| | |
|---|---|
| **Official Title** | Randomized Phase 2 Trial of CPX-351 (Vyxeos) vs. CLAG-M (Cladribine,Cytarabine, G-CSF, and Mitoxantrone) in Medically Less-Fit Adults with Acute Myeloid Leukemia (AML) or Other High-Grade Myeloid Neoplasm |
| **NCT Number** | NCT04195945 |
| **Document Type** | Protocol and Statistical Analysis Plan |
| **Document Date** | 10/18/2023 |

**FRED HUTCHINSON CANCER CENTER**
**UNIVERSITY OF WASHINGTON SCHOOL OF MEDICINE**

Current version: 09/16/2022
Previous version: 07/30/2020

# Randomized Phase 2 Trial of CPX-351 (Vyxeos™) vs. CLAG-M (Cladribine, Cytarabine, G-CSF, and Mitoxantrone) in Medically Less-Fit Adults with Acute Myeloid Leukemia (AML) or Other High-Grade Myeloid Neoplasm

**Principal Investigator:**

- Roland B. Walter, MD PhD MS: Professor, Fred Hutch; Professor, UW (pager: 206-560-0657; Email: rwalter@fredhutch.org)

**Co-Investigators:**

- Anna B. Halpern, MD: Assistant Professor, Fred Hutch; Assistant Professor, UW (phone: 206-606-1978)

**Biostatistician:**

- Megan Othus, PhD: Professor, Fred Hutch (phone: 206-667-5749).

**Study Coordinator:**

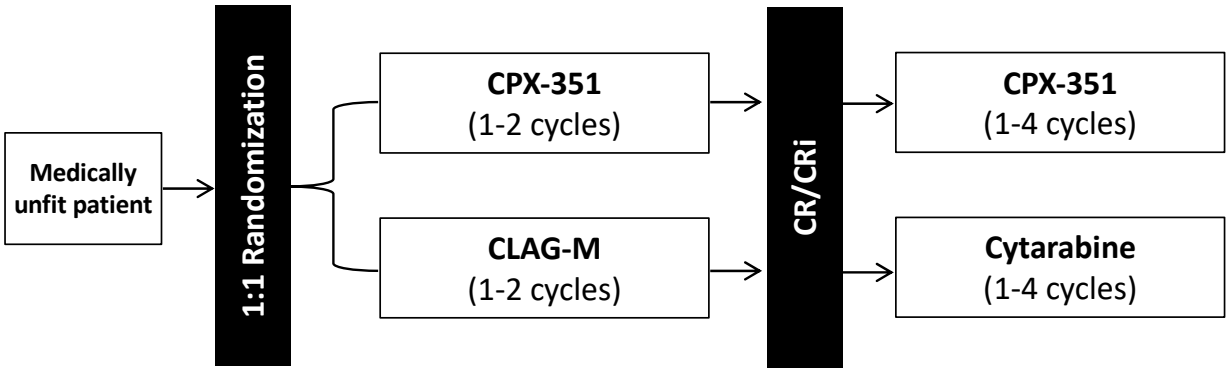
- Nicole Stinnett (phone: 206-667-5226; Fax: 206-667-1113; Email: nstinnet@fredhutch.org)

**Regulatory Coordinator:**

- Judy Allen (phone: 206-667-6840; Email: jaallen@fredhutch.org)

**Emergency Phone (24 hours):**
Call the paging operator at the University of Washington Medical Center at 206-598-6190 and ask for the Fellow on call for Hematology/Oncology.

## TREATMENT SCHEME



# TABLE OF CONTENTS

# 1.0 BACKGROUND AND RATIONALE

## 1.1 Trial synopsis

The need for new therapies in medically less-fit adults with acute myeloid leukemia (AML) is unquestioned.[1,2] Increasing evidence indicates the vast majority of such individuals may derive greater benefit from intensive than non-intensive therapy.[3-6] However, which intensive therapy provides optimal treatment outcomes with regard to quality of life (QOL) and survival is unknown. One candidate regimen is CPX-351 (Vyxeos™), a liposomal formulation of daunorubicin and cytarabine that was found to be superior to 7+3 in medically fit older adults with secondary AML in a large, randomized multicenter trial.[7] Another candidate regimen is CLAG-M (cladribine, high-dose cytarabine, G-CSF, and mitoxantrone) with escalated doses of mitoxantrone – a regimen we developed at our institution and found superior to 7+3 in non-randomized comparisons in medically fit adults with AML.[8,9] Here, we propose to evaluate two single-arm Phase 2 trials in one protocol in adults ≥18 years with newly-diagnosed AML or analogous high-grade myeloid neoplasms (≥10% blasts in either peripheral blood and/or bone marrow) that are medically less-fit, as defined by a treatment-related mortality (TRM) score of ≥13.1. Derived from a validated, multivariate model composed of weighted information from 8 covariates (age, performance status, white blood cell count, peripheral blood blast percentage, type of AML [de novo vs. secondary], platelet count, albumin, and serum creatinine), this score corresponds to a ≥10-15% 28-day mortality with intensive chemotherapy.[10] Patients will be randomized 1:1 to one of two arms: CPX-351 (given at the doses [daunorubicin 44 mg/m$^2$, cytarabine 100 mg/m$^2$] used in the randomized Phase 3 trial in older medically-fit adults with AML that led to the drug's approval in 2017[7]) and CLAG-M (given at the doses used in fit adults with AML), provided both arms are open to accrual at the time. If only one arm is open, patients will be assigned to the open arm. Using 3-month overall survival (OS) as the primary endpoint, each experimental arm will be compared to historic data from an institutional trial with CPX-351 given at an attenuated dose (daunorubicin 14 mg/m$^2$, cytarabine 32 mg/m$^2$) in this patient population. Each arm will have a two-stage design with 15 patients in each stage, for a total accrual of up to 60 patients. Secondary endpoints are related to the collection of other treatment efficacy data and information on medical resource utilization as well as quality of life (QOL; using established questionnaires as well as a newly-developed AML-specific questionnaire) and will be used to inform the design of a subsequent, larger trial.

## 1.2 Scientific basis/rationale

Over the last 4 decades, outcomes for medically less-fit adults with AML – individuals who are typically, but not invariably, older – have not substantially improved and most still die from treatment-related toxicities or therapeutic resistance.[1,2] The need for new approaches for these patients is therefore unquestioned. Increasing evidence from population-based registries and institutional experiences support the use of intensive chemotherapy rather than low-intensity therapy (or no therapy) in most patients up to age 80 even with comorbidities.[3-6] Consistent with this notion, we found unsatisfactory efficacy in an institutional randomized study (FH #2642, NCT01804101) with attenuated doses of CPX-351 at 32 or 64 units/m$^2$ per dose in this patient population (equivalent to daunorubicin 14 mg/m$^2$/cytarabine 32 mg/m$^2$ or daunorubicin 28 mg/m$^2$/cytarabine 64 mg/m$^2$) in adults with newly diagnosed AML who were medically less-fit, as defined by a treatment-related mortality (TRM) score of ≥13.1, a score corresponding to a ≥10-15% 28-day mortality with intensive chemotherapy.[10]

Two intensive regimens of potential interest in less-fit adults with AML are standard-dose CPX-351 and CLAG-M. The interest in CPX-351 is based on findings from a randomized Phase 3 trial, in which CPX-351 was demonstrated to have superior response rates and survival compared to 7+3 in fit adults ≥60 years with secondary AML.[7] The observation that early death rates were lower with CPX-351 than 7+3 suggests this regimen may be useful in less-fit individuals as well. The interest in CLAG-M is based on our institutional data using this regimen in fit adults with newly-diagnosed AML. Since 2014, our institution has treated >200 newly-diagnosed AML patient with CLAG-M, and in multivariable comparison of our newly-diagnosed study cohort to a similar cohort treated with 7+3, we found superior rates of $MRD^{neg}$ CR and CR/CR with incomplete hematologic recovery (CR/CRi).[8,9] Furthermore, we found high response rates even in those aged >65 years, those with adverse risk cytogenetics and those with secondary disease. In an ongoing institutional trial (FH #9759, NCT03012672), we are comparing full-dose CLAG-M to reduced-dose CLAG-M in less-fit AML patients with a TRM score of ≥13.1. Within the limitations of a small sample size, preliminary analyses from this ongoing trial indicate that both regimen intensities are equally tolerated with similar early death rates while remission rates may be slightly higher with full-dose CLAG-M, arguing for further testing of full-dose CLAG-M in medially less-fit adults with AML.

### 1.3 Hypothesis to be tested in this randomized trial

The proposed trial was designed to test the idea that CPX-351 and CLAG-M given at doses used typically for medically-fit adults with AML will both lead to better outcomes (overall survival and $MRD^{neg}$ complete remission [CR] rates) than attenuated doses of CPX-351 in less-fit adults with AML. While our trial will not be powered to compare CPX-351 and CLAG-M directly, we also hypothesize patients who receive CPX-351 will have better quality of life and less healthcare resource utilization than those who receive GCLAM and will experience similar rates of $MRD^{neg}$ CRs, 60-day mortality, and event-free survival.

## 2.0 OBJECTIVES

### 2.1 Primary objectives

**2.1.1** To evaluate whether CPX-351 or CLAG-M, at doses typically used for medically-fit adults with AML, improve 3-month overall survival in medically-unfit adults with AML compared to attenuated dose CPX-351 as used in our previous institutional trial (32 units/$m^2$ per dose).

### 2.2 Secondary objectives

**2.2.1** To compare CR rates, $MRD^{neg}$ CR rates, response duration, and RFS between the study arms.

**2.2.2** To describe the toxicity profile and infectious complications of each study treatment as well as 30- and 60-day mortality rate.

**2.2.3** To evaluate the impact of treatment on quality of life (QOL) for patients undergoing the two therapies.

**2.2.4** To describe the impact of each study treatment on medical resource utilization.

# 3.0 PATIENT ELIGIBILITY

## 3.1 Inclusion criteria

**3.1.1** Age ≥18 years.

**3.1.2** Diagnosis of untreated "high-grade" myeloid neoplasm (≥10% blasts in blood or bone marrow) or AML other than acute promyelocytic leukemia (APL) with t(15;17)(q22;q12) or variants according to the 2016 WHO classification.[11] Outside diagnostic material is acceptable to establish diagnosis; submission of peripheral blood specimen for flow cytometry performed at the study institution should be considered. Diagnostic material must have been submitted for cytogenetic and/or molecular testing as clinically appropriate.

**3.1.3** Treatment-related mortality (TRM) score ≥13.1 as calculated with simplified model (see **Appendix A**).[10]

**3.1.4** The use of hydroxyurea before enrollment is permitted; hydroxyurea should be discontinued prior to start of study treatment. Patients with symptoms/signs of hyperleukocytosis or WBC >100,000/μL or with concern for other complications of high tumor burden or leukostasis (e.g., hypoxia, disseminated intravascular coagulation) can be treated with leukapheresis or may receive up to 2 doses of cytarabine (up to 500 mg/m$^2$ each) any time prior to enrollment.

