University of California
Hematologic Malignancies Consortium
UCD UCI UCLA UCSD UCSF

Phase II study of the combination of CPX-351 and Glasdegib in previously untreated patients with Acute Myelogenous Leukemia with MDS related changes or therapy-related Acute myeloid leukemia: A University of California Hematologic Malignancies Consortium Protocol (UCHMC1913/UCI 18-105)

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Study Agent: Daunorubicin and Cytarabine liposomal CPX-351 (CPX-351®)
Glasdegib (Daurismo™)

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(v7.0)	August 4, 2021
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Signature Page

The signature below constitutes the approval of this protocol and the attachments, and provides the necessary assurances that this trial will be conducted according to all stipulations of the protocol, including all statements regarding confidentiality, and according to local legal and regulatory requirements and applicable U.S. federal regulations and ICH guidelines.

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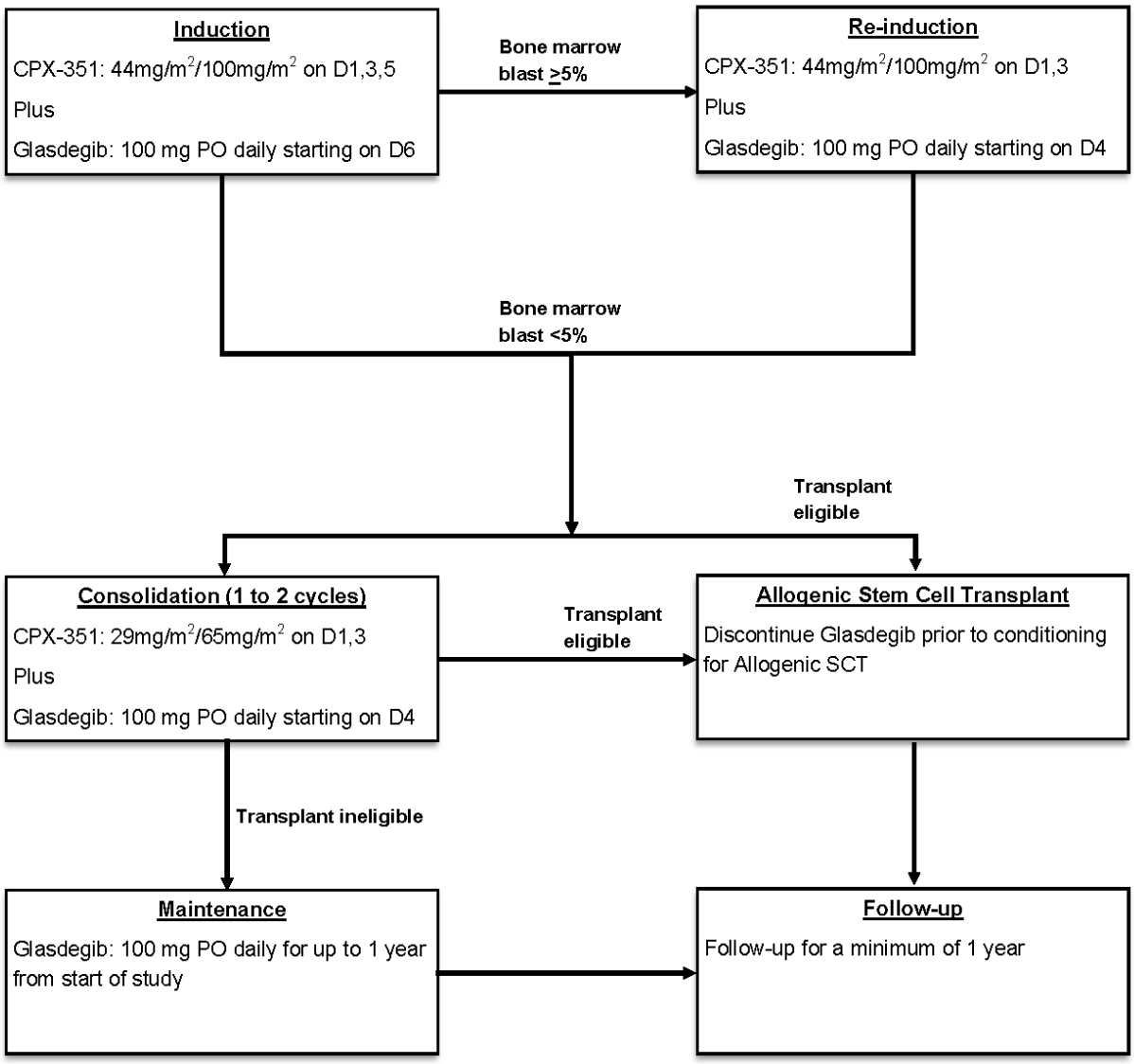
LIST OF ABBREVIATIONS

AE	Adverse event
ALT	Alanine aminotransferase
AML	Acute Myeloid Leukemia
ANC	Absolute neutrophil count
aPTT	Activated partial thromboplastin time
AST	Aspartate aminotransferase
CBC	Complete blood count
CML	Chronic Myelogenous Leukemia
CMML	Chronic Myelomonocytic Leukemia
CMP	Comprehensive metabolic panel
CNS	Central Nervous System
CR	Complete Remission
CrCl	Creatinine clearance
CRF	Case Report Form
CRi	Complete Remission with incomplete recovery
CTCAE	Common Terminology Criteria for Adverse Events
DLT	Dose limiting toxicity
DSMB	Data and Safety Monitoring Board
ECG	Electrocardiogram
ECHO	Echocardiogram
ECOG	Eastern Cooperative Oncology Group
EFS	Event-free survival
ET	Essential Thrombocythemia
FDA	Food and Drug Administration
FISH	Fluorescence in situ hybridization
GCP	Good Clinical Practice
GFR	Glomerulus filtration rate
GI	Gastrointestinal
HCG	Human chorionic gonadotropin
Hgb	Hemoglobin
HIPAA	Health Insurance Portability and Accountability Act
HIV	Human Immunodeficiency virus
HSCT	Hematopoietic Stem Cell Transplantation
ICF	Informed consent form
INR	International normalized ratio
IRB	Institutional Review Board
LAIP	Leukemia-associated immunophenotypes
LDAC	Low dose cytarabine

LDH	Lactate dehydrogenase
LSC	Leukemic stem cells
LVEF	Left Ventricular Ejection Fraction
MDS	Myelodysplastic Syndrome
MFC	Multiparameter flow cytometry
MPN	Myeloproliferative Neoplasm
MRD	Minimal/Measurable Residual Disease
NCI	National Cancer Institute
NGS	Next Generation Sequencing
NYHA	New York Heart Association
ORR	Overall response rate
OS	Overall survival
PI	Principal investigator
Plt	Platelet
PO	per os/by mouth/orally
PT	Prothrombin time
PV	Polycythemia Vera
RFS	Relapse-free survival
RSC	Radiation Safety Committee
RT-PCR	Reverse transcription polymerase chain reaction
SAE	Serious adverse event
SGOT	Serum Glutamic Oxaloacetic Transaminase
SMO	Smoothened
SPGT	Serum Glutamic Pyruvic Transaminase
Sub-I	Sub-investigator
ULN	Upper limit of normal
UPR	Unanticipated problem
WBC	White blood cell
WHO	World Health Organization

STUDY SCHEMA



*Treatment will be discontinue for induction failure, relapsed or progressed disease, treatment intolerance, continuation to HSCT or at any point based on the investigator's discretion. At discontinuation, subjects will enter the follow-up portion of the study.

STUDY SUMMARY

Title	Phase II study of the combination of CPX-351 and Glasdegib in previously untreated patients with Acute Myelogenous Leukemia with MDS related changes or therapy-related Acute myeloid leukemia**:** A University of California Hematologic Malignancies Consortium Protocol (UCHMC1913/UCI 18-105)
Short Title	CPX-351 and Glasdegib for newly diagnosed acute myelogenous leukemia with MDS related changes or therapy-related Acute myeloid leukemia
Phase	Phase 2
Sponsor	University of California Hematologic Malignancies Consortium
Methodology	Single-arm, open-label trial
Study Duration	2-3 years
Study Center(s)	The University of California Hematologic Malignancies Consortium: University of California, Irvine University of California, Los Angeles University of California, San Diego University of California, San Francisco University of California, Davis
Objectives	*Primary objective*: • Determine the efficacy of the combination of CPX-351 and Glasdegib for newly diagnosed AML with MDS related changes and therapy-related AML *Secondary objectives*: • Determine the toxicity of the combination of CPX-351 and Glasdegib in adults with newly diagnosed AML with MDS related changes • Determine the rate of response by measuring overall remission rate (ORR) of the combination. The overall remission rate includes complete remission (CR) and complete remission with incomplete recovery (CRi) • Determine the durability of response by measuring relapse free survival (RFS) • Determine the survival and length of survival by measuring Overall Survival (OS) • Determine the time to return of normal hematopoiesis, duration of response • Determine the proportion of patients who go on to receive allogeneic HSCT *Exploratory objectives*: • Determine if MRD status based on multiparameter flow cytometry from University of Washington can be used as a surrogate marker for survival • To determine if gene expression profiling can be biomarkers of response
Number of Subjects	30 evaluable subjects
Diagnosis and Main Inclusion Criteria	1. Previously untreated therapy-related AML or AML with myelodysplastic related changes as described by WHO

	2016 a. AML arising in MDS (including CMML) or MDS/MPN syndrome b. AML with MDS-related cytogenetic abnormalities (Appendix A, metaphase FISH allowable as surrogate for cytogenetics) c. AML with multilineage dysplasia involving the presence of 50% or more dysplastic cells in at least two cell lines and in the absence of mutation in NPM1 or biallelic CEBPA (as per WHO 2016) 2. Adults 18 years of age or older 3. ECOG performance status 0 to 2 4. Adequate organ function as defined as: a. Left Ventricular Ejection Fraction (LVEF) > 50% b. Serum total bilirubin < 2.0 mg/dL, unless considered due to Gilbert's disease or leukemic involvement c. AST, ALT and alkaline phosphatase < 3 times the upper limit of normal, unless considered due to leukemic involvement d. Serum creatinine < 2.0 mg/dL, or creatinine clearance > 40 mL/min based on Cockcroft-Gault GFR 5. Absence of unstable cardiac disease defined as myocardial infarction within 6 months, uncontrolled heart failure, or uncontrolled cardiac arrhythmia 6. Ability to understand and the willingness to sign a written informed consent or subject's legally authorized representative (LAR) has provided informed consent prior to any study-specific activities/procedures being initiated when the subject has any kind of condition that, in the opinion of the investigator, may compromise the ability of the subject to give written informed consent 7. Women of child-bearing potential and men with partners of child-bearing potential must agree to use 2 methods of birth control or be surgically sterile, or abstain from heterosexual activity for the course of the study through 120 days after the last dose of study medication A woman of child-bearing potential is any female (regardless of sexual orientation, having undergone a tubal ligation, or remaining celibate by choice) who meets the following criteria: • Has not undergone a hysterectomy or bilateral oophorectomy; or • Has not been naturally postmenopausal for at least 12 consecutive months (i.e., has had menses at any time in

	the preceding 12 consecutive months) Women of child-bearing potential has negative pregnancy test within 72 hours of initiating study drug dosing Male subjects must agree to use a latex condom during sexual contact with females of childbearing potential even if they have had a successful vasectomy starting with the first dose of study therapy through 120 days after the last dose of study therapy 8. Leukapheresis, corticosteroid and hydroxyurea are permitted as initial management of hyperleukocytosis at the investigator's discretion for up to 7 days after starting study therapy. Hyperleukocytosis is defined as greater than 30k WBC. When possible, a bone marrow biopsy for screening should be performed prior to the initiation hyperleukocytosis management
Exclusion Criteria	1. Prior treatment with Glasdegib or CPX-351 2. Previously treated AML except for initial management of hyperleukocytosis. Treatment with hypomethylating therapy for MDS is allowable but not since their diagnosis of AML. No prior treatment with cytarabine or daunorubicin are allowed 3. Concurrent *FLT3* mutation that the treating physician deems necessary to treat with midostaurin, whereas patients with *FLT3-mutated* AML not treated with midostaurin can be enrolled. Patients with known Core Binding Factor –t(8;21), inv(16), t(16;16) are allowed for study participation at the treating investigator's discretion 4. Active CNS or testicular involvement by leukemia; diagnostic lumbar puncture is not required 5. History of neurologic disorder including but not limited to: prior seizure, epilepsy, structural brain abnormality, benign brain tumor, stroke, brain injuries, dementia, movement disorder or other significant CNS abnormalities 6. Baseline QT corrected interval based on Fridericia's formula (QTcF) interval > 450 ms 7. Acute coronary syndrome in the past 12 months, NYHA class III or VI 8. Known history of Wilson's disease or other copper handling disorder

	9. History of GI malabsorptive disease 10. Has a known additional malignancy that is progressing or requires active treatment. Exceptions include basal cell carcinoma of the skin, squamous cell carcinoma of the skin, or in situ cervical cancer that has undergone potentially curative therapy 11. Known HIV infection 12. Active hepatitis B or hepatitis C infection (patients who successfully completed curative hepatitis C therapy can be enrolled) 13. Any uncontrolled infection, active bacterial or viral infection manifesting as fevers or hemodynamic instability within the past 72 hours 14. Proven active invasive fungal infection 15. Is pregnant or breastfeeding, or expecting to conceive or father children within the projected duration of the trial, starting with the pre-screening or screening visit through 120 days after ^{the} last dose of trial treatment 16. Severe or uncontrolled medical disorder that would, in the investigator's opinion, impair ability to receive study treatment (i.e., uncontrolled diabetes, chronic renal disease, chronic pulmonary disease or active, uncontrolled infection, psychiatric illness/social situations that would limit compliance with study requirements 17. Current or anticipated use of other investigational agents 18. For patients with prior anthracycline exposure, the cumulative life-time dose should not exceed 386mg/m^2 at the time of study entry (to convert different anthracycline to daunorubicin-equivalent, see Appendix H for conversion factors)
Study Product(s)	CPX-351 and Glasdegib
Duration of administration	• CPX-351 will be administer during Induction on days 1, 3 and 5. Glasdegib will be given starting on day 6 and continuing until beginning of consolidation • Consolidation can be either 1 or 2 cycles. CPX-351 will be administered during days 1 and 3. Glasdegib will begin on day 4 and continue daily • If the patient is a candidate for HSCT and moves forward with HSCT, then Glasdegib will be discontinued at least 7 days prior

	• During Maintenance, Glasdegib will be taken daily for up to 1 year
Reference therapy	Lancet Phase II CPX-351 versus 7+3. Blood 2014
Study Outcome Measures	*Safety* • Common Terminology Criteria for Adverse Events (CTCAE) version 5.0 • Adverse events • Serious adverse events • Adverse events leading to discontinuation of study therapy *Efficacy* • Event-free survival • Objective response rate → complete remission (CR) plus complete remission with incomplete hematologic recovery (CRi) • Relapse free survival • Duration of response • Time to return of normal hematopoiesis • Overall survival • Proportion of patients who go on to receive allogeneic HSCT *Exploratory outcome measures* • Determine if MRD status can be used as a surrogate marker for survival • Determine if using gene expression profiling can identify subset of patients who are more likely to respond
Rationale	In the phase III trial of CPX-351 versus 7+3 chemotherapy for first line treatment of secondary AML in patients 60-75 years of age, 309 patients were treated with either of the two regimen. There was a statistically significant improvement in overall survival as well as overall remission rate in the CPX-351 arm. Glasdegib in combination with LDAC has been shown to have tolerable side effect profile while improving survival outcomes in some patients with elderly AML who are unfit for chemotherapy. In the phase II trial of Glasdegib with cytarabine and daunorubicin, 69 patients with newly diagnosed AML were treated with the combination. The overall survival of the combination was improved to historical controls. We hypothesize that the combination of CPX-351 with Glasdegib will demonstrate improvements in event-free survival as well as being well tolerated.

