

CCCWFU 22215

Comprehensive Cancer Center of Wake Forest University

An Open Label Study to Evaluate the Feasibility of CPI-613 Given with High Dose Cytarabine and Mitoxantrone in Patients with Relapsed or Refractory Acute Myeloid Leukemia (AML)

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## SCHEMA

This is a Pilot open label trial to establish the feasibility of CPI-613 in combination with high dose cytarabine and mitoxantrone:

*Salvage Induction:* CPI-613 at doses of 1,500 mg/m<sup>2</sup>/day will be given over 2 hours on days 1-5. Cytarabine will be given at 3gm/m<sup>2</sup> for age <60 or 1.5 gm/m<sup>2</sup> for age >60 in 500 mL NS over 3 hours every 12 hours for 5 doses starting on day 3. Mitoxantrone will be given at 6mg/m<sup>2</sup> daily for 3 doses given in 50 mL NS over 15 minutes after 1st, 3rd and 5th doses of Cytarabine. A day 14 marrow will be obtained to assess disease response. If there is a response to therapy but residual disease remains patients may receive either a repeated courses identical to the above or a shortened 3 day course with CPI-613 on days 1-3, cytarabine starting on day 2 for 3 total doses and Mitoxantrone after 1<sup>st</sup> and 3<sup>rd</sup> doses at the discretion of the treating physician.

There will be 20 patients recruited at a CPI-613 dose of 500mg/m<sup>2</sup>/day following the same treatment guidelines outlined above. Individuals recruited to this dose level of CPI-613 will remain on this dose level for consolidation and maintenance therapy.

*Salvage Consolidation:* All responding patients are eligible for consolidation therapy with up to 2 cycles of the shortened 3 course of CPI-613 (same dose as induction cycle), high dose cytarabine and mitoxantrone. Responding patients can be removed from trial at any time to receive a stem cell transplant at the discretion of the treating physician. Patients can move to maintenance following 1, 2 or no cycles of consolidation at the discretion of the treating physician.

*Maintenance Therapy:* Any patient who has completed all planned consolidation therapy (i.e. 0, 1 or 2 cycles) and is not eligible for, faces a significant delay or refuses a stem cell transplant may receive maintenance therapy with CPI-613 at a dose of 2,500 mg/m<sup>2</sup>/day over 2 hours on days 1-5 of a 28 day cycle. Patients treated during induction and consolidation at the 500 mg/m<sup>2</sup> dose will receive that dose during maintenance therapy. Patients may continue on maintenance therapy until evidence of disease progression or occurrence of intolerable side effects.

### Eligibility:

- A. Pathologic or cytologic evidence of relapsed or refractory acute myeloid leukemia or granulocytic sarcoma.
- B. ECOG Performance Status of  $\leq 3$ .
- C. Must be  $\geq 18$  years of age.
- D. Expected survival  $>3$  months.
- E. Women & Men of child-bearing potential must use accepted contraceptive methods and must have a negative serum or urine pregnancy test within 1 week prior to treatment initiation. (Note: Pregnant patients are excluded because the effects of CPI-613 on a fetus are unknown.)
- F. No pregnant/lactating women
- G. Mentally competent, ability to understand and willingness to sign the informed consent form.
- H. No radiotherapy, treatment with cytotoxic agents (except CPI-613), treatment with biologic agents or any anti-cancer therapy within the 2 weeks prior to treatment with CPI-613. Hydroxyurea and oral tyrosine kinase inhibitors being used without  $\leq$  Grade 2 toxicity can be taken until day 1 of therapy.
- I. No serious medical illness that would potentially increase patients' risk for toxicity.

- J. No patients with active central nervous system (CNS) or epidural tumor.
- K. No active uncontrolled bleeding/bleeding diathesis.
- L. No life expectancy shorter than 3 months.
- M. No condition or abnormality which may, in the opinion of the investigator, compromise the safety of patients.
- N. No unwillingness or inability to follow protocol requirements.
- O. No large and recurrent pleural or peritoneal effusions or clinically significant pericardial effusion.
- P. No active heart disease including myocardial infarction within previous 6 months, symptomatic coronary artery disease, arrhythmias requiring medication, or symptomatic congestive heart failure.
- Q. No evidence of ongoing, uncontrolled infection.
- R. No patients with known HIV infection.
- S. No patients receiving any other standard or investigational treatment for their cancer, or any other investigational agent for any indication within the past 2 weeks prior to initiation of CPI-613 treatment (the use of Hydrea is allowed).
- T. No patients who have received immunotherapy of any type within the past 4 weeks prior to initiation of CPI-613 treatment.
- U. No requirement for immediate palliative treatment of any kind including surgery.
- V. No patients that have received a chemotherapy regimen with stem cell support in the previous 6 months.
- W. No history of additional risk factors for torsade de pointes (e.g., clinically significant heart failure, hypokalemia, family history of Long QT Syndrome).
- X. Laboratory values  $\leq$  2 weeks must be:
  - Adequate hepatic function (aspartate aminotransferase [AST/SGOT]  $\leq$  3x upper normal limit [UNL], alanine aminotransferase [ALT/SGPT]  $\leq$  3x UNL ( $\leq$  5x UNL if liver metastases present), bilirubin  $\leq$  1.5x UNL).
  - Adequate renal function (serum creatinine  $\leq$  1.5 mg/dL or 133  $\mu$ mol/L).
- Y. Left Ventricular Ejection Fraction sufficient to safely administer mitoxantrone as determined by the treating physician

## ABBREVIATIONS USED

|               |  |        |   |
|---------------|--|--------|---|
| AE            | = adverse events                                   | IUD    | = intrauterine device   |
| AEMD          | = altered energy metabolism-directed               | IV     | = intravenous or intravenously  |
| ADR           | = adverse drug reactions                           | Kel    | = terminal elimination rate constant  |
| ALT           | = alanine aminotransferase                         | EPS    | = ECOG Performance Status   |
| ALP           | = alkaline phosphatase                             | LC-MS  | = Liquid Chromatography - Mass Spectroscopy                                       |
| ANC           | = absolute neutrophil count                        | LD10   | = the dose that induce death or significant toxicity in 10% of the animals tested |
| AST           | = aspartate aminotransferase                       | LDH    | = lactate dehydrogenase   |
| AUC           | = area under the curve                             | MRT    | = mean residence time   |
| AUC0-t        | = AUC from time 0 to last measurable concentration | MTD    | = maximum tolerated dose  |
| AUC0-infinity | = AUC from time 0 to infinity                      | NCI    | = National Cancer Institute   |
| BUN           | = blood urea nitrogen                              | NSCLC  | = non-small cell lung carcinoma   |
| CAS           | = Chemical Abstract Society                        | PDC    | = pyruvate dehydrogenase complex  |
| Cl            | = clearance  | PK     | = pharmacokinetic   |
| Cmax          | = maximum observed concentration                   | QA     | = Quality Assurance   |
| Cend          | = concentration immediately post-infusion          | RECIST | = Response Evaluation Criteria in Solid Tumors                                    |
| CFR           | = Code of Federal Regulations                      | RPMI   | = Roswell Park Memorial Institute   |
| CK or CPK     | = creatine kinase                                  | RSA    | = Research Study Assistant  |
| CNS           | = central nervous system                           | SAE    | = serious adverse event   |
| Rafael        | = Rafael Pharmaceuticals, Inc.                     | SGOT   | = serum glutamic-oxaloacetic transaminase   |
| CRF           | = case report form                                 | SGPT   | = serum glutamic-pyruvic transaminase   |
| CTC           | = common toxicity criteria                         | SOP    | = Standard Operating Procedures   |
| D5W           | = 5% dextrose water                                | STD    | = the dose that induces 10% incidence of significant toxicity                     |
| DLT           | = dose-limiting toxicity                           | t1/2   | = elimination half-life   |
| FBS           | = Fetal Bovine Serum                               | TEA    | = triethanol, triethanolamine or tri-ethanolamine                                 |
| FDA           | = Food and Drug Administration                     | TLS    | = tumor lysis syndrome  |
| GLP           | = Good Laboratory Practices                        | UNL    | = upper normal limit  |
| GCP           | = Good Clinical Practices                          | US     | = United States   |
| GGT           | = gamma-glutamyl transferase                       | USP    | = United States Pharmacopoeia   |
| GI            | = gastrointestinal                                 | Vd     | = volume of distribution  |
| hERG          | = Ether-a-Go-Go-Related Gene                       | WBC    | = white blood cell  |
| Hgb           | = hemoglobin                                       |        |   |
| IEC           | = Independent Ethics Committee                     |        |   |
| IND           | = Investigational New Drug                         |        |   |
| INR           | = International Normalized Ratio                   |        |   |
| IRB           | = Institutional Review Board                       |        |   |

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## 1.0 Introduction and Background

### 1.1 Proposed Mechanism of Action

CPI-613, the investigational drug, is a novel anti-tumor compound presumably with a novel mechanism of action that does not belong to any existing pharmacological class of anticancer agents currently used in the clinics. Specifically, CPI-613 is referred to as an Altered Energy Metabolism-Directed (AEMD) compound, and it is selective against tumor cells (but not normal cells) according to preclinical studies. The anti-tumor effects of CPI-613 are believed to be exerted by the inhibition of the pyruvate dehydrogenase complex (PDC).

In both normal and tumor cells, energy is derived from glucose, first by breaking down glucose to pyruvate via the glycolytic cycle in the cell cytoplasm. Once formed in mammalian cells, pyruvate is then converted by PDC to acetyl-CoA that is in turn metabolized via the tricarboxylic acid (TCA) cycle in the mitochondria.

Most tumor cells display profound perturbation of energy metabolism that tightly correlates with malignant transformation (Baggetto 1992). The PDC is regulated by the phosphorylation state of the E1 subunit. When phosphorylated by the PDC kinase the enzyme is inhibited and the conversion of pyruvate to acetyl-CoA is inhibited. Preclinical studies have shown that CPI-613 causes phosphorylation of the E1 subunit in tumor cells with little to no effect on normal cells. As a result of this phosphorylation ATP levels in tumors cells fall and cancer cell death ensues.

Consistent with the proposed mechanism is the fact that CPI-613 has been shown to have anti-tumor activity in cell culture and animal tumor models against diverse cancers independent of multiple drug resistance, cell cycle phase and activated signal transduction pathways. The novelty in the presumed mechanism of action for CPI-613 is further supported by the results from an *ex vivo* study demonstrating that CPI-613 is effective against various types of tumor cells excised from patients that were resistant to different anti-cancer drugs currently used in the clinics.

The significance of CPI-613 having a novel mechanism of action that is not shared by any existing pharmacological class of anti-cancer agents currently used in the clinics is that CPI-613 may be effective not only against naive tumors that have never been treated with any anti-cancer agents, but also effective against tumors that are resistant to anti-cancer agents currently used in the clinics. This is an important aspect because tumors frequently develop resistance to anti-cancer agents, rendering a shortage of treatment options. The availability of a novel anti-cancer agent would provide a new tool to treat cancer.

## 1.2 Background on Preclinical Studies

CPI-613 is being developed as an anti-tumor agent for the treatment of cancer. A number of preclinical anti-tumor efficacy studies; Administration, Distribution, Metabolism, and Elimination (ADME) studies; safety pharmacology studies; and toxicity studies of CPI-613 have been conducted. These studies are briefly described below, and the Investigator's Brochure provides detailed information regarding these preclinical studies.

### In Vitro and Animal Efficacy Studies

*In vitro* cell culture studies have shown that CPI-613 is effective against a variety of tumor cell lines such as human BxPC-3 pancreatic tumors, human AsPC-1 pancreatic tumors, human H-460 non-small cell lung carcinoma (NSCLC), and human A2780 ovarian tumors, as well as explants of different types of fresh human tumors including NSCLC, colon, breast, and pancreatic tumors. Additionally the drug has activity against human AML cell lines including MV4-11 and HL60. Additional work has shown that the immortalized NIH 3T3 cell line is not affected by CPI-613. Once these cells have been transformed by oncogenic RAS expression they become sensitive. This is a mutation commonly found in hematologic malignancies including the acute leukemias. Consistent with the *in vitro* studies are animal efficacy studies, which showed that CPI-613 was effective against xenograft of human BxPC-3 and AsPC-1 pancreatic tumors, and human H-460 NSCLC.