**3.1.5** Patients may have received low-intensity treatment (e.g., azacitidine/decitabine, lenalidomide, growth factors) for antecedent low-grade myeloid neoplasm (i.e. <10% blasts in blood and bone marrow).

**3.1.6** Adequate organ function.

**3.1.6.1** Bilirubin <2.0 mg/mL unless elevation is thought to be due to hepatic infiltration by neoplastic cells, Gilbert's syndrome, or hemolysis (assessed within 14 days prior to study day 0).

**3.1.6.2** Left ventricular ejection fraction (LVEF) ≥45%, assessed within 12 months prior to registration, e.g., by MUGA scan or echocardiography or another appropriate diagnostic modality.

**3.1.7** Women of childbearing potential and men must agree to use adequate contraception beginning at the signing of the consent until at least 4 weeks after the last dose of study drug.

**3.1.8** Ability to understand and the willingness to sign a written informed consent document.

## 3.2 Exclusion criteria

**3.2.1** Myeloid blast crisis of chronic myeloid leukemia (CML), unless patient is not considered candidate for tyrosine kinase inhibitor treatment.

**3.2.2** Concomitant illness associated with a likely survival of <1 year.

**3.2.3** Active systemic fungal, bacterial, viral, or other infection, unless disease is under treatment with anti-microbials and/or controlled or stable. Patients with fever thought to be likely secondary to leukemia are eligible.

**3.2.4** Known hypersensitivity to any study drug used in this trial.

**3.2.5** Pregnancy or active breast feeding.

**3.2.6** Concurrent treatment with any other approved or investigational anti-leukemia agent. Treatment with a FLT3-inhibitor for FLT3-mutated AML is permissible as described in section 6.0.

# 4.0 EVALUATION AND COUNSELING OF PATIENT

The patient will be completely evaluated with a history, physical examination, diagnostic testing if necessary, and review of outside slides and records if available. The protocol will be discussed thoroughly with the patient and family (if present), with description of all known risks to the patient. Alternative forms of treatment will be presented objectively, and the risks and hazards of the study explained to the patient. Consent will be obtained using forms approved by the local IRB.

# 5.0 PROTOCOL REGISTRATION

To register, the provider(s) involved in the care of the potential study participant must contact a Study Investigator or the Study Coordinator and fax the Research Subject Registration Form (**Appendix B**) to the study team (FAX: +1-206-667-1113). For registration, a completed Research Subject Registration Form including completed eligibility checklist (**Appendix B**), a copy of the signed consent form, and a signed HIPAA authorization must be available, and all eligibility requirements according to section 3.0 must be met. To complete the registration process, the Principal Investigator or his designee will assign a patient study number and register the patient on the study.

# 6.0 TREATMENT PLAN

This study is a single-institution, randomized, non-blinded trial in which eligible patients will be randomized in a 1:1 ratio to receive either CPX-351 or CLAG-M for induction therapy. If a response other than an $MRD^{neg}$ CR is achieved, the patient will receive re-induction with either CPX-351 or CLAG-M at the same dosing. Patients who achieve a CR/CRi with up to 2 courses of therapy can receive post-remission therapy with either CPX-351 at a reduced dose or intermediate-dose cytarabine for up to 4 additional treatment cycles, for a total of up to 6 courses of therapy. All patients will be assessed for treatment response/outcome, quality of life, and healthcare resource utilization. The treatment plan is depicted on page 2.

## 6.1 Baseline/Pre-Treatment Assessment

The following procedures should be obtained at baseline before initiation of study therapy to establish trial eligibility and allow patient characterization and disease prognostication. Results of tests and/or procedures conducted as per standard of care may be used to determine study eligibility if conducted within an appropriate window prior to screening. Outside testing and previously collected clinical data may be used if within the appropriate time frame.

**6.1.1** History and physical examination (assessed within 14 days prior to study day 0).

**6.1.2** Bone marrow examination with morphologic and flow cytometric assessment, routine cytogenetic analysis, and molecular testing (e.g., FLT3/ITD, NPM1, CEBPA) as appropriate; a bone marrow biopsy should be obtained if spicules are absent from the aspirate sample. Bone marrow examination is not required if there are immunophenotypically malignant blasts comprising ≥10% of total white blood cells in the peripheral blood or pathologically-confirmed extramedullary disease as per International Working Group recommendations[12,13] (assessed up to 2 months prior to study day 0). If diagnosis is based on outside diagnostic material, submission of peripheral blood specimen for flow cytometric assessment at UW/SCCA should be considered to establish leukemia-associated immunophenotype.

**6.1.3** Complete blood counts with differential blood count, including immature cells/blasts; platelet count (assessed within 14 days prior to study day 0).

**6.1.4** Metabolic panel, including bilirubin, albumin, and creatinine (assessed within 14 days prior to study day 0).

**6.1.5** MUGA scan or echocardiography, or other appropriate diagnostic modality, to assess left ventricular ejection fraction (LVEF; assessed within 12 months prior to study day 0).

## 6.2 Pre-treatment

At the discretion of the treating physician for clinical management only, allopurinol 300 mg PO daily (or equivalent dose adjusted for renal function) may be considered in all patients without known allergies to allopurinol to reduce the risk of tumor lysis. Higher doses of allopurinol are permitted if patients develop tumor lysis syndrome. Patients may receive rasburicase, a recombinant uric acid oxidase, for the prevention and/or treatment of tumor lysis syndrome at the discretion of the treating physician if clinically indicated. All patients should be adequately hydrated and receive anti-emetics as necessary.

## 6.3 Administration of CPX-351: INDUCTION

**6.3.1** Patients will receive CPX-351 at a dose of daunorubicin 44 mg/m$^2$, cytarabine 100 mg/m$^2$ on days 1, 3, and 5. CPX-351 should be administered IV over 90 minutes.

**6.3.2** The doses of CPX-351 are calculated using the patient's actual weight (measured before each treatment cycle).

**6.3.3** Administration of CPX-351 in the outpatient clinic is permitted.

**6.3.4** All treatment is given as intent-to-treat; missed doses will not be made up.

**6.3.5** For patients with FLT3 internal tandem duplication mutations (FLT3-ITD) or FLT3 tyrosine kinase domain (FLT3-TKD) mutations, use of commercially-available tyrosine kinase inhibitors on published schedules is allowed. No other investigational or commercial agents or therapies other than those described herein may be administered with the intent to treat the patient's malignancy.

## 6.4 Administration of CLAG-M: INDUCTION

**6.4.1** The doses of the elements of CLAG-M will be as follows: cladribine 5 mg/m$^2$ IV daily over 2 hours on Days 1-5; cytarabine 2,000 mg/m$^2$ IV daily over 2 hours on Days 1-5; G-CSF 300 or 480 µcg/ (based on weight <76 kg vs. ≥76kg) daily subcutaneously daily on Days 0-5; and Mitoxantrone 18 mg/m$^2$ IV daily over 60 minutes on Days 1-3. Note that often day 0 G-CSF is given as outpatient and the remainder of therapy is given as inpatient. Thus, a >24-hour delay between day 0 G-CSF and the start of day 1 therapy is allowed.

**6.4.2** The doses of all medications are calculated using the patient's actual weight (measured before each treatment cycle).

**6.4.3** If WBC >20,000/µL, the patient has recently received treatment with cytarabine and/or hydroxyurea, or if patient has signs/symptoms from high tumor burden (e.g., hypoxia) Days 0 and 1 G-CSF may be omitted at physician discretion.

**6.4.4** All treatment is given as intent-to-treat; missed doses will not be made up.

**6.4.5** Administration in the outpatient clinic can be considered but should be discussed with the study investigators.

**6.4.6** For patients with FLT3 internal tandem duplication mutations (FLT3-ITD) or FLT3 tyrosine kinase domain (FLT3-TKD) mutations, use of commercially-available tyrosine kinase inhibitors on published schedules is allowed. No other investigational or commercial agents or therapies other than those described herein may be administered with the intent to treat the patient's malignancy.

**6.4.7** If the patient has significant organ-specific dysfunction at baseline (e.g., abnormal liver or kidney function), dose reduction can be considered as described in section 6.8 at the physician discretion in conjunction with the oncology pharmacist.

## 6.5 Monitoring during/after induction therapy

For patient monitoring, the following assessments and study intervals are suggested:

**6.5.1** Complete blood counts with differential blood count, including immature cells/blasts, and platelet count at least 3 times weekly until absolute neutrophil count [ANC] >500/µL and self-sustained platelet count >20,000/µL.

**6.5.2** Metabolic panel, including electrolytes (Na, K), bilirubin, ALT/AST, and creatinine at least weekly until ANC >500/µL and self-sustained platelet count >20,000/µL.

**6.5.3** If patients develop signs or symptoms suggestive of cardiac dysfunction, LVEF should be assessed using the same method to evaluate baseline LVEF status (MUGA scan or echocardiography, or another appropriate diagnostic modality).

## 6.6 Assessment for response after first induction course

A bone marrow aspirate should be obtained upon blood count recovery (i.e. ANC >1,000/µL and platelet count >100,000/µL) or between Days +25 to +35 after start of chemotherapy, whichever occurs first. Marrow may be delayed in discussion with PI if clinically significant reason to do so (e.g., patient in ICU). A bone marrow biopsy should be obtained if spicules are absent from the aspirate sample. In patients with unclear response status, the bone marrow examination should be repeated every 7-10 days until the response can be assessed or until Day +42. Responses are defined in section 8.1.

**6.6.1** Achievement of MRD-negative CR: Patients are eligible for post-remission chemotherapy as described in section 6.7.

**6.6.2** Achievement of remission (CR/CRi) other than MRD-negative CR: patients are eligible for a second course of induction chemotherapy provided all non-hematologic toxicities have resolved to Grade <2. Treatment will be with either CPX-351 or CLAG-M at identical doses as given during the first cycle of chemotherapy. For patients who experienced ≥Grade 3 non-hematologic toxicities during the first induction, a dose reduction is recommended as described in section 6.8. If there is clinical concern about re-induction chemotherapy, patients may be given post-remission chemotherapy as described in section 6.7.

**6.6.3** Response other than CR/CRi: patients are eligible for a second course of induction chemotherapy provided all non-hematologic toxicities have resolved to Grade <2. Treatment will be with either CPX-351 or CLAG-M at identical doses as given during the first cycle of chemotherapy. For patients who experienced ≥Grade 3 non-hematologic toxicities during the first induction, a dose reduction is recommended as described in section 6.8.

**6.6.4** Persistent severe cytopenias (as defined in section 8.1) without evidence of disease after Day +42: Patients will be removed from the treatment portion of the protocol.

## 6.7 Post-remission therapy

After a maximum of 2 cycles of induction therapy, patients are eligible for post-remission therapy if CR/CRi is achieved by the end of induction.

**6.7.1** For patients who received CPX-351 during induction: patients can receive up to 4 courses of post-remission therapy with CPX-351 at a dose of daunorubicin 29 mg/m$^2$, cytarabine 65 mg/m$^2$ on days 1 and 3.