Study Title: Phase II study of the combination of Glasdegib and CPX-351 in previously untreated patients with Acute Myelogenous Leukemia with MDS related changes or therapy-related Acute myeloid leukemia: A University of California Hematologic Malignancies Consortium Protocol (UCHMC1913/UCI 18-105)

PI: Deepa Jeyakumar, MD, Assistant Clinical Professor of Medicine
Institution: Chao Comprehensive Cancer Center, University of California Irvine, Orange, CA

	Screening	Induction/ Re-induction[E] (Days 1-75)							Consolidation[J] (Days 1-55)				Maintenance[K] (Days 1-28)	EOT	Follow-up
Protocol Activity	**≤ 28 days prior to D1**	**D1**	**D3**	**D5**	**D6**	**Weekly (+/- 2 days)**	**Induction response D20 (+1 day)**	**Remission evaluation D28 to D60**	**D1**	**D3**	**D4**	**Weekly (+/- 2 days)**	**D1 (+/- 7 days)**	**Within 7 days of last dose**	**Every 3 month (+/- 14 days)**
Informed Consent[A]	X														
Clinical Evaluation and Procedures															
Eligibility Review	X														
Disease Classification	X														
Medical History	X														
Concomitant Medication Review	X	For the entire duration of study participation													
AE/ SAE Review		From when participant start study therapy on induction day 1 up until 28 days after the last dose of study therapy/ and until resolution of any treatment-related AE/ SAE													
Physical Exam	X	X				X			X			X	X	X	X
ECOG Performance	X	X				X			X			X	X	X	X
12-lead ECG	X				X[G]	X[G,H]					X[G]			X	
ECHO	X														
BMA/BMBX	X[C]						X	X				X[N]		X[L]	
MRD (send to UW)							X	X						X[L]	
Cytogenetics /Molecular profiling	X[C]						X	X						X[L]	

Research sample for gene expression correlatives	X[C, D]						X[D]	X[D]						X[D,L]	
HSCT information/ Survival Status															X[M]
Laboratory Assessments															
Hematology	X	X				X	X	X	X			X	X	X	X
Chemistry	X	X				X			X			X	X	X	
Urinalysis	X														
Coagulation	X														
Pregnancy Test[B]	X								X				X		
Study treatment															
CPX-351 Infusion		X	X	X[F]					X	X					
Glasdegib					X[I]						X[I]		X		

Abbreviations:
AE=Adverse Event, SAE=Serious Adverse Event, ECOG=Eastern Cooperative Oncology Group, ECG=Electrocardiogram, ECHO=Echocardiogram, BMA=Bone Marrow Aspirate, BMBX=Bone Marrow Biopsy, MRD=Minimal/Measurable Residual Disease, UW=University of Washington, HSCT=Hematopoietic Stem Cell Transplant, D=Day, EOT=End of Treatment

Footnotes:
[A] Must be obtained before undergoing any protocol-specific study procedures, unless as part of standard of care
[B] Serum beta-HCG should be done for any female of child-bearing potential
[C] Bone marrow collections do not need to be repeated if a diagnostic bone marrow procedure was done prior to informed consent and is done within 28 days of starting day 1 of induction
[D] Collect bone marrow aspirate for research sample for gene expression correlatives; if patient has any circulating blasts, then peripheral blood can be collected instead of aspirate; if bone marrow is a “dry tap,” then this sample does not need to be collected
[E] Re-induction is based on response evaluation bone marrow done on day 20 of induction. If there is greater than 5% blast count, re-induction is recommended. The final decision for re-induction is based on investigator’s discretion. For patients who will be treated with re-induction, an ECHO and pregnancy test (for female patients of child-bearing potentials) will be done before starting re-induction
[F] Omit CPX-351 on day 5 for participants receiving re-induction

[G] ECG is done pre-dose and can be done up to 24 hours before planned glasdegib dosing
[H] During induction, repeat an ECG a week after starting glasdegib (around day 13-15). If clinically significant abnormal ECG or clinically significant changes in QTc, then refer to section 6.4 for further guidance. If normal or non-clinically significant abnormalities and/or changes in QTc, additional ECG monitoring is not required and is done per the treating investigator's discretion
[I] Glasdegib should continue until day 1 of the next cycle of CPX-351
[J] Up to two cycles of consolidation is allowed. These are 28 day cycles, unless delays are necessary. In the case of a delay, glasdegib will continue daily until the start of CPX-351 infusion in the next cycle. If the patient will proceed to allogenic SCT, then consolidation can be skipped or shorten. Glasdegib will be stopped at least 7 days before transplant.
[K] These are 28 days cycle. Patients who are not receiving HSCT will be allowed to proceed to glasdegib maintenance for up to 1 year of study start
[L] At the time of suspected relapse, a bone marrow aspirate/ biopsy will be done and samples will be collected. Patients will discontinue glasdegib in anticipation of start of treatment for relapsed disease
[M] Patients who undergo HSCT will have their HSCT information collected and will only require survival follow up. No other procedures or requirements will be collected
[N]At the end of consolidation, a bone marrow biopsy is recommended but is not required by the protocol. If it is done, it is suggested to send for cytogenetics, molecular studies, and MRD.

1.0 BACKGROUND AND RATIONALE

1.1 Disease Background

According to the SEER database in 2018, there are an estimated 19,250 cases of AML diagnosed [1]. Unfortunately, there are 10,670 estimated deaths attributed to AML that same year [1]. The prognosis of patients with acute myelogenous leukemia with MDS related changes and secondary AML is poor [2]. The long term survival of these patients with the standard of care “7+3” chemotherapy is low. This is related to lower rates of complete remission as well as relapse after obtaining complete remission related to residual disease.

1.2 AML with myelodysplastic changes

The presence of multilineage dysplasia alone does not classify a case as AML with myelodysplastic-related changes when a mutation of NPM1 or biallelic mutation of CEBPA is present [3]. The outcome of 318 cases of NPM1 mutated AML were examined retrospectively [4]. Multilineage dysplasia was present in 23% of them. The outcomes of the NPM1 mutated AML were equivalent independent of the status of multilineage dysplasia. These results were confirmed in another retrospective analysis of 130 patients [5]. NPM1 mutations were present in 68 patients. There were 19 cases of multilineage dysplasia in AML with NPM1 mutation and 13 cases of multilineage dysplasia in AML without NPM1 mutation. The outcomes of the patients with AML with NPM1 mutation were similar whether multilineage dysplasia was present or not. The outcome of 108 cases of CEPBA mutated AML were examined retrospectively [6]. The cases with multilineage dysplasia had lower white blood cell counts. However, the biologic characteristics, cytogenetic and mutational analysis were similar. There was no difference in the 2 year overall survival or event free survivals in patients with multilineage dysplasia or without multilineage dysplasia.

In cases lacking these mutations, the morphologic detection of multilineage dysplasia (defined as the presence of 50% of more dysplastic cells in at least 2 cell lines) remains a poor prognostic indicator and is sufficient to make a diagnosis of AML with myelodysplastic changes [3]. The outcome of 177 cases of AML with multilineage dysplasia without NPM1 were analyzed retrospectively [7]. There were 43 cases of AML with WHO criteria of multilineage dysplasia. There were 16 cases of AML with significant dysplasia but not sufficient for WHO criteria for multilineage dysplasia. There were 80 cases of AML without evidence of multilineage dysplasia. The presence of multilineage dysplasia was associated with lower complete remission rates after initial frontline chemotherapy. Furthermore, if patients were censored for going to transplant, cases of AML with multilineage dysplasia were associated with a shorter survival. These results were confirmed in another series of cases of AML without NPM1 mutation, there was an inferior response to induction chemotherapy at 53% versus 85% [5]. Furthermore, in these cases, multilineage dysplasia was an unfavorable prognostic value for response rate and survival in multivariable analysis.

1.3 Minimal/Measurable Residual Disease (MRD) in AML

While assessment of “measurable” residual disease in AML has been standardized in ALL, the assessment of measurable residual disease (MRD) in AML is still evolving. There are three different methods of assessing MRD which are multiparameter flow cytometry (MFC), NGS or RT-PCR based [8]. In the US, MFC has been more widely tested while in Europe, RT-PCR based assays are more common. MFC based assays will measure for leukemia-associated

immunophenotypes (LAIP) with CD2, CD4, CD7, CD13, CD15, CD19, CD33, CD34, CD45, CD56, CD123, CD117 and HLA-DR. RT-PCR will measure for mutations in CBFB-MYH11, FTL3-ITD, IDH1 and IDH2, NPM1, RUNX1/RUNXITI, t(10,11)-KMT2A-MLLT10, t(11,19)-KMT2A-ELL, t(6,11)- KMT2A-MLLT4, t(9,11)- KMT2A-MLLT3 and WT1.

Recently, NGS based assays are being present for certain mutations including NPM1, RUNX1, FLT3-IRD, IDH1 and IDH2. However, particular attention was made to the sensitivities of the various assays. Furthermore, it is important to separate out age-related clonal hematopoiesis from leukemia-specific signature. Specific examples of mutations that are more likely to be clonal hematopoiesis including DNMT3A, TET2 and ASXL1. In the recent study that utilized NGS testing, when mutations related to clonal hematopoiesis is separated, then the difference in relapse rate was clearly different between the MRD positive and MRD negative group [9].

Assessment of MRD by MFC has been tested in various trials. Recently, in patients with biallelic CEPBA mutated AML, the assessment of MRD by MFC at the end of consolidation was able to distinguish a high and low risk group of patients [10]. Patients that were MRD positive at the end of consolidation had lower relapse-free survival than patients who were MRD negative at the end of consolidation.

Similarly, there are been several trials using MRD by MFC to determine if we can determine higher risk patient population for relapse in patients with AML undergoing induction chemotherapy [11,12].

1.4 Glasdegib

Aberrant signaling in the hedgehog pathway has been identified in leukemia and specifically in leukemia stem cells. Upregulation of these pathways has been shown in resistant AML cell lines. Therefore, inhibition of this pathway with an inhibitor is an attractive target for anti-leukemia therapy. Glasdegib is a small molecule inhibitor of smoothened (SMO) in the Sonic Hedgehog pathway [13].

1.4.1 Preclinical work with Glasdegib

Glasdegib inhibits SMO in vitro and induces significant antitumor activity in vivo [14-15]. Furthermore, SMO inhibition has been shown to reduce leukemia stem cells (LSC) population in xenograft models by inhibition of the Hedgehog (Hh) signaling and reduction in cell populations expressing LSC markers [16].

1.4.2 Early clinical work with Glasdegib

In the phase 1 dose-escalation study in patients with advanced myeloid malignancies, Glasdegib was well tolerated as a single agent [17]. The most common treatment related adverse effects were dysgeusia, decreased appetite and alopecia. Based on these results, subsequent phase II trial were focused on patients with acute myeloid leukemia, myelodysplastic syndrome and myelofibrosis. In a separate Phase 1 trial in Japanese patients with hematologic malignancies, patients received Glasdegib as a single agent as a once a daily for each 28 days cycle after they had received a single dose five days prior to starting the first cycle. There were similar treatment related adverse events noted in patients who received Glasdegib as a single agent [18]. Furthermore, the GLI1 was downregulated in the skin of these patients by 80%. Downregulation of GLI1 is associated with inhibition of tumor growth. While there is no direct evidence that GLI1 suppression in skin correlates with suppression in

hematologic malignancies, this pathway has been shown to be part of the pathogenesis of the basal cell carcinoma [19, 20].

1.4.3 Early clinical trials with Glasdegib in combination

In the phase 1b study, Glasdegib was studied in combination with other anti-leukemic therapies in patients with newly diagnosed AML or high risk MDS [21]. There were three arms. Arms A and B for patients who were unfit for standard chemotherapy. Arm A was Glasdegib with low dose cytarabine. Arm B was Glasdegib with decitabine. Arm C was Glasdegib with standard cytarabine and daunorubicin for patients who were fit for standard induction chemotherapy. The study was following the standard 3+3 dose escalation design. The primary endpoint was dose limiting toxicity (DLT). There were 10 additional patients in the expansion cohorts of arms A and C. There were no DLT's observed in arms A and B. In Arm C, there was one patient with grade 4 neuropathy. The most common treatment related adverse events were mostly grade 1 or 2. There were some cases of dysgeusia, muscle spasms and alopecia. Overall, thirty one percent of patients had complete remission (CR) or complete remission with incomplete recovery (CRi). In the phase 2 portion of this trial, Glasdegib with low dose cytarabine was found to improve overall survival compared to low dose cytarabine alone [22]. Based on the results of this trial, FDA approved Glasdegib in combination with low dose cytarabine with patients with newly diagnosed AML who are over the age of 75 or who have chronic health problems that preclude intensive chemotherapy on November 21, 2018 [23]. These results have been updated and published [24]. Of note, Glasdegib has not been studied in patients with severe renal or moderate-to-severe hepatic impairment.

Based on the results of the phase I trial of the combination of Glasdegib with standard chemotherapy, a phase II open-label study of Glasdegib in combination with cytarabine and daunorubicin with patients with newly diagnosed AML or high-risk MDS was initiated [25]. Patients received Glasdegib started on day -3 at 100mg orally daily in continuous 28 days cycles. They also received cytarabine at 100mg/m2 on day 1-7 and daunorubicin at 60mg/m2 on day 1-3. Once in remission, they received cytarabine consolidation at 1gm/m2 twice daily on days 1, 3, 5 of each cycle for 2-4 cycles total. This was followed by maintenance Glasdegib for up to 6 cycles. The complete remission rate was 46%. Among patients older than 55, the complete remission rate was 40%. Among all 69 patients, the median overall survival was 14.9 months. The most common treatment related adverse reactions were diarrhea and nausea. The combination was well tolerated.

In the non-intensive arm of the phase II trial with LDAC with Glasdegib, there were several genes that correlated with improved OS [26]. Lower levels of expression of FOXM1 and MSI2 and higher expression levels of BCL2 and CCND2 correlated with improved overall survival. In the intensive treatment arm with Glasdegib and cytarabine/daunorubicin, higher PTCH1 expression correlated with improved overall survival. Furthermore, in the intensive arm, mutations in FLT3, TP53, CEP170, NPM1 and ANKRD26 correlated with overall survival. Interesting to note, that patients with AML with mutated FLT3 (which is generally a poor risk group) did better than AML with wild type FLT3. Therefore, we will be measuring some of these genes to see if this observation of their correlation with improved overall survival is confirmed.

1.5 CPX-351

CPX-351 was designed as a fixed 5:1 molar ratio of cytarabine to daunorubicin within a liposomal carrier.

1.5.1 Preclinical work with CPX-351

There is strong supporting pre-clinical evidence that CPX-351 may be more effective than 7+3. Based on in vitro work, the highest proportion of synergy occurs at 5:1 molar ratio [27]. There is relatively high accumulation and persistence of the liposomal drug within the marrow [28].

Finally, there is selective uptake within the leukemic cells [29].

1.5.2 Early clinical work with CPX-351

In the first-in-man of CPX-351 in relapsed and refractory AML, CPX-351 was found to be safe and producing complete remissions in eight out of 33 patients with refractory leukemia [30]. There was a dose-limiting toxicity (DLT) noticed in 3 out of 6 patients in the phase 1 trial at dose level 134 units/m^2 that led to dose reduction. The DLT was congestive heart failure, hypertensive crisis and cytopenias beyond day 56. This led to using a lower dose level of 101 units/m^2 in the next cohort which was well tolerated without DLTs. Subsequent trials have used the dose to 100units/m^2.

In the phase II trial, CPX-351 was compared to investigator's choice of first salvage chemotherapy in 125 patients with AML in first relapse [31]. In this study, CPX-351 did not meet the 1 year survival improvement in the overall population. However, there were higher response rates in the poor-risk group as well as event-free survival and overall survival. Also, the 60-day mortality rate was lower than with salvage chemotherapy in the poor-risk group.

