

Document Coversheet

Study Title:

A Phase II Study of CPX-351 in Younger Patients < 60 Years Old with Secondary Acute Myeloid Leukemia

Institution/Site:	Roswell Park Comprehensive Cancer Center
Document (Approval/Update) Date:	02/13/2026
NCT Number:	NCT04269213
IRB Number	I 501719

Roswell Park Protocol No.: I-501719



PROTOCOL TITLE:

A Phase II Study of CPX-351 in Younger Patients < 60 Years Old with Secondary Acute Myeloid Leukemia

PROTOCOL NUMBER:

I-501719

PRINCIPAL INVESTIGATOR:

Steven Green, MD
Roswell Park Comprehensive Cancer Center
Elm and Carlton Street
Buffalo, New York 14263
716-845-7110
Steven.Green@roswellpark.org

VERSION NUMBER:

11

DATE: 23JAN2026

Confidentiality Statement

Any and all information presented in this document shall be treated as confidential and shall remain the exclusive property of the party(ies) mentioned above (Roswell Park Cancer Institute Corporation d/b/a Roswell Park Comprehensive Cancer Center). The use of such confidential information must be restricted to the recipient for the agreed purpose and must not be disclosed, published, or otherwise communicated to any unauthorized persons, for any reason, in any form whatsoever without the prior written consent of the party(ies) above.

Roswell Park Protocol No.: I-501719

Table of Contents

1	Objectives	3
2	Background.....	3
3	Inclusion and Exclusion Criteria	5
4	Local and Study-Wide Number of Subjects	7
5	Local and Study-Wide Recruitment Methods	7
6	Multi-Site Research	8
7	Study Timelines	8
8	Study Endpoints.....	8
9	Design	9
10	Treatment.....	9
11	Procedures Involved	14
12	Withdrawal of Subjects.....	17
13	Risks to Subjects.....	18
14	Potential Benefits to Subjects	18
15	Data and Specimen Banking.....	18
16	Measurement of Effect	19
17	Safety Evaluation.....	19
18	Data Management and Confidentiality	24
19	Statistical Plan	25
20	Provisions to Monitor the Data to Ensure the Safety of Subjects.....	26
21	Vulnerable Populations.....	27
22	Community-Based Participatory Research.....	27
23	Sharing of Results with Subjects	27
24	Setting	27
25	Provisions to Protect the Privacy Interests of Subjects	27
26	Resources Available	27
27	Prior Approvals.....	27
28	Compensation for Research-Related Injury.....	27
29	Economic Burden to Subjects.....	27
30	Consent Process	28
31	Process to Document Consent in Writing.....	28
32	Drugs or Devices	28
33	References.....	31
34	Appendices/ Supplements.....	33

Roswell Park Protocol No.: I-501719

1 OBJECTIVES

Hypothesis

Induction therapy with CPX-351 administered to patients between the ages 18-59 with secondary AML results in response rates not significantly different to those patients aged 60 and above.

1.1 Primary Objective

- To determine the complete response rate including morphologic complete remission (CR) and morphologic complete remission with incomplete blood count recovery (CRi) as defined by the International Working Group Criteria (1).

1.2 Secondary Objectives

- To determine CR + CRi duration, event free survival (EFS), overall survival (OS), patients successfully proceeding to allogeneic hematopoietic cell transplant, and adverse events (AE).

2 BACKGROUND

2.1 Secondary acute myeloid leukemia

Patients with secondary acute myeloid leukemia (s-AML) have poor long-term outcomes following standard induction chemotherapy with 7+3 (2). This was a population-based study within the Swedish Acute Leukemia Registry. Within this study, s-AML was defined as AML with antecedent hematological disease (AHD-AML) or therapy-related AML (t-AML). A total of 3,363 patients diagnosed with AML between 1997 and 2006 were included. The majority of patients (2,474; 73.6%) were classified as de novo AML. Patients defined as having AHD-AML constituted 630 (18.7%) individuals, and 259 (7.7%) of patients had t-AML. Of the patients undergoing intensive induction chemotherapy, CR rates were significantly decreased in AHD-AML (39% CR) and t-AML (54% CR), compared to de novo AML (72% CR) ($P < 0.001$ for both comparisons). Furthermore, these decreased CR rates in s-AML were observed independent of cytogenetic risk group. Through a multivariate analysis, AHD-AML (HR 1.51; 95% CI 1.26-1.79) and t-AML (HR 1.72, 95% CI 1.38-2.15) were independent risk factors for poor survival. In particular, the impact of s-AML on survival was highly dependent on age. The median survival observed in AHD-AML for patients aged < 55 , 55-74 and ≥ 75 years was 7, 7, and 6 months, respectively, and 14, 9, and 8 months in t-AML. This is in stark contrast to individuals with de novo AML who experienced a median survival of 158, 16, and 7 months for patients aged < 55 , 55-74 and ≥ 75 years. AHD-AML and t-AML demonstrated inferior overall survival compared to de novo AML in each of the three cytogenetic risk groups, demonstrating that poor outcomes are independent of karyotype.

2.2 CPX-351

The standard of care therapy for fit patients with AML over the last four decades has consisted of induction with 7+3 which is comprised of cytarabine and anthracycline (daunorubicin or idarubicin) (3). This combination has exhibited synergy *in vitro*; however the ratio which synergy occurs *in vivo* cannot be tightly controlled as the individual agents will be distributed and eliminated independently of each other (4). To overcome this barrier, CPX-351 was developed.

Roswell Park Protocol No.: I-501719

This agent is a liposome formulation fixing cytarabine and daunorubicin at the synergistic ratio of 5:1. Preclinical AML models demonstrated improved *in vivo* efficacy utilizing CPX-351 likely due to increased and prolonged exposure of synergistic cytarabine: daunorubicin ratios in bone marrow (5-7). In addition, these animal studies demonstrated that the synergistic ratio of cytarabine to daunorubicin was preserved 24 hours following administration. This was confirmed in the Phase 1 study of CPX-351 in patients with relapsed and refractory AML at all dose levels for up to 24 hours (8).

CPX-351 was then evaluated in a randomized, controlled Phase 2 trial in patients aged 60 – 69 with newly diagnosed AML (9). Patients were randomized 2:1 to receive induction chemotherapy with CPX-351 or 7+3. This study was designed to determine efficacy and identify patient subgroups who may benefit from CPX-351. 126 patients were enrolled and were balanced for patient-specific and disease risk factors. Higher response rates overall were observed in patients receiving CPX-351 (66.7% vs 51.2%, $P=0.07$), meeting the predefined criteria for success. However, no statistically significant differences in event-free survival (EFS) or OS were observed. Patients with s-AML were found to have an improved response rate (57.6% vs 31.6%, $P=0.06$) with prolongation of EFS (hazard ratio [HR] = 0.59, $P=0.08$) and OS (HR = 0.46, $P=0.01$). It was noted that a prolonged time to recovery from cytopenias occurred in the group receiving CPX-351 with more grade 3-4 infections, but without increase in infection-related deaths (3.5% vs 7.3%) or 60-day mortality (4.7% vs. 14.6%) indicating an acceptable safety profile.

These findings paved the way for the landmark Phase III study evaluating CPX-351 for patients aged 60-75 years old with s-AML as compared to standard induction chemotherapy (7+3) (10). A total of 309 patients aged 60 to 75 years with newly diagnosed s-AML were enrolled and went on to receive one to two cycles of induction chemotherapy with either CPX-351 or 7+3, followed by consolidation therapy. Median OS (primary endpoint) was significantly greater in patients receiving CPX-351 as compared to 7+3 (9.56 vs. 5.95 months; HR 0.69; 95% CI, 0.52 – 0.9; one-sided $P=0.003$). In addition, overall remission rate was significantly higher with CPX-351 vs 7+3 (47.7% vs. 33.3%; two-sided $P=0.016$). These improved outcomes were observed across all age groups and s-AML subtypes. The prolonged time to cytopenia recovery observed in the CPX-351 group within the Phase 2 study was also observed in this study, however there were no differences in the incidences of nonhematologic toxicities. Furthermore, early mortality rates with CPX-351 and 7+3 were 5.9% and 10.6% (two-sided $P=0.149$) through day 30 and 13.7% and 21.2% (two-sided $P=0.097$) through day 60. Although the age of patients enrolled in these studies were limited to older AML patients, CPX-351 went on to receive FDA approval for use in all adults aged ≥ 18 years with s-AML.

As our center uses CPX-351 for all patients per the FDA label, including those younger than 60, we performed a retrospective analysis along with three other large academic centers to assess our real world experience of CPX-351 in patients < 60 years old (11). We identified twenty-one patients with confirmed s-AML who received CPX-351. Median age was 55 years (range 42 – 59), 13 were male (62%). The majority (62%, N=13) had AML-MRC, 4 (19%) had treatment-related AML (t-AML) and 4 (19%) had MDS-MRC. Four of 5 patients had received prior hypomethylating therapy. Fourteen patients had a complex karyotype (67%), and 4 patients were found to have a normal karyotype (12%). The most common molecular event was *TP53* mutation seen in 9 patients (43%), followed by *FLT3*-ITD identified in 3 patients (14%). At the time of analysis, response assessments were available for 16 pts. Overall response rate (CR/CRi/PR) was 25% with 1 CR (6%, 1/16), 1 CRi (6%, 1/16), and 2 PR (13%, 2/16). The remaining patients

Roswell Park Protocol No.: I-501719

(12/16, 75%) were non-responders. One patient has received an allogenic stem cell transplant. The most common adverse event was infection (81%, 17/21) with 3 clinically significant bleeding events. Thirty-day mortality was 14.3%, with 60-day mortality of 19.1%. Overall survival in all evaluable patients (N=21) was 7.1 months (range 0.5 – 7.4 months), with mean follow up of 14.8 weeks.

This multi-institutional retrospective analysis suggests that CPX-351 results in lower response rates (CR/CRi 13%) and shorter overall survival (7.1 mos) than reported in the recently published Phase 3 trial data in patients aged 60-75 years old. However, there are many potential explanations for this discrepancy which include short duration of follow up, small sample size, the retrospective design of this study, and the significant proportions of patients with complex karyotype and *TP53* mutations. At this point it is unclear whether age truly impacts outcome for patients with s-AML, but we do believe that response rates between these two cohorts (younger vs. older s-AML) should not be statistically different as the biology underlying the disease is similar. Therefore, we are proposing to evaluate this prospectively in a Phase II, single arm multi-institutional study.

3 INCLUSION AND EXCLUSION CRITERIA

NOTE: For blood Chemistry labs, Roswell Park clinical blood chemistries are performed on plasma unless otherwise indicated.

