives will be fully discussed with potentially eligible patients. Only patients who provide informed consent will be enrolled into the study. The investigators will be responsible for keeping a record of all subjects who sign an informed consent form for entry into the study. Screening must take place within 28 days of initiation of therapy.

Initial Evaluation

- At screening subjects will have a general history, vitals, physical exam and ECOG status noted
- Laboratories that are routine for patients with MDS and AML will be completed including CBC with diff, CMP [which is BMP+LFT] within 14 days of treatment initiation.
- A baseline CXR [or CT chest] and Urinalysis will also be performed within 14 days of treatment initiation, which is routine for patients with MDS and AML in consideration for intensive chemotherapy
- Routine cardiology evaluation is performed for all AML and MDS patients in consideration for intensive chemotherapy. An EKG and ECHO (or MUGA) will be done as part of this routine care within 28 days of treatment initiation
- Bone marrow biopsy and aspirate with histological evaluation, is routinely performed for patients presenting to Stanford hematology for AML and MDS for disease assessment.

Molecular and cytogenetic evaluation may be repeated as clinically indicated. Prior cytogenetic and molecular findings may be notated as available. This evaluation will be performed as part of standard of care. Bone marrow evaluation is to be done within 21 days of treatment initiation. Note: patients may be treated prior to return of full results of molecular and cytogenetic analysis. If there is a dilute or aspiculate aspirate, or insufficient aspirate specimen, bone marrow biopsy can be allowed to estimate blast count and cytogenetics; of note in these situations, there may be insufficient material to obtain full cytogenetic analysis. Bone marrow biopsy and/or peripheral blood can be used to obtain molecular mutational analysis (if there are blasts in peripheral blood). If there is insufficient material for cytogenetics or molecular analysis, this can be noted.

CPX-351 Administration

CPX-351 is administered through a peripheral or central venous access, over approximately 90-minute infusions. The doses of CPX-351 are calculated using the patient's actual weight. Both inpatient and outpatient administration of CPX-351 is permitted.

First Induction:

In this study, enrolled patients will receive CPX-351 for induction therapy at a dose of 65 units/m2/day, on days 1, 3, and 5 intravenously.

Second Induction:

Bone marrow biopsy will be completed 14 days (+/- 3 days based on bone marrow biopsy scheduling logistics) after day 1 of first induction therapy.

- Patients who have evidence of morphological leukemia free state with < 5% blast count on Day 14 marrow (+/-3 days) will be monitored for count recovery, followed by consolidation therapy for those patients achieving a CR/CRi.
- For patients who have a reduced blast count on the Day 14 marrow (+/- 3 days) compared to baseline but have not yet achieved a morphological leukemia free state (< 5% blasts), a second course of induction with CPX-351 will be given, at a dose of 65 units/m2/day on Days 1 and 3.
- Patients who have absolutely no change in the blast count on the Day 14 marrow (+/- 3 days) compared to baseline will be discontinued from study treatment and followed for survival.
- Patients whose assessment of a morphological leukemia free state on the Day 14 (+/-3 days) marrow is equivocal by pathology, will have a repeat bone marrow biopsy done 7+/-3 days later. If repeat marrow shows morphological leukemia free state with < 5% blasts, patients will be monitored for count recovery followed by consolidation therapy for patients achieving a CR/CRi. If repeat marrow shows ≥ 5% blasts, patients will undergo a second induction course with CPX-351 at a dose of 65 units/m2/day on days 1 and 3.
- For patients who achieve an initial morphologic leukemia free state after first induction but have disease relapse within (≤) 15 days (defined by > 5% blasts on bone marrow biopsy or peripheral circulating blasts) will be eligible for a second course of induction therapy at PI discretion, if safe to administer.
- Patients who achieve a CR/CRi after a second course of induction will be treated with consolidation therapy. Patients who are unable to achieve a CR/CRi after a second course of induction, will be discontinued from the study and followed for survival.

Consolidation

If bone marrow biopsy post 1st induction or post 2nd induction is significant for complete remission or complete remission with incomplete count recovery (CRi), patient will then be treated with up to 2 cycles of consolidation therapy with 65 units/m2/day on Days 1 and 3 for each course of consolidation. The first consolidation course with CPX-351 must be given no earlier than 28 days after the start of the last induction and no later than 75 days after the start of the last induction. Patients must have recovered to ANC ≥ 500/uL and platelets >50,000/uL to be eligible for the first or second consolidation. The second consolidation course is administered between 28-75 days after the start of the first consolidation.

- Consolidation with stem cell transplant (HSCT) is permitted either in place of CPX-351 chemotherapy consolidation or following CPX-351 chemotherapy consolidation for transplant eligible patients
- No other chemotherapy consolidation is permitted for those patients achieving CR/CRi with CPX-351 induction therapy
- Performance status must be 0-2 prior to consolidation treatment with CPX-351
- LVEF prior to consolidation treatment must be documented to be ≥ 45%

Evaluation during Treatment Phase (of each course of treatment)

- Physical Exam and Vital Signs on Day 1, and post induction(s): during count recovery (ANC ≥ 500/uL, platelets ≥ 50,000/uL) or by Day 42+/-3.
- CBC with differential on Day 1, 14+/-3 (for induction(s)), and post induction(s)s: during count recovery (ANC ≥ 500/uL, platelets ≥ 50,000/uL) or by Day 42+/-3.
- Chemistry (CMP or BMP+LFT panel) on Day 1 and post induction(s)s: during count recovery (ANC ≥ 500/uL, platelets ≥ 50,000/uL) or by Day 42+/-3.
- Additional Labs (including uric acid, LDH, Coagulation studies) as per institutional standard of care or medical needs.
- Bone Marrow aspirate and biopsy evaluation is required at Day 14+/- 3 days after first induction course to evaluate response to therapy. For equivocal samples or non-evaluable samples, a repeat bone marrow evaluation will be repeated 7+/- 3 days later to determine the need for a second induction (after first induction).
- After induction(s): Bone marrow biopsy is required in count recovery (ANC ≥ 500, plt ≥ 50,000) or by Day 42+/-3 to confirm response to CPX-351
- Repeat cytogenetic analysis and molecular analysis is at the discretion of the treating physician based on baseline findings and standard of care
- A repeat ECHO or MUGA and EKG must be completed within 14 days of starting consolidation #1 and consolidation #2.
- Adverse events/toxicity via CTCAE version 4.0 assessment guidelines will be assessed on Day 1, and after induction(s): during count recovery (ANC ≥ 500/uL, platelets ≥ 50,000/uL) or by Day 42+/-3.

End of Active Treatment Phase or Early Termination

- At the end of active study treatment or at the time of early termination, patient visit information will include vital signs, physical exam, ECOG performance status, CBC with

DIFF, chemistries, toxicity notation. This may be combined with another visit, depending on patient status.

- Patients will have a follow-up visit 30 days +/- 3 days after the last dose of CPX-351 for toxicity assessment and collection of adverse event data
  - Patients who have significant residual non-hematopoietic toxicity will be followed up to around 4 weeks after the last dose of study drug until toxicity resolves to ≤ grade 1, stabilizes or initiation of new therapy, whichever comes first. Patients with unresolved AEs after 4 weeks will have the events classified as permanent sequelae.
- Not less than 30 days after the last dose of CPX-351, AND at the start of HSCT or non-protocol consolidation or non-protocol salvage therapy, adverse event data collection stops.

Follow-up

- Patients will be followed until death or up to 1 year following study enrollment
- Patient status report will be obtained at 1 year following study enrollment by either clinic visit or by telephone or correspondence or discussion with treating physician or evaluation of survival using the state/county/federal death reports. Patient status report will include survival status, and as possible: duration of remission, relapse/refractory status, and whether a new anti-leukemic therapy has been initiated.
- Clinic visits and laboratories will be done during follow-up time period at the discretion of the treating physician or institutional standard of care
- Bone marrow evaluations will be done as per standard of care or institutional guidelines at discretion of treating physician (example, any suspicion of relapse or change in counts without other explanation for lasting > 1 month)

4.2 General Concomitant Medication and Supportive Care Guidelines

- Placement of peripheral or central venous access will be per standard of care for AML and MDS treatment
- Hydrea may be used up to 24 hours before first dose of CPX-351
- The use of anti-infectives, intravenous fluids, growth factor support, and transfusion support will be at the discretion of the treating physician per institutional standard of care for AML and MDS treatment
- Treatment of infusion related reaction and hypersensitivity management will be per institutional standards
- Allopurinol and/or rasburicase are allowed as per discretion of treating physician for patients for prevention of tumor lysis or treatment of tumor lysis
- Pre-medications for CPX-351 will include routine anti-emetics and hydration as needed given routinely for anthracycline and cytarabine based therapy
- All additional laboratory evaluations as needed for institutional standard of care are allowed
- Patients with signs/symptoms of hyperleukocytosis or WBC > 100,000/uL can be treated with leukapheresis if needed prior to first dose of CPX-351

4.3 Study Modification/Discontinuation

Any modifications to the study will be documented in a revised protocol with a new assigned

version. The trial may be stopped early for the following reasons:

- Unacceptable toxicity
- Discontinued drug development
- Poor enrollment
- Request from regulatory authority

In case of study discontinuation, all study participants will be informed.

4.4 Criteria for Removal from Study

Patients will be discontinued from the study under the following circumstances:

- Completion of protocol
- Persistent disease with a lack of any response to treatment
- Persistent disease without achievement of CR/CRi despite two induction courses with CPX-351
- Relapsed disease: presence of > 5% blasts in the bone marrow following CR or CRi (note however patients who achieve morphologic leukemia free state after first induction but have disease relapse within (≤) 15 days will be eligible for a second course of induction)
- Patient non-adherence with protocol
- Administration of non-protocol consolidation or non-protocol salvage therapy
- Inter-current illness which in the judgment of the investigator affects assessment of clinical status to a significant degree, and requires discontinuation of protocol therapy for patient safety
- Withdrawal of informed consent by the study participant at any time. The patient will be classified as withdrawal of consent.