1.5.3 Further development of CPX-351

In the phase II trial, the outcomes were compared of CPX-351 versus traditional cytarabine/daunorubicin (7+3) chemotherapy in 126 patients with newly diagnosed AML [32]. CPX-351 had higher response rates than traditional cytarabine/daunorubicin (7+3) chemotherapy at 66.7% versus 51.2% with p=0.07 which met the predefined criteria of p<0.1. There was a prolongation of event-free survival as well as overall survival but this was not significant. The recovery after cytopenias were more prolonged after CPX-351 with more grade 3-4 infections but without increased deaths due to infection. Aside for risk of infection, patients did have diarrhea, nausea, edema, constipation, rash, febrile neutropenia. However, these side effects were also seen with the cytarabine/daunorubicin arm. Furthermore, the 60-day mortality was not increased in the CPX-351 arm. This provided the rationale for a phase III trial.

In the phase 3 clinical trial, CPX-351 has improved overall survival rates, event-free survival and response rate (complete response and complete responses with incomplete recovery) to traditional 7+3 chemotherapy in the patients with previously untreated AML with MDS related changes as well as AML evolving out of MDS [33]. There was a prolongation in recovery of cytopenias seen again. There were similar rates of grade 3-5 infections between CPX-351 and standard cytarabine/daunorubicin induction chemotherapy. At median follow-up of 21 months, the median overall survival was 9.5 months in CPX-351 arm versus 5.9 months in the standard 7+3 arm. The complete remission/complete remission with incomplete recovery (CR/CRi) rate were 47% with CPX-351 versus 33% in 7+3 arm (p=0.008). The duration of remission was similar between the two groups at 6.9 months versus 6.1 months in CPX-351 and 7+3 arm, respectively. As a result of improved response rates, more patients receiving CPX-351 were also able to go to transplant than 7+3 arm at 34% versus 25% p=0.049 [34]. Furthermore, as an exploratory endpoint, there was improved post-transplant survival in patients who received CPX-351 versus 7+3 chemotherapy [35].

1.6 Rationale for the combination of Glasdegib and CPX-351

While either of these drugs separately has proven to improve the outcome of this patient population, it remains clear that effective treatment options for this patient population still is an unmet medical need. CPX-351 has been shown to have better response rates and survival rates compared to 7+3 chemotherapy. Glasdegib has been shown to improve upon survival outcomes when added to 7+3 chemotherapy. Given the increased cytoreduction from CPX-351 which can lead to higher rates of complete remission and the improvement in survival outcomes seen with Glasdegib in combination with cytotoxic chemotherapy like cytarabine/daunorubicin, it is reasonable that the combination may prove to have improvements in outcomes for patients.

1.7 Correlative Studies

In the non-intensive arm of the phase II trial with LDAC with Glasdegib, there were several genes that correlated with improved OS [26]. Lower levels of expression of FOXM1 and MSI2 and higher expression levels of BCL2 and CCND2 correlated with improved overall survival. In the intensive treatment arm with Glasdegib and cytarabine/daunorubicin, higher PTCH1 expression correlated with improved overall survival. Furthermore, in the intensive arm, mutations in FLT3, TP53, CEP170, NPM1 and ANKRD26 correlated with overall survival. Interesting to note, that patients with AML with mutated FLT3 (which is generally a poor risk group) did better than AML with wild type FLT3. Therefore, we will be measuring some of these genes to see if this observation of their correlation with improved overall survival is confirmed.

Furthermore, we will be measuring MRD at the end of induction by MFC at University of Washington. We would like to determine if MRD negative status at the end of induction correlated with survival outcomes in this patient population.

2.0 STUDY OBJECTIVES

The purpose of this trial is to examine the combination of Glasdegib and liposomal daunorubicin/cytarabine CPX-351 in previously untreated patients with AML with MDS related changes or therapy-related AML.

2.1 Primary Objective/ Primary Endpoint

2.1.1 Primary Objective	2.1.2 Primary Endpoint
• To determine the efficacy when using the combination of CPX-351 and Glasdegib to treat patients with newly diagnosed AML with MDS-related changes or treatment related AML	• Efficacy will be measured by following the 6 month event-free survival (EFS). EFS is defined as the as the time from screening biopsy to the date of confirmed disease progression, relapse from CR/CRi, treatment failure, or death, whichever comes first. Of interest, a 6 month EFS will be important to follow

2.2 Secondary Objectives/ Secondary Endpoints

2.2.1 Secondary Objectives	2.2.2 Secondary Endpoints
• To evaluate any toxicities associated with the combination	• Adverse events are to be captured and characterized by type, frequency, severity (as graded by NCI CTCAE v.5.0), timing, seriousness and relationship to study drugs
• To evaluate the rate of response	• The overall response rate (ORR) includes the rate of complete remission (CR) and complete remission with incomplete count recovery (CRi)
• To evaluate the durability of response	• Durability of response will be measured by relapse-free survival (RFS), defined as the amount of time a patient remains in remission after having achieve a CR or CRi
• To evaluate survival and the length of survival	• Survival follow up information will be collected to determine overall survival (OS)
• To evaluate the time to return of normal hematopoiesis	• Laboratory studies including complete blood counts (CBCs) will be collected to evaluate the recovery of bone marrow hematopoiesis
• To evaluate the proportion of subjects who go on to receive allogenic HSCT	• HSCT information will be collected for patients who proceed to allogenic HSCT

2.3 Exploratory Objectives/ Exploratory Endpoints

2.3.1 Exploratory Objectives	2.3.2 Exploratory Endpoints
• To determine if minimal residual disease (MRD) status can be used as a surrogate marker for survival	• MRD status based on multiparameter flow cytometry from University of Washington will be collected at each response assessment time points
• To determine if gene expression profiling can be biomarkers of response	• Molecular, cellular and soluble biomarkers in peripheral blood and bone marrow samples will be collected

3.0 PATIENT ELIGIBILITY

3.1 Inclusion Criteria

Subjects must meet all of the inclusion criteria to participate in this study.

1. Previously untreated therapy-related AML or AML with myelodysplastic related changes as described by WHO 2016
    a. AML arising in MDS (including CMML) or MDS/MPN syndrome
    b. AML with MDS-related cytogenetic abnormalities (Appendix A, metaphase FISH allowable as surrogate for cytogenetics)
    c. AML with multi-lineage dysplasia involving the presence of 50% or more dysplastic cells in at least two cell lines and in the absence of mutation in NPM1 or biallelic CEBPA (as per WHO 2016)

2. Adults 18 years of age or older

3. ECOG performance status 0 to 2

4. Adequate organ function as defined as:
    a. Left Ventricular Ejection Fraction (LVEF) > 50%
    b. Serum total bilirubin < 2.0 mg/dL, unless considered due to Gilbert's disease or leukemic involvement
    c. AST, ALT and alkaline phosphatase < 3 times the upper limit of normal, unless considered due to leukemic involvement
    d. Serum creatinine < 2.0 mg/dL, or creatinine clearance > 40 mL/min based on Cockcroft-Gault GFR

5. Absence of unstable cardiac disease defined as myocardial infarction within 6 months, uncontrolled heart failure, or uncontrolled cardiac arrhythmia

6. Ability to understand and the willingness to sign a written informed consent or subject's legally authorized representative (LAR) has provided informed consent prior to any study-specific activities/procedures being initiated when the subject has any kind of condition that, in the opinion of the investigator, may compromise the ability of the subject to give written informed consent

7. Women of child-bearing potential and men with partners of child-bearing potential must agree to use 2 methods of birth control or be surgically sterile, or abstain from heterosexual activity for the course of the study through 120 days after the last dose of study medication

    A woman of child-bearing potential is any female (regardless of sexual orientation, having undergone a tubal ligation, or remaining celibate by choice) who meets the following criteria:
    - Has not undergone a hysterectomy or bilateral oophorectomy; or
    - Has not been naturally postmenopausal for at least 12 consecutive months (i.e., has had menses at any time in the preceding 12 consecutive months)

    Women of child-bearing potential has negative pregnancy test within 72 hours of initiating study drug dosing

    Male subjects must agree to use a latex condom during sexual contact with females of childbearing potential even if they have had a successful vasectomy starting with the first dose of study therapy through 120 days after the last dose of study therapy

8. Leukapheresis, corticosteroid and hydroxyurea are permitted as initial management of hyperleukocytosis at the investigator's discretion for up to 7 days after starting study therapy. Hyperleukocytosis is defined as greater than 30k WBC. When possible, a bone marrow biopsy for screening should be performed prior to the initiation hyperleukocytosis

3.2 Exclusion Criteria

Subjects meeting any of the exclusion criteria at baseline will be excluded from study participation.

1. Prior treatment with Glasdegib or CPX-351

2. Previously treated AML except for initial management of hyperleukocytosis. Treatment with hypomethylating therapy for MDS is allowable but not since their diagnosis of AML. No prior treatment with cytarabine or daunorubicin are allowed

3. Concurrent *FLT3* mutation that the treating physician deems necessary to treat with midostaurin, whereas patients with *FLT3-mutated* AML not treated with midostaurin can be enrolled. Patients with known Core Binding Factor –t(8;21), inv(16), t(16;16) are allowed for study participation at the treating investigator's discretion

4. Active CNS or testicular involvement by leukemia; diagnostic lumbar puncture is not required

5. History of neurologic disorder including but not limited to: prior seizure, epilepsy, structural brain abnormality, benign brain tumor, stroke, brain injuries, dementia, movement disorder or other significant CNS abnormalities

6. Baseline QT corrected interval based on Fridericia's formula (QTcF) interval > 450 ms

7. Acute coronary syndrome in the past 12 months, NYHA class III or VI

8. Known history of Wilson's disease or other copper handling disorder

9. History of GI malabsorptive disease

10. Has a known additional malignancy that is progressing or requires active treatment. Exceptions include basal cell carcinoma of the skin, squamous cell carcinoma of the skin, or in situ cervical cancer that has undergone potentially curative therapy

11. Known HIV infection

12. Active hepatitis B or hepatitis C infection (patients who successfully completed curative hepatitis C therapy can be enrolled)

13. Any uncontrolled infection, active bacterial or viral infection manifesting as fevers or hemodynamic instability within the past 72 hours

14. Proven active invasive fungal infection

15. Is pregnant or breastfeeding, or expecting to conceive or father children within the projected duration of the trial, starting with the pre-screening or screening visit through

120 days after the last dose of trial treatment

16. Severe or uncontrolled medical disorder that would, in the investigator's opinion, impair ability to receive study treatment (i.e., uncontrolled diabetes, chronic renal disease, chronic pulmonary disease or active, uncontrolled infection, psychiatric illness/social situations that would limit compliance with study requirements

17. Current or anticipated use of other investigational agents

18. For patients with prior anthracycline exposure, the cumulative life-time dose should not exceed 386mg/m^2 at the time of study entry (to convert different anthracycline to daunorubicin-equivalent, see Appendix H for conversion factors)

4.0 REGISTRATION PROCEDURES

Subjects will be evaluated for eligibility by the site principal investigator to ensure that the inclusion and exclusion criteria have been met.

4.1 Patient Registration Procedures

Patients that have signed informed consent to participate in a UCHMC protocol must be registered with the initiating site and enrolled on the protocol.

Patients must be entered into the OnCore system the same day the informed consent is signed.

All patients will be assigned a specific study ID which will correlate with the study number, site number and patient enrollment numbers. Patient ID's will be assigned by the lead site and formatted as follows: UCHMC1913-XX-XX.

Study specific ID will be provided by the initiating site once eligibility is confirmed by the initiating center.

All patients must obtain a study ID number from the initiating center before initiation of treatment.

4.2 Patient Eligibility

Eligibility of the patient is determined by the clinical protocol and confirmed prior to registration. Participating sites need to send a redacted copy of the eligibility checklist signed by the treating investigator and accompanying redacted source which may include but is not limited to, pathology report, physical exam including ECOG, medical and oncology history and screening labs, must be provided to the initiating site for the specific study. Approval by initiating site PI and the initiating site clinical research manager is required prior to initiating treatment. Participating sites should send the requested redacted information above to uci18105@hs.uci.edu for confirmation of eligibility at least 3 business days prior to the planned start date of treatment.

5.0 TREATMENT PLAN

5.1 Treatment Dosage and Administration

Agent	Dose	Route	Schedule
CPX-351 for Induction	Daunorubicin 44mg/m^2-cytarabine 100mg/m^2	IV infusion for 90 minutes	Days 1, 3 and 5
CPX-351 for Reinduction	Daunorubicin 44mg/m^2 -cytarabine 100mg/m^2	IV infusion for 90 minutes	Days 1 and 3
CPX-351 for Consolidation	Daunorubicin 29mg/m^2-cytarabine 65mg/m^2	IV infusion for 90 minutes	Days 1 and 3
Glasdegib	100 mg	PO daily in the a.m.	Begins day after completion of CPX-351 infusion and continues daily until Day 1 of subsequent cycle of CPX-351

5.2 Induction

During induction, patients will receive the combination of Glasdegib and CPX-351. The dose of Glasdegib is 100mg orally daily on days 6 to 28. CPX-351 will be given at a dose of daunorubicin 44mg/m^2-cytarabine100mg/m^2 via 90 minute infusion on days 1, 3, 5. Induction can last longer than 28 days and up to 60 days. If induction last more than 28 days, patient should continue to take glasdegib daily and as prescribed until day 1 of next cycle of CPX-351. Patient will be instructed to hold glasdegib on the day they receive CPX-351 infusion..

5.3 Reinduction

Patients who are responding to the initial induction but not yet less than 5% blasts can receive a second induction. Patients who have not had any reduction in blasts count should be considered as refractory and should be considered for other treatment options off protocol. However, if there is a greater than 50% reduction in blast count but greater than 5% blasts present on marrow, re-induction is strongly recommended. The use of re-induction will be at the treating physician's discretion based on bone marrow biopsy performed on day 20 (+1 day). The regimen for re-induction will be CPX-351 at a dose of daunorubicin 44mg/m^2–cytarabine 100mg/m^2 on days 1 and 3. Glasdegib will be administered at 100mg daily on days 4-28. Reinduction can last longer than 28 days and up to 60 days. If reinduction last more than 28 days, patient should continue to take glasdegib daily and as prescribed until day 1 of next cycle of CPX-351. Patient will be instructed to hold glasdegib on the day they receive CPX-351 infusion.

5.4 Consolidation

Patients who achieve CR or CRi, can be continued on consolidation therapy for up to two cycles. In general, patients who have achieve CRi, consolidation should be initiated once the platelet count ≥ 50,000/uL and ANC ≥ 500/uL. The first consolidation cycle should start between 28 to 75 days after initiation of the last induction therapy. Each subsequent cycle of consolidation should be initiated between 28 to 55 days after the start of previous cycle of

consolidation. The exact day is at the treating physician's discretion. The number of consolidation cycles will depend on the time required for identification and availability of a suitable stem cell donor for patients going to stem cell transplantation.

The dose of CPX-351 will be at a dose of daunorubicin 29 mg/m^2–cytarabine 65 mg/m^2 on days 1 and 3. Glasdegib will be administered at 100mg daily for days 4-28. Consolidation cycles can last longer than 28 days. If cycles last more than 28 days, patient should continue to take glasdegib daily and as prescribed until day 1 of next cycle of CPX-351. Patient will be instructed to hold glasdegib on the day they receive CPX-351 infusion.

5.6 Allogenic stem cell transplantation

The decision to go to allogeneic transplant once the patient is in remission is based on the treating's physician discretion as well as the desire of the patient. Patients who are considered candidates for allogeneic transplant and have a donor stem cell source available can proceed to allogeneic transplant. Alternatively, patients can receive up to two cycles of consolidation chemotherapy prior to allogeneic transplant.

For patients going to transplant, Glasdegib will be discontinued within 7 days prior to start of conditioning for their transplant.

5.7 Maintenance

For patients who complete consolidation chemotherapy and not proceeding to allogeneic transplant, they will proceed to maintenance therapy. Glasdegib oral daily will be continued for up to one year. The patients will proceed with monthly assessments of disease status if they are on Glasdegib maintenance. If they are adults of child-bearing age and potential, they will need to be reminded of contraception. If they are a woman of child-bearing age and potential, they will need to have pregnancy test.

