Phase II Trial of CPX (Cytarabine:Daunorubicin) Liposome Injection in Patients >/=60 Years of Age With AML Previously Untreated By Intensive Chemotherapy

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PHASE II TRIAL OF CPX-351 (CYTARABINE:DAUNORUBICIN) LIPOSOME INJECTION IN PATIENTS WITH ACUTE MYELOID LEUKEMIA ≥60 YEARS OF AGE WHO HAVE NOT BEEN TREATED WITH INTENSIVE CHEMOTHERAPY

Sponsor
Weill Cornell Medicine

Investigator Initiated Trial

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PROTOCOL SYNOPSIS

Title:

PHASE II TRIAL OF CPX-351—(CYTARABINE:DAUNORUBICIN) LIPOSOME INJECTION IN PATIENTS WITH ACUTE MYELOID LEUKEMIA ≥60 YEARS OF AGE WHO HAVE NOT BEEN TREATED WITH INTENSIVE CHEMOTHERAPY

Sponsor: Weill Cornell Medicine
Investigator Initiated Trial:
Principal Investigator: Ellen Ritchie
Weill-Cornell Medical Center

Objectives:

Primary

- To assess the suitability of CPX-351 as first intensive therapy in older (age ≥60 years) patients with AML based on safety and efficacy. The primary efficacy endpoint will be overall survival (OS). The primary safety endpoint will be 30-day mortality.

Secondary

- To assess efficacy by response (CR, CRp, CRi, and CR+CRp+CRi)) rate, response duration, and Event Free Survival (EFS)
- To assess safety by 30-day mortality, serious adverse events (SAE) and adverse event frequency and severity
- To assess QOL using FACT-LEU
- To assess the relationship of cognitive function to outcome using the Blessed Orientation-Memory-Concentration Test and the Montreal Cognitive Assessment
- To confirm the safety of CPX-351 as a post-remission (consolidation) therapy
- To supplement efficacy assessment by determining the rate of morphologic leukemia-free state (MLFS)

Study Design:

This is an open label study to assess the safety and efficacy of CPX-351 as first intensive therapy in elderly (age ≥60 years) patients with AML with companion cognitive function testing to determine whether this contributes to outcome in these patients. Patients may have received prior AML treatment with non-intensive regimens, e.g. hypomethylating agents, low-dose cytarabine, or lenolidomide, but may not have received intensive AML treatment with anthracyclines and/or infusional cytarabine prior to enrollment on this trial. The cohort will include 30 patients treated with single-agent CPX-351. These patients will be assessed for efficacy and safety. Quality of life will be assessed using the FACT-LEU in all patients. Cognitive function will be assessed using the Blessed Orientation-Memory-Concentration Test and the Montreal Cognitive Assessment.

Study enrollment is expected to be completed within approximately 2 years.

Sample Size:

30 patients

Study Drugs:
CPX-351 (cytarabine:daunorubicin) Liposome Injection is a liposomal formulation of a fixed combination of the antineoplastic drugs cytarabine and daunorubicin. The two drugs are present inside the liposome in a 5:1 molar ratio shown to act synergistically in pre-clinical studies. The liposome membrane is composed of a 7:2:1 molar ratio of distearoylphosphatidylcholine, distearoylphosphatidylglycerol and cholesterol.

CPX-351 is provided as a sterile, pyrogen-free, purple, lyophilized product in 50 mL glass, single-use vials. Each 50 mL vial after reconstitution contains 20 mL of CPX-351 (5 units/mL). Each unit (u) contains 1.0 mg cytarabine and 0.44 mg daunorubicin base in liposomes suspended in sucrose. Product is stored at 5˚ ± 3ºC.

Efficacy Variables & Analysis:

- To assess the suitability of CPX 351 in older patients with AML and the relationship of cognitive function to outcome
- Response rate (CR, CRp, CRi, and CR+CRp+CRi), (morphologic, cytogenetic and molecular response)
- Response duration (relapse-free survival)
- EFS
- Evaluation of QOL of CPX treated patients
- Evaluation of relationship of cognitive function to outcome in treated patients

Safety Variables & Analysis:
Patients will be monitored for all clinical adverse events as well as laboratory evaluations.

- Induction Mortality: assessed at Day 30 and 60; therapies may be changed after 30 days.
- Serious Adverse Events
- Adverse Events: Grades 1-5 and Grades 3-5
- Laboratory Evaluations
  - Routine hematology (CBC+diff+Platelet count) and chemistry (with LDH)
  - Time to hematologic recovery and proportion with prolonged cytopenias (≥ 56 days)
- Cardiac Evaluations
  - Cardiac AEs: Grades 1-5 and Grades 3-5
  - ECG changes (pre-dose for each course, and at the end of each course)
  - LVEF changes (pre and post treatment)

Other Variables & Analysis:
Quality of Life Assessment: FACT-Leu will be used to assess patients at the start of treatment and one month after treatment completion.

Cognitive Assessment: The Blessed Orientation-Memory-Concentration Test and the Montreal Cognitive Assessment Mini will be administered at the start of treatment and one month after completion of therapy.

Cardiac Assessments: All ECG and ECHO/cardiac MRI assessments will be obtained and read locally for patient care.

ABBREVIATIONS

7+3	Seven days of continuous infusion of cytarabine at 100 mg/m^2/day and three days of daunorubicin at 60 mg/m^2/day
5+2	Five days of continuous infusion of cytarabine at 100 mg/m^2/day and 2 days of daunorubicin at 60 mg/m^2/day
ADR	Adverse Drug Reaction
AE	Adverse Event
AHD	Antecedent Hematologic Disorders
ALL	Acute Lymphocytic Leukemia
ALT	Alanine Transaminase (SGPT)
AML	Acute Myeloid Leukemia
ANC	Absolute Neutrophil Count
Ara-U	Arabinosyluracil
ASCO	American Society of Clinical Oncology
AST	Aspartate Transaminase (SGOT)
ATPase	Adenosine triphosphatase
AUC	Area under the plasma concentration-time curve
BID	Twice daily
BSA	Body Surface Area
BUN	Blood Urea Nitrogen
C	Celsius
Cmax	Maximum plasma concentration
CL	Clearance
CNS	Central nervous system
CPX-351	CPX-351 (cytarabine:daunorubicin) Liposome Injection
CR	Complete Remission
CRi	Complete Remission with incomplete hematologic recovery
CRp	Complete remission with incomplete platelet recovery
CRF	Case Report Form
CMMoL	Chronic Myelomonocytic Leukemia
CTCAE	Common Terminology Criteria for Adverse Events
d	day
DEHP	di(2-ethylhexyl)phthalate
dL	deciliter
DSMB	Data and Safety Monitoring Board
DSPG	Distearoylphosphatidylglycerol
DSPC	Distearoylphosphatidylcholine
EC	Ethics Committee
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
EFS	Event-free Survival
ELN	European LeukemiaNet
EOI	End of Infusion
FDA	Food and Drug Administration
FISH	Fluorescence in situ Hybridization
g	gram(s)

GCP	Good Clinical Practice
HCl	Hydrogen Chloride
HIPAA	Health Information Protection and Portability Act
HIV	Human Immunodeficiency Virus
HMA	Hypomethylating Agent
HOVON	Hemato-Oncologie voor Volwassenen Nederland
HP	High Purity
HSCT	Hematopoietic Stem Cell Transplantation
ICF	Informed Consent Form
ICH	International Committee on Harmonization
ITT	Intent-to-treat
IRB/EC	Institutional Review Board/Ethics Committee
iv, IV	intravenous
K-M	Kaplan-Meier
L	liter
LDH	Lactate Dehydrogenase
LVEF	Left ventricular ejection fraction
m^2	square meters
MDR	Multi-drug Resistance
MDS	myelodysplastic syndrome
MedDRA	Medical Dictionary for Regulatory Activities
mg	milligram(s)
mL	milliliter(s)
MLL	Mixed Lineage Leukemia
MPN	Myeloproliferative neoplasm
MLS	Morphologic Leukemia-free State
MRU	Medical Resource Usage
MTD	Maximum Tolerated Dose
MUGA	Multiple Gated Acquisition scan
mw	molecular weight
N	Number, Population
NF	National Formulary
OS	Overall Survival
PD	Persistent Disease
PhEur	European Pharmacopoeia
PHI	Protected Health Information
PK	Pharmacokinetics
PS	Performance Status
q.s.	quantum sufficiat
RBC	Red blood cells
SAE	Serious Adverse Event
SD	Standard deviation
sAML	Secondary AML
$T_{1/2}$	Half-life
t-AML	Therapy-related AML
Tmax	Time of occurrence of Cmax

u	Units
µL	Microliter
ULN	Upper Limits of Normal
USP	United States Pharmacopeia
V	Volume
WHO	World Health Organization

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1 General Information

This document is a protocol for a human research study. This study is to be conducted according to United States and international standards of Good Clinical Practice (FDA Title 21 parts 11, 50, 54, 56, 312, International Conference on Harmonization and the Declaration of Helsinki), applicable government regulations and Institutional research policies and procedures.

2 Background Information

2.1 Acute Myeloid Leukemia in the Elderly and its Treatment

Acute Myeloid Leukemia in older patients is a poor prognosis disease. While progress in supportive care, such as better antibiotic and antifungal therapy, have improved outcomes for younger persons with this disease, the overall survival of older patients has not changed through the years. The reasons for the poorer prognosis of elderly patients are multifocal and include disease biology, comorbid illness, geriatric syndromes and social factors. Intensive treatment and consolidation chemotherapy can be difficult to administer to an older population. The intensiveness of treatment can be difficult to tolerate in older patients with other comorbid illnesses and geriatric syndromes. Physicians may modify doses to standard regimens to decrease presumed toxicities and inadvertently decrease the efficacy of treatment. Once patients have recovered from induction chemotherapy, they may be too weak to withstand subsequent cycles of consolidation therapy and never achieve a deep, MRD negative, response to treatment and a durable response to therapy.