**6.7.2** For patients who received CLAG-M during induction: patients can receive up to 4 courses of post-remission therapy intermediate-dose cytarabine (500 mg/m$^2$ per dose) once daily on Days 1-6.

**6.7.3** Post-remission courses should start within 6 weeks of achieving CR/CRi and once patients have recovered to ≤Grade 2 toxicities from the previous course of therapy.

**6.7.4** For patients with FLT3 internal tandem duplication mutations (FLT3-ITD) or FLT3 tyrosine kinase domain (FLT3-TKD) mutations, use of commercially-available tyrosine kinase inhibitors on published schedules is allowed.

**6.7.5** Patients can proceed to transplantation barring contraindications and if a suitable donor is available.

## 6.8 Dose modifications of chemotherapeutic drugs

**6.8.1** CPX-351 arm: for patients who experienced ≥Grade 3 non-hematologic toxicities excluding neutropenic fever and infections during the first induction or any subsequent treatment cycle, a dose reduction of 33% can be considered for subsequent treatment courses.

**6.8.2** CLAG-M arm: for patients who have organ dysfunction at baseline or those who experienced ≥Grade 3 non-hematologic toxicities excluding neutropenic fever and infections during the first induction, a dose reduction can be considered as follows:

**6.8.2.1** If a patient develops Grade ≥3 non-hematologic toxicity other than Grade 3 infections within 28 days from the last dose of CLAG-M, the next treatment course will be given once toxicity is ≤ grade 2; doses for this course will be cladribine 4 mg/m$^2$ days 1-5, cytarabine 1,500mg/m$^2$ days 1-5, mitoxantrone 14 mg/m$^2$ days 1-3, and G-CSF dose unchanged.

**6.8.2.2** Cladribine: If the serum creatinine exceeds 2.0 mg/dL and/or estimated creatinine clearance (calculated by Cockcroft-Gault) decreases to less than 50 mL/min during therapy, we will consider dose reduction in discussion with the Oncology Pharmacist.

**6.8.2.3** Cytarabine: If the serum creatinine exceeds 2.0 mg/dL and/or estimated creatinine clearance (calculated by Cockcroft-Gault) decreases significantly during therapy, we will consider dose reduction in discussion with the Oncology Pharmacist.

## 6.9 Supportive Therapy

**6.9.1** All patients will be adequately hydrated and receive appropriate anti-emetics based upon institutional standard of care guidelines.

**6.9.2** Additional growth factors may be used according to institutional standard of care guidelines or the preference of the attending physician.

**6.9.3** Antimicrobial prophylaxis should be used according to institutional standard of care guidelines. In case of neutropenic fever, standard of care diagnostic testing will be performed, and empiric antibiotic coverage will be utilized as per standard of care institutional practices.

**6.9.4** Transfusion support should be carried out according to institutional standard of care guidelines.

## 6.10 Treatment of CNS disease

Treatment of CNS disease is done according to institutional practice guidelines or the preference of the attending physician.

## 6.11 Recommended follow-up care

After completion of protocol treatment or early termination of treatment (see section 6.12), patients should be evaluated according to institutional and/or national guidelines or the discretion of the attending physician. These evaluations may include peripheral blood studies and/or bone marrow examinations, as clinically indicated.

## 6.12 Criteria for removal from treatment prior to completion of protocol treatment

All reasons for discontinuation of treatment must be documented:

**6.12.1** Consolidation with hematopoietic cell transplantation after achievement of CR or CRi.

**6.12.2** Failure to achieve CR or CRi after up to 2 cycles of induction therapy.

**6.12.3** Persistent severe cytopenias (as defined in section 8.1) without evidence of leukemia after Day +42.

**6.12.4** Relapse after achievement of CR or CRi during treatment.

**6.12.5** Adverse toxicities that prevent continuation with study treatment.

**6.12.6** Withdrawal of consent; the patient may withdraw from the study at any time for any reason.

# 7.0 DRUG INFORMATION ON CPX-351

## 7.1 Drug description

CPX-351 (daunorubicin and cytarabine) is a liposomal formulation for injection and is supplied as a sterile, preservative-free, purple, lyophilized cake in a single-dose vial. Each vial of CPX-351 contains 44 mg daunorubicin and 100 mg cytarabine. The liposomes are composed of distearoylphosphatidylcholine, distearoylphosphatidylglycerol, and cholesterol, and are suspended in sucrose. After reconstitution (but before final dilution), each mL contains 2.2 mg daunorubicin and 5 mg cytarabine. CPX-351 is administered as an IV infusion over approximately 90 minutes. See Section 7.2 for details on preparation for infusion.

**7.1.1** Supplies: CPX-351 is supplied refrigerated in a carton containing 2 clear glass, single-use vials, each containing a lyophilized cake of drug product.

**7.1.2** Storage of CPX-351: CPX-351 cartons must be stored refrigerated (5°C ± 3°C) in an upright position until the time of use.

**7.1.3** Stability: Materials released for clinical trials will be periodically tested during the investigational period and monitored for acceptable product attributes. The current shelf life is 48 months from date of manufacture. Any material that fails to comply with specifications will be promptly removed from the clinic and replaced with new clinical supplies.

## 7.2 Drug preparation

As described in the prescribing information for CPX-351 (Vyxeos US PI 2017), the CPX-351 drug is prepared as follows:

**7.2.1** Calculate the CPX-351 dose based on daunorubicin and individual subject's body surface area (BSA).

**7.2.2** Calculate the number of vials of CPX-351 based on the daunorubicin dose.

**7.2.3** Remove the appropriate number of vials of CPX-351 from the refrigerator and equilibrate to the room temperature for 30 minutes.

**7.2.4** Reconstitute each vial with 19 mL of sterile water for injection using a sterile syringe and immediately thereafter start a 5-minute timer.

**7.2.5** 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.

**7.2.6** 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.

**7.2.7** Gently invert each vial 5 times prior to withdrawing the reconstituted product for further dilution. If the reconstituted product is not diluted into an infusion bag immediately, store in refrigerator at 2ºC to 8ºC for up to 4 hours.

**7.2.8** Calculate the volume of reconstituted CPX-351 required using the following formula: [volume required (mL) = dose of daunorubicin (mg/$m^2$) X subject's BSA ($m^2$) ÷ 2.2 (mg/mL)].

**7.2.9** 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.

**7.2.10** 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.

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

**7.2.12** 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.

Please note that aseptic technique must be strictly observed throughout the handling of CPX-351 Liposome for Injection since no bacteriostatic agent or preservative is present. The infusion of CPX-351 Liposome for Injection must be started within 4 hours of dilution. Vials are for single use. Unused material should be recorded as such and discarded according to institutional policies. Procedures for proper handling and disposal of anticancer drugs should be implemented.

## 7.3 Drug administration

CPX-351 is for IV use only and should never be given by the intramuscular or subcutaneous route. Do not mix CPX-351 with or administer as an infusion with other drugs. The infusion of CPX-351 Liposome for Injection will be performed through a central venous catheter or a peripherally inserted central catheter, using an infusion pump to ensure that the drug is infused over the specified time period. DO NOT USE AN IN-LINE FILTER. Administer CPX-351 over 90 minutes via an infusion pump. Flush the line with 0.9% Sodium Chloride Injection, USP or 5% Dextrose Injection, USP to ensure administration of the full dose. The dosage of each active ingredient (total mg and mg/$m^2$) and start time of the infusion must be documented in the subject's chart.

## 7.4. Side effects of CPX-351

Among 375 subjects treated with CPX-351, the most frequently reported adverse events (AEs) were in the system organ class (SOC) categories "Gastrointestinal Disorders" (338 subjects, 90.1%), "General Disorders" and "Administration Site Conditions" (338 subjects, 90.1%), "Skin and Subcutaneous Disorders" (315 subjects, 84.0%), and "Respiratory, Thoracic

and Mediastinal Disorders" (292 subjects, 77.9%). Among the 236 subjects in the All Controls group, the most frequently reported AEs were in the SOC categories "Gastrointestinal Disorders" (224 subjects, 94.9%), "General Disorders and Administration Site Conditions" (209 subjects, 88.6%), "Respiratory, Thoracic and Mediastinal Disorders" (166 subjects, 70.3%) and "Infections and Infestations" (163 subjects, 69.1%).

**7.4.1** Within the SOC Gastrointestinal Disorders, a lower incidence was reported for subjects receiving CPX-351 than for subjects receiving control treatment (90.1% vs. 94.9%, respectively). This difference is mainly attributable to the reduced incidence of Diarrhea reported for subjects receiving CPX-351 compared with All Control treatment (45.6% vs. 65.7%). Other Preferred Terms within the SOC Gastrointestinal Disorders were reported with similar frequency.

**7.4.2** Infections and infestations were reported more frequently for subjects receiving CPX-351 than for All Control treated subjects (77.1% vs. 69.1%, respectively). In particular, Bacteremia occurred more frequently among CPX-351 treated subjects compared with control treated subjects (10.7% vs. 4.2%, respectively).

**7.4.3** In the SOC Nervous System Disorders, an imbalance was also observed between subjects treated with CPX-351 and All Controls (63.7% vs. 55.1%), which was primarily driven by differences in the incidence of headache (32.0% vs. 25.4%, respectively).

**7.4.4** Within the SOC Skin and Subcutaneous Tissue Disorders, subjects treated with CPX-351 experienced more AEs than control treated subjects (84.0% vs. 63.6%). Rash (39.2% vs. 24.6%), petechiae (18.9% vs. 12.3%) and pruritus (17.3% vs. 9.7%) were all reported more frequently in subjects treated with CPX-351 compared with All Controls.

# 8.0 DRUG INFORMATION ON CLAG-M

## 8.1 Drug information on G-CSF (granulocyte colony-stimulating factor)

**8.1.1** Mechanism of action: G-CSF is a growth factor that stimulates the production, maturation, and activation of neutrophils. Further, it promotes premature release of neutrophils from the bone marrow and enhances their phagocytic capacity.

**8.1.2** Pharmacokinetics: Peak G-CSF concentrations after sub-cutaneous dosing occur in 2 to 8 hours, though the onset of action is approximately 24 hours, with plateau concentrations in 3-5 days, and elimination over an 11-20 day period. G-CSF is cleared by systemic degradation. Notably, as G-CSF binds neutrophils, plasma levels are controlled in large part by the absolute neutrophil count.[14]

**8.1.3** Adverse effects (AEs): *Common drug-related AEs (occurring in >10% of patients)* include fever, petechiae, elevated uric acid, splenomegaly, bone pain, and epistaxis.

*Less common drug-related AEs (occurring in 1% -10% of patients)* include hyper- or hypotension, arrhythmias, headache, nausea, vomiting, leukocytosis, and transfusion reaction.