3.1 Inclusion Criteria

To be included in this study, participants must meet the following criteria:

- 1 Aged 18-59.
- 2 Newly diagnosed:
 - a. therapy-related AML
 - b. AML with antecedent MDS or CMML
 - c. AML with MDS-related changes (as per WHO)
- 3 Have an ECOG Performance Status of ≤ 2 . Refer to **Appendix A**.
- 4 Have the following clinical laboratory values:
 - a. Plasma creatinine ≤ 1.5 x UNL
 - b. Total bilirubin < 2.0 mg/dL
 - c. Serum alanine aminotransferase and aspartate aminotransferase < 3 x ULN
- 5 Left ventricular ejection fraction by echocardiogram or multiple-gated acquisition $\geq 50\%$.
- 6 Participants of child-bearing potential must agree to use adequate contraceptive methods (e.g., hormonal or barrier method of birth control; abstinence) prior to study entry. Should a woman become pregnant or suspect she is pregnant while she or her partner is participating in this study, she should inform her treating physician immediately.
- 7 Women of childbearing potential must have a negative serum or urine pregnancy test within 72 hours prior to enrollment and commit to two forms of birth control.

Roswell Park Protocol No.: I-501719

- 8 Men must use a latex condom during any sexual contact with women of childbearing potential.
- 9 Willing to adhere to protocol specific requirements.
- 10 Participant must understand the investigational nature of this study and sign an Independent Ethics Committee/Institutional Review Board approved written informed consent form prior to receiving any study related procedure.

Please refer to **Appendix B** for the Investigator Study Eligibility Verification form: Inclusion Criteria.

3.2 Exclusion Criteria

Participants will be excluded from the study for the following:

- 1 Prior treatment of AML.
- 2 Known clinically active CNS leukemia.
- 3 Core-binding factor leukemia.
- 4 Acute promyelocytic leukemia.
- 5 Uncontrolled other malignancy.
- 6 Prior anthracycline exposure > 368 mg/m² of daunorubicin or equivalent.
- 7 Cardiovascular disease resulting in heart failure (New York Heart Association Class III or IV), unstable angina (angina symptoms at rest), or new onset angina (began within the last 3 months) or myocardial infarction within the past 6 months.
- 8 Hypersensitivity to cytarabine, daunorubicin, or liposomal drugs.
- 9 Known active HIV infection.
- 10 Known history of active hepatitis B or C infection.
- 11 Pre-existing liver disease (e.g. cirrhosis, chronic hepatitis B or C, nonalcoholic steatohepatitis, sclerosing cholangitis).
- 12 Evidence of ongoing, uncontrolled systemic infection.
- 13 Pregnant or breastfeeding women.
- 14 Subject with concurrent severe and/or uncontrolled medical or psychiatric conditions that in the opinion of the investigator may impair the participation in the study or the evaluation of safety and/or efficacy.
- 15 History of Wilson disease or other copper-handling disorders.
- 16 Any condition which in the Investigator's opinion deems the participant an unsuitable candidate to receive study drug.

Please refer to **Appendix C** for the Investigator Study Eligibility Verification Form: Exclusion Criteria.

Roswell Park Protocol No.: I-501719

3.3 Special Populations

The following special populations are excluded from this study:

- Cognitively impaired adults/adults with impaired decision-making capacity
- Individuals who are not yet adults (infants, children, teenagers)
- Pregnant women
- Prisoners

3.4 Inclusion of Women and Minorities

Both men and women and members of all races and ethnic groups are eligible for this study.

4 LOCAL AND STUDY-WIDE NUMBER OF SUBJECTS

A maximum of 46 participants at multiple sites, including Roswell Park will be enrolled and treated on this study. We expect successful enrollment with 6 years of study activation across all sites.

Prior studies in this population have shown about 25% of enrolled patients become ineligible or unevaluable and are replaced. On this basis, up to 46 patients will be enrolled, of which 34 are expected to be evaluable.

4.1 Criteria for Replacement

Patients who are enrolled on the study may be replaced for the following reasons:

1. Withdrawal or removal from the study prior to receiving any of the study drug.
2. Subjects who withdraw or are removed prior to adequate attempt at cytoreduction (bone marrow cellularity < 20%) with completion of up to 2 cycles of induction.
 - a. If second induction is not attempted due to persistent disease or disease progression after the first induction, patient will not be replaced. If second induction is not administered due to safety concerns on the part of the PI or co-investigator despite not achieving hypocellularity but would otherwise be eligible for second induction, the patient will be replaced.
3. Subjects non-compliant with study procedures.
4. Subject is found to have significantly deviated from any 1 of the inclusion or exclusion criteria after enrollment.
5. Death prior to response assessment.

5 LOCAL AND STUDY-WIDE RECRUITMENT METHODS

Participants will be identified and recruited from the patients followed by or referred to the Roswell Park leukemia service or through the leukemia programs at participating network sites.

Given the rarity of patients < 60 years old with s-AML, this study will require a collaborative group of co-investigators. This study is planned to open at multiple academic institutions within the USA, including Roswell Park. The primary endpoint of this study (CR + CRi) would be informed by a relatively small sample size (34 patients). Secondary endpoints (CR + CRi duration,

Roswell Park Protocol No.: I-501719

EFS, OS, and patients successfully proceeding to allogeneic hematopoietic stem cell transplantation) will provide additional valuable information.

- Patients will be referred to any of the leukemia physicians where the study is open and, will be offered the opportunity to enroll on protocol.
- An IRB approved letter will be distributed to local hematologists/oncologist who sees potentially eligible patients. These physicians can then refer patients for consideration of trial participation. The study will be registered on clinicaltrials.gov. Patients may review the study on Roswell Park's website and other collaborating institutional external websites.
- All study related advertising documents used at any site would first be reviewed by the IRB at any participating institution prior to their use.

6 MULTI-SITE RESEARCH

- The study will be opened initially at Roswell Park and three additional sites. To ensure that all patients are treated appropriately and in a consistent fashion we will ensure the following:
 - All sites will have the most current version of the protocol; consent document, and HIPAA authorization.
 - All required approvals (initial, continuing review and modifications) have been obtained at each site (including approval by the site's IRB of record).
 - All modifications have been communicated to sites and approved (including approval by the site's IRB of record) before the modification is implemented.
 - All engaged participating sites will safeguard data, including secure transmission of data, as required by local information security policies.
 - All local site investigators will conduct the study in accordance with applicable federal regulations and local laws.
 - All non-compliance with the study protocol or applicable requirements will be reported in accordance with local policy.

In addition, see **Appendix D**: Instructions for Multiple Site Studies.

7 STUDY TIMELINES

Participant accrual (see **Section 4**) is expected to take 6 years, with follow-up for 5 years from the start of investigational treatment. Participants are monitored for 1 year ($\pm$ 2 months) for disease, survival status, bone marrow transplant status (including the 30-day follow-up visit) for up to 5 years following last dose of study drug every 3 months.

8 STUDY ENDPOINTS

8.1 Primary Endpoints

- Complete response rate including morphologic complete remission (CR) and morphologic complete remission with incomplete blood count recovery (CRi) as defined by the International Working Group Criteria (1) within 45 days of beginning therapy.

Roswell Park Protocol No.: I-501719

8.2 Secondary Endpoints

- CR + CRi duration, event free survival (EFS), overall survival (OS), patients successfully proceeding to allogenic hematopoietic cell transplant, and adverse events (AE).

9 DESIGN

This is a Phase II single arm study with two stages, with up to 46 patients enrolling. Subjects will be treated with daunorubicin/cytarabine liposomal according to the FDA dose and schedule. In the first stage, 10 subjects will be enrolled. If 1 or fewer complete responses are observed in stage 1, then the proposed treatment will not be considered promising and the study will be terminated. If 2 or more patients demonstrate a complete response, then an additional 26 patients will be enrolled in the second stage. Accrual will be suspended while awaiting the data from stage 1 to mature. Eligible patients would be between the ages of 18-59 and carry a diagnosis of newly diagnosed secondary AML, including AML with myelodysplasia related changes and therapy-related AML. These patients should be deemed fit by the treating physician to receive high dose induction chemotherapy. Enrollment would be completed following confirmation of secondary AML, prior to initiation of therapy.

Patients would then go on to receive daunorubicin/cytarabine liposomal as induction chemotherapy. Bone marrow samples for documentation of disease status and response assessments will be performed at baseline, and between days 14-21 for assessment of response to therapy and determination of need for second induction. Adequate response is defined as cellularity less than 20% with residual blasts < 5% (1). Patients not achieving adequate cyto-reduction following second induction (if required) will be withdrawn from study. At count recovery patients would undergo bone marrow biopsy and aspiration. Patients achieving a CR would go on to receive up to two cycles of consolidation with daunorubicin/cytarabine liposomal. Bone marrow aspiration and biopsy can be performed following each cycle of consolidation per institutional care. Patients will be permitted to proceed to allogenic hematopoietic stem cell transplantation at the discretion of the treating physician.

10 TREATMENT

The following pre-medications are to be administered:

- Ondansetron 8 mg by oral administration 30 minutes prior to first dose of daunorubicin/cytarabine liposomal, then every 8 hours for a total of 18 doses days 1-6 of therapy
- Dexamethasone 12 mg by oral administration 30 minutes prior to first dose of daunorubicin/cytarabine liposomal.

Prior to initiating each cycle of daunorubicin/cytarabine liposomal, the prior cumulative anthracycline exposure for the patient will be calculated. Patients will not be permitted to receive daunorubicin/cytarabine liposomal if the lifetime cumulative anthracycline exposure is greater than 368 mg/m².

10.1 Induction Therapy

Induction with daunorubicin/cytarabine liposomal: 100 mg/m² cytarabine and 44 mg/m² daunorubicin, will be administered as a 90-minute intravenous infusion via an infusion pump through a central venous catheter or a peripherally inserted central catheter on days 1, 3, and 5 in

Roswell Park Protocol No.: I-501719

an inpatient setting. **Do not use an in-line filter.** Flush the line after administration with 0.9% Sodium Chloride Injection, USP or 5% Dextrose Injection, USP. A bone marrow assessment will be obtained between days 14-21 to assess cyto-reduction. A second induction course (44 mg/m² daunorubicin/100 mg/m² cytarabine liposomal) will be administered on days 1 and 3 via intravenous infusion over 90 minutes for patients who did not achieve hypoplastic bone marrow (< 20% cellularity and < 5% blasts) so long as ECOG ≤ 2, so long as the treating physician deems there is no contraindication to proceeding with treatment. If the patient has disease progression, they will not receive a second induction and will be taken off treatment.