5.8 Duration of Therapy

In the absence of treatment delays due to adverse events, treatment may continue until completion or protocol-defined therapy or until:

- Disease progression
- Inter-current illness that prevents further administration of therapy
- Unacceptable adverse events
- Patient decided to withdraw from the study
- General or specific examples in the patient's condition render the patient unacceptable for further treatment in the judgement of the investigator

Subjects who become medically incapacitated or cognitively impaired after enrollment into this trial may continue with protocol therapy as long as they are benefiting from treatment in the judgement of the investigator. In the event that this occurs, a surrogate or legally authorized representative (LAR) must sign the ICF. The surrogate/LAR will assist the subject in completion of study procedures and diary. If a subject regains ability to regains the cognitive ability to consent, they must be re-consented using standard consenting procedure

5.9 Duration of Follow Up

Patients will be followed every 3 months for one year after removal from or completion of treatment or death, whichever comes first. Patients removed from treatment for unacceptable adverse events will be followed until resolution or stabilization of the adverse event then for relapse and survival afterwards. Patients who undergo allogeneic stem cell transplant will only be followed for survival.

5.10 Other therapeutic Agents

The use of therapeutic agents or approaches for malignancy outside of what is expressly stated in this protocol is strictly forbidden. This includes any study undefined use of the study specific therapeutic agents, the same class of agents, or agents not expressly defined in the protocol with potential or known anti-leukemic activity. Institutional standard of care supportive medications are allowed as long as they do not have known or predicted anti-leukemic activity or are in conflict with study dictated supportive care.

If hyperleukocytosis is present (when greater than 30k), cytoreduction is allowed with leukapheresis, corticosteroids or hydroxyurea for up to 7 days at the investigator's discretion.

5.11 Pre-Medications

Anti-emetics should be given prior to CPX-351. The exact antiemetic should be used per the institutional protocol or treating physician discretion. One common regimen is ondansetron 8mg IV on days 1, 3 and 5 given 30 minutes prior to CPX-351 administration. Monitor for infusion reactions during and at least 1 hour after the end of the infusion.

5.12 Infection prophylaxis

5.12.1 Prophylaxis during neutropenia

Prophylaxis during neutropenia including antibacterial and antifungal therapies is to be administered per local standard of care. For antibacterial prophylaxis, levofloxacin 500mg daily is recommended. Cefpodoxime is an allowable alternative to avoid QTc prolongation. Acyclovir is strongly recommended for viral prophylaxis.

5.12.2 Fungal prophylaxis during neutropenia

During periods of neutropenia patients should receive fungal prophylaxis. Recommended treatment is: isavuconazole due to drug interactions with glasdegib for absolute neutrophil count <500/mcl. Alternate prophylactic regimens are up to individual investigator's discretion.

5.13 Permitted concomitant therapy

Growth factors including granulocyte colony-stimulating factors and granulocyte-macrophage colony-stimulating factors are permitted and should be used based on American Society of Clinical Oncology guidelines.

5.14 Prohibited concomitant therapy

Antineoplastic agents other than CPX-351, Glasdegib and hydroxyurea prior to the start of the study are not allowed.

Glasdegib can lead to QTc prolongation. Therefore, drugs that can prolong QTc should be avoided. Please refer to list of drugs in Appendix D.

Caution must be taken with moderate/strong CYP3A4/5 inhibitor in conjunction with Glasdegib. If possible, it is best to avoid the combination. If this is not possible, then QTc monitoring is recommended.

When there is an urgent need to start a moderate/strong CYP3A4/5 inhibitor or TdP drug, administration of these medications should not be delayed, the Investigator should consider temporarily interrupting Glasdegib dosing and should implement these additional monitoring procedures as soon as it is reasonably possible.

6.0 Toxicities and Dosing Delays/Dose Modifications

Any patient who receives treatment on this protocol will be evaluable for toxicity. Each patient will be assessed for the development of toxicity according to the NCI Common Toxicity Criteria for Adverse Events (CTCAE), version 5.0. Dose adjustments should be made according to the system showing the greatest degree of toxicity.

6.1 CPX-351 dose modification

The dose of CPX-351 should not be modified. The dose can be delayed due to prolonged cytopenias or due to infections at any time.

CPX-351 should remain the same dose for entire cycle. For subsequent cycles, if body surface area (BSA) change is $\geq$10%, then the dose should be recalculated using the new BSA. If BSA remains <10% of baseline BSA (at time of screening), then dose of CPX-351 should not change and is calculated using baseline BSA

6.2 Glasdegib dose modification for non-hematologic toxicities

If a grade 3 non-hematologic toxicity occurs, interrupt the treatment until symptoms reduce or return to baseline. Resume Glasdegib at the same dose level if the event is not attributable to the study drug as determined by the Investigator. If the investigator deems the event as being possibly related to the study drug, then reduce the dose in increments of 25 mg. If a dose reduction is necessary after 50 mg, then the study treatment should be discontinued.

6.3 Glasdegib dose modification for hematologic toxicities

The dose of Glasdegib should not be modified for any hematologic toxicities.

6.4 Glasdegib dose modification for QTc prolongation

The dose of Glasdegib should be modified if there is evidence of QTc prolongation.

If the QTc is found to be between 480 to 500 ms, the recommendations are as follows:

- Correct any electrolyte abnormalities
- Review and adjust any medications that may be contributing to QTc prolongation. Refer to Appendix D for medications that are associated with QTc prolongation.
- Monitor ECG at least weekly for two weeks following resolution of the QTc prolongation to less than 480 ms
- If the QTc is found to be greater than 500, the recommendations are as follows:
  - Correct any electrolyte abnormalities
  - Review and adjust any medications that may be contributing to QTc prolongation
  - Interrupt Glasdegib
  - Resume Glasdegib at a reduced dose of 50 mg once daily when QTc is less than 480 ms or if the QTc returns to within 30 ms of baseline
  - Monitor ECG at least weekly for two weeks following resolution of the QTc prolongation to less than 480 ms
  - Consider re-escalating the dose to 100 mg daily if an alternative etiology for QTc prolongation is identified
- If QTc interval prolongation is associated with life-threatening arrhythmia, then Glasdegib should be discontinued permanently.

7.0 STUDY PROCEDURES

7.1 Screening/Baseline Procedures

Assessments performed exclusively to determine eligibility for this study will be done only after obtaining informed consent. Assessments performed for clinical indications (not exclusively to determine study eligibility) may be used for baseline values even if the studies were done before informed consent was obtained.

All screening procedures must be performed within 28 days prior to registration unless otherwise stated. The screening procedures include:

7.1.1 Informed Consent

A complete description of the study is to be presented and discussed with each potential subject or the subject's legally authorized representative, if applicable, and a signed and dated informed consent form is to be obtained before any study specific procedure is performed. A copy of the signed and dated consent form should be given to the subject before participation in the study.

The initial informed consent form, any subsequent reviewed written informed consent form and any written information provided to the subject must receive the IRB approval in advance of use. The subject should be informed in a timely manner if new information become available that may be relevant to the subject's willingness to continue participation in the trial. The communication of the information will be provided and documented via a revised consent form that captures the subject's dated signature. The informed consent will adhere to IRB requirements, applicable laws and regulations and sponsor requirements.

7.1.2 Medical history

Complete medical, surgical and oncology history as well as history of infections are obtained at screening. Any changes from Screening (e.g. worsening severity or abnormal findings) are considered to be adverse events (AEs).

7.1.3 Demographics

Demographic profile will include date of birth, gender, race, and ethnicity.

7.1.4 Review subject eligibility criteria

At the initiating site, the information below must be reviewed with the initiating site PI and research manager prior to the assignment of the subject study ID and initiation of treatment. For participating sites, the following information must be redacted of any patient identifiers and sent at least 3 business days prior to the planned start date of treatment for eligibility confirmation and subject ID assignment to uci18105@hs.uci.edu via secure email:

- Signed informed consent
- Signed eligibility checklist
- Bone marrow biopsy report
- Physical exam including ECOG and medical history
- All screening labs
- Baseline ECG

Review of eligibility criteria, as described in Section 3, is required to ensure subject qualification for study entry.

The signed eligibility checklist, redacted source documentation as mentioned above and signed informed consent for each enrolled patient must be emailed to uci18105@hs.uci.edu per section 4.1.

7.1.5 Review previous and concomitant medications

All concomitant medications taken by the subject during the study are to be recorded up until 28 days after last study dose. If a reportable adverse event occurs within 28 days after last study dose, recording of concomitant medications should continue until resolution of adverse event.

7.1.6 Physical exam including vital signs, height and weight

Vital signs (temperature, pulse, respirations, blood pressure), height, weight will be collected at screenings and during each physical exam. Subjects will be examined by an investigator during study visits. (Note: height is only required at screening.)

7.1.7 Performance status

The Eastern Cooperative Oncology Group (ECOG) Performance status will be evaluated prior to study entry, on day 1 of induction and day 28 of induction, on day 1 and day 28 of each subsequent consolidation cycles, and on day 1 of each cycle of maintenance. (See appendix A)

7.1.8 Hematology

Hematology to include hemoglobin (Hgb), platelets, total white blood cell count (WBC), and differential.

7.1.9 Serum chemistries

Comprehensive metabolic panel (CMP) to include: albumin, alkaline phosphatase, ALT/SGPT, AST/SGOT, BUN, creatinine, electrolytes (sodium, potassium, calcium, chloride, bicarbonate), glucose, and total bilirubin. Additional chemistries: lactate dehydrogenase (LDH), phosphate, magnesium, and uric acid.

7.1.10 Coagulation

Coagulation profile includes International Normalized Ratio (INR), prothrombin time (PT) and activated partial thromboplastin time (PTT).

7.1.11 ECG

Resting 12-lead ECG will be taken at screening.

7.1.12 Echocardiogram

An ECHO should be performed during screening before starting treatment with CPX-351.

7.1.13 Urinalysis

Standard urinalysis dipstick assessment (pH, protein, glucose, blood, ketones, and leukocytes) should be performed.

7.1.14 Pregnancy test (for females of child bearing potential)

Serum or urine beta HCG test are acceptable and should be done prior to starting treatment. Sites should follow local institutional guidelines.

7.1.15 Bone marrow procedures

Bone marrow aspirate and biopsy should be done during screening. It should be completed within 28 days. Cytogenetic and molecular profiling will be analyzed with these samples.

7.1.16 Research samples

Additional bone marrow aspirate or peripheral blood will be collected for gene expression testing.

7.2 Procedures during Treatment

7.2.1 Induction

- Physical exam will be done weekly
- Review previous and concomitant medications
- ECOG Performance Status Review
- Blood draws for laboratory studies will be done weekly
- ECGs will be done on day 6 before starting Glasdegib and approximately one week after day 6 (on day 13-15)
- Review of concomitant medications
- Adverse event assessment
- Assessment of minimal residual disease assessed by multi-parameter flow cytometry. This should be done according to local institutional guidelines.

- Bone marrow aspiration and biopsy
  - Day 20
  - Upon recovery of cytopenias typically around day 28 to 60, at the discretion of treating physician. If counts has not recovered by day 60, then complete on day 60.
- Additional BMA or PB will be collected for gene expression testing

7.2.2 Rationale for the timeline of bone marrow assessments

During the phase II and III trials with CPX-351, there was evidence of relatively delayed clearance of bone marrow blasts compared to standard induction chemotherapy. Therefore, bone marrow assessments should be performed on day 20, in order to avoid labeling a patient as requiring re-induction if the bone marrow biopsy is done on day 14 inadvertently.

Similarly, the subsequent bone marrow should be delayed until there is evidence of normal hematopoiesis between days 28-60. The exact day to perform the bone marrow assessment is at the discretion of the treating physician. It is strongly encouraged to avoid performing the bone marrow biopsy prematurely. If peripheral counts do not recover by day 60, bone marrow should be performed to assess the status of the disease.

7.2.3 Adequacy of bone marrow specimen

An adequate bone marrow specimen is required to evaluate for remission (during induction days 28-60). An adequate bone marrow specimen is defined as having nucleated cells in the aspirate with spicules. The nucleated cell count is determined by the pathologist and the presence of spicules can be determined by the provider performing the bone marrow biopsy at the time of obtaining the aspirate. If the sample is inadequate, the bone marrow should be repeated within one week. In case of a dry tap without any aspirate, two cores are preferred; however, local institutional guidelines should be followed.

7.2.4 Bone marrow blasts of 5-10%

In the case of the bone marrow specimen has 5-10% blasts on bone marrow obtained prior to induction day 46, it is encouraged to reassess the marrow in 1-2 weeks (no later than day 60), instead of labeling the patient as not in remission. This will allow more time for the relatively delayed effects of CPX-351. The final decision is at the discretion of the treating physician.

7.2.5 Assessment of remission status

The date of CR and CRi or relapse is based on the date of the bone marrow biopsy that was performed. The exact date of achievement of CR is based on the date when the bone marrow biopsy demonstrates less than 5% blasts with the peripheral ANC ≥ 1,000/uL and the platelet count ≥ 100,000/uL. If the bone marrow biopsy shows less than 5% blasts prior the day the peripheral counts recover, then the date of CR is based on the date when the peripheral counts recover.

7.2.6 Reinduction

- Prior to reinduction, an ECHO should be completed
- Review of concomitant medications
- Adverse event assessment
- ECOG performance status

- Physical exam will be done weekly
- Blood draws for laboratory studies will be done weekly
- ECGs will be done within 24 hours of day 4 before starting Glasdegib
- For females with childbearing potential, a pregnancy test will be done
- Assessment of minimal residual disease assessed by multi-parameter flow cytometry. This should be done according to local institutional guidelines.
- Bone marrow aspiration and biopsy
  - Day 20
  - Upon recovery of cytopenias typically around day 28 to 60, at the discretion of the physician. If counts has not recovered by day 60, then complete on day 60.
- Additional BMA or PB will be collected for gene expression testing

7.2.7 Consolidation

- Physical exam will be done weekly
- Review of concomitant medications
- Adverse event assessment
- Blood draws for laboratory studies will be done weekly
- For females with childbearing potential, a pregnancy test will be done
- ECOG performance status
- ECGs will be done on within 24 hours of day 4 of every cycle
- Adverse event assessment
- Bone marrow at the end of consolidation is recommended but is not required by the study.

7.2.8 Maintenance

- Physical exam will be done on day 1 of every cycle
- Review of concomitant medications
- Adverse event assessment
- ECOG performance status
- Blood draws for laboratory studies will be done on day 1 of every cycle
- For females with childbearing potential, a pregnancy test will be done

7.3 End of Treatment Visit

All subjects will undergo an end of treatment evaluation. End of study is defined as at least 12 months after the final subject is enrolled, or sooner if all subjects have died, discontinued the study, are lost to follow-up, or withdrew consent prior to the two years after the last subject is enrolled.

- Physical exam
- Review of concomitant medications
- Adverse event assessment
- ECOG Performance Status Review
- ECG will be done
- Blood draws for laboratory studies
- Assessment of minimal residual disease assessed by multi-parameter flow cytometry. This should be done according to local institutional guidelines.
- Bone marrow aspiration and biopsy

    - At any time of suspected relapsed disease, at the discretion of treating physician
- Additional BMA or PB will be collected for gene expression testing

7.4 Follow-up Procedures

Patients will be followed every 3 months for a minimum of one year after removal from or completion of treatment or death, whichever comes first. Patients who undergo allogeneic stem cell transplant will only be followed up for survival status. Patients removed from treatment for unacceptable adverse events will be followed until resolution or stabilization of the adverse event then for relapse and survival afterwards.

- Survival status (either in clinic during standard visit or by phone)
- Physical Exam
- ECOG Performance Status Review
- Blood draws for laboratory studies
- Bone marrow aspiration and biopsy
    - At any time of suspected relapsed disease, at the discretion of treating physician
- Assessment of minimal residual disease assessed by multi-parameter flow cytometry. This should be done according to local institutional guidelines.