Additionally, *in vitro* cell culture studies have shown that CPI-613 was equally effective against tumor cell lines with well-characterized mechanisms of drug resistance and their parental tumor cell lines. The equal effectiveness against resistant and parental tumor cell lines is consistent with the proposed novel mechanism of action of CPI-613 that is not shared by any chemotherapeutic agents currently used in the clinics. The drug-resistant tumor cell lines and the parental studied are listed below:

| Parental Tumor Cell Lines            | Drug-Resistant Derivative   |
|--------------------------------------|---|
| MCF-7 breast carcinoma line          | NCI/ADR-RES adriamycin-resistant derivative(Recently reclassified as an Ovarian Cancer derivative of OVCAR-8 FYI) |
| A2780 ovarian carcinoma cell line    | A2780DX doxorubicin-resistant derivative  |
| NCI/H69 small cell lung cancer cells | H69-AR anthracycline-resistant derivative   |
| MES-SA uterine sarcoma cells         | MES-SA/MX2 mitoxanthrone-resistant derivative   |

### Pharmacokinetic Studies

In rats, the toxicokinetic profile of CPI-613 administered 2x weekly for 3 weeks by IV administration at dose levels of 25, 30 or 35 mg/kg (i.e., 150, 180 or 210 mg/m<sup>2</sup>, respectively) was characterized by an apparent biphasic profile – an initial distribution phase followed by an elimination phase.

Systemic exposure was proportional to dose level, and there was no evidence of test article accumulation or sex differences in exposure. In minipigs, the toxicokinetic profile of CPI-613 administered 2x weekly for 3 weeks by IV administration at dose levels of 45, 42 and 46 mg/kg (i.e., 1575, 1470 and 1617 mg/m<sup>2</sup>, respectively) was also characterized by an apparent biphasic profile. There was also no evidence of test article accumulation or sex differences in exposure.

#### ADME Studies

A PK study in minipigs showed that the log scale of the half-life (t<sub>1/2</sub>) values tended to be directly and linearly related to the log of the dose. Specifically, t<sub>1/2</sub> was ~1hour at 3 mg/kg (105 mg/m<sup>2</sup>), ~1.7 hours at 10 mg/kg (350 mg/m<sup>2</sup>), and 10 hours at 30 mg/kg (1050 mg/m<sup>2</sup>).

The tissue distribution pattern of radioactivity, after an intravenous (IV) administration of <sup>14</sup>C-labeled CPI-613 in rats showed that:

1. The liver might be involved in the metabolism of CPI-613 and/or <sup>14</sup>C-containing metabolites of CPI-613.
2. Both the GI tract and the kidneys might be involved in the elimination of CPI-613 and/or <sup>14</sup>C-containing metabolites of CPI-613.
3. CPI-613 and <sup>14</sup>C-containing metabolites of CPI-613 were mostly present in the extracellular space in the circulation.

An *in vitro* human plasma protein binding study showed that CPI-613 exhibited 99.7% binding to human plasma proteins, a value that was similar to warfarin. These results are consistent with findings from tissue distribution studies (see above) which showed CPI-613 was mostly present in the extracellular space in the circulation, consistent with findings of extensive plasma protein binding.

An *in vitro* human CYP450 enzyme inhibition study showed CPI-613 does not significantly inhibit various CYP450 isozymes, including 1A2, 2C9, 2C19, 2D6, and 3A4.

An *in vitro* human liver S9 fraction hepatocyte study showed that CPI-613 was oxidized to form a sulfoxide metabolite rapidly, with a half-life of <19 minutes. CPI-613 was also glucuronidated rapidly at the terminal carboxyl group, with a half-life of <15 minutes. Due to oxidation and glucuronidation, potential metabolites are a sulfoxide, a metabolite with glucuronidation in the terminal carboxyl group; and/or a metabolite with combination of sulfoxidation and glucuronidation.

*In Vitro and Animal Pharmacology Safety Studies*

An *in vitro* study showed that CPI-613 did not inhibit Ether-a-Go-Go-Related Gene (hERG) channels. Since hERG channel inhibition is the predominant cause of QTc interval prolongation which has been linked to Torsades de Pointes conditions such as sudden cardiac death and ventricular arrhythmia, this study suggested that CPI-613 may not induce Torsades de Pointes conditions. This is consistent with the subsequent animal toxicology studies showing that CPI-613 did not induce abnormal ECG pattern.

The potential influence of air in the dead space of an IV catheter on the acute toxicity of CPI-613 in rats has been evaluated. The results suggested that standard drug administration procedures in the elimination of dead air space within indwelling IV catheters should be followed, since air in the catheter air space may enhance the acute toxicity of CPI-613 at supra-antitumor doses.

The acute toxicity of CPI-613 administered IV as a bolus vs. by infusion has been compared in a preliminary study in rats. The results suggested that CPI-613 at supra-antitumor doses might be less toxic when administered as a 1-hr IV infusion than as a 1-min IV bolus.

*Animal Toxicology Studies*

Single Dose: A toxicology study involving a single IV administration of CPI-613 in mice has been conducted. The results indicated that 0.3-3 mg/kg (0.9-9 mg/m<sup>2</sup>) of CPI-613 did not induce any toxicity, whereas 10-100 mg/kg (30-300 mg/m<sup>2</sup>) also did not induce toxicity, except inflammatory reactions at or around the site of injection with intensity that was dose-related.

Twice Weekly for 1 Week Dosing: Animal toxicology studies involving IV administrations of CPI-613 twice weekly for 1 week have been conducted in mice and minipigs. In mice, CPI-613 at 100 mg/kg (300 mg/m<sup>2</sup>) induced mortality in all female mice but not male mice. Also, CPI-613 at 30 and 75 mg/kg (90 and 215 mg/m<sup>2</sup>, respectively) did not induce any toxicity, except inflammation around the site of injection and a small increase in the spleen weight in mice treated with 75 mg/kg (215 mg/m<sup>2</sup>) and in the surviving mice treated with 100 mg/kg (300 mg/m<sup>2</sup>) of CPI-613.

In minipigs, when given 2x weekly for 1 week, CPI-613 at doses up to 30 mg/kg (1,050 mg/m<sup>2</sup>), the highest dose investigated in this study, did not induce toxicity, other than local inflammatory reactions at and around the site of injection. These results are consistent with those observed with the mouse study (see above).

**Twice Weekly for 3 Weeks Dosing:** Animal toxicology studies involving IV administrations of CPI-613 twice weekly for 3 weeks have been conducted in rats and minipigs, as described below.

In rats, when administered at dose levels of 25, 30 or 35 mg/kg (i.e., 150, 180 or 210 mg/m<sup>2</sup>, respectively), CPI-613 enhanced inflammatory responses in the body in a dose related manner, as reflected by dose-related exaggeration in the incidence and severity of granulomatous or acute, chronic, or chronic active inflammation at the administration site (inguinal vein), skin and subcutaneous tissue near the port, and inguinal skin and subcutaneous tissue near the inguinal vein, when compared to control treatment. CPI-613 at the toxicological doses of 30-35 mg/kg (180-210 mg/m<sup>2</sup>) in rats induced dose-related incidence of mortality. The cause of death was due to significant systemic inflammation, and might be related to an over enhancement of the inflammatory responses induced by CPI-613. Deaths due to significant systemic inflammation were also observed in minipigs treated with the minipig toxicological dose of 46.2 mg/kg (i.e., 1617 mg/m<sup>2</sup>) of CPI-613 in another toxicology study. CPI-613 at 25, 30 and 35 mg/kg (i.e., 150, 180 and 210 mg/m<sup>2</sup>, respectively) elevated GGT levels in a dose-dependent manner in rats. This elevation is not associated with histopathology findings or other parameters of kidney or liver functions, and therefore not related to toxicity of the kidney or liver. However, it may be related to systemic inflammation (Yamada J, Tomiyama H, *et. al.* 2006), since systemic inflammation was observed in CPI-613 treated rats in this study. Finally, CPI-613 at the rat toxicological doses of 30 and 35 mg/kg (i.e., 180 and 210 mg/m<sup>2</sup>, respectively) increased reticulocyte levels, which appeared to be associated with hematopoietic cell proliferation of the spleen, and sternal bone marrow hyperplasia that were secondary to inflammation initiated at the administration site or port in rats. The no-observable-adverse effect levels were 25 mg/kg (150 mg/m<sup>2</sup>) CPI-613. The LD10 or STD10 is approximately 35 mg/kg (210 mg/m<sup>2</sup>).

In minipigs, when administered at dose levels of 42, 45, 46.2, 50 and 55 mg/kg (i.e., 1470, 1575, 1617, 1750 and 1925 mg/m<sup>2</sup>, respectively), CPI-613 at all dose levels induced transient vomiting that was transient and reversible. Mortality (2 of 8 minipigs) was observed in minipigs treated with CPI-613 at 46.2 mg/kg (i.e., 1617 mg/m<sup>2</sup>), due to significant systemic inflammation. Significant systemic inflammation was also observed in rats treated with CPI-613, resulting in dose-dependent incidence of mortality at the toxicological doses of 30-35 mg/kg (180-210 mg/m<sup>2</sup>) and might be due to an over enhancement of inflammatory responses induced by toxic doses of CPI-613, as supported by dose-related exaggeration in inflammatory effects according to gross necropsy and histopathology findings (see below).

**Overall Summary of Preclinical Studies**

Preclinical efficacy studies, ADME studies, tissue distribution studies, and toxicology studies on CPI-613 have been conducted. The efficacy studies demonstrated the anti-tumor effects of CPI-613, whereas the ADME studies provided PK, biodistribution, metabolism and plasma protein binding information on CPI-613 in the body. Finally, for the toxicology studies, CPI-613 was administered in a way that mimicked that in the proposed clinical study, which involved IV administration given twice weekly. The results of the animal toxicology showed that CPI-613 is sufficiently non-toxic.

**1.3 Background on Clinical Studies**

Six single-patient physician-sponsored clinical studies have been conducted for compassionate use. Three of these single-patient studies were conducted in the US, whereas the other 3 were conducted in Israel.

Additionally, a Phase I clinical study involving CPI-613 as a single agent in patients with solid tumors and lymphomas is ongoing. A phase I clinical study involving CPI-613 as a single agent in patients with advanced hematologic malignancies is ongoing. A phase I study of CPI-613 in combination with high dose cytarabine and mitoxantrone has recently been completed. This trial established the MTD of CPI-613 as 2,500 mg/m<sup>2</sup>. A Phase I/II clinical study involving CPI-613 in combination with Gemcitabine is ongoing.

**1.4 Rationale**

Chemotherapy resistance is a major cause of death in patients with relapsed or refractory AML. CPI-613 can increase the sensitivity of leukemia cells to chemotherapy in petri dishes and mice. As a single agent in a phase I clinical trial several relapsed/refractory AML patients had an objective response. Additionally, a phase I study of CPI-613 in combination with high dose cytarabine and mitoxantrone has recently been completed. This trial established the MTD of CPI-613 as 2,500 mg/m<sup>2</sup>. Preliminary analysis of the study revealed an overall complete remission or complete remission with incomplete count recovery rate of 45%. This compares favorably with our historical experience of this regimen without CPI-613. In this trial patients with poor risk cytogenetics had a 46% response rate, far superior to the 19% response seen with historical data. This trial established that CPI-613 can be safely administered at 2,500 mg/m<sup>2</sup> in this combination and results in superior response rates. The novel mechanism of action, non-cross resistance with chemotherapeutic agents, lack of CPI-613-related myelosuppression clinically and increase response rate make this regimen a suitable candidate for the proposed pilot study.

### **1.5 Justification of the Dose of CPI-613**

WFUCCC 22112, a phase I study of CPI-613 in combination with high dose cytarabine and mitoxantrone given exactly as proposed in the current study established the MTD of CPI-613 to be 2,500 mg/m<sup>2</sup>. A detailed analysis of the response data indicated that similar response rates were seen at the 2,000 mg/m<sup>2</sup> dose with less toxicity. Further studies have indicated a dose of 1500 mg/m<sup>2</sup> has a similar efficacy profile as 2,000 mg/m<sup>2</sup> but with even less toxicity. The rationale behind using a dose of 500mg/m<sup>2</sup> is supported by three lines of evidence: 1) pre-clinical evidence in mice suggesting lower doses may be more efficacious overtime than higher doses, 2) a traditional dose response effect of CPI-613 is not observed in AML patients thus far, and 3) a previous study in pancreatic cancer that showed remarkable synergy between CPI-613 at 500mg/m<sup>2</sup> in combination with standard chemotherapy.