10.2 Consolidation Therapy

Patients achieving a CR following induction will go on to receive up to two cycles of consolidation therapy. The first cycle of consolidation will be administered 5-8 weeks following the start of the last induction, so long as the patient meets the criteria for morphologic CR (platelets are ≥ 100 x 10⁹/L, absolute neutrophil count > 1,000/mcL (blasts < 5%) and no evidence of extramedullary disease). Each cycle of consolidation therapy will be administered over a 90-minute intravenous infusion on days 1 and 3 at a dose of cytarabine 65 mg/m² and daunorubicin 29 mg/m². A repeat bone marrow assessment can be performed prior to proceeding with the second cycle of consolidation per institutional care, and the patient meets criteria for morphologic CR.

10.3 Dose Modifications and Treatment Delays

Missed Doses of daunorubicin/cytarabine liposomal

If a planned dose of daunorubicin/cytarabine liposomal is missed, administer the dose as soon as possible and adjust the dosing schedule accordingly, maintaining the treatment interval.

Hypersensitivity Reactions

For hypersensitivity reactions of any grade/severity, interrupt daunorubicin/cytarabine liposomal infusion immediately and manage symptoms. Reduce the rate of infusion or discontinue treatment as outlined below, with definitions of severity of reaction per CTCAE v5.0:

- Mild symptoms (Grade 2): Once symptoms resolve, reinstate infusion at half the prior rate of infusion. Consider premedication with antihistamines and/or corticosteroids for subsequent doses of daunorubicin/cytarabine liposomal.
- Moderate symptoms (Grade 3): Do not reinstate infusion. For subsequent doses of daunorubicin/cytarabine liposomal, pre-medicate with antihistamines and/or corticosteroids prior to initiating infusion at same rate.
- Severe/life-threatening symptoms (Grade 4): Permanently discontinue daunorubicin/cytarabine liposomal treatment, treat according to the standard of care to manage symptoms, and monitor patient until symptoms resolve.

Cardiotoxicity

Discontinue daunorubicin/cytarabine liposomal in patients who exhibit impaired cardiac function unless the benefit of continuing treatment outweighs the risk.

For additional information see FDA package insert.

10.4 Reference Toxicities during Daunorubicin/Cytarabine Liposomal Treatment

10.4.1 Do Not Interchange with Other Daunorubicin – and/or Cytarabine Containing Products

Due to substantial differences in the pharmacokinetic parameters, the dose and schedule recommendations for daunorubicin/cytarabine liposomal are different from those for daunorubicin hydrochloride injection, cytarabine injection, daunorubicin citrate liposome injection, and cytarabine liposome injection. Verify drug name and dose prior to preparation and administration to avoid dosing errors. Do not substitute other preparations of daunorubicin or cytarabine for daunorubicin/cytarabine liposomal.

10.4.2 Hemorrhage

Serious or fatal hemorrhage events, including fatal central nervous system (CNS) hemorrhages, associated with prolonged severe thrombocytopenia, have occurred in patients treated with daunorubicin/cytarabine liposomal. In Study 1 (NCT01696084), the incidence of any grade hemorrhagic events during the entire treatment period was 74% of patients on the daunorubicin/cytarabine liposomal arm and 56% on the control arm. The most frequently reported hemorrhagic event was epistaxis (36% in daunorubicin/cytarabine liposomal arm and 18% in control arm). Grade 3 or greater events occurred in 12% of daunorubicin/cytarabine liposomal treated patients and 8% of patients treated with 7+3. Fatal treatment-emergent CNS hemorrhage not in the setting of progressive disease occurred in 2% of patients on the daunorubicin/cytarabine liposomal arm and in 0.7% of patients on the control arm. Monitor blood counts regularly until recovery and administer platelet transfusion support as required.

10.4.3 Cardiotoxicity

Daunorubicin/cytarabine liposomal contains the anthracycline daunorubicin, which has a known risk of cardiotoxicity. Prior therapy with anthracyclines, pre-existing cardiac disease, previous radiotherapy to the mediastinum, or concomitant use of cardiotoxic drugs may increase the risk of daunorubicin induced cardiac toxicity. Prior to administering daunorubicin/cytarabine liposomal, obtain an electrocardiogram (ECG) and assess cardiac function by multi-gated radionuclide angiography (MUGA) scan or echocardiography (ECHO). Repeat MUGA or ECHO determinations of left ventricular ejection fraction (LVEF) prior to consolidation with daunorubicin/cytarabine liposomal and as clinically required. Discontinue daunorubicin/cytarabine liposomal in patients with impaired cardiac function unless the benefit of initiating or continuing treatment outweighs the risk. daunorubicin/cytarabine liposomal treatment is not recommended in patients with LVEF that is less than normal.

Total cumulative doses of non-liposomal daunorubicin greater than 550 mg/m² have been associated with an increased incidence of drug-induced congestive heart failure. The tolerable limit appears lower (400 mg/m²) in patients who received radiation therapy to the mediastinum.

Calculate the lifetime cumulative anthracycline exposure prior to each cycle of daunorubicin/cytarabine liposomal. Daunorubicin/cytarabine liposomal treatment is not recommended in patients whose lifetime anthracycline exposure has reached the maximum cumulative limit. The exposure to daunorubicin following each cycle of CPX-351 is shown in **Table 1**.

Roswell Park Protocol No.: I-501719

Table 1 Cumulative Exposure of Daunorubicin per Cycle of Daunorubicin/Cytarabine Liposomal

Therapy	Daunorubicin per Dose	Number of Doses per Cycle	Daunorubicin per Cycle
First Induction Cycle	44 mg/m ²	3	132 mg/m ²
Second Induction Cycle	44 mg/m ²	2	88 mg/m ²
Each Consolidation Cycle	29 mg/m ²	2	58 mg/m ²

10.4.4 Hypersensitivity Reactions

Serious or fatal hypersensitivity reactions, including anaphylactic reactions, have been reported with daunorubicin and cytarabine. Monitor patients for hypersensitivity reactions. If a mild or moderate hypersensitivity reaction occurs, interrupt or slow the rate of infusion with daunorubicin/cytarabine liposomal and manage symptoms. If a severe or life-threatening hypersensitivity reaction occurs, discontinue daunorubicin/cytarabine liposomal permanently, treat symptoms according to the standard of care, and monitor until symptoms resolve.

10.4.5 Copper Overload

Reconstituted daunorubicin/cytarabine liposomal contains 5 mg/mL copper gluconate, of which 14% is elemental copper. There is no clinical experience with daunorubicin/cytarabine liposomal in patients with Wilson's disease or other copper-related metabolic disorders. The maximum theoretical total exposure of copper under the recommended daunorubicin/cytarabine liposomal dosing regimen is 106 mg/m². Consult with a hepatologist and nephrologist with expertise in managing acute copper toxicity in patients with Wilson's disease treated with daunorubicin/cytarabine liposomal. Monitor total serum copper, serum nonceruloplasmin bound copper, 24-hour urine copper levels and serial neuropsychological examinations in these patients. Use daunorubicin/cytarabine liposomal in patients with Wilson's disease only if the benefits outweigh the risks. Discontinue daunorubicin/cytarabine liposomal in patients with signs or symptoms of acute copper toxicity.

10.4.6 Tissue Necrosis

Daunorubicin has been associated with severe local tissue necrosis at the site of drug extravasation. Administer daunorubicin/cytarabine liposomal by the intravenous route only. Do not administer by intramuscular or subcutaneous route.

For additional information see FDA package insert.

10.5 General Concomitant Medication and Supportive Care

10.5.1 Daunorubicin/Cytarabine Liposomal Drug interactions

Cardiotoxic agents: Concomitant use of cardiotoxic agents may increase the risk of cardiotoxicity. Assess cardiac function more frequently when daunorubicin/cytarabine liposomal is co-administered with cardiotoxic agents.

Roswell Park Protocol No.: I-501719

Hepatotoxic agents: Concomitant use with hepatotoxic agents may impair liver function and increase the toxicity of CPX-351. Monitor hepatic function more frequently when daunorubicin/cytarabine liposomal is co-administered with hepatotoxic agents.

10.5.2 Daunorubicin/Cytarabine Liposomal Contraindications

The use of daunorubicin/cytarabine liposomal is contraindicated in patients with a history of hypersensitivity reaction to cytarabine, daunorubicin, or any component of the formulation.

10.5.3 Permitted Concomitant Medication

Hydroxyurea is permitted prior to and after the start of induction chemotherapy if needed at the discretion of the investigator for significant leukocytosis.

In subjects who have a high-risk of CNS disease (i.e., $WBC \geq 40 \times 10^9/L$, monocyte phenotypes, extramedullary disease, signs of neurologic deficit), a lumbar puncture with intrathecal chemotherapy per institutional standard will be permitted once as prophylaxis per standard-of-care.

10.5.4 Supportive Care

In general, institutional guidelines should be followed. The following supportive care guidelines are provided as examples.

- **Nausea/vomiting:** Standard anti-emetic therapy may be used as necessary.
- **Tumor lysis syndrome:** Evidence of tumor lysis syndrome should be managed with intravenous fluids, allopurinol, rasburicase, and renal consultation per institutional standards.
- **Neutropenic prophylaxis:** Anti-microbial prophylaxis in the setting of neutropenia is strongly suggested for all subjects. Recommended agents are listed below with equivalent alternatives permitted per the investigator's discretion. As posaconazole is considered to be a hepatotoxic agent, it is recommended to initiate prophylaxis on day 6 of induction or day 4 of consolidation to avoid interaction with daunorubicin. As levofloxacin and posaconazole may increase the risk of torsades and QTc prolongation, monitoring of patients for QTc prolongation with EKGs as clinically indicated during treatment is recommended.

Type	Recommended agent	Dose	Period
Antibacterial	Levofloxacin	500-750 mg oral QD	During neutropenia
Antiviral	Acyclovir	400 mg oral BID	During neutropenia
Antifungal	Posaconazole	300 mg oral QD	During neutropenia

Neutropenic fever/infection: Treatment of active infection in the setting of myelosuppression associated with disease and/or study therapy will be at the discretion of the treating physician.

Roswell Park Protocol No.: I-501719

10.6 Duration of Treatment

Participants may remain on study and continue to receive treatment up to two cycles of consolidation therapy in the absence of disease progression, unacceptable toxicity or withdrawal from study, intercurrent illness that prevents further administration of treatment, participant demonstrates an inability/refusal to comply with oral medication regime, and participant withdraws from study.

11 PROCEDURES INVOLVED

The study-specific assessments are detailed in this section and outlined in **Appendix E** (Study Calendar). Baseline and/or Screening assessments must be performed within 28 days prior to the first dose of investigational product (unless otherwise noted). Any results falling outside of the reference ranges may be repeated at the discretion of the investigator. All treatment dosing and on-study visit procedures are allowed a window of ± 3 days unless otherwise noted.