7.5 Correlative Studies

In the non-intensive arm of the phase II trial with LDAC with Glasdegib, there were several genes that correlated with improved OS [11]. Lower levels of expression of FOXM1 and MSI2 and higher expression levels of BCL2 and CCND2 correlated with improved overall survival. In the intensive treatment arm with Glasdegib and cytarabine/daunorubicin, higher PTCH1 expression correlated with improved overall survival. Furthermore, in the intensive arm, mutations in FLT3, TP53, CEP170, NPM1 and ANKRD26 correlated with overall survival. Interesting to note, that patients with AML with mutated FLT3 (which is generally a poor risk group) did better than AML with wild type FLT3. Therefore, we will be measuring some of gene expression to see if this observation of their correlation with improved overall survival is confirmed.

Furthermore, we will be measuring MRD by MFC at the end of induction. University of Washington is the preferred facility who will receive the samples and assess MRD. If samples cannot be sent to University of Washington, sites should send their samples for MRD assessment according to their local institutional guidelines. We will determine if the status of MRD by MFC at the end of induction correlates with survival.

8.0 Removal of Subjects from Study Treatment and Study

Patients can be taken off the study treatment and/or study at any time at their own request, or they may be withdrawn at the discretion of the investigator for safety, behavioral or administrative reasons. The reason(s) for discontinuation will be documented and may include:

1. Patient completed study treatment;
2. Patient voluntarily withdraws from treatment (follow-up permitted);
3. Patient withdraws consent (termination of treatment and follow-up);
4. Patient/LAR is unable to comply with protocol requirements;
5. Patient demonstrates disease progression (unless continued treatment with study drug is deemed appropriate at the discretion of the investigator);
6. Patient experiences toxicity that makes continuation in the protocol unsafe;

7. Treating physician judges continuation on the study would not be in the patient's best interest;
8. Patient becomes pregnant (pregnancy to be reported along same timelines as a serious adverse event);
9. Development of second malignancy (except for basal cell carcinoma or squamous cell carcinoma of the skin) that requires treatment, which would interfere with this study;
10. Lost to follow-up.
    If a research subject cannot be located to document survival after a period of 2 years, the subject may be considered "lost to follow-up." All attempts to contact the subject during the two years must be documented.

9.0 DATA AND SPECIMEN SUBMISSION GUIDELINES

9.1 Labeling Samples

Each sample to be labeled with patient specific study ID, initials, visit type, date of collection and time of collection.

9.2 Sample Collection Guidelines

MRD Testing

For minimal residual disease testing, a first pull aspirate sample should be collected and sent overnight to the University of Washington or the facility designated by your local institutional guidelines for analysis. The aspirate should be collected in a 1mL to 5mL EDTA vial or according to local institutional guidelines.

Gene Expression

For gene expression testing, 2 mL will be collected from the bone marrow biopsy sample. In the event that there is a dry tap, the gene expression sample will be collected using peripheral blood if there are any circulating blasts present. If there are no circulating blasts, the gene expression sample will not be collected for testing. The sample needs to be processed immediately and carefully handled. Sites are responsible for providing their own tubes and vials for collection of all research related samples. In the event that a site does not have funding for supplies, the sample will not be collected and will not be considered a deviation. All samples will be shipped to and stored at UCI Clinical Trials Biospecimen Laboratory until analysis, which will be done at another laboratory. Please refer to the study sample lab manual for further processing, storage, and shipment instructions.

10.0 Measurement of Effect

10.1 Antitumor Effect- Hematologic Tumors

Response criteria for bone marrow are as per International Working Group Response Criteria in AML listed in Table 2.

10.2 Complete remission

Complete remission is defined as no circulating blasts or extramedullary disease with a bone marrow biopsy with trilineage hematopoiesis with less than 5% blasts and ANC greater/equal than 1,000/uL and platelet count greater/equal than 100,000/uL.

Refractory disease is the failure to achieve CR at the end of induction.

Progressive disease is the increase of at least 25% in the absolute number of circulating or bone marrow leukemic blasts or appearance of extramedullary disease.

Relapsed disease is the reappearance of blasts in the bone marrow (greater than 5%) or in the blood after achieving CR or CRi.

MRD negative CR is the absence of detectable leukemic blasts using multiparameter flow cytometry at the University of Washington.

10.3 Progressive disease

Progressive disease is the evidence for an increase in bone marrow blast percentage and/or increase of absolute blast counts in blood by 50% or new extramedullary disease.

10.4 Event-free survival

Event-free survival is defined as the time from screening biopsy to the date of confirmed disease progression, relapse from CR/CRi, treatment failure, or death, whichever comes first. This was chosen as an endpoint for several reasons. It is known to incorporate several endpoints of interest including efficacy of the treatment as well as toxicity that both contribute to the outcome of the patient. Complete remission may not capture the full benefits of Glasdegib since the drug may prevent relapse through different mechanisms than enhanced cytotoxicity.

10.5 Final Response Assessment

Overall survival is measured as the time from the date of diagnostic biopsy which confirmed disease to the date of death from any cause. Patients not known to have died at last follow-up are censored on the date they were last known to be alive. Patients will be followed for a minimum of one year from the completion of the treatment.

Patients who go on to allogeneic transplant will be censored for survival on the dates that they start conditioning regimen to avoid transplant as a confounding factor in analysis of overall survival.

11.0 ADVERSE EVENTS

All adverse events will be graded as toxicity using the CTCAE version 5.0 grading system. Graded toxicity should be recorded in the CRF.

Analyses will be performed for all patients having received at least one dose of study drug.

11.1 Event Definitions

- **Adverse event (AE)** - An adverse event is any untoward medical experience or change of an existing condition that occurs during or after treatment, whether or not it is considered to be related to the protocol intervention. An AE can therefore be any unfavorable and unintended sign (including a clinically significant abnormal laboratory finding), symptom, or disease temporally associated with the use of an experimental intervention, whether or not related to the intervention.
- **Unexpected Adverse Event** [Modified from the definition of unexpected adverse drug experience in FDA regulations at 21 CFR 312.32 (a)] – An adverse event is unexpected if it is not listed in the investigator's brochure and/or package insert; is not listed at the specificity or severity that has been observed; is not consistent with the risk information described in the protocol and/or consent; is not an expected natural progression of any underlying disease, disorder, condition, or predisposed risk factor of the research participant experiencing the adverse event.
- **Expected Adverse Event** - Any event that does not meet the criteria for an unexpected event OR is an expected natural progression of any underlying disease, disorder, condition, or predisposed risk factor of the research participant experiencing the adverse event.
- **Serious Adverse Event (SAE)** [21 CFR 312.32] - defined as any expected or unexpected adverse event that result in any of the following outcomes:
    - Death
    - Is life-threatening experiences (places the subject at immediate risk of death from the event as it occurred)
    - Unplanned hospitalization equal or greater than 24 hours)) or prolongation of existing hospitalization
    - A persistent or significant disability/incapacity
    - A congenital anomaly/birth defect
    - Any other adverse event that, based upon appropriate medical judgment, may jeopardize the subject's health and may require medical or surgical intervention to prevent one of the outcomes listed above (examples of such events include allergic bronchospasm requiring intensive treatment in the emergency room or at home, blood dyscrasias of convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse).
- **Unanticipated problem (UP)** - Any incident, experience or outcome that meets all three of the following criteria:
    1. Unexpected (in term nature, severity, or frequency) given the following: a) the research procedures described in the protocol-related documents such as the IRB approved research protocol, informed consent document or Investigator Brochure (IB); and b) the characteristics of the subject population being studied; AND
    2. Related or possibly related to participation in the research (possibly related means there is a reasonable possibility that the incident, experience, or outcomes may have been caused by the drugs, devices or procedures involved in the research); AND
    3. Suggests that the research places subjects or others at greater risk of harm (including physical, psychological, economic, or social harm) than previously known or recognized.
- **Protocol Violation**- A protocol violation is an accidental or unintentional change to or noncompliance with the IRB-approved protocol that increases risk or decreases benefit and/or affects the subject's rights, safety, welfare, and/or the integrity of the data.

Examples of incidents that may be considered violations include: enrolling a participant who does not meet the inclusion criteria; obtaining verbal consent before the initiation of study procedures when the IRB requires signed, written informed consent; and failure to collect screening labs before initiation of study procedures [Reference: Policy #57 UCI HRPP Policy and Procedure Glossary].

- **Protocol Deviation**- a protocol deviation is an accidental or unintentional change to the research protocol that does not increase risk or decrease benefit or have a significant effect on the participant's rights, safety or welfare, or on the integrity of the data. Deviations may result from the action of the participant, researcher, or staff. Examples: a rescheduled study visit, an omitted routine safety lab for a participant with previously normal values; or failure to collect an ancillary self-report questionnaire data (e.g., quality of life) [Reference: Policy #57 UCI HRPP Policy and Procedure Glossary].

11.2 Adverse Event Monitoring

All patients who have received at least one dose of CPX-351 will be considered evaluable for safety. After initiation of study drug, all adverse events (AEs) and serious adverse events (SAEs) regardless of attribution will be collected at every visit until 28 days following the last administration of study drug, until study discrimination/termination, or until initiation of subsequent anticancer therapy, whichever comes first. Subjects will be assessed at each follow-up visit to determine if there are any new AEs. Adverse events will no longer be reported in patients who go on to allogeneic transplant. AEs and SAEs will be recorded on the adverse event report section within OnCore. Please reference section 11.3 and 11.4 for a complete list of all entities who require notifications of AEs and SAEs.

Adverse event data collection and reporting, which are required as part of every clinical trial, are done to ensure the safety of subjects enrolled in the studies as well as those who will enroll in future studies using similar agents. Adverse events are reported in a routine manner at scheduled times during a trial. Additionally, certain adverse events must be reported in an expedited manner to allow for optimal monitoring of patient safety and care.

As far as possible, each adverse event should be evaluated to determine:

- duration (start and end dates)
- severity (grade)
- seriousness
- relationship to study agent
- action taken (i.e., none, study agent modification, medical intervention)
- outcome (i.e., resolved without sequelae, resolved with sequelae, ongoing)

Adverse events monitoring begins after initiation of study treatment and ends 28 days following the last administration of study treatment or study discontinuation/termination, whichever is earlier.

All patients experiencing an adverse event, <u>at least possibly</u> related to the drug, will be monitored until:

- the adverse event resolves or the symptoms or signs that constitute the adverse event return to baseline;
- any clinically significant abnormal laboratory values have returned to baseline;
- there is a satisfactory explanation other than the study drug for the changes observed; or
- death.

11.2.1 Severity

All non-hematologic adverse events will be graded according to the NCI Common Terminology Criteria for Adverse Events (CTCAE) version 5.0. The CTCAE v5.0 is available at http://ctep.cancer.gov/reporting/ctc.html

If no CTCAE grading is available, the severity of an AE is graded as follows:

Mild (grade 1): the event causes discomfort without disruption of normal daily activities.
Moderate (grade 2): the event causes discomfort that affects normal daily activities.
Severe (grade 3): the event makes the patient unable to perform normal daily activities or significantly affects his/her clinical status.
Life-threatening (grade 4): the patient was at risk of death at the time of the event.
Fatal (grade 5): the event caused death.

11.2.2 Seriousness

A “serious” adverse event is defined in regulatory terminology as any untoward medical occurrence that:

1. Results in death.
   If death results from (progression of) the disease, the disease should be reported as event (SAE) itself.
2. Is life-threatening.
   (the patient was at risk of death at the time of the event; it does not refer to an event that hypothetically might have caused death if it were more severe).
3. Requires in-patient hospitalization or prolongation of existing hospitalization for ≥ 24 hours.
4. Results in persistent or significant disability or incapacity.
5. Is a congenital anomaly/birth defect
6. Is an important medical event
   Any event that does not meet the above criteria, but that in the judgment of the investigator jeopardizes the patient, may be considered for reporting as a serious adverse event. The event may require medical or surgical intervention to prevent one of the outcomes listed in the definition of “Serious Adverse Event“.
   For example: allergic bronchospasm requiring intensive treatment in an emergency room or at home; convulsions that may not result in hospitalization; development of drug abuse or drug dependency.

11.2.3 Relationship

Attribution categories for adverse events in relationship to protocol therapy are as follows:

Related – The AE is *clearly related* to the study treatment
Unrelated – The AE *is clearly NOT related* to the study treatment.

11.2.4 Prior experience

Expected events are those that have been previously identified as resulting from administration of the agent. An adverse event is considered unexpected, for expedited reporting purposes only, when either the type of event or the severity of the event is not listed in the current known adverse events listed in the agent clinical experience section of this protocol or Product Label.

11.3 Reporting Requirements for Adverse Events

Adverse events, serious adverse events, deviations, violations, and unanticipated problems must be entered into the clinical trial management system (CTMS), OnCore, and must also be reported to the following entities according to the timelines mentioned in the chart below. Serious adverse events collection will start at the time patient signs consent until 28 days after the end of treatment. Adverse events will be collected from the time the research patient begins treatment until 28 days after the end of treatment. All adverse events/serious adverse events should be followed until resolution or stabilization.

Event Type	Coordinating Center/Medical Monitor	UCI IRB	Local IRB	Jazz Pharmaceuticals	Pfizer	CFCCC DSMB
Unanticipated Problem	Within 24 hours from date the site is aware of the event, the site should enter this information into OnCore. An email notification should also be sent via email to djeyakum@hs.uci.edu and uci18105@hs.uci.edu.	Within 5 business days submit an Unanticipated Problem Report (UP) through Kuali Research Protocols. Current policy can be found here.	According to local institutional policies and guidelines	Within 1 business day of learning of the event. Submit all UPs to AEreporting@jazzpharma.com and submit any copies of the FDA submissions to PVcomms@jazzpharma.com when the FDA submission is made. All follow up information must be sent to Jazz Pharmaceuticals within 1 business day of PI's receipt of new information.	Within 1 business day of learning of the event. Submit all UPs via CIOMS form or a Pfizer approved SAE form.	Within 5 days from date PI is aware of the event. This information must be reported into OnCore.
AEs and SAEs (non-Unanticipated Problem)	Please refer to section 11.4 for reporting timeframes on AEs and SAEs	N/A		All SAEs should be reported in the same manner as a UP. All other adverse events will be reported to Jazz Pharmaceuticals in summary or line-item form upon Jazz Pharmaceuticals' request and at the conclusion of the study.	All SAEs should be reported in the same manner as a UP.	Please refer to section 11.4 for clarification on reporting timeframes for AEs and SAEs
Non-compliance	N/A	N/A		N/A	N/A	Please refer to section 11.4 for reportable deviations/violations
Serious or continuing non-compliance	Within 24 hours via email to djeyakum@hs.uci.edu and uci18105@hs.uci.edu.	Within 5 business days submit a reportable event through Kuali Research Protocols.		N/A	N/A	Within 5 days from date PI is aware of the event.
Prospective/Planned Deviations	At least 5 business days prior to the event via email to djeyakum@hs.uci.edu	At least 48 hours prior to date the request is		N/A	N/A	At the time of progress review as aggregate reports

	and uci18105@hs.uci.edu for approval.	needed by. Submit a Prospective Deviation Request form through Kuali Research Protocols.				