*Infrequent drug-related AEs (occurring in <1% of patients)* include acute respiratory distress syndrome, allergic reactions, alopecia, alveolar hemorrhage, arthralgia, bone density decrease, capillary leak syndrome, cerebral hemorrhage, vasculitis, dyspnea, edema, erythema nodosum, hematuria, hemoptysis, hepatomegaly, hypersensitivity, injection site reaction, pericarditis, proteinuria, psoriasis exacerbation, pulmonary infiltrates, renal insufficiency, sickle cell crisis, splenic rupture, Sweet's syndrome, tachycardia, and thrombophlebitis.

**8.1.4** Recommended dose adjustments for organ dysfunction: There is limited or no data examining the toxicity of G-CSF in patients with renal or liver dysfunction. Therefore, administration of G-CSF to patients with liver or kidney disease must be done with caution.

## 8.2 Drug Information on cladribine (2-chloro-2'-deoxyadenosine, 2-CdA)

**8.2.1** Mechanism of action: Cladribine is a prodrug that is converted to an adenosine deaminase-resistant triphosphate derivative (2-CdATP). This molecule is then activated by deoxycytidine kinase to a 5'-triphosphate derivative (2-CdAMP), which is incorporated into DNA where it acts as a transcription regulator. In addition to its cytotoxic properties in dividing cells, cladribine induces death in quiescent cells of lymphoid origin through an unknown mechanism.[15]

**8.2.2** Pharmacokinetics: Cladribine is renally excreted, with 18-35% as unchanged drug. It is able to penetrate the CSF, where it achieves 25% of plasma concentrations. It is 20% protein-bound. The half-life for elimination after a 2-hour infusion is 6.7±2.5 hours in patients with normal renal function.

**8.2.3** Adverse effects: *Common adverse effects (occurring in >10% of patients)* include fever, fatigue, headache, rash, nausea, anorexia, vomiting, myelosuppression (including grade 3/4 neutropenia/thrombocytopenia), injection site reaction, and infection.

*Less common adverse effects (occurring in 1 to 10% of patients)* include edema, tachycardia, thrombosis, chills, dizziness, insomnia, malaise, diarrhea or constipation, weakness, myalgias and arthralgias, cough, dyspnea, epistaxis, and diaphoresis.

*Rare adverse effects (occurring in <1% of patients)* include aplastic anemia, bacteremia, opportunistic infections, lymphocytopenia, altered mental status, hemolytic anemia, hypersensitivity, myelodysplastic syndrome, quadriparesis, and renal dysfunction/failure.

**8.2.4** Reconstitution: Cladribine is supplied as a sterile, preservative-free, isotonic solution containing 10 mg of cladribine (1 mg/mL) in 10 mL single-use vials. Cladribine should be passed through a sterile 0.22μm filter prior to introduction into the infusion bag containing 0.9% Sodium Chloride Injection, USP.

**8.2.5** Administration and compatibility: The use of 5% dextrose is not recommended as a diluent because of increased degradation of cladribine. The infusion solution is stable for 24 hours at room temperature.

**8.2.6** Storage and stability: Store refrigerated 2° to 8°C (36° to 46°F). Protect from light during storage.

**8.2.7** Recommended dose adjustments for organ dysfunction: Specific guidelines for cladribine dosing in patients with hepatic/renal dysfunction or hypoalbuminemia are not clearly defined. Because of the potential for compensatory elimination of cladribine in patients with hepatic and/or renal dysfunction, specific guidelines for dosing are difficult to define. Thus, when deciding whether to adjust cladribine doses for renal dysfunction, the risks for potential toxicities (e.g., myelosuppression, neurotoxicity) against the benefits and goals of treatment must be considered.

## 8.3 Drug information on cytarabine (cytosine arabinoside)

**8.3.1** Mechanism of action: Cytarabine is a synthetic pyrimidine analog, in which the sugar moiety (normally a ribose or deoxyribose) has been replaced with arabinose. Although its mechanism of action is not completely understood, the active form of cytarabine is probably incorporated into the DNA and interferes with DNA synthesis. As such, cytarabine has been found to primarily effect dividing cells, blocking their progression from $G_1$ to S phase.

**8.3.2** Pharmacokinetics: Cytarabine is metabolized by deoxycytidine kinase and other kinases into its most active form (aracytidine triphosphate). Aracytidine triphosphate is converted to nontoxic uracil derivatives by pyrimidine nucleoside deaminases. This balance between the levels of kinases and deaminases is critical for regulating the sensitivity/resistance of cells to the drug. The plasma clearance of cytarabine is biphasic, with an initial rapid phase and more prolonged second clearance phase. The rapid clearance phase has a relatively short half-life ($t_{1/2\alpha}$ = 10 minutes), while the half- life of the second clearance phase is slightly longer ($t_{1/2\beta}$ = 1-3 hours). The nontoxic metabolites from the drug are excreted in the urine, and within 24 hours after the infusion, approximately 80% of these nontoxic metabolites can be recovered from the urine.

**8.3.3** Adverse effects: The dose-limiting toxicity for cytarabine is myelosuppression. *Adverse Events Associated with Standard Dose Cytarabine: Frequent AEs (not definitely quantified)* include the following: myelosuppression (leucopenia, anemia, neutropenia, thrombocytopenia), pyrexia, rash, anorexia, diarrhea, nausea, vomiting, mucositis, anal inflammation or ulceration, hepatic dysfunction or increased liver enzymes, and local thrombophlebitis.

*Less frequent AEs (not definitely quantified)* include chest pain, pericarditis, dyspnea dizziness, headache, neural toxicity, neuritis, alopecia, pruritis, skin freckling, skin ulceration, urticaria, abdominal pain, bowel necrosis, esophageal ulceration, esophagitis, pancreatitis, sore throat, urinary retention, jaundice/hyperbilirubinemia, local site cellulites, renal dysfunction, allergic edema or anaphylaxis, sepsis, and sudden respiratory distress syndrome.

*Infrequent AEs (not definitely quantified)* include aseptic meningitis, cardiopulmonary arrest, cerebral dysfunction, cytarabine syndrome (bone pain, chest pain, conjunctivitis, fever, maculopapular rash, malaise, myalgia), exanthematous pustulosis, hyperuricemia, intestinal pneumonitis, increased lipase,

paralysis with intrathecal and IV combination therapy, rhabdomyolysis, veno-occlusive disorder, and death.

*Adverse events associated with high-dose cytarabine* include cardiomegaly and cardiomyopathy, coma, severe neurotoxicity, personality change, somnolence, total body alopecia, severe rash or skin desquamation, gastrointestinal ulceration, peritonitis, intestinal pneumatosis, necrotizing colitis, liver abscess or damage, peripheral neuropathy, corneal toxicity, hemorrhagic conjunctivitis, pulmonary edema, sudden respiratory distress syndrome, and sepsis.

**8.3.4** Reconstitution: Cytarabine should be reconstituted in sterile water and can be further diluted using either 5% dextrose or sodium chloride solutions into appropriate concentrations for infusion.

**8.3.5** Administration and compatibility: The diluted cytarabine solution should be inspected for particulate matter, discoloration, and haze prior to infusion. If there is evidence of particulate matter, discoloration, or haze the solution should not be infused. Patients should be medicated with standard anti-emetic therapy. Cytarabine is not compatible (1) during Y-site administration with allopurinol, amphotericin B, ganciclovir; (2) in syringe with metoclopropamide; or (3) admixed with fluorouracil, heparin, insulin (regular), nafcillin, oxacillin, penicillin G. Cytarabine may have variable compatibility when admixed with gentamycin, hydrocortisone, and methylpredinsolone.

**8.3.6** Storage and stability: Vials of non-reconstituted cytarabine should be stored at room temperature 15°C - 30°C (59°F - 86°F). The diluted cytarabine solution may be stable for up to 48 hours if stored at room temperature.

**8.3.7** Drug-drug interaction: Reversible decreases in the plasma steady-state concentration for digoxin and cardiac glycosides may occur. Cytarabine may diminish the therapeutic effect of flucytosine. There is *ex vivo* data suggesting that cytarabine may reduce the effectiveness gentamycin for killing *K. pneumoniae*.

**8.3.8** Warnings and precautions: *Ex vivo* and *in vivo* studies have found that cytarabine causes extensive chromosomal damage and potential malignant transformation. Although there have been some case reports describing cytarabine use in pregnant humans, these cases reports are few. Thus, cytarabine is considered Pregnancy Category D. Women should be advised not to become pregnant while receiving cytarabine, and men should be advised not to father a child while receiving cytarabine and for at least 3 months after completing the therapy. It is not known whether cytarabine or its metabolites are excreted in breast milk; thus, it is not recommended for lactating females who are breast-feeding. As with any highly immunosuppressive medication, cytarabine may diminish the effectiveness of dead and live vaccines and enhance the toxic/adverse effect of live vaccines. One should avoid use of live vaccines while receiving it. A small percentage of patients will have a hypersensitivity reaction to cytarabine, and these individuals should not receive the drug again.

**8.3.9** Recommended dose adjustments for organ dysfunction: Guidelines for adjusting cytarabine dose due to renal or liver dysfunction are not standardized, but many clinicians will adjust the dose based upon the function of these organs.

## 8.4 Drug information on mitoxantrone

**8.4.1** Mechanism of action: Mitoxantrone (dihydroxyanthracenedione) is an anthracenedione derivative that intercalates with DNA, resulting in inhibition of nucleic acid synthesis.

**8.4.2** Pharmacokinetics: Mitoxantrone is 78% bound to plasma proteins. A three-compartment model was described after a single intravenous dose of mitoxantrone. The mean alpha half-life is 6 to 12 minutes, the mean beta half-life is 1.1 to 3.1 hours, and the mean terminal (gamma) or elimination half-life is 23 to 215 hours (median 75 hours). Mitoxantrone has extensive distribution into body tissues and is metabolized in the liver to two main inactive metabolites (monocarboxylic acid derivative and dicarboxylic acid derivative). The major route of excretion for mitoxantrone appears to be biliary into the feces; approximately 11% of the dose is recovered in the urine within 5 days of drug administration, with 65% of this being unchanged drug.

**8.4.3** Adverse effects: *Common adverse effects (occurring in >10% of patients)* include edema, fever, fatigue, headache, alopecia, nausea/vomiting, diarrhea, mucositis/stomatitis, myelosuppression, weakness, dyspnea, cough, and infection.

*Less common adverse effects (occurring in 1 to 10% of patients)* include congestive heart failure, decreased left ventricular ejection fraction (LVEF), hypertension, chills, anxiety, cutaneous mycosis, hypcalcemia, hypokalemia, hyponatremia, menorrhagia, jaundice, myalgia, arthralgia, renal failure, proteinuria, rhinitis, diaphoresis, and infection.