Unless otherwise defined in the written protocol text, all procedures/assessments will be conducted in accordance with site specific Standard Operating Procedures. Informed consent **MUST** be completed prior to receiving any study related procedures.

11.1 Baseline Evaluations

The following will be performed within 28 days prior to first dose of study drug unless otherwise noted:

- Medical history and Pre-Existing conditions (including all prior anti-leukemic therapy)
- Concomitant Medications: List any medications that are ongoing, or that will be discontinued, within 1 week prior to first dose of study drug.
- Physical examination
- Vital signs (i.e., temperature, heart rate, respiratory rate, blood pressure, body weight, and height)
- ECOG Performance status **Appendix A**
- Hematology
- Chemistry
- Bone marrow aspirate and biopsy (with flow cytometry, conventional cytogenetics $\pm$ FISH as appropriate)
- Pregnancy test (urine) in females of childbearing potential within 3 days of starting treatment
- Urinalysis
- Chest x-ray or CT chest
- 12-lead Electrocardiogram (ECG)
- ECHO or MUGA scan

Roswell Park Protocol No.: I-501719

11.2 Evaluations Performed Day 1 of Induction and Re-Induction Cycles

- Concomitant medications
- Adverse events
- Physical examination
- Vital signs (refer to **Appendix E**)
- ECOG performance status
- Hematology
- Chemistry
- ECHO or MUGA if receiving Re-Induction
- EKG if receiving Re-Induction

11.3 Evaluations Performed at Day 14-21 following Induction

- Concomitant medications
- Adverse events
- Physical examination
- Vital signs (refer to **Appendix E**)
- ECOG performance status
- Hematology
- Chemistry
- Bone marrow biopsy and aspirate (with MRD flow cytometry, conventional cytogenetics ± FISH as appropriate)

11.4 Evaluations Performed day on 28 – 45 Following Last Dose of Induction or Re-Induction

- Concomitant medications
- Adverse events
- Physical examination
- Vital signs (refer to Appendix E)
- ECOG performance status
- Hematology
- Chemistry
- Bone marrow biopsy and aspirate (with MRD flow cytometry, conventional cytogenetics ± FISH as appropriate)
- ECHO or MUGA

Roswell Park Protocol No.: I-501719

- EKG

11.5 Evaluations Performed day on 1 of Consolidation

- Concomitant medications
- Adverse events
- Physical examination
- Vital signs (refer to **Appendix E**)
- ECOG performance status
- Hematology
- Chemistry

11.6 Evaluations Performed day on 28 – 45 Following Last Dose of Consolidation

- Concomitant medications
- Adverse events
- Physical examination
- Vital signs (refer to **Appendix E**)
- ECOG performance status
- Hematology
- Chemistry
- ECHO or MUGA
- EKG

11.7 Evaluations Performed at End of Treatment ($\pm$ 3 days)

The following evaluations will be performed at end of treatment or at time of treatment discontinuation:

- Concomitant medications
- Adverse events
- Physical examination
- Vital signs
- ECOG performance status
- Hematology
- Chemistry
- Bone marrow biopsy and aspirate (with MRD flow cytometry, conventional cytogenetics $\pm$ FISH as appropriate)

Roswell Park Protocol No.: I-501719

11.8 Post-Treatment Follow-Up Evaluation

Follow-up safety evaluations will occur 30 days ($\pm$ 3 days) after last dose of study drug or until resolution of any drug-related toxicity (telephone contact is acceptable):

- Concomitant medications: List any ongoing medications with dose changes, as applicable
- Adverse events.

11.9 Long-Term Follow-Up Evaluation

Participants are monitored for 1 year ($\pm$ 2 months) for disease, survival status, bone marrow transplant status (including the 30-day follow-up visit) for up to 5 years following last dose of study drug every 3 months. Telephone contact for any changes in the adverse event profile and outcome will be performed. Participants who are unavailable for follow-up evaluations should be classified as lost to follow-up for 1 of the following reasons:

- Lost to follow-up: For a participant to be considered lost to follow-up, the investigator must make two separate attempts to re-establish contact with the participant. The attempts to reestablish participant contact must be documented (e.g., certified letter).
- Death: Date and cause of death will be recorded for those participants who die within 30 days after last dose of study drug (telephone verification is acceptable).

12 WITHDRAWAL OF SUBJECTS

Upon treatment discontinuation all end of treatment evaluations and tests will be conducted. All participants who discontinue due to an AE must be followed until the event resolves or stabilizes.

Appropriate medical care should be provided until signs and symptoms have abated, stabilized, or until abnormal laboratory findings have returned to acceptable or pre-study limits. The final status of the AE will be reported in the participant's medical records and the appropriate eCRF.

Reasons for treatment discontinuation should be classified as follows:

- Death
- Progressive disease
- Toxicity; treatment related or unrelated
- Investigator judgment
 - The Investigator may discontinue a participant if, in his/her judgment, it is in the best interest of the participant to do so.
- Noncompliance
- Participant voluntary withdrawal
 - A participant may withdraw from the study at any time, for any reason. If a participant discontinues treatment, an attempt should be made to obtain information regarding the reason for withdrawal.
- Sponsor decision.

Roswell Park Protocol No.: I-501719

13 RISKS TO SUBJECTS

13.1 Embryo-Fetal Toxicity

Based on its mechanism of action and findings from animal studies with daunorubicin and cytarabine, CPX-351 can cause embryo-fetal harm when administered to a pregnant woman. There are no adequate and well-controlled studies of CPX-351, daunorubicin, or cytarabine in pregnant women. Daunorubicin and cytarabine are reproductive and developmental toxicants in multiple species (mice, rats, and/or dogs), starting at a dose that was approximately 0.02 times the exposure in patients at the recommended human dose on an mg/m² basis. Patients should be advised to avoid becoming pregnant while taking CPX-351. If this drug is used during pregnancy or if the patient becomes pregnant while taking this drug, apprise the patient of the potential risk to a fetus. Advise females and males of reproductive potential to use effective contraception during treatment and for 6 months following the last dose of CPX-351.

13.2 Carcinogenesis, Mutagenesis and Impairment of Fertility

Carcinogenicity, mutagenicity, and impairment of fertility studies with (daunorubicin and cytarabine) liposome for injection have not been conducted.

Carcinogenicity and mutagenicity studies have been conducted with daunorubicin. Published literature reported data that suggest daunorubicin (5 mg/kg) could be tumorigenic in rats at 0.68 times the recommended human dose on an mg/m² basis. A high incidence of mammary tumors was observed about 120 days after a single intravenous dose of 12.5 mg/kg daunorubicin in rats (about 1.7 times the recommended human dose on an mg/m² basis). A carcinogenic evaluation of daunorubicin by the IARC Working Group classified daunorubicin as a possible human carcinogen based on sufficient evidence in animals and inadequate data in humans. Daunorubicin was mutagenic in in vitro tests (Ames assay, V79 hamster cell assay), and clastogenic in in vitro (CCRF-CEM human lymphoblasts) and in in vivo (SCE assay in mouse bone marrow) tests.

Daunorubicin intravenous doses of 0.25 mg/kg/day (about 0.12 times the recommended human dose on a mg/m² basis) in male dogs caused testicular atrophy and total aplasia of spermatocytes in the seminiferous tubules.

Cytarabine was mutagenic in in vitro tests and was clastogenic in vitro (chromosome aberrations and SCE in human leukocytes) and in vivo (chromosome aberrations and SCE assay in rodent bone marrow, mouse micronucleus assay). Cytarabine caused the transformation of hamster embryo cells and rat H43 cells in vitro.

No studies assessing the impact of cytarabine on fertility are available in the literature. Cytarabine was clastogenic to meiotic cells; a dose-dependent increase in sperm-head abnormalities and chromosomal aberrations occurred in mice given IP cytarabine.

In addition, see **Section 10.4** and FDA package insert.

14 POTENTIAL BENEFITS TO SUBJECTS

There is no direct benefit to patients as this therapy is FDA approved.

15 DATA AND SPECIMEN BANKING

N/A

Roswell Park Protocol No.: I-501719

16 MEASUREMENT OF EFFECT

For the purposes of this study, patients should be re-evaluated for response by bone marrow aspirate and biopsy 4-6 weeks following last dose of induction or re-induction. If there is no measurable effect on disease status and/or likely drug and/or disease related toxicities, then patients not achieving clinical benefit will be taken off treatment and enter follow-up. If CR/CRi is achieved following induction or re-induction, patients will go on to receive consolidation. Further evaluation of response by bone marrow aspirate and biopsy will be performed 4-6 weeks following last dose of consolidation.

Refer to **Appendix F** for Criteria for Response.

17 SAFETY EVALUATION

17.1 Adverse Events

An adverse event or adverse experience (AE) is any untoward medical occurrence associated with the use of a drug in humans, whether or not considered drug related. Therefore, an AE can be ANY unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal (investigational) product, whether or not considered related to the medicinal (investigational) product (attribution of ‘unrelated’, ‘unlikely’, ‘possible’, ‘probable’, or ‘definite’).

An AE is considered “unexpected” if it is not listed in the investigator brochure or is not listed at the specificity or severity that has been observed; or if an investigator brochure is not required or available, is not consistent with the risk information described in the general investigational plan in other study-related documents.

17.2 Diagnosis Versus Signs and Symptoms

If known, a diagnosis should be recorded on the CRF rather than individual signs and symptoms (e.g., record only liver failure or hepatitis rather than jaundice, asterixis, and elevated transaminases). However, if a constellation of signs and/or symptoms cannot be clinically characterized as a single diagnosis or syndrome at the time of reporting, each individual event should be recorded as an AE or SAE on the CRF. If a diagnosis is subsequently established, it should be reported as follow-up information.

17.3 Adverse Events Occurring Secondary to Other Events

In general, AEs occurring secondary to other events (e.g., cascade events or clinical sequelae) should be identified by their primary cause. For example, if severe diarrhea is known to have resulted in dehydration, it is sufficient to record only diarrhea as an AE or SAE on the CRF.

However, clinically significant AEs occurring secondary to an initiating event that are separated in time should be recorded as independent events on the CRF. For example, if a severe gastrointestinal hemorrhage leads to renal failure, both events should be recorded separately on the CRF.

17.4 Abnormal Laboratory Values

Only clinically significant laboratory abnormalities that require active management will be recorded as AEs or SAEs on the CRF (e.g., abnormalities that require study drug dose

Roswell Park Protocol No.: I-501719

modification, discontinuation of study treatment, more frequent follow-up assessments, further diagnostic investigation, etc.).

If the clinically significant laboratory abnormality is a sign of a disease or syndrome (e.g., alkaline phosphatase and bilirubin 5 x the upper limit of normal associated with cholecystitis), only the diagnosis (e.g., cholecystitis) needs to be recorded on the Adverse Event CRF.