11.4 Additional Reporting of Events from Investigators at Participating Sites to the Sponsor Investigator

- Investigators at participating institutions must report AE, SAE, deviations, violations, and unanticipated problems according to their institutional policies.
- Investigators at participating institutions must also report AE, SAE, deviations, violations, and unanticipated problems to the PI of the coordinating center (or other entity such as a contract research organization) in the following timeframes:

Adverse Event/ Serious Adverse Events

Event Type	**Reporting Timeframe to CFCCC DSMB (Notification is done by entering this information into OnCore within the timelines below)**	**Reporting Timeframe to Coordinating Center (Notification is done via email to djeyakum@hs.uci.edu and uci18105@hs.uci.edu within the timelines below)**
Serious Adverse Events (all attributions) that meet all of the following criteria: • Unexpected • Grades 3-5 • Occurring during treatment or within 28 days of the end of treatment*	5 business days from date the PI is aware of the event	24 hours from date the site is aware of the event.
Adverse Events that meet all of the following criteria: • Unexpected • Study related (possibly, probably, or definitely) • Grades 3-4 • Occurring during treatment or within 28 days of the end of treatment*	5 business days from date the PI is aware of the event	24 hours from date the site is aware of the event.
All other Adverse Events and Serious Adverse Events should be reported as noted in the 'Reporting Requirements for Adverse Events' section	Prior to each scheduled progress review.	5 business days from the date the site is aware of the event
** Investigators are not obligated to actively seek information regarding the occurrence of new AEs or SAEs beginning after the 28-day post-treatment period. However, if the investigator learns of such an event and that event is deemed relevant to the study, he/she should promptly document and report the event.*		

Deviations/Violations

Event Type	Reporting Timeframe to CFCCC DSMB (Notification is done by entering this information into OnCore within the timelines below)	Reporting Timeframe to Coordinating Center (Or other entity monitoring/coordinating the trial)
Violations as defined above (e.g. wrong dosage of drug administered, safety procedures not being conducted at specific time points).	5 business days from the date the PI is aware of the event	24 hours from the date the site is aware of the event
Deviations as defined above, including: • Planned deviations (e.g. rescheduling a visit that will be out of window due to a holiday) • Unplanned deviations (e.g. rescheduled visit, a missed routine safety laboratory test for a participant with previously normal values)	Prior to each scheduled progress review	5 business days from the date the site is aware of the event

12.0 AGENT INFORMATION

12.1 Glasdegib

Please refer to product label for more comprehensive information.

Other names for the drug: Daurismo

Mechanism of action (or Product description): Hedgehog pathway inhibitor

Availability: Provided by funder,

How supplied: Glasdegib will be supplied in 30 count pill bottles. Initial dose will be supplied in 100 mg tablets. If dose modifications are needed, Glasdegib will be supplied in 25 mg tablets.

Storage and stability: Store at 20℃ to 25℃ (68℉ to 77℉); excursions permitted between 15℃ to 30℃ (59℉ to 86℉).

Route of administration for this study: Oral dose, given daily in the morning with or without food

Side effects: Anemia, fatigue, hemorrhage, febrile neutropenia, musculoskeletal pain, nausea, edema, thrombocytopenia, dyspnea, decreased appetite, dysguesia, mucositis, constipation, rash.

12.1.1 Return and Retention of Study Drug

Remaining drug is to be destroyed, according to Chao Cancer Center Investigational Drug Services destruction policy. Participating sites are to follow their institutional practice for destruction of study drug.

12.1.2 Drug Accountability/Subject Compliance

Records of study medications used, dosages administered, and intervals between visits will be kept during the study. Patients will be asked to fill out a pill diary and bring with them for review after each cycle of study treatment. (Appendix E)

Drug accountability will be noted at the completion of the trial. Patients will be asked to return all unused medication at the end of the study.

12.2 CPX-351

Please refer to product label for more comprehensive information.

Other names for the drug: Vyxeos; Liposomal Cytarabine and Daunorubicin

Mechanism of action (or Product description): liposomal formulation of cytarabine and daunorubicin in fixed 5:1 molar ratio which was developed to treat AML.

Availability: Provided by funder,

How supplied: CPX-351 will be supplied as 100mg cytarabine plus 44mg daunorubicin in a 50ml vial.

Storage and stability: Store unreconstituted VYXEOS vials in a refrigerator at 2°C to 8°C (36°F to 46°F) in an upright position. The vial should be stored in its original carton to protect from light.

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

The IV bags and infusion sets must follow the Vyxeos package insert). Per Vyxeos package insert, nondi(2-ethylhexyl)phthalate (DEHP) IV bags and infusion sets are not required. Aseptic technique must be strictly observed throughout the handling of CPX-351 since no bacteriostatic agent or preservative is present. The infusion of CPX-351 must be started within 4 hours of dilution. Vials are for single use only. 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.

The infusion of CPX-351 will be performed though a central venous catheter, using an infusion pump to ensure that the drug is infused over the specific time period. Do not use an in-line filter. CPX-351 should never be given by intramuscular or subcutaneous route. Administer CPX-351 over approximately 90 minutes vial an infusion pump. Flush the line to ensure the administration of the full dose.

Side effects: Hemorrhagic events, febrile neutropenia, rash, edema, nausea, mucositis, diarrhea, constipation, musculoskeletal pain, fatigue, abdominal pain, dyspnea, headache, cough, decreased appetite, arrhythmia, pneumonia, bacteremia, chills, sleep disorders, and vomiting

13.0 STATISTICAL CONSIDERATIONS

13.1 Study Design

This is an investigator-initiated trial which will evaluate the outcome of the combination of CPX-351 and Glasdegib in patients with newly diagnosed AML. This is a single-arm, open-label, Phase-IIA clinical trial to estimate the efficacy and tolerability of the combination of CPX-351 and Glasdegib in the study population.

UC Irvine will be the primary site of enrollment and additional sites within the University of California Hematologic Malignancies Consortium (UCHMC), including UCSF, UCLA, UCSD, and UCD can be added. Total of 1-5 U.S. centers. Enrollment can occur at any site as long as the trial is open at that site.

13.2 Data Analyses Plans

13.2.1 Primary Objectives

For efficacy, the primary objective is to estimate proportion of evaluable participants who are event-free at six months (EFS6) and compare to the historical figure of 50 percent.

13.2.2 Primary Endpoint

The primary endpoint for efficacy is EFS6. The event-free interval begins with the date of diagnostic biopsy, and ends as described in Section 2.1.

13.2.3 Primary Analysis

The null hypothesis is that EFS6 is 50%. The alternative hypothesis is that EFS6 will be 65% or more. The figure of 65% is the minimum thought to indicate the treatment regimen is worthy of further study. We will construct an exact (Clopper-Pearson), one-sided (lower), 90% confidence interval about the observed EFS6. If that the lower limit of that confidence interval is greater than 0.5, the treatment regimen will be deemed worthy of further study.

13.3 Sample Size and Accrual Goal

The accrual goal is 30 evaluable participants. The table below shows the lower bound of the 90%, one-sided, exact confidence interval as a function of sample size and true proportion (precision = 0.14). As the table shows, given the true proportion EFS6 is at least 65%, then 28 observations from evaluable subjects have at least 90% probability to yield a lower, one-sided confidence bound that excludes the historical-control value of 50%. Our goal is 30 evaluable subjects to allow for unanticipated loses.

Sample Size (evaluable)	True Proportion	Lower Bound*
28	60%	46%
28	65%	51%
28	70%	56%

- Rounded so as to assure coverage

13.4 Other Analyses

13.4.1 Description of Participants

Participants will be described by sex, age, and other host or clinical factors, using means, medians, and percentiles for continuous variables and counts and percentages for categorical variables. To the extent possible, participants will be compared to those who decline to participate in order to assess representativeness of the studied sample.

13.4.2 Analyses of Secondary Endpoints and Ad-Hoc Comparisons

13.4.2.1 General Philosophy

Consistent with the phase-ii nature of the project, we will examine the data in many ways to inform decisions about further research, including plots, tables, and statistical tests. Secondary analyses will be performed on intent-to-treat, per protocol, and ad-hoc data sets, as warranted. Given the total sample size of 28 to 30, probability values from statistical tests will be used as a guide to interpretation, which will also depend on clinical judgment. Therefore, we will not be concerned with overall, study-wise, type-1 error rates for secondary and ad-hoc analyses. As may be indicated, we will transform data to approach more closely analytic requirements, using logit transforms for percent data and log (for first choice) for continuous measures. If transformations fail, we will fall back on the analysis of ranks or use non-parametric methods.

13.4.2.2 Proportions

Proportions, such as, overall remission rates and proportion who go to HSCT will be characterized by exact, binomial interval estimates and compared with Fisher's exact test.

13.4.2.3 Survival

Time-to-event measures, such as, overall survival, time to normal hematopoiesis, duration of response, and influence of MRD status will be characterized by Kaplan-Meier methods, both overall and by strata of interest. Differences in times/survival between or among groups will be evaluated by the log-rank test. If assumptions are reasonably met, then Cox proportional-hazards models will be made to examine the effects on survival of covariates adjusting for other covariates. Ties in survival time will be broken by the subtracting a small, randomly generated amount from each tied observation (Borucka, 2014).

13.4.2.4 Gene Expression

We will use differential gene-expression analysis to try to identify genes or sets of genes where change in expression levels correlate with response to study treatment.

13.4.2.5 Analyses of Intolerability or Toxicity

We will examine the data to discover factors that may predict adverse reactions to the study treatment. We will proceed in the same way as outlined above for secondary analyses. Adverse events will be classified by type, frequency, severity, timing, grade, and other factors that may aid interpretation, and be summarized by proportions, overall and within groups of subjects.

14.0 STUDY MANAGEMENT

14.1 Conflict of Interest

Any investigator who has a conflict of interest with this study (patent ownership, royalties, or financial gain greater than the minimum allowable by their institution, etc.) must have the conflict reviewed according to their local conflict of interest policy. If there is a positive disclosure, the site must communicate this information to the initiating site to determine if any revisions to the consent form are required with the IRB of record based on the COI outcome.

14.2 Regulatory Issues

Regulatory requirements both at the federal level and the institutional level must be followed. The federal regulations for human subject protections and for clinical trials can be found in the

Federal Code of Regulations for the Department of Health and Human Services (DHHS) and the websites for federal agencies such as the National Institutes of Health (NIH) and the Food and Drug Administration (FDA).

14.3 Scientific Review Committees

Each participating institution must submit the protocol to their individual scientific review committees per their institutional policies. Scientific Review Committee approval is required prior to IRB approval through individual IRBs and reliance on the initiating site's IRB. Site may rely on Scientific Review Committee approval by another NCI designated cancer center.

14.4 Institutional Review Boards

Each clinical site must obtain approval by their local Institutional Review Board (IRB) prior to the initiation of any UCHMC clinical trial. Communication between a site and the respective IRB is the responsibility of the site investigator. Copies of IRB correspondence, including protocol approval letters, must be kept on file at the site. A site may begin accrual upon contacting the Clinical Trials Operations Core by e-mail to assure any outstanding regulatory issues have been addressed and resolved. The UCHMC Clinical Trial Operations Core will be responsible for ensuring that all necessary essential documents as listed below in the trial master file are in place and kept up to date throughout the study. It is not required to wait until all UCHMC sites secure local IRB approval to begin enrolling at an approved site. Each site is responsible for the annual renewal of IRB approval if not operated through UC Reliance. Each investigator must report to the IRB any problems, serious adverse drug reactions or proposed changes in the protocol that may affect the status of the investigation and the willingness of patients to participate in the trial. The investigator must also report to the IRB at intervals appropriate to the degree of risk in the study, but no less frequently than once a year or at study closure.

14.5 SMART IRB Process

The initiating site's IRB will act as IRB of record through the SMART IRB reliance agreement.

14.5.1 Initial Review Process

1. All relying PIs agree to reliance through the SMART IRB process
2. The initiating site PI will proceed with local IRB submission and notify the initiating site's IRB about the participating sites
3. Reviewing IRB approves the study
4. IRB approved documents are pulled by the initiating site and distributed to the participating sites
5. Each participating site will begin their local IRB submission and obtain approval and acceptance of the reliance
6. Once accepted, the smart IRB agreement will be finalized and distributed to the sites

14.5.2 Continuing Review

Continuing Reviews (Annual Reviews) are the responsibility of the Reviewing PI. If the Continuing Review approval is not obtained in a timely manner, none of the relying sites will be allowed to continue research. The initiating site will inform the relying sites once the Continuing Review approval has been granted.

If the participating sites are relying on the initiating site's IRB, participating sites are to provide the initiating site of all requested documents and information approximately 120 days prior to the expiration date of the study. Sites utilizing their local IRB must submit the continuing review approximately 90 days prior to expiration date of the study. Once the Continuing Review has been approved, the initiating site will update the expiration date in OnCore. Any sites utilizing their local IRB must submit their continuing review approval to the lead site upon receipt by sending the form to uci18105@hs.uci.edu.

The Office of the President notes: "... no relying UC site on your study will be able to continue work if you don't obtain IRB renewal [continuing review approval] on time: it is your responsibility as a Reviewing Campus PI to apply for the renewal [continuing review] on time!"

14.5.3 Amendments

You are required to promptly inform the Reviewing PI/RC of the need for amendments.

Protocol and ICF amendments will be submitted to the IRB of record by the initiating site. Once approval is granted by the IRB of record, approved documents will be provided to the sub-sites.

14.5.4 Adverse Events

You are required to report to the Reviewing PI/RC and the IRB of record any adverse or unanticipated events. Each site is responsible for notifying the Reviewing Campus IRB following the Reviewing Campus's guidelines and notifying their local IRB, Jazz Pharmaceuticals, the study's DSMB, as applicable. Any decision, change in protocol, etc. will be reported and uploaded to the Registry by the Reviewing Campus IRB.

14.5.5 Protocol Amendment Procedures

Should amendments to the protocol be required, the amendments will be originated and documented by the Study Chair. It should also be noted that when an amendment to the protocol substantially alters the study design or the potential risk to the patient, a revised consent form might be required.

The written amendment, and if required the amended consent form, must be sent to the IRB for approval prior to implementation.

Any substantial change should be discussed during the UCHMC Monthly Teleconference. If the need for a protocol revision is agreed upon, the originator of the protocol is responsible for modifying the protocol, and sending the revised version electronically to the UCHMC Coordinating Center and sites along with the summary of the proposed changes. The originator of the protocol also has responsibility for submitting the amendment to the FDA, if applicable.

If the changes are solely administrative and do not alter trial conduct, UCHMC Clinical Trials Steering Committee approval is not required. Steering Committee Members should be made aware of all amendments. Each Steering Committee member should be provided with a list of changes implemented in an amendment.

The initiating site's IRB will be utilized for all protocol amendment approvals. Each center must submit the revision to their respective IRB for approval if not relying through the SMART IRB reliance agreement. A copy of the IRB approval is to be sent to uci18105@hs.uci.edu.

The primary site will ensure that all sites are operating off the correct protocol and ICF version and will obtain training documentation from each site. Each site will follow their institutional policy on protocol training. A copy of each site's institutional policy must be sent to the initiating site prior to the site initiation visit.

14.5.6 Institutional Review Board (IRB) Approval and Consent

The IRB should approve the consent form and protocol prior to any study-related activities. It is expected that the IRB will have the proper representation and function in accordance with federally mandated regulations.

In obtaining and documenting informed consent, the investigator should comply with the applicable regulatory requirement(s), and should adhere to Good Clinical Practice (GCP) and to ethical principles that have their origin in the Declaration of Helsinki.

Before recruitment and enrollment onto this study, the patient will be given a full explanation of the study and will be given the opportunity to review the consent form. Each consent form must include all the relevant elements currently required by the FDA Regulations and local or state regulations. Once this essential information has been provided to the patient and the investigator is assured that the patient understands the implications of participating in the study, the patient will be asked to give consent to participate in the study by signing an IRB-approved consent form.

Prior to a patient's participation in the trial, the written informed consent form should be signed and personally dated by the patient and by the person who conducted the informed consent discussion.