## **2.0 Objectives**

### **2.1 Primary Objective**

To determine the feasibility of CPI-613 when administered with high dose cytarabine, and mitoxantrone in all three phases of salvage therapy (induction, and maintenance). The regimen will be considered feasible if  $\geq 50\%$  of patients eligible for maintenance therapy complete at least 3 cycles.

### **2.2 Secondary Objectives**

To observe the response rate (CR, and CRi) of CPI-613 in combination with high dose cytarabine and mitoxantrone.

To observe the overall survival of patients treated with CPI-613 in combination with high dose cytarabine and mitoxantrone in induction, consolidation and maintenance.

To monitor toxicities experienced by patients treated with CPI-613 in combination with high dose cytarabine and mitoxantrone in induction, consolidation and maintenance.

## **3.0 Patient Selection**

This clinical trial can fulfill its objective only if patients appropriate for this trial are enrolled. All relevant medical and other considerations should be taken into account when deciding whether this protocol is appropriate for a particular patient. Physicians should consider the risks and benefits of any therapy, and therefore only enroll patients for whom this treatment is appropriate.

### 3.1 Inclusion Criteria

- 3.1.1 Patients must have histologically or cytologically documented relapsed and/or refractory Acute Myeloid Leukemia or granulocytic sarcoma.
- 3.1.2 ECOG Performance Status of  $\leq 3$ .
- 3.1.3 Must be  $\geq 18$  years of age.
- 3.1.4 Expected survival  $> 3$  months.
- 3.1.5 Women of child-bearing potential (i.e., women who are pre-menopausal or not surgically sterile) must use accepted contraceptive methods (abstinence, intrauterine device [IUD], oral contraceptive or double barrier device), and must have a negative serum or urine pregnancy test within 1 week prior to treatment initiation. (Note: Pregnant patients are excluded because the effects of CPI-613 on a fetus are unknown.)
- 3.1.6 Fertile men must practice effective contraceptive methods during the study period, unless documentation of infertility exists.
- 3.1.7 Mentally competent, ability to understand and willingness to sign the informed consent form.
- 3.1.8 No radiotherapy, treatment with cytotoxic agents (except CPI-613), treatment with biologic agents or any anti-cancer therapy within the 2 weeks prior to treatment with CPI-613. Hydroxyurea and oral tyrosine kinase inhibitors being used without Grade  $\leq 2$  toxicity can be taken until day 1 of therapy. Patients must have fully recovered from the acute, non-hematological, non-infectious toxicities of any prior treatment with cytotoxic drugs, radiotherapy or other anti-cancer modalities (returned to baseline status as noted before most recent treatment). Patients with persisting, non-hematologic, non-infectious toxicities from prior treatment  $\leq$  Grade 2 are eligible, but must be documented as such.
- 3.1.9 Laboratory values  $\leq 2$  weeks must be:
  - Adequate hepatic function (aspartate aminotransferase [AST/SGOT]  $\leq 3$  times upper normal limit [UNL], alanine aminotransferase [ALT/SGPT]  $\leq 3$  times UNL ( $\leq 5$  times ULN if liver metastases present), bilirubin  $\leq 1.5$  times UNL).
  - Adequate renal function (serum creatinine  $\leq 1.5$  mg/dL or 133  $\mu$ mol/L).
- 3.1.10 Left Ventricular Ejection Fraction (by TTE, MUGA or cardiac MRI) sufficient to safely administer mitoxantrone as determined by the treating physician

### 3.2 Exclusion Criteria

- 3.2.1 Serious medical illness, such as significant cardiac disease (e.g. symptomatic congestive heart failure, unstable angina pectoris, myocardial infarction within the past 6 months, uncontrolled cardiac arrhythmia, pericardial disease or New York Heart Association Class III or IV), or

severe debilitating pulmonary disease, that would potentially increase patients' risk for toxicity.

- 3.2.2 Patients with active central nervous system (CNS) or epidural tumor.
- 3.2.3 Albumin <2.0 g/dL or <20 g/L.
- 3.2.4 Any active uncontrolled bleeding, and any patients with a bleeding diathesis (e.g., active peptic ulcer disease).
- 3.2.5 Pregnant women, or women of child-bearing potential not using reliable means of contraception (because the teratogenic potential of CPI-613 is unknown).
- 3.2.6 Lactating females because the potential of excretion of CPI-613 into breast milk. (**Note:** Lactating females are excluded because the effects of CPI-613 on a nursing child are unknown.)
- 3.2.7 Fertile men unwilling to practice contraceptive methods during the study period.
- 3.2.8 Life expectancy less than 3 months.
- 3.2.9 Any condition or abnormality which may, in the opinion of the investigator, compromise the safety of patients.
- 3.2.10 Unwilling or unable to follow protocol requirements.
- 3.2.11 Patients with large and recurrent pleural or peritoneal effusions requiring frequent drainage (e.g. weekly). Patients with any amount of clinically significant pericardial effusion.
- 3.2.12 Active heart disease including symptomatic coronary artery disease, uncontrolled arrhythmias, or symptomatic congestive heart failure.
- 3.2.13 Evidence of ongoing, uncontrolled infection.
- 3.2.14 Patients with known HIV infection. (**Note:** Patients with known HIV infection are excluded because patients with an immune deficiency are at increased risk of lethal infections when treated with marrow-suppressive therapy, and because there may be unknown or dangerous drug interactions between CPI-613 and anti-retroviral agents used to treat HIV infections.)
- 3.2.15 Patients receiving any other standard or investigational treatment for their cancer, or any other investigational agent for any indication within the past 2 weeks prior to initiation of CPI-613 treatment (the use of Hydrea is allowed).
- 3.2.16 Patients who have received immunotherapy of any type within the past 4 weeks prior to initiation of CPI-613 treatment.
- 3.2.17 Requirement for immediate palliative treatment of any kind including surgery.
- 3.2.18 Patients that have received a chemotherapy regimen with stem cell support in the previous 6 months.

### **3.3 Inclusion of Women and Minorities**

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

CCCWFU 22215

Comprehensive Cancer Center of Wake Forest University

An Open Label Study to Evaluate the Feasibility of CPI-613 Given with High Dose Cytarabine and  
Mitoxantrone in Patients with Relapsed or Refractory Acute Myeloid Leukemia (AML)

**NCT Clinicaltrials.gov:** NCT02484391

## 4.0 Registration Procedures

All patients entered on any CCCWFU trial, whether treatment, companion, or cancer control trial, **must** be linked to the study in EPIC within 24 hours of Informed Consent. Patients **must** be registered prior to the initiation of treatment.

You must perform the following steps in order to ensure prompt registration of your patient:

1. Complete the Eligibility Checklist (Appendix A)
2. Complete the Protocol Registration Form (Appendix B)
3. Alert the Cancer Center registrar by phone, *and then* send the signed Informed Consent Form, Eligibility Checklist and Protocol Registration Form to the registrar, either by fax or e-mail.

Contact Information:

Protocol Registrar PHONE (336) 713-6767

Protocol Registrar FAX (336) 713-6772

Protocol Registrar E-MAIL ([registra@wakehealth.edu](mailto:registra@wakehealth.edu))

\*Protocol Registration is open from 8:30 AM - 4:00 PM, Monday-Friday.

4. Fax/e-mail ALL eligibility source documents with registration. Patients **will not** be registered without all required supporting documents.

Note: If labs were performed at an outside institution, provide a printout of the results. Ensure that the most recent lab values are sent.

To complete the registration process, the Registrar will:

- assign a patient study number
- assign the patient a dose
- register the patient on the study

## 5.0 Treatment Plan

Patients recruited at 500 mg/m<sup>2</sup> will receive this dose for all treatment phases.

Salvage Induction Cycle 1:

The dose of CPI-613 will be 500 mg/m<sup>2</sup>/day or 1,500 mg/m<sup>2</sup>/day given over 2 hours on days 1-5. Immediately following CPI-613 dosing 50 ml of D5W will be run through the central line. Cytarabine will be given following CPI-613 at 3gm/m<sup>2</sup> for age <60 or 1.5 gm/m<sup>2</sup> for age >60 in 500 mL NS over 3 hours every 12 hours for 5 doses starting on day 3. Mitoxantrone will be given at 6mg/m<sup>2</sup> daily for 3 doses given in 50 mL NS over 15 minutes after 1st, 3rd and 5th doses of cytarabine.

Dose modifications for cytarabine and mitoxantrone are as follows (Please see section 6 for CPI-613 dose modifications):

Hold Cytarabine and notify physician if:

- Bilirubin 1.5-3: Consider Decrease dose by 25%.
- Bilirubin greater than 3: Consider Decrease dose by 50%.
- Cr Cl less than 60 mL/min: Consider dose reduction.
- Hold mitoxantrone and notify physician if:
- Bilirubin greater than 3: Consider Decrease dose by 25%.

All dose modifications are at the discretion of the treating physician.

Salvage Induction Cycle 2 (Optional, at the discretion of the treating physician):

A repeat of the initial cycle as outlined above or at the discretion of the treating physician an abbreviated second cycle can be given. In the abbreviated course CPI-613 is given as above on days 1-3, cytarabine given as above for 3 doses starting on day 2, mitoxantrone given as above after the first and third cytarabine doses.

Salvage Consolidation:

All responding patients are eligible for consolidation therapy with up to 2 cycles of the abbreviated course of CPI-613 at 500 mg/m<sup>2</sup>/day or 1,500 mg/m<sup>2</sup>/day, high dose cytarabine and mitoxantrone. Responding patients can be removed from trial at any time to receive a stem cell transplant at the discretion of the treating physician. Patients can move to maintenance following 1, 2 or no cycles of consolidation at the discretion of the treating physician.

Maintenance Therapy:

Any patient that has completed all planned consolidation therapy (i.e. 0, 1 or 2 cycles) and refuses or is not eligible for a stem cell transplant may receive maintenance therapy with CPI-613. The dose for the maintenance phase of treatment in this study is 2,500 mg/m<sup>2</sup> except for patients who received 500 mg/m<sup>2</sup> at induction. Patients receiving 500 mg/m<sup>2</sup> at induction will continue with this dose during maintenance therapy. Patients may continue on maintenance therapy until evidence of disease progression, availability of stem cell transplant or occurrence of intolerable side effects.