2.2 CombiPlex® Technology and CPX-351

Combination chemotherapy regimens have traditionally been designed empirically on the basis of tolerability. However, in vitro, where the ratio of drugs used in combination can be controlled, it has been demonstrated that drug combinations providing synergy at one ratio may be simply additive or even antagonistic at other ratios.[15] When individual free drugs are administered, each agent is handled differently by the body, resulting in varying distribution of the individual drugs to tumor sites which can result in drug ratios that are suboptimal or ineffective. Jazz's technology is based on the findings that in vitro synergistic activity of antineoplastic drugs depends on specific drug ratios and that the in vivo activity of a combination depends on maintaining the synergistic ratio. In this way, the development of a particular chemotherapeutic regimen can be based on the most efficacious ratio rather than empirically based on toxicity.

The development of CPX-351 (cytarabine:daunorubicin) Liposome Injection was based on 1) defining a synergistic ratio of the two active moieties, cytarabine and daunorubicin, using cell-based screening assays and 2) designing a liposomal drug carrier to maintain this ratio after intravenous administration. This ratio was not based on the empirically-derived, toxicity-guided regimens currently used for cytarabine and anthracyclines.

CPX-351 is a liposomal formulation of a fixed combination of the antineoplastic drugs cytarabine and daunorubicin. The two drugs are present inside the liposome in a 5:1 molar

ratio. The liposome membrane is composed of distearoylphosphatidylcholine, distearoylphosphatidylglycerol and cholesterol in a 7:2:1 molar ratio. These liposomes have a nominal diameter of approximately 100nm and are suspended in sucrose. Sterilization is achieved by filtration through a 0.22 μm filter.

CPX-351 is provided as a sterile, pyrogen-free lyophilized formulation in 50 mL glass, single-use vials. Each vial contains 100 units of CPX-351 where each unit contains 1.0 mg cytarabine and 0.44 mg daunorubicin base in liposomes. The lyophilized cake is reconstituted with sterile water for injection to obtain a homogeneous dispersion at 5 units/mL. The composition of the formulation after reconstitution is listed in Table 1 below.

Table 1: Quantitative Composition

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	149	7 mg	0.07 mg
Sucrose, NF	342	2054 mg	20.54 mg

2.3 CPX-351 Product Label

CPX-351 (cytarabine:daunorubicin) LIPOSOME FOR INJECTION 100 units/Vial
Each unit contains 1.0 mg (±10%) Cytarabine and 0.44 mg (±10%) Daunorubicin (base) in liposomes containing DSPC, DSPG and cholesterol. Also contains copper as copper gluconate, triethanolamine and sucrose.
Store refrigerated at 5°C (±3°C) in an upright position.
FRAGILE: Do not drop
Caution: New Drug – Limited by Federal Law to Investigational Use
Manufactured for
Jazz Pharmaceuticals, Inc., 200 PrincetonSouth Corporate Center
Ewing, NJ 08628

Lot #_____ Expiration Date:_____

2.4 Rationale for CPX-351 use in Patients suitable for non-intensive therapy

Three clinical studies have been completed with CPX-351 and a detailed presentation is available in the Investigator's Brochure. A brief summary of observations pertinent to treatment of AML patients, particularly those with co-morbidities and patients whose age tends of limit treatment to non-intensive regimens is discussed below.

The rationale for using CPX-351 to treat older patients thought to be unsuitable for treatment with intensive chemotherapy is rooted in the characteristics of AML in older patients, the pharmacology and mechanism of CPX-351 action, and clinical observations

of the dose-response and safety of CPX-351. It is well known that both the incidence of AML and the risk of AML resistance to chemotherapy increase in an age related manner. Younger patients, particularly those younger than 45 years of age, have higher response rates, lower rates of primary refractory disease, and longer survival than patients over the age of 70. This is associated with an age related rising risk of adverse cytogenetics and multidrug resistance phenotype. CPX-351 packages cytarabine and daunorubicin within liposomes at a 5:1 molar ratio, found *in vitro* to maximize drug synergy and minimize antagonism. CPX-351 liposomes are stable and persist in the plasma for extended periods of time leading to cytarabine and daunorubicin half-lives of approximately 24 hours. This result suggests that CPX-351 may be effective for both in rapidly and slowly cycling leukemias. Exposure of leukemia cells from cell lines and circulating blast cells from patients demonstrate direct entry of CPX-351 liposomes and subsequent intracytoplasmic release of drug. These observations suggest that effective treatment may be possible even in patients with multidrug resistance phenotype due to increased P-glycoprotein expression. Clinical observations of CPX-351 safety and efficacy come almost exclusively from patients considered fit for intensive chemotherapy and indicate a safety profile that is very similar to that of 7+3 chemotherapy except for more prolonged myelosuppression. In the clinic the dose-toxicity/response curve appears to be shallow with most of the grade 3/4 adverse events associated with prolonged myelosuppression rather than severe non-hematologic toxic events.

Taken together these findings suggest that treatment at the MTD (100 units/m^2/dose on day 1, 3, and 5) is likely to be feasible, even in patients of advanced age and with some co-morbidities because the toxicities of treatment are mostly confined to myelosuppression and because supportive care with anti-infective prophylaxis is effective. It is thought that full dose treatment is likely to maximize the probability of response and that response is possible even in patient populations enriched for adverse cytogenetics and multi-drug resistance phenotype. The mode of action of CPX-351 should enable rapid clearance of leukemia from the peripheral blood and bone marrow with most patients achieving complete response after one induction course of treatment with recovery from neutropenia usually within 5-7 weeks.

Treating an AML patient population usually considered suitable for non-intensive regimens with CPX-351 is not without risk. This patient population is expected to be older with some baseline comorbidities and cannot be expected to be as resilient as the fit older population treated in Phase II with CPX-351. In that study induction mortality was assessed at Day 30 and 60 and a lower rate of early mortality was observed for CPX-351 treated patients (4/85, 4.7% vs. 6/41, 14.6% at 60 days, p=0.053). This result is the best evidence that CPX-351 treatment at full dose is likely to be acceptably safe and suggests that rapid clearance of leukemia due to full dose treatment may assist in reducing the contribution of leukemia to the early death rate.

The greater myelosuppression and more prolonged neutropenia following CPX-351 treatment was associated with a higher frequency of febrile neutropenia (63.5% vs. 51.2%), grade 3 and 4 infections (e.g. bacteremia (42.4% vs. 22%)), and bleeding events (e.g. epistaxis (36.5% vs. 19.5%)). In spite of this the lower mortality rate at 30 and 60 days

indicates that CPX-351 was safe and strongly suggests that anti-infection prophylaxis was effective in preventing infection-related deaths in spite of risks of myelosuppression.

Most recently, a phase 3 trial comparing CPX-351 to standard induction chemotherapy with daunorubicin and cytarabine in older patients aged 60-75 with high risk AML was completed. The Phase 3 trial compared to the standard of care regimen of cytarabine and daunorubicin known as 7+3.

The median overall survival for patients treated with CPX-351 in the study was 9.56 months compared to 5.95 months for patients receiving 7+3, representing a 3.61 month improvement in favor of CPX-351. The hazard ratio (HR) was 0.69 (p=0.005) which represents a 31% reduction in the risk of death versus 7+3. The percentage of patients alive 12 months after randomization was 41.5% on the VYXEOS arm compared to 27.6% on the 7+3 arm. The percentage of patients alive 24 months after randomization was 31.1% on the CPX-351 arm compared to 12.3% on the 7+3 arm.

Event-free survival was also statistically significant in favor of CPX-351. The HR was 0.74 (p-value=0.021). The median event-free survival was 2.53 months in the CPX-351 arm compared to 1.31 months in the 7+3 arm.

CPX-351 also demonstrated a statistically significant improvement in induction response rate (CR+CRi of 47.7% versus 33.3%; p=0.016) and this significance was maintained for the analysis of CR alone (CR of 37.3% versus 25.6%, p=0.040).

Thirty-four percent of CPX-351 treated patients received a stem cell transplant (SCT) compared to 25% of 7+3 treated patients. In a landmark survival analysis of patients receiving a SCT, CPX-351 patients had significantly improved survival post-transplant (HR was 0.46 (p-value=0.0046)). The median overall survival had not been reached in the CPX-351 treated patients compared to 10.25 months in the 7+3 treated patients.

Thirty-day and sixty-day all-cause mortality favored CPX-351. Thirty-day mortality was 5.9% compared to 10.6% and sixty-day mortality was 13.7% versus 21.2%.
Grade 3-5 non-hematologic and hematologic adverse events were similar between the VYXEOS and 7+3 arms.

On the basis of the phase 3 trial data, CPX 351 was approved by the FDA for treatment of older patients aged 60-75 with prior myeloid hematologic disease.

2.5 Rationale for Assessment of Non-Hematologic Factors that Influence Outcome in Older AML Patients

Treatment outcome of older AML patients is closely linked to the age of the patient. Data from the Swedish Acute Leukemia Registry confirms that patient outcome worsens with increasing age. Presumably, the older the age of the patient, the more complicated the disease: the biology of the disease is more severe in the elderly and patients have more

difficulty tolerating the consequences of chemotherapy treatment. Determining the fitness of an older patient for chemotherapy treatment can be quite challenging. The biologic age of an older person may differ significantly from the numeric age: there can tremendous variability in the fitness and function of older people at any given chronologic age after age 60. There is no scientific algorithm to assess the actual biologic age of an older adult. Adverse disease related prognostic factors are more easily measured. Older patients are much more likely to have adverse cytogenetics and unfavorable molecular mutations. Older patients have a higher rate of multi-drug resistant phenotypes and antecedent hematologic disorders. The patient-specific prognostic factors such as severity of comorbid illness, fitness and social support are more difficult to quantify. Many older patients have comorbid illnesses that may or may not be apparent at the time of leukemia diagnosis. Drug metabolism is different in older patients and is influenced by diminished renal and hepatic function that also may not be clinically apparent at the time of diagnosis. The elderly have deficits in immune function that make the tolerance of infections less robust. Patients often have diminished physical conditioning and endurance that may not be visible on routine physical examination. In addition, numerous psychosocial factors influence the outcome of older adults with AML including cognitive decline, social isolation, and lack of a caretaker. The patient-related prognostic factors are more difficult to measure and their significance may not emerge until after treatment for their leukemia has already been given.