If the clinically significant laboratory abnormality is not a sign of a disease or syndrome, the abnormality itself should be recorded as an AE or SAE on the CRF. If the laboratory abnormality can be characterized by a precise clinical term, the clinical term should be recorded as the AE or SAE. For example, an elevated blood potassium level of 7 mEq/L should be recorded as “hyperkalemia”.

Observations of the same clinically significant laboratory abnormality from visit to visit should not be repeatedly recorded as AEs or SAEs on the CRF, unless their severity, seriousness, or etiology changes.

17.5 Preexisting Medical Conditions (Baseline Conditions)

A preexisting medical condition should be recorded as an AE or SAE only if the frequency, severity, or character of the condition worsens during the study. When recording such events on an Adverse Event CRF, it is important to convey the concept that the preexisting condition has changed by including applicable descriptors (e.g., “more frequent headaches”).

17.6 Grading and Reporting Adverse Events

17.6.1 Grading and Relationship to Drug

The descriptions and grading scales found in the CTEP Version 5.0 of the NCI Common Terminology Criteria for Adverse Events (CTCAE) will be utilized for AE reporting. CTEP Version 5.0 of the CTCAE is identified and located at:

http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm.

AEs not covered by specific terminology listed should be reported with common medical terminology and documented according to the grading scales provided in the CTCAE Version 5.0.

The relationship of event to study drug will be documented by the Investigator as follows:

Unrelated: The event is clearly related to other factors such as the participant’s clinical state, other therapeutic interventions or concomitant drugs administered to the participant.

Unlikely: The event is doubtfully related to investigational agent(s). The event was most likely related to other factors such as the participant’s clinical state, other therapeutic interventions, or concomitant drugs.

Possible: The event follows a reasonable temporal sequence from the time of drug administration but could have been produced by other factors such as the participant’s clinical state, other therapeutic interventions or concomitant drugs.

Probable: The event follows a reasonable temporal sequence from the time of drug administration and follows a known response pattern to the study drug. The event cannot be reasonably explained by other factors such as the participant’s clinical state, therapeutic interventions or concomitant drugs.

Roswell Park Protocol No.: I-501719

Definite: The event follows a reasonable temporal sequence from the time of drug administration, follows a known response pattern to the study drug, cannot be reasonably explained by other factors such as the participant's condition, therapeutic interventions or concomitant drugs; AND occurs immediately following study drug administration, improves upon stopping the drug, or reappears on re-exposure.

17.6.2 Reporting Adverse Events

Routine AEs occurring between the start date of intervention until 30 days after the last intervention, or until the event has resolved, the study participant is lost to follow-up, the start of a new treatment, or until the study investigator assesses the event(s) as stable or irreversible, will be reported. New information will be reported after it is received.

Guidelines for Routine Adverse Event Reporting for Phase 1 Studies (Regardless of Expectedness)

Attribution	Grade 1	Grade 2	Grade 3	Grade 4
Unrelated	X	X	X	X
Unlikely	X	X	X	X
Possible	X	X	X	X
Probable	X	X	X	X
Definite	X	X	X	X

Guidelines for Routine Adverse Event Reporting for Pilot, Phase 2, and Phase 3 Studies (Regardless of Expectedness)

Attribution	Grade 1	Grade 2	Grade 3	Grade 4
Unrelated			X	X
Unlikely			X	X
Possible	X	X	X	X
Probable	X	X	X	X
Definite	X	X	X	X

17.7 Serious Adverse Events

A serious adverse event (SAE) is any adverse event (experience) that in the opinion of either the investigator or sponsor results in **ANY** of the following:

- Death.
- A life-threatening adverse event (experience). Any AE that places a participant or participants, in the view of the Investigator or sponsor, at immediate risk of death from the reaction as it occurred. It does NOT include an AE that, had it occurred in a more severe form, might have caused death.
- Inpatient hospitalization or prolongation of existing hospitalization (for > 24 hours).
- A persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions.
- A congenital anomaly or birth defect.

Roswell Park Protocol No.: I-501719

- Important Medical Event (IME) that, based upon medical judgment, may jeopardize the participant and may require medical or surgical intervention to prevent one of the outcomes listed above.

17.7.1 Reporting Serious Adverse Events

All new SAEs occurring from the date the participant signs the study consent until 30 days after the last intervention or a new treatment is started, whichever comes first, will be reported. The Roswell Park SAE Source Form is to be completed with all available information, including a brief narrative describing the SAE and any other relevant information.

SAEs occurring after the 30 day follow-up period that the investigator determines to be possibly, probably, or definitely related to the study intervention should be reported.

SAEs that are unexpected and possibly-, probably- or definitely- related must be reported as an Unanticipated Problem by the Investigator must be reported. Please refer to **Section 17.10.1** for details on reporting Unanticipated Problems.

17.8 Investigator Reporting: Notifying the Study Sponsor

Investigators MUST report within 1 business day upon becoming aware, to the sponsor ANY Serious Adverse Events, whether or not they are considered related to the investigational agent(s)/intervention.

17.8.1 Reporting SAEs to Jazz Pharmaceuticals

All SAEs (initial and follow-up) that require collection and reporting per protocol, and which occur in a subject who received CPX-351, must also be reported to Jazz Pharmaceuticals within 1 business day of their awareness of the SAE (AREporting@jazzpharma.com). The Investigator will also provide Jazz (PVcomms@jazzpharma.com) with a copy of all submissions made to the FDA at the time the submission is made. In addition, the Sponsor should provide all other adverse events to Jazz in summary or line-item form upon Jazz's request and at the conclusion of the study.

17.9 Follow-Up for Serious Adverse Events

All related SAEs should be followed to their resolution, until the study participant is lost to follow-up, the start of a new treatment, or until the study investigator assesses the event(s) as stable or irreversible. New information will be reported when it is received.

17.10 Unanticipated Problems

An Unanticipated Problem (UP) is any incident, experience, or outcome that meets all of the following criteria:

- Unexpected (in terms of nature, severity, or frequency) given:
 - The research procedures that are described in the study-related documents, including study deviations, as well as issues related to compromise of participant privacy or confidentiality of data.
 - The characteristics of the participant population being studied.

Roswell Park Protocol No.: I-501719

- Related or possibly related to participation in the research (possibly related means there is a reasonable possibility that the incident, experience, or outcome may have been caused by the procedures involved in the research).
- Suggests that the research places participants or others at a greater risk of harm (including physical, psychological, economic, or social harm) than was previously known or recognized and if in relation to an AE is also deemed Serious per Section 17.7.

17.10.1 Reporting Unanticipated Problems

The Reportable New Information (RNI) Form will be submitted to the CTO Quality Assurance (QA) Office within 1 business day of becoming aware of the Unanticipated Problem. After review, the CTO QA Office will submit the RNI to the IRB.

When becoming aware of new information about an Unanticipated Problem, submit the updated information to the CTO QA Office with an updated Reportable New Information Form. The site Investigator or designated research personnel will report all unanticipated problems to the IRB in accordance with their local institutional guidelines.

17.11 FDA Reporting

When Roswell Park is the IND holder the following describes the FDA reporting requirements by timeline for AEs and new safety findings that meet the criteria outlined below:

Within 7 Calendar Days

Any adverse event that meets ALL the following criteria:

- Related or possibly related to the use of the study drug;
- Unexpected; and
- Fatal or life-threatening.

Within 15 Calendar Days

Any adverse event that meets ALL the following criteria:

- Related or possibly related to the use of the study drug;
- Unexpected; and
- Serious but not fatal or life-threatening;

Or, meets ANY of the following criteria:

- A previous adverse event that is not initially deemed reportable but is later found to fit the criteria for reporting (report within 15 days from when event was deemed reportable).
- Any findings from other studies, including epidemiological studies, pooled analysis of multiple studies, or other clinical studies conducted with the study drug that suggest a significant risk in humans exposed to the drug.
- Any findings from animal or in vitro testing that suggest a significant risk for human participants including reports of mutagenicity, teratogenicity, or carcinogenicity or reports of significant organ toxicity at or near the expected human exposure.

Roswell Park Protocol No.: I-501719

- Any clinically important increase in the rate of occurrence of a serious, related or possibly related adverse event over that listed in the protocol or investigator brochure.

Sponsors are also required to identify in IND safety reports, all previous reports concerning similar adverse events and to analyze the significance of the current event in the light of the previous reports.

Reporting Process

The principal investigator or designee will complete and submit a FDA Form 3500A MedWatch for any event that meets the above criteria. Forms will be submitted to the CTO QA Office via email to CTO-QA@RoswellPark.org.

18 DATA MANAGEMENT AND CONFIDENTIALITY

Full build studies are managed by Roswell Park CTO Data Management for analysis by Roswell Park Biostatisticians. All electronic case report form (eCRF) data are captured for these studies.

Data management activities are performed using a CTMS system that enables the collection, cleaning and viewing of clinical trial data. CTO data management designs the study-specific database and facilitates development by the Information Technology team. Once the database design is approved by the Investigator, Statistician, and Clinical Research Coordinator, the database is put into production and data entry can begin. Data can be entered and changed only by those with the rights to do so into the eCRFs.

18.1 Maintenance of Study Documents

Essential documents will be retained per Roswell Park's policy for 6 years from the study termination date. These documents could be retained for a longer period, however, if required by the applicable local regulatory requirements or by an agreement with Roswell Park.

18.2 Revisions to the Protocol

Roswell Park may make such changes to the protocol as it deems necessary for safety reasons or as may be required by the U.S. FDA or other regulatory agencies. Revisions will be submitted to the IRB/ERC for written approval before implementation.

18.3 Termination of the Study

It is agreed that, for reasonable cause, either the Roswell Park Investigators or the Sponsor, may terminate this study, provided a written notice is submitted within the time period provided for in the Clinical Trial Agreement. In addition, Roswell Park may terminate the study at any time upon immediate notice if it believes termination is necessary for the safety of participants enrolled in the study.

18.4 Confidentiality

Any data, specimens, forms, reports, video recordings, and other records that leave the site will be identified only by a participant identification number (Participant ID, PID) to maintain confidentiality. All records will be kept in a limited access environment. All computer entry and networking programs will be done using PIDs only. Information will not be released without written authorization of the participant.

Roswell Park Protocol No.: I-501719

19 STATISTICAL PLAN

19.1 Design

This is a multi-center, open-label, single-arm Phase II study of CPX-351 in younger patients (< 60 years old) with secondary acute myeloid leukemia. All statistical analyses will be performed by the Department of Biostatistics and Bioinformatics at Roswell Park.