4.5 Alternatives

4.5.1 Risk Reduction

Hematologic toxicity is a known and expected adverse event from intensive chemotherapy due to the mechanism of action of intensive chemotherapy, and due to the underlying pathophysiology of acute myeloid leukemia and MDS. Patients with MDS have dysplastic hematopoiesis and cytopenias at baseline. To minimize duration of cytopenia more than expected from CPX-351, we have decreased the induction and consolidation dose in our study compared to prior phase II studies of CPX-351, as our patient population includes patients > 75 and has both patients with MDS and AML. Additionally cytopenias both as a result of the underlying disease and treatment will be treated aggressively as per institutional guidelines. Infections as a result of underlying disease and treatment will be aggressively treated as per institutional guidelines.

Anthracyclines have a risk of cardiotoxicity that increases with pre-existing cardiomyopathy, possibly via reactive oxygen species generation. Based on AE seen in the initial CPX-351 phase study, we have excluded patients who have had prior lifetime daunorubicin exposure > 368 mg/m^2 or equivalent other anthracycline dose. We are also excluding patients with uncontrolled current myocardial impairment. Given the partial hepatic metabolism of both daunorubicin and cytarabine, patients with active hyperbilirubinemia or active transaminitis will be excluded. An exception is however patients who have active hyperbilirubinemia or transaminitis secondary to leukemia, in which case, treatment of leukemia may improve liver dysfunction. Similarly patients with significant renal dysfunction will be excluded. An exception is in patients with renal dysfunction secondary to leukemia (example tumor lysis or hyperleukocytosis), in whom treatment of leukemia

may improve renal dysfunction. High dose cytarabine therapy (≥ 1.5 grams/ m^2 or 1500 mg/m^2) has risks of neurotoxicity. The dose of cytarabine as part of CPX-351 in this protocol does not commonly cause neurotoxicity.

Acute Myeloid Leukemia and higher risk MDS that has failed HMA therapy has a poor outcome. There are very limited therapy options for patients in this population. Therefore inclusion criteria have been generated to be inclusive of this population, while excluding patients with factors that may place patients at higher than expected risk for intensive chemotherapy.

4.5.2 Alternatives

There are no standard guidelines for therapy for patients with AML and MDS who are relapsed/refractory to HMA therapy. Therefore the alternatives to this clinical study include patients not participating. Patients may opt for no treatment, best supportive care (transfusions, treatment of infections etc.), hydroxyurea (a general myelosuppressive agent for palliative care), low dose subcutaneous cytarabine, another clinical trial that they are eligible for, or other alternatives after discussion with their treating physician.

5. INVESTIGATIONAL AGENT/DEVICE/PROCEDURE INFORMATION

5.1 Investigational Agent/Device/Procedure

Please refer to the investigator's brochure provided by Celator pharmaceuticals. We will review and summarize the investigational agent here.

5.1.1 Introduction

CPX-351 is a liposomal formulation of a fixed combination of cytarabine and daunorubicin in a 5:1 molar ratio within a liposome. *In vitro* studies have shown that maintaining this fixed molar ratio maximizes antitumor efficacy in cell lines and animal models compared to conventional free drug treatment. The rationale for use in patients with AML and higher risk MDS, is that delivery of a fixed, maintained ratio of 5:1 of cytarabine: daunorubicin will enhance efficacy compared to treatment with conventional free drugs in the 7+3 regimen.

5.1.2 Dosage Form, Route of Administration, and Dosage Regimen

CPX-351 is a liposomal formulation of cytarabine and daunorubicin in a fixed molar ratio of 5:1, contained within the liposome. The liposomal membrane is composed of distearylphosphatidylcholine (DSPC), distearylphosphatidylglycerol (DSPG) and cholesterol in a 7:2:1 molar ratio. A copper based loading process is used to encapsulate daunorubicin. The size of these liposomes is approximately 100 nm and the drug is filtered through a 0.22 micromolar filter for sterilization. One unit of CPX-351 contains 1.0 mg cytarabine (+/- 10%) plus 0.44 mg daunorubicin (+/-10%).

CPX-351 is provided by Celator pharmaceuticals as a sterile, pyrogen free, purple lyophilized formulation in 50 mL glass, single use vials. Each vial contains 100 units of CPX-351. The lyophilized cake is reconstituted with sterile water for injection to obtain a homogenous dispersion at 5 units/mL (ex. 20 mL sterile water with 100 units of drug, with final concentration 5 units per mL). After dilution in either normal saline or dextrose injection to a final concentration of 0.10 units/ml to 1.32 units/ml, CPX-351 is infused over 90 minutes intravenously. CPX-351 will be administered through peripheral or central venous access, using an infusion pump or other means to ensure drug administered over appropriate time period.

The dosing regimen for induction course #1 will be CPX-351 65 units/m2/day on Days 1, 3, and 5., with CPX-351 65 units/m2/day on Days 1 and 3 for induction course #2 for patients requiring a second course of induction. The dosing regimen for consolidation courses will be 65 units/m2/day on Days 1 and 3.

Table 1: Components of CPX-351 Liposome Injection
(image from CPX-351 Investigator's Brochure provided by Celator Pharmaceuticals)

Component	mw	Amount per Vial	Amount per unit
Cytarabine, USP/PhEur	243	100 mg	1.0 mg
Daunorubicin HCl USP/ PhEur (reported as the free base)	528	44 mg	0.44 mg
Distearoylphosphatidylcholine	790	454 mg	4.5 mg
Distearoylphosphatidylglycerol	801	132 mg	1.3 mg
Cholesterol, HP	387	32 mg	0.3 mg
Copper gluconate, USP	454	92 mg	0.9 mg
Triethanolamine, NF, PhEur	149	7 mg	0.07 mg
Sucrose, NF, PhEur	342	2054 mg	20.54 mg

5.1.3 Drug Preparation, Storage, and Stability

The appropriate number of vials of CPX-351 based on patient's body surface area (BSA) should be removed from the refrigerator and reconstituted with sterile water to obtain a homogenous dispersion of 5 units/mL, before further dilution. Further dilution can be completed with either sodium chloride or dextrose injection. CPX-351 can be diluted to a final concentration between 0.10 to 1.32 units/mL prior to administration. CPX-351 should not be heated. Aspetic technique should be maintained throughout its preparation given no preservative is present.

Infusion must be started within 4 hours of dilution. Solutions for administration should be prepared in glass bottles or NON-DEHP polypropylene or polyolefin bags. Per company recommendations, only DEHP-free administration sets such as those that are polyethylene-lined should be used. An in-line filter with CPX-351 should not be used. Unused material in vials should be discarded using proper technique for handling and disposal of antineoplastic agents.

CPX-351 liposome injection cartons should be stored refrigerated at 5 degrees Celsius +/- 3 degrees Celsius in an upright position until the vials are used. Each carton contains 2 clear glass, single vial use vials. Drug material released by the company will be periodically tested and monitored for acceptable product attributes. The current shelf-life of CPX-351 is 24 months from the date of manufacture. Drug that fails to comply with specifications will be removed.

5.1.4 Proposed Mechanism of action of Cytarabine, an active component of CPX-351

Cytarabine (or cytosine arabinoside) is a traditional anti-metabolite chemotherapy agent used for a variety of leukemias and non-Hodgkin's lymphomas. It is thought to work by interfering with DNA synthesis for its main anti-neoplastic activity, by affecting rapidly dividing cells that require significant DNA synthesis. Cytarabine is metabolized intracellularly into an active triphosphate form (cytosine arabinoside triphosphate). This metabolite is able to become incorporated into DNA, and may inhibit alpha-DNA polymerase and inhibit DNA repair through effects on beta-DNA polymerase.

5.1.5 Proposed Mechanism of action of Daunorubicin, an active component of CPX-351

Daunorubicin is a traditional chemotherapy agent of the anthracycline family. The anthracycline family of chemotherapeutic agents are used to treat a wide variety of cancers including leukemias, non-Hodgkin lymphomas, genitourinary and breast cancer. Anthracyclines are thought to cause DNA damage by affecting topoisomerase II, leading to changes in DNA coiling/uncoiling, ligation/religation [20] ultimately affecting DNA and RNA synthesis. Anthracyclines may also cause reactive oxygen species generation.

5.1.6 Proposed Mechanism of Action of CPX-351

Given that chemotherapy drug combinations may have synergistic, additive, or antagonistic effects based on the ratio of agents being used, but that their combinatorial effects are difficult to control *in vivo* because of the independent pharmacokinetics of conventional free drug cocktails, there has been considerable interest in developing liposomal drug delivery vehicles that allow control of drug ratio exposure via coordinated pharmacokinetics to try to improve therapy efficacy via prolonged maintenance of optimal drug ratios *in vivo*.

In the preclinical studies [15] various fixed ratio liposomal formulations of combined cytarabine and daunorubicin were tested in leukemia cell lines and murine models. *In vitro* cytotoxicity curves from various tumor cell lines analyzed for synergy showed that the 5:1 cytarabine:daunorubicin drug ratio (CPX-351) was the most synergistic (53% synergy, 33% antagonism, 13% additive). *In vivo* pharmacokinetics in a mouse model comparing free drug cocktail versus CPX-351, were significant for findings of a longer elimination half-life with CPX-351, with the maintenance of a ratio of cytarabine:daunorubicin of 5:1-9:1 for over 24 hours whereas free drug was noted to be rapidly removed from the circulation. The absolute plasma concentrations of both drugs were also higher in the CPX-351 group in this model, compared to administration of free drug cocktail. Interestingly, bone marrow samples in this model were also found to have higher drug concentrations when CPX-351 was used, in comparison to free drug combination. Finally, fixed drug ratio liposomal formulations ranging from 1:1 to 12:1 were evaluated in a P388 leukemia mouse model, with findings of the 5:1 drug ratio being most therapeutically active with findings of increased survival.

Thus the proposed mechanism of action for improved efficacy of CPX-351 compared to conventional free drug administration of cytarabine and daunorubicin includes: 1) the maintenance of a synergistic 5:1 molar ratio for periods > 24 hours after infusion because of the encapsulation of the drugs; 2) the drug liposome has also been found to be stable and able to circulate for more than 7 days after drug infusion; 3) an additional mechanism may be the accumulation of CPX-351 in the bone marrow, as shown in mouse models, and 4) the preferential uptake of CPX-351 within cytoplasm of leukemic cells [15].