Through using the Comprehensive Geriatric Assessment (CGA) to evaluate elderly patients with AML, studies have shown that there appears to be a relationship between cognitive function and outcome in older patients treated for AML. This study will explore this relationship further by implementing cognitive testing to determine this relationship in patients treated with CPX 351. Klepin et al. conducted a study of 74 older AML patients treated with intensive daunorubicin/cytarabine induction and used the CGA to assess patients for chemotherapy fitness. This study demonstrated that impaired cognition (defined as <77 by the Modified Mini-Mental State Exam) and impaired objective physical function (defined as an SPPB<9) predicted a worse overall survival in older adults with AML. Ritchie et al. (unpublished data) completed an analysis using the CGA to predict overall survival in patients aged 60 or older receiving induction therapy for AML with either standard induction with daunorubicin and cytarabine or low intensity induction with decitabine. One hundred and twenty-six patients were enrolled. Cognitive function as measured by the Blessed Orientation-Memory-Concentration Test. Patients with impaired cognitive function had worse overall survival in univariate analysis but in multivariate analysis this variable lost significance. A small percentage of patients with normal cognitive function on the Blessed Test were given the Montreal Cognitive Assessment and were impaired by measurement on this test. The Blessed may not have been sensitive enough to stratify the cognitive deficits in the population tested. Alternatively, the level of family and social support given to these patients may be more important than cognitive function in the survival of older patients with AML. Given that Klepin's analysis of patients suggested that cognitive function is important to the survival of older patients with AML and that more sensitive testing may be needed to determine the level of cognitive impairment in this population, cognitive testing using both the Blessed and the MOCA will be used in this study to determine whether this is an important factor in the survival of older patients with AML.

3 Study Objectives and Rationale

3.1 Primary Objectives

- To assess the feasibility of CPX-351 as first intensive therapy in elderly (age ≥60 years) patients with AML based on safety and efficacy and to evaluate cognitive function in these patients and its relationship to outcome. CPX-351 alone will be declared feasible if one or two induction courses (3 doses or 5 doses) can be delivered to patients with acceptable 30-day mortality. The primary efficacy endpoint will be overall survival (OS). The primary safety endpoint will be early mortality defined as 30-day mortality.

3.2 Secondary Objectives

- To assess efficacy by response (CR, CRp, CRi, and CR + CRp + CRi) rate and duration and Event Free Survival (EFS)
- To assess safety by 30-day mortality, serious adverse events (SAE) and adverse event frequency and severity
- To assess QOL using FACT-LEU
- To assess the relationship of cognitive function to outcome using the Blessed Orientation-Memory-Concentration Test and the Montreal Cognitive Assessment
- To confirm the safety and practicality of CPX-351 as consolidation therapy
- To supplement efficacy assessment by determining the rate of morphologic leukemia-free state (MLFS)

4 Study Design

This is an open label study to assess the suitability of CPX-351 as first intensive therapy in elderly (age ≥60 years) patients with AML. Patients may have received prior AML treatment with non-intensive regimens, e.g. hypomethylating agents, low dose Ara C or lenolidomide, but may not have received intensive AML treatment with anthracyclines and/or cytarabine prior to enrollment on this trial. The outcome of elderly patients following intensive treatment with CPX-351 will be measured by clinical endpoints for efficacy and safety and by biological/functional response.

4.1 Patient Recruitment

All patients will be screened for study suitability by a principal investigator or sub-investigator prior to entry on the study. An explanation of the study and discussion of the expected risks and benefits will be fully discussed with patients prior to the screening process in order for the patient to provide a voluntary written informed consent. Only eligible and consenting patients will be entered into the study.

4.2 Patient Sample Size

Early mortality (30 day mortality) in newly diagnosed fit older (age ≥ 60 years) patients with AML initially treated with standard induction therapy with daunorubicin and cytarabine is approximately 20%. Older patients with AML who are less fit, particularly those initially treated with non-intensive regimens, are expected to have 60-day mortality of approximately 40%. After 15 patients have been treated and followed for 30 days or more, early mortality will be assessed. If 30-day mortality exceeds 20% (>3 of the initial 15 patients), *all further accrual will stop*. Subsequent enrollment after the first 15 subjects should ideally resume after the safety analysis is complete, however recognizing the acute nature of AML, it might not be possible to deny treatment to subjects in screening for ethical reasons sufficiently long to evaluate safety or efficacy. In other words, if the 30-day mortality for the preceding patients is less than 20%, study accrual will continue during the DSMB's safety analysis.

In the event that more than 15 subjects have enrolled before the safety analysis, only the first 15 subjects dosed will be informative for determining need for dose reduction.

Study enrollment will be completed within approximately 2 years.

4.3 Induction

Following registration, patients will be monitored closely for response and safety. Depending on the type and extent of response as well as toxicity, the patient may continue on to consolidation therapy, receive a second induction, or be discontinued from the Treatment Phase and monitored in the Follow-up Phase.

Dosing for first induction: CPX-351 alone

- CPX-351 at 100u/m^2 will be administered on study days 1, 3 and 5

4.4 Repeat of Induction

Patients achieving aplasia/hypoplasia (<5% blast count) will not receive second inductions. Patients with reduced tumor burden and evidence of persistent leukemia who remain fit for additional intensive chemotherapy can be given second inductions up to 60 days (measured from day 1 of chemotherapy treatment) after the first induction treatment date.

Patients unable to achieve a response (CR, CRp, or CRi) after up to 2 inductions are discontinued from further treatment and followed for survival.

Dosing for second induction:

- CPX-351 at 100 u/m^2 will be administered on days 1 and 3

4.5 Consolidation Therapy

Only patients with confirmed response (CR or CRp or CRi) and who remain fit for additional chemotherapy are eligible for chemotherapy consolidation. Investigators may

use post remission therapy of their choice or they may choose to use CPX-351. Before consolidation treatment can begin, patients need a repeat echocardiogram and labs to evaluate renal and liver function and must fulfill eligibility criteria initiation of treatment. For patients given CPX-351 post remission therapy: prior to starting consolidation, LVEF must be documented to be ≥50% and patients must have recovered to ANC >500/μL and platelets >50,000/μL within 56 days after last dose of CPX-351. A second consolidation cycle is permitted provided the first consolidation course was well tolerated and repeat echocardiogram shows an LVEF > 50% and ANC and platelets have recovered within 56 days of the start of the last consolidation cycle. Up to 2 consolidation courses are permitted. Scheduling and dose of consolidation treatment may be adjusted depending on degree and rate of patient recovery.

Dosing for consolidation:

- CPX-351 at 65 u/m^2 will be administered on days 1 and 3

4.6 Follow-up Phase

Patients will be followed at monthly intervals or more frequently depending on clinical circumstances until start of the next salvage treatment, death or for 1 year from date of enrollment. Patients alive and in remission after 1 year will be followed annually or more frequently depending on clinical circumstances for up to 5 years from enrollment. For EFS evaluation, events include: documentation of persistent AML after induction, relapse after achievement of CR/CRp/ CRi, or death. Bone marrow assessments will be performed at any time during follow up when recurrent cytopenias raise the suspicion of AML relapse. After documentation of persistent leukemia or relapse, follow-up for OS will continue. At the start of HSCT or non-protocol AML treatment of any sort or 30-days following the last dose, whichever occurs first, AE data collection will stop.

4.7 Study Modification/Discontinuation

Any modifications to the study will be documented in a revised protocol with a new assigned version. The revised protocol will have an appendix which will detail the revisions to the document.

5 Selection and Withdrawal of Patients

5.1 Study Population

5.1.1 Inclusion criteria

5.1.1.1 Ability to understand and voluntarily give informed consent

5.1.1.2 Age≥60 years at the time of study treatment

5.1.1.3 Pathological diagnosis of AML according to WHO criteria (with >20% blasts in the peripheral blood or bone marrow) including:

5.1.1.4 De novo AML with normal karyotype or adverse karyotypes (including patients with karyotypic abnormalities characteristic of MDS)

5.1.1.5 Secondary AML: transformed from prior MDS or MPN, confirmed by bone marrow documentation of prior antecedent hematologic disorder

5.1.1.6 Therapy-related AML: t-AML, requires documented history of prior cytotoxic therapy or ionizing radiotherapy for an unrelated disease

5.1.1.7 Performance status >50% KPS, ECOG 0-2

5.1.1.8 Laboratory values fulfilling the following:

5.1.1.9 Serum creatinine < 2.5 mg/dL

5.1.1.10 Serum total bilirubin < 2.5 mg/dL,

5.1.1.11 Serum alanine aminotransferase or aspartate aminotransferase < 3 times the ULN

5.1.1.12 Patients with elevated liver enzymes and serum creatinine values secondary to AML are eligible after discussion with PI

5.1.1.13 Cardiac ejection fraction ≥ 50% by echocardiography, MUGA, or Cardiac MRI

5.1.1.14 Patients with history of second malignancies in remission may be eligible if there is clinical evidence of disease stability off cytotoxic chemotherapy, documented by imaging, tumor marker studies, etc., at screening. Patients maintained on long-term non-chemotherapy treatment, e.g., hormonal therapy, are eligible.