14.5.7 Required Documentation

Trial Master File (TMF)
Prior to initiating a UCHMC protocol and enrolling subjects, the initiating site must insure that all essential documents are in place and activate the site.
Before the study can be initiated at any site, the following documentation must be provided to the UCI Clinical Trials Office:

UC Irvine Health
Chao Family Comprehensive Cancer Center
Clinical Trials
200 Manchester Drive, Suite 400
Orange, CA, 92868
Phone: 714-456-5153
Fax: 714-456-2242
Email : uci18105@hs.uci.edu

- A copy of the official IRB approval letter for the protocol and informed consent document OR documentation of agreement to accept UCI IRB approval of the protocol and consent through the UC IRB Reliance Registry by means of the SMART IRB reliance agreement
- IRB membership list or FWA letter
- A copy of the IRB approved consent form
- CAP and CLIA Laboratory certification numbers and institution lab normal values for those listed on the 1572
- Executed clinical research contract

- Delegation of Authority Log
- 1572
- Financial Disclosure Forms
    - For PI and each Sub-I
- CVs and Medical Licenses
    - For PI and each Sub-I
- GCP Training
    - For PI, Sub-Is and study personnel
- Protocol Signature Page
- IATA Training Certificate for Coordinators
- Site Drug Destruction SOPs
- Institutional SOPs
- Site contact sheet

Sub-sites will receive activation notice upon receipt of all required documents by the initiating site.

14.5.8 Protocol Initiation

When a protocol has been submitted for IRB approval at a site, the initiating site must be notified. Protocols will be tracked in OnCore. Each clinical site must ensure that the protocol has been approved by a local IRB prior to the initiation of a trial. A copy of the protocol approval letter must be sent to the UCI by emailing uci18105@hs.uci.edu. If a site is not relying on the initiating site's IRB, each site is responsible for annual renewal of IRB approval and should email a copy of the renewal letter to central study email when it is received. If run through the smart IRB reliance, the initiating site will be responsible for providing documentation of annual renewal approval to each of the participating centers.

Site Initiation Visits
Prior to activation and patient enrollment on a protocol a site initiation visit must occur. All PIs must be in attendance along with the coordinator, regulatory associate and pharmacy when appropriate. SIV's may be conducted in person or remotely per the initiating PI's preference.

Site Activation
Prior to enrolling the first patient, all sites must obtain notice of activation from the initiating site. At a minimum, sites must show documentation of IRB approval, IRB Stamped ICF, completed delegation of authority log, and if applicable with the site policy, SIV training documentation.

14.5.9 Protocol Amendments and Continuing Renewal Approvals

Protocol Amendments
For all protocol amendments, each site must follow their institutional policy on protocol training. A copy of this policy must be sent to initiating site for review prior to the site initiation visit.

Signed protocol signature pages must also be completed by each PI for each version of the protocol.

Prior to submitting the revised ICF, the initiating site is to work with each site to ensure that changes to the ICF per the amendment are appropriate per their institutional requirements. The initiating site will provide each site with their IRB stamped version of the amended ICF if applicable and clearly indicate whether or not patients must be re-consented. If necessary, foreign language

translations of the ICF and other patient facing materials will be provided to each site by the initiating site.

IRB approval documentation to be provided by the initiating site to each sub-site for each amended protocol.

Continuing Renewals
Prior to submitting the continuing renewal to the IRB, the initiating site will work with each sub-site to obtain patient narratives and non-UPR logs (deviation log) per their IRBs operating procedures. Once continuing renewal has been granted, it is the responsibility of the initiating site to provide each site with the IRB approval notice and stamped ICF with updated expiration date. If necessary, all translated materials will be provided at this time.

Site Close out Visit
A Site close out visit must be performed prior to a site closing a study with the IRB. During the site close out visit, final data review will occur, review and collection of all regulatory documents will be performed, and final drug accountability will occur. This visit may be an on-site visit or can be completed remotely.

14.5.10 Electronic Data Capture "OnCore EDC"

Data must be entered within 10 business days of each study visit. Data progress will be monitored by the clinical research manager to ensure that all data is entered in a timely manner per the UCHMC guidelines.

User Training
Instruction concerning the use of eCRF forms is provided by the clinical research manager. Instruction concerning the use of the OnCore EDC Database, remote training concerning the proper use of the EDC system is available to sites by request, or if training appears is needed based on inconsistency or errors in data reported.

- The PI at the initiating site will have access to view the data of all patients at all sites
- Local PI and coordinator for individual sub-sites will have access to view only the data pertaining to their patients.

Changes in study status must be promptly recorded in the OnCore EDC System. Case report forms (CRFs) are to be entered into OnCore by clinical site personnel within 10 business days of the patient's visit.

Registration/Baseline Data
The Registration/Baseline data is captured by the OnCore EDC System. Clinical staff is required to check with their IRB and the initiating site for current protocol accrual before consenting or attempting to enroll patients in any clinical trial.

If errors are made in attempting to enroll in a protocol, the data entry can only be corrected by contacting the study team at uci18105@hs.uci.edu.

Clinical Data
The Clinical case report forms are intended to capture laboratory values and clinical visit information at time intervals specified by each protocol. These values are to be entered into the OnCore EDC system within 10 business days of the patient visit.

14.5.11 Data Forms and Submission Schedule via OnCore EDC

Data Forms Completion
Data forms are to be completed following Screening, and then after each study visit.

Data Forms Submission
Data forms are to be completed in the OnCore EDC system and corresponding source documentation uploaded within 2 weeks after each study visit. Timeline for Data Form submission is as follows:

Screening Forms: to be completed within 24 hours following confirmation of eligibility and enrollment on the study.

Treatment Visit Forms: within 2 weeks of the end of each visit, to include Con Med forms.

Off-Study Form/Death Form: within 1 week of knowledge of off-study status or death of patient.

AE Forms: please refer to the reporting requirements section 11.3 and 11.4 to determine the appropriate timeline in which this information should be entered. All AEs should always be entered prior to scheduled Study Conference Calls (scheduled monthly)

SAE Forms: to be sent within 24 hours of knowledge of the event, and then as soon as a final report can be done. Please refer to the reporting requirements section 11.3 and 11.4 to determine the appropriate timeline in which this information should be entered.

14.5.12 Data Monitoring

It is the responsibility of the clinical research manager and study coordinator to review all of the case report forms submitted using the OnCore EDC Database. Electronic submission of clinical data should be reviewed monthly, of all data entered in that month. Any problems with the OnCore EDC System (e.g. system access, errors, bugs) should be reported to the lead institution immediately. The OnCore team can be reached via email at OnCore_Admin@hs.uci.edu. You may also contact the central study email, uci18105@hs.uci.edu, with any OnCore issues as well.

14.5.13 Study Monitoring Conference Calls

During the study, we will hold **bi-weekly or monthly** teleconferences to be attended by the study investigators or their representatives, the principal investigator, data management, and the statistical data center to review adverse events, accrual and other issues that arise over the course of the study. This teleconference is only required for those sites with patients on study.

14.5.14 Subject Data Protection

In accordance with the Health Information Portability and Accountability Act (HIPAA), subjects who have provided written informed consent must also sign a subject authorization to release medical information to the study Sponsor and allow a regulatory authority, or Institutional Review Board access to subject's medical information relevant to the study.

14.5.15 Data and Safety Monitoring/Auditing

This study will also use the UCI Data Safety and Monitoring Board (DSMB) to provide oversight in the event that this treatment approach leads to unforeseen toxicities. This is a risk level 1 study, as defined in the Chao Family Comprehensive Cancer Center (CFCCC) Data and Safety Monitoring Plan (DSMP) because although Glasdegib and Vyxeos are FDA approved, the toxicity of the combination is not well established.

The Principal Investigator (PI), co-investigator, clinical research coordinator, and statistician are responsible for monitoring of data and safety for this study. For studies that have stopping rules for safety and efficacy, the PI will be responsible for the implementation and make changes as applicable. The CFCCC Data and Safety Monitoring Board (DSMB) is an independent body responsible for the safety of study subjects as well as the data integrity of the protocol. Data and safety will be reported to the DSMB with submission of progress reports that include aggregated reports of adverse events, serious adverse events, deviations, and violations. In addition, certain adverse events, serious adverse events, deviations, violations, and unanticipated problems will be reported promptly to the DSMB for review according to Section 11.3 and Section 11.4.

The CFCCC Stern Center for Cancer Clinical Trials and Research Quality Assurance Unit will conduct monitoring and auditing activities as per the UC Irvine CFCCC Quality Assurance Monitoring and Auditing Plan and at the discretion of the CFCCC DSMB in order to ensure patient safety and data integrity oversight. By conducting internal monitoring and auditing, the CFCCC will ensure compliance with high quality standards and all applicable regulations, guidelines, and institutional policies. Trial monitoring and auditing may be completed remotely or on-site. Participating sites may follow their own internal quality assurance policies in order to maintain patient safety and data integrity oversight. The investigator must permit study-related monitoring/auditing and provide access to study-related materials.

Risk Levels

Risk Level	Definition	Monitoring
Level 1	**High Risk** - UCI investigator-initiated interventional trials for which the PI holds Investigational New Drug (IND) or Investigation Device Exemption (IDE). Example: Gene therapy, dendritic cell products from GMP suite, phase I/II development and phase I studies, first in human, etc.	Two months after subject enrollment

14.5.16 Adherence to the Protocol

Except for an emergency situation in which proper care for the protection, safety, and well-being of the study patient requires alternative treatment, investigators are required to conduct their research according to the plans reviewed and approved by the IRB. Any planned or prospective deviations must require proper approval from the initiating site and the IRB. Please refer to section 11.3 and 11.4 to ensure when and who must be informed of any planned deviations.

14.5.17 Emergency Modifications

Investigators may implement a deviation from, or a change of, the protocol to eliminate apparent immediate hazards/risks to trial subjects without prior IRB approval. Any such emergency modification implemented must be noted and reported to the IRB and inform the initiating site PI along the lines of a protocol deviation or violation, depending on the nature of the modification.

14.5.18 Protocol Violations

Any unplanned variance from an IRB approved protocol is considered a violation and must be reported to the IRB in a timely fashion.

A. All major protocol deviations will be reported in accordance with UCI IRB, UCI CFCCC Stern Center policies, UCI DSMB and the participating site's IRB policies.
Major violations include:
- Instances that have harmed or increased the risk of harm to one or more research participants.
- Instances that have damaged the scientific integrity of the data collected for the study.
- Results from willful or knowing misconduct on the part of the investigator(s).
- Demonstrates serious or continuing noncompliance with federal regulations, State laws, or University policies.

B. Minor violations may be reported to the IRB at the time of the continuing review.
Minor violations have no substantive effect on the risks to participants or on the scientific integrity of the research plan or the value of the data collected.

14.5.19 Amendments to the Protocol

Should amendments to the protocol be required, the amendments will be originated and documented by the Study Chair. It should also be noted that when an amendment to the protocol substantially alters the study design or the potential risk to the patient, a revised consent form might be required.

The written amendment, and if required the amended consent form, must be sent to the IRBs and any applicable entities or committees (FDA, RSC, IBC, when applicable) for approval prior to implementation.

14.5.20 Record Retention

Study documentation includes all Case Report Forms, data correction forms or queries, source documents, correspondence, monitoring logs/letters, and regulatory documents (e.g., protocol and amendments, IRB correspondence and approval, signed patient consent forms).

Source documents include all recordings of observations or notations of clinical activities and all reports and records necessary for the evaluation and reconstruction of the clinical research study.

Government agency regulations and directives require that the study investigator must retain all study documentation pertaining to the conduct of a clinical trial. Study documents should be kept on file until 10 years after the completion and final study report of this investigational study.

14.5.21 Obligations of Investigators

The Principal Investigator is responsible for the conduct of the clinical trial at the site in accordance with Title 21 of the Code of Federal Regulations and/or the Declaration of Helsinki.

The Principal Investigator is responsible for personally overseeing the treatment of all study patients. The Principal Investigator must assure that all study site personnel, including sub-investigators and other study staff members, adhere to the study protocol and all FDA/GCP/NCI regulations and guidelines regarding clinical trials both during and after study completion.

The Principal Investigator at each institution or site will be responsible for assuring that all the required data will be collected and entered onto the Case Report Forms. Periodically, monitoring visits will be conducted and the Principal Investigator will provide access to his/her original records to permit verification of proper entry of data. At the completion of the study, all case report forms will be reviewed by the Principal Investigator and will require his/her final signature to verify the accuracy of the data.

15.0 UCHMC Publication Policy

15.1 Overview

The process of preparation, clearance, and publication of any manuscript which results from a UCHMC study is complete when the study results are disseminated to the scientific community by means of a formal referred publication. The UCHMC Steering Committee has oversight over the use and publication of UCHMC data. Each institution participating in protocol studies must be acknowledged and each contributing institution should have the opportunity to review the manuscript.

15.2 Publication Preparation and Review

The responsibility for writing manuscripts describing a UCHMC study belongs to the Study Principal Investigator. The Biostatistics Core provides analytic assistance and review for manuscripts based on UCHMC clinical protocols, and as requested by the Study Chair. The Clinical Trials Steering Committee reviews manuscripts based on UCHMC clinical protocols. The timeline for preparing, reviewing, and revising the manuscript will be decided by the Study Chair and the UCHMC Steering Committee on a case-by-case basis.

15.3 Publication Acknowledgements

All manuscripts should acknowledge in the title of the paper that the manuscript is a group effort. A suggested mechanism is to follow the title of the paper with the phrase "University of California Hematologic Malignancies Consortium (UCHMC) Study." The manuscript should indicate UCHMC protocol by number.

15.4 Authorship

First author will be assigned to the study chair or PI at the initiating site. Senior authorship will be assigned based on contribution to protocol development, not specifically to study enrollment. The order of authorship assignments outside of first and last (senior) author will be based on study enrollment numbers with highest enrolling sites placed earlier in authorship order. Both the local PI and steering committee member, if different, from each site will be included as authors on the publication. References to Patient Data in Publications
In order to ensure that the privacy and confidentiality of UCHMC patients is maintained in publications, measures must be taken to ensure that no personal identifiable data (PID) is

released in any publication. When publishing information pertaining to the given patient data and/or samples, investigators are to utilize the study specific ID number.

16.0 REFERENCES

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17.0 APPENDICES

Appendix A. Cytogenetic abnormalities

Cytogenetic abnormalities sufficient to diagnose AML with myelodysplasia-related changes when ≥ 20% PB or BM blasts are present and prior therapy has been excluded

Cytogenetic abnormalities
Complex karyotype (3 or more abnormalities)
Unbalanced abnormalities
-7/del(7q)
del(5q)/t(5q)
i(17q)/t(17p)
-13/del(13q)
del(11q)
del(12p)/t(12p)
idic(X)(q13)
Balanced abnormalities
t(11;16)(q23.3;p13.3)
t(3;21)(q26.2;q22.1)
t(1;3)(p36.3;q21.2)
t(2;11)(p21;q23.3)
t(5;12)(q32;p13.2)
T(5;7)(q32;q11.2)
t(5;17)(q32;p13.2)
t(5;10)(q32;q21.2)
t(3;5)(q25.3;q35.1)

Appendix B. Performance Status

ECOG Performance Status Scale	
Grade	Descriptions
0	Normal activity. Fully active, able to carry on all pre-disease performance without restriction.
1	Symptoms, but ambulatory. Restricted in physically strenuous activity, but ambulatory and able to carry out work of a light or sedentary nature (e.g., light housework, office work).
2	In bed < 50% of the time. Ambulatory and capable of all self-care, but unable to carry out any work activities. Up and about more than 50% of waking hours.
3	In bed > 50% of the time. Capable of only limited self-care, confined to bed or chair more than 50% of waking hours.
4	100% bedridden. Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair.
5	Dead.

Appendix C. CYP35A Inhibitors/Inducers

Strong CYP3A4/5 Inducers	
Inducer	**Therapeutic Class**
Rifampin	Antibiotics
Rifabutin	Antibiotics
Avasimibe	Antilipedimics
Phenytoin	Anticonvulsants
Carbamazepine	Anticonvulsants
Phenobarbital	Anticonvulsants
Enzalutamide	Antiandrogens
St. John's Wort	Herbal Medications
Mitotane	Antineoplastic
Moderate CYP3A4/5 Inducers	
Inducer	**Therapeutic Class**
semagacestat	Alzheimers
efavirenz	NNRTI
bosentan	Endothelin Receptor Antagonist
genistein	Food Product
Thioridazine	Antipsychotics
Naficillin	Antibiotics
Talviraline	NNRTI
Lopinavir	Protease Inhibitor
Modafinil	Psychostimulant
Etravirine	NNRTI
Lersivirine	NNRTI

Source: University of Washington Drug Interaction Database. "Copyright University of Washington 1999-2015, UW Metabolism and Transport Drug Interaction Database, accessed: May 2017"

Strong CYP3A4/5 Inhibitors	
Inhibitor	**Therapeutic Class**
Ketoconazole	Antifungal
Itraconazole	Antifungal
Voriconazole	Antifungal
Posaconazole	Antifungal
Troleandomycin	Antibiotics
Clarithromycin	Antibiotics
Telithromycin	Antibiotics
Mibefradil	Calcium Channel Blocker
Conivaptan	Diuretics

Nefazodone	Antidepressants
Cobicistat	--
Indinavir/Ritonavir	Protease Inhibitors
Tipranavir/Ritonavir	Protease Inhibitors
Ritonavir	Protease Inhibitors
Indinavir	Protease Inhibitors
Nelfinavir	Protease Inhibitors
Saquinavir	Protease Inhibitors
Saquinavir/Ritonavir	Protease Inhibitors
Lopinavir/Ritonavir	Protease Inhibitors
Telaprevir	Antivirals
Boceprevir	Antivirals
Danoprevir/Ritonavir	Antivirals
Elvitegravir/Ritonavir	Antivirals
LCL161	Antivirals
Idelalisib	Kinase Inhibitors
Grapefruit Juice DS	Food Products

Source: University of Washington Drug Interaction Database. “Copyright University of Washington 1999-2015, UW Metabolism and Transport Drug Interaction Database, accessed: May 2017”

Moderate CYP3A4/5 Inhibitors	
Inhibitor	**Therapeutic Class**
Fluconazole	Antifungals
Erythromycin	Antibiotics
Ciprofloxacin	Antibiotics
Diltiazem	Calcium Channel Blockers
Verapamil	Calcium Channel Blockers
Dronedarone	Antiarrhythmics
Aprepitant	Antiemetics
Casopitant	Antiemetics
Netupitant	Antiemetics
Tofisopam	Benzodiazepines
Cyclosporine	Immunosuppressant
Schisandra sphenanthera	Herbal Medication
ACT-178882	Renin Inhibitor
Cimetidine	H2 Receptor Antagonist
FK1706	Central Nervous System Agent
Faldaprevir	Antivirals
Crizotinib	Kinase Inhibitor
Nilotinib	Kinase Inhibitor

Atazanivir/Ritonavir	Protease Inhibitor
Darunavir	Protease Inhibitor
Darunavir/Ritonavir	Protease Inhibitor
Atazanavir	Protease Inhibitor
Amprenavir	Protease Inhibitor
Imatinib	Antineoplastic agent
Grapefruit Juice	Food Products
Isavuconazole	Antifungal
GSK2647544	Alzheimer's/Dementia

Source: University of Washington Drug Interaction Database. "Copyright University of Washington 1999-2015, UW Metabolism and Transport Drug Interaction Database, accessed: May 2017"

Appendix D. Drugs known to prolong QTc

Drugs that have known risk for QT prolongation			
Generic Name	**Drug Class**	**Therapeutic Use**	**Route**
Amiodarone	Anti-arrhythmic	Abnormal heart rhythm	oral,injection
Anagrelide	Phosphodiesterase 3 inhibitor	Thrombocythemia	oral
Arsenic trioxide	Anti-cancer	Leukemia	injection
Azithromycin	Antibiotic	Bacterial infection	oral,injection
Chloroquine	Anti-malarial	Malaria infection	oral
Chlorpromazine	Anti-psychotic /Anti-emetic	Schizophrenia/nausea	oral, injection
Cilostazol	Phosphodiesterase 3 inhibitor	Intermittent claudication	oral
Ciprofloxacin	Antibiotic	Bacterial Infection	oral, injection
Citalopram	Anti-depressant, SSRI	Depression	oral
Clarithromycin	Antibiotic	Bacterial infection	oral
Disopyramide	Anti-arrhythmic	Abnormal heart rhythm	oral
Dofetilide	Anti-arrhythmic	Abnormal heart rhythm	oral
Donepezil	Cholinesterase inhibitor	Dementia	oral
Dronedarone	Anti-arrhythmic	Atrial Fibrillation	oral
Droperidol	Anti-psychotic / Anti-emetic Anesthesia	adjunct, nausea	injection
Erythromycin	Antibiotic	Bacterial infection; increase GI motility	oral, injection
Escitalopram	Anti-depressant, SSRI	Major depression/ Anxiety Disorders	oral
Flecainide	Anti-arrhythmic	Abnormal heart rhythm	oral
Fluconazole	Anti-fungal	Fungal infection	oral, injection
Halofantrine	Anti-malarial	Malaria infection	oral
Haloperidol	Anti-psychotic	Schizophrenia, agitation	oral, injection
Ibutilide	Anti-arrhythmic	Abnormal heart rhythm	injection
Levofloxacin	Antibiotic	Bacterial infection	oral, injection
Methadone	Opiate	Pain control, narcotic dependence	oral, injection
Moxifloxacin	Antibiotic	Bacterial infection	oral, injection
Ondansetron	Anti-emetic	Nausea, vomiting	oral, injection
Pentamidine	Antibiotic	Pneumocystis pneumonia	injection, inhaled
Pimozide	Anti-psychotic	Tourette's tics	oral
Propofol	Anesthetic	Anesthesia	injection

Quinidine	Anti-arrhythmic	Abnormal heart rhythm	oral, injection
Sevoflurane	Anesthetic, general	Anesthesia	inhaled
Sotalol	Anti-arrhythmic	Abnormal heart rhythm	oral
Thioridazine	Anti-psychotic	Schizophrenia	oral
Vandetanib	Anti-cancer	Thyroid cancer	oral

Source: Credible Meds.org (http://crediblemeds.org/healthcare-providers/drug-list/?rf=All). TdP risk category filtered on Drugs with known TdP risk. Assessed 11 October 2015.

Appendix E. IWG Response Criteria

International Working Group Response Criteria in AML

Classification	Definition
Complete remission (CR)	Bone marrow blasts < 5 percent; absence of blasts with Auer rods; absence of extramedullary disease; ANC > 1000/μL; platelet count > 100,000/μL; independence of red cell transfusions
Complete remission with incomplete hematologic recovery (CRi)	All CR criteria except for residual thrombocytopenia (platelet counts < 100,000/μL) and neutropenia (ANC < 1000/uL)
Complete remission with partial hematologic recovery (CRp)*	Bone marrow blasts < 5 percent; absence of blasts with Auer rods; absence of extramedullary disease; ANC > 500/μL; platelet count > 50,000/μL; independence of red cell transfusions
Morphologic leukemic-free state	Bone marrow blasts < 5 percent; absence of blasts with Auer rods; absence of extramedullary disease; no hematologic recovery required
Partial remission (PR)	Relevant in the setting of phase I and II clinical trials only; all hematologic criteria of CR; decrease of bone marrow blast percentage to 5 to 25 percent; and decrease of pretreatment bone marrow blast percentage by at least 50 percent
Cytogenetic remission	Reversion to a normal karyotype at the time of morphologic CR (or CRi) in cases with an abnormal karyotype at the time of diagnosis; based on the evaluation of 20 metaphase cells from bone marrow
Molecular remission	No standard definition; depends on molecular target
Resistant disease	Failure to achieve CR or CRi (general practice; Phase 2/3 trials), or failure to achieve CR, CRi or PR (Phase 1 trials); only includes subjects surviving ≥ 7 days following completion of initial treatment, with evidence of persistent leukemia by blood and/or bone marrow examination
Death in aplasia	Deaths occurring ≥ 7 days following completion of initial treatment while cytopenic; with an aplastic or hypoplastic bone marrow obtained within 7 days of death, without evidence of persistent leukemia
Death from indeterminate cause	Deaths occurring before completion of therapy, or < 7 days following its completion; or deaths occurring ≥ 7 days following completion of initial therapy with no blasts in the blood, but no bone marrow examination available
Relapse	Bone marrow blasts ≥ 5 percent; or reappearance of blasts in the blood; or development of extramedullary disease
Stable disease	Failure to achieve a response and not meeting the criteria for disease progression

Disease progression	For subjects with 5% to 70% bone marrow blasts at the last assessment (including the pretreatment assessment prior to study entry): - a > 50% increase in bone marrow blast count percentage from the last bone marrow blast count to ≥ 20% that persists for at least 2 bone marrow assessments separated by at least 1 month. For subjects with ≥ 70% bone marrow blasts at the last assessment: - a doubling of the nadir absolute peripheral blood blast count that persists for at least 1 month and the final absolute peripheral blood blast count is > 10×10^9/L. The date of progressive disease is defined as the first date that there was either a > 50% increase in bone marrow blast count from the last assessment for subjects with 5 to 70% bone marrow blasts or a doubling of the peripheral blood blast count to > 10×10^9/L for subjects with ≥ 70% bone marrow blasts.

Appendix F. Pill Diary

Glasdegib _____ mg			
Instructions: • Do not take Glasdegib on the same day as CPX-351 infusion. • Take by mouth in the morning, with 8 ounces of water. • Take with or without food. Swallow the tablet whole. • Do not chew or crush the tablet before swallowing. • If you forget to take your dose at the regular time, and **LESS** than 10 hours have passed since the dosing time, take the dose as soon as possible. If **MORE** than 10 hours have passed since the dosing time, skip the dose and continue on your normal dose schedule the next day. • If you miss a dose, do **NOT** make it up by taking an extra tablet. If you vomit at any time after you have taken your study pill, do **NOT** make it up by taking an extra tablet.			
Date (MM/DD/YY)	Time pills taken	Number of glasdegib pills taken	Use the space below to make notes about things you would like to tell the doctor (including unusual symptoms you experience, other medicine you have taken and anything else you think would be of interest.
Example: *5/22/2020*	*9:20 AM*	*1*	*First dose today, taken with breakfast and glass of water.*
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Additional space for comments:			

When completed, please sign below:

Patient Signature: _____ Date: ____/_____/_____

Site Staff Signature: _____Date: ____/_____/_____

Appendix G. Eligibility Checklist

Study Title: Phase II study of the combination of Glasdegib and CPX-351 in previously untreated patients with Acute Myelogenous Leukemia with MDS related changes or therapy-related Acute myeloid leukemia

Patients Initials: _____ SID: _____
DOB:_____

Inclusion Criteria		*Yes*	*No*
1	Previously untreated therapy-related AML or AML with myelodysplastic related changes as described by WHO 2016 a. AML arising in MDS (including CMML) or MDS/MPN syndrome b. AML with MDS-related cytogenetic abnormalities (Appendix A) (metaphase FISH allowable as surrogate for cytogenetics) c. AML with multilineage dysplasia involving the presence of 50% or more dysplastic cells in at least two cell lines and in the absence of mutation in NPM1 or biallelic CEBPA (as per WHO 2016).		
2	Adults 18 years of age or older		
3	ECOG performance status 0 to 2		
4	Adequate organ function as defined as: 1. Left Ventricular Ejection Fraction (LVEF) > 50% 2. Serum total bilirubin < 2.0 mg/dL, unless considered due to Gilbert's disease or leukemic involvement 3. AST, ALT and alkaline phosphatase < 3 times the upper limit of normal, unless considered due to leukemic involvement 4. Serum creatinine < 2.0 mg/dL, or creatinine clearance > 40 mL/min based on Cockcroft-Gault GFR		
5	Absence of unstable cardiac disease defined as myocardial infarction within 6 months, uncontrolled heart failure, or uncontrolled cardiac arrhythmia		
6	Ability to understand and the willingness to sign a written informed consent or subject's legally authorized representative (LAR) has provided informed consent prior to any study-specific activities/procedures being initiated when the subject has any kind of condition that, in the opinion of the investigator, may compromise the ability of the subject to give written informed consent		

7	Women of child-bearing potential and men with partners of child-bearing potential must agree to use 2 methods of birth control or be surgically sterile, or abstain from heterosexual activity for the course of the study through 120 days after the last dose of study medication A woman of child-bearing potential is any female (regardless of sexual orientation, having undergone a tubal ligation, or remaining celibate by choice) who meets the following criteria: • Has not undergone a hysterectomy or bilateral oophorectomy; or • Has not been naturally postmenopausal for at least 12 consecutive months (i.e., has had menses at any time in the preceding 12 consecutive months) • Women of child-bearing potential has negative pregnancy test within 72 hours of initiating study drug dosing. • Male subjects must agree to use a latex condom during sexual contact with females of childbearing potential even if they have had a successful vasectomy starting with the first dose of study therapy through 120 days after the last dose of study therapy		
8	Leukapheresis, corticosteroid and hydroxyurea are permitted as initial management of hyperleukocytosis at the investigator's discretion for up to 7 days after starting study therapy. Hyperleukocytosis is defined as greater than 30k WBC. When possible, a bone marrow biopsy for screening should be performed prior to the initiation hyperleukocytosis management		

Exclusion Criteria		***Yes***	***No***
1	Prior treatment with Glasdegib or CPX-351		
2	Previously treated AML except for initial management of hyperleukocytosis. Treatment with hypomethylating therapy for MDS is allowable but not since their diagnosis of AML. No prior treatment with cytarabine or daunorubicin are allowed		
3	Concurrent *FLT3* mutation that the treating physician deems necessary to treat with midostaurin, whereas patients with *FLT3-mutated* AML not treated with midostaurin can be enrolled. Patients with known Core Binding Factor –t(8;21), inv(16), t(16;16) are allowed for study participation at the treating investigator's discretion		
4	Active CNS or testicular involvement by leukemia; diagnostic lumbar puncture is not required		
5	History of neurologic disorder including but not limited to: prior seizure, epilepsy, structural brain abnormality, benign brain tumor, stroke, brain injuries, dementia, movement disorder or other significant CNS abnormalities		

6	Baseline QT corrected interval based on Fridericia's formula (QTcF) interval > 450 ms		
7	Acute coronary syndrome in the past 12 months, NYHA class III or VI		
8	Known history of Wilson's disease or other copper handling disorder		
9	History of GI malabsorptive disease		
10	Has a known additional malignancy that is progressing or requires active treatment. Exceptions include basal cell carcinoma of the skin, squamous cell carcinoma of the skin, or in situ cervical cancer that has undergone potentially curative therapy		
11	Known HIV infection		
12	Active hepatitis B or hepatitis C infection (patients who successfully completed curative hepatitis C therapy can be enrolled)		
13	Any uncontrolled infection, active bacterial or viral infection manifesting as fevers or hemodynamic instability within the past 72 hours		
14	Proven active invasive fungal infection		
15	Is pregnant or breastfeeding, or expecting to conceive or father children within the projected duration of the trial, starting with the pre-screening or screening visit through 120 days after the last dose of trial treatment		
16	Severe or uncontrolled medical disorder that would, in the investigator's opinion, impair ability to receive study treatment (i.e., uncontrolled diabetes, chronic renal disease, chronic pulmonary disease or active, uncontrolled infection, psychiatric illness/social situations that would limit compliance with study requirements		
17	Current or anticipated use of other investigational agents		
18	For patients with prior anthracycline exposure, the cumulative life-time dose should not exceed 386mg/m^2 at the time of study entry (to convert different anthracycline to daunorubicin-equivalent, see Appendix H for conversion factors)		

Investigator Signature: _____ Date: _____

Coordinator Signature: _____ Date: _____

Supervisor Signature: _____ Date: _____

Appendix H: Anthracyclines Equivalent Guidelines[a]

Drug	Conversion factor[b]
Daunorubicin	1
Doxorubicin	2
Epirubicin	1
Idarubicin	4
Mitoxantrone	4.4

[a]Adapted from Keefe D, et al. Anthracycline-induced cardiomyopathy. Seminars in Oncology. 2001;28(4 Suppl 12):2-7.
[b]To calculate the equivalent dose of daunorubicin, the total cumulative dose of anthracycline was multiplied by the conversion factor.