## 5.1 Table of Study-Related Interventions

| Assessments  | Pre-Enrollment Screening                           | Salvage Induction Cycle 1   |                  |                  |                  |                  |                  |                  |                  |
|--|--|---|------------------|------------------|------------------|------------------|------------------|------------------|------------------|
|  |  | Day 1   | Day 2            | Day 3            | Day 4            | Day 5            | Day 6            | Day 7            | Day 8            |
| Treatment with CPI-613   |  | ✓   | ✓                | ✓                | ✓                | ✓                |                  |                  |                  |
| Treatment with Cytarabine  |  |   |                  | ✓                | ✓                | ✓                |                  |                  |                  |
| Treatment with Mitoxantrone  |  |   |                  | ✓                | ✓                | ✓                |                  |                  |                  |
| Medical history <sup>7</sup>   | ✓  |   |                  |                  |                  |                  |                  |                  |                  |
| Physical exam <sup>7</sup> and vital signs <sup>1</sup>  | ✓ <sup>1</sup>                                     | ✓ <sup>4</sup>  | ✓ <sup>4</sup>   | ✓ <sup>4</sup>   | ✓ <sup>4</sup>   | ✓ <sup>4</sup>   |                  |                  |                  |
| Pregnancy test for woman of child-bearing potential  | ✓  |   |                  |                  |                  |                  |                  |                  |                  |
| TTE, MUGA or MRI   | ✓  |   |                  |                  |                  |                  |                  |                  |                  |
| ECOG performance status  | ✓  |   |                  |                  |                  |                  |                  |                  |                  |
| Evaluation of symptoms & medications   | ✓  |   |                  |                  |                  |                  |                  |                  |                  |
| Clinical chemistry <sup>2</sup> , hematology & coagulation <sup>7,11</sup>   | ✓  | ✓ <sup>5,6</sup>  | ✓ <sup>5,6</sup> | ✓ <sup>5,6</sup> | ✓ <sup>5,6</sup> | ✓ <sup>5,6</sup> | ✓ <sup>5,6</sup> | ✓ <sup>5,6</sup> | ✓ <sup>5,6</sup> |
| Creatinine, BUN  |  | ✓ <sup>10</sup>   | ✓ <sup>10</sup>  | ✓ <sup>10</sup>  | ✓ <sup>10</sup>  | ✓ <sup>10</sup>  | ✓ <sup>10</sup>  | ✓ <sup>10</sup>  | ✓ <sup>10</sup>  |
| Anti-Tumor Efficacy (i.e., imaging for granulocytic sarcoma, bone marrow biopsy for AML) <sup>3,7</sup>  | Obtained within 2 weeks prior to the first dose.   | Obtained on day 14 of cycle 1.  |                  |                  |                  |                  |                  |                  |                  |
| Optional blood, urine and plasma samples, as well as bone marrow via biopsy <sup>9</sup> for possible testing of biomarkers, predictors of biological responses, toxicity, genotype vs. drug response relationship, etc. | Obtained within 2-4 weeks prior to the first dose. | Blood sample to be obtained prior to and following the dose of CPI-613 at 2, 4, and 6 hours from end of CPI-613 infusion on day 1 and bone marrow sample to be obtained on day 14 of Cycle 1. Bone marrow samples may be collected +/- 1-2 days if falls on a weekend or holiday. Optional urine samples will be collected from the first void after the first infusion of CPI-613. Details of the collection will be recorded on Appendix G. |                  |                  |                  |                  |                  |                  |                  |

<sup>1</sup> Height, weight are also determined during pre-enrollment screening.<sup>2</sup> Renal function will be assessed utilizing the Cockcroft-Gault formula.<sup>3</sup> The Response Criteria will be assessed by standard criteria (Blood. 2010;115:453-474).<sup>4</sup> Vital signs will be performed immediately after CPI-613 administration and the patient only re-examined if clinically indicated.<sup>5</sup> These tests are performed within 24 hrs prior to dosing. Only the results of the creatinine are needed before CPI-613 is dosed.<sup>6</sup> For Day 1 of Treatment Cycle 1, the pre-enrollment test results can be used for all labs except creatinine which must be rechecked 24 hours prior to dosing.<sup>7</sup> The frequency of assessment beyond Cycle 1 is:

- For medical history, physical exam and vital signs, ECOG PS, evaluation of symptoms and medications, they are assessed within 5 days of the next cycle doses.
- Clinical chemistry and hematology are assessed on day 5 of each cycle (or day 3 if short dosing cycle is given).

<sup>9</sup> Bone Marrow via biopsy will only be collected if deemed appropriate by physician<sup>10</sup> Creatinine and BUN to be checked within 24 hours of every dose and at 24, 48 and 72 hours post last dose of CPI-613, mitoxantrone, and cytarabine (i.e., days 6, 7, and 8)<sup>11</sup> Coagulation (PT/PTT) to be completed Day 1 and weekly during Cycle 1.

| Assessments   | Salvage Consolidation Cycle 1 and 2  |                |                |       |       |       |       |       |
|---|--|----------------|----------------|-------|-------|-------|-------|-------|
|   | Day 1  | Day 2          | Day 3          | Day 4 | Day 5 | Day 6 | Day 7 | Day 8 |
| Treatment with CPI-613  | ✓  | ✓              | ✓              |       |       |       |       |       |
| Treatment with Cytarabine   |  | ✓              | ✓              |       |       |       |       |       |
| Treatment with Mitoxantrone   |  | ✓              | ✓              |       |       |       |       |       |
| Medical history <sup>7</sup>  | ✓ <sup>7</sup>   |                |                |       |       |       |       |       |
| Physical exam <sup>7</sup> and vital signs <sup>1</sup>   | ✓ <sup>4</sup>   | ✓ <sup>4</sup> | ✓ <sup>4</sup> |       |       |       |       |       |
| Pregnancy test for woman of child-bearing potential   | ✓  |                |                |       |       |       |       |       |
| TTE, MUGA or MRI  | ✓ <sup>11</sup>  |                |                |       |       |       |       |       |
| ECOG performance status   | ✓  |                |                |       |       |       |       |       |
| Evaluation of symptoms & medications  | ✓  |                |                |       |       |       |       |       |
| Clinical chemistry <sup>2</sup> and hematology <sup>7,11</sup>  | ✓ <sup>5</sup>   | ✓ <sup>5</sup> | ✓ <sup>5</sup> |       |       |       |       |       |
| Creatinine, BUN   | ✓  | ✓              | ✓              |       |       |       |       |       |
| Anti-Tumor Efficacy (i.e., imaging for granulocytic sarcoma, bone marrow biopsy for AML) <sup>3,7</sup>   | Obtained upon completion of all planned consolidation therapy.   |                |                |       |       |       |       |       |
| Optional blood and plasma samples, as well as bone marrow via biopsy <sup>9</sup> for possible testing of biomarkers, predictors of biological responses, toxicity, genotype vs. drug response relationship, etc. | Blood sample to be obtained prior to and following the dose of CPI-613 at 2, 4, and 6 hours from end of CPI-613 infusion on day 1 and bone marrow sample to be obtained at the end of planned consolidation therapy. Bone marrow samples may be collected +/- 1-2 days if falls on a weekend or holiday. |                |                |       |       |       |       |       |

<sup>1</sup> Height, weight are determined during pre-enrollment screening.  
<sup>2</sup> Renal function will be assessed utilizing the Cockcroft-Gault formula.  
<sup>3</sup> The Response Criteria will be assessed by standard criteria (Blood. 2010;115:453-474).  
<sup>4</sup> Vital signs will be performed immediately after CPI-613 administration and the patient only re-examined if clinically indicated.  
<sup>5</sup> These tests are performed within 24 hrs prior to dosing. Only the results of the creatinine are needed before CPI-613 is dosed.  
<sup>7</sup> The frequency of assessment is:  
- For medical history, physical exam and vital signs, ECOG PS, evaluation of symptoms and medications, they are assessed within 5 days of the next cycle doses.  
<sup>9</sup> Bone Marrow via biopsy will only be collected if deemed appropriate by physician  
<sup>10</sup> Creatinine and BUN to be checked within 24 hours of every dose of CPI-613  
<sup>11</sup> TTE/MUGA/Cardiac MRI can be obtained within 2 weeks of consolidation as long as no other cardiac toxins have been administered. Prior to cycle 2 of consolidation TTE/MUGA/Cardiac MRI is at the discretion of the treating physician

| Assessments   | Maintenance Therapy  |                |                |                |                |       |       |       |
|---|--|----------------|----------------|----------------|----------------|-------|-------|-------|
|   | Day 1  | Day 2          | Day 3          | Day 4          | Day 5          | Day 6 | Day 7 | Day 8 |
| Treatment with CPI-613  | ✓  | ✓              | ✓              | ✓              | ✓              |       |       |       |
| Medical history <sup>7</sup>  | ✓ <sup>7</sup>   |                |                |                |                |       |       |       |
| Physical exam <sup>7</sup> and vital signs <sup>1</sup>   | ✓ <sup>4</sup>   | ✓ <sup>4</sup> | ✓ <sup>4</sup> | ✓ <sup>4</sup> | ✓ <sup>4</sup> |       |       |       |
| Pregnancy test for woman of child-bearing potential   | ✓  |                |                |                |                |       |       |       |
| ECOG performance status   | ✓ <sup>7</sup>   |                |                |                |                |       |       |       |
| Evaluation of symptoms & medications  | ✓ <sup>7</sup>   |                |                |                |                |       |       |       |
| Clinical chemistry <sup>2</sup> and hematology <sup>7,11</sup>  | ✓ <sup>5</sup>   | ✓ <sup>5</sup> | ✓ <sup>5</sup> | ✓ <sup>5</sup> | ✓ <sup>5</sup> |       |       |       |
| Creatinine, BUN   | ✓  | ✓              | ✓              | ✓              | ✓              |       |       |       |
| Anti-Tumor Efficacy (i.e., imaging for granulocytic sarcoma, bone marrow biopsy for AML) <sup>3,7</sup>   | Obtained upon completion of every fourth cycle.  |                |                |                |                |       |       |       |
| Optional blood and plasma samples, as well as bone marrow via biopsy <sup>9</sup> for possible testing of biomarkers, predictors of biological responses, toxicity, genotype vs. drug response relationship, etc. | Blood sample to be obtained prior to and immediately following the dose of CPI-613 on day 1 and bone marrow sample to be obtained at the end of planned maintenance therapy. Bone marrow samples may be collected +/- 1-2 days if falls on a weekend or holiday. |                |                |                |                |       |       |       |

<sup>1</sup> Height, weight are determined during pre-enrollment screening.  
<sup>2</sup> Renal function will be assessed utilizing the Cockcroft-Gault formula.  
<sup>3</sup> The Response Criteria will be assessed by standard criteria (Blood. 2010;115:453-474).  
<sup>4</sup> Vital signs will be performed immediately after CPI-613 administration and the patient only re-examined if clinically indicated.  
<sup>5</sup> These tests are performed within 24 hrs prior to dosing. Only the results of the creatinine are needed before CPI-613 is dosed.  
<sup>7</sup> The frequency of assessment for cycles after cycle 1 is:  
- For medical history, physical exam and vital signs, ECOG PS, evaluation of symptoms and medications, they are assessed within 7 days of the next cycle doses.  
<sup>9</sup> Bone Marrow via biopsy will only be collected if deemed appropriate by physician.  
<sup>10</sup> Creatinine and BUN to be checked within 24 hours of every dose of CPI-613.

## 5.2 Pre-Enrollment Medical Screening

Informed consent must be obtained prior to pre-enrollment medical screening. Investigators who are listed on US “Food and Drug Administration (FDA) Form 1572” or Canadian “Clinical Trial Site Information Form” are authorized to obtain informed consent. Pre-enrollment medical screening is used to determine the eligibility of each candidate. All enrollment evaluations must be performed within the time frame listed below, prior to CPI-613 treatment and include:

Within 2 weeks:

- Bone marrow biopsy or cytologic evidence of relapsed or refractory AML or granulocytic sarcoma
- Optional blood, plasma and bone marrow biopsy sample for biomarker evaluation
- a complete medical history
- physical exam, including vital signs, height, and weight
- ECOG PS
- baseline evaluation of symptoms and medications
- clinical chemistry (including renal function), hematology and coagulation (see Section 5.6 for specifics)

Within 1 week:

- a pregnancy test for women of child-bearing potential (performed within 1 week prior to CPI-613 treatment)

## 5.3 CPI-613 Dosing

This is a Pilot trial to determine the feasibility of CPI-613 given with high dose cytarabine and mitoxantrone in salvage induction, consolidation and maintenance. This is an open-label study, and investigators and subjects are not blinded to the treatment. The reason this is an open-label study is because this is a feasibility trial, and the investigators need to determine whether this regimen is feasible to be tested in larger clinical trials. The assignment of patients will not be randomized, since this is a feasibility trial. The doses of CPI-613 for the induction and consolidation phases of treatment in this study are 500 mg/m<sup>2</sup> or 1,500 mg/m<sup>2</sup> with 20 patients in each cohort for both 500 and 1,500 the study has already accrued 17 patients at 2,000 mg/m<sup>2</sup> cohort; the dose for the maintenance phase of treatment in this study is 2,500 mg/m<sup>2</sup> except for patients who received 500mg/m<sup>2</sup> at induction. Patients receiving 500mg/m<sup>2</sup> at induction will continue with this dose for all phases of therapy including maintenance.

CPI-613 must be diluted from 50 mg/mL to 12.5 mg/mL with D5W (i.e., 1 portion of CPI-613 diluted with 3 portions of D5W) and must be administered IV at a rate of ~0.5 mL/min via a central venous catheter with D5W running at a rate of about 125-150 mL/hr. Please refer to Section 5.4 for methods of administering CPI-613.

#### **5.4 CPI-613 Administration Guidelines**

Since information on the use of CPI-613 in humans is limited, investigators should be aware of potential AEs and toxicities observed in preclinical studies, as described below.