5.1.2 Exclusion Criteria

5.1.2.1 Acute promyelocytic leukemia [t(15;17)]

5.1.2.2 Clinical or morphologic evidence of active CNS leukemia

5.1.2.3 Prior intensive chemotherapy for AML with anthracycline/cytarabine-based regimens and/ or prior HSCT. Patients may have been treated with commercially available or investigational hypomethylating agents (e.g. decitabine, azacitidine, SGI-110), lenalidomide, or low-dose cytarabine (not to exceed 20 mg/m2 daily for 14 days for ≤ 6 cycles)

5.1.2.4 Prior treatment including HMA, systemic chemotherapy, surgery, or radiation therapy must have been completed at least 7 days before start of study treatment or after discussion with PI. Treatment with investigational agents must have been completed at least 14 days prior to study drug treatment. Hydroxyurea is permitted for control of blood counts before the start of study treatment. Toxicities associated with prior therapies must have recovered to grade 1 or less prior to start of study treatment.

5.1.2.5 Patients with prior cumulative anthracycline exposure of greater than 368 mg/m2 daunorubicin (or equivalent).

5.1.2.6 Any serious medical condition, laboratory abnormality or psychiatric illness that would prevent obtaining informed consent

5.1.2.7 Patients with myocardial impairment of any cause (e.g. cardiomyopathy, ischemic heart disease, significant valvular dysfunction, hypertensive heart disease, and congestive heart failure) resulting in heart failure by New York Heart Association Criteria (Class III or IV staging)

5.1.2.8 Active or uncontrolled infection. Patients with an infection receiving treatment (antibiotic, antifungal or antiviral treatment) may be entered into the study but must be afebrile and hemodynamically stable for ≥72 hrs.

5.1.2.9 Patients with current or recent evidence of invasive fungal infection (blood or tissue culture); patients with recent fungal infection must have a subsequent negative cultures to be eligible

5.1.2.10 Known HIV (new testing not required) or evidence of active hepatitis B or C infection (with rising transaminase values)

5.1.2.11 Hypersensitivity to cytarabine, daunorubicin or liposomal products

5.1.2.12 History of Wilson's disease or other copper-metabolism disorder

5.1.2.13 History of prior bone marrow or solid organ transplantation

5.2 Withdrawal of Patients

Patients will be discontinued from the Treatment Phase and enter the Follow-up Phase for assessment of efficacy endpoints under the following circumstances:

- Completion of Treatment Phase
- Persistent disease: lack of a response to treatment
- Relapsed disease: re-appearance of disease following CR, CRp, or CRi
- Unacceptable toxicity
- Patient non-compliance with protocol
- Administration of non-protocol chemotherapy
- Concurrent illness which, in the judgment of the investigator, effects assessment of clinical status to a significant degree, and requires discontinuation of protocol therapy.

Any adverse event that, in the judgement of the investigator, may cause severe or permanent harm if the study intervention is continued will result in subject discontinuation from the study. Any treatment related grade 3 or higher non-hematological toxicity that does not resolve to grade 2 within 14 days of receiving treatment for the event will result in subject discontinuation from the study.

During any phase of the study, if a patient requests to stop treatment and/or follow-up, the patient will be discontinued and no further information will be collected. The patient will be classified as withdrawal of consent.

6 Treatment of Patients

See APPENDIX 1: Patient Evaluation Flow Sheet

6.1 Pre-Treatment Evaluations

After providing informed consent, eligible patients are registered to the study.

The date of the first test or exam will be considered as the date of the screening visit.

Procedure	Evaluation	Timing
Informed Consent	It should be personally signed and dated by the patient. The responsible investigator must also personally sign and date the document. A copy of the Informed Consent must be given to the patient. The patient's study screening must be conspicuously noted in the source documentation.	Informed consent should be obtained prior to initiation of screening procedures. If the period between ICF signature date and induction 1, day 1 visit is ≥30 days the patient must sign another ICF.
Demography	Date of birth, sex, race, ethnicity	Within 14 days prior to Registration
Medical History	Complete medical history • Resolved conditions • Intermittent conditions • Concurrent illnesses • Previous surgeries	Within 14 days prior to registration
Leukemia History	Leukemia, MDS, and MPN History Prior chemotherapies Prior leukemia treatment	Within 14 days prior to registration
Physical Exam	Objective review of body systems Height Weight BSA ECOG Performance Status	Within 3 days prior to registration
Vital Signs	Heart rate Blood pressure Temperature Respiratory rate	Within 3 days prior to registration
Hematology	Hemoglobin White Blood Count Platelets Differential Count	Within 1 day prior to registration
Biochemistry	BUN Creatinine Uric Acid Electrolytes (Sodium, Potassium, Chloride) Bilirubin Alkaline phosphatase AST or ALT LDH Protein Calcium Albumin Glucose	Within 1 day prior to registration
Urinalysis	pH specific gravity glucose protein ketones blood	Within 3 days prior to registration
Questionnaires	MOCA, Blessed, FACT-Leu	Within 7 days prior to registration

Procedure	Evaluation	Timing
Bone Marrow Aspiration/Biopsy	Morphology	Within 14 days prior to registration
Diagnostic Imaging	Chest X-ray or Chest CT	Within 28 days prior to registration
Diagnostic Imaging	Echocardiography, MUGA or cardiac MRI scan	Within 14 days prior to registration
Electrocardiogram (ECG)	ECG	Within 14 days prior to registration
Cytogenetics	Cytogenetics (performed locally)	Within 3 months prior to registration
Molecular Studies	Central or local laboratory evaluation of CEBPA, FLT3, and NPM1 (either PB or BM)	Within 3 months prior to registration

6.2 Evaluation during Treatment Phase

Inductions and consolidations are administered as courses. A course consists of the administration of therapy with scheduled assessments to evaluate the response to treatment. The first induction may end before the completion of all evaluations if a second induction is necessary, (see Section 4.4). Induction is completed when a patient has

- A confirmed CR (see section 8.4)
- A CRp or CRi (see section 8.4) and is to begin consolidation treatment before hematologic count recovery
- Persistent/recurrent disease (PD/relapse)
- Response evaluation cannot be performed because of the patient's condition and no further study treatment can or will be administered.

Patients with a CR or CRi may receive up to 2 consolidation treatments.

Procedure	Evaluation	Timing
Physical Exam	Objective review of body systems Weight BSA	Days 14 and 42
Vital Signs	Heart rate Blood pressure Temperature Respiratory rate	Days 14 and 42
Hematology	Hemoglobin White Blood Count Platelets Differential Count	Days 1, 3, 5, 7±3, 10±1, 14±2, then weekly (±2days) until whichever occurs last: - Day 42 - peripheral blood count recovery - removed from Treatment Phase

Procedure	Evaluation	Timing
Biochemistry	BUN Creatinine Uric Acid Electrolytes (Sodium, Potassium, Chloride) Bilirubin Alkaline phosphatase AST or ALT LDH Protein Calcium Albumin Glucose	Days 1, 3, 5, 7±3, 10±1, 14±2, then weekly (±2days) until whichever occurs last: - Day 42 - peripheral blood count recovery - removed from Treatment Phase
Bone Marrow Evaluation	Morphology	As needed to confirm response or determine antileukemic effect and need for second induction.
Cytogenetics Molecular Studies	Cytogenetics Molecular Studies	Required in patients with a CR, CRp, or CRi with positive baseline findings (perform at the time of bone marrow assessment for CR or CRi). Optional in patients with normal baseline cytogenetics/molecular studies.
Diagnostic Imaging	Echocardiography, MUGA or cardiac MRI scan	After the last induction and before each consolidation cycle.
Questionnaires	MOCA, Blessed, FACT-Leu	Days 7±3, 42±3, Induction 2 Day 1(±3)
Adverse Events/Toxicity	CTCAE v.4 assessment	Continual assessment starting from the first dose until 30 days after completion of the Treatment Period.
Concomitant Medications		Continual assessment during Treatment Period.

6.3 Early Termination or End of Treatment Phase

Any patient that completes or discontinues treatment must have the following evaluations performed within 30 days after termination and prior to the initiation of any salvage therapy, if not performed within the last 30 days:

Procedure	Evaluation	Timing
Diagnostic Imaging	Echocardiography, MUGA or cardiac MRI	Within 30 days after discontinuation if a study has not been performed since last treatment or before the initiation of any non-protocol treatment
Electrocardiogram (ECG)	ECG	Within 30 days after discontinuation
Adverse Events/Toxicity	CTCAE v.4 assessment	Assess Adverse events that were ongoing at the time of discontinuation and record and report any new serious adverse events (up to 30 days after discontinuation)
Response Assessment	Best Response Reason for End of Treatment	Within 30 days after discontinuation
Questionnaires	MOCA, Blessed, FACT-Leu	Within 30 days after discontinuation

6.4 Evaluation during Follow-up Phase

The following evaluations are completed during the follow-up phase:

Procedure	Evaluation	Timing
Patient status report	Survival status	Once monthly until 1 year from first treatment. After the first year record only the date of death or alive at Year 5 (Day 1825).
	Relapse status New anti-leukemic therapies	Once monthly until 1 year from first treatment. After the first year record only the date of relapse and any new leukemic therapies.
Hematology	Hemoglobin White Blood Count Platelets Differential Count	Once monthly until 1 year from first treatment. After the first year record only the date of relapse and any new leukemic therapies.
Bone Marrow Evaluation	Morphology	For patients in CR or CRi perform at any time that there is a suspicion of relapse. Following the first year of follow up, record relapse information, including any bone marrow evaluations. Not required following relapse.
Diagnostic Imaging	Echocardiography, MUGA or cardiac MRI	If last treatment phase LVEF was reduced >10% from baseline and is less than 50% repeat every 3 months until LVEF returns to baseline ± 5% or until 1 year from first treatment. Persistent reductions in LVEF of >10% with nadir values below 50% documented at 1 year are considered permanent sequelae.
Biochemistry	BUN Creatinine Electrolytes (Sodium, Potassium, Chloride) Bilirubin Alkaline phosphatase AST or ALT Protein Calcium Albumin Glucose	Perform monthly only if abnormality(ies) persists at the end of the Treatment Phase. Perform until abnormality(ies) returns to baseline, until 1 year from first treatment or the initiation of new therapy and/or relapse. (whichever is earliest)
Adverse Events/Toxicity	CTCAE v.4 assessment	Assess AEs that were ongoing at the time of discontinuation. Do NOT record any new AEs. AEs that persist without evidence of recovery for >30 days are considered permanent sequelae and do not require further follow-up.