5.1.7 Summaries of animal and clinical studies

Summary of CPX-351 in Animal Studies

In the P388 leukemia model, mice who received CPX-351 (5:1 ratio of cytarabine: daunorubicin) had a higher survival at Day 55 compared to mice who received other ratios (1:1, 3:1, 12:1). CPX-351 has been compared to free drug cocktail in the P388, L1210, WEHI-3B, CCRF-CEM and HL-60B murine models. CPX-351 has also been compared to individual liposomal formulations in the P388 and WEHI-3B murine models. In these models, CPX-351 was found to have improved anti-leukemic activity over free drug cocktail and individual liposomal formulations.

Pharmacokinetic studies of CPX-351 have additionally been done in rat and dog toxicokinetic studies, showing 3:1 – 7:1 ratio maintenance for 24 hours following administration. Total plasma drug concentrations were higher for extended time periods with CPX-351 compared to free drug administration.

In the bone marrow engrafting CCRF-CEM human leukemia xenograft model, CPX-351 was found to deliver higher amounts of cytarabine and daunorubicin compared to free drug cocktails. Prolonged drug exposure with maintenance near the 5:1 molar ratio was also found with CPX-351 on the order of days. Extended leukemia clearance and improved survival were noted in this model. Interestingly, the concentrations of cytarabine and daunorubicin were found to be higher in leukemic cells compared to normal bone marrow cells. The mechanism of action for this is thought to be preferential direct uptake of intact liposomes in leukemic cells.

Of note, toxicology studies were completed using single dose and repeated dose administrations of CPX-351 in the Beagle dog and Sprague-Dawley rat models. These studies helped to identify the starting dose of CPX-351 at 3 units/m2 for the subsequent Phase I dose escalation study in humans.

Summary of CPX-351 in Human Studies

There have been three clinical trials with CPX-351 that have completed accrual. A complete analysis has been published for the initial phase I trial [16] and accrual has been completed for two phase II trials, with ongoing followup. Data available for these trials is summarized here with additional information available in the investigator's brochure.

Phase I Study of CPX-351: CLTR0305-101

In this initial phase I study, the primary goal was to establish the maximum tolerated dose (MTD) for CPX-351 for recommendations on dosing for further phase II studies.

Pharmacokinetic assessments of plasma samples were made at every dose level and patients were monitored for signs of antileukemic activity. An induction course with CPX-351 administered on days 1, 3, and 5 over 90 minute infusions was designed to mimic the 7 day drug exposure with conventional 7+3 treatment. Patients with relapsed/refractory AML, ALL, and high risk MDS were eligible for the study. There were 43 pts with AML, 3 pts with ALL, and 2 pts with MDS who were treated. The median age of patients was 62 with an age range of 23-81. The starting dose of CPX-351 was 3 units/m2, and studied dose levels were 3 (1 patient),6 (1 patient),12 (2 patients), 24 (4 patients), 32 (4 patients), 43 (4 patients), 57 (3 patients),76 (3 patients),101 (6 patients), and 134 units/m2 (6 patients). There were 34 patients who were studied in the dose escalation part of the study.

Dose limiting toxicities were observed at the 10th dose level of 134 u/m2 (3 DLTs in 3 patients of 6), including congestive heart failure (CHF; 1 pt), hypertensive crises (1 pt) and persistent cytopenia past 56 days (1 patient; recovery occurred at day 112). The patient with the CHF episode had prior 369 mg/m2 daunorubicin and a total of 556 mg/m2 including CPX-351, and as a result, phase II studies have included a cap of 500 mg/m2 on cumulative anthracycline dose after one induction course of CPX-351 and patients with significant pre-existing cardiac disease were excluded. Thus 101 units/m2 was found to be the MTD. An additional 14 patients were subsequently added to the 101 units/m2 cohort during the expansion phase of the study to obtain additional safety and potential efficacy data, for a total of 48 patients. Grade 3 and 4 Non-hematologic toxicities included mucositis (1 pt), vomiting (1 pt), skin rash (3 pts), CHF (2 pts), elevated bilirubin (1 pt), and elevated transaminases (2 pts). In terms of initial efficacy data, of the total 48 patients, there were

11 patients who experienced a response (AML- 9 CR, 1 CRp; ALL- 1 CR). 8 of the patients with AML with CR had prior cytarbine + anthracycline therapy, confirming anti-leukemic activity. Of the total patients with CR, 5 pts were ≥ age 60. The median duration of remission was 6.9 months.

In terms of pharmacokinetic analysis, this phase I study assessed the concentrations of cytarabine, daunorubicin, uracil arabinoside, and daunorubicinol and found that they exhibited mono-exponential, first order elimination with minimal early phase distribution.

The day 1 single-dose and day 5 multiple-dose plasma cytarabine and daunorubicin showed linear pharmacokinetic characteristics (Cmax and AUC (0-T)) and the 5:1 molar ratio of cytarabine to daunorubicin was maintained for up to 24 hours on days 1 and 5 at all dose levels.

CPX-351 was found to have a markedly prolonged mean half-life and greater drug exposure (AUC) for both cytarabine and daunorubicin, compared to expected mean half-life and AUC with conventional free drug; and measurable drug levels of cytarabine and daunorubicin were detected > 7 days after last dose with CPX-351.

Phase II Study of CPX-351: CLTR0308-204

Study 204 is a randomized, open label, multi-center phase II trial comparing CPX-351 to conventional 7+3 in older patients ages 60-75 with newly diagnosed AML (including both de novo AML and secondary AML). One hundred twenty-seven patients were randomized 2:1 to CPX-351 or 7+3. 126 patients were treated, 85 on CPX-351 and 41 on 7+3. The primary endpoint was rate of response (CR+CRi). Success was defined as achievement of a trend towards superior efficacy with a one sided p value of < 0.1 with approximately 80% power. Secondary endpoints were overall survival, event-free survival, CR+CRi duration, leukemia-free after induction, safety and practicality of CPX-351 as consolidation therapy and the response rate of CPX-351 between de novo and secondary AML. At entry patients were stratified by age 60-69 vs. age 70-75, cytogenetics < 3 or ≥ 3 cytogenetic abnormalities, and type of AML, de novo vs. secondary. High risk patients were ≥ 70 years of age, or had complex cytogenetics, or had secondary AML. Standard risk patients were age 60-69 and had non-complex cytogenetics (< 3 abnormalities) and had de novo AML. After accrual was complete, Dr. Jeffrey Lancet from the Moffitt Cancer Center, Tampa, FL, reviewed all of the cytogenetic reports and made the final cytogenetic group determination. Randomization and stratification were successful in balancing demographic and leukemia associated risk factors between the two study arms.

CPX-351 produced superior rates of leukemic-free state and response, with similar duration of remission. The improvement in response occurred predominately in the form of CRi (CR with incomplete hematologic recovery). The study met the primary endpoint with a response rate (CR+Cri) of 66.7% compared to 51.2%with a p-value of 0.0712 (single sided, p < 0.1). Further analysis of response demonstrated consistent benefit for CPX-351 in response rate across every patient subgroup, including stratifications based on age, cytogenetic group, and presence of secondary leukemia. Kaplan-Meier (K-M) analysis after a minimum follow up of 1-year demonstrated non-significant improvements for CPX-351 for Event Free Survival (EFS) and Overall Survival (OS) in the overall population and the high risk strata. Overall survival and EFS in the secondary AML group did reach statistical significance favoring the CPX-351 arm (p=0.01, HR 0.40; and p=0.04, HR 0.51 respectively). Of the 33 patients in the CPX-351 arm who had secondary AML, 13/33 (39%) had prior HMA exposure and 16/33 (48%) had not. There were 19 patients in the 7+3 arm with secondary AML; 7 of them had prior HMA exposure. The response rate in patients receiving CPX-351 who had secondary AML and prior HMA exposure was 54% (7/13

responded with CR/CRi); in contrast, the response rate in patients receiving 7+3 who had secondary AML and prior HMA exposure was 29% (2/7 responded with CR/CRi).

Induction mortality was assessed at Day 30 and 60. A trend towards a lower rate of early mortality was observed for CPX-351 treated patients at 60 days (4/85, 4.7% vs. 6/41, 14.6%, p=0.053), evidence that CPX-351 treatment is acceptably safe and that higher rates of leukemia clearance may assist in reducing the early death rate. CPX-351 treatment was associated with greater myelosuppression and more prolonged cytopenias, with a higher frequency of febrile neutropenia (63.5% vs. 51.2%), bacteremia (35.3% vs.19.5%), fungal infections (15.4% vs 0%), and bleeding events, compared to 7+3. There were 4 deaths in the total CPX-351 group (1 from pneumonia, 3 from bleeding events; 1 fall in a thrombocytopenic patient; 1 intracranial hemorrhage; 1 respiratory tract hemorrhage). Thus a low threshold for platelet transfusions for critical thrombocytopenia is recommended. However the lower mortality rate of CPX-351 indicates the safety of CPX-351 despite the greater myelosuppression and its consequences. Given the reduced early mortality and OS advantage in secondary AML, a phase III study is currently underway, comparing CPX-351 vs 7+3 in secondary AML age 60-75.

Phase II Study of CPX-351: CLTR0308-205

Study 205 is a randomized, open label phase II trial comparing CPX-351 (100 units/m2 given on Day 1, 3, 5) with intensive salvage therapy in patients adult patients < 65 years of age with AML in first relapse. The trial accrued 125 patients with a 2:1 randomization to CPX-351 to CPX-351 versus investigator's choice of salvage therapy. The primary endpoint was survival at one year. Secondary endpoints were CR+CRi rate, remission duration, event-free survival and 30/60/90 day mortality. CPX-351 was able to increase the rate of CR+CRi rate 49% vs. 41%, and had comparable 60-day mortality 15% vs. 16%. After 1-year of follow up there were trends favoring CPX-351 for event free survival (HR=0.66, p=0.08) and overall survival (HR=0.75, p=0.19). In the subset analysis of patients with unfavorable risk group by the European Prognostic Index there was a significant improvement in overall survival (HR=0.55, p=0.02). The proportion of CPX-351 versus control treated patients alive at 1-year was 37% vs. 30%, and the proportion of unfavorable risk patients alive at one year was 30% vs. 10%.