According to animal toxicology studies, IV administration of CPI-613 can induce reactions at and around the site of administration. These reactions are consistent with local inflammation, which include red/purple/black color, swelling, necrosis, warm to touch, etc. These local reactions occurred more severely when there was accidental leakage of CPI-613 into the perivascular space during IV administration. This is possibly because of low perfusion in the perivascular areas, causing prolonged exposure of local tissues to CPI-613. Therefore, care must be taken to avoid perivascular leakage of CP-613.

CPI-613 must be administered IV by infusion (not bolus), via a central venous catheter that is free flowing, with D5W running at a rate of about 125-150 mL/hr, and free of air in the dead space of the IV catheter. This is to minimize vascular irritation, inflammation and acute toxicity of CPI-613. Accidental co-administration of extra air that is present in the dead space of an IV catheter has been shown to induce excessive acute toxicity of CPI-613 according to animal studies (Study NCL-049).

CPI-613 must be diluted prior to administration, as described in Section 5.3. Dilution of CPI-613 prior to administration reduces the rates of delivery of CPI-613 to the body, thus minimizing the acute toxicity of CPI-613.

Accordingly, the following procedures in administering CPI-613 should be taken to minimize local reactions and acute toxicity of CPI-613:

- A. Confirmation of the placement of the IV line to ensure that there is a lack of leakage of CPI-613 into the perivascular space.
- B. Confirmation that the IV line is free flowing and with D5W running at a rate of about 125-150 mL/hr.
- C. Confirmation that the IV line is free of air in the dead space.
- D. If necessary, rotate the site of administration for different doses of CPI-613.
- E. Dilute CPI-613 drug product with D5W, as instructed in the study protocol.
- F. Administer CPI-613 by infusion, not bolus, as instructed in the study protocol.
- G. Upon completion of administering CPI-613, “slowly” flush the IV line with ~10 mL of D5W to remove residual CPI-613.

Investigators should be aware of the following toxicity observed in animals treated with toxic doses of CPI-613:

1. CPI-613 at the toxicological doses of 30-35 mg/kg (180-210 mg/m<sup>2</sup>) induced dose-related incidence of mortality in rats. The cause of death in most rats was due to significant systemic inflammation, and might be related to an over enhancement in the inflammatory responses induced by CPI-613. Deaths due to significant systemic inflammation were also observed in minipigs treated with the minipig toxicological dose of 46.2 mg/kg (i.e., 1617 mg/m<sup>2</sup>) of CPI-613. Additionally, CPI-613 at 30 and 35 mg/kg (i.e., 180 and 210 mg/m<sup>2</sup>, respectively) in minipigs increased reticulocyte levels, which appeared to be associated with hematopoietic cell proliferation of the spleen, and sternal bone marrow hyperplasia that were secondary to inflammation initiated at the administration site or port. Therefore, investigators should be aware of significant increases in reticulocyte levels, which can be used as an indication of severe inflammation.
2. CPI-613 at 42-55 mg/kg (i.e., 1470-1925 mg/m<sup>2</sup>) induced transient vomiting in minipigs.
3. CPI-613 at 42-46.2 mg/kg (1470-1617 mg/m<sup>2</sup>, respectively) induced transient and reversible increases in troponin I and creatine kinase (CPK) isoenzyme. The transient and reversible nature of the troponin and CPK isoenzyme results were consistent with necropsy exam and histopathology, which indicated that there was no cardiac damage after the 3-week treatment of different doses of CPI-613.

## **5.5 General Concomitant Medication and Supportive Care Guidelines**

Patients will receive standard prophylactic treatment for drug-related symptoms. Supportive treatments may include anti-emetic, anti-diarrhea, anti-allergic, anti-hypertensive medications, analgesics, antibiotics, allopurinol, and others such as blood products and bone marrow growth factors. The treating physician may utilize marrow growth factors, or blood or platelet transfusions at their discretion. For patients with an ANC  $\geq$  500/mm<sup>3</sup> at the time of CPI-613 administration loperamide can be administered as a premedication at a dose of 2 to 4 mg PO 30 minutes prior to CPI-613.

## **5.6 Study Procedures – Assessment of Safety, Plasma Concentration, and Possible Anti-Tumor Efficacy**

*Safety Assessment:* The safety of CPI-613 will be assessed based on:

- physical exams
- vital signs
- clinical pathology

- clinical chemistry
- renal function
- hematology

For physical exams and vital signs, they are to be performed during screening (performed within 2 weeks prior to treatment with CPI-613) and after CPI-613 administration in Cycle 1. Beyond Cycle 1, physical exam and vital signs will be assessed within 5 days of the next cycle doses.

For clinical pathology (i.e., clinical chemistry, renal function, hematology and coagulation), they are to be performed during screening (performed within 2 weeks prior to treatment with CPI-613), and within 24 hrs prior to dosing. Creatinine results within the last 24 hours must be reviewed prior to CPI-613 dosing. For Day 1 of Treatment Cycle 1, pre-dose assessments of clinical pathology are not needed because the pre-enrollment results can be used. Beyond cycle 1, laboratory assessments will be assessed on at least day 1 and 5 of each cycle rather than prior to beginning each cycle.

For left ventricular ejection fraction assessments, they are evaluated during screening and prior to consolidation therapy. Additional assessments can be made at the discretion of the treating physician.

*Anti-Tumor Efficacy – A Secondary Endpoint:* Baseline anti-tumor efficacy (i.e., bone marrow biopsy) will be obtained within 2 weeks prior to the first dose of treatment cycle 1. Follow-up anti-tumor efficacy will be obtained on day 14 of cycle 1. In patients treated with additional treatment cycles beyond Cycle 1, anti-tumor efficacy will be assessed upon count recovery (defined as ANC>1000, freedom from RBC transfusions and platelets>100k) or day 42 from the first day of the cycle whichever comes first. Anti-tumor efficacy assessment will also be based on investigator and institutional routine monitoring of the disease progression of the patients, together with baseline evaluations performed prior to treatment with CPI-613. During maintenance therapy anti-tumor efficacy will be assessed after every 4<sup>th</sup> cycle.

*Optional Sampling and “Banking” of Blood, Plasma, urine and Bone Marrow Biopsy Samples:* Optional blood samples (5 mL), urine (5-10 ml) as well as bone marrow via biopsy (if deemed appropriate by physician), will be obtained and “banked” for possible testing of biomarkers, predictors of biological responses, toxicity, relationship between genotype and drug responses, etc. These samples will be obtained prior to treatment initiation, as well as prior to and following administration of CPI-613 during salvage Cycle 1. The specific procedures are outlined below.

#### Whole Blood Sample

- One (5 mL) Lavendar Top K EDTA Vacutainer Tube will be used.

- Do not centrifuge or freeze sample.
- Label sample and store at refrigerated temperature (2-8°C).
- Samples will be shipped on ice pack to the address shown at the bottom of this section.

Fresh Bone Marrow Biopsy for Banking of Tumor Cells

- Samples will be collected into a green top lithium heparin tube. Harvested fresh tumor specimens are placed on ice and shipped to the address below. (Note the tumor bank will Ficoll separate mononuclear cells and freeze aliquots in RPMI media containing 10% DMSO.)

Urine Samples

Urine samples will be collected from the first void after the first infusion of CPI-613 in the first induction cycle only. Details of the collection will be recorded on Appendix G.

- Approximately 5-10 ml of urine will be collected in a 15 mL conical tube
- The tube will placed at 4°C until placed into the Tumor Tissue Core Facility (see below)

All optional samples and specimens should be shipped to:

Wake Forest Cancer Center  
Tumor Tissue Core Facility  
Care of Dr. Greg Kucera  
Hanes Building Rm 4049  
Medical Center Blvd  
Winston-Salem NC 27157

## 5.7 Specifics of Tests Performed During the Study

*ECOG PS:* The ECOG performance status (see Table below) will be used to classify patient's functional impairment. The higher the score, the worse the survival for most serious illnesses including AML.

### ECOG Performance Scale (EPS)

| Score    | Definition   |
|----------|--|
| <b>0</b> | Fully active, able to carry on all pre-disease performance without restriction   |
| <b>1</b> | Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light house work, office work. |
| <b>2</b> | Ambulatory and capable of all self-care but unable to carry out any work activities. Up and about more than 50% of waking hours.                           |
| <b>3</b> | Capable of only limited self-care, confined to bed or chair more than 50% of waking hours.   |
| <b>4</b> | Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair.  |
| <b>5</b> | Dead.  |

CCCWFU 22215

Comprehensive Cancer Center of Wake Forest University

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Mitoxantrone in Patients with Relapsed or Refractory Acute Myeloid Leukemia (AML)

**NCT Clinicaltrials.gov:** NCT02484391

*Lab Studies:* Clinical chemistry assessed includes the following parameters.

Renal function will be assessed utilizing the Cockcroft-Gault formula.

|                  |  |
|------------------|--|
| glucose          | uric acid  |
| creatinine       | blood urea nitrogen (BUN)                          |
| total protein    | AST/serum glutamic-oxaloacetic transaminase (SGOT) |
| albumin          | ALT/serum glutamic-pyruvic transaminase (SGPT)     |
| Na <sup>+</sup>  | alkaline phosphatase (ALP)                         |
| K <sup>+</sup>   | lactate dehydrogenase (LDH)                        |
| Cl <sup>-</sup>  | total bilirubin                                    |
| Mg               |  |
| Ca <sup>+2</sup> |  |
| PO <sub>4</sub>  |  |
| CO <sub>2</sub>  |  |

Hematology includes:

Complete blood count with differential

Coagulation includes:

|     |                             |
|-----|-----------------------------|
| INR | partial thromboplastin time |
|-----|-----------------------------|

## 5.8 Future Research

Optional blood samples will be collected before and at various times after the 1<sup>st</sup> dose of CPI-613. Provisions should be made to record and report the actual clock times when samples are drawn. Whenever possible samples should be taken 5 minutes before and at completion of the infusion of CPI-613 on day 1 and at 2, 4 and 6 hours after the completion of the infusion. Blood (5 mL for each sample) should be obtained from an IV catheter that is not used for administration of CPI-613. The blood samples should be collected in 5-mL lavender top collection tubes containing K2- or K3-EDTA anticoagulant. Immediately after blood collection, gently invert tube 3 times to ensure proper mixing of blood and anticoagulant. Blood should then be immediately placed at 4 degrees Celsius. Additionally, several milliliters of urine from the first void following completion of the CPI-613 infusion on day one will be collected in consenting subjects. Once collected 5-10 ml of urine should be placed in a 15 ml conical tube and placed at 4 degrees Celsius until it can be sent to the tumor tissue core facility (see below).

When all samples have been collected, they should be sent to:

Wake Forest Cancer Center  
Tumor Tissue Core Facility  
Care of Dr. Greg Kucera  
Hanes Building Rm 4049  
Medical Center Blvd  
Winston-Salem NC 27157

Email: [gkucera@wakehealth.edu](mailto:gkucera@wakehealth.edu)

### **5.9 Criteria for Removal from Study**

Listed below are criteria for the discontinuation of the study. However, patients who fail to return for the follow-up visits will be contacted and queried as to the reason they have failed to complete the study with special attention to health status.

- A. Patients have the right to withdraw from the study at any time for any reason.
- B. The investigator has the right to withdraw patients from the study according to his/her discretion, if the investigator determines that continued participation is not in the patient's best interest. As an excessive rate of withdrawals can render the study not interpretable, unnecessary withdrawal of patients should be avoided. When a patient discontinues investigational treatment, the investigator should make every effort to contact the patient and to perform a final evaluation. The reason(s) for withdrawal must be recorded. Criteria for terminating subject's participation in the study are listed below:
  - Protocol defined disease progression significantly greater than expected
  - Unacceptable toxicity of the investigational product
  - Patient withdrawal of consent
  - Investigator's discretion
  - Undercurrent illness: a condition, injury, or disease unrelated to the intended disease for which the study is investigating, that renders continuing the treatment unsafe or regular follow-up impossible
  - General or specific changes in the patient's condition that renders the patient ineligible for further investigational treatment
  - Non-compliance with investigational treatment, protocol-required evaluations or follow-up visits
  - Termination of the clinical trial by the sponsor

### **6.0 Dosing Delays/Dose Modifications for CPI-613**

The occurrence of Grade 1 toxicity does not generally require dose modification for subsequent doses for that patient. However, if Grade 2 non-hematologic, non-infectious toxicity develops attributed as at least probably related to CPI-613, treatment can resume only after the Grade 2 toxicity has been reduced to Grade 1 or below, and the dose level for subsequent doses for that patient will be reduced by 25% of the dose at which such Grade 2 toxicity occur. If Grade 3 or 4 non-hematologic, non-infectious toxicity develops, dosing of that patient will be withheld and the patient shall be monitored for recovery from, and reversibility of, such Grade 3 or 4 toxicity. To resume treatment for a patient who has had Grade 3 or 4 toxicity, the Grade 3 or 4 toxicity must be reduced to Grade 1 or below, and the dose level for subsequent doses for that patient will be reduced

to 50% of the dose at which such Grade 3 or 4 toxicity occur. If the reduced dose of CPI-613 results in no toxicity, patients may be dose escalated to the prior dose at the discretion of the treating physician.