7 Drug Administration

The responsibility for treatment of patients rests with the individual investigator. Protocol treatment must begin within 72 hours of registration.

First Induction:

Agent	Dose	Route	Duration	Schedule
CPX-351	100u/m^2/day	IV	90 minutes*	Days 1, 3 and 5

Second Induction:

Agent	Dose	Route	Duration	Schedule
CPX-351	100u/m^2/day	IV	90 minutes*	Days 1 and 3

Consolidations (up to 2 are permitted):
*Approximately

Agent	Dose	Route	Duration	Schedule
CPX-351	65u/m^2/day	IV	90 minutes*	Days 1 and 3

7.1 Drug Preparation and Administration

7.1.1 CPX-351

7.1.1.1 Drug Preparation

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

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

7.1.1.2 Drug Administration

The infusion of CPX-351 (cytarabine:daunorubicin) Liposome Injection will be performed through a central venous catheter, using an infusion pump to ensure that the drug is infused over the specified time period. Non-DEHP containing administration sets should be used. **Do not use an in-line filter.** CPX-351 should never be given by the intramuscular or subcutaneous route. Administer CPX-351 over approximately 90 minutes via an infusion pump. Flush the line to ensure administration of the full dose.

The dosage (total units and u/m^2), start/stop time of the infusion, total volume infused, must be documented in the patient's chart.

(Reconstitution information to be obtained from pharmacy as well as infusional instruction)

7.2 Drug Accountability

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

7.3 Dose Reductions and Delays

It is the intention of the study to treat every patient at full dose. Dose delays or modifications will be recommended at the discretion of the treating physician and PI. Doses may be delayed due to toxicities (for example hypersensitivity reactions). Any doses missed or delayed due to toxicity may be administered as soon as the patient has recovered from the toxicity. Toxicities will be graded using the CTCAE Version 4.0. See APPENDIX 4: Common Terminology Criteria for Adverse Events V4.0 (CTCAE)). Toxicities for cytarabine and daunorubicin are relatively well known, and are outlined in the product information for each of these drugs. Furthermore, dose reductions or protocol closure will be considered:

1) If >2 of the first 5 patients or >3 of the first 15 patients experience grade 4 toxicities, accrual will stop, the protocol reviewed, and dose modifications considered. If the incidence of grade 4 toxicity exceeds 20% of patients at any point after the first 15 patients have been treated, accrual will stop, the protocol will be reviewed, and dose modifications considered.

2) If 30-day mortality exceeds 20% (>3 of the initial 15 patients), *all further accrual will stop.* Subsequent enrollment after the first 15 subjects should ideally resume after the safety analysis is complete, however recognizing the acute nature of AML, it might not be possible to deny treatment to subjects in screening for ethical reasons sufficiently long to evaluate safety or efficacy. In other words, if the 30-day mortality for the preceding patients is less than 20%, study accrual will continue during the DSMB's safety analysis.

   In the event that more than 15 subjects have enrolled before the safety analysis, only the first 15 subjects dosed will be informative for determining need for dose reduction as outlined in section 4.2.

7.4 Concomitant Therapy

7.4.1 Premedication

7.4.1.1 CPX-351

Nausea and vomiting:
Patients may be premedicated for nausea and vomiting according to institutional standards.

Hypersensitivity/Infusion-related reactions:
Patients will not be routinely premedicated for hypersensitivity or infusion-related reactions initially during the first infusion of the first treatment course. If the patient develops a hypersensitivity reaction then he/she should be pre-medicated at all subsequent infusions.

Suggested guidelines for management of hypersensitivity reactions:

Mild symptoms (e.g., mild flushing, rash, pruritus):
Stop infusion and supervise at bedside with monitoring of vital signs
Reinitiate infusion slowly (halving the rate of infusion) +/- premedication

Moderate symptoms (e.g. moderate rash, flushing, mild dyspnea, chest discomfort):
Stop infusion and give IV diphenhydramine, 20-25 mg (or equivalent) and IV dexamethasone 10 mg.
Do not reinitiate infusion. Premedicate on re-treatment. Retreat at same dose and rate.

Severe/life-threatening symptoms (e.g. hypotension requiring vasopressor therapy, angioedema, respiratory distress requiring bronchodilation therapy, generalized urticaria):
Stop infusion. Administer IV diphenhydramine and dexamethasone as indicated above. Add epinephrine (adrenaline) or bronchodilators if indicated. Do not reinitiate infusion. Do not retreat. Report as a serious adverse event.

If hypersensitivity or infusion-related reactions become a clinically relevant toxicity, then premedication for hypersensitivity reactions will be instituted with drugs, doses and schedule according to each investigator's preference. Additionally, a decision may be made to prolong the infusion time to two hours or more.

Permitted therapy
Patients may receive ongoing supportive and palliative care (e.g. pain control) as clinically indicated throughout the study.

Infection Prophylaxis: Prophylactic use of antibiotics, antifungals, and antiviral drugs is highly recommended during the period of profound neutropenia until ANC returns to 500/μL or greater. The choice of medications will be according to institutional protocol. Use of anti-infective agents as prophylaxis and treatment must be documented on the case report forms.

Growth Factor support: The use of growth factors will be according to institutional protocol and according to ASCO criteria.[16] Use of growth factors must be documented on the case report forms.

Transfusion support: The use of transfusion support (RBCs and platelets) will be according to institutional protocol. Use of transfusion support must be documented on the case report forms.

7.4.2 Therapy that is not permitted

Other anti-cancer treatment and other investigational therapy(ies) are not permitted during the Treatment Phase. In the event of persistent disease or relapse the patient may receive other anti-leukemic therapies and is followed for survival.

7.5 Duration of Protocol Treatment

Patients may continue on study provided they have not met the criteria for discontinuation of therapy (See Section 5.2). Patients may receive up to 2 induction courses followed by up to 2 consolidation courses. After the Treatment Phase, patients will be followed for up to 5 years.

8 Assessment of Efficacy

8.1 Efficacy Population

All registered patients are evaluable for efficacy. Patients that die on or before Day 7 will be replaced.

8.2 Overall Survival

Overall survival is measured from the date of registration to death from any cause. Patients not known to have died will be censored on the date they were last known to be alive. Patients will be followed for up to 5 years.

8.3 Event-free Survival

Event-free survival is defined as the time from study registration to the date of induction treatment failure (persistent disease), progressive disease (PD) or death from any cause, whichever comes first. Patients alive and not known to have any of these events will be censored on the date of their last tumor assessment.

8.4 Response Assessment Criteria

During the Treatment Phase patients will be assessed for response according to the following criteria[1]:

Complete remission (CR)[a]	Bone marrow blasts <5%; absence of blasts with Auer rods; absence of extramedullary disease; absolute neutrophil count ≥1.0 x 10^9/L (1000/μL); platelet count ≥100 x 10^9/L (100,000/μL); independence from red cell transfusions
CR with incomplete recovery (CRi)[b]	All CR criteria except for residual neutropenia (<1.0 x 10^9/L [1000/μL]) **or** thrombocytopenia (<100 x 10^9/L [100,000/μL])
Best Response	See Section 8.4.1
Treatment failure	
Persistent Disease (PD)	Failure to achieve CR or CRi; only includes patients surviving ≥7 days following completion of initial treatment, with evidence of persistent leukemia (blasts in peripheral blood, extramedullary leukemia, or persistence in the bone marrow)
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 with no blasts in the blood, but no bone marrow examination available at recovery
Relapse[c]	Bone marrow blasts ≥5%; or reappearance of blasts in the blood after achievement of a CR or CRi; or development of extramedullary disease

[a]Bone marrow assessment REQUIRED to confirm CR. All criteria need to be fulfilled; marrow evaluation should be based on a count of 200 nucleated cells in an aspirate with spicules; if ambiguous, consider repeat exam after 5 to 7 days; flow cytometric evaluation may help to distinguish between persistent leukemia and regenerating normal marrow; a marrow biopsy should be performed in cases of dry tap, or if no spicules are obtained; no minimum duration of response required.

[b]Bone marrow assessment REQUIRED to confirm CRi. Some patients may not achieve complete hematologic recovery prior to initiation of consolidation. CRi cannot be declared earlier than Day 35 to allow adequate time for documentation of peripheral blood recovery. Consolidation may begin no earlier than 35 days after the last induction course.

[c]In cases with low blast percentages (5-10%), a repeat marrow should be performed to confirm relapse. Appearance of new dysplastic changes should be closely monitored for emerging relapse. In a patient who has been recently treated, dysplasia or a transient increase in blasts may reflect a chemotherapy effect and recovery of hematopoiesis.

A subject who is alive in a state of aplasia with no evidence of continued disease will be considered as having "no response."

The response of patients with no post-baseline bone marrow assessment will be entered as not done.