In summary, data from the Phase I and both randomized Phase II studies demonstrate consistent high level activity of CPX-351 in AML, with increases in leukemia-free state and clinical response (CR+CRi) compared to conventional therapy.

5.2 Availability

Celator pharmaceuticals will be providing CPX-351. Letter of intent has been accepted by Celator pharmaceuticals for provision of the drug for this study.

5.3 Agent Ordering

The study drug will be obtained from Celator pharmaceuticals by the research pharmacy. See Appendix L.

Requests will be made to:

Celator Pharmaceuticals
200 Princeton South Corporate Center, Suite 180
Ewing, NJ 08628
(609) 243-0123: Office

(609) 243-0202: Fax
Attn: Donna Cabral-Lilly

5.4 Agent 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.

6. DOSE MODIFICATIONS

6.1 Dose Delays and Modification during Induction Therapy:

6.1.1 No further study therapy will be given if a patient experiences grade 4 non-hematologic toxicity during induction #1, with the exception of febrile neutropenia/infection or constitutional symptoms or if there is recovery to grade ≤ grade 2 within 14 days

6.1.2 If a subject experiences grade 3 or higher non-hematologic toxicity during induction #1 with the exception of febrile neutropenia/infection or constitutional symptoms, the dose of CPX-351 will be reduced by ~33% (to 43 units/m2/day) for induction course #2 (if patient requires a second induction), if 6.1.1 is met.

6.2 Dose Modification during Consolidation Therapy

6.2.1 If a dose reduction was required because of grade 3 or higher non-hematologic toxicity (except for febrile neutropenia/infection or constitutional symptoms) or if blood count recovery required > 56 days during induction therapy, the dose of CPX-351 during consolidation #1 will be reduced to 43 units/m2/day.

6.1.3 If a subject experiences grade 3 or higher non-hematologic toxicity during consolidation #1 with the exception of febrile neutropenia/infection or constitutional symptoms or if blood count recovery required > 56 days during consolidation #1, the dose of CPX-351 will be reduced by 33% for consolidation #2 (that is, either 43 units/m2/day X 2 doses or 30 units/m2/day X 2 doses depending on dose used for consolidation #1).

6.3 Dosing Comparisons of CPX-351

CPX-351 (Prior Phase I study)

- 1 unit = 1.0 mg of cytarabine + 0.44 mg daunorubicin
- MTD: 100 units/m2/day on Days 1, 3, and 5 for induction
- Cytarabine 100 units/m2 = 100 mg/m2
- Total Cytarabine administered for induction: 100 mg/m2 X 3 days = 300 mg/m2 total
- Daunorubicin 100 units/m2=44 mg/m2
- Total Daunorubicin administered for induction: 44 mg/m2 X 3 days=132 mg/m2 total

CPX-351 (Current Phase II study for HMA refractory or relapsed AML or MDS)

- 1 unit = 1.0 mg of cytarabine + 0.44 mg daunorubicin
- Dose for induction #1: 65 units/m2/day on Days 1, 3, 5

- Cytarabine 65 units/m2 = 65 mg/m2
- Total Cytarabine administered for induction #1: 65 mg/m2 X 3 days = 195 mg/m2 total
- Daunorubicin 65 units/m2 = 28.6 mg/m2
- Total Daunorubicin administered for induction #1: 28.6 mg/m2 X 3 days = 85.8 mg/m2 total

7. ADVERSE EVENTS AND REPORTING PROCEDURES

7.1 Potential Adverse Events

There have been 3 completed trials of CPX-351: (1) Study 101, a phase I study of CPX-351 in patients with advanced leukemia and high risk MDS, (2) Study 204, a phase IIB multicenter, randomized study of CPX-351 versus 7+3 therapy in elderly patients with untreated AML between the ages of 60-75, (3) Study 205, a phase IIB multicenter randomized, open label trial of CPX-351 versus control salvage therapy in adult patients between the ages of 18-65 with AML in first relapse after initial CR > 1 month. We will summarize the adverse effects reported by Celator pharmaceuticals. Please additionally refer to the Celator pharmaceuticals investigators brochure.

Study 204

Overall Adverse Events for Study 204

The most common AEs of any severity following CPX-351 in Study 204 were: rash, diarrhea, nausea, febrile neutropenia, localized edema, constipation, pain, bacteremia, fatigue, decreased appetite, chills, cough, pyrexia, epistaxis, stomatitis, headache, petechie, insomnia, vomiting, pruritis, abdominal pain.

Grade 3-5 Adverse Effects with > 5% frequency with CPX-351 treatment in Study 204

Grade 3-5 Adverse effects with > 5% frequency in the CPX-351 arm from Study 204 include: febrile neutropenia, bacteremia, pneumonia, hypokalemia, neutropenia, sepsis, thrombocytopenia, diarrhea, acute renal failure, dyspnea, syncope, hypoxia, rash, clostridial infection, epistaxis, pain, fungal pneumonia, bacterial urinary tract infection.

CPX-351 Arm	7+3 arm
30 day mortality 3.5%	30 day mortality 7.3%
60 day mortality 4.7%	60 day mortality 14.6%
At least one grade 3 AE: 97.6% (83/85)	At least one grade 3 AE: 87.8% (36/41)
At least one grade 4 AE: 27.1% (23/85)	At least one grade 4 AE: 26.8% (11/41)
Grade 5 AE (Death): 11.8% (10/85)	Grade 5 AE (Death): 17.1% (7/41)
Grade 5 bleeding events: 3/85 (fall, intracranial hemorrhage, respiratory tract hemorrhage)	Grade 5 bleeding events: 0% (0/41)
Febrile neutropenia grade 3 and 4: 63.5% (54/85)	Febrile neutropenia grade 3 and 4: 51.2% (21/41)
Bacteremia grade 3 and 4: 35.3% (30/85)	Bacteremia grade 3 and 4: 19.5% (8/41)
Fungal infection Grade 3 and 4 : 15.4% (13/85)	Fungal infection Grade 3 and 4: 0%
Grade 3 rash: 8.2% (7/85)	Grade 3 rash: 0% (0/41)

Study 204: Grade 3-5 Cardiac Events

	Grade 3 and 4 AE		Grade 5 AE	
Preferred Term/Event	CPX-351 (N=85) N	7+3 (N=41) N	CPX-351 (N=85) N	7+3 (N=41) N
Atrial Fibrillation	3	1	0	0
Cardiac Failure	2	1	0	0
Tachycardia (SVT)	1	1	0	0
Angina Pectoris	0	1	0	0
Cardiac Arrest	0	0	0	1
Myocardial Infarction	1	1	0	1
Restrictive cardiomyopathy	1	0	0	0
Acute myocardial infarction	0	1	0	0
Myocarditis	0	1	0	0
Troponin increased	1	0	0	0

Study 205

Grade 3-5 Adverse Events > 5% frequency with CPX-351 from Study 205

Grade 3-5 Adverse effects with > 5% frequency in the CPX-351 arm from Study 205 include: febrile neutropenia, bacteremia, pneumonia, sepsis, fatigue, hypokalemia, urinary tract infection, rash, pyrexia, neutropenia, syncope, septic shock.

Grade 5 Adverse Events in Study 205

There were a total of 19 grade 5 events in the CPX-351 arm. Grade 5 events include 4 deaths from pneumonia, 4 deaths from sepsis, 2 deaths from AML, 2 deaths from septic shock, 1 death from acute respiratory failure, 1 death from respiratory distress, 1 death from respiratory failure, 1 death from cardio-respiratory arrest, 1 death from cerebral hemorrhage, 1 death from subdural hematoma, 1 death from sudden cardiac death. There were 9 deaths in the control salvage arm.

Adverse Event Incidence (any grade) in all patients treated with CPX-351 at a dose of 100 units/m^2

The CPX-351 investigator's brochure reviews the adverse event incidence of any grade in all patients treated with CPX-351 at a dose of 100 units/m2 (N=196). The most common adverse events of any grade with > 15% frequency include (in rounded percentages):

- Rash – 66%
- Fever & Infection (Febrile Neutropenia) - 57%
- Nausea - 57%
- Diarrhea - 50%
- Pain - 45%
- Constipation - 44%
- Fatigue - 43%
- Bacteria in the blood (Bacteremia) - 37%
- Fever (Pyrexia□ □- 36%
- Chills - 36%

- Swelling □Localized edema□ □- 33%
- Decreased Appetite - 33%
- Vomiting - 32%
- Cough - 32%
- Headache - 31%
- Shortness of Breath (Dyspnea) - 26%
- Nosebleed (Epistaxis) - 26%
- Mouth Swelling (Stomatitis) - 25%
- Low Potassium Levels (Hypokalemia) - 25%
- Small Red or Purple Skin Spots (Petechiae) - 24%
- Dizziness - 22%
- Hypotension - 22%
- Pneumonia - 22%
- Anxiety - 22%
- Abdominal Pain - 21%
- Insomnia - 21%
- Itching (Pruritus) - 20%
- Fast Heart Rate (Tachycardia) – 16%
- Weakness (Asthenia) – 15%
- Swelling of Limbs (Edema Peripheral) – 15%
- Hypertension – 15%
- In some cases, side effects can be serious, long lasting, or may never go away. There is also a risk of death.

Adverse Event Addendum 3/3/2015:

This protocol addendum is to report a recent unexpected severe adverse event that occurred in a patient receiving CPX-351 on the multi-center CLTR0310-301 trial at another facility. This is a phase III company sponsored trial comparing CPX-351 versus 7+3. The patient was reported to have demyelinating motor neuropathy (grade 3) and hypothyroidism (grade 2), which was possibly related to CPX-351. The complete study results (in terms of both safety data and efficacy are pending). The report of this event provided by the company will be submitted to the IRB and the informed consent form will be updated with this information.