Mitoxantrone may cause cardiac toxicity with prolonged administration and doses exceeding 80 to 100 mg/m$^2$. When used after doxorubicin, cardiotoxicity is more frequent; an analysis by the Southwest Oncology Group revealed a risk of 6% at 134 mg/m$^2$ prior doxorubicin and 60 mg/m$^2$ mitoxantrone, rising to a 15% risk at 120 mg/m$^2$ mitoxantrone. Cardiac events reported included arrhythmias, decreased left ventricular function, chronic heart failure, tachycardia, ECG changes, and, infrequently, myocardial infarction. Bradycardia has been rarely reported. Patients with prior treatment with anthracyclines, prior mediastinal radiotherapy, or with preexisting cardiovascular disease may have more frequent occurrences of cardiac toxicity.

**8.4.4** Reconstitution: Mitoxantrone must be diluted prior to use. The dose of mitoxantrone should be to at least 50 mL with either 0.9% Sodium Chloride Injection (USP) or 5% Dextrose Injection (USP). Mitoxantrone may be further diluted into Dextrose 5% in Water, Normal Saline or Dextrose 5% with Normal Saline and used immediately.

**8.4.5** Administration and compatibility: Care in the administration of mitoxantrone will reduce the chance of extravasation. Mitoxantrone should be administered into the tubing of a freely running intravenous infusion of 0.9% Sodium Chloride Injection, USP or 5% Dextrose Injection, USP. Care should be taken to avoid extravasation at the infusion site and to avoid contact of mitoxantrone with the skin, mucous membranes, or eyes. If any signs or symptoms of extravasation have

occurred, including burning, pain, pruritis, erythema, swelling, blue discoloration, or ulceration, the injection or infusion should be immediately terminated and restarted in another vein.
Mitoxantrone should not be mixed in the same infusion as heparin since a precipitate may form.

**8.4.6** Storage and stability: Mitoxantrone should be stored between 15°C - 25°C (59°F - 77°F).

# 9.0 EVALUATION AND END POINT DEFINITIONS

## 9.1 Treatment response and outcome

Treatment response (e.g. morphologic/cytogenetic/molecular complete remission, partial remission) or treatment failure (e.g. resistant disease, morphologic leukemia-free state, morphological or molecular/cytogenetic relapse) as well as treatment outcome (e.g. overall survival, relapse-free survival, event-free survival, and remission duration) are categorized according to criteria recommended by International Working Groups.[12,13] Since persistent severe cytopenias are not defined per International Working Groups, here we define persistent severe cytopenias as absolute neutrophil count <200/μL AND platelets <20,000/μL (self-sustained without transfusion) without evidence of leukemia on bone marrow aspirate beyond day +42 after therapy.

## 9.2 Toxicity criteria

This study will use the CTCAE (NCI Common Terminology Criteria for Adverse Events) Version 5.0 for Toxicity and Adverse Event reporting. A copy of the CTCAE v5.0 can be downloaded from the CTEP home page (http://ctep.cancer.gov). Only grade ≥3 adverse events other than hematologic toxicities will be graded and recorded.

## 9.3 Evaluation of medical complications and use of medical resources

Information on medical complications (e.g. neutropenic fever, documented infections including nosocomial infections, bleeding, reasons for hospitalization, etc.) and use of medical resources (e.g. transfusions) will be abstracted from the medical records from the inpatient and outpatient facilities similar to what we have done in previous studies.[16,17]

## 9.4 Assessment of patients' quality of life (QOL)

QOL of patients will be assessed longitudinally using the EORTC core QOL questionnaire (QLQ-C30) and the newly-developed AML-specific QOL instrument ("AML-QOL")[18] via electronic data capture or paper version of the instruments (**Appendix C**). Socio-demographic information will be collected at baseline with questions on race, gender, marital status, dependent children at home, residential type and distance from the study center, work status, etc.

**9.4.1** The EORTC QLQ-C30 is a questionnaire for patient self-completion composed of multi-items and single scales. These include five functional scales (physical, role, emotional, social, and cognitive), three symptom scales (fatigue, nausea and vomiting and pain) and a global health status/QOL scale and six single items (dyspnea, insomnia, appetite loss, constipation, diarrhea, and financial

difficulties). The EORTC QLQ-C30 will be scored according to the recommendations of the developers. We estimate it will take 6 minutes to complete the EORTC QLQ-C30.

**9.4.2** The AML-QOL is organized into the following domains: Physical, Social, Cognitive, Anxiety, and Depression (called 'Mood' on the questionnaire). Additionally, there are 7 stand-alone items that can be scored individually or together to form a Symptom Index. Finally, there is a single item assessing global QOL. Scoring for the AML-QOL is as follows: all single items, domains, and the Symptom Index are scored from 1-5, where 5 indicates the best health status. All items within each domain/index contribute equally. A summary score is calculated as an average of all 5 domains, the Symptom Index, and the single-item QOL question. The summary score ranges from 0-100, where 100 indicates best overall QOL. We estimate it will take 5 minutes to complete the AML-QOL.

QOL questionnaires should be completed for baseline assessment at the time of enrollment, either through self-administration or with the assistance of research staff or caregiver(s). A second assessment should occur after completion of the first cycle prior to starting the second cycle of therapy.

Obtaining complete patient-reported data has been historically challenging in AML trials. Given that participants do not always fill out questionnaires due to acute illness, hospitalization, feeling poorly, and/or time or other constraints, we will measure the percentage of returned surveys as one of our feasibility outcomes. Given the factors above, surveys not returned will not be considered a protocol deviation. However, we will make the following allowances to minimize missing data:

**9.4.3** When possible, participants will complete all questionnaires on their own. Patients may return questionnaires to study team in person, by mail, or electronically.

**9.4.3.1** A REDCap survey has been set up to capture these data. REDCap is a secure web application for building and managing online surveys and databases with servers located at Fred Hutchinson Cancer Center. It is specifically designed to support data capture for research studies. A unique access code is provided to participants to access their individual surveys. The online version of all surveys mirrors the paper version. The online version allows participants to save their answers at any point and return to complete it later. In this case, participants will be given a unique return code that will allow them to return to access the questionnaire. Only study staff and the PI will have administrative privileges for the online questionnaires.

**9.4.4** If participants are unable to physically complete questionnaires by hand, they may designate a representative to help with completion by reading items, reading answer choices, and marking the participant’s response. Representatives will be told not to prompt or discuss responses until the end of the survey.

**9.4.5** If participants are not able to complete questionnaires in person, we will send them questionnaires by mail with a stamped return envelope.

**9.4.6** If participants are not able to complete questionnaires in person and are also unable to fill out questionnaires on paper, we will contact them by phone and ask if they are able to complete the questionnaires over the phone. If they agree, a member of the research team may call them. The researcher will read each question and response and will mark down the answer given by the participant.

**9.4.7** At each time point, participants will be asked to complete questionnaires in a designated order: first AML-QOL, second QLQ-C30. This way, if participants are unable to complete the full battery of questionnaires, we will be most likely to capture the most relevant aspects.

### 9.5 Duration of cytopenias

The duration of neutropenia and thrombocytopenia will be determined as time from day 1 of treatment until an absolute neutrophil count of 500 or a self-sustained platelet count of 50,000 is reached, respectively. Time to achievement of absolute neutrophil count >1,000/μL and platelet count >100,000/μL will also be recorded.

### 9.6 Duration of follow-up

After removal from protocol, patients will be followed to determine event-free survival and disease-free survival (for patients achieving CR or CRi) as well as overall survival (for all patients) for a maximum of 5 years. Follow-up may include periodic (e.g., every 3 months) review of medical records, and, only if absolutely necessary, direct contact of the study participant.

## 10.0 RECORDS

Research data will be recorded in a study-specific, password protected database using a unique study ID for each patient to assure patient confidentiality. Data from source documents will be transcribed into this database. Source documents are documents where patient data are recorded and documented for the first time. They include, but are not limited to, hospital records, clinical and office charts, laboratory notes, memoranda, quality of life assessments, pharmacy dispensing records, recorded data from automated instruments, copies of transcriptions that are certified after verification as being accurate and complete, X-rays, patient files, and records kept at the pharmacy, laboratories, and medico-technical departments involved in the clinical trial. There will be no case reports forms (CRFs) used for this trial.

The Principal Investigator will ensure that data collected conform to all established guidelines. Each subject is assigned a unique subject number to protect subject confidentiality. Subjects will not be referred to by this number, by name, or by any other individual identifier in any publication or external presentation.

The licensed medical records department, affiliated with the institution where the subject receives medical care, maintains all original inpatient and outpatient chart documents. Patient research files will be maintained under control of the local site Principal Investigator and/or study team as designated by institutional policies.

Access to the study database will be restricted by electronic password protection and restricted access to computers per institutional policies and/or guidelines.

# 11.0 PROTOCOL ENROLLMENT AND SPECIAL CONSIDERATIONS

All eligible patients will be included in this study without regard to gender or ethnicity. The incidence of AML is slightly higher in men, so it is expected that the distribution of these patients will reflect a slight male predominance of the disease as well as the general demographic distribution of AML patients seen at our institution. Based on our statistical approach, we will require no more than 60 patients to compare with patients treated historically at our institution.

**Projected Target Accrual**
**ETHNIC AND GENDER DISTRIBUTION CHART**

| **TARGETED / PLANNED ENROLLMENT: Number of Subjects = 60** | | | |
|---|---|---|---|
| Ethnic Category | **Sex / Gender** | | |
| | **Females** | **Males** | **Total** |
| Hispanic or Latino | 2 | 4 | 6 |
| Not Hispanic or Latino | 22 | 32 | 54 |
| Ethnic Category Total of All Subjects* | 24 | 36 | 60 |
| Racial Categories | | | |
| American Indian/Alaska Native | 0 | 0 | 0 |
| Asian | 2 | 2 | 6 |
| Native Hawaiian or Other Pacific Islander | 1 | 1 | 2 |
| Black or African American | 2 | 2 | 4 |
| White | 19 | 29 | 48 |
| Other/More Than One Race/Unknown | 0 | 0 | 0 |
| Racial Categories: Total of All Subjects* | 24 | 36 | 60 |

# 12.0 GUIDELINES FOR SERIOUS ADVERSE EVENT REPORTING

## 12.1 Expedited reporting requirements

In accordance with Fred Hutch/UW Cancer Consortium IRB policy, all adverse events (AEs; whether occurring on-site or off-site), which in the opinion of the principal investigator (PI) are (1) unexpected, and (2) related or possibly related to the research, and (3) serious or suggests that the research places research participants or others at a greater risk of physical or psychological harm than was previously known or recognized, will be submitted to the IRB within ten (10) calendar days of learning of the problem. Both the "Expedited Reporting Form for Unanticipated Problems or Noncompliance" and the "Adverse Event Reporting Form", or equivalent forms, will be completed for this reporting.

All SAEs (initial and follow-up) that require collection and reporting per protocol, and which occur in a subject who received CPX-351 will also be submitted to Jazz Pharmaceuticals at

AEreporting@jazzpharma.com within 5 business day of their awareness of the SAE. The Principal 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, all other adverse events will be reported to Jazz in summary or line-item form upon Jazz's request and at the conclusion of the study.