8.4.1 Best Response

Patients who complete the induction(s) with a response of CRp or CRi may be upgraded to CR during or after consolidation if the patient's peripheral blood counts meet the criteria for CR (ANC≥1000/μL and Platelets ≥100,000/μL). To upgrade a response to CR after peripheral blood count recovery, a new bone marrow assessment must be performed within 14 days of documented peripheral blood count recovery.

8.5 Remission Duration

Only patients achieving CR or CRp or CRi are assessed for remission duration. Remission duration is measured from the date of achievement of a remission until the date of relapse or death from any cause; patients not known to have relapsed or died at last follow-up will be censored on the date of their last tumor assessment.

8.6 Morphologic Leukemia-free State

All registered patients that have at least one evaluable post–registration bone marrow assessment performed on or after Day 14 after the last induction will be assessed for morphologic leukemia-free state. Morphologic leukemia-free state is defined as bone marrow blasts <5% AND absence of Auer rods and/or extramedullary disease.[1]

8.7 Stem Cell Transplant

The number and percentage of patients transferred for stem cell transplant will be summarized.

9 Assessment of Safety

9.1 Safety Population

All patients who receive at least one dose of study drug will be considered evaluable for safety.

9.2 Adverse Events

9.2.1 Definition of an Adverse Event

An adverse event is any untoward medical occurrence in a patient or clinical investigation subject administered with a pharmaceutical product and which does not necessarily have to have a causal relationship with this treatment. An adverse event can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding, for example), symptom, or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product. This includes worsening of a pre-existing condition or increase in frequency of a pre-existing condition. An adverse event is considered serious if it meets any of the serious criteria listed in Section 9.2.2. To ensure no confusion or misunderstanding of the difference between the terms "serious" and "severe", which are not synonymous, the following clarification is provided:

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

Adverse events are to be recorded in the case report form from the start of the infusion on Day 1 to the last day of the treatment period, 30 days after the last dose, with the exception of serious adverse events. (See Section 9.2.2).

Adverse drug reactions (ADRs) are all noxious and unintended responses to a medicinal product related to any dose that a causal relationship between the medicinal product and an adverse event is at least a reasonable possibility, i.e., the relationship cannot be ruled out. An unexpected ADR is any adverse reaction not identified in nature or intensity in the current Investigator's Brochure.

9.2.2 Definition of a Serious Adverse Event

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

Results in death (grade 5)
Is life-threatening
Requires inpatient hospitalization or prolongation of existing hospitalization
Results in persistent or significant disability or incapacity
Is a congenital anomaly/birth defect

These events are to be reported as serious from the start of the infusion on Day 1 to 30 days after completion of the treatment period. Medical and scientific judgment should be exercised in deciding whether expedited reporting is appropriate in other situations such as 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 events listed above.

9.2.3 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 the Sponsor or its designee. 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 at the study site.

Follow-up information should be sent to the Sponsor or its designee via the original Serious Adverse Event Form, re-stating the date of the original report. Either a new Serious Adverse Event Form should be 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.

The telephone and fax numbers of the local Clinical Research contact person and the contact person in the local department of Clinical Safety, specific to the site, must be listed in the investigator folder provided for each individual site and provided to the Sponsor or its designee at the start of the trial. Questions referring to a specific serious adverse event occurring in a study patient should be directed to the local Clinical Research contact person specified in the investigator folder provided for the site.

9.2.4 Reporting Serious Adverse Events to Regulatory Agencies and Review Boards

All SAEs must be reported to Jazz Pharmaceuticals, Inc. within 24 hrs of awareness, irrespective of relatedness, causality, expectedness. The WCM research team will complete and submit the US-FDA Form 3500A (MedWatch form) to AEreporting@jazzpharma.com within 1 business day of the awareness of the SAE.

All AEs and SAEs will be reported to the WCM IRB per the policies outlined below:

All SAEs will be reported with an SAE cover sheet that documents relatedness, expectedness, and risk determination. SAE reports will be saved in the study's regulatory binder. SAE reports will be compiled to complete the Data and Safety Monitoring Board (DSMB) periodic report.

The WCM IRB must be notified within 7 calendar days of investigator notification of an SAE when all of the following conditions are met, as determined by the Principal Investigator. These SAEs are considered "immediately reportable":

a. The event is unexpected – when its specificity and severity are not accurately reflected in the WCM consent document, Investigators Brochure, or package insert; AND
b. The harm is "related" or "possibly related" – where there is a reasonable possibility that the harm may have been caused by the research procedure(s), or interventions; AND
c. The harm suggests that the research places WCM subjects at greater risk of harm (including physical, psychological, economic or social harm) than was previously known or recognized.

For events that are considered immediately reportable to the WCM IRB, the SAE report must be emailed to irb@med.cornell.edu.

AEs grade 3 or higher and all SAEs will be listed on the Adverse Event & IND Safety Reporting Cumulative Table and reported to the WCM IRB at the time of continuing renewal.

All AEs that are serious, unexpected and associated with the use of CPX-351 will be reported to the applicable regulatory authority (FDA in the US and to Health Canada in Canada). The period we have to report the SAE to the FDA depends on the severity of the SAE, as follows:

- **Within 7 days** of becoming aware of the SAE for fatal (Grade 5), life-threatening (Grade 4) events

- **Within 15 days** of becoming aware of all other qualifying SAEs (i.e., hospitalizations, second cancers, etc.)

9.3 Cardiac Toxicity Monitoring

As anthracyclines are known to have an adverse effect on cardiac function, each patient's cardiac function will be monitored through the treatment and follow-up phases and LVEF below 50% will be recorded as an adverse event. Any decrease in LVEF >10% resulting in a nadir LVEF <50% will be reported as an SAE.

9.4 Laboratory Data

Laboratory data obtained according to the schedule of assessments will be recorded on the CRF or other data collection instrument. Only laboratory data requested by the protocol should be recorded unless specific findings result in a clinical event such as an adverse event or documentation of peripheral blood count recovery. These results will be collected and recorded on the CRF.

10 Other Evaluations

10.1 Blessed Orientation-Memory-Concentration Test (BOMC)

This is a short six item test designed to evaluate older patients for early dementia. The assessment is not affected by age or educational level. The six-item Blessed Orientation-Memory-Concentration (BOMC) test was developed by Katzman, Brown, Fuld, et al. (1983) from the longer (29-item) Blessed Information-Memory-Concentration (BIMC) test (Blessed, Tomlinson, and Roth, 1968). Katzman and colleagues (1983) selected 6 of the original 29 BIMC items based on a series of statistical analyses. The scores from each of the six items are multiplied as detailed below to yield a weighted score. Possible total scores on the BOMC range from 0 (all items answered correctly) to 28 (all items answered incorrectly). Weighted error scores greater than 10 are consistent with dementia, according to Katzman et al. (1983).

10.2 Montreal Cognitive Assessment (MOCA)

The MoCA test is a one-page 30-point test administered in approximately 10 minutes. The test and administration instructions are freely accessible for clinicians at **www.mocatest.org**. The test is available in 35 languages or dialects. There are 3 alternate forms in English, designed for use in longitudinal settings.

The MoCA assesses several cognitive domains. The short-term memory recall task (5 points) involves two learning trials of five nouns and delayed recall after approximately 5 minutes. Visuospatial abilities are assessed using a clock-drawing task (3 points) and a three-dimensional cube copy (1 point). Multiple aspects of executive functions are assessed using an alternation task adapted from the trail-making B task (1 point), a phonemic fluency task (1 point), and a two-item verbal abstraction task (2 points). Attention, concentration and working memory are evaluated using a sustained attention task (target detection using tapping; 1 point), a serial subtraction task (3 points), and digits forward and backward (1 point each). Language is assessed using a three-item confrontation naming task with low-familiarity animals (lion, camel, rhinoceros; 3 points), repetition of two syntactically complex sentences (2 points), and the aforementioned fluency task. Finally, orientation to time and place is evaluated (6 points).

10.3 The Functional Assessment of Cancer Therapy – Leukemia (FACT-Leu)

The FACT-Leu is a validated measurement of quality of life parameters for patients undergoing treatment for acute leukemia. This questionnaire is standardly used in leukemia treatment protocols to measure quality of life parameters.

10.4 Medical Resource Use

Medical resource use (MRU) data will be collected for all study participants and analyzed by health outcomes (overall survival and response (CR+CRp+CRi) for CPX-351. The MRU data collected in the trial will be used to identify costs associated with planned induction and consolidation treatment and for unplanned medical interventions necessary for patient support. Specific MRU data collected will include but may not be limited to:

- hospitalization nights (general ward and intensive care);
- blood product support (PRBC, Platelets, other);
- non-chemotherapy drugs (anti-infectives, growth factors, etc.); and
- AML chemotherapy (induction vs. consolidation).

11 Statistical Considerations

The primary objective of this non-randomized open label study is to evaluate the safety and efficacy of CPX-351 as a treatment for AML in elderly (≥ 60 years of age) patients. Dose reductions or protocol closure will be considered:

1) If >2 of the first 5 patients or >3 of the first 15 patients experience grade 4 toxicities, accrual will stop, the protocol reviewed, and dose modifications considered. If the incidence of grade 4 toxicity exceeds 20% of patients at any point after the first 15 patients have been treated, accrual will stop, the protocol will be reviewed, and dose modifications considered.

2) If 30-day mortality exceeds 20% (>3 of the initial 15 patients), *all further accrual will stop.* Subsequent enrollment after the first 15 subjects should ideally resume after the safety analysis is complete, however recognizing the acute nature of AML,

it might not be possible to deny treatment to subjects in screening for ethical reasons sufficiently long to evaluate safety or efficacy. In other words, if the 30-day mortality for the preceding patients is less than 20%, study accrual will continue during the DSMB's safety analysis.