19.2 Sample Size Determination

The sample size calculations are based on the primary analysis, which evaluates the complete response rate (morphologic CR and CRi). A Phase III trial of CPX-351 in older patients (60-75 years old) demonstrated a complete response rate of 47.7%. However, a recent multi-institutional retrospective study indicated a complete response rate of only 13% in younger patients. Therefore, if a prospective study can demonstrate that the true complete response rate is greater than 30% (mid-point between the Phase III and retrospective study), then that would be sufficient evidence to warrant further study of this treatment in younger patients. If the true complete response rate is 48% in younger patients, then the two-stage minimax design ($n_1=10$ and $n_2=26$) achieves 81.1% power at a significance level of 0.1.

Across all centers, we expect to enroll an average of 0.8 patients per month. Therefore, we expect accrual to be completed in 6 years.

19.3 Primary Analysis

The primary objective is to determine whether CPX-351 is effective in treating younger patients with secondary acute myeloid leukemia. The primary outcome is complete response (morphologic CR or CRi), which is treated as a dichotomous variable and will be summarized using frequencies and relative frequencies. A Phase III trial of CPX-351 in older patients (60-75 years old) demonstrated a complete response rate of 47.7%. However, a recent multi-institutional retrospective study indicated a complete response rate of only 13% in younger patients. Therefore, we will prospectively evaluate whether the true complete response rate in the younger population is greater than 30% (mid-point between the Phase III and retrospective study). We will test the following hypotheses using a two-stage minimax design:

$$H_0: \pi \leq 0.3 \text{ versus } H_A: \pi > 0.3,$$

where π is the true complete response rate for younger patients with secondary acute myeloid leukemia. In stage 1, $n_1=10$ patients will be enrolled. If $T_1=2$ or more complete responses are observed, then an additional $n_2=26$ patients will be enrolled in stage 2. Otherwise, the treatment will not be considered promising and the study will be terminated. In stage 2, if $T=15$ or more complete responses are observed in the total $n=36$ patients, then the treatment will be considered promising in younger patients; otherwise, the treatment will not be considered promising.

Additionally, an 90% confidence interval about the true complete response rate will be obtained using Jeffrey's prior method.

Patients will be considered eligible for inclusion in primary endpoint analysis if:

- 1) Subjects who underwent adequate attempt to achieve cytoreduction was made as defined above through the administration of up to 2 cycles of CPX-351 to achieve cellularity < 20%.

Roswell Park Protocol No.: I-501719

- 2) Subjects alive at timepoint for endpoint analysis (day +45).
- 3) Subjects compliant with study procedures.
- 4) Subjects without significant deviation from any 1 of the inclusion or exclusion criteria after enrollment.

19.4 Secondary Analysis

The secondary objectives are to evaluate CR+CRi duration, event-free survival (EFS), overall survival (OS), and successfully proceeding to allogenic hematopoietic cell transplant.

The time-to event outcomes (CR+CRi duration, EFS, and OS) will be summarized using standard Kaplan-Meier methods, where estimates of the median obtained with 90% confidence intervals. The CR+CRi duration is defined as the time from CR or CRi until relapse or last follow-up. EFS is defined as the time from treatment until disease progression/relapse, death due to disease, or last follow-up. OS is defined as the time from treatment until death due to any cause or last follow-up.

The allogenic hematopoietic cell transplant status will be summarized using frequencies and relative frequencies; with the transplant rate estimated using a 90% confidence interval obtained using Jeffrey's prior method.

19.5 Safety Analysis

All adverse events and toxicities will be reported by grade using frequencies and relative frequencies. Additionally, the study will be monitored by the Roswell Park Data Safety and Monitoring Committee (DSMC), who may make recommendations about study continuation and termination.

Potential Adverse Events

Cytopenias	Infection	Bleeding
Anemia	Febrile Neutropenia	Pulmonary Hemorrhage
Neutropenia	Bacteremia	GI Bleed
Thrombocytopenia	Sepsis	
	Pneumonia	

20 PROVISIONS TO MONITOR THE DATA TO ENSURE THE SAFETY OF SUBJECTS

The Roswell Park Data Safety Monitoring Committee will assess the progress of the study, the safety data, and critical efficacy endpoints (Phase I studies will be reviewed quarterly Phase II, III and pilot investigator-initiated studies will be reviewed semi-annually). The DSMC will review the study and will make recommendations that include but not limited to; (a) continuation of the study, (b) modifications to the design, (c) suspension of or, (d) termination of the study.

Roswell Park Protocol No.: I-501719

21 VULNERABLE POPULATIONS

N/A

22 COMMUNITY-BASED PARTICIPATORY RESEARCH

N/A

23 SHARING OF RESULTS WITH SUBJECTS

Individual response data is shared with the participant as a part of their clinical care.

24 SETTING

All research visits and procedures will take place at Roswell Park or a participating network site. Patients will be identified and recruited from the patient population followed by the Leukemia service team at Roswell Park or other participating network sites.

25 PROVISIONS TO PROTECT THE PRIVACY INTERESTS OF SUBJECTS

Any data, specimens, forms, reports, video recordings, and other records that leave the site will be identified only by a participant identification number (Participant ID, PID) to maintain confidentiality. All records will be kept in a limited access environment. All computer entry and networking programs will be done using PIDs only. Information will not be released without written authorization of the participant.

26 RESOURCES AVAILABLE

N/A

27 PRIOR APPROVALS

N/A

28 COMPENSATION FOR RESEARCH-RELATED INJURY

If the subject believes they have been injured as a direct result of their participation in this research study, they will be advised to notify the Roswell Park Patient Advocate at (716) 845-1365 or the Study Doctor at (716) 845-7110.

Medical diagnosis and treatment for the injury will be offered, and a determination will be made regarding appropriate billing for the diagnosis and treatment of the injury. A financial counselor (716-845-4782) will be able to provide an explanation of coverage and to answer questions the subject may have regarding study related billing.

The subject is not prevented from seeking to collect compensation for injury related to malpractice, fault, or blame on the part of those involved in the research.

29 ECONOMIC BURDEN TO SUBJECTS

The participants will not be subject to any economic burden.

Roswell Park Protocol No.: I-501719

30 CONSENT PROCESS

This study will not be initiated until the protocol and informed consent document(s) have been reviewed and approved by a properly constituted Institutional Review Board (IRB) or Independent Ethics Committee (IEC). Each participant shall read, understand, and sign an instrument of informed consent prior to performance of any study-specific procedure. It is the responsibility of the investigator to ensure that the participant is made aware of the investigational nature of the treatment and that informed consent is given.

The Investigator is responsible for the retention of the participant log and participant records; although personal information may be reviewed by authorized persons, that information will be treated as strictly confidential and will not be made publicly available. The investigator is also responsible for obtaining participant authorization to access medical records and other applicable study specific information according to Health Insurance Portability and Accountability Act regulations (where applicable).

This study will be conducted in compliance with all applicable laws and regulations of the state and/or country and institution where the participant is treated. The clinical trial should be conducted in accordance with the ethical principles embodied in the Belmont Report: Ethical Principles and Guidelines for the Protection of Human Subjects of Research, consistent with good clinical practice and the applicable regulatory requirements and according to the guidelines in this protocol, including attached appendices.

31 PROCESS TO DOCUMENT CONSENT IN WRITING

The Investigator (or IRB specified designee) is responsible for obtaining written consent from each participant in accordance with GCP guidelines using the approved informed consent form, before any study specific procedures (including screening procedures) are performed. The informed consent form acknowledges all information that must be given to the participant according to applicable GCP guidelines, including the purpose and nature of the study, the expected efficacy and possible side effects of the treatment(s), and specifying that refusal to participate will not influence further options for therapy. Any additional information that is applicable to the study must also be included. Additional national or institutionally mandated requirements for informed consent must also be adhered to. The participant should also be made aware that by signing the consent form, processing of sensitive clinical trial data and transfer to other countries for further processing is allowed.

The Investigator or designee shall provide a copy of the signed consent form to the participant and the signed original shall be maintained in the Investigator File. A copy of the signed consent form must be filed in the participant file. At any stage, the participant may withdraw from the study and such a decision will not affect any further treatment options.

32 DRUGS OR DEVICES

32.1 Daunorubicin/Cytarabine Liposomal Active Substance and Source

Each vial of daunorubicin/cytarabine liposomal contains 44 mg daunorubicin and 100 mg cytarabine.

Roswell Park Protocol No.: I-501719

32.1.1 Drug Shipment

Drug will not be supplied by the study.

32.1.2 Preparation

- Calculate the daunorubicin/cytarabine liposomal dose based on daunorubicin and individual patient's BSA.
- Calculate the number of vials of daunorubicin/cytarabine liposomal based on the daunorubicin dose.
- Remove the appropriate number of vials of daunorubicin/cytarabine liposomal from the refrigerator and equilibrate to the room temperature for 30 minutes.
- Then, reconstitute each vial with 19 mL of Sterile Water for Injection using a sterile syringe and immediately thereafter start a 5-minute timer.
- Carefully swirl the contents of the vial for 5 minutes while gently inverting the vial every 30 seconds.
- Do not heat, vortex, or shake vigorously.
- After reconstitution, let rest for 15 minutes.
- The reconstituted product should be an opaque, purple, homogeneous dispersion, essentially free from visible particulates. After reconstitution (but before final dilution), each mL will contain 2.2 mg of daunorubicin and 5 mg of cytarabine.
- Gently invert each vial 5 times prior to withdrawing the reconstituted product for further dilution. If the reconstituted product is not diluted into an infusion bag immediately, store in refrigerator at 2°C to 8°C for up to 4 hours.
- Calculate the volume of reconstituted daunorubicin/cytarabine liposomal required using the following formula: $[\text{volume required (mL)} = \text{dose of daunorubicin (mg/m}^2\text{)} \times \text{patient's BSA (m}^2\text{)} \div 2.2 \text{ (mg/mL)}]$.
- Aseptically withdraw the calculated volume of the reconstituted product from the vial(s) with a sterile syringe and transfer it to an infusion bag containing 500 mL of 0.9% Sodium Chloride Injection, USP or 5% Dextrose Injection, USP. There may be residual product remaining in the vial. Discard unused portion.
- Gently invert the bag to mix the solution. The dilution of the reconstituted product results in a deep purple, translucent, homogeneous dispersion, free from visible particulates.
- If the diluted infusion solution is not used immediately, store in refrigerator at 2°C to 8°C for up to 4 hours.
- Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit. Only solutions without visible particles should be used.

Roswell Park Protocol No.: I-501719

32.1.3 Storage and Stability

Unreconstituted daunorubicin/cytarabine liposomal vials will be stored in a refrigerator at 2°C to 8°C (36°F to 46°F) in an upright position. The vial should be stored in its original carton to protect from light.