## 12.2 Definitions

**12.2.1** Adverse event (AE): Any harm or untoward medical occurrence in a research participant administered a medical product, medical treatment or procedure even if it does not necessarily have a causal relationship with the product, treatment, or procedure. An adverse event can be any unfavorable and unintended sign (including an abnormal laboratory finding, for example), symptom, or disease temporally associated with the use of a medical product, medical treatment, or procedure whether or not considered to be related. Mechanisms of obtaining information on AE include monthly transcripts, assessment forms obtained after each clinic visit, and hospital progress and discharge notes. Grade ≥3 adverse events other than hematologic toxicities will be recorded, graded, and reported as appropriate.

**12.2.2** Related or possibly related AE: An AE is "related or possibly related to the research procedures" if in the opinion of the principal investigator, it was more likely than not caused by the research procedures. AEs that are solely caused by an underlying disease, disorder or condition of the subject or by other circumstances unrelated to either the research or any underlying disease, disorder or condition of the subject are not "related or possibly related". If there is any question whether or not an AE is related or possibly related, the AE should be reported.

**12.2.3** Serious AE (SAE): An adverse event that results in any of the following outcomes:

- Death
- Life-threatening adverse event (real risk of dying)
- Prolongation of hospitalization*
- Persistent or significant disability/incapacity/or change in psychosocial status
- Congenital anomaly
- Requires intervention to prevent permanent impairment of damage

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

**12.2.4** Unexpected AE: An unexpected adverse event is defined as an event that has a nature or severity, or frequency that is not consistent (a) the known or foreseeable risk of adverse events associated with the research procedures described in the protocol-related documents, such as the IRB-approved research protocol, informed consent document and other relevant sources of information such as

product labeling and package inserts; and also are not consistent with (b) the characteristics of the subject population being studied including the expected natural progression of any underlying disease, disorder or condition or any predisposing risk factor profile. with the applicable investigator brochure, or the prior medical condition of the subject or other treatment given to the subject. "Unexpected," as used in this definition, refers to an adverse drug experience that has not been previously observed and reported in preclinical or clinical studies rather than an experience that has not been anticipated based on the pharmacological properties of the study drug.

### 12.3 Grading adverse event severity

All AEs will be graded in severity according to the NCI Common Terminology Criteria for Adverse Events (CTCAE) Version 5.0 (http://ctep.cancer.gov). If a CTCAE criterion does not exist, the investigator should use the grade or adjectives: Grade 1 (mild), Grade 2 (moderate), Grade 3 (severe), Grade 4 (life-threatening), or Grade 5 (fatal) to describe the maximum intensity of the adverse event.

### 12.4 Monitoring, recording, and standard reporting of adverse events

Only grade ≥3 adverse events (AEs) other than hematologic toxicities will be recorded, graded, and reported as appropriate per 12.1. AEs will be monitored and recorded in the study database from the time of first exposure to the therapy in this study (i.e., the start of the first drug administration infusion on day 1) until 4 weeks after the last dose of study treatment. AEs with an onset date prior to the first exposure to an investigational product will not be recorded. However, in the case of clinically significant worsening of the AE during the specified AE monitoring time frame, the AE will be recorded.

Adverse events that do not meet the requirement for expedited reporting will be summarized for the institutional annual protocol review. Myelosuppression and associated complications are expected events during leukemia therapy; therefore, myelosuppression and associated complications such as fever, infections, bleeding, and related hospitalizations will not be reported as individual AE but will be summarized in the annual report to the IRB.

## 13.0. DATA AND SAFETY MONITORING PLAN

Institutional support of trial monitoring will be in accordance with the Fred Hutch/University of Washington Cancer Consortium Institutional Data and Safety Monitoring Plan (DSMP). Under the provisions of this plan, Fred Hutch Clinical Research Support (CRS) coordinates data and compliance monitoring conducted by consultants, contract research organizations, or Fred Hutch employees unaffiliated with the conduct of the study. Independent monitoring visits occur at specified intervals determined by the assessed risk level of the study and the findings of previous visits per the institutional DSMP. In addition, protocols are reviewed at least annually and as needed by the Consortium Data and Safety Monitoring Committee (DSMC), Fred Hutch Scientific Review Committee (SRC) and the Fred Hutch /University of Washington Cancer Consortium Institutional Review Board (IRB). The review committees evaluate accrual, adverse events, stopping rules, and adherence to the applicable data and safety monitoring plan for studies actively enrolling or treating subjects. The IRB reviews the study progress and safety information to assess continued acceptability of the risk-benefit ratio for human subjects. Approval of committees as applicable is necessary to continue the

study. The trial will comply with the standard guidelines set forth by these regulatory committees and other institutional, state and federal guidelines.

# 14.0 INVESTIGATOR OBLIGATIONS

The Principal Investigator (PI) is responsible for the conduct of the clinical trial at the site and is responsible for personally overseeing the treatment of all study subjects. The PI must assure that all study site personnel, including sub-Investigators and other study staff members, adhere to the study protocol and to all applicable regulations and guidelines regarding clinical trials both during and after study completion. All subjects are informed of the nature of the program, its possible hazards, and their right to withdraw at any time, and each subject signs a form indicating their consent to participate prior to receiving any study-related procedures.

# 15.0 ADMINISTRATIVE AND REGULATORY CONSIDERATIONS

## 15.1 Protocol interpretation and compliance

The procedures defined in the protocol are carefully reviewed by the PI, co-investigators and study staff prior to the time of study initiation to ensure accurate representation and implementation. Protocol amendments, if any, are reviewed and implemented promptly following IRB/EC and relevant Competent Authorities approval.

## 15.2 Ethical considerations

Each named Investigator agrees to conduct this study in accordance with applicable United States clinical trial regulations and guidelines, the ICH (E6) GCP guidelines, the IRB/EC and local legal requirements and with the Declaration of Helsinki (1989). The Investigator will conduct all aspects of this study in accordance with all national, state, and local laws of the applicable regulatory agencies.

## 15.3 Informed consent

Per local institutional policies/guidelines, the PI, sub-Investigators and qualified designees assume the responsibility of obtaining written Informed Consent for each subject or the subject's legally authorized representative before any study-specific procedures are performed. Subjects meeting the criteria set forth in the protocol will be offered the opportunity to participate in the study. To avoid introduction of bias, the Investigator must exercise no selectivity with regard to offering eligible subjects the opportunity to participate in the study.

Subjects or legal guardians of all candidate subjects will receive a comprehensive explanation of the proposed treatment, including the nature of the therapy, alternative therapies available, any known previously experienced adverse reactions, the investigational status of the study drug, and other factors that are part of obtaining a proper Informed Consent. Subjects will be given the opportunity to ask questions concerning the study, and adequate time to consider their decision to or not to participate. Informed Consent will be documented by the use of a written Consent Form that includes all the elements required by FDA regulations and ICH guidelines. The form is to be signed and dated by the subject and by the person who administers the consent process. The original signed Consent Form will be filed in the research record. One copy of the signed form will be given to the patient; another copy will be filed in the patient's medical record.

If an amendment to the protocol changes the subject participation schedule in scope or activity, or increases the potential risk to the subject, the Informed Consent Form must be amended. The revised Informed Consent Form must be used to obtain re-consent from any subjects currently enrolled in the study if the subject is affected by the amendment (as determined by the PI or designee) and must be used to document consent from any new subjects enrolled after the approval date of the amendment.

### 15.4 Institutional Review Board/Ethics Committee

The PI will assure that an appropriately constituted IRB/EC that complies with the requirements of 21 CFR Section 56 or written assurance of compliance with ICH (E6) guidelines will be responsible for the initial and continuing review and approval of the clinical study. Before initiation of the study, the PI or designee will forward copies of the protocol and Consent Form to be used for the study to the IRB/EC for its review and approval. The PI or designee will also assure that all changes in the research activity and all unanticipated problems involving risks to human subjects or others will be reported promptly to the IRB/EC, and that no changes will be made to the protocol without prior IRB/EC approval, except where necessary to eliminate apparent immediate hazards to human subjects. The Investigator or designee will be responsible for submitting periodic progress reports to the IRB/EC at intervals appropriate to the degree of subject risk involved in the study, but not less than once per year and at the completion or termination of the study.

### 15.5 Publication statement

The results of this clinical trial may be used for public dissemination in the form of papers, abstracts, posters, or other informational materials to be presented at scientific meetings, or published in professional journals, or as a part of an academic thesis by an investigator. Identifiable patient data may not be used for any of these presentations, manuscripts, or reports unless directed by law.

## 16.0 STATISTICAL CONSIDERATIONS

### 16.1 Efficacy assessment

This study will evaluate two single-arm Phase 2 trials in one protocol. Patients will be randomized 1:1 to one of two arms: CPX-351 and CLAG-M, provided both arms are open to accrual at the time. If only one arm is open, patients will be assigned to the open arm. We will use 3-month overall survival (OS) from date of start of protocol therapy as the primary endpoint: Based on our previous institutional randomized trial comparing CPX-351 at 32 vs 64 units/$m^2$ per dose in this patient population (corresponding to daunorubicin 14 mg/$m^2$/cytarabine 32 mg/$m^2$) or daunorubicin 28 mg/$m^2$/cytarabine 64 mg/$m^2$),[19] we assume a historical 3-month OS of 50% (null hypothesis). Either regimen would be of interest for further study if the true 3-month OS were 70% or higher (alternative hypothesis). Each arm will have a two-stage design with 15 patients in each stage. At the first stage, if 8 or more patients is alive at 3-months, then an additional 15 patients will be enrolled to the arm in the second stage. Observing 19 or more of the 30 patients alive at 3 months will be considered evidence that a regimen warrants further investigation. For each arm, this design has a one-sided type-1 error rate of 9% and power of

83%. The probability of stopping after the first stage of accrual under the null hypothesis is 50% and under the alternative hypothesis is 5%.

### 16.2 Toxicity assessment

In each arm of this trial, we will evaluate each arm separately for early death (death within 28 days of starting protocol therapy) after 10 patients have been enrolled on each arm (note: futility analyses may not be performed at the same time depending on accrual patterns). On our previous randomized trial of CPX-351 as well as our ongoing trial comparing full-dose CLAG-M with reduced-dose CLAG-M in adults with AML and TRM scores >13.1, the median TRM scores were around 25-30, corresponding to an approximately 25-30% estimated early death rate.[10] Based on these historical data, we would not be interested in regimens with true early death rates greater than 25%. For each arm, if we observe 5 or more early deaths in the first 10 patients treated on that arm, we will close the arm to accrual due to the early death rate. If the true early death rate is 25%, the probability of (incorrectly) closing the arm early due to the early death rate is 8%. If the true early death rate is 60%, the probably of (correctly) closing the arm early due to the early death rate is 62%.

### 16.3 Medical resource and quality of life assessments

Resource utilization endpoints and quality of life endpoints will be estimated along with 95% confidence intervals and summarized descriptively.

### 16.4 Trial monitoring

There is no formal data and safety monitoring committee for this study. Toxicity and accrual monitoring as well as response monitoring will be done by the Principal Investigator, Study Coordinator and study Biostatistician. Accrual reports will be generated monthly, and formal toxicity reports will be generated every 6 months.