In the event that more than 15 subjects have enrolled before the safety analysis, only the first 15 subjects dosed will be informative for determining need for dose reduction as outlined above.

Patients who die within the first 7 days because of leukemia related toxicity will be replaced. Those patients will be included in the analysis given the intention to treat for 30 day mortality and overall survival.

Analyses will primarily be descriptive in nature. Categorical variables will be summarized as frequency counts with associated percentages and continuous variables will be summarized as mean, standard deviation, median and range. Exact confidence intervals will be computed using the Clopper-Pearson method.

All analyses will be performed using SAS version 9.2 or higher.

Additional details regarding statistical analyses may be presented in a Statistical Analysis Plan (SAP).

11.1 Primary and Secondary Endpoints

11.1.1 Primary Endpoints

In the CPX-351 cohort, the primary efficacy endpoint is overall survival (OS) as defined in Section 8.2; the primary safety endpoint is the 30-day mortality rate.

11.1.2 Secondary Endpoints

Secondary efficacy endpoints include complete response (CR, CRp, CRi, and CR+CRp+CRi), the relationship of cognitive function to treatment response and OS, event-free survival and morphologic leukemia free state (as defined in Section 8). Secondary safety endpoints include incidence of AEs and SAEs, laboratory measurements (hematology and biochemistry), vital signs and physical examinations.

11.2 Sample Size and Power Justification for Primary Endpoint

With 24 months for accrual, and a minimum of 36 months of follow-up, using a one-sided alpha-level of 0.05, a sample size of 30 patients has 80% power to detect a difference between the null hypothesis of 10 months median survival versus 16 months median survival in this patient population.

In regards to safety, with a sample size of 30 the maximum width of the one-sided 95% exact confidence interval for estimated 30-day or 60-day mortality rates is less than 19%.

Analysis of the relationship of cognitive function to outcome and overall survival will be hypothesis generating.

11.3 Analysis Populations

Efficacy and safety analysis populations will be comprised of all patients who receive at least one dose of study drug.

11.4 Analysis of Primary Endpoints

Overall survival will be analyzed using Kaplan-Meier methods. Patients who have not died at the time of analysis will be censored on the date they were last known to be alive. Median survival and the associated 95% confidence interval will be computed using the Brookmeyer-Crowley method. The estimated survival curve will be generated.

Estimates of 30- and 60-day mortality rates will be computed using Kaplan-Meier methods along with associated two-sided 95% confidence intervals computed using the Brookmeyer-Crowley method.

11.5 Analysis of Secondary Endpoints

Time dependent endpoints, such as remission duration (relapse-free survival) and event-free survival (EFS), will be evaluated using Kaplan-Meier methods; estimates of event rates will be computed and a survival curve generated.

Binary Endpoints

The response (CR, CRp, CRi, and CR+CRp+CRi) rate and best response (CR, CRp, CRi, and CR+CRp+CRi) rate will be calculated based on the responses achieved as defined in section 8.4. The number of patients who achieve response will be divided by the number of patients in the efficacy population to determine response rate.

Likewise, the morphologic leukemia-free rate will be calculated as the number of patients who achieve morphologic leukemia-free state, as defined in section 8.6, divided by the number patients in the safety population who have at least one evaluable post-randomization bone marrow assessment.

The rate of stem cell transplant will be calculated by the number of patients who have a stem cell transplant divided by the number of patients in the safety population.

11.6 Safety Analysis

Safety data will be analyzed and reported for all patients who receive at least one dose of study drug. Safety data summarized will include hematology, chemistries, vital signs,

adverse events (AEs) and physical examinations. Safety data will be summarized using descriptive statistics.

The number and proportion of patients with reported AEs and SAEs will be summarized by maximum grade. AEs that are related to study drug will be summarized in a separate table.

Laboratory values will be summarized both by actual result and by CTC toxicity grade (for selected laboratory parameters). Summaries of laboratory results at each scheduled time point will reflect the observed value at that time point as well as change from baseline. For selected laboratory parameters, the maximum grade for each patient will be summarized for each type of toxicity; a shift table will reflect baseline toxicity grade versus maximum observed on-treatment toxicity grade.

Vital signs and physical exam data will be summarized at each scheduled time point.

11.7 Data Safety Monitoring Board (DSMB)

Weill Cornell Medical College requires that all research approved by the WCMC IRB include an appropriate plan for the monitoring of data to ensure the safety of human subjects. Research supported by Federal agencies will be monitored according to all regulations and guidelines of the relevant Federal agency.

The WCMC Data and Safety Monitoring Board (DSMB) will review the IRB approved protocol, informed consent documents, and data and safety monitoring plan prior to study initiation. During the course of the study, the DSMB will perform safety analysis as outlined in 4.2 after 15 subjects have enrolled.

After the initial safety analysis period, the DSMB will review the cumulative study data semiannually to evaluate safety, efficacy, study conduct, and scientific validity and integrity of the trial. In particular, the results of the Day 30 echocardiogram will be included in the DSMB Periodic Reports. The WCMC DSMB may also convene as needed if stopping criteria are met or other safety issues arise that the Principal Investigator and/or IRB would like the WCMC DSMB to address. The study PI will submit all written DSMB recommendations to the IRB upon receipt.

12 Administrative, Regulatory and Ethical Issues

12.1 Direct Access to Source Documents

Source data is all information, original records of clinical findings, observations, or other activities in a clinical trial necessary for the reconstruction and evaluation of the trial. Source data are contained in source documents. Examples of these original documents and data records include but are not limited to: hospital records, clinical and office charts, laboratory notes, memoranda, patients' diaries or evaluation checklists, pharmacy dispensing records, recorded data from automated instruments, copies or transcriptions

certified after verification as being accurate and complete, microfiches, photographic negatives, microfilm or magnetic media, x-rays, patient files, and records kept at the pharmacy, at the laboratories, and at medico-technical departments involved in the clinical trial. All data will be collected and stored on a computerized database using a REDCAP program.

Case report forms, all copies of test results, and study-related regulatory documents [e.g., Informed Consents, Institutional Review Board (IRB)/Ethics Committee (EC) approvals/correspondence, etc.] must be available at all times for regulatory agency inspection and review by the sponsor or its designee. During the periodic site monitoring visits, the source documents will be verified against data entered onto the CRF in order to assure that all data is accurately and completely reflected on the patient's CRF.

12.2 Study Monitoring and Quality Inspections/Audits

This study will be monitored by the WCM PI and/or research team according to GCP/ICH guidelines. An internal site initiation visit will be held prior to initiation of patient enrollment. The protocol, CRFs, study drug supplies, and relevant procedures will be explained in detail at the site visit. Subsequent to patient enrollment, the WCM PI and/or research team will review the CRFs and source documents to ensure that the study is conducted according to the protocol and GCP/ICH guidelines.

To ensure compliance with GCP/ICH guidelines and all applicable regulatory requirements, WCM PI and/or research team may conduct an internal quality assurance audit. Regulatory agencies may also conduct a regulatory inspection of this study. Such audits or inspections can occur at any time during or after completion of the study. If audits or inspections occur, the WCM PI and WCM's research team agree to allow the auditor/inspector direct access to all relevant documents and to allocate his/her time and the time of his/her staff to the auditor/inspector to discuss findings and any relevant issues.

12.3 Ethics

This study will be conducted in accordance with local regulations, GCP, ICH guidelines and the Declaration of Helsinki. The WCM PI will be responsible for the overall conduct of the clinical trial for the site and will be responsible for ensuring the trial is conducted according to the protocol and all regulatory requirements and IRB/EC regulations.

12.4 Adherence to the Protocol

Except for a change that is intended to eliminate an immediate hazard to patients, the approved protocol will be conducted as described. If a change in the conduct is made to eliminate an immediate hazard, the FDA and IRB/EC are notified immediately.

Deviations from the protocol will be considered in two categories, Protocol Violations and Protocol Deviations. Protocol Violations include patients who are not eligible according to the inclusion/exclusion criteria in effect at the time of registration. Protocol Deviations include other non-compliance with the protocol, such as missing or skipped procedures or

evaluations, evaluations performed outside given window, incorrect administration of investigational product, etc.

12.5 Protocol Revisions

All revisions must be discussed with, and be prepared by, the WCM PI. If the revision is an Administrative Letter, the investigator should submit it to the IRB/EC and FDA for their information. If the revision is an Amendment, it will be signed by the WCM PI. The WCM PI must submit the Amendment to the IRB/EC for review and approval prior to implementation. Documentation of approval signed by the Chairperson or designee of the IRB/EC must be sent to the FDA.

If an Amendment substantially alters the study design or increases the potential risk to the patient: (1) the consent form must be revised and submitted to the IRB/EC for review and approval; (2) the revised form must be used to obtain consent from patients currently enrolled in the study if they are affected by the Amendment; and (3) the new form must be used to obtain consent from new patients prior to enrollment. The revised consent form must then also be submitted to the FDA for review and approval.

All revisions will be sent to the national competent authorities in North America.

12.6 Retention of Patient Records and Study Files

CRFs and other reports (e.g., investigator trial files, source documents, original, signed/dated informed consent forms) pertaining to this clinical investigation must be maintained for a minimum of 2 years.

12.7 Patient Confidentiality

The WCM PI and research team will preserve the confidentiality of all patients taking part in this trial. In the event of patient names inadvertently appearing on the trial documentation, this information will not be entered into the computer database for this trial. The WCM PI and research team will seek access to clinical information only after approval to do so has been given by the patient and the relevant authorities. The data from this trial may be used in publications and submissions to regulatory authorities.