Effects on Mutagenicity, Carcinogenicity, Impairment of Fertility, Pregnancy, Nursing Mothers

Mutagenicity, carcinogenicity, and impairment on fertility with CPX-351 have not been conducted. Cytarabine is known to cause extensive chromosomal damage. As reviewed in the investigator's brochure, Daunorubicin has been reported to cause fibrosarcomas, adenocarcinomas, and peritoneal sarcomas. Given the mutagenicity of daunorubicin and cytarabine, patients undergoing treatment with CPX-351 will be advised to use a reliable contraceptive method. CPX-351 has not been studied in pregnant animals. Both Cytarabine and Daunorubicin have been designated as Pregnancy Category D due to known teratogenicity. It is not known if CPX-351 is excreted in human milk. Given possible drug excretion in human mild and because of possible serious adverse risks in nursing infants, patients receiving CPX-351 should not breast feed. Given the advanced age of patients in this study, we do not anticipate any women in this study to be pregnant in this study, be

of child-bearing age, or be breast-feeding. Men in this study are still at risk of mutagenicity of spermatozoa. Therefore all patients will be advised to use a reliable contraceptive method.

SUMMARY: Discussion of Adverse Effect Profile of CPX-351

In summary, the risk and side effect profile of CPX-351 has been found to be comparable to that of traditional induction therapy with 7+3 (study 204) and control salvage therapy (study 205). There is an increased incidence of febrile neutropenia, bacteremia, and fungal infections with CPX-351, which is thought to be consistent with the longer duration of myelosuppression with CPX-351 given its pharmacokinetics. Though infections were common, deaths from infections were not common, indicating effective supportive care.

In terms of 60-day mortality, the CPX-351 arms in Study 204 and Study 205 had lower or similar 60-day mortality compared to the control arms respectively (4.7% vs 14.6% in Study 204; 14.8% vs 15.9% in Study 205).

Risk Reduction

Given the anticipated older patient population in our study cohort of patients with HMA refractory or relapsed AML or MDS, with possible risks of prolonged myelosuppression given older age and underlying MDS in patients with MDS or AML secondary to MDS, we are dose reducing CPX-351 in our study to 65 units/m2/day on Days 1, 3, and 5 for initial induction therapy.

7.2 Adverse Event Reporting

Adverse events will be graded according to CTCAE v4.0. Both Serious and Non-Serious Adverse Events will be clearly noted in source documentation and listed on study specific Case Report Forms (CRFs). The Protocol Director (PD) or designee will assess each Adverse Event (AE) to determine whether it is unexpected according to the Informed Consent, Protocol Document, or Investigator's Brochure, and related to the investigation. All Serious Adverse Events (SAEs) will be followed until resolution to ≤ grade 1, or until 4 weeks after the last dose of the study treatment, or until other therapy is initiated for AML, whichever comes first.

Patients with unresolved AEs after 4 weeks will have the events classified as permanent sequelae.

7.3 Serious Adverse Event Reporting Instructions

The investigator must complete the Serious Adverse Event Report Form in English, assess the relationship to study treatment and send the completed form by fax within 24 hours to Celator and to the local IRB Office. The original and the duplicate copies of the Serious Adverse Event Form, and the fax confirmation sheet must be kept with the case report forms.

Follow-up information is sent to Celator or its designee as well as the local IRB office via the original Serious Adverse Event Form, re-stating the date of the original report. Either a new Serious Adverse Event Form is sent (stating that this is a follow-up), or the original one resent (with the new information highlighted and a new date provided). The follow-up should describe whether the event has resolved or continues, if and how it was treated, whether the patient continued or discontinued study participation. The form and fax confirmation sheet must be retained.

7.3.1 Reporting Serious Adverse Events to Regulatory Agencies and Review Boards

The need for an expedited report to regulatory authorities will be determined by the Sponsor-Investigator. All AEs that are serious, unexpected and associated with the use of CPX-351 will be reported to the Food and Drug Administration (FDA) by the Sponsor-Investigator.

7.3.2 Report of Adverse Events to the Institutional Review Board

The Sponsor-Investigator will report serious adverse events to the Stanford Institutional Review Board (IRB) per institutional policy.

7.3.3 Investigator Reporting to the FDA

Serious adverse events (SAEs) that are unlisted/unexpected, and at least possibly associated to the drug, and that have not previously been reported in the Investigators brochure, or reference safety information document should be reported promptly by the principal investigator to the Food and Drug Administration (FDA) by telephone or by fax. Fatal or life threatening SAEs that meet the criteria for reporting to the FDA must be reported to the FDA within 7 calendar days after awareness of the event. All other SAEs that meet the criteria for reporting to the FDA must be reported to the FDA within 15 calendar days after awareness of the event. A clear description of the suspected reaction should be provided along with an assessment as to whether the event is drug or disease related.

7.3.4 Adverse event updates/IND safety reports

Celator shall notify the Investigator via an IND Safety Report of the following information:

- Any AE associated with the use of study drug in this study or in other studies that is both serious and unexpected.
- Any finding from tests in laboratory animals that suggests a significant risk for human subjects including reports of mutagenicity, teratogenicity, or carcinogenicity.

The Investigator shall notify his/her IRB/EC promptly of these new serious and unexpected AE(s) or significant risks to subjects.

The Investigator must keep copies of all AE information, including correspondence with Celator and the IRB/EC, on file.

7.4 Adverse Event Definition based on CTCAE v4.0 criteria

An Adverse Event is any untoward medical occurrence (any symptom, sign, or abnormal lab/radiology/pathology finding) in a patient administered with a pharmaceutical product and which does not necessarily have to have a causal relationship with this treatment, only temporal association. This is inclusive of worsening of pre-existing conditions or any increases in the frequency of a pre-existing condition. As previously described in other CPX-351 protocols, there is a difference between seriousness and severity that should be clarified:

- Severe is used to describe the intensity of a specific event; the event itself may of varying medical significance
- Serious relates to patient or event outcome that is associated with the patient's life or functioning

7.4.1 Definition of Serious Adverse Event based on CTCAE v4.0 criteria

A serious adverse event (SAE) is any adverse event that at any dose:

- Results in Death
- Is life threatening
- Requires prolongation of existing hospitalization*
- Results in persistent or significant disability or incapacity

- Is a congenital anomaly/birth defect
- Is an important medical event[#]

*Hospitalization itself will not be considered a serious adverse event if required for complications of AML or co-morbid conditions. Hospitalization will be considered SAE if it fulfills the criteria for a serious and unexpected adverse event as otherwise described.

*Exceptions to the definition of SAE are myelosuppression and associated complications (Ex. uncomplicated febrile neutropenia, infection, grade 1-3 bleeding events (with or without platelet transfusions)). These are common and expected events in patients with AML and MDS. These events will be reported as AEs, not SAEs. Hospitalizations for routine procedures, investigations, and chemotherapy administration are not considered an SAE in this protocol.

Medical and scientific judgment should be exercised in deciding whether expedited reporting is appropriate in situations where none of the outcomes listed above occurred. Important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the patient or may require intervention to prevent one of the other outcomes listed in the definition above should also usually be considered serious. Examples of such events include allergic bronchospasm requiring intensive treatment in an emergency room or at home or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse. A new diagnosis of cancer during the course of a treatment should be considered as medically important.

Non-hematologic SAEs CTCAE Grade 3 and above, and all subsequent follow-up reports will be reported to the Stanford Cancer Center Data and Safety Monitoring Committee (DSMC) using the study specific CRF regardless of the event's relatedness to the investigation. Following review by the DSMC, events meeting the IRB definition of 'Unanticipated Problem' will be reported to the IRB using eProtocol within 10 working days of DSMC review, or within 5 working days for deaths or life-threatening experiences.

AEs that do not meet the requirement for expedited reporting will be reported to the IRB as part of the annual renewal of the protocol.

8. CORRELATIVE/SPECIAL STUDIES

8.1 Laboratory Correlative Studies: the following studies are completed for patients in the study as part of institutional routine care. We will evaluate molecular and cytogenetic data as available and compare to response.

8.2 Collection of Correlative Studies: Mutational and cytogenetic evaluation and bone marrow biopsy are routinely clinically obtained on initial evaluation at Stanford to confirm and evaluate current status of disease. These studies may be evaluated as clinically indicated at the time of relapse or progression of disease depending on diagnosis (AML or MDS). They will be collected as per standard institutional guidelines.

8.3 Handling of Specimens: Specimens are obtained as part of institutional routine care. They will be handled as per institutional standard guidelines.

8.4 Specimen Shipping. Mutational tests may be performed as a send out test by the institution. Specimens will be shipped per institutional guidelines by the institution lab.

8.5 Specimen Coding. Specimens are obtained as per routine care. Specimens will be coded as per institutional routine.

9. STUDY CALENDAR

Please see Appendix for patient calendar.

10. MEASUREMENTS

10.1 Primary and Secondary Outcome measures

Primary outcome measures will be the following:

- Safety data. Safety data will be assessed using CTCAE v4.0:
    - 30 and 60 Day mortality
    - SAEs
    - Grade 3-5 AE frequency
- Determine the response rate (CR + CRi for AML + CR for MDS) following induction with CPX-351 **Secondary outcome measures will be the following:**
- Determine the duration of remission following induction with CPX-351.
- Determine overall survival at 12 months.
- Determine the early induction mortality at Day 60 after 1st induction.

10.1.1 Relevant Subset

- Safety data will be determined on all patients who have received at least one dose of CPX-351
- Response rate will be determined using all patients who have received at least one dose of CPX-351
- The duration of remission will be determined for all patients who achieve a CR or CRi.
- Overall Survival will be determined on all patients
- Early induction mortality will be determined on all patients who have received at least one dose of CPX-351

10.1.2 Measurement Time Points

- Safety data will be assessed for 4 weeks following completion or discontinuation of treatment, or until initiation of new therapy, whichever one comes first.
- The response rate will be determined following the initial course of therapy (e.g. up to two courses of induction therapy with CPX-351).
- Overall survival will be determined at 12 months
- Early induction mortality will be determined on Day 60 after 1st induction (Day 1=first dose of CPX-351)
- Remission duration is from the start of response until disease relapse or death. A response will be classified as CR or CRi for AML, and CR for MDS

10.1.3 Response Review

Responses are based on pathological responses. Pathology is routinely determined by hematopathologists at Stanford who are independent of the study at Stanford.