Dose adjustments during maintenance therapy will be done as described above with the addition that should patients experience hematologic toxicity  $\geq$  Grade 2 attributed to CPI-613 the next dose of maintenance therapy must be held until the Grade 2 toxicity has been reduced to Grade 1 or below, and the dose level for subsequent doses for that patient will be reduced by 25% of the dose at which such Grade 2 toxicity occurred. If Grade 3 or 4 hematologic toxicity develops, dosing of that patient will be withheld and the patient shall be monitored for recovery from, and reversibility of, such Grade 3 or 4 hematologic toxicity. To resume treatment for a patient who has had Grade 3 or 4 hematologic toxicity, the Grade 3 or 4 hematologic toxicity must be reduced to Grade 1 or below, and the dose level for subsequent doses for that patient will be reduced to 50% of the dose at which such Grade 3 or 4 hematologic toxicity occurred. If the reduced dose of CPI-613 results in no toxicity, patients may be dose escalated to the prior dose at the discretion of the treating physician.

## 7.0 Adverse Events List and Reporting Requirements

Given the severe nature of the disease and treatment modalities associated with this patient population, any adverse event lower than grade 3 during a patient's treatment AE evaluation period will not be part of data analysis or subject to expedited reporting.

### 7.1 Adverse Event Characteristics

- **CTCAE term (AE description) and grade:** The CTEP Active Version of the NCI Common Terminology Criteria for Adverse Events (CTCAE 4.0) will be utilized for AE reporting. The CTEP Active Version of the CTCAE is identified and located on the CTEP website at [http://ctep.cancer.gov/protocolDevelopment/electronic\\_applications/ctc.htm](http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm). All appropriate treatment areas should have access to a copy of the CTEP Active Version of CTCAE.
- **‘Expectedness’:** AEs can be ‘Unexpected’ or ‘Expected’ (see Section 7.1 above) for expedited reporting purposes only.
- **Attribution** of the AE:
  - Definite – The AE is *clearly related* to the study treatment.
  - Probable – The AE is *likely related* to the study treatment.
  - Possible – The AE *may be related* to the study treatment.
  - Unlikely – The AE is *doubtfully related* to the study treatment.
  - Unrelated – The AE is *clearly NOT related* to the study treatment.

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**List of Adverse Events to be Reported:**

- \*Abdominal pain
- \*Creatinine
- \*Diarrhea
- \*Injection site Reaction
- \*Nausea
- \*Vomiting

All adverse events should be reported on the adverse event log and in ORIS regardless of whether they are on this list.

Asterisk (\*) denotes expected Adverse Events.

All SAEs are required to be reported to Rafael Pharmaceuticals via the provided SAE Reporting Form. All completed forms must be sent to Claudia Moore at Rafael. The Comprehensive Cancer Center of Wake Forest University will submit any applicable SAEs to the FDA.

SAE reports must be submitted to Rafael by fax to the following address:

Department of Regulatory and Clinical Affairs  
Rafael Pharmaceuticals, Inc.  
25 Health Sciences Drive  
Stony Brook, NY 11790  
Telephone: 631-444-6868  
Telefax: 631-794-2319

**7.2 STRC SAE Reporting Requirements**

The Safety and Toxicity Review Committee (STRC) is responsible for reviewing SAEs for CCCWFU Institutional studies as outlined in Appendix B. STRC currently requires that all unexpected grade 4 and all grade 5 SAE's on these trials be reported to them for review. This procedure is a part of the CCCWFU Data Safety Monitoring Plan that our institution has on file at the NCI. All CRM staff members assisting a PI in investigating, documenting and reporting an SAE qualifying for STRC reporting are responsible for informing a clinical member of the STRC committee as well as the entire committee via the email notification procedure of the occurrence of an SAE.

**7.3 WFUHS IRB AE Reporting Requirements**

Any unanticipated problems involving risks to subjects or others and adverse events shall be promptly reported to the IRB, according to institutional policy. Reporting to the IRB is required regardless of the funding source, study sponsor, or whether the event involves an investigational or marketed drug, biologic or device. Reportable events are not limited to physical injury, but include psychological, economic and social harm. Reportable events may arise as a result

of drugs, biological agents, devices, procedures or other interventions, or as a result of questionnaires, surveys, observations or other interactions with research subjects.

All members of the research team are responsible for the appropriate reporting to the IRB and other applicable parties of unanticipated problems involving risk to subjects or others. The Principal Investigator, however, is ultimately responsible for ensuring the prompt reporting of unanticipated problems involving risk to subjects or others to the IRB. The Principal Investigator is also responsible for ensuring that all reported unanticipated risks to subjects and others which they receive are reviewed to determine whether the report represents a change in the risks and/or benefits to study participants, and whether any changes in the informed consent, protocol or other study-related documents are required.

Any unanticipated problems involving risks to subjects or others occurring at a site where the study has been approved by the WFUHS IRB (internal events) must be reported to the WFUHS IRB within 7 calendar days of the investigator or other members of the study team becoming aware of the event.

Any unanticipated problems involving risks to subjects or others occurring at another site conducting the same study that has been approved by the WFUHS IRB (external events) must be reported to the WFUHS IRB within 7 calendar days of the investigator or other members of the study team becoming aware of the event.

Any event, incident, experience, or outcome that alters the risk versus potential benefit of the research and as a result warrants a substantive change in the research protocol or informed consent process/document in order to insure the safety, rights or welfare of research subjects.

## 8.0 Pharmaceutical Information

### 8.1 Pharmaceutical Accountability

Drug accountability logs will be maintained for all investigative agents used under this protocol. These logs shall record quantities of study drug received and quantities dispensed to patients, including lot number, date dispensed, patient identifier number, patient initials, protocol number, dose, quantity returned, balance remaining, and the initials of the person dispensing the medication.

### 8.2 Study Drug

#### Various Names of Investigational Drug

Chemical Name:

6,8-bis-benzylsulfanyloctanoic acid

Alternative Name:

6,8-bis(benzylthio)octanoic acid; or

6,8-bis-benzylsulfonyloctanoic acid

|                                      |  |
|--------------------------------------|--|
| Chemical Abstract Society (CAS) No.: | 95809-78-2   |
| Pharmacologic Class:                 | altered energy metabolism-directed (AEMD) compound |
| Code Name:                           | CPI-613  |
| Trade Name:                          | Bylantra (tentative)                               |
| Generic Name:                        | None   |

#### Description of CPI-613 Drug Product

CPI-613 is provided in 10-mL amber glass vials. Each 10-mL vial contains 10 mL of CPI-613 at a concentration of 50 mg/mL (in 1M triethanolamine [TEA, also called trolamine]), which is equivalent to 500 mg of CPI-613. The drug product of CPI-613 is a clear and colorless solution that is free of any particulate matter.

#### Handling of CPI-613

CPI-613 is an investigational drug and the toxicity in humans is not fully understood. All necessary precautions in handling potentially toxic chemicals must be strictly adhered to. Gloves and protective clothing must be worn when handling CPI-613. Avoid contact by all modes of exposure. If the solution contacts the skin, it must be washed immediately and thoroughly with soap and water. If the solution comes in contact with mucous membranes, the membranes must be flushed thoroughly with water. Spills should be picked up with absorbent material and the area must be washed at least 3 times with ethyl alcohol followed by water.

CPI-613 drug product is slightly photosensitive (Study# PHO-001). Therefore, after removal of CPI-613 drug product from the amber vials, CPI-613 drug product should be protected from excessive light before administration to patients.

#### Storage of CPI-613

CPI-613 should be stored under refrigeration, at 2°-8°C (36°-46°F), except when being prepared for administration.

If CPI-613 is to be transferred from one storage area to another, or is to be prepared for dosing, care must be taken to maintain appropriate product temperature.

UNDER NO CIRCUMSTANCES SHOULD CPI-613 BE FROZEN.

#### IV Infusion Sets, Syringes and IV Bags to be Used for Administration of CPI-613

CPI-613 must be administered IV by infusion, via a central IV catheter with D5W running at a rate of about 125-150 mL/hr. Subsequent sections describe the appropriate types of IV catheters, IV bags, syringes and clinical solutions that can be used in mixing and administering CPI-613 to patients.

Leaching of Diethylhexyl Phthalate (DEHP): CPI-613 can cause leaching of DEHP from IV infusion sets and IV bags (Study COM-003). Therefore, DEHP-containing IV infusion sets, IV bags or syringes should not be used in mixing or administration of CPI-613. Examples of syringes and extension set for syringe pump that do not contain DEHP (and therefore can be used in the administration of CPI-613) are:

Syringes: Kendall Monoject syringes, all mono-ject syringes are DEHP free.

Extension Set for Syringe Pump Use: All extension sets from MED-RX do not contain DEHP.

IV Infusion Sets: A compatibility study has been conducted showing that CPI-613 is compatible with 4 commonly used IV infusion sets (Study# COM-001). Therefore, these 4 types of IV infusion sets, and IV infusion sets that are made with the same materials, can be used to administer CPI-613. These IV infusion sets are:

PVC material - ADDitIV® Primary IV Set with Universal Spike, Backcheck Valve, 2 Injection Sites, DEHP-Free and Latex-Free, 15 drops/mL, REF V14453, B Braun Medical Inc.

Latex material - Interlink® System Secondary Medication Set, 10 drops/mL, 2C7451, Baxter Healthcare Corporation

PVC material - Surshield™ Safety Winged Infusion Set, 0.19 mL Volume, Latex-Free, DEHP-Free, SV\*S25BLS, Terumo Medical Products Hangzhou Co. Ltd.

Polyethylene material - Interlink® System Paclitaxel Set by Baxter HealthCare, Non DEHP: Polyethylene tubing with a 0.22 microfilter Item # 2C7558 10 drops/mL

Syringes: Compatibility studies (Studies# COM-001 and COM-002) have shown that CPI-613 drug product (50 mg/mL), and drug product diluted with D5W to various concentrations (1.6-25 mg/mL) are compatible with various types of syringes, as listed below. Therefore, any of these types of syringes, and syringes that are made with the same materials, can be used to administer CPI-613. Also, glass syringes can also be used, since glass (such as glass containers) is compatible with CPI-613 drug product.

Norm-Ject, polythelyene barrel, polyethylene plunger, latex free (Henke Sass Wolf GMBH) syringes  
Becton Dickinson syringes  
Terumo syringes  
Monoject syringes  
Glass syringes

Reconstitution and Administration of CPI-613

CPI-613 must be diluted from 50 mg/mL to 12.5 mg/mL with 5% Dextrose Water or D5W (i.e., 1 portion of CPI-613 diluted with 3 portions of D5W) prior to administration. The diluted drug product should be visually inspected for clarity. If haziness or precipitate is observed, do not use the diluted drug product for dosing. After dilution with sterile D5W, the solution is clear and has a pH of 8.4-8.8. The diluted CPI-613 drug product has been found to be stable for 24 hrs at room temperature and refrigeration temperature (Studies STA-010).

CPI-613 must be administered IV, via a central venous catheter that is free flowing, free of air in the dead space, and with D5W running at a rate of about 125-150 mL/hr. This is to minimize vascular irritation, inflammation and acute toxicity of CPI-613 (Study NCL-049). Accidental co-administration of extra air in the dead space of IV catheters during administration of CPI-613 has demonstrated the potential to induce acute toxicity of CPI-613 according to animal studies (Study NCL-049). Also, accidental leakage of CPI-613 into the perivascular space during IV administration, which prolongs exposure of perivascular tissue to CPI-613, can induce significant local inflammation according to animal studies (Studies NCL-027 and NCL-030).