## 17.0 STUDY TERMINATION

The Principal Investigator reserves the right to terminate this study at any time.

## 18.0 REFERENCES

1. Walter RB, Estey EH. Management of older or unfit patients with acute myeloid leukemia. *Leukemia*. 2015;29(4):770-775.

2. Michaelis LC, Klepin HD, Walter RB. Advancements in the management of medically less-fit and older adults with newly diagnosed acute myeloid leukemia. *Expert Opin Pharmacother*. 2018;19(8):865-882.

3. Juliusson G, Antunovic P, Derolf A, et al. Age and acute myeloid leukemia: real world data on decision to treat and outcomes from the Swedish Acute Leukemia Registry. *Blood*. 2009;113(18):4179-4187.

4. Oran B, Weisdorf DJ. Survival for older patients with acute myeloid leukemia: a population-based study. *Haematologica*. 2012;97(12):1916-1924.

5. Medeiros BC, Satram-Hoang S, Hurst D, Hoang KQ, Momin F, Reyes C. Big data analysis of treatment patterns and outcomes among elderly acute myeloid leukemia patients in the United States. *Ann Hematol*. 2015;94(7):1127-1138.

6. Sorror M, Storer B, Elsawy M, et al. Relative benefit for intensive versus non-intensive induction therapy for patients with newly diagnosed acute myeloid leukemia (AML) using a composite, age-comorbidity-cytogenetic, model [abstract]. *Haematologica*. 2016;101(S1):221-222.

7. Lancet JE, Uy GL, Cortes JE, et al. 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):2684-2692.

8. Halpern AB, Othus M, Huebner EM, et al. Phase 1/2 trial of GCLAM with dose-escalated mitoxantrone for newly diagnosed AML or other high-grade myeloid neoplasms. *Leukemia*. 2018;32(11):2352-2362.

9. Halpern AB, Walter RB. CLAG-M with dose-escalated mitoxantrone for adults with acute myeloid leukemia. *Oncotarget*. 2018;9(93):36543-36544.

10. Walter RB, Othus M, Borthakur G, et al. Prediction of early death after induction therapy for newly diagnosed acute myeloid leukemia with pretreatment risk scores: a novel paradigm for treatment assignment. *J Clin Oncol*. 2011;29(33):4417-4423.

11. Arber DA, Orazi A, Hasserjian R, et al. The 2016 revision to the World Health Organization classification of myeloid neoplasms and acute leukemia. *Blood*. 2016;127(20):2391-2405.

12. Cheson BD, Bennett JM, Kopecky KJ, et al. 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):4642-4649.

13. Döhner H, Estey E, Grimwade D, et al. Diagnosis and management of AML in adults: 2017 ELN recommendations from an international expert panel. *Blood*. 2017;129(4):424-447.

14. Carton E, Bellesoeur A, Mir O. Colony-stimulating factors for febrile neutropenia. *N Engl J Med*. 2013;369(3):285-286.

15. Reiss AL, Aylward E, Freund LS, Joshi PK, Bryan RN. Neuroanatomy of fragile X syndrome: the posterior fossa. *Ann Neurol*. 1991;29(1):26-32.

16. Walter RB, Lee SJ, Gardner KM, et al. Outpatient management following intensive induction chemotherapy for myelodysplastic syndromes and acute myeloid leukemia: a pilot study. *Haematologica*. 2011;96(6):914-917.

17. Vaughn JE, Othus M, Powell MA, et al. Resource utilization and safety of outpatient management following intensive induction or salvage chemotherapy for acute myeloid leukemia or myelodysplastic syndrome: a nonrandomized clinical comparative analysis. *JAMA Oncol*. 2015;1(8):1120-1127.

18. Buckley SA, Jimenez-Sahagun D, Othus M, Walter RB, Lee SJ. Quality of life from the perspective of the patient with acute myeloid leukemia. *Cancer*. 2018;124(1):145-152.

19. Walter RB, Othus M, Orlowski KF, et al. Unsatisfactory efficacy in randomized study of reduced-dose CPX-351 for medically less fit adults with newly diagnosed acute myeloid leukemia or other high-grade myeloid neoplasm. *Haematologica*. 2018;103(3):e106-e109.

# APPENDIX A: TREATMENT-RELATED MORTALITY (TRM) SCORE

## Calculation of Simplified Treatment-Related Mortality (TRM) Score

Includes covariates: performance status (PS), age, platelet count, albumin, secondary AML, white blood cell count (WBC), peripheral blood blast percentage, and creatinine

Score = $100/(1+e^{(-x)})$, with $x$ = -4.08 + 0.89*PS + 0.03*age - 0.008*platelet count - 0.48*albumin + 0.47*(have secondary AML) + 0.007*WBC - 0.007*(peripheral blood blast percentage) + 0.34*creatinine

## Probability of TRM Above and Below Various Simplified TRM Score Cut-offs

| TRM Score Interval | Patients below/ within/above TRM Score Interval (%) | TRM Probability if below TRM Score Interval (%) | TRM Probability if within TRM Score Interval (%) | TRM Probability if above TRM Score Interval (%) |
|---|---|---|---|---|
| 0 – 1.9 | 0/20/80 | - | 1 | 12 |
| 1.91 – 3.9 | 20/20/60 | 1 | 2 | 16 |
| 3.91 – 6.9 | 40/20/40 | 1 | 7 | 20 |
| 6.91 – 9.2 | 60/10/30 | 3 | 7 | 24 |
| 9.21 – 13.1 | 70/10/20 | 4 | 12 | 31 |
| 13.11 – 22.8 | 80/10/10 | 5 | 20 | 41 |
| 22.81 – 100 | 90/10/0 | 6 | 41 | - |

From: Walter RB, Othus M, Borthakur G, Ravandi F, Cortes JE, Pierce SA, Appelbaum FR, Kantarjian HM, Estey EH. Prediction of early death after induction therapy for newly diagnosed acute myeloid leukemia with pretreatment risk scores: a novel paradigm for treatment assignment. *J Clin Oncol*. 2011;29(33):4417-4424.

# APPENDIX B: RESEARCH SUBJECT REGISTRATION FORM

Protocol # RG1005577 Patient Demographics and Eligibility Form
Please fax this completed form to 206-667-1113 for patient registration.
Questions regarding eligibility should go to Dr. Roland B. Walter, pager: 206-560-0657

**#:**_____

Patient Name: _____ _____ ___
Last First MI

Date of Birth: ___ ___/___ ___/ ___ ___ ___ ___
Month Day Year

Planned starting day of treatment: ___ ___/___ ___/ ___ ___ ___ ___
Month Day Year

Ethnicity *(<u>choose one</u>)*: instruct the patient to <u>select one</u> of the following:

- ☐ **Hispanic or Latino** (A person of Cuban, Mexican, Puerto Rican, South or Central American, or other Spanish culture or origin, regardless of race). Term "Spanish Origin" can also be used in addition to "Hispanic" or "Latino"
- ☐ **Not Hispanic or Latino**
- ☐ **Declined to Report**

Race *(<u>check all that apply</u>)*: instruct the patient to <u>select one or more</u> of the following:

- ☐ **American Indian/Alaska Native** (A person having origins in any of the original peoples of North, Central, or South America, and who maintains tribal affiliations or community attachment)
- ☐ **Asian** (A person having origins in any of the original peoples of the Far East, Southeast, Asia, or the Indian subcontinent including, for example, Cambodia, China, India Japan, Korea, Malaysia, Pakistan, the Philippine Islands, Thailand and Vietnam)
- ☐ **Native Hawaiian/Pacific Islander** (A person having origins in any of the original peoples of Hawaii, Guam, Samoa or other Pacific Islands)
- ☐ **Black/African American** (A person having origins in any of the black racial groups of Africa.
- ☐ **White** (A person having origins in any of the original peoples of Europe, the Middle East or North Africa)
- ☐ **Research Subject does not know race**
- ☐ **Declined to Report**

Gender:

- ☐ Male
- ☐ Female
- ☐ Unknown

**<u>ATTACH SIGNED CONSENT AND HIPAA AUTHORIZATION FORMS AND SEND TO THE COORDINATING CENTER STUDY TEAM FOR REGISTRATION.</u>**

## APPENDIX B cont'd
**Protocol # RG1005577 Eligibility**

**I) Inclusion Criteria:**
**Each of the following questions (1-10) must be marked "Yes" (or N/A) for the patient to enroll on Protocol # RG1005577**

1) Yes ☐ No ☐ Patient signed and dated consent form
Date: _____

2) Yes ☐ No ☐ Patient signed and dated HIPAA authorization

3) Yes ☐ No ☐ Age ≥18 years

4) Yes ☐ No ☐ Diagnosis of untreated "high-risk" myeloid neoplasm (≥10% blasts in blood or bone marrow) or AML other than acute promyelocytic leukemia (APL).

5) Yes ☐ No ☐ Treatment-related mortality (TRM) score ≥13.1 as calculated by simplified model available at https://cstaging.fhcrc-research.org/TRM

| | |
|---|---|
| Age: | WBC: Date: |
| Secondary AML ☐ YES ☐ NO | Creatinine: Date: |
| Platelets: Date: | % PB Blasts: Date: |
| Albumin: Date: | Performance Status: Date: |
| **TRM score:** | |

6) Yes ☐ No ☐ No prior therapy for AML other than hydroxyurea or prior low-intensity therapy for low-grade hematologic disorder. Patients with symptoms/signs of hyperleukocytosis or WBC>100,000/μL or with concern for other complications of high tumor burden or leukostasis (e.g. hypoxia, disseminated intravascular coagulation) can be treated with leukapheresis or may receive up to 2 doses of cytarabine (up to 500 mg/m$^2$/dose) prior to enrollment

7) Yes ☐ No ☐ Bilirubin ≤2.0 x mg/dL unless elevation is thought to be due to hepatic infiltration by AML, Gilbert's syndrome, or hemolysis (assessed within 14 days prior to study day 0)

9) Yes ☐ No ☐ Left ventricular ejection fraction ≥45%, assessed within 12 months prior to study day 0, e.g. by MUGA scan or echocardiography, or other appropriate diagnostic modality and no clinical evidence of congestive heart failure.

10) Yes ☐ No ☐ N/A ☐ Women of childbearing potential and men must agree to use adequate contraception.

**II) Exclusion Criteria:**

**The following question (11-16) must be marked "No" for the patient to enroll on Protocol # RG1005577**

11) Yes ☐ No ☐ Myeloid blast crisis of chronic myeloid leukemia (CML), unless patient is not considered candidate for tyrosine kinase inhibitor treatment

12) Yes ☐ No ☐ Concomitant illness associated with a likely survival of <1 year

13) Yes ☐ No ☐ Active systemic fungal, bacterial, viral, or other infection, unless disease is under treatment with anti-microbials and/or controlled or stable (e.g. if specific, effective therapy is not available/feasible or desired [e.g. chronic viral hepatitis, HIV]).