Drug storage temperature will be maintained and recorded, as applicable.

33 REFERENCES

1. Cheson BD, Bennett JM, Kopecky KJ, Buchner T, Willman CL, Estey EH, Schiffer CA, Doehner H, Tallman MS, Lister TA, Lo-Coco F, Willemze R, Biondi A, Hiddemann W, Larson RA, Lowenberg B, Sanz MA, Head DR, Ohno R, Bloomfield CD, International Working Group for Diagnosis SoRCTO, Reporting Standards for Therapeutic Trials in Acute Myeloid L. Revised recommendations of the International Working Group for Diagnosis, Standardization of Response Criteria, Treatment Outcomes, and Reporting Standards for Therapeutic Trials in Acute Myeloid Leukemia. *J Clin Oncol.* 2003;21(24):4642-9. doi: 10.1200/JCO.2003.04.036. PubMed PMID: 14673054.
2. Hulegardh E, Nilsson C, Lazarevic V, Garelius H, Antunovic P, Rangert Derolf A, Mollgard L, Uggla B, Wennstrom L, Wahlin A, Hoglund M, Juliusson G, Stockelberg D, Lehmann S. Characterization and prognostic features of secondary acute myeloid leukemia in a population-based setting: a report from the Swedish Acute Leukemia Registry. *Am J Hematol.* 2015;90(3):208-14. doi: 10.1002/ajh.23908. PubMed PMID: 25421221.
3. Wang ES. Treating acute myeloid leukemia in older adults. *Hematology Am Soc Hematol Educ Program.* 2014;2014(1):14-20. doi: 10.1182/asheducation-2014.1.14. PubMed PMID: 25696830.
4. Mayer LD, Harasym TO, Tardi PG, Harasym NL, Shew CR, Johnstone SA, Ramsay EC, Bally MB, Janoff AS. Ratiometric dosing of anticancer drug combinations: controlling drug ratios after systemic administration regulates therapeutic activity in tumor-bearing mice. *Mol Cancer Ther.* 2006;5(7):1854-63. doi: 10.1158/1535-7163.MCT-06-0118. PubMed PMID: 16891472.
5. Kim HP, Gerhard B, Harasym TO, Mayer LD, Hogge DE. Liposomal encapsulation of a synergistic molar ratio of cytarabine and daunorubicin enhances selective toxicity for acute myeloid leukemia progenitors as compared to analogous normal hematopoietic cells. *Exp Hematol.* 2011;39(7):741-50. doi: 10.1016/j.exphem.2011.04.001. PubMed PMID: 21530609.
6. Lim WS, Tardi PG, Dos Santos N, Xie X, Fan M, Liboiron BD, Huang X, Harasym TO, Bermudes D, Mayer LD. Leukemia-selective uptake and cytotoxicity of CPX-351, a synergistic fixed-ratio cytarabine:daunorubicin formulation, in bone marrow xenografts. *Leuk Res.* 2010;34(9):1214-23. doi: 10.1016/j.leukres.2010.01.015. PubMed PMID: 20138667.
7. Tardi P, Johnstone S, Harasym N, Xie S, Harasym T, Zisman N, Harvie P, Bermudes D, Mayer L. In vivo maintenance of synergistic cytarabine:daunorubicin ratios greatly enhances therapeutic efficacy. *Leuk Res.* 2009;33(1):129-39. doi: 10.1016/j.leukres.2008.06.028. PubMed PMID: 18676016.
8. Feldman EJ, Lancet JE, Kolitz JE, Ritchie EK, Roboz GJ, List AF, Allen SL, Asatiani E, Mayer LD, Swenson C, Louie AC. First-in-man study of CPX-351: a liposomal carrier containing cytarabine and daunorubicin in a fixed 5:1 molar ratio for the treatment of relapsed and refractory acute myeloid leukemia. *J Clin Oncol.* 2011;29(8):979-85. doi: 10.1200/JCO.2010.30.5961. PubMed PMID: 21282541; PMCID: PMC4520927.

Roswell Park Protocol No.: I-501719

9. Lancet JE, Cortes JE, Hogge DE, Tallman MS, Kovacsovics TJ, Damon LE, Komrokji R, Solomon SR, Kolitz JE, Cooper M, Yeager AM, Louie AC, Feldman EJ. Phase 2 trial of CPX-351, a fixed 5:1 molar ratio of cytarabine/daunorubicin, vs cytarabine/daunorubicin in older adults with untreated AML. *Blood*. 2014;123(21):3239-46. doi: 10.1182/blood-2013-12-540971. PubMed PMID: 24687088; PMCID: PMC4624448.
10. Lancet JE, Uy GL, Cortes JE, Newell LF, Lin TL, Ritchie EK, Stuart RK, Strickland SA, Hogge D, Solomon SR, Stone RM, Bixby DL, Kolitz JE, Schiller GJ, Wieduwilt MJ, Ryan DH, Hoering A, Banerjee K, Chiarella M, Louie AC, Medeiros BC. CPX-351 (cytarabine and daunorubicin) Liposome for Injection Versus Conventional Cytarabine Plus Daunorubicin in Older Patients With Newly Diagnosed Secondary Acute Myeloid Leukemia. *J Clin Oncol*. 2018;36(26):2684-92. doi: 10.1200/JCO.2017.77.6112. PubMed PMID: 30024784; PMCID: PMC6127025.
11. Przepolewski AT, C.; Vachhani, P.; Sanikommu, S.R.; Thota, S.; Baron, J.; Griffiths, E.A.; Thompson, J.E.; Sweet, K.L.; Wang, E.S. Safety and Efficacy of Liposomal Cytarabine/Daunorubicin (CPX-351) in Younger Patients < 60 Years Old with Secondary Acute Myeloid Leukemia. American Society of Hematology Annual Meeting; San Diego, CA: *Blood*; 2018. p. 2677.

Roswell Park Protocol No.: I-501719

34 APPENDICES/ SUPPLEMENTS

Appendix A	ECOG Performance Status Scores	34
Appendix B	INVESTIGATOR STUDY ELIGIBILITY VERIFICATION FORM INCLUSION CRITERIA	35
Appendix C	INVESTIGATOR STUDY ELIGIBILITY VERIFICATION FORM EXCLUSION CRITERIA	36
Appendix D	Instructions for Multi-Site (External) Studies	37
Appendix E	Schedule of Procedures and Observations	39
Appendix F	Instructions for AML Response criteria	42

Roswell Park Protocol No.: I-501719

Appendix A ECOG Performance Status Scores

Description	Status
Fully active, able to carry on all pre-disease performance without restriction.	0
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.	1
Ambulatory and capable of all self-care but unable to carry out any work activities.	2
Capable of only limited self-care, confined to bed or chair more than 50% of waking hours.	3
Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair.	4
Dead	5

Roswell Park Protocol No.: I-501719

Appendix B INVESTIGATOR STUDY ELIGIBILITY VERIFICATION FORM INCLUSION CRITERIA

Participant Name: (Multi-site: use participant initials): _____

Medical Record No.: (Multi-site: use participant ID): _____

Title: A Phase II Study of CPX-351 in Younger Patients < 60 Years Old with Secondary Acute Myeloid Leukemia

INCLUSION CRITERIA				
Yes	No	N/A	All answers must be "Yes" or "N/A" for participant enrollment.	Date
☐	☐	☐	1. Aged 18-59.	
☐	☐	☐	2. Newly diagnosed: - Therapy-related AML - AML with antecedent MDS or CMML - AML with MDS-related changes (as per WHO)	
☐	☐	☐	3. Have an ECOG Performance Status of ≤ 2 . Refer to Appendix A .	
☐	☐	☐	4. Have the following clinical laboratory values: - Plasma creatinine ≤ 1.5 x UNL - Total bilirubin < 2.0 mg/dL - Serum alanine aminotransferase and aspartate aminotransferase < 3 x ULN	
☐	☐	☐	5. Left ventricular ejection fraction by echocardiogram or multiple-gated acquisition $\geq 50\%$	
☐	☐	☐	6. Participants of child-bearing potential must agree to use adequate contraceptive methods (e.g., hormonal or barrier method of birth control; abstinence) prior to study entry. Should a woman become pregnant or suspect she is pregnant while she or her partner is participating in this study, she should inform her treating physician immediately.	
☐	☐	☐	7. Women of childbearing potential must have a negative serum or urine pregnancy test within 72 hours prior to enrollment and commit to two methods of birth control.	
☐	☐	☐	8. Men must use a latex condom during any sexual contact with women of childbearing potential.	
☐	☐	☐	9. Willing to adhere to protocol specific requirements.	
☐	☐	☐	10. Participant must understand the investigational nature of this study and sign an Independent Ethics Committee/Institutional Review Board approved written informed consent form prior to receiving any study related procedure.	

Investigator Signature: _____ **Date:** _____

Printed Name of Investigator: _____

Roswell Park Protocol No.: I-501719

Appendix C INVESTIGATOR STUDY ELIGIBILITY VERIFICATION FORM EXCLUSION CRITERIA

Participant Name: (Multi-site: use participant initials): _____

Medical Record No.: (Multi-site: use participant ID): _____

Title: A Phase II Study of CPX-351 in Younger Patients < 60 Years Old with Secondary Acute Myeloid Leukemia

EXCLUSION CRITERIA				
Yes	No	N/A	All answers must be "No" or "N/A" for participant enrollment.	Date
☐	☐	☐	1. Prior treatment of AML.	
☐	☐	☐	2. Known clinically active CNS leukemia.	
☐	☐	☐	3. Core-binding factor leukemia.	
☐	☐	☐	4. Acute promyelocytic leukemia.	
☐	☐	☐	5. Uncontrolled other malignancy.	
☐	☐	☐	6. Prior anthracycline exposure > 368mg/m ² of daunorubicin or equivalent.	
☐	☐	☐	7. Cardiovascular disease resulting in heart failure (New York Heart Association Class III or IV), unstable angina (angina symptoms at rest), or new onset angina (began within the last 3 months) or myocardial infarction within the past 6 months.	
☐	☐	☐	8. Hypersensitivity to cytarabine, daunorubicin, or liposomal drugs.	
☐	☐	☐	9. Known active HIV infection.	
☐	☐	☐	10. Known history of active hepatitis B or C infection.	
☐	☐	☐	11. Pre-existing liver disease (e.g. cirrhosis, chronic hepatitis B or C, nonalcoholic steatohepatitis, sclerosing cholangitis).	
☐	☐	☐	12. Evidence of ongoing, uncontrolled systemic infection.	
☐	☐	☐	13. Pregnant or breastfeeding women.	
☐	☐	☐	14. Subject with concurrent severe and/or uncontrolled medical or psychiatric conditions that in the opinion of the investigator may impair the participation in the study or the evaluation of safety and/or efficacy.	
☐	☐	☐	15. History of Wilson disease or other copper-handling disorders.	
☐	☐	☐	16. Any condition which in the Investigator's opinion deems the participant an unsuitable candidate to receive study drug.	