CPI-613 must not be administered as a bolus, but by infusion via a central venous catheter, over a total of 2 hours. All doses of CPI-613 will be administered over 2 hours to simplify PK/PD analysis. The infusion will also minimize potential acute toxicity of CPI-613, according to animal studies (Study NCL-049). The following precautions must be taken when administering CPI-613:

- A. Confirmation of the placement of the IV line to ensure a lack of leakage of CPI-613 into the perivascular space.
- B. Confirmation that the IV line is free flowing, and with D5W running at a rate of about 125-150 mL/hr.
- C. Confirmation that the IV line is free of dead air space.
- D. Rotate the site of administration for different doses of CPI-613.
- E. Dilute CPI-613 drug product with D5W, as instructed in the study protocol.
- F. Administer CPI-613 by infusion, not as a bolus.

G. After administration of CPI-613, “slowly” flush the IV line with ~10 mL of D5W to remove residual CPI-613.

*Request for CPI-613*

CPI-613 must be requested from Rafael by the Principal Investigator (or authorized designees). CPI-613 may not be used outside the scope of this protocol, nor can it be transferred or licensed to any party not participating in this clinical study. Rafael policy requires that CPI-613 be shipped directly to the institution where the patient is to be treated. Rafael does not permit the transfer of CPI-613 between institutions (unless with prior written approval from Rafael). Requests must be submitted to Rafael by fax or email to the following address:

Department of Regulatory and Clinical Affairs  
Rafael Pharmaceuticals, Inc.  
1 Duncan Dr  
Cranbury NJ 08512  
Telephone: 631-444-6868  
Telefax: 631-794-2319  
Email: [sanjeev@Rafaelpharma.com](mailto:sanjeev@Rafaelpharma.com)

The following information must be provided in the request of CPI-613 from Rafael:

- Names of the principal investigator and the requestor (if different)
- Name of the study site
- Name of the pharmacist responsible for receiving and storing CPI-613
- Name of the person and address where CPI-613 is to be shipped to
- Amount (# vials) requested
- Date of request
- Date shipment expected
- Study Protocol (title and protocol#) for which the requested CPI-613 is to be used

*Procurement of Investigational Drug*

Relevant regulations require investigators to establish a record of the receipt, use and disposition of all investigational products. Investigators may delegate responsibility of drug ordering, storage, accountability and preparation to their designees.

The investigator, or the designee, will be responsible for dispensing and accounting of CPI-613 provided by Rafael and for exercising accepted medical and pharmacy practices.

Records of inventory, dispensation and disposition (vials received, source and dates) must be maintained. In addition, all doses dispensed should be accounted for by recording the date, study number and name, patient identification, patient initials, patient medical record number and balance forward. These records must be maintained and kept at the study site, and will be reviewed by Rafael, or its designee, during periodic monitoring visits.

#### Disposal of CPI-613

The following procedures are to be taken in disposal of CPI-613:

- During the study, store the used CPI-613 vials (which must be separate from the unused CPI-613 vials) at room temperature in an access-limited area. Alternatively, destroy the used CPI-613 vials according to institutional policy after documentation of the number of used CPI-613 vials and remaining volume in each used vial.
- At the end of the study, deface the label (both used and unused vials) with a permanent marking pen.
- For used CPI-613 vials (if not already destroyed according to institutional policy), after documentation of the number of used CPI-613 units and remaining volume in each container, the used containers should be destroyed at the site according to the institutional procedures for destroying toxic chemicals. A certificate documenting the destruction of used vials must be kept on file.
- All unused CPI-613 vials must be returned to Rafael at the address shown below. (Note: The return of the CPI-613 to Rafael, as well as the quantity returned, must be documented.)

Department of Regulatory and Clinical Affairs  
Rafael Pharmaceuticals, Inc.  
25 Health Sciences Drive  
Stony Brook, NY 11790  
Telephone: 631-444-6868  
Telefax: 631-794-2319  
Email: king@Rafaelpharma.com

## **9.0 Measurement of Effect**

### **9.1 Antitumor Effect**

Although response is not the primary endpoint of this trial, patients with measurable disease will be assessed by standard criteria for AML (*Blood*).

2010;115:453-474). Peripheral blood (PB) cell counts and samples of bone marrow aspirates will be assessed for changes in disease status. Hematologic improvement (HI) requires improvement in one of the three hematopoietic lineages compared with baseline measurements, and stable disease (SD) requires the absence of objective disease progression for at least 2 months. Relevant responses have to be confirmed by a repeat measurement at least 1 wk later. Assessments will be done as described above.

### 9.1.1 Definitions

Evaluable for toxicity. All patients will be evaluable for toxicity from the time of their first treatment with CPI-613.

Evaluable for objective response. Only those patients who have measurable disease present at baseline, have received at least one cycle of therapy, and have had their disease re-evaluated will be considered evaluable for response. These patients will have their response classified according to the definitions stated above. (Note: Patients who exhibit objective disease progression prior to the end of cycle 1 will also be considered evaluable.)

Overall Survival (OS): Time from enrollment on trial to death from any cause.

## 10.0 Statistical Considerations

This is a pilot trial investigating three doses of CPI-613 (500, 1500, and 2,000 mg/m<sup>2</sup>). We plan to accrue between 10 and 15 patients per year for a total of 67 patients (20 at 500, 1,500 mg/m<sup>2</sup> and 3 additional patients at 2,000 mg/m<sup>2</sup>). Of note 17 patients at 2,000 mg/m<sup>2</sup> and 7 patients at 2,500 mg/m<sup>2</sup> were already accrued.

### Analysis Plan:

The primary objective of determining the feasibility of administering CPI-613 in combination with high dose cytarabine and mitoxantrone during induction, consolidation and maintenance therapies will be completed by determining the percentage of patients eligible for maintenance therapy who complete at least 3 cycles. If  $\geq 50\%$  of eligible patients complete 3 cycles of maintenance therapy we will consider this regimen feasible for future study. Given an estimated response rate of 50% and a 25% attrition to stem cell transplant, if we enroll 60 patients we should be able to assess feasibility of maintenance in approximately 22 patients. With 22 evaluable patients, a two-sided 95.0% confidence interval using the large sample normal approximation will extend 22% in either direction from the observed value when the expected value is 50%. Within a dose we should be able to estimate feasibility in 7 patients with a 95% confidence interval extending 36% in either direction.

Participants will also be followed and analyzed for secondary outcomes of response rate and overall survival both overall and by dose. Participants will be monitored for survival through routine follow-up visits. Confidence intervals will be calculated around the estimates of the response rate (CR and CRi). Assuming a response rate of 0.5, with 60 participants, we would be able to create 95 percent confidence intervals with a 0.13 margin of error (0.37, 0.63). We will use Kaplan-Meier estimation to analyze overall survival. The frequency of toxicities experienced by the participants will be presented by type and grade in an effort to monitor and report safety of the treatment.

In exploratory analysis we plan to compare both complete response and early mortality (death within 60 days of beginning of treatment) to the observed rates in a historical cohort of subjects (CCCFWFU 22111), both overall and by dose. In the historical cohort the response rate was estimated to be 41%. Using a one-sided chi-square test, a 0.05 significance level, null hypothesis of 41%, and assuming 70% power, we would be able to show significant improvement in response if we are able to achieve a response rate of 56% or higher. Early mortality in the historical cohort was estimated to be 29% at 60 days. We will use a one-sided exact test for a single proportion, a 0.05 significance level, a null hypothesis of 29%, and 70% power. To show a significant decrease in early mortality in this study we would need to observe a 60 day mortality rate of 16.8% or lower.

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Study COM-002. Bhasin R. 2008. Compatibility Testing of CPI-613 Drug Product Dosing Solutions with Different Types of Syringes.

Study COM-003. Gupta D. 2009. Investigation of the Release Behavior of Diethylhexyl Phthalate (DEHP) from the Polyvinyl-Chloride Containing Infusion Sets and Bags for Intravenous Administration by CPI-613 Drug Product.

Study CL-CPI613-002. Ongoing. An Open Label, Dose-Escalation Study to Evaluate Safety, Tolerability, Maximum Tolerated Dose (MTD), Efficacy, and Pharmacokinetics (PKs) of CPI-613 Given Twice Weekly for Three Consecutive Weeks in Cancer Patients.

Study NCL-027. Seng J. 2006. Escalating Dose Toxicology Study of Intravenously Administered CPI-613 to Miniature Pigs.

Study NCL-030. Seng J. 2006. An Acute Toxicity Study of CPI-613 Administered Via the intravenous (Slow Bolus) Route to Mice.

Study NCL-044. Seng J. 2007. A 21-Day Toxicokinetic Study of CPI-613 Administered Twice Weekly via the Intravenous Route to Sprague-Dawley Rats with a 14-Day Recovery Period.

Study NCL-045. Seng J. 2008. Evaluation of the Toxicity Potential of CPI-613, Given Twice Weekly for 3 Weeks by Intravenous Administration, in Hanford Minipigs with a 14-Day Recovery Period.

Study NCL-049. Moore C, Karnik S, Lee K. 2007. Preliminary Studies of Comparative Toxicity of CPI-613 Administered Intravenously (IV) as Bolus Vs. Infusion, Effects of Air in Dead Space of Butterfly IV Infusion Set on Toxicity of CPI-613, and Acute Effects of CPI-613 on Clinical Chemistry in Rats.

Study PHO-001 (Covance Study# 7769-101). Potts B. 2007. Photostability Testing of CPI-613 Drug Product.

Study STA-004. (CR Study# LRH00017SX). McFarlene J. 2006. Long Term Matrix Stability Assessment of CPI-613 in K2 EDTA and K3 EDTA Human Plasma.

Study STA-010. Bhasin R. 2007. Stability of CPI-613 Injection dosing solutions after Dilution with 5% Dextrose (D5W).

Study VLD-002 (CR Study# LRH00016LX). McFarlene J. 2006. Validation of a High Performance Liquid Chromatographic-Mass Spectrometric Method for the Analysis of CPI-613 in K3 and K2 EDTA Human Plasma.

Yamada J, Tomiyama H, et. al. 2006. Elevated serum levels of alanine aminotransferase and gamma glutamyltransferase are markers of inflammation and oxidative stress independent of the metabolic syndrome. Atherosclerosis. 189(1):198-205.

## APPENDIX A – REGISTRATION GUIDELINES

The following guidelines have been developed in order to ensure timely registration of your patient.

All patients entered on any CCCWFU trial, whether treatment, companion, or cancer control trial, **must** be linked to the study in EPIC within 24 hours of Informed Consent . Patients **must** be registered prior to the initiation of treatment.

In order to ensure prompt registration of your patient, please:

5. Complete the Eligibility Checklist (attached)
6. Complete the Protocol Registration Form (attached)
7. Alert the WFUHS registrar by phone, *and then* send the signed Informed Consent Form, Eligibility Checklist and Protocol Registration Form to the registrar, either by fax or e-mail.

### Contact Information:

Protocol Registrar PHONE (336) 713-6767

Protocol Registrar FAX (336) 713-6772

Protocol Registrar E-MAIL ([registra@wakehealth.edu](mailto:registra@wakehealth.edu))

\*Protocol Registration is open from 8:30 AM - 4:00 PM, Monday-Friday.

8. Please fax/e-mail ALL eligibility source documents with registration. Patients **will not** be registered without all required supporting documents.

Note: If labs were performed at an outside institution, please provide a printout of the results. Please ensure that the most recent lab values are sent.