14) Yes ☐ No ☐ Known hypersensitivity to any study drug

15) Yes ☐ No ☐ Confirmed or suspected pregnancy or active breastfeeding.

16) Yes ☐ No ☐ Treatment with any other investigational anti-leukemia agent except commercially-available FLT3 inhibitor for FLT3-mutated patient

Name of person completing form:_____

Signature of Study Investigator:_____Date:_____

# FAX COVER PAGE

**DATE:_____**

**TO: Nicole Stinnett**

**FAX (206) 667-1113**

**RE: RESEARCH SUBJECT REGISTRATION FORM**
**PROTOCOL # RG1005577**

**FROM:_____**

**FAX:_____**

**PHONE:_____**

# APPENDIX C: PATIENT-REPORTED MEASURES

**Date: _____ Subject Initials: _____ Study Subject #: _____**

## EORTC QLQ-C30 (version 3)

We are interested in some things about you and your health. Please answer all of the questions yourself by circling the number that best applies to you. There are no "right" or "wrong" answers. The information that you provide will remain strictly confidential.

Please fill in your initials: |_|_|_|_|
Your birthdate (Day, Month, Year): |_|_|_|_|_|_|_|_|
Today's date (Day, Month, Year): 31 |_|_|_|_|_|_|_|_|

| | | Not at All | A Little | Quite a Bit | Very Much |
|---|---|---|---|---|---|
| 1. | Do you have any trouble doing strenuous activities, like carrying a heavy shopping bag or a suitcase? | 1 | 2 | 3 | 4 |
| 2. | Do you have any trouble taking a long walk? | 1 | 2 | 3 | 4 |
| 3. | Do you have any trouble taking a short walk outside of the house? | 1 | 2 | 3 | 4 |
| 4. | Do you need to stay in bed or a chair during the day? | 1 | 2 | 3 | 4 |
| 5. | Do you need help with eating, dressing, washing yourself or using the toilet? | 1 | 2 | 3 | 4 |

**During the past week:**

| | | Not at All | A Little | Quite a Bit | Very Much |
|---|---|---|---|---|---|
| 6. | Were you limited in doing either your work or other daily activities? | 1 | 2 | 3 | 4 |
| 7. | Were you limited in pursuing your hobbies or other leisure time activities? | 1 | 2 | 3 | 4 |
| 8. | Were you short of breath? | 1 | 2 | 3 | 4 |
| 9. | Have you had pain? | 1 | 2 | 3 | 4 |
| 10. | Did you need to rest? | 1 | 2 | 3 | 4 |
| 11. | Have you had trouble sleeping? | 1 | 2 | 3 | 4 |
| 12. | Have you felt weak? | 1 | 2 | 3 | 4 |
| 13. | Have you lacked appetite? | 1 | 2 | 3 | 4 |
| 14. | Have you felt nauseated? | 1 | 2 | 3 | 4 |
| 15. | Have you vomited? | 1 | 2 | 3 | 4 |
| 16. | Have you been constipated? | 1 | 2 | 3 | 4 |

Please go on to the next page

**Date: _____ Subject Initials: _____ Study Subject #: _____**

| **During the past week:** | **Not at All** | **A Little** | **Quite a Bit** | **Very Much** |
|---|---|---|---|---|
| 17. Have you had diarrhea? | 1 | 2 | 3 | 4 |
| 18. Were you tired? | 1 | 2 | 3 | 4 |
| 19. Did pain interfere with your daily activities? | 1 | 2 | 3 | 4 |
| 20. Have you had difficulty in concentrating on things, like reading a newspaper or watching television? | 1 | 2 | 3 | 4 |
| 21. Did you feel tense? | 1 | 2 | 3 | 4 |
| 22. Did you worry? | 1 | 2 | 3 | 4 |
| 23. Did you feel irritable? | 1 | 2 | 3 | 4 |
| 24. Did you feel depressed? | 1 | 2 | 3 | 4 |
| 25. Have you had difficulty remembering things? | 1 | 2 | 3 | 4 |
| 26. Has your physical condition or medical treatment interfered with your family life? | 1 | 2 | 3 | 4 |
| 27. Has your physical condition or medical treatment interfered with your social activities? | 1 | 2 | 3 | 4 |
| 28. Has your physical condition or medical treatment caused you financial difficulties? | 1 | 2 | 3 | 4 |

**For the following questions please circle the number between 1 and 7 that best applies to you**

29. How would you rate your overall health during the past week?

| 1 | 2 | 3 | 4 | 5 | 6 | 7 |
|---|---|---|---|---|---|---|
| Very poor | | | | | | Excellent |

30. How would you rate your overall quality of life during the past week?

| 1 | 2 | 3 | 4 | 5 | 6 | 7 |
|---|---|---|---|---|---|---|
| Very poor | | | | | | Excellent |

**Date:** _____ **Subject Initials:** _____ **Study Subject #:** _____

# AML-QOL

Please mark the answer for how you felt over the last **7 days**...

| | Never | Rarely | Sometimes | Often | Almost always | |
|---|---|---|---|---|---|---|
| **Physical** | | | | | | |
| 1. I felt fatigued | 1 | 2 | 3 | 4 | 5 | |
| 2. I had enough energy to go about my day. | 1 | 2 | 3 | 4 | 5 | |
| 3. I had enough energy to enjoy the things I do for fun | 1 | 2 | 3 | 4 | 5 | |
| 4. I felt weak all over | 1 | 2 | 3 | 4 | 5 | |
| 5. I felt short of breath | 1 | 2 | 3 | 4 | 5 | |
| **Social** | | | | | | |
| 6. I felt satisfied with my current level of social activity | 1 | 2 | 3 | 4 | 5 | |
| 7. I felt isolated from others | 1 | 2 | 3 | 4 | 5 | |
| **Cognitive** | | | | | | |
| 8. I had trouble concentrating | 1 | 2 | 3 | 4 | 5 | |
| 9. This disease / treatment has taken a toll on my ability to remember things | 1 | 2 | 3 | 4 | 5 | |
| **Anxiety** | | | | | | |
| 10. I felt anxious | 1 | 2 | 3 | 4 | 5 | |
| 11. My worries overwhelmed me | 1 | 2 | 3 | 4 | 5 | |
| 12. I worried about the impact my disease is having on my family | 1 | 2 | 3 | 4 | 5 | |
| 13. It troubled me that I don't feel in control of my own life | 1 | 2 | 3 | 4 | 5 | |
| 14. I was self-conscious about how my appearance has changed | 1 | 2 | 3 | 4 | 5 | |
| 15. I worried about the cost of my treatment | 1 | 2 | 3 | 4 | 5 | |

**Date:** _____ **Subject Initials:** _____ **Study Subject #:** _____

Please mark the answer for how you felt over the last **7 days**...

| **Mood** | Never | Rarely | Sometimes | Often | Almost always | |
|---|---|---|---|---|---|---|
| 16. I felt sad | 1 | 2 | 3 | 4 | 5 | |
| 17. I felt that I have nothing to look forward to | 1 | 2 | 3 | 4 | 5 | |
| 18. I felt hopeless | 1 | 2 | 3 | 4 | 5 | |
| 19. I felt emotionally exhausted | 1 | 2 | 3 | 4 | 5 | |

| **Disease / Treatment Effects** | | | | | | |
|---|---|---|---|---|---|---|
| 20. I was bothered by changes in the way food tastes | 1 | 2 | 3 | 4 | 5 | |
| 21. I have been bleeding easily | 1 | 2 | 3 | 4 | 5 | |
| 22. I had nausea | 1 | 2 | 3 | 4 | 5 | |
| 23. I had fevers | 1 | 2 | 3 | 4 | 5 | |
| 24. I had trouble with my bowels (constipation, diarrhea, cramping, etc.) | 1 | 2 | 3 | 4 | 5 | |
| 25. I had pain | 1 | 2 | 3 | 4 | 5 | |
| 26. I have been able to get a good night's sleep | 1 | 2 | 3 | 4 | 5 | |

| **Quality of Life** | Excellent | Very Good | Good | Fair | Poor | |
|---|---|---|---|---|---|---|
| 27. In general, would you say your quality of life is... | 1 | 2 | 3 | 4 | 5 | |

**Date: _____ Subject Initials: _____ Study Subject #: _____**

**Please tell us about yourself**

**1.** Do you consider yourself to be Latino/a or Hispanic?

No ……..…….. 1
Yes …….. 2

**2.** How would you best describe your race? (Circle all that apply):

Black……..…….. 1
American Indian/Alaskan Native……. 2
Asian ……..……. 3
Hawaiian Native/Pacific Islander…… 4
White…… ……..…….. 5
Other, please specify _____ 6

**3.** What is your gender?

Male……..…… 1
Female…… 2

**4.** How old are you? _____ years

**5.** What is your marital status?

Married/Living with partner…… 1
Single, Never married……..…… 2
Divorced, Separated…… 3
Widowed……..…… 4
Other, specify _____5

**6.** How many children do you have?

None……..…… 0
One…… 1
Two…… 2
Three or more…… 3

If you have children, please tell us how old they are _____

**7.** What is your current living arrangement?

Alone…….. 1
With other adults(s), no dependents*……. 2
With other adults(s) and dependents*……. 3
With dependents* only…… 4
In an institution or retirement home…… 5

* Dependents can include children, elderly or the infirm

**8.** Please estimate the distance from your home to the Fred Hutchinson Cancer Center clinic

_____ miles

**9.** What is your current work status? (Circle all that apply)

In school……. 1
Working full time…… 2
Working part time…….. 3
Homemaker…… 4
Disabled……. 5
On medical leave from work…….. 6
Unemployed, looking for work…….. 7
Unemployed, not looking for work…… 8
Retired…… 9
Other, please specify_____11

**10a.** What type of insurance coverage do you have? (Circle all that apply)

None.....1
Group insurance through an employer (yours or family member) ....2
Private insurance or COBRA.....3
Military, TRICARE, CHAMPVA or Veterans Administration.....4
Medicaid .....5
Medicare .....6
State high-risk pool for persons previously denied insurance .....7
Other, specify _____8

**10b.** If you have **private or group insurance**, does it provide:

Full coverage for almost any physician, clinic, or hospital…..…… A
Full coverage for physicians, clinics or hospitals within the plan… B

**11.** What is the highest grade of school you have completed?

Grade school…….. 1
Some high school…… 2
High school graduate……. 3
Some college…….. 4
College graduate…… 5
Postgraduate degree…….. 6

**12.** What was your approximate annual family income in the year prior to your diagnosis?

Under $15,000…… 1
$15,000 - $24,999…….. 2
$25,000 - $49,999…….. 3
$50,000 - $74,999…….. 4
$75,000 - $99,999…….. 5
$100,000 or above…….. 6

**13.** To what extent does religion or spirituality guide you in your daily activities?

Not at all……. 1
Very little……. 2
Somewhat……. 3
Quite a bit……. 4
A great deal…….. 5