Participant meets all entry criteria: ☐ Yes ☐ No

If "NO", do not enroll participant in study.

Investigator Signature: _____ **Date:** _____

Printed Name of Investigator: _____

Roswell Park Protocol No.: I-501719

Appendix D Instructions for Multi-Site (External) Studies

1. CONTACT INFORMATION

All questions related to the protocol or study implementation should be directed to:

Roswell Park Cancer Institute
CTO Quality Assurance (QA) Office
CTO-QA@RoswellPark.org
Elm and Carlton Streets
Buffalo, New York 14263

Telephone:

Monday - Friday; 8: 00 AM to 4: 00 PM EST
716-845-3870

After hours, weekends, and holidays request the Roswell Park Investigator
716-845-2300

2. INFORMED CONSENT

- Informed consent must be obtained by the **site Investigator/designee** from any participants wishing to participate, **prior to any procedures or treatment**.
- An informed consent template is provided by Roswell Park and can be amended to reflect institutional requirements.
- All consent changes **must** be reviewed by Roswell Park CTO QA Office prior to submission to the site IRB.
- The informed consent must be IRB approved.
- Always check that the most up to date version of the IRB approved consent is being used.
- Within 5 business days, notify the Roswell Park CTO QA Office of all participant withdrawals or consent to limited study participation and appropriately document the discontinuation and the reason(s) why.

3. PARTICIPANT REGISTRATION

The participant completes the Gender, Race, and Ethnicity Form and this is placed in the study binder.

Roswell Park does not grant exceptions to eligibility criteria.

Phase 2 Protocol Registration Instructions

The Subject Screening and Enrollment Log must be emailed to the Roswell Park CTO QA Office (CTO-QA@RoswellPark.org) within 1 business day of the date the participant is consented. Once the Investigator has determined that eligibility has been met, complete the eligibility check list and email it to the Roswell Park QA Coordinator at CTO-QA@RoswellPark.org.

4. STUDY DEVIATIONS

- If a deviation has occurred to eliminate hazard, this must be reported to the Roswell Park Network, site IRB and any other regulatory authority involved in the study.
- ALL study deviations will be recorded on the **Study Deviation Log**.

Roswell Park Protocol No.: I-501719

- Participants inadvertently enrolled with significant deviation(s) from the study-specified criteria will be removed from the study, at the discretion of the Principal Investigator.

5. **STUDY DOCUMENTATION**

- Study documents must be filled out completely and correctly. Ditto marks are not allowed.
- If an entry has been documented in error put a single line through the entry and initial and date the change. The Roswell Park CTO QA Coordinator must be able to read what has been deleted.
- Do **NOT** use white-out, magic marker, scratch-outs.
- Do **NOT** erase entries.
- Use only black ink for documentation on the accountability form and any other study forms.
- It is the responsibility of Roswell Park to inform the Investigator/ institution as to when these documents no longer need to be retained. If, for any reason, the Investigator desires to no longer maintain the study records, they may be transferred to another institution, another investigator, or to Roswell Park upon written agreement between the Investigator and Roswell Park.

6. **SERIOUS ADVERSE EVENT REPORTING**

The site Investigator or designated research personnel will report all SAEs, whether related or unrelated to the investigational agent(s) to the **IRB in accordance with their local institutional guidelines**. The site will notify the Roswell Park CTO QA Coordinator within 1 business day of being made aware of the SAE to SafetyEventReporting@roswellpark.org. A preliminary written report must follow within 1 business day of the first notification using the following forms:

- Roswell Park SAE Source form
- MedWatch 3500A or AdEERs.

A complete follow-up report must be sent to the Roswell Park CTO QA Coordinator when new information becomes available.

7. **UNANTICIPATED PROBLEM REPORTING**

An unanticipated problem (UP) is any incident, experience, or outcome that meets all of the criteria in **Section 17.10**.

For all adverse events occurring that are unanticipated and related or possibly related to the research drug, biologic or intervention, the participating physician or delegated research staff from each site will notify their local **IRB in accordance with their local institutional guidelines**. The site must also notify the Roswell Park CTO QA Coordinator within 1 business day of being made aware of the Unanticipated Problem by completing the **Roswell Park Unanticipated Problem Report Form** and emailing it to the Roswell Park CTO QA Coordinator.

Appendix E Schedule of Procedures and Observations

Time point	Screening ¹	Induction					Re-Induction (If required)			Consolidation Cycles			End of Treatment (± 3 days)	Follow-Up ²	Long Term Follow-Up ³
Day of cycle	1	1	3	5	14-21	28-45*	1	3	28-45	1	3	28-45	N/A	N/A	N/A
Pre-Existing Conditions ¹⁰	X														
Concomitant Medications	X ⁸	X			X		X		X	X		X	X	X	
Adverse Events	X	X			X		X		X	X		X	X	X	X
Clinical Procedures															
Medical History	X ¹⁰														
Physical Examination	X	X			X		X		X	X		X	X		
Vital signs ⁴	X	X			X		X		X	X		X	X		
Height/Weight ⁹	X														
ECOG Performance Status	X	X			X		X		X	X		X	X		
Disease Status															X
Survival Status															X
BMT Status															X
Laboratory Procedures															
Hematology ⁵	X	X			X		X		X	X		X	X		
Chemistry ⁶	X	X			X		X		X	X		X	X		
Pregnancy Test (Urine or Serum) ⁷	X														

Time point	Screening ¹	Induction					Re-Induction (If required)			Consolidation Cycles			End of Treatment (± 3 days)	Follow-Up ²	Long Term Follow-Up ³
Day of cycle	1	1	3	5	14-21	28-45*	1	3	28-45	1	3	28-45	N/A	N/A	N/A
Urinalysis	X														
Bone Marrow Biopsy and Aspirate	X				X				X				X		
Imaging Procedures															
ECG/EKG	X						X		X			X			
Chest X-ray or CT Chest	X														
Cardiac Assessment (ECHO, MUGA)	X					X**	X		X			X			
Treatment/Drug Administration															
CPX-351		X	X	X			X	X		X	X				

Time point	Screening ¹	Induction					Re-Induction (If required)			Consolidation Cycles			End of Treatment (± 3 days)	Follow-Up ²	Long Term Follow-Up ³
Day of cycle	1	1	3	5	14-21	28-45*	1	3	28-45	1	3	28-45	N/A	N/A	N/A

Footnotes:

1. Performed within 4 weeks prior to treatment start.
2. Follow-up safety evaluations will occur 30 days (± 3 days) after last dose of study drug or until resolution of any drug related toxicity (telephone contact is acceptable).
3. Participants are monitored for 1 year (± 2 months) for disease, survival status, bone marrow transplant status (including the 30-day follow-up visit) for up to 5 years following last dose of study drug every 3 months. Telephone contact is acceptable.
4. Vital signs: temperature, heart rate, respiratory rate, blood pressure.
5. Hematology [(i.e., complete blood count (CBC) with manual differentials)]: WBC, RBC, HGB, HCT, platelet, MCV, MCH, MCHC, % neutrophils, absolute neutrophils, % monocytes, absolute monocytes, % eosinophils, absolute eosinophils, % basophils, absolute basophils, % absolute lymphocyte, platelet confirmation (as clinically indicated), and differential confirmation (as clinically indicated). Note: Participants experiencing Grade 4 neutropenia should be monitored according to institutional guidelines. As needed at each study visit as determined by the Investigator or study physician.
6. Chemistry (i.e., complete metabolic panel (CMP): chloride, CO₂, potassium, sodium, BUN, glucose, calcium, creatinine, total protein, albumin, total bilirubin, alkaline phosphatase, AST, ALT, A/G ratio, BUN/creatinine ratio, osmol (Calc), anion gap).
7. Pregnancy test to be performed within 3 days of starting treatment.
8. Medications ongoing, or discontinued, within 1 week prior to first dose of study drug.
9. Height collected at baseline only.
10. Baseline signs and symptoms with an onset between the time subject signs consent and first dose of drug.

* This column only applies if patient undergoes one induction, not applicable if patient requires re-induction

** To be performed following last dose of Induction or Re-Induction

Appendix F Instructions for AML Response criteria

Response category	Definition
Complete remission (CR)	Bone marrow blasts < 5%; absence of blasts with Auer rods; absence of extramedullary disease; absolute neutrophil count > $1.0 \times 10^9/L$ ($1000/\mu L$); platelet count > $100 \times 10^9/L$ ($100\,000/\mu L$); independence of red cell transfusions
CR with incomplete recovery (CRi)	All CR criteria except for residual neutropenia (< $1.0 \times 10^9/L$ [$1000/\mu L$]) or thrombocytopenia (< $100 \times 10^9/L$ [$100\,000/\mu L$])
Morphologic leukemia-free state	Bone marrow blasts < 5%; absence of blasts with Auer rods; absence of extramedullary disease; no hematologic recovery required
Partial remission (PR)	Relevant in the setting of Phase 1 and 2 clinical trials only; all hematologic criteria of CR; decrease of bone marrow blast percentage to 5% to 25%; and decrease of pretreatment bone marrow blast percentage by at least 50%
Cytogenetic CR (CRc)	Reversion to a normal karyotype at the time of morphologic CR (or CRi) in cases with an abnormal karyotype at the time of diagnosis; based on the evaluation of 20 metaphase cells from bone marrow
Molecular CR (CRm)	No standard definition; depends on molecular target
Hematologic improvement	Response criteria (responses must last at least 8 wk.)
Erythroid response (pretreatment, < 11 g/dL)	Hgb increase by ≥ 1.5 g/dL, Relevant reduction of units of RBC transfusions by an absolute number of at least 4 RBC transfusions/8 wk. compared with the pretreatment transfusion number in the previous 8 wk. Only RBC transfusions given for a Hgb of ≤ 9.0 g/dL pretreatment will count in the RBC transfusion response evaluation
Platelet response (pretreatment, < $100 \times 10^9/L$)	Absolute increase of $\geq 30 \times 10^9/L$ for patients starting with > $20 \times 10^9/L$ platelets, Increase from < $20 \times 10^9/L$ to > $20 \times 10^9/L$ and by at least 100%†
Neutrophil response (pretreatment, < $1.0 \times 10^9/L$)	At least 100% increase and an absolute increase > $0.5 \times 10^9/L$
Progression or relapse after HI‡	At least 1 of the following: At least 50% decrement from maximum response levels in granulocytes or platelets Reduction in Hgb by ≥ 1.5 g/dL Transfusion dependence