## CCCWFU # 22215 Eligibility Checklist

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| Yes                      | No                       | N/A                      | Inclusion Criteria (All responses must be YES in order to enter study)  | Eligibility Confirmation (registrar) |
|--------------------------|--------------------------|--------------------------|---|--------------------------------------|
| <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | Patients must have histologically or cytologically documented relapsed and/or refractory Acute Myeloid Leukemia or granulocytic sarcoma.  |                                      |
| <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | ECOG Performance Status of $\leq 3$ .   |                                      |
| <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | Must be $\geq 18$ years of age.   |                                      |
| <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | Expected survival $>3$ months.  |                                      |
| <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | Women of child-bearing potential (i.e., women who are pre-menopausal or not surgically sterile) must use accepted contraceptive methods (abstinence, intrauterine device [IUD], oral contraceptive or double barrier device), and must have a negative serum or urine pregnancy test within 1 week prior to treatment initiation.<br>Pregnancy Test: Positive or Negative   |                                      |
| <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | Fertile men must practice effective contraceptive methods during the study period, unless documentation of infertility exists.  |                                      |
| <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | Mentally competent, ability to understand and willingness to sign the informed consent form.  |                                      |
| <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | No radiotherapy, treatment with cytotoxic agents (except CPI-613), treatment with biologic agents or any anti-cancer therapy within the 2 weeks prior to treatment with CPI-613. Hydroxyurea and oral tyrosine kinase inhibitors being used without Grade $\leq 2$ toxicity can be taken until day 1 of therapy. Patients must have fully recovered from the acute, non-hematological, non-infectious toxicities of any prior treatment with cytotoxic drugs, radiotherapy or other anti-cancer modalities (returned to baseline status as noted before most recent treatment). Patients with persisting, non-hematologic, non-infectious toxicities from prior treatment $\leq$ Grade 2 are eligible, but must be documented as such |                                      |
| <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | Laboratory values $\leq 2$ weeks must be:   |                                      |
| <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <ul style="list-style-type: none"> <li>• Adequate hepatic function (aspartate aminotransferase [AST/SGOT] <math>\leq 3</math> x upper normal limit [UNL])</li> </ul>  |                                      |
| <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <ul style="list-style-type: none"> <li>• alanine aminotransferase [ALT/SGPT] <math>\leq 3</math> x UNL (<math>\leq 5</math> x UNL if liver metastases present)</li> </ul>   |                                      |
| <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <ul style="list-style-type: none"> <li>• bilirubin <math>\leq 1.5</math> x UNL</li> </ul>   |                                      |
| <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <ul style="list-style-type: none"> <li>• Adequate renal function (serum creatinine <math>\leq 1.5</math> mg/dL or 133 <math>\mu</math>mol/L).</li> </ul>  |                                      |
| <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <ul style="list-style-type: none"> <li>• Left Ventricular Ejection Fraction (by TTE, MUGA or cardiac MRI) sufficient to safely administer mitoxantrone as determined by the treating physician</li> </ul>   |                                      |
| Yes                      | No                       | N/A                      | Exclusion Criteria (All responses must be NO in order to enter study)   |                                      |
| <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | Serious medical illness, such as significant cardiac disease (e.g. symptomatic congestive heart failure, unstable angina pectoris, myocardial infarction within the past 6 months, uncontrolled cardiac arrhythmia, pericardial disease or New York Heart Association Class III or IV), or severe debilitating pulmonary disease, that would potentially increase patients' risk for toxicity   |                                      |
| <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | Patients with active central nervous system (CNS) or epidural tumor   |                                      |
| <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | Any active uncontrolled bleeding, and any patients with a bleeding diathesis (e.g., active peptic ulcer disease)  |                                      |

|                          |                          |                          |  |  |
|--------------------------|--------------------------|--------------------------|--|--|
| <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | Pregnant women, or women of child-bearing potential not using reliable means of contraception (because the teratogenic potential of CPI-613 is unknown)  |  |
| <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | Lactating females because the potential of excretion of CPI-613 into breast milk   |  |
| <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | Fertile men unwilling to practice contraceptive methods during the study period  |  |
| <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | Life expectancy less than 3 months   |  |
| <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | Any condition or abnormality which may, in the opinion of the investigator, compromise the safety of patients  |  |
| <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | Unwilling or unable to follow protocol requirements  |  |
| <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | Patients with large and recurrent pleural or peritoneal effusions requiring frequent drainage (e.g. weekly). Patients with any amount of clinically significant pericardial effusion   |  |
| <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | Active heart disease symptomatic coronary artery disease, uncontrolled arrhythmias, or symptomatic congestive heart failure  |  |
| <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | Albumin <2.0 g/dL or <20 g/L   |  |
| <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | Evidence of ongoing, uncontrolled infection.   |  |
| <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | Patients with known HIV infection  |  |
| <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | Patients receiving any other standard or investigational treatment for their cancer, or any other investigational agent for any indication within the past 2 weeks prior to initiation of CPI-613 treatment (the use of Hydrea is allowed) |  |
| <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | Patients who have received immunotherapy of any type within the past 4 weeks prior to initiation of CPI-613 treatment  |  |
| <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | Requirement for immediate palliative treatment of any kind including surgery   |  |
| <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | Patients that have received a chemotherapy regimen with stem cell support in the previous 6 months   |  |

This subject is  eligible /  ineligible for participation in this study.

ORIS Assigned PID: \_\_\_\_\_

Signature of research professional confirming eligibility: \_\_\_\_\_ Date: \_\_\_\_\_

Signature of Treating Physician: \_\_\_\_\_ Date: \_\_\_\_\_

Signature of Principal Investigator\*\*: \_\_\_\_\_ Date: \_\_\_\_\_

\* Examples of source documents include clinic note, pathology report, laboratory results, etc. When listing the source, specifically state which document in the medical record was used to assess eligibility. Also include the date on the document. Example: "Pathology report, 01/01/14" or "Clinic note, 01/01/14"

\*\*Principal Investigator signature can be obtained following registration if needed

**CCCWFU # 22215****Protocol Registration Form****Page 2****DEMOGRAPHICS**

Patient: Last Name: \_\_\_\_\_

First Name: \_\_\_\_\_

MRN: \_\_\_\_\_

DOB (mm/dd/yy): \_\_\_\_\_ / \_\_\_\_\_ / \_\_\_\_\_

SEX: \_\_\_\_\_

 Male Hispanic Female Non-Hispanic

Race (choose all that apply): \_\_\_\_\_

 WHITE       BLACK ASIAN PACIFIC ISLANDER NATIVE AMERICAN

Height: \_\_\_\_\_ inches

Weight: \_\_\_\_\_ lbs. (actual)

Surface Area: \_\_\_\_\_ m<sup>2</sup>

Zip Code: \_\_\_\_\_ (required if no MRN)

Primary Diagnosis: \_\_\_\_\_

Date of Diagnosis: \_\_\_\_\_ / \_\_\_\_\_ / \_\_\_\_\_

Dose assignment:  500mg/m<sup>2</sup>/day       1,500mg/m<sup>2</sup>/day (2,500mg/m<sup>2</sup>/day maintenance)**The following are required prior to registration:****CURRENT DISEASE STATUS AT REGISTRATION:** \_\_\_\_\_(1<sup>ST</sup> relapse, 2<sup>ND</sup> relapse, 3<sup>RD</sup> relapse, refractory etc., including allo or auto bone marrow transplant)

| Prior Therapies/<br>Protocol # if applicable | Start / End Date of<br>Prior Therapy | Best Response<br>(CR, PR,<br>Treatment Failure) | Date of<br>Best Response | Date of<br>Relapse | Duration of<br>Best Response<br>(in Months) |
|--|--------------------------------------|---|--------------------------|--------------------|---|
| #1 _____                                     | _____ / _____                        | _____   | _____                    | _____              | _____                                       |
| #2 _____                                     | _____ / _____                        | _____   | _____                    | _____              | _____                                       |
| #3 _____                                     | _____ / _____                        | _____   | _____                    | _____              | _____                                       |
| #4 _____                                     | _____ / _____                        | _____   | _____                    | _____              | _____                                       |

COMMENT: \_\_\_\_\_

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**PROTOCOL INFORMATION**

Date of Registration: \_\_\_\_\_ / \_\_\_\_\_ / \_\_\_\_\_

MD Name (last) : \_\_\_\_\_

Date protocol treatment starts: \_\_\_\_\_ / \_\_\_\_\_ / \_\_\_\_\_

Informed written consent: \_\_\_\_\_

 YES       NO

(consent must be signed prior to registration)

Date Consent Signed: \_\_\_\_\_ / \_\_\_\_\_ / \_\_\_\_\_

PID # (to be assigned by ORIS): \_\_\_\_\_

*Protocol Registrar can be contact by calling 336-713-6767 between 8:30 AM and 4:00 PM, Monday – Friday.*

*Completed Eligibility Checklist and Protocol Registration Form must be hand delivered, faxed or e-mailed to the registrar at 336-7136772 or [registra@wakehealth.edu](mailto:registra@wakehealth.edu)*

**CCCWFU # 22215 Eligibility Source Documentation Checklist  
(to be submitted with Protocol Registration Form)**

Page 3

| <b>Source Documents Needed</b> |   | ✓ or<br>N/A |
|--------------------------------|---|-------------|
| 1                              | Pathology report confirming patient has relapsed and/or refractory Acute Myeloid Leukemia   |             |
| 2                              | Documentation of ECOG Performance Status of $\leq 3$ .  |             |
| 3                              | Most recent H&P documenting patient is $\geq 18$ years of age   |             |
| 4                              | Documentation of expected survival $> 3$ months   |             |
| 5                              | Documentation that WOCBP agree to use accepted contraceptive methods  |             |
| 6                              | Negative serum or urine pregnancy test within 1 week prior to treatment initiation  |             |
| 7                              | Documentation that fertile men agree to practice effective contraceptive methods during the study period  |             |
| 8                              | Copies of all informed consent documents  |             |
| 9                              | Documentation of No radiotherapy, treatment with cytotoxic agents (except CPI-613), treatment with biologic agents or any anti-cancer therapy within the 2 weeks prior to treatment with CPI-613. Patients must have fully recovered from the acute, non-hematological, non-infectious toxicities of any prior treatment with cytotoxic drugs, radiotherapy or other anti-cancer modalities (returned to baseline status as noted before most recent treatment). Patients with persisting, non-hematologic, non-infectious toxicities from prior treatment $\leq$ Grade 2 are eligible, but must be documented as such. |             |
| 10                             | Lab report documenting all initial required lab values  |             |
| 11                             | Documentation that patient has no serious medical illness, such as significant cardiac disease (e.g. symptomatic congestive heart failure, unstable angina pectoris, myocardial infarction within the past 6 months, uncontrolled cardiac arrhythmia, pericardial disease or New York Heart Association Class III or IV), or severe debilitating pulmonary disease, that would potentially increase patients' risk for toxicity   |             |
| 12                             | Documentation that patient does not have an active central nervous system (CNS) or epidural tumor   |             |
| 13                             | Documentation that patient does not have any active uncontrolled bleeding, and any patients with a bleeding diathesis (e.g., active peptic ulcer disease).  |             |
| 14                             | Documentation that patient is not pregnant, lactating or a WOCBP not using reliable means of contraception  |             |
| 15                             | Documentation that patient is not a fertile man unwilling to practice contraceptive methods during the study period   |             |
| 16                             | Documentation that patient does not have a life expectancy less than 3 months.  |             |
| 17                             | Documentation that patient does not have any condition or abnormality which may, in the opinion of the investigator, compromise the safety of patients.   |             |
| 18                             | Documentation that patient is not unwilling or unable to follow protocol requirements.  |             |
| 19                             | Documentation that patient does not have large and recurrent pleural or peritoneal effusions requiring frequent drainage (e.g. weekly). Patients with any amount of clinically significant pericardial effusion.  |             |
| 20                             | Documentation that patient does not have active heart disease including myocardial infarction within previous 6 months, symptomatic coronary artery disease, uncontrolled arrhythmias, or symptomatic congestive heart failure.   |             |
| 21                             | Lab report showing Albumin $\geq 2.0$ g/dL or $\geq 20$ g/L.  |             |

|    |  |  |
|----|--|--|
| 22 | Documentation that patients do not have evidence of ongoing, uncontrolled infection.   |  |
| 23 | Documentation that patients do not have known HIV infection.   |  |
| 24 | Documentation that patient is not receiving any other standard or investigational treatment for their cancer, or any other investigational agent for any indication within the past 2 weeks prior to initiation of CPI-613 treatment (the use of Hydrea is allowed). |  |
| 25 | Documentation that patient has not received immunotherapy of any type within the past 4 weeks prior to initiation of CPI-613 treatment.  |  |
| 26 | Documentation that patