CASE WESTERN RESERVE UNIVERSITY | CASE COMPREHENSIVE CANCER CENTER

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STUDY TITLE: Phase I/II Trial of CPX-351 + Palbociclib in Patients with Acute Myeloid Leukemia

PRINCIPAL INVESTIGATOR: Sudipto Mukherjee, MD
Case Comprehensive Cancer Center
Cleveland Clinic
Taussig Cancer Center
9500 Euclid Avenue
Cleveland, OH 44195
Tel: [redacted]
E-mail: [redacted]

STATISTICIAN: [redacted]

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IND #: [redacted]

OTHER AGENT(S): None

SUMMARY OF CHANGES

Protocol Date	Section	Change
3/8/2019	Title	Protocol title changed to reflect Phase I/II update and further clarify included diseases
3/8/2019	2.0	2.1.1 and 2.1.2 - Phase IIa and Phase IIb were changed to Phase I and Phase II respectively
3/8/2019	3.0	Further changes as a result of Phase IIa and IIb being changed to Phase I and Phase II
3/8/2019	3.1	Section 3.1 "Number of Subjects" changed to "Study Design including dose escalation/cohorts" Added DLT table and updated starting dose of Palbo to 75mg. Added details about the Phase I design. Phase II will begin after maximum tolerated dose is defined. Phase II will have palbociclib administered at the recommended phase II dose chosen from the 3 dose levels evaluated in Phase I. Added section about using hydrea at physician discretion for pts with >25,000 WBC; patients cannot be treated with palbociclib and CPX-351 until WBC is less than or equal to 25,000 to prevent overt tumor lysis syndrome
3/8/2019	3.2	Simplified text for number of subjects to just a total to be enrolled between Phase I and Phase II
3/8/2019	3.3	Added specification on how/if subjects will be replaced
3/8/2019	3.4	Added: "Patients will be taken off the study after they complete their induction and consolidation chemotherapy will be at the discretion of the treating physician."
3/8/2019	4.1	Inclusion Criteria split into Phase I and Phase II portions
3/8/2019	4.1	Inclusion Criteria age for Phase 1 is now ≥18 years of age instead of ≥18-65 Further clarified the types of acute myeloid leukemia allowed on trial Added an Inclusion Criteria section for the Phase II portion
3/8/2019	6.1	Changed details of dosing schema to reflect changes made earlier in the protocol; added option for FLT3-ITD patients to choose between staying on trial or switching to midostaurin; Hydrea discretion added here too Updated study schema graphic to reflect the palbociclib starting dose change

Protocol Date	Section	Change
3/8/2019	6.1.2	Clarified CPX-351 dosing
3/8/2019	6.2	Further clarified DLT and added Hy's Law
3/8/2019	6.3	Missed doses of palbociclib will not be made up
3/8/2019	7.0	Updated dose delay/modification guidelines updated
3/8/2019	8.0-8.2	Added additional risks and side effects
3/8/2019	14.2	Further defined primary endpoint for Phase II safety monitoring
3/8/2019	14.0–14.3	Updates to statistical analysis plan and safety/efficacy monitoring
3/8/2019	Appendix III	Duplicate Appendix III regarding Palbociclib 125mg dose schedule was deleted
3/8/2019	Throughout	Updated CPX-351 dose units from u/m^2 to specify how much of daunorubicin and cytarabine is being used Minor administrative and formatting changes
3/8/2019	13.2	Updated section to reflect the use of multiple databases
7/18/2019	Throughout	Administrative, formatting, and consistency updates were made throughout the protocol
7/18/2019	Throughout	CTCAE version was corrected from version 4.0 version 5.0
7/18/2019	3.1; 3.4; 6.1	Day 28 (±5 days) biopsy was changed to Day 35 (±7 days)
7/18/2019	3.1; 6.2	Clarification was added to DLT timing and definition
7/18/2019	4.1	Phase II eligibility clarification of age range
7/18/2019	6.1; 6.2; 7.0	Dose modification guidelines were revised to instruct to skip palbociclib dosing if QTcB is above 480 ms
7/18/2019	6.1	Study schema was revised to be consistent with the text and to illustrate the treatment schedule for re-induction
7/18/2019	6.4	Early removal criteria was clarified to be separate than End Of Treatment criteria
7/18/2019	6.5	Duration of follow up was revised to more closely align with institutional standard of care
7/18/2019	9.1.1	Palbociclib dispensing instructions were revised to more accurately reflect institutional guidelines and procedures.
7/18/2019	10.0	Contact information was updated for collecting and sending correlative samples
7/18/2019	11.1.3; 11.3	Addition of instructions for re-induction
7/18/2019	11.1.4	Addition of instructions for End of Treatment timing and procedures
7/18/2019	11.2	Added an ECHO or MUGA to be done at screening to test for LVEF
7/18/2019	11.3	Added separate calendar for re-induction for clarity
7/18/2019	13.1	Added revised language for database to include Forte EDC

Protocol Date	Section	Change
10/24/19	Appendix IV	Cytogenetics were made to not be required on the Day 14 bone marrow biopsy
10/24/19	throughout	Minor formatting and consistency updates were made throughout the protocol
3/9/2020	3.1; 14.0	Modified the requirements to allow 3 (instead of 6) patients in phase 1 to be enrolled at the recommended phase II dose
3/9/2020	3.2	Changed the overall enrollment goal from 36 to 35
3/9/2020	8.1; 8.2	Revised the risk tables to match the consent
3/9/2020	11.2	Removed the Day 14 ECG from the study calendar
3/9/2020	14.0; 14.1; 14.2	Revised the Phase II efficacy and safety monitoring statistical plan
4/22/2020	Cover Page	Adding UH as a site to the study
4/22/2020	10.0	Updated workflow for correlative blood draw at screening
1/15/2021	Throughout	Administrative, formatting, and consistency updates were made throughout the protocol to reflect transition from Dr. Nazha to Dr. Mukherjee
1/15/2021	9.1.1	Added in changes to reflect the use of either capsules or tablets for Palbociclib.
1/15/2021	9.1.1	Information added to show the different characteristics of the Palbociclib tablets
1/15/2021	9.1.1	Removed dosing levels of 75mg and 100mg of Palbociclib since study has moved past the dose escalation phase and only using 125mg now.
1/25/2022	Throughout	Removed UH as they are no longer participating

ABBREVIATIONS

CCCC	Case Comprehensive Cancer Center
CRF	Case Report Form
DSTC	Data Safety and Toxicity Committee
FDA	Food and Drug Administration
ICF	Informed Consent Form
IRB	Institutional Review Board
PRMC	Protocol Review and Monitoring Committee
SOC	Standard of Care
CCF	Cleveland Clinic Foundation
MDS	Myelodysplastic Syndromes
CMML	Chronic Myelomonocytic Leukemia
MPN	Myeloproliferative Neoplasm
AML	Acute Myeloid Leukemia
DNA	Deoxyribonucleic acid
FDA	The Food and Drug Administration
HMAs	Hypomethylating Agents
ORR	Overall Response Rate
SC	Subcutaneous
NCI	National Cancer Institute
PO	Orally
Sp	Specificity protein
EOT	End of Treatment
CR	Complete Remission
PR	Partial Remission
HI	Hematologic Improvement
IWG	International Working Group
WHO	World Health Organization
APL	Acute promyelocytic leukemia
WBC	White Blood Cell
CSF	Colony-Stimulating Factor
CTCAE	Common Terminology Criteria for Adverse Events
AE	Adverse Event
SAE	Serious Adverse Event
DSMP	Data and Safety Monitoring Plan
PRBC	Packed Red Blood Cell
ALT	Alanine transaminase
AST	Aspartate aminotransferase
ECOG	Eastern Cooperative Oncology Group
RBC	Red Blood Cells
CRi	Complete Response (CR) with incomplete hematologic recovery
CRp	Complete Response (CR) with incomplete platelets

IEC	Independent Ethics Committee
GCP	Good Clinical Practice
ICH	International Conference on Harmonization
HIPAA	Health Insurance Portability and Accountability Act of 1996
EOS	End of Study
BUN	Blood Urea Nitrogen
MCV	Mean Corpuscular Volume
MCHC	Mean Cell Hemoglobin Concentration

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1.0 Introduction

1.1 Background of Study Disease

Approximately 20,000 patients were diagnosed with acute myeloid leukemia (AML) with greater than 10,000 AML patient deaths in the United States in 2017(1). While the response rate to current induction standard chemotherapy (7+3) is approximately 70-75%, only 20-30% of AML patients will survive beyond 5 years and the majority will relapse within the first year of treatment (1). Further, approximately 20-30% of newly diagnosed patients is refractory to induction chemotherapy and have very poor outcome with a median overall survival of 3 months (2). Induction chemotherapy with 7+3 has been the standard of care treatment for newly diagnosed AML for the last 4 decades. Novel approaches to enhance the efficacy of treatment and decrease relapse is desperately needed.

1.2 Name and Description of Investigational Agent CPX-351

1.2.1 Preclinical Data

CPX-351 is a liposomal formulation of a fixed combination of the antineoplastic drugs cytarabine and daunorubicin. The two drugs are present inside the liposome in a 5:1 molar ratio. The liposome membrane is composed of distearoylphosphatidylcholine, distearoylphosphatidylglycerol and cholesterol in a 7:2:1 molar ratio (3). These liposomes have a nominal diameter of approximately 100nm and are suspended in sucrose. Sterilization is achieved by filtration through a 0.22 µm filter.CPX-351 is provided as a sterile, pyrogen-free lyophilized formulation in 50 mL glass,single-use vials. Each vial contains 100 units of CPX-351 where each unit contains 1.0 mg cytarabine and 0.44 mg daunorubicin base in liposomes. The lyophilized cake is reconstituted with sterile water for injection to obtain a homogeneous dispersion at 5 units/mL (3). The pre-clinical pharmacology and toxicology are summarized in the Investigator's Brochure for CPX-351.

1.2.2 Clinical Data

Phase I study of CPX-351

In a phase 1 dose-escalation trial, CPX-351 induction was administered on days 1, 3, and 5 by 90-minute infusion to 48 relapsed or refractory patients with acute myeloid leukemia (AML) or high-risk myelodysplasia (4). Doses started at 3 units/m2 with dose doublings in single-patient cohorts until a pharmacodynamic effect (treatment-related adverse events or reduction in bone marrow cellularity or blast count) was observed, followed by 33% escalations in three patient cohorts until dose-limiting toxicity (DLT) occurred. The maximum-tolerated dose was 101 units/m2 (4). DLTs consisted of hypertensive crisis, congestive heart failure, and prolonged cytopenias (4). Adverse events were consistent with cytarabine and daunorubicin treatment. Response occurred at doses as low as 32 units/m2. Of 43 patients with AML, nine had complete response (CR) and one had CR with incomplete platelet recovery; of patients with acute lymphoblastic leukemia, one of three had CR. Eight CRs were achieved among the 31 patients with prior cytarabine and daunorubicin treatment. CR in AML occurred in five of 26 patients age >/= 60 years and in five of 17 patients younger than age 60 years. Median half-life was 31.1 hours (cytarabine) and 21.9 hours (daunorubicin), with both drugs and their metabolites detectable > 7 days after the last dose. The targeted 5:1 molar ratio was maintained at all dose levels for up to 24 hours (4).

Phase II studies of CPX-351

A randomized, multicenter, open-label, phase 2 trial was conducted to evaluate the efficacy and safety of CPX-351 with investigators' choice of first salvage treatment in adult patients with first relapse AML (5). The primary endpoint of the study was 1-year overall survival (OS), and Kaplan-Meier analysis did not show a significant difference between the two treatment groups (HR, 0.75; $P = 0.33$). Survival at 1-year was 36% and 27% ($P = 0.33$) for CPX-351 and salvage treatment arms, respectively (5). Patients were stratified at baseline according to the European Prognostic Index (EPI), and results showed that CPX-351 treated patients with the EPI-defined poor-risk strata demonstrated higher response rates (39.3% CPX-351 versus 27.6% salvage arm) and improvements in

event-free survival (EFS) (HR, 0.63; $P = 08$) and OS (HR, 0.55; $P = 0.02$). The overall rates of grade 5 AEs were similar between the CPX-351 (23.5%) and salvage treatment arms (20.5%) (5).

A second phase 2, randomized, multicenter, parallel-arm, open-label study evaluated the efficacy and safety of CPX-351 compared with conventional 7 + 3 regimen in newly diagnosed elderly patients with AML (6). The primary efficacy endpoint was response rate, defined as complete response (CR) + complete response with incomplete blood count recovery (CRi). The study was powered to detect a 23% increase in response rate with at least 85% power and a one-sided significance level of 0.1. CPX-351produced higher response rates (66.7% vs 51.2%, $P = 0.07$), meeting predefined criteria for success ($P < 0.1$) (6). The common AEs were similar between the two treatment groups, however, median time to ANC and platelet recovery times were longer in the CPX-351group compared with 7 + 3 group (6).

Phase III study of CPX-351

The phase 3, randomized, multicenter, open-label study evaluated the efficacy and safety of CPX-351 compared with conventional 7 + 3 (cytarabine for 7 days plus daunorubicin for 3 days) regimen in adult patients (60 to 75 years) with newly-diagnosed tAML or AML-MRC (7). The primary efficacy endpoint was overall survival (OS). The results showed OS was significantly greater in the CPX-351 group compared with the 7 + 3 group (7). The median OS was 9.56 months with CPX-351and 5.95 months with 7 + 3 (Hazard Ratio [HR] 0.69; $P = 0.005$). Grade 3-5 non-hematologic adverse events (AEs) occurring ≥ 5% were similar between the two groups, except pneumonia (20% vs 15%) and bacteremia (10% vs 2%) were numerically higher in the CPX-351compared with 7 + 3 groups, respectively. Also, median time to recovery of absolute neutrophil count (ANC) ≥ 500/μL and platelets ≥ 50,000/μL were longer in the CPX-351group than 7 + 3 group.2-4 (7).

1.3 Name and Description of Palbociclib

1.3.1 Preclinical Data

Treatment of cultured tumor cells with Palbociclib causes growth arrest that is accompanied by the inhibition of specific Rb phosphorylation by CDK4 or CDK6 on residues serine -780 and -795 of Rb. The IC50 values for reduction of Rb phosphorylation at serine -780 and -795 in MDA-MB-435 breast carcinoma cells were 0.066 and 0.063 μM, respectively. The IC50 values for reduction of Rb phosphorylation are similar to the IC50 values of inhibition of thymidine incorporation across a range of cultured tumor and normal cells.

Palbociclib was tested in vitro on molecularly characterized human breast cancer cell lines. Results from these experiments indicate that those cell lines that are more sensitive to Palbociclib (IC50 < 150 nM) have low levels of CDKN2A (p16) and high levels of Rb1, while resistant cell lines show the opposite characteristics. Sensitive cell lines in this panel represent mostly the luminal ER+ subtype.

Palbociclib has been evaluated in safety pharmacology, genetic toxicity, reproductive and development (fertility and early embryonic development, embryofetal development), and repeat-dose toxicity studies of up to 15-weeks duration in the rat and dog. Based on the nonclinical safety studies conducted with Palbociclib, the primary Palbociclib-related systemic toxicities were observed in hematolymphopoietic tissues (decreased cellularity, increased iron pigment, decreases in peripheral leukocytes and RBC parameters) and male reproductive organs (degeneration of seminiferous tubules, secondary epididymal hypospermia and increased intratubular cellular debris). Partial to complete reversibility of toxicities was demonstrated following a 4 week recovery period, with the exception of the male reproductive organ findings in the dog. These toxicities occurred in both rats and dogs, and are consistent with the intended pharmacologic effect of Palbociclib (i.e., cell cycle inhibition) (Fink et al, 2001; Arguello et al, 1998; Bartkova et al, 2003). Palbociclib was also identified with the potential to cause QT prolongation, developmental effects, and aneugenicity. Developmental effects that were considered adverse included a decrease in fetal body weights in rats and a low incidence of small phalanges on the forepaws in rabbits. A no effect level for aneugenicity was observed at

approximately 7-fold higher than unbound systemic AUC24 exposures associated with the human clinical dose of 125 mg QD.

1.3.2 *Clinical Data*

Palbociclib has been tested in a Phase 1 dose escalation Study (A5481001) in 74 patients with advanced cancer. Two dosing schedules were evaluated: Schedule 3/1 (3 weeks on treatment/1 week off treatment) and Schedule 2/1 (2 weeks on treatment/1 week off treatment). All DLTs observed in this study were related to myelosuppression and mainly consisted of Grade 3 neutropenia lasting more than 7 days after the end of the treatment cycle. However, neutropenia was reversible and non-cumulative. Other most common adverse events included fatigue, anemia, diarrhea, constipation, vomiting and dyspnea, all with mild to moderate severity. At the MTD, a greater proportion of patients on the 200 mg QD, 2/1 schedule had treatment-related TEAEs during and after Cycle 1 than patients on the 125 mg QD, 3/1 schedule although the proportion of patients with treatment-related neutropenia was similar with respect to the 2 dosing schedules, both during and after Cycle 1. One partial response was reported in a patient with testicular cancer. A total of 13/37 patients treated with Schedule 3/1 evaluable for efficacy experienced stable disease (SD), including 6 patients with SD lasting 40 weeks or longer. Based on the preclinical evidence that Palbociclib is highly active in ER(+) cell lines and the encouraging safety and PK profiles observed in the initial clinical studies, a randomized, multicenter active-controlled Phase 1/2 Study (A5481003) was designed to assess the efficacy, safety and pharmacokinetics of letrozole 2.5 mg QD (continuously) in combination with Palbociclib 125 mg QD (schedule 3/1) versus single agent letrozole 2.5 mg QD (continuously) for the first-line treatment of ER(+), HER2 (-) advanced breast cancer in postmenopausal women. Letrozole was selected as the active control based on its worldwide approval and use as standard of care for the first-line hormonal treatment of postmenopausal women with ER(+) advanced breast cancer. Study A5481003 was comprised of a limited Phase 1 portion, aimed at confirming the safety and tolerability of the combination and excluding a PK interaction with the combination, and a randomized Phase 2 portion aimed at evaluating the efficacy and safety of letrozole in combination

with Palbociclib when compared to letrozole alone in the first-line treatment of postmenopausal patients with ER(+), HER2(-) advanced breast cancer. The Phase 2 portion consisted of 2 parts. In Part 1, patient selection was based only on ER/HER2 status. In Part 2, patients were prospectively selected also taking into account tumor CCND1 amplification and/or p16 loss. In May 2012, 177 patients have been enrolled in this study and enrollment is closed. Twelve (12) were enrolled in the Phase 1 portion and 165 (66 and 99 in Part 1 and 2, respectively) were enrolled in the Phase 2 portion. Results from the Phase 1 portion, 83 indicated no PK interaction between Palbociclib and letrozole with mean AUC (0-24) of 2002 and 2043 nghr/mL (n=11) for Palbociclib in the absence and presence of letrozole, respectively, and 1990 and 1730 ng•hr/mL (n=10) for letrozole in the absence and presence of Palbociclib, respectively. The RP2D was determined GBG 78 - PENELOPEB Study Protocol E (Version 10 – 12 April 2016)– Confidential 55 to be 125 mg QD on Schedule 3/1 (3 weeks continuous treatment followed by 1 week off treatment) in combination with letrozole 2.5 mg QD continuously. Partial responses were reported for 3 (33%) out of 9 patients with measurable disease (3 had bone-only disease). Another 5 patients (42%) had stable disease for ≥ 6 months and the clinical benefit rate (PR + SD ≥ 6 months) was 67%. Eight (8) patients discontinued from the study due to disease progression, including 2 patients with clinical progression, 1 patient withdrew consent and 3 patients are still ongoing. Two (2) interim analyses for the Phase 2 portion of the study have been conducted. The results of the interim analyses showed consistent trend of clinically meaningful improvements in progression-free survival (PFS; primary endpoint). In the first interim analysis (Part 1; N=66), the median PFS for the PD 0332991 plus letrozole arm was 18.2 months versus 5.7 months for the letrozole alone arm (HR=0.35; 95% CI: 0.17, 0.72; p=0.006). The second interim analysis (N=165) continued to demonstrate a statistically significant improvement in PFS (26.1 vs. 7.5 months, respectively; HR=0.37; 95% CI: 0.21, 0.63; p <0.001).

The combination of Palbociclib plus letrozole was generally well tolerated with safety profile similar to Palbociclib as a single agent. The most frequently reported treatment-related adverse events included neutropenia, leukopenia, anemia, and fatigue. There were febrile neutropenia reported to date in this study. Overall, 8 patients in the

combination arm were discontinued from the study treatment due to an adverse event, of which 5 were considered treatment-related (grade 3 neutropenia [n=4] and ischemic colitis) and 1 patient from the letrozole alone arm.

These results indicate that the combination of Palbociclib with letrozole is well tolerated with AEs similar to those seen with either Palbociclib or letrozole when administered alone.

1.3.3 *Clinical Pharmacokinetics*

As of 10 December 2014, twenty-one clinical studies have evaluated the PK of Palbociclib. Four of these trials were conducted in patients with advanced malignant disease.

Phase 1 clinical pharmacology and biopharmaceutic studies of Palbociclib were conducted in healthy subjects. Ten of these 17 clinical trials were clinical pharmacology studies conducted to investigate the absorption, distribution, metabolism, and excretion of Palbociclib as well as examine the potential for DDI with Palbociclib. The remaining 7 of the 17 clinical trials were biopharmaceutic studies conducted to examine the bioavailability, bioequivalence, and food effect of the palbociclib formulations.

Pharmacokinetic parameters are available from all 74 patients enrolled in Study A5481001 (a first-in-human dose-escalation study in patients with advanced cancer) following multiple-dose administration (Day 8 of Cycle 1) at daily doses ranging from 25 to 225 mg of Palbociclib. In addition, PK parameters are also available for nine patients on Day 14 of Cycle 1 (from patients on Schedule 2/1, i.e., 2 weeks on treatment followed by 1 week off treatment) and 4 patients on Day 21 of Cycle 1 (from patients on Schedule 3/1, i.e., 3 weeks on treatment followed by 1 week off treatment). The exposure (AUC(0-10) and Cmax) increased in a dose proportional manner (i.e. dose linearity) over the dose range of 25 to 225 mg QD following Palbociclib administration on Days 1 and 8 of Cycle 1, although some variability (low to moderate) around these doses was observed particularly at the 150 mg QD dose level. Following repeated daily dosing to Day 14 and Day 21 Palbociclib was absorbed with a median Tmax of ~4 hours when fasting 2 hours

before and after Palbociclib administration. The mean Palbociclib Vz/F was 3103 L, which is significantly greater than total body water (42 L), indicating that Palbociclib extensively penetrates into peripheral tissues. The ability for Palbociclib to cross the blood brain barrier in humans is unknown. In rats, Palbociclib displayed minimal ability to cross the intact blood brain barrier. Palbociclib was eliminated slowly; the mean t½ was 26.5 hours (ranged 15.8 to 36.2 hours) and the mean CL/F was 86.1 L/hour. Palbociclib accumulated following repeated dosing with a median Rac of 2.4, which is consistent with a half-life of ~27 hours.

The solubility of the Palbociclib free base is pH dependent—Palbociclib is water soluble at low pH (2.1-4.5), while the solubility dramatically decreases as pH rises above 4.5. Concomitant administration of agents which increase gastric pH can alter the solubility and absorption of Palbociclib free base formulations.

Palbociclib is metabolized to multiple metabolites in a qualitatively similar manner in rat, dog and human liver microsomes. In vitro, Palbociclib is primarily metabolized by CYP3A4 enzymes. An exploratory evaluation of the circulating metabolites for Palbociclib was conducted in plasma samples obtained from patients treated with Palbociclib 200 mg QD (Schedule 2/1) in Study A5481001. Assessment of the pooled plasma samples on Day 14 of Cycle 1 indicated that the glucuronide conjugate of Palbociclib and the lactam of Palbociclib (PF-05089326) were the main metabolites present in plasma. Glucuronide conjugate of Palbociclib is unlikely to be active vs the intended target (CDK4/6). Although PF-05089326 showed similar in vitro activity vs CDK4/6 as with Palbociclib, the unbound exposure of this metabolite is considerably lower than the parent drug. Therefore, contribution of this metabolite to the pharmacologic activity in humans is anticipated to be low. Other metabolites observed were the glucuronide conjugates of hydroxylated Palbociclib and the glucuronide conjugate of reduced Palbociclib. PF-05089326 was also observed in the circulation of rats following repeated daily oral administration of Palbociclib. Plasma protein binding of Palbociclib and PF-05089326 is ~85% and 95%, respectively.

In vitro (hERG) and in vivo (dog telemetry) studies revealed a potential for QT prolongation at unbound concentrations ≥14-fold the unbound steady-state Cmax

associated with the clinical dose of 125 mg QD (refer to the Palbociclib investigator's brochure for additional details).

A preliminary pharmacokinetic/pharmacodynamic analysis has been conducted to explore the QT/QTc and plasma PD-032991 concentration relationship for Study A5481001 (FIH study) by using graphical methods and mixed effects linear modeling (NONMEM). Data from 73 patients were used for the analysis, and an analysis of the QTcF and QTcB data demonstrated that QTcF was the more appropriate correction method based on plots of the QTc versus RR interval. No patient had a maximum on treatment QTcF value of $\geq$ 500 msec. The QTcF changes from the baseline at the mean Cmax calculated for 200 mg dose were simulated for 10000 patients. The mean and upper 95%

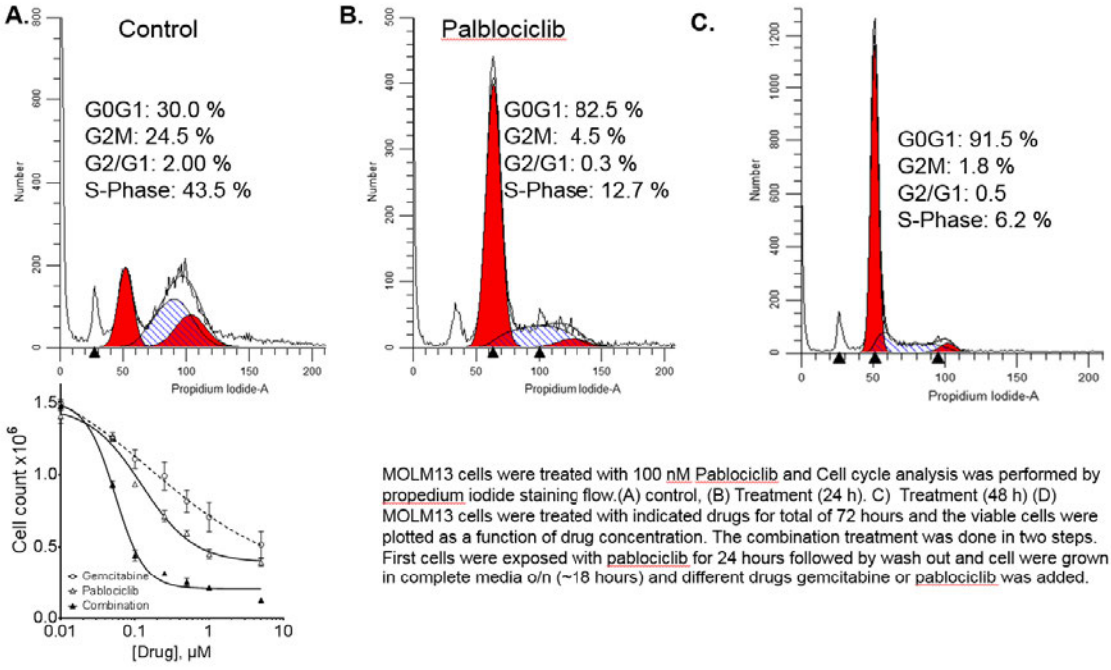
1.4 Rationale

The lack of response or resistance to current therapies in patients with AML is mainly related to resistance to cytarabine or anthracyclines (the most effective drugs in AML). Overcoming cytarabine resistance can provide an attractive treatment strategy compared to current practice of adding more cytotoxic agents or targeted therapies such as FLT3 inhibitors or IDH1/2 inhibitors that can only be given to a small fraction of patients.

Cytarabine is a pyrimidine nucleoside analog that can inhibit DNA synthesis. Its action is specific to the S phase of the cell cycle (8). It has been demonstrated that leukemia cells are at different stages in their cell cycle with some cells at G0 /G1 phase while others are at different phases like S and M phase (9). These cells remain quiescent and resist treatment with S phase dependent chemotherapy such as cytarabine. Treatment with cell cycle inhibitors can potentially synchronize these cells to enter the S phase and increase its response to cytarabine. It can also induce apoptosis in the cells that remain in G0/G1 phase thus providing an attractive strategy to overcome cytarabine resistance.

Cyclin-dependent kinase (CDKs) are frequently overexpressed or hyperactivated in human cancers and represent a key therapeutic target (10). Palbociclib, a cell permeable pyridopyrimidine with oral bioavailability, is an exceptionally selective and potent

inhibitor of CDK4 and CDK6 (IC50~10 nM for recombinant proteins) (10). In vitro and in vivo studies have shown that Palbociclib can effectively induce early G1 arrest by inhibiting CDK4/6 in AML cell lines and xenografts suggestive of unique opportunity to target specific phases of the cell cycle in AML (10). Treatment of HL-60 AML cell lines with Palbociclib can induce G1 arrest followed by synchronous progression of surviving AML cells into S phase after withdrawing the drug, thereby creating a time window to incorporate cytarabine and enhance its activity (10). Sequential administration of palbociclib and chemotherapy resulted in dramatic increase in the cytotoxic killing of cytarabine in vivo (10). More importantly, it trigged apoptosis of AML cells through inhibition of the *homeobox (HOX)A9* oncogene expression by reducing the transcription of its target *PIM1*. Reduced PIM1 synthesis attenuates PIM1-mediated phosphorylation of the pro-apoptotic BAD and activates BAD-dependent apoptosis.



MOLM13 cells were treated with 100 nM Pablociclib and Cell cycle analysis was performed by propedium iodide staining flow.(A) control, (B) Treatment (24 h). C) Treatment (48 h) (D) MOLM13 cells were treated with indicated drugs for total of 72 hours and the viable cells were plotted as a function of drug concentration. The combination treatment was done in two steps. First cells were exposed with pablociclib for 24 hours followed by wash out and cell were grown in complete media o/n (~18 hours) and different drugs gemcitabine or pablociclib was added.

These observations coupled with the ability of Palbociclib to induce apoptosis in leukemic cells that are at G0/G1 phase suggest that CDK4/6 inhibitors can be particularly effective when administered prior to chemotherapy and then sequentially during chemotherapy every 48 hours to allow for AML cell cycle reset and S phase entry (based

on the drug half-life). We have also shown that prior administration of Palbociclib for 48 hours can arrest 91% of the cells in G0/G1 phase and these cells will proceed to S phase after the cessation of Palbociclib highlighting the importance of administrating Palbociclib for 48 hours prior to starting chemotherapy.

Herein, we propose to start Palbociclib prior to CPX-351 and then every 48 hours during therapy (since the half-life of Palbociclib is 24-27 hours) to enhance CPX-351 cytotoxic activity by synchronizing AML cell entry to S phase and also induce apoptosis in the cells that remain in G0/G1 phase.

2.0 Objectives

2.1 Primary Objectives

2.1.1 Phase I

Evaluate the safety and tolerability of Palbociclib in combination with CPX-351

2.1.2 Phase II

Evaluate the efficacy of Palbociclib in combination with chemotherapy as measured by overall response rate (ORR), i.e. complete response (CR) and CR with incomplete blood count recovery (CRi) by IWG criteria (11).

2.2 Secondary Objective(s)

1. Time to response (TTR)
2. Evaluate duration of response (DOR)
3. Evaluate the event-free survival (EFS)
4. Evaluate Overall Survival (OS) probability

3.0 Study Design

3.1 Study design including dose escalation / cohorts

This is a single arm, open label study of the combination of Palbociclib with CPX-351 in adults with AML. The trial consists of two components: phase I to evaluate the safety with dose escalation of Palbociclib in combination with CPX-351 and phase II to evaluate the

overall response rate of the combination in the targeted patient population. A cycle is 35 days.

The phase I portion of the study will be 3+3 design. Palbociclib will be given at dose level 1 (75 mg po) (Please see schema in section 6 for dose levels) on day -1 and -2, day 0 will be rest and then CPX-351 (daunorubicin 44 mg/m^2 and cytarabine 100 mg/m^2) will be started on day 1, 3, and 5 along with Palbociclib on day 2, 4, and 6 followed by rest/monitoring period (days 7-35).

Dose escalation will proceed within each cohort according to the following scheme. Before escalating to the next dose level, the final subject in the previous dose level must have reached the Day 35 biopsy in order to allow sufficient time to observe for dose-limiting toxicities (DLT). DLTs are defined in section 6.2.

Number of Subjects with DLT at a Given Dose Level	**Escalation Decision Rule**
0 out of 3	Enter 3 subjects at the next dose level.
1 out of 3	Enter 3 more subjects at this dose level. • If 0 of these 3 subjects experience DLT, proceed to the next dose level. • If 1 or more of this group suffer DLT, then dose escalation is stopped, and this dose is declared the maximally administered dose. Three (3) additional subjects will be entered at the next lowest dose level if only 3 subjects were treated previously at that dose.
≥2	Dose escalation will be stopped. This dose level will be declared the maximally administered dose (highest dose administered). Three (3) additional subjects will be entered at the next lowest dose level if only 3 subjects were treated previously at that dose.

≤1 out of 6 or 0 out of 3 at highest dose level below the maximally administered dose	This is generally the recommended maximally tolerated dose.

After the phase I is completed and the maximum tolerated dose (MTD) is defined, the study will proceed with phase II with Palbociclib administered at the recommended phase 2 dose (RP2D). RP2D of Palbociclib for the combination therapy will be selected among the 3 dose levels evaluated in phase I following evaluation of safety data acquired from all phase patients completing at least 1 cycle of therapy. The phase II part of the study is Simon two stage design with objective to assess the efficacy of the combination in the targeted patient population.

Patients will receive 1-2 induction courses of the combination of Palbociclib and CPX-351.

Hydrea with a dose at the discretion of treating physician is allowed for patients with WBC ≥ 25,000 and treatment with Palbociclib and CPX-351 cannot be started until WBC is less ≤ 25,000 to prevent overt tumor lysis syndrome. Prophylaxis for tumor lysis is required during this period. Prophylactic antibiotics are allowed at the discretion of the treating physician and in accordance with the institutional guidelines.

3.2 Number of Subjects

A total of 35 patients will be enrolled on phase I/II.

3.3 Replacement of Subjects

Subjects that fail the screening process will be replaced. No subject will be replaced after receiving treatment.

3.4 Expected Duration of Treatment and Subject Participation

The intent of the study design is for all patients to receive up to 2 induction cycles with the combination of Palbociclib and CPX-351. Treatment will be continued during the duration of the study unless patients meet any or all of the early withdrawal criteria stated in appendix II. The expected duration of the treatment period for subjects is

approximately 35 days, with a 2 year follow up period. Subsequent consolidation chemotherapy will be given at the discretion of the treating physician off study.

4.0 Subject Selection

Each of the criteria in the sections that follow must be met in order for a subject to be considered eligible for this study. Use the eligibility criteria to confirm a subject's eligibility.

4.1 Inclusion Criteria

For Phase I only

Subjects must meet all of the following inclusion criteria to be eligible for enrollment:

1. Subjects must be $\geq$ 18
2. Primary refractory (to 1 or 2 induction cycles of chemotherapy) or relapsed AML according to 2016 WHO criteria
3. Higher-risk newly diagnosed AML (diagnosed according to 2016 WHO criteria). Higher-risk defined as higher-risk per ELN 2017 criteria.
4. Eastern Cooperative Oncology Group (ECOG) Performance Status $\leq$ 2
5. Subjects must have normal organ function as defined below:
    - Total bilirubin $\leq$ 2 times upper limit of normal ($\leq$ 3 x ULN if considered to be due to leukemic involvement or Gilbert's syndrome) or if higher than 2 times upper limit of normal with approval from the PI
    - Serum Creatinine $\leq$ 2 x ULN or if higher than 2 times upper limit of normal with approval from the PI
    - Left ventricular ejection fraction of $\geq$ 45%
6. Women of childbearing potential should be advised to avoid becoming pregnant and men should be advised to not father a child while receiving treatment. All men

and women of childbearing potential must use acceptable methods of birth control throughout the study.

7. Subjects must have the ability to understand and the willingness to sign a written informed consent document.

For Phase II part:

Subjects must meet all of the following inclusion criteria to be eligible for enrollment:

1. Subjects must be 18-65 years of age
2. Newly diagnosed acute myeloid leukemia according to 2016 WHO criteria (excluding APL [AML-M3])
3. Eastern Cooperative Oncology Group (ECOG) Performance Status ≤ 2
4. Subjects must have normal organ function as defined below:
    - Total bilirubin ≤ 2 times upper limit of normal ((≤ 3 x ULN if considered to be due to leukemic involvement or Gilbert's syndrome) or if higher than 2 times upper limit of normal with approval from the PI
    - Serum Creatinine ≤ 2 x ULN or if higher than 2 times upper limit of normal with approval from the PI
    - Left ventricular ejection fraction of $\geq 45\%$
5. Patients with secondary AML arising out of MDS (all subtypes under WHO classification), chronic myelomonocytic leukemia (CMML) and therapy-related AML are eligible.
6. Women of childbearing potential should be advised to avoid becoming pregnant and men should be advised to not father a child while receiving treatment. All men and women of childbearing potential must use acceptable methods of birth control throughout the study.
7. Subjects must have the ability to understand and the willingness to sign a written informed consent document.

4.2 Exclusion Criteria

The presence of any of the following will exclude a subject from study enrollment:

1. Prior treatment with CPX-351, Palbociclib or other cell cycle inhibitors.
2. Any serious medical condition, laboratory abnormality, or psychiatric illness that, in the view of the treating physician, would place the participant at an unacceptable risk if he or she were to participate in the study or would prevent that person from giving informed consent.
3. Any active malignancy (unrelated, non-hematological malignancy) diagnosed within the past 6 months of starting the study drug (other than curatively treated carcinoma-in-situ of the cervix or non-melanoma skin cancer).
4. History of allergic reactions attributed to compounds of similar chemical or biologic composition to CPX-351, Palbociclib or other cell cycle inhibitors.
5. Subjects with uncontrolled intercurrent illness including, but not limited to ongoing or active infection, symptomatic congestive heart failure, unstable angina pectoris, uncontrolled cardiac arrhythmia, or psychiatric illness/social situations that would limit compliance with study requirements.
6. Known history of HIV or active hepatitis B or C.
7. No major surgery within 2 weeks prior to study enrollment.
8. Pregnancy or breast feeding
9. Male and female patients who are fertile who do not agree to use an effective barrier methods of birth control (i.e. abstinence) to avoid pregnancy while receiving study treatment.
10. Acute promyelocytic leukemia (APL)

4.3 Inclusion of Women and Minorities

Men, women and members of all races and ethnic groups are eligible for this trial.

5.0 Registration

All subjects who have been consented are to be registered in the OnCore™ Database. For those subjects who are consented, but not enrolled, the reason for exclusion must be recorded.

All subjects will be registered through Cleveland Clinic and will be provided a study number by contacting the study coordinator listed.

6.0 Treatment Plan

6.1 Treatment Regimen Overview

Induction

Palbociclib will be administered orally on day -2 and -1 starting at level 1 (please see schema below) during the phase I portion. Day 0 will be rest and then CPX-351 (daunorubicin 44 mg/m^2 and cytarabine 100 mg/m^2) will be started on days 1, 3, and 5 along with Palbociclib day 2, 4, and 6 followed by rest/monitoring period (days 7-35).

Patients will be treated with CPX-351 based on a calculation determined from the patient's body surface area (BSA). BSA will be calculated before each course and will be based on the patient's height (measured at baseline) and weight (measured each cycle). If a patient's QTcB is above 480ms on a day of palbociclib, dosing will be skipped for that day. The dose should not be made up and treatment should continue as planned the next day.

A bone marrow biopsy and aspirate should be obtained on day 14 (+3 day window) after starting CPX-351. If residual leukemia is present (blasts percentage > 5%), per the discretion of the treating physician, another induction course of the combination of Palbociclib and CPX-351 is possible and will be administered as follows:

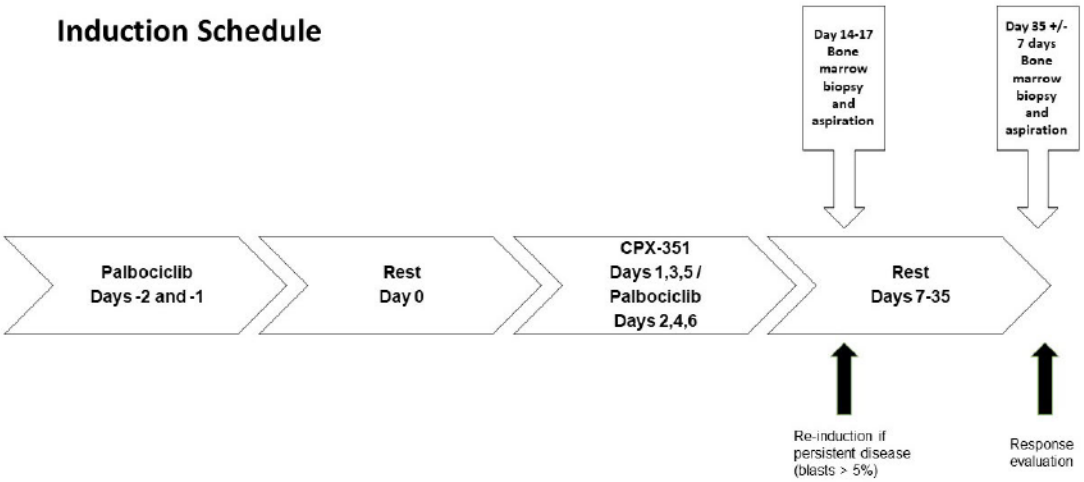
Palbociclib will be started at designated dose level on day -2 and -1 , day 0 is rest and CPX-351 will be started at (daunorubicin 44 mg/m^2 and cytarabine 100 mg/m^2) on day 1 and 3 and Palbociclib on day 2 and 4.

Patient with FLT3-ITD who are enrolled on the study will be giving the option to continue on the study without receiving midostaurin or will be taken off the study to start midostaurin.

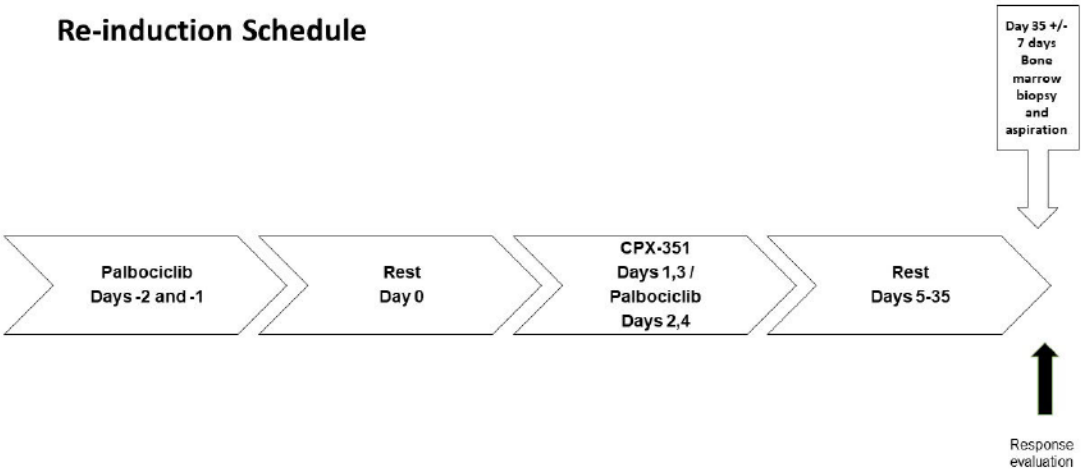
Study Schema

Palbociclib Cohorts	Dose
1	75 mg
2	100 mg
3	125 mg

Induction Schedule



Re-induction Schedule



Hydrea with a dose at the discretion of treating physician is allowed for patients with WBC $\geq$ 25,000 and treatment with Palbociclib and CPX-351 cannot be started until WBC is less $\leq$ 25,000 to prevent overt tumor lysis syndrome. Prophylaxis for tumor lysis is required during this period. Prophylactic antibiotics are allowed at the discretion of the treating physician and in accordance with the institutional guidelines.

6.1.1 Name of **Investigational Agent** Administration

Patients will receive Palbociclib orally at designated dose level based on dosing schedule described in the study calendar.

6.1.2 Name of **Investigational Agent** Administration

Patients will receive CPX-351 intravenously at daunorubicin 44 mg/m^2 and cytarabine 100 mg/m^2. Dosing Schedule is described in study calendar.

6.2 Definition of Dose-Limiting Toxicity (Applicable for dose escalation studies only)

Dose limiting toxicities will be according to the NCI CTEP criteria. A non-hematologic dose-limiting toxicity (DLT) is defined as Grade 3 or 4 adverse event or abnormal laboratory value (according to CTCAE criteria) assessed by treating physician as at least possibly related to either/both study drug(s), unless clearly and incontrovertibly related to active AML or intercurrent illness, during treatment or within 28 days after the last dose of Palbociclib, and does not resolve to below grade 3 within 28 days of onset.

Exclusion of these criteria may include:

i. Grade 3 fatigue, asthenia, fever, anorexia, or constipation

ii. Grade 3 nausea, vomiting or diarrhea not requiring tube feeding, total parenteral nutrition, or requiring or prolonging hospitalization

iii. Infection, bleeding, or other expected direct complication of cytopenias due to active underlying leukemia

iv. Grade 3 infusion reaction including cytokine release syndrome (CRS), if successfully managed and which resolves within 72 hours

v. Grade 3 or 4 tumor lysis syndrome (TLS) if it is successfully managed clinically and resolves within 7 days without end-organ damage.

vi. Grade 3 or 4 isolated electrolyte abnormalities that last < 72 hours will not be considered DLT.

A hematologic dose-limiting toxicity is defined as severe myelosuppression with a hypoplastic marrow with less than 5% cellularity and no evidence of leukemia 45 days from start of therapy. This will define severe and delayed myelosuppression not related to persistent leukemia and likely related to treatment.

Non-hematologic toxicities will be counted as DLTs if they are "at least possibly related to the study drugs. Any treatment related death or confirmed Hy's law cases will be considered DLTs.

Hy's law cases satisfy each of the following 3 components:

a. The drug causes hepatocellular injury, defined as an elevated ALT or AST ≥ 3 times the upper limit of normal.
b. They also have elevation of their serum total bilirubin > 2 times the upper limit of normal, without findings of cholestasis (often defined as serum alkaline phosphatase activity < 2 times the upper limit of normal).
c. No other reason can be found to explain the combination of increased aminotransferase and serum total bilirubin, such as viral hepatitis, alcohol abuse, ischemia, preexisting liver disease, or another drug capable of causing the observed injury.

It is assumed that low counts at diagnosis are due to involvement by the disease process and require therapy for improvement.

6.3 General Concomitant Medications and Supportive Care Guidelines

Necessary supportive measures for optimal medical care will be given throughout the treatment as determined by the treating physician and the patient's medical need. No

concomitant chemotherapy, immunotherapy, or therapy with monoclonal antibodies will be allowed during the study with the exception of hydroxyurea or corticosteroids for control of blood counts.

Use of a colony-stimulating factor or combinations thereof (e.g. G-CSF, GM-CSF, or erythropoietin) are at the discretion of the treating physician and is permitted if judged in the patient's best medical interest.

Prophylactic antibiotics, antifungal, and antiviral agents (e.g. levofloxacin, valacyclovir, etc.) are strongly recommended; however, the use of these or other drugs will be left to institutional guidelines.

Missed doses of Palbociclib will not be made up. Patients who vomit any time after taking a dose must be instructed NOT to "make it up," and to resume treatment as per schedule.

Palbociclib is metabolized to multiple metabolites in a qualitatively similar manner in rat, dog and human liver microsomes. In vitro, Palbociclib is primarily metabolized by CYP3A4 enzymes. Co-administration with drugs that are CYP3A inhibitors and inducers may change the plasma concentrations of Palbociclib in humans. The concurrent use of CYP3A inhibitors, including amprenavir, atazanavir, boceprevir, clarithromycin, conivaptan, delavirdine, diltiazem, erythromycin, fosamprenavir, indinavir, itraconazole, ketoconazole, lopinavir, mibefradil, miconazole, nefazodone, nelfinavir, posaconazole, ritonavir, saquinavir, telaprevir, telithromycin, verapamil, voriconazole, and grapefruit, grapefruit juice or any product containing grapefruit, are not allowed during the time that palbociclib is administered. The concurrent use of CYP3A inducers, including carbamazepine, felbamate, nevirapine, phenobarbital, phenytoin, primidone, rifabutin, rifampin, rifapentin, and St. John's wort, are not allowed in during the time that palbociclib is administered.

Hydrea with a dose at the discretion of treating physician is allowed for patients with WBC $\geq$ 25,000 and treatment with Palbociclib and CPX-351 cannot be started until WBC is less $\leq$ 25,000 to prevent overt tumor lysis syndrome. Prophylaxis for tumor lysis is required during this period. Prophylactic antibiotics are allowed at the discretion of the treating physician and in accordance with the institutional guidelines.

6.4 Criteria for Removal from Study

In the absence of treatment delays due to adverse events treatment can continue until one of the criteria applies for early removal (see appendix II).

6.5 Duration of Follow Up

Following completion of active treatment, patients will be followed for survival and AML-related treatment every 6 months for up to 2 years as part of standard of for CCF leukemia patients. This follow up will be completed based on what is available in the patient's medical record.

7.0 Dose Delays/Dose Modifications

If a patient's QTcB is above 480ms on a day of palbociclib, dosing will be skipped for that day. The dose should not be made up and treatment should continue as planned the next day.

8.0 Potential Risks and Adverse Events

8.1 Palbociclib

COMMON, SOME MAY BE SERIOUS
In 100 people receiving Palbociclib more than 20 and up to 100 may have:
▪ Anemia ▪ Neutropenia ▪ Fatigue ▪ Diarrhea ▪ Nausea

OCCASIONAL, SOME MAY BE SERIOUS

In 100 people receiving Palbociclib from 5 to 10 may have:

- Decreased appetite
- Constipation
- Vomiting
- Rash
- Flatulence
- Abdominal pain
- Shortness of breath
- Fever
- Cough
- Back pain

RARE, AND SERIOUS

In 100 people receiving Palbociclib 5 or fewer may have:

- Hair loss
- Headache
- Nosebleed
- Muscle spasm
- Upper respiratory tract infection
- Dry mouth
- Itching
- Dizziness
- Abdominal swelling
- Chills
- Runny nose

Inflammation of the lungs

Palbociclib—used to treat some patients with advanced breast cancer—may cause rare but severe inflammation of the lungs. According to the FDA, patients should notify their health-care professional right away if they have any new or worsening symptoms involving their lungs, as they may indicate a rare but life-threatening condition. Symptoms to watch for include difficulty or discomfort with breathing and shortness of breath while at rest or with low activity.

8.2 CPX-351

COMMON, SOME MAY BE SERIOUS
In 100 people receiving CPX-351 more than 10 and up to 100 may have:
▪ Anemia ▪ Neutropenia ▪ Fatigue ▪ Diarrhea ▪ Nausea ▪ Constipation ▪ Hemorrhage ▪ Rash ▪ Edema ▪ Mucositis ▪ Musculoskeletal pain ▪ Abdominal Pain ▪ Cough ▪ Headache ▪ Dyspnea ▪ Arrhythmia ▪ Pneumonia ▪ Sleep Disorder ▪ Chills ▪ Dizziness ▪ Non-conduction Cardiotoxicity (cardiotoxicity caused by the anthracylcine doxorubicin) ▪ Fungal infection ▪ Upper respiratory induction (excluding fungal) ▪ Hypoxia ▪ Hypertension ▪ Hypotension ▪ Vomiting

- Chest Pain
- Decreased appetite
- Bacteremia (excluding sepsis)
- Delirium
- Pyrexia
- Pleural effusion
- Anxiety
- Pruritus
- Sepsis (excluding fungal)
- Hemorrhoids
- Petechiae
- Renal insufficiency
- Transfusion reactions
- Visual impairment (except bleeding)
- Catheter/device/injection site reaction
- Prolonged low platelets
- Prolonged low neutrophil count
- Hair loss

OCCASIONAL, SOME MAY BE SERIOUS
In 100 people receiving CPX-351 more than 5 may have:

- Hyponatremia
- Hypokalemia
- Hypoalbuminemia
- Hyperbilirubinemia
- Alanine aminotransferase abnormalities

OCCASIONAL, SOME MAY BE SERIOUS
In 100 people receiving CPX-351 less than 10 may have:

- Ear and labyrinth disorders: Deafness, Deafness unilateral

- Eye Disorders: Eye conjunctivitis, Dry eye, Eye edema, Eye swelling, Eye irritation, Eye pain, Ocular discomfort, Ocular hyperemia, Periorbital edema, Scleral hyperemia
- Gastrointestinal disorders: Dyspepsia
- Psychiatric disorders: Hallucinations
- Respiratory, thoracic and mediastinal disorders: Pneumonitis

8.3 Definitions

8.3.1 Adverse Event

An **adverse event** (AE) is any unfavorable or unintended event, physical or psychological, associated with a research study, which causes harm or injury to a research participant as a result of the participant's involvement in a research study. The event can include abnormal laboratory findings, symptoms, or disease associated with the research study. The event does not necessarily have to have a causal relationship with the research, any risk associated with the research, the research intervention, or the research assessments.

Adverse events may be the result of the interventions and interactions used in the research; the collection of identifiable private information in the research; an underlying disease, disorder, or condition of the subject; and/or other circumstances unrelated to the research or any underlying disease, disorder, or condition of the subject.

8.3.2 Serious Adverse Events

A **serious adverse event** (SAE) is any adverse experience occurring at any dose that results in any of the following outcomes:

- Results in **death.**
- Is a **life-threatening** adverse experience. The term life-threatening in the definition of serious refers to an adverse event in which the subject was at risk of death at the time of the event. It does not refer to an adverse event which hypothetically might have caused death if it were more severe.

- Requires **inpatient hospitalization or prolongation of existing hospitalization**. Any adverse event leading to hospitalization or prolongation of hospitalization will be considered as Serious, UNLESS at least one of the following expectations is met:
    - The admission results in a hospital stay of less than 24 hours OR
    - The admission is pre-planned (e.g., elective or scheduled surgery arranged prior to the start of the study) OR
    - The admission is not associated with an adverse event (e.g., social hospitalization for purposes of respite care.

  However, it should be noted that invasive treatment during any hospitalization may fulfill the criteria of "medically important" and as such may be reportable as a serious adverse event dependent on clinical judgment. In addition where local regulatory authorities specifically require a more stringent definition, the local regulation takes precedent.
- Results in **persistent or significant disability/incapacity**. The definition of disability is a substantial disruption of a person's ability to conduct normal life's functions.
- Is a **congenital anomaly/birth defect**.
- Is an **important medical event**. Important medical events that may not result death, be life-threatening, or require hospitalization may be considered a serious adverse experience when, based upon appropriate medical judgment, they may jeopardize the subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood disease or disorders, or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse. The development of a new cancer is always considered an important medical event.

8.3.3 Adverse Event Evaluation

The investigator or designee is responsible for ensuring that all adverse events (both serious and non-serious) observed by the clinical team or reported by the subject which occur after the subject has signed the informed consent are fully recorded in the subject's medical records. Source documentation must be available to support all adverse events.

A laboratory test abnormality considered clinically relevant as deemed by the treating physician should be reported as an adverse event.

The investigator or sub-investigator (treating physician if applicable) will provide the following for all adverse events (both serious and non-serious):

- Event term (as per CTCAE 5.0)
- Description of the event
- Date of onset and resolution
- **Expectedness of the toxicity**
- **Grade of toxicity**
- **Attribution of relatedness to the investigational agent- (this must be assigned by an investigator, sub-investigator, or treating physician)**
- Action taken as a result of the event, including but not limited to; no changes, dose interrupted, reduced, discontinued, etc. or action taken with regard to the event, i.e. no action, received conmed or other intervention, etc.
- Outcome of event

Descriptions and **grading scales** found in the NCI Common Terminology Criteria for Adverse Events (CTCAE) version **5** will be utilized for AE reporting.

An expected adverse event is an event previously known or anticipated to result from participation in the research study or any underlying disease, disorder, or condition of the subject. The event is usually listed in the Investigator Brochure, consent form or research protocol.

An unexpected adverse event is an adverse event not previously known or anticipated to result from the research study or any underlying disease, disorder, or condition of the subject.

Attribution* is the relationship between an adverse event or serious adverse event and the study drug. Attribution will be assigned as follows:

- Definite – The AE is clearly related to the study drug.
- Probable – The AE is likely related to the study drug.
- Possible – The AE may be related to the study drug.
- Unlikely – The AE is doubtfully related to the study drug.
- Unrelated – The AE is clearly NOT related to the study drug.

*Attribution is required for each individual components of the treatment regimen.

8.4 SAE Report Form

SAEs will be recorded on the FDA Form 3500A (MedWatch) and Study SAE coversheet but should only be reported as instructed below. The electronic FDA SAE reporting forms should not be used.

8.5 Reporting Procedures for Serious Adverse Events

For the purposes of safety reporting, all adverse events will be reported that occur through 30 days after the final dose of study drug. Adverse events, both serious and non-serious, and deaths that occur during this period will be recorded in the source documents. All SAEs should be monitored until they are resolved or are clearly determined to be due to a subject's stable or chronic condition or intercurrent illness(es). Related AEs will be followed until resolution to baseline or grade 1 or stabilization.

8.5.1 SAE Reporting Requirements

- Participating investigators (all sites) must report all serious adverse events to the Lead Site Principal Investigator (e.g. Sponsor-Investigator) within **24 hours** of discovery or notification of the event. The participating investigator must also provide follow-up information on the SAE until final resolution.
- The Lead Site Principal Investigator will review the SAE and report the event to the FDA, external collaborator(s), and IRB as applicable.
- It is the Sponsor-Investigator's responsibility (e.g. lead site PI) to ensure that ALL serious adverse events that occur on the study (e.g. ALL SAEs that occur at each enrolling institution) are reported to all participating sites.

Drug Supplier / Manufacturer / Financial Supporter Reporting Requirements:

- Drugs (CPX-351, will be supplied by Jazz Pharmaceuticals and Palbociclib purchase will be funded by Jazz Pharmaceuticals). The trial will be supported by Jazz Pharmaceuticals. The Sponsor-Investigator (e.g. lead site PI) will be responsible for reporting all SAEs that are treatment-emergent for CPX-351 to Jazz Pharmaceuticals within 1 business day of their awareness of the SAE via email at AEReporting@jazzpharma.com.

Institutional Review Board Reporting Requirements:

- Investigative sites will report adverse events to their respective IRB according to the local IRB's policies and procedures in reporting adverse events.

8.6 SAEs and OnCore

- All SAEs will be entered into OnCore.
- A copy of the SAE form(s) submitted to the sponsor-investigator is also uploaded into Oncore.

8.7 Data Safety and Toxicity Committee

It is the responsibility of each site PI to ensure that ALL SAEs occurring on this trial (internal or external) are reported to the Case Comprehensive Cancer Center's Data and Safety Toxicity Committee. This submission is simultaneous with their submission to Jazz Pharmaceuticals and/or other regulatory bodies.

The sponsor-investigator is responsible for submitting an annual report to the DSTC as per CCCC Data and Safety Monitoring Plan.

8.8 Data and Safety Monitoring Plan (DSMP)

This protocol will adhere to the policies of the Case Comprehensive Cancer Center Data and Safety Monitoring Plan in accordance with NCI guidelines.

9.0 PHARMACEUTICAL INFORMATION

9.1 Investigational Agents

9.1.1 Name of Agent Palcociclib

Other Names: IBRANCE

Product description:

Palbociclib will be supplied as capsules or tablets containing 125 mg equivalents of Palbociclib free base. Capsules will be supplied in HDPE bottles containing 23 capsules. Please see the chart below regarding the medication in capsule form.

Dosage	Color	Shape
125mg	Caramel/Caramel	Oval

Tablets will be supplied in blister packs of 21 tablets. Please see the chart below regarding the medication in tablet form.

Dosage	Color	Shape
125mg	Light Pink	Oval

Preparation and Dispense:

Palbociclib will be provided in non-patient-specific bottles or blister packs. The patient name should be recorded on the bottle label or on the packing in the spaces provided by site personnel at the time of assignment to patient. Palbociclib will be administered by the research and/or inpatient staff and the dispensing will be recorded on the patient's electronic medical record. Returned unused medication MUST NOT be re-dispensed to a patient.

Storage requirements:

Palbociclib is an agent that must be handled and administered with care. Due to possible unknown hazards associated with topical and environmental exposure to experimental agents, capsules and tablets must not be opened and/or emptied into any vehicle for oral ingestion; capsules must be swallowed intact. Only one capsule or tablet strength will be dispensed to the patient at each dispensing visit. In the event of dose modification, new capsules or tablets will be dispensed.

Route of administration:

Palbociclib will be administered at the dose and schedule described in section 6. Patients should take Palbociclib with food. Patients should be instructed to swallow palbociclib capsules or tablets whole and not to chew them prior to swallowing. No capsule or tablet should be ingested if it is broken, cracked, or otherwise not intact. Patients should be encouraged to take their dose at approximately the same time each day.

Drug Procurement:

Palbociclib will not be directly supplied by Jazz Pharmaceuticals, however Jazz Pharmaceuticals will providing funds to purchase Palbociclib for the study.

Packing, labeling, and drug Accountability:

Palbociclib capsules and tablets should be stored at controlled room temperature (15-30 C, 59-86 F) in their original container.

Drug Destruction:

At the completion of the study, there will be a final reconciliation of drug shipped, drug consumed, and drug remaining. This reconciliation will be logged on the drug reconciliation form, signed and dated. Any discrepancies noted will be investigated, resolved, and documented prior to return or destruction of unused study drug. Drug destroyed on site will be documented in the study files.

9.2 Investigational Agents

9.2.2 Name of Agent CPX-351

Other Names: VYXEOS

Product description: CPX-351 (daunorubicin and cytarabine) liposome for injection is a combination of daunorubicin and cytarabine in a 1:5 molar ratio encapsulated in liposomes for intravenous administration. The liposome membrane is composed of distearoylphosphatidylcholine (DSPC), distearoylphosphatidylglycerol (DSPG), and cholesterol in a 7:2:1 molar ratio.

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

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

Storage requirements: 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.

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

Route of administration: The infusion of CPX-351 (cytarabine:daunorubicin) Liposome Injection will be performed through a central venous catheter, using an infusion pump to ensure that the drug is infused over the specified time period. Non-DEHP containing administration sets should be used. **Do not use an in-line filter.** CPX-351 should never be given by the intramuscular or subcutaneous route. Administer CPX-351 over approximately 90 minutes via an infusion pump. Flush the line to ensure administration of the full dose. The dosage (total units and u/m2), start/stop time of the infusion, total volume infused, must be documented in the patient's chart.

Drug Procurement: CPX-351 will be supplied for this study by Jazz Pharmaceuticals.

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

Drug Destruction: At the completion of the study, there will be a final reconciliation of drug shipped, drug consumed, and drug remaining. This reconciliation will be logged on the drug reconciliation form, signed and dated. Any discrepancies noted will be investigated, resolved, and documented prior to return or destruction of unused study drug. Drug destroyed on site will be documented in the study files.

10.0 EXPLORATORY or CORRELATIVE STUDIES

Peripheral blood samples will be collected prior to starting treatment for future correlative studies.

CASE 1918: List of Specimens Expected to Collect

Screening	Tubes Expected
Peripheral Blood	10mL Sodium Heparin Green Top Tube (2)

CCF PROCEDURE

1. If drawn at Cancer Center, Page 26781 for pick up
2. If drawn elsewhere, tube to Cancer Center and page 26781 on sample arrival
3. Email [redacted] with any questions

11.0 STUDY PARAMETERS AND CALENDAR

11.1 Study Parameters

11.1.1 Screening Evaluation

History and physical (including weight and blood pressure), vitals, CBC with differential and platelets, chemistry profile (total bilirubin, serum creatinine, SGPT or SGOT, uric acid, LDH, phosphorus, potassium, magnesium, glucose), ECHO, and an ECG should be performed within 14 days of therapy start. Serum or urine HCG should be obtained at screening within 3 days prior of treatment start.

A bone marrow aspirate and/or biopsy should be performed within 28 days of therapy start. The bone marrow evaluation will include immunophenotyping by flow cytometry and cytogenetic studies.

11.1.2 Treatment Period

CBC with differential and chemistry profile will be monitored per institutional standard of care until remission. Labs that are drawn in this time frame will be captured in the database.

11.1.3 Re-induction Period

If a patient undergoes re-induction therapy after the Day 14 biopsy (+3 day window), the re-induction schedule of events should then be followed starting with Day -2.

11.1.4 End of Treatment (EOT)

EOT procedures should be performed at least within 7 days of the Day 35 bone marrow biopsy/aspirate taking place. If a subject has met criteria for early removal from the study, EOT procedures must be performed within 7 days.

11.2 Induction Calendar

Period	Screening Period[A]	Treatment Period																		End Of Treatment (EOT)	Follow up[H]
Day		-2[M]	-1	0	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15-35		
Informed consent form	X																				
History and physical exam[D]	X																			X	
Concomitant Medication[B]	← X →																				
ECOG performance status[C]	X																			X	
Hematology[D]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X[K]	
Serum Chemistry[D]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X[K]	
Uric Acid	X	X	X	X	X	X	X	X	X	X											
Phosphate Level	X	X	X	X	X	X	X	X	X	X											
Magnesium Level	X	X	X	X	X	X	X	X	X	X											
Pregnancy test	X																				
ECG[J]	X	X	X	X	X	X	X	X	X	X											
ECHO or MUGA	X																				
Vital sign	X	X	X			X		X		X								X	X[L]	X[K]	
Bone marrow biopsy	X																	X[F]	X[G]		
Bone marrow aspirate	X																	X[F]	X[G]		
Survival Follow up																					X
Record RBC/ platelets transfusion	X																				
Disease response assessment																			X[E]		
Disease related follow up																					X
Correlative Samples	X																				

LDH/Tumor Lysis Syndrome	X																				
AE Assessment[I]	← X →																				
Study Drugs																					
Palbociclib		X	X			X		X		X											
CPX-351					X		X		X												

A: Screening period is defined as the time period from the day of consent to start of study therapy.
B: Con Meds will be collected for medications that were administered because of an AE or medical history
C: See Appendix I for grading criteria
D: See Appendix IV for required tests
E: See Appendix III for response assessment criteria
F: Day 14 bone marrow biopsy/aspirate have a +3 days window; this is not required during re-induction
G: Day 35 bone marrow biopsy/aspirate have a +/- 7 days window
H: Follow up occurs every 6 months (+/- 7 days window) for 2 years after EOT visit
I: SAE follow up must be reported through 30 days after last dose
J: Skip palbociclib dose if QTcB > 480ms
K: Does not need to be repeated at EOT if being done same day as Day 35 bone marrow biopsy/aspirate
L: To be performed on same day as Day 35 biopsy
M: Day -2 pre-dose assessments do not need to be repeated if being done same day as screening. If the same assessments are being used for both screening and day -2, the data should be entered at screening in the database.

11.3 Re-induction Calendar

Period	Treatment Period																		End Of Treatment (EOT)	Follow up[H]
Day	-2	-1	0	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15-35		
History and physical exam[D]																			X	
Concomitant Medication[B]	← X →																			
ECOG performance status[C]																			X	
Hematology[D]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X[K]	
Serum Chemistry[D]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X[K]	
Uric Acid	X	X	X	X	X	X	X													
Phosphate Level	X	X	X	X	X	X	X													
Magnesium Level	X	X	X	X	X	X	X													
ECG[J]	X	X	X	X	X	X	X													
Vital sign	X	X			X		X											X[L]	X[K]	
Bone marrow biopsy																		X[G]		
Bone marrow aspirate																		X[G]		
Survival Follow up																				X
Disease response assessment																		X[E]		
Disease related follow up																				X
AE Assessment[I]	← X →																			
Study Drugs																				
Palbociclib	X	X			X		X													
CPX-351				X		X														

12.0 MEASUREMENT OF EFFECT

Response criteria will be defined by Cheson et al 2003 (11). Patients will be assessed for response at the end of induction (or at the end of re-induction if applicable). Overall response rate includes CR and CRi.

Response criteria will be defined as follow:

Response	**Definition**
Complete remission (CR)	Bone marrow blasts <5%; absence of circulating blasts and blasts with Auer rods; absence of extramedullary disease; absolute neutrophil count >1.0 x 109/L (1,000/µL); platelet count >100 x 109/L (100,000/µL)
CR with incomplete hematologic recovery (CRi)	All CR criteria except for residual neutropenia [<1.0 x 109/L (1,000/µL)] or thrombocytopenia [<100 x 109/L (100,000/µL)]
Morphologic leukemia-free state (MLFS)	Bone marrow blasts <5%; absence of blasts with Auer rods; absence of extramedullary disease; no hematologic recovery required
Partial remission (PR)	All hematologic criteria of CR; decrease of bone marrow blast percentage to 5% to 25%; and decrease of pretreatment

	bone marrow blast percentage by at least 50%
Stable disease	Absence of CRMRD-, CR, CRi, PR, MLFS; and criteria for PD not met
Progressive disease (PD)	Evidence for an increase in bone marrow blast percentage and/or increase of absolute blast counts in the blood: • >50% increase in marrow blasts over baseline (a minimum 15% point increase is required in cases with <30% blasts at baseline; or persistent marrow blast percentage of >70% over at least 3 months; without at least a 100% improvement in absolute neutrophil count (ANC) to an absolute level [>0.5 x 109/L (500/µL), and/or platelet count to >50 x 109/L (50,000/µL) non-transfused]; or • >50% increase in peripheral blasts (WBC x % blasts) to >25 x 109/L (>25,000/µl) (in the absence of

	differentiation syndrome); or • New extramedullary disease

13.0 DATA REPORTING / REGULATORY CONSIDERATIONS

Adverse event lists, guidelines, and instructions for AE reporting can be found in Section 8.0 (Adverse Events: List and Reporting Requirements).

13.1 Data Reporting

The Forte EDC™ and OnCore™ databases will be utilized, as required by the Case Comprehensive Cancer Center and Cleveland Clinic, to provide data collection for both accrual entry and trial data management. Forte EDC and OnCore™ are Clinical Trials Management Systems housed on secure servers. Access to data through Forte EDC and OnCore™ is restricted by user accounts and assigned roles. Once logged into the Forte EDC or OnCore™ system with a user ID and password, Forte EDC™ and OnCore™ define roles for each user which limits access to appropriate data. User information and password can be obtained by contacting the OnCore™ Administrator at OnCore-registration@case.edu for OnCore™ access, and taussigoncore@ccf.org for Forte EDC™ access.

Forte EDC™ is designed with the capability for study setup, activation, tracking, reporting, data monitoring and review, and eligibility verification. When properly utilized, Forte EDC™ is 21 CFR 11 compliant. This study will utilize electronic Case Report Form completion in the Forte EDC™ database. A calendar of events and required forms are available in Forte EDC™.

13.2 Regulatory Considerations

The study will be conducted in compliance with ICH guidelines and with all applicable federal (including 21 CFR parts 56 & 50), state or local laws.

13.2.1 Written Informed consent

Provision of written informed consent must be obtained prior to any study-related procedures. The Principal Investigator will ensure that the subject is given full and adequate oral and written information about the nature, purpose, possible risks and benefits of the study as well as the subject's financial responsibility. Subjects must also be notified that they are free to discontinue from the study at any time. The subject should be given the opportunity to ask questions and be allowed time to consider the information provided.

The original, signed written Informed Consent Form must be kept with the Research Chart in conformance with the institution's standard operating procedures. A copy of the signed written Informed Consent Form must be given to the subject. Additionally, documentation of the consenting process should be located in the research chart.

13.2.2 Subject Data Protection

In accordance with the Health Information Portability and Accountability Act (HIPAA), a subject must sign an authorization to release medical information to the sponsor and/or allow the sponsor, a regulatory authority, or Institutional Review Board access to subject's medical information that includes all hospital records relevant to the study, including subjects' medical history.

13.2.3 Retention of records

The Principal Investigator of The Case Comprehensive Cancer Center supervises the retention of all documentation of adverse events, records of study drug receipt and dispensation, and all IRB correspondence for as long as needed to comply with local, national and international regulations. No records will be destroyed until the Principal Investigator confirms destruction is permitted.

13.2.4 Audits and inspections

Authorized representatives of the sponsor, a regulatory authority, an Independent Ethics Committee (IEC) or an Institutional Review Board (IRB) may visit the site to perform audits or inspections, including source data verification. The purpose of an audit or inspection is to systematically and independently examine all study-related activities and documents to determine whether these activities were conducted, and data were recorded,

analysed, and accurately reported according to the protocol, Good Clinical Practice (GCP), guidelines of the International Conference on Harmonization (ICH), and any applicable regulatory requirements. For multi-center studies, participating sites must inform the sponsor-investigator of pending audits.

14.0 STATISTICAL CONSIDERATIONS

This phase I-II study is devised to evaluate the safety and preliminary efficacy of Palbociclib in combination with CPX-351 for treatment of AML in a total of 35 patients. Phase I will identify the MTD and recommended phase 2 dose (RP2D) of Palbociclib when administered with CPX-351 using a conventional 3+3 design with 3 dose levels. Dose escalation will proceed within each cohort according to the following scheme. Dose-limiting toxicities (DLT) are defined in section 6.2.

Number of Subjects with DLT at a Given Dose Level	**Escalation Decision Rule**
0 out of 3	Enter 3 subjects at the next dose level.
1 out of 3	Enter 3 more subjects at this dose level. • If 0 of these 3 subjects experience DLT, proceed to the next dose level. • If 1 or more of this group suffer DLT, then dose escalation is stopped, and this dose is declared the maximally administered dose. Three (3) additional subjects will be entered at the next lowest dose level if only 3 subjects were treated previously at that dose.
≥2	Dose escalation will be stopped. This dose level will be declared the maximally administered dose (highest dose administered). Three (3) additional subjects will be entered at the next

	lowest dose level if only 3 subjects were treated previously at that dose.
≤1 out of 6 or 0 out of 3 at highest dose level below the maximally administered dose	This is generally the recommended maximally tolerated dose.

After completion of phase I, the study will proceed to phase II with Palbociclib administered at the recommended phase 2 dose (RP2D). Phase II will evaluate both the safety and tolerability as well as preliminary efficacy of Palbociclib in combination with CPX-351 as measured by overall response rate (ORR), defined as complete response (CR) and CR with incomplete blood count recovery (CRi) by 2003 IWG criteria. Adverse Events will be assessed according to the Common Terminology Criteria for Adverse Events (CTCAE) version 5.0).

14.1 Phase II Efficacy Monitoring

Phase II will use Simon's two-stage design (Simon, 1989). The null hypothesis that the true ORR after induction <0.60 will be tested against a one-sided alternative hypothesis that the ORR > 0.80 with type I error 0.1 and power 0.80. The phase II part has a maximum sample size of 26 patients, with 14 patients in stage I. Futility stopping rules and design operating characteristics are provided in Table 14.1.

Table 14.1 Futility stopping boundaries for efficacy and operating characteristics of the two-stage Simon design with type I error 0.1 and power of 0.8. N1 is the sample size in the first stage. R1 is the drug rejection number in the first stage. R is the final rejection number should the trial proceed to full accrual. PET is the probability of early termination of the study under the null hypothesis.

Phase II sample size	N1	R1	R	PET under null
26	14	9	18	0.72

The trial will accrue 14 patients in stage I, if 9 or less patients achieve OR then the trial will stop early for futility. Otherwise, the trial will accrue additional 12 patients to full sample size of 26. The combination will be considered effective if 19 or more out of 26 patients achieved OR.

14.2 Phase II Safety Monitoring

Safety monitoring will continue in phase II where a maximum of 26 patients will be enrolled. The primary endpoint for safety monitoring is the occurrence of a DLT during the entire treatment period of 1-2 cycles of induction therapy. The method of Thall et al (1995) (12) will be used to monitor the safety of the combined regimen. The safety monitoring scheme was devised to pause the study for review of toxicities given sufficient evidence that the DLT rate exceeds 0.20. Specifically, the trial will pause for toxicity review if the posterior probability is 0.8 or higher, i.e. Pr (Toxicity Rate > 0.20 | data) > 0.80. Additionally, it is assumed that the prior probability of experiencing a DLT is distributed in accordance with a non-informative prior Beta (0.2, 0.8) distribution with effective sample size of 1. Monitoring will be carried out in cohorts of 5 patients and will initiate from the 5th patient. Table 14.2 summarizes the resultant stopping boundaries. Table 14.3 summarizes the trial's operating characteristics with the Bayesian design.

Table 14.2. Summary of early stopping boundaries in cohorts of 5 starting from the 5th patient. For example, if 3 or more patients experience a DLT out of the first 5 patients, the trial will stop early due to toxicity.

Stop Early if #Patients Experienced Toxicity	3-5	4-10	5-15	6-20
Total #Patients Treated	5	10	15	20

Table 14.3. Summary of operating characteristics based on 10,000 simulations using boundaries in Table 14.2 for early stopping. For example, if the true toxicity rate is 20%, the probability of early stopping is 0.26. If the true toxicity rate is 40%, the probability of early stopping is 0.90.				
Scenario	True Toxicity Rate	Pr(Early Stop)	Average #Patients Treated	Average #Toxicities
1	0.10	0.03	24.6	2.5
2	0.20	0.26	21.7	4.3
3	0.30	0.64	16.5	4.9
4	0.40	0.90	11.7	4.7

14.3 Analysis Plan

Descriptive statistical analysis will be calculated, including histograms or box-plots, proportions, range, means and standard deviations. Fisher's exact test and Wilcoxon rank test will be used in univariate analyses of categorical and continuous variables, respectively. Summary statistics of toxicities will be provided in frequencies and percentages. Toxicity rate and ORR will be estimated along with 95% CIs. Other statistical analyses will be carried out as appropriate. All p-values presented will be nominal.

REFERENCES

1. Dohner H, Estey E, Grimwade D, Amadori S, Appelbaum FR, Buchner T, et al. Diagnosis and management of AML in adults: 2017 ELN recommendations from an international expert panel. Blood. 2017 Jan 26;129(4):424-47. PubMed PMID: 27895058. Pubmed Central PMCID: PMC5291965. Epub 2016/11/30. eng.

2. Ravandi F, Cortes J, Faderl S, O'Brien S, Garcia-Manero G, Verstovsek S, et al. Characteristics and outcome of patients with acute myeloid leukemia refractory to 1 cycle of high-dose cytarabine-based induction chemotherapy. Blood. 2010;116(26):5818-23.

3. Kim HP, Gerhard B, Harasym TO, Mayer LD, Hogge DE. Liposomal encapsulation of a synergistic molar ratio of cytarabine and daunorubicin enhances selective toxicity for acute myeloid leukemia progenitors as compared to analogous normal hematopoietic cells. Experimental hematology. 2011 Jul;39(7):741-50. PubMed PMID: 21530609. Epub 2011/05/03. eng.

4. Feldman EJ, Lancet JE, Kolitz JE, Ritchie EK, Roboz GJ, List AF, et al. First-in-man study of CPX-351: a liposomal carrier containing cytarabine and daunorubicin in a fixed 5:1 molar ratio for the treatment of relapsed and refractory acute myeloid leukemia. Journal of clinical oncology : official journal of the American Society of Clinical Oncology. 2011 Mar 10;29(8):979-85. PubMed PMID: 21282541. Pubmed Central PMCID: PMC4520927. Epub 2011/02/02. eng.

5. Cortes JE, Goldberg SL, Feldman EJ, Rizzeri DA, Hogge DE, Larson M, et al. Phase II, multicenter, randomized trial of CPX-351 (cytarabine:daunorubicin) liposome injection versus intensive salvage therapy in adults with first relapse AML. Cancer. 2015 Jan 15;121(2):234-42. PubMed PMID: 25223583. Pubmed Central PMCID: PMC5542857. Epub 2014/09/17. eng.

6. Medeiros BC, Lancet JE, Cortes JE, Newell LF, Lin TL, Ritchie EK, et al. Analysis of Efficacy By Age for Patients Aged 60-75 with Untreated Secondary Acute Myeloid Leukemia (AML) Treated with CPX-351 Liposome Injection Versus Conventional Cytarabine and Daunorubicin in a Phase III Trial. Blood. 2016;128(22):902-.

7. Lancet JE, Uy GL, Cortes JE, Newell LF, Lin TL, Ritchie EK, et al. CPX-351 (cytarabine and daunorubicin) Liposome for Injection Versus Conventional Cytarabine

Plus Daunorubicin in Older Patients With Newly Diagnosed Secondary Acute Myeloid Leukemia. Journal of clinical oncology : official journal of the American Society of Clinical Oncology. 2018 Jul 19:JCO2017776112. PubMed PMID: 30024784. Epub 2018/07/20. eng.

8. Kufe DW, Major PP. Studies on the mechanism of action of cytosine arabinoside. Medical and pediatric oncology. 1982;10 Suppl 1:49-67. PubMed PMID: 6761569. Epub 1982/01/01. eng.

9. Schnerch D, Yalcintepe J, Schmidts A, Becker H, Follo M, Engelhardt M, et al. Cell cycle control in acute myeloid leukemia. American Journal of Cancer Research. 2012 08/20
06/21/received
07/27/accepted;2(5):508-28. PubMed PMID: PMC3433102.

10. Aleem E, Arceci RJ. Targeting cell cycle regulators in hematologic malignancies. Frontiers in cell and developmental biology. 2015;3:16. PubMed PMID: 25914884. Pubmed Central PMCID: PMC4390903. Epub 2015/04/29. eng.

11. Cheson BD, Bennett JM, Kopecky KJ, Büchner T, Willman CL, Estey EH, et al. Revised Recommendations of the International Working Group for Diagnosis, Standardization of Response Criteria, Treatment Outcomes, and Reporting Standards for Therapeutic Trials in Acute Myeloid Leukemia. Journal of Clinical Oncology. 2003;21(24):4642-9. PubMed PMID: 14673054.

12. Thall PF, Simon RM, Estey EH. Bayesian sequential monitoring designs for single-arm clinical trials with multiple outcomes. Statistics in medicine. 1995 Feb 28;14(4):357-79. PubMed PMID: 7746977. Epub 1995/02/28. eng.

APPENDIX I: ECOG / KARNOFSKY PERFORMANCE STATUS CRITERIA

ECOG Performance Status Scale		**Karnofsky Performance Scale**	
Grade	Description	Percent	Description
0	Normal activity. Full active, able to carry on all pre-disease performance without restriction.	100	Normal, no complaints, no evidence of disease.
		90	Able to carry on normal activity; minor signs or symptoms of disease.
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).	80	Normal activity with effort; some signs or symptoms of disease.
		70	Cares for self, unable to carry on normal activity or to do active 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% if waking hours.	60	Requires occasional assistance, but is able to care for most of his/her needs.
		50	Requires considerable assistance and frequent medical care.

3	In bed > 50% of the time. Capable of only limited self-care, confined to bed or chair more than 50% of waking hours.	40	Disabled, requires special care and assistance.
		30	Severely disabled, hospitalization indicated. Death not imminent.
4	100% bedridden. Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair.	20	Very sick, hospitalization indicated. Death not imminent.
		10	Moribund, fatal processes progressing rapidly.
5	Dead.	0	Dead

APPENDIX II: EARLY REMOVAL CRITERIA

- Intercurrent illness that prevents further administration of treatment
- The investigator and/or treating physician considers it to be in the best interest of the subject to permanently discontinue study treatment
    - This includes if the treatment is deemed to be of excessive toxicity to the patient by the treating physician
- Patient decision to withdraw from treatment (partial consent) or from the study (full consent)
- Pregnancy during the course of the study for a child-bearing participant
- Death

- Unacceptable adverse events defined as following:
    - Unacceptable treatment related toxicity, NCI CTC AE version 5.0 Grade 3 or 4 that fails to recover to baseline or < Grade 3 in the absence of treatment within 4 weeks
    - Any toxicity or other issue that causes a delay of study drug administration by more than 4 weeks

APPENDIX III: RESPONSE CRITERIA

Response	**Definition**
Complete remission (CR)	Bone marrow blasts <5%; absence of circulating blasts and blasts with Auer rods; absence of extramedullary disease; absolute neutrophil count >1.0 x 109/L (1,000/µL); platelet count >100 x 109/L (100,000/µL)
CR with incomplete hematologic recovery (CRi)	All CR criteria except for residual neutropenia [<1.0 x 109/L (1,000/µL)] or thrombocytopenia [<100 x 109/L (100,000/µL)]
Morphologic leukemia-free state (MLFS)	Bone marrow blasts <5%; absence of blasts with Auer rods; absence of extramedullary disease; no hematologic

	recovery required
Partial remission (PR)	All hematologic criteria of CR; decrease of bone marrow blast percentage to 5% to 25%; and decrease of pretreatment bone marrow blast percentage by at least 50%
Stable disease	Absence of CRMRD-, CR, CRi, PR, MLFS; and criteria for PD not met
Progressive disease (PD)	Evidence for an increase in bone marrow blast percentage and/or increase of absolute blast counts in the blood: • >50% increase in marrow blasts over baseline (a minimum 15% point increase is required in cases with <30% blasts at baseline; or persistent marrow blast percentage of >70% over at least 3 months; without at least a 100% improvement in absolute neutrophil count (ANC) to an absolute level [>0.5 x 109/L (500/µL), and/or platelet count to >50 x 109/L

	(50,000/µL) non-transfused]; or • >50% increase in peripheral blasts (WBC x % blasts) to >25 x 109/L (>25,000/µl) (in the absence of differentiation syndrome); or • New extramedullary disease

APPENDIX IV: CLINICAL LABORATORY PARAMETERS

Hematology	Serum Chemistry	Vitals	Physical Exam	Bone Marrow Biopsy & Aspiration
Red blood cell count	Sodium	Temp	Height (only at C1D1)	Marrow blast percent
Hemoglobin	Potassium	Pulse	Weight	Marrow Cellularity
Hematocrit	Chloride	Resp		Auer Rods
White blood cell count	Bicarbonate	Blood Pressure		Dysplasia
Neutrophil	BUN	SpO2*		Cytogenetics (not required on D14 biopsy (+3 day window)
Platelets	Glucose (non-fasting)			
Blasts percent	Albumin			
MCV	AST			

MCHC	ALT			
Eosinophils	Serum creatinine			
Basophils	Protein			
Monocytes	Calcium			
Lymphocyte	Bilirubin			
	Alkaline phosphate			

APPENDIX V: WHO classification of myeloid neoplasms and acute leukemia

Arber et al, 2016

WHO myeloid neoplasm and acute leukemia classification
Myeloproliferative neoplasms (MPN)
Chronic myeloid leukemia (CML), *BCR-ABL1*$^{+}$
Chronic neutrophilic leukemia (CNL)
Polycythemia vera (PV)
Primary myelofibrosis (PMF)
PMF, prefibrotic/early stage

WHO myeloid neoplasm and acute leukemia classification
PMF, overt fibrotic stage
Essential thrombocythemia (ET)
Chronic eosinophilic leukemia, not otherwise specified (NOS)
MPN, unclassifiable
Mastocytosis
Myeloid/lymphoid neoplasms with eosinophilia and rearrangement of *PDGFRA*, *PDGFRB*, or *FGFR1*, or with *PCM1-JAK2*
Myeloid/lymphoid neoplasms with *PDGFRA* rearrangement
Myeloid/lymphoid neoplasms with *PDGFRB* rearrangement
Myeloid/lymphoid neoplasms with *FGFR1* rearrangement
Provisional entity: Myeloid/lymphoid neoplasms with PCM1-JAK2
Myelodysplastic/myeloproliferative neoplasms (MDS/MPN)
Chronic myelomonocytic leukemia (CMML)
Atypical chronic myeloid leukemia (aCML), *BCR-ABL1*$^{-}$
Juvenile myelomonocytic leukemia (JMML)

WHO myeloid neoplasm and acute leukemia classification
MDS/MPN with ring sideroblasts and thrombocytosis (MDS/MPN-RS-T)
MDS/MPN, unclassifiable
Myelodysplastic syndromes (MDS)
MDS with single lineage dysplasia
MDS with ring sideroblasts (MDS-RS)
MDS-RS and single lineage dysplasia
MDS-RS and multilineage dysplasia
MDS with multilineage dysplasia
MDS with excess blasts
MDS with isolated del(5q)
MDS, unclassifiable
Provisional entity: Refractory cytopenia of childhood
Myeloid neoplasms with germ line predisposition
Acute myeloid leukemia (AML) and related neoplasms

WHO myeloid neoplasm and acute leukemia classification
AML with recurrent genetic abnormalities
AML with t(8;21)(q22;q22.1);*RUNX1-RUNX1T1*
AML with inv(16)(p13.1q22) or t(16;16)(p13.1;q22);*CBFB-MYH11*
APL with *PML-RARA*
AML with t(9;11)(p21.3;q23.3);*MLLT3-KMT2A*
AML with t(6;9)(p23;q34.1);*DEK-NUP214*
AML with inv(3)(q21.3q26.2) or t(3;3)(q21.3;q26.2); *GATA2, MECOM*
AML (megakaryoblastic) with t(1;22)(p13.3;q13.3);*RBM15-MKL1*
Provisional entity: AML with BCR-ABL1
AML with mutated *NPM1*
AML with biallelic mutations of *CEBPA*
Provisional entity: AML with mutated RUNX1
AML with myelodysplasia-related changes
Therapy-related myeloid neoplasms

WHO myeloid neoplasm and acute leukemia classification
AML, NOS
AML with minimal differentiation
AML without maturation
AML with maturation
Acute myelomonocytic leukemia
Acute monoblastic/monocytic leukemia
Pure erythroid leukemia
Acute megakaryoblastic leukemia
Acute basophilic leukemia
Acute panmyelosis with myelofibrosis
Myeloid sarcoma
Myeloid proliferations related to Down syndrome
Transient abnormal myelopoiesis (TAM)
Myeloid leukemia associated with Down syndrome

WHO myeloid neoplasm and acute leukemia classification
Blastic plasmacytoid dendritic cell neoplasm