Information about study patients will be kept confidential and managed according to the requirements of the Health Insurance Portability and Accountability Act (HIPAA). Those regulations require a signed patient authorization informing the patient of the following:
What protected health information (PHI) will be collected from patients in this study
Who will have access to that information and why
Who will use or disclose that information

<u>The rights of a research patient to revoke their authorization for use of their PHI:</u>
In the event that a patient revokes authorization to collect or use PHI, the Investigator, by regulation, retains the ability to use all information collected prior to the revocation of patient authorization. For patients that have revoked authorization to collect or use PHI,

attempts should be made to obtain permission to collect at least vital status (i.e. that the patient is/is not alive) at the end of their scheduled study period.

12.8 Informed Consent

Patients will be required to sign a statement of informed consent that meets the requirements of the US Code of Federal Regulations (21 CFR 50), Canadian regulations, local regulations, ICH guidelines and the IRB/EC of the study center. The medical record will include a statement that written informed consent was obtained before the patient was enrolled in the study and the date written consent was obtained.

Members of the treating team will review the nature of the study, its purpose, the procedures involved, the expected duration, the potential risks and benefits and alternative therapies including best supportive care. Patients must be informed that participation in the study is voluntary, he/she may withdraw from the study at any time and withdrawal from the study will not affect his/her subsequent medical treatment or relationship with the treating physician. Financial costs that will or may be incurred as a result of participation in the study, as well as the efforts to maintain patient confidentiality will also be discussed.

This consent must be witnessed and dated and retained by the WCM PI as part of the study records. A copy of the informed consent form must be given to the patient. In the event the patient is re-screened, the patient is not required to sign another informed consent form unless the patient is re-screened more than 30 days from the previous informed consent form signature date.

If an Experimental Subject's Bill of Rights is applicable in the Investigator's US state, that form must also be prepared and signed by each patient and retained as a part of the required study records. A copy of the Bill of Rights must be given to the patient or the patient's legally authorized representative.

A copy of the IRB approved consent form must be submitted to the FDA and Jazz Pharmaceuticals, Inc. prior to shipment of drug supplies to WCM. Each patient's signed informed consent must be kept on file by the Investigator for regulatory authority inspection at any time.

For all US sites, the HIPAA Privacy Rule Authorization language must be included in the Informed Consent/authorization form (or a separate authorization document) and approved by the IRB (or Privacy Board). The elements of the HIPAA Privacy Rule Authorization are found in APPENDIX 5: Elements of the HIPAA Privacy Rule Authorization.

The Declaration of Helsinki, as amended, recommendations (2008 version), guiding doctors in clinical research must be signed by the Investigator and returned to the Sponsor or its designee. A copy must also be kept on file by the Investigator.
The IRB/EC of an institution must approve the consent form document to be used at that center prior to its local activation; changes to the consent form during the course of the study will also require IRB/EC notification/approval.

The following elements must appear in the consent form: a description of the purpose of the study (indication, that the drug is investigational); potential side effects; potential benefits; study design; voluntary participation; and confidentiality. It is essential that the consent form contain a clear statement that gives permission for 1) information to be sent to and 2) source medical records to be reviewed by the Sponsor and other agencies as necessary.

12.9 Publication Policy

The results of this study will be published by the study investigator and sub-investigators.

The Sponsor requires review of written and oral presentation at least 45 days prior to initial submission to the publishing authority. If necessary to protect proprietary rights of information to be disclosed in the publication, the Sponsor may request a further 45 day delay in submission for publication, and the investigators agree to make all reasonable efforts to grant such further delay to the Sponsor.

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14 APPENDIX 1: Patient Evaluation Flow Sheet – Treatment Phase

Each INDUCTION[1, 2] and CONSOLIDATION:

Day:	Screening	1	2	3	4	5	6	7 ±3	10 ±1	14 ±2	21 ±2	28 ±2	35 ±2	42 ±2	Weekly[3] ±2	150[8] ±10	End of Phase/Early Term. ±30
Informed Consent[4]	x																
Medical/Leukemia History	x																
Physical Exam	x									x				x			
Vital Signs	x									x				x			
ECOG Performance Status	x																
ECG	x	x[8]														x	x[8]
Registration	x																
Hematology	x	x		x		x		x	x	x	x	x	x	x	x		
Biochemistry	x	x		x		x		x	x	x	x	x	x	x	x		
Urinalysis	x																
Bone Marrow Evaluation	x									x[5]	**As needed to confirm response/persistence**						
Chest X-ray/Chest CT	x																
Echocardiography/MUGA/cardiac MRI	x													x[7]		x	x
Blessed Orientation Memory Concentration	x[9]							x[9]						x[9]			x[9]
MOCA	x[9]							x[9]						x[9]			x[9]
FACT-Leu	x[9]							x[9]						x[9]			x[9]
Response Assessment										x[6]							
Cytogenetics/Molecular Studies	x	**At the time of CR or CRi**															
Adverse Events		**Assess throughout Induction and Consolidation**															
Concomitant Medications		**Assess throughout Induction and Consolidation**															
Treatment Administration	CPX-351	**See relevant protocol section(s).**															x

[1]The first induction may end prematurely if a second induction is necessary, see Section 4.4. The schedule of evaluations for the first induction is followed until the second induction starts, then the evaluations are followed as indicated in the flow sheet, beginning with Day 1

[2] Second inductions and consolidations of are CPX-351 on Days 1 and 3, see Sections 4.4 & 4.5, See Section 7 for an alternative consolidation regimen of intermediate dose cytarabine, e.g. for patients that exceed 500mg/m^2 cumulative daunorubicin-equivalent dose, or as decided by the investigator

[3]Continue weekly evaluations until confirmation of response (CR/CRi) or persistent disease is declared

[4] Within 30 days prior to start of screening, if informed consent was collected, 30 days elapse and the patient is still not screened he/she must sign another ICF

[5]Required after first induction (in case the Day 14 bone marrow is non-evaluable or assessment of aplasia is equivocal, a repeat evaluation may be performed 5-14 days later, at the discretion of the treating physician, in order to determine effect and need for second induction

[6]Day 150 or 45 Days after the last treatment whichever is later

[7]See Section 9.3, Repeat ECHO/MUGA/cardiac MRI before the second consolidation

[8] ECG will be performed pre-dose for each course of treatment, and at the end of each course or EOT.

[9] Blessed, MOCA and FACT-Leu can be administered +/- 3 days from indicated day

15 APPENDIX 2: Patient Evaluation Flow Sheet –Follow-up

	Monthly for 1 Year (±10 Days)	**Once Years 2-5**	**Early Termination**
Patient status report	**x**	**x**	**x**
Hematology	**x**		**x**
Biochemistry	Perform monthly only if abnormality(ies) persists at the end of the Treatment Phase. Perform until abnormality(ies) returns to baseline, until 1 year from registration, or the initiation of new therapy and/or relapse. (whichever is earliest)		
Bone Marrow Aspiration/Biopsy	For patients in CR or CRi perform at any time that there is a suspicion of relapse. For patients in CR, perform if peripheral blood counts fall below 1000/µL for ANC or 100,000/µL for platelets for >1 month or at any time there is suspicion of relapse. For patients in CRi perform if counts fall significantly below peak recovery levels. If the peripheral blood counts in a patient with a CRi recover to CR levels (≥1000/µL for ANC or ≥100,000/µL for platelets), perform a bone marrow evaluation within 14 days to confirm CR. Following the first year of follow up, record relapse information, including any bone marrow evaluations. Not required following the initiation of new therapy and or relapse.		
Echocardiography, MUGA or Cardiac MRI	If last LVEF treatment phase or Day 150 was reduced >10% from baseline and is less than 50% repeat every 3 months until LVEF returns to baseline (±5%) or until 1 year from registration. Persistent reductions in LVEF of >10% with nadir values below 50% documented at 1 year are considered permanent sequelae.		
Adverse Events/Toxicity	Assess AEs that were ongoing at the time of discontinuation. Do NOT record any new AEs. AEs that persist without evidence of recovery for >30 days are considered permanent sequelae and do not require further follow-up.		

16 APPENDIX 3: Performance Status – ECOG

Grade	Description
0	Fully active, able to carry on all pre-disease performance without restriction (Karnofsky 90-100)
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature (e.g., light housework, office work) (Karnofsky 70-80).
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 (Karnofsky 50-60).
3	Capable of only limited self-care, confined to bed or chair more than 50% of waking hours (Karnofsky 30-40).
4	Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair (Karnofsky 10-20).

17 APPENDIX 4: Common Terminology Criteria for Adverse Events V4.0 (CTCAE)

This 72 page document can be obtained as a pdf file from http://ctep.cancer.gov.
The publication date is June 14, 2010

18 APPENDIX 5: 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 (i.e., "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).

19 APPENDIX 6: 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/)

20 APPENDIX 7: Anthracyclines Equivalents Guidelines

According to the exclusion criteria patients with a total lifetime anthracycline exposure exceeding the equivalent of 368 mg/m^2 of daunorubicin (or equivalent) prior to start of study therapy [100 u/m^2 of CPX-351 contains 44 mg/m^2 of daunorubicin x 3 doses (1 induction) = 132 mg/m^2 + 368 mg/m^2 = 500 mg/m^2 = maximum allowable limit of daunorubicin from all sources at the end of the 1st induction] are excluded from Protocol CLTR0310-301.

	Conversion factor*
Daunorubicin	1
Doxorubicin	2
Epirubicin	1
Idarubicin	4
Mitoxantrone	4.4

Multiply the number in the second column by the total cumulative dose a patient has received.

For example:
200mg/m^2 of mitoxantrone x 4.4(conversion factor) = 880mg/m^2
This means 200mg/m^2 of mitoxantrone is equivalent to 880 mg/m^2 of daunorubicin

*Adapted from Keefe D., Anthracycline-Induced Cardiomyopathy. Seminars in Oncology, Vol 28, No 4, Suppl 12 (August), 2001: pp 2-7