10.1.4 Measurement Definitions

Measurement definitions for patients:

- Safety Data will be measured by CTCAE 4.0 criteria
- The response rate is the sum of the rate of CR plus CRi (Total of CR + CRi for AML patients + CR for MDS)
- For the following definitions involving blast percentages, blast percentages are routinely evaluated from bone marrow aspirate specimens by morphology. Evaluation of bone marrow biopsy is allowed for evaluation if the aspirate is insufficient for analysis, equivocal, dilute or aspicular.
- Responses for AML will use the European Leukemia Net (ELN) classification [21]
- Responses for MDS will use the International Working Group (IWG) guidelines [22]
- For treatment failure definitions as per the IWG criteria, we will consider up to two courses of induction therapy as the "initial course of therapy"

Response Criteria for AML:

- Morphologic leukemia-free state is defined as having < 5% blasts by morphology from the Day 14 bone marrow aspirate following induction therapy. Day 14 bone marrows may be obtained +/- 3 days due to logistic purposes of institutional bone marrow processing. There should be no blasts with auer rods or persistence of extramedullary disease.
- Complete remission (CR) is defined as having < 5% blasts, with count recovery to platelets ≥ 100,000/uL and ANC > 1000/uL. There should be no blasts with auer rods and no persistence of extramedullary disease. Patient should have transfusion independence.
- Complete remission with incomplete count (CRi) recovery is defined meeting all the parameters for CR, with the exception of platelets ≥ 100,000/uL and/or ANC > 1000/uL.
- Partial response is defined as normalization of blood counts (ANC > 1000/uL and platelets > 100,000/uL); a decrease of bone marrow blast percentage to 5-25%; and decrease of pretreatment bone marrow blast percentage by at least 50%; or ≤ 5% blasts with auer rods still present.
- Resistant disease is defined as failure to achieve a CR/CRi following up to two courses of induction therapy with CPX-351. It only includes patients surviving ≥ 7 days following completion of initial treatment with evidence of persistent leukemia by blood or bone marrow aspiration
- Death in aplasia: deaths occurring ≥ 7 days following completion of initial treatment while cytopenic; with an aplastic or hypoplastic bone marrow obtained within 7 days of death, without evidence of persistent leukemia
- Death from indeterminate cause: deaths occurring before completion of therapy or < 7 days following its completion; or deaths occurring ≥ 7 days following completion of initial therapy but no blasts in the blood, but no bone marrow examination available
- Disease relapse after CR/CRi: bone marrow blasts ≥ 5% (not attributable to any other causes such as regenerating bone marrow; if equivocal after recent therapy whether from marrow regeneration, a repeat bone marrow biopsy at least one week later should be done); reappearance of blasts in the blood; development of extramedullary disease
- Overall survival is defined as the number/percentage of patients alive at 12 months (starting from date of entry into trial). Includes death from any cause.

- Early induction mortality at Day 30 is defined as the number of patients who died during the first 30 days of treatment (with Day 1=first day of treatment) of the first induction
- Early induction mortality at Day 60 is defined as the number of patients who died during the first 60 days of treatment (with Day 1=first day of treatment) of the first induction
- Remission duration: is the number of days from remission until disease relapse (day when blasts > 5% are observed). It is defined for only patients who achieve a CR/CRi.
- Relapse free survival is defined for patients who achieve a CR/CRi in AML and is measured from the date of attaining remission until date of AML relapse or death from any cause.
- Event free survival is defined as time from date of entry into study until treatment failure, relapse from CR/CRi, or death from any cause (whichever occurs first). For patients who do not achieve a CR, EFS is defined as the point of progression or death (whichever comes first).

Response Criteria for MDS: Responses must last for at least 4 weeks as per IWG criteria

- Complete remission is defined as ≤ 5% blasts with normal maturation of all cell lines; persistent dysplasia will be noted; there must be normalization of peripheral blood counts to: Hb ≥ 11 g/dL, platelets ≥ 100,000/uL, ANC ≥ 1000/uL with no blasts in the peripheral blood.
- Partial remission is defined as meeting all CR criteria except: bone marrow blasts are decreased by ≥ 50% over pretreatment value but still > 5%
- Marrow CR is defined as having bone marrow ≤ 5% myeloblasts and decrease by ≥ 50% over pretreatment
- Stable disease is defined as failure to achieve at least PR, but no evidence of progression for > 8 weeks
- Treatment failure is defined as:
  - death during treatment; or
  - disease progression characterized by worsening of cytopenias; or
  - increase in percentage of bone marrow blasts;
  - or progression to a more advanced MDS FAB subtype than pretreatment
- Relapse after CR or PR: 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 Hb concentration by ≥ 1.5 g/dL or transfusion dependence
- Disease progression. For patients with:
  - Less than 5% blasts: ≥ 50% increase in blasts to > 5% blasts
  - 5-10% blasts: ≥ 50% increase in blasts to > 10% blasts
  - 10-20% blasts: ≥ 50% increase in blasts to > 20% blasts
  - 20-30% blasts: ≥ 50% increase in blasts to > 30% blasts
  - Any of the following:
    - At least 50% decrement from maximum remission/response in granulocytes or platelets
    - Reduction in Hb ≥ 2 g/dL
    - Transfusion dependence
- Overall survival is defined as the number/percentage of patients alive at 12 months (starting from date of entry into trial). Includes death from any cause.

- Early induction mortality at Day 30 is defined as the number of patients who died during the first 30 days of treatment (with Day 1=first day of treatment) of the first induction
- Early induction mortality at Day 60 is defined as the number of patients who died during the first 60 days of treatment (with Day 1=first day of treatment) of the first induction
- Remission duration: is the number of days from CR until disease relapse.
- Event free survival is defined as time from date of entry into study until treatment failure or death from any cause (whichever occurs first).

11. REGULATORY CONSIDERATIONS

11.1 Institutional Review of Protocol

The protocol, the proposed informed consent and all forms of participant information related to the study (e.g. advertisements used to recruit participants) will be reviewed and approved by the Stanford IRB and Stanford Cancer Center Scientific Review Committee (SRC). Any changes made to the protocol will be submitted as a modification and will be approved by the IRB prior to implementation. The Protocol Director will disseminate the protocol amendment information to all participating investigators and research coordinators involved in the study.

11.2 Data and Safety Monitoring Plan

The Stanford Cancer Center Data and Safety Monitoring Committee (DSMC) will be the monitoring entity for this study. The DSMC will audit study-related activities to determine whether the study has been conducted in accordance with the protocol, local standard operating procedures, FDA regulations, and Good Clinical Practice (GCP). In addition, the DSMC will regularly review serious adverse events and protocol deviations associated with the research to ensure the protection of human subjects. Results of the DSMC audit will be communicated to the IRB and the appropriate regulatory authorities at the time of continuing review, or in an expedited fashion, as needed.

11.3 Data Management Plan

The Protocol Director, or his/her designee, will prepare and maintain adequate and accurate participant case histories with observations and data pertinent to the study. A Unique Study ID will be created for each patient to maintain patient confidentiality and the unique study ID will be used on case report forms (CRFs). The protocol director and his/her designee will keep the key linking patients with their unique study ID.

Study specific CRFs will document treatment outcomes for data analysis. Data from source documents are used to transcribe critical protocol data on CRFs. The REDCAP database system will be used to assist in data analysis and will be maintained by the protocol director or his/her designee. For any printed or paper CRFs, they will be kept in a locked office. Access to electronic study databases will be restricted by electronic password protection.

12. STATISTICAL CONSIDERATIONS

12.1 Statistical Design

This study is a phase 2 open label, fixed dose administration of CPX-351 to patients with HMA refractory or relapsed AML or higher risk MDS. In order to minimize the Phase II sample size in the event of an unfavorable response, a Simon two-stage minimax design will be followed. Dr. Alex McMillan is the biostatistician assisting with the project.

Sample Size Justification

Using a desired significance of 0.05 (alpha; type I error) and power of 80% (beta 0.20; power=1-beta) with a two stage minimax design using p0=0.20 and pA=0.40, a total of 33 patients will be accrued in this study.

Eighteen patients will be accrued during stage 1 and 15 patients during stage 2. For the first 18 patients, if no more than four out of 18 treated achieve the primary end point of CR/CRi after 2 induction cycles (i.e. response rate of 22%), then the regimen will be considered ineffective and the study will be terminated; if five or more of the 18 patients achieve a CR/CRi, the study will accrue to a minimum total of 33 patients.

Effect Size Justification:

The null hypothesis (p0=0.20) is based on estimated predicted average CR/CRi rate of 20% based on several studies. In the retrospective review study by [23] outcomes of 61 patients with secondary AML who received traditional types of induction therapy were evaluated; of patients who had prior HMA therapy or revlimid, 32% achieved CR/CRi (compared to those who had induction chemotherapy after best supportive care; OR 1.13, 95% CI 0.04-0.42; p=0.001). The median OS in this patient cohort was 3.7 months. In the retrospective study of outcomes of 74 patients with secondary AML after azacitidine treatment failure, 13 patients were noted to have been treated with "active therapies" after AZA failure; of 4 patients who received intensive chemotherapy, none responded [12]. In a study of outcomes of MDS after AZA failure, of 35 patients who received intensive chemotherapy, there was a 14% overall response with 8.9 months as the median survival ([13]; p=0.04 for patients in the intensive chemotherapy group for outcome compared to best supportive care). Given the wide range above, we estimate that the predicted response to traditional induction therapy in this group will be between 15-20% (lower than 32%) given the older age cohort in our study.

The alternative hypothesis of predicted CR/CRi response with CPX-351 in our study patients will be 40% (pA=0.40). In the preliminary Phase IIb data of CPX-351 induction therapy versus 7+3 therapy in newly diagnosed AML patients aged 60-75, the CR rate was 48.8% and the CRi rate was 17.9% with total response rate of 66.7%; patients with secondary AML had CR rate of 36.4% and CRi 21.2% with total response rate of 57.6%. Amongst the patients with secondary AML in the CPX-351 arm (N=33), 13 patients had prior hypomethylation therapy exposure and 16 had not; 4 patients had prior treatment with other agents. In the patients with prior HMA therapy receiving CPX-351, the CR rate was 23% (3/13) and CRi rate was 31% (4/13) with overall CR/CRi rate of 54% (7/13). We anticipate that the patients enrolled in our study will have an older age and include patients with MDS, and potentially lower CR/CRi rate. Thus our alternative hypothesis will conservatively be established at pA=0.40.

12.1.1 Randomization

This is a fixed dose study of CPX-351. There will be no randomization.

12.2 Interim analyses

As described above, for the first 18 patients, if no more than four out of 18 treated achieve the primary end point of CR/CRi after 2 induction cycles (i.e. response rate of 22%), then the regimen will be considered ineffective and the study will be terminated; if five or more of the 18 patients achieve a CR/CRi, the study will accrue to a minimum total of 33 patients.

12.3 Descriptive Statistics and Exploratory Data Analysis

We will describe the following for the group of patients in the study:

- We will describe age, sex, race/ethnicity, performance status of the patient group
- Descriptive analysis of how many patients have AML versus MDS; and how many patients have de novo AML versus secondary AML
- Descriptive analysis of prior therapies
- Descriptive analysis of IPSS score for patients with MDS at baseline
- Descriptive analysis of peripheral blood and blast percentage for the total group, and then subsets of AML and MDS at baseline
- Descriptive analysis of baseline ANC, hemoglobin, and platelet count at the time of study entry
- Descriptive analysis of cytogenetics and molecular features as available
- Baseline EF

12.4 Primary Analysis

The primary outcome measures will be the following. Please refer to section 10 for details on definitions and time-frame of measurement.

- Safety data.
- Determining the response rate (CR + CRi) following up to two induction courses with CPX-351.

12.4.1 Analysis Population

- All patients enrolled in the trial who receive any dose of CPX-351 will be analyzed for safety
- All patients enrolled in the trial who receive any dose of CPX-351 will be analyzed for response (CR/CRi)
- Missing data for CR or CRi status will be considered as non-response as the conservative measure as a response cannot be definitely imputed in this population

12.4.2. Analysis Plan

- To analyze the safety data, adverse events recorded using CTCAE 4.0 for each patient will reviewed and totaled, for the total number of adverse events for each adverse event compared to total group of patients (rate of outcome of each adverse event in study population).
- The response rate will be calculated by adding the total CR + CRi (total number of CR + CRi for AML + CR for MDS) events after up to two courses of induction therapy, and comparing it to the total number of patients undergoing induction with CPX-351.

12.5 Secondary Analysis

The secondary outcome measures will be the following:

- Determine the duration of remission following induction with CPX-351.
- Determine overall survival at 12 months.
- Determine the early induction mortality at Day 60 after 1st induction.

12.5.1 Analysis Population

- All patients who are initiated into the study will be analyzed for overall survival.
- All patients who receive at least one dose of CPX-351 will be included in the analysis of early induction mortality at Day 60.
- All patients who achieve CR will be included in the analysis of remission duration

12.5.2 Secondary Outcomes: Analysis Plan

Analysis of secondary outcome measures will be done by the following:

- The remission of duration will be calculated by counting the number of days from the date of remission until date of disease relapse for patients who achieve a CR (and CRi for AML). The average days of remission will be calculated to determine the median duration of remission.
- Induction mortality at Day 60 for patients for first induction therapy will be calculated by determining the number of deaths within the first 60 days, using Day 1 of the first induction therapy as the first day, compared to the total number of patients who have received any dose of CPX-351.
- The overall survival will be determined by the number of patients who are alive at 12 months compared to the number of patients who initiated into the study.

12.6 Sample Size

12.6.1 Accrual estimates

The sample size of the patients in this study will be 33. We anticipate that 1-2 patients/month will be accrued with overall accrual taking approximately 2-3 years based on patient volume seen in our clinic currently.

12.6.2 Sample size justification

Please refer to 12.1

12.6.3 Effect size justification

Please refer to 12.1

12.7 Criteria for future studies

If we do see a significant response rate in this study, we will plan on proceeding with a larger registration trial in a phase III randomized study as it will be important to establish that the effect was causative from CPX-351 use specifically including patients with both AML and MDS. This will be used in preparation to analyze whether CPX-351 will be standard of care for patients with higher risk MDS and AML who are refractory/relapsed to HMA therapy and intensive chemotherapy candidates.

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APPENDICES

APPENDIX A**: Participant Eligibility Checklist**

A Participant Eligibility Checklist must be completed in its entirety for each subject prior to registration. The completed, signed, and dated checklist must be retained in the patient's study file and the study's Regulatory Binder.

Protocol Title:	A Phase II Study of CPX-351 for treatment of higher risk MDS or AML relapsed or refractory to Hypomethylation (HMA) therapy
Protocol Number:	**IRB-28524 / HEM0036**
Principal Investigator:	Rondeep Singh Brar, MD

II. Subject Information:

Subject Name/ID:
Gender: ☐ Male ☐ Female

III. Inclusion/Exclusion Criteria

Inclusion Criteria (From IRB approved protocol)	**Yes**	**No**	**Supporting Documentation***
1. Ability to understand and voluntarily give informed consent	☐	☐	
2. Age 60 and older	☐	☐	
3. Pathological diagnosis of AML (by WHO criteria) or higher risk MDS (includes int-2 and high risk MDS by IPSS) along with one the following: - Patients with de novo or secondary MDS with progression/refractoriness after HMA treatment who have not transformed to AML - Patients with MDS and prior HMA treatment for MDS who transform to AML - Patients with AML who are refractory/relapsed after HMA therapy for their AML are eligible	☐	☐	
4. Life expectancy > 1 month	☐	☐	
5. ECOG Performance Status 0-2	☐	☐	
6. Able to adhere to study visit schedule and other protocol requirements	☐	☐	
7. Serum creatinine < 2.0	☐	☐	

8. Serum total bilirubin ≤ 2.5 (Patients with Gilbert's syndrome will be included if total bilirubin at time of study entry is ≤ 2X their baseline total bilirubin)	☐	☐	
9. AST and ALT < 3X ULN	☐	☐	
10. Cardiac EF ≥ 45% by ECHO or MUGA	☐	☐	
11. Patients with second malignancies may be eligible at discretion of PI given acute life threatening nature of untreated AML or higher risk MDS. Patients maintained on long-term non-chemotherapy treatment, eg, hormonal therapy, are also eligible.	☐	☐	☐ (N/A=not applicable)
Exclusion Criteria (From IRB-approved protocol)			
1. Patients who have previously undergone allogeneic hematopoietic stem cell transplant	☐	☐	
2. Patients with > 368 mg/m^2 prior daunorubicin or daunorubicin equivalent anthracycline therapy	☐	☐	
3. Acute promyelocytic leukemia	☐	☐	
4. Any serious medical condition, laboratory abnormality, or psychiatric illness that would prevent from obtaining informed consent	☐	☐	
5. Prior conventional cytotoxic induction chemotherapy for the treatment of MDS or AML is excluded	☐	☐	
6. Patient has not had prior HMA therapy	☐	☐	
7. Clinical evidence of CNS leukemia	☐	☐	
8. Uncontrolled current myocardial impairment (ischemic heart disease or arrhythmia or valve dysfunction or HTN or CHF that is uncontrolled)	☐	☐	
9. Active uncontrolled infection (if infection being treated and patient hemodynamically stable for 48 hours, patient can be entered into	☐	☐	

study)			
10. Active known uncontrolled HIV or hepatitis C infection	☐	☐	
11. Known hypersensitivity to cytarabine, daunorubicin, or liposomal products	☐	☐	
12. Known history of Wilson's disease or copper related disorders	☐	☐	
13. Medical or psychiatric illness or organ dysfunction or lab abnormality that in the discretion of the PI would compromise patient safety or interfere with interpretation of the data	☐	☐	
14. Serum creatinine ≥ 2.0 mg/dL	☐	☐	
15. Serum bilirubin > 2.5 (patient's with Gilbert's syndrome will be excluded if their total bilirubin at study entry is > 2X baseline total bilirubin)	☐	☐	
16. Serum ALT/AST > 3X ULN	☐	☐	

*****All subject files must include supporting documentation to confirm subject eligibility. The method of confirmation can include, but is not limited to, laboratory test results, radiology test results, subject self-report, and medical record review.

IV. Statement of Eligibility

This subject is ☐ **eligible** / ☐ **ineligible** for participation in the study.

Signature:	Date:
Printed Name:	

Signature:	Date:
Printed Name:	

Signature:	Date:
Printed Name:	

APPENDIX B: ECOG Performance Status

GRADE	ECOG Performance Status
0	Fully Active, able to carry on all pre-disease performance without restriction
1	Restricted in physically strenuous activity but ambulatory and bale to carry out work of a light or sedentary nature, eg, light house work, office work
2	Ambulatory and capable of all self-care but unable to carry out any work activities. Up and about more than 50% of waking hours.
3	Capable of only limited self-care, confied to bed or chair more than 50% of waking hours
4	Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair
5	Dead

APPENDIX C: New York Heart Association Heart Failure Functional Classification

CLASS	Patient Symptoms
Class I (Mild)	No limitation of physical activity. Ordinary physical activity does not cause undue fatigue, palpitation, or dyspnea (shortness of breath)
Class II (Mild)	Slight limitation of physical activity. Comfortable at rest, but less than ordinary activity causes fatigues, palpitation, or dyspnea
Class III (Moderate)	Marked limitation of physical activity. Comfortable at rest, but less than ordinary activity causes fatigue, palpitation, or dyspnea
Class IV (Severe)	Unable to carry out any physical activity without discomfort. Symptoms of cardiac insufficiency at rest. If any physical activity is undertaken, discomfort is increased.

APPENDIX D: Definitions of De Novo AML and Secondary AML

- De Novo AML refers to patients with AML with no clinical history of prior myelodysplastic syndrome, myeloproliferative disorder, or exposure to potentially leukemogenic therapies or agents
- Secondary AML refers to patients who have a history of MDS, MPD, or exposure to potentially leukemogenic therapies or agents; this includes alkylating agent related MDS/AML and topoisomerase II related AML
- AML : the blast count must be ≥ 20% in either the peripheral blood or bone marrow aspirate. Exceptions include t(8;21), inv(16), t(15;17) disease, in which case the diagnosis of AML is made regardless of blast count

APPENDIX E: CTCAE Version 4.0 Grading Definition

We will use CTCAE version 4.0 to classify adverse events. It is available from the NIH/NCI website: http://evs.nci.nih.gov/ftp1/CTCAE/About.html

This publication is from 06/14/2010.

Grading used to grade the severity of AEs for CTCAE 4.0:

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

Self-care ADLs: refers to bathing/showering, dressing/undressing/personal hygiene, feeding/eating self, using the toilet, transferring, taking medications, and not bed-ridden

Instrumental ADLs: refers to preparation of meals, shopping for groceries or clothes, using the telephone, managing money, etc.

APPENDIX F: Elements of the HIPAA Privacy Rule Authorization

- Written in plain language understandable to the patient or the representative;
- A "specific and meaningful" description of Protected Health Information (PHI) to be used and disclosed;
- The specific identification of the person/class authorized to make the use or disclosure;
- The specific identification of the persons/class to whom the covered entity may make the requested use or disclosure;
- Description of the purpose of the disclosure;
- An expiration date or event (ie, "no expiration date" for data repository use, or "for the duration of a specific research study" permits use until end of study plus time for wrapping up and reporting);
- A statement of the patient's right to revoke the authorization and any exceptions to the right to revoke;
- Conditions, if any, on authorization;
- A statement about possible re-disclosures of PHI by the recipient and that the PHI will no longer be protected by the Privacy Rule in the event of such re- disclosures; and
- The signature and date of the patient (or of the patient's personal representative, along with the personal representative's authority to act).

APPENDIX G: Declaration of Helsinki

WORLD MEDICAL ASSOCIATION DECLARATION OF HELSINKI ETHICAL PRINCIPLES FOR MEDICAL RESEARCH INVOLVING HUMAN SUBJECTS

Available at http://www.wma.net/en/20activities/10ethics/10helsinki/

APPENDIX H: Anthracycline Equivalents Guidelines

Anthracycline	Conversion Factor*
Daunorubicin	1
Doxorubicin	2
Epirubicin	1
Idarubicin	4
Mitoxantrone	4.4

The dose of equivalent daunorubicin can be calculated by multiplying the anthracycline amount previously received by the conversion factor to determine the equivalent dose of daunorubicin received [24].

APPENDIX I: 2008 WHO Classification of Acute Myeloid Leukemia

Acute myeloid leukemia and related neoplasms

1. Acute myeloid leukemia with recurrent genetic abnormalities
    a. AML with t(8;21)(q22;q22); *RUNX1-RUNX1T1*
    b. AML with inv(16)(p13.1q22) or t(16;16)(p13.1;q22); *CBFB-MYH11*
    c. APL with t(15;17)(q22;q12); *PML-RARA*
    d. AML with t(9;11)(p22;q23); *MLLT3-MLL*
    e. AML with t(6;9)(p23;q34); *DEK-NUP214*
    f. AML with inv(3)(q21q26.2) or t(3;3)(q21;q26.2); *RPN1-EVI1*
    g. AML (megakaryoblastic) with t(1;22)(p13;q13); *RBM15-MKL1*
    h. *Provisional entity: AML with mutated NPM1*
    i. *Provisional entity: AML with mutated CEBPA*
2. Acute myeloid leukemia with myelodysplasia-related changes
3. Therapy-related myeloid neoplasms
4. Acute myeloid leukemia, not otherwise specified
    a. AML with minimal differentiation
    b. AML without maturation
    c. AML with maturation
    d. Acute myelomonocytic leukemia
    e. Acute monoblastic/monocytic leukemia
    f. Acute erythroid leukemia
    g. Pure erythroid leukemia
    h. Erythroleukemia, erythroid/myeloid
    i. Acute megakaryoblastic leukemia
    j. Acute basophilic leukemia
    k. Acute panmyelosis with myelofibrosis
5. Myeloid sarcoma

Reference: [25]

APPENDIX J: 2008 WHO Classification and Criteria for MDS

Disease	Blood findings	BM findings
Refractory cytopenia with unilineage dysplasia (RCUD): (refractory anemia [RA]; refractory neutropenia [RN]; refractory thrombocytopenia [RT])	Unicytopenia or bicytopenia* No or rare blasts (< 1%)†	Unilineage dysplasia: ≥ 10% of the cells in one myeloid lineage < 5% blasts < 15% of erythroid precursors are ring sideroblasts
Refractory anemia with ring sideroblasts (RARS)	Anemia No blasts	≥ 15% of erythroid precursors are ring sideroblasts Erythroid dysplasia only < 5% blasts
Refractory cytopenia with multilineage dysplasia (RCMD)	Cytopenia(s) No or rare blasts (< 1%)† No Auer rods < 1×10^9/L monocytes	Dysplasia in ≥ 10% of the cells in ≥ 2 myeloid lineages (neutrophil and/or erythroid precursors and/or megakaryocytes) < 5% blasts in marrow No Auer rods ± 15% ring sideroblasts
Refractory anemia with excess blasts-1 (RAEB-1)	Cytopenia(s) < 5% blasts† No Auer rods < 1×10^9/L monocytes	Unilineage or multilineage dysplasia 5%-9% blasts† No Auer rods
Refractory anemia with excess blasts-2 (RAEB-2)	Cytopenia(s) 5%-19% blasts‡ Auer rods ±‡ < 1×10^9/L monocytes	Unilineage or multilineage dysplasia 10%-19% blasts‡ Auer rods ±‡
Myelodysplastic syndrome—unclassified (MDS-U)	Cytopenias < 1% blasts†	Unequivocal dysplasia in < 10% of cells in one or more myeloid lineages when accompanied by a cytogenetic abnormality considered as presumptive evidence for a diagnosis of MDS (see Table 6) < 5% blasts
MDS associated with isolated del(5q)	Anemia Usually normal or increased platelet count No or rare blasts (< 1%)	Normal to increased megakaryocytes with hypolobated nuclei < 5% blasts Isolated del(5q) cytogenetic abnormality No Auer rods

Reference: [26]

APPENDIX K: Patient Study Calendar
Each Induction[1] and Consolidation

DAY	Screen	1	3	5	14+/-3	During[3] Count recovery or by Day 42+/-3	End of Active Treatment Phase[15]/Early Termination	30-day post last dose of study drug +/-3 days	1-year Follow-up (+/- 2 weeks)[13]
Informed Consent[5]	X								
Medical history	X								
Vital Signs[11]	X	X				X	X		
Physical Exam	X	X				X	X		
ECOG Perf Status	X	X[8]							
CBC with Diff	X	X			X[9]	X	X		
Chemistries[10]	X	X				X			
Urianalysis[12]	X								
CXR or CT Chest[12]	X								
ECHO or MUGA[7]	X								
EKG[7]	X								
Bone Marrow Evaluation	X				X[6]	X[4]			
Cytogenetics and Molecular Evaluation[14]	X								
Concomitant medications	X	X				X	X		
Toxicity Notation		X				X	X	X[16]	
Treatment Admin		X	X	X[2]					
Followup Assessment									X

1 The first induction can end prematurely if a second induction is necessary. The schedule of evaluations for the first induction is followed until the second induction starts; then the evaluations are followed as indicated in the calendar, beginning with Day 1.

2 Second inductions and consolidations use a different dosing regimen with treatment on Days 1 and 3.

3 Only after completion of induction(s), during count recovery (ANC $\geq$ 500/uL, plt $\geq$ 50,000/uL) or by Day 42+/-3.

4 Only after completion of induction(s) to confirm response to CPX-351

5 If 30 days elapse after the initial informed consent was signed and screening has not been completed, the patient must sign another ICF

6 Required after first induction course (in case the initial day 14+/-3 days bone marrow is non-evaluable or assessment of aplasia is equivocal, a repeat evaluation will be performed 7+/-3 days later, in order to determine effect and need for a second induction); as needed thereafter to confirm response/disease persistence/relapse

7 ECHO or MUGA and EKG repeated before each consolidation course (within 14 days of starting each course of consolidation). Initial screening ECHO or MUGA and EKG obtained within 28 days of treatment initiation

8 ECOG performance status must be 0-2 to receive treatment

9 Only during first induction course

10 Chemistries include basic metabolic panel and liver function panel (also called a CMP at Stanford).

11 Height and weight as part of vital signs will be obtained at screening and repeated as medically needed.

12 Baseline CXR or CT Chest and UA to be obtained within 14 days of treatment initiation

13 Followup can be obtained by clinic visit, telephone, or other correspondence, discussion with treating physician, or state/country/federal resources such as date of death lists.

14 After initial screening cytogenetics/molecular testing, can be repeated as needed as per discretion of treating physician or institutional standard of care. Of note, for insufficient or poor aspirate samples in which cytogenetics or molecular testing are not obtainable, this can be noted.

15 End of active treatment phase or early termination. End of active treatment phases refers to after both consolidation

treatments are completed. May be combined with another visit depending on patient status.
16 Patients will have a followup visit 30 days +/- 3 days after the last dose of study drug for toxicity assessment and collection of adverse event data. This may be combined with another visit depending on patient status.

Appendix L:
Study Drug Re-Supply Form

To order re-supply of CPX-351 vials, complete all sections below and fax to:

Celator Pharmaceuticals, Inc.
Fax:
Office Phone:

Ensure sufficient time is provided for drug shipment. Drug will be shipped within 1 week of request.

Date	
Investigator	
Site Number	
Current Balance of CPX-351 Vials	
# of Requested CPX-351 Vials (shipped as 4 vials/box)	

Name of Pharmacist/Site Staff to receive shipment	
Address where shipment is to be sent (include phone number)	

Name (print) **Signature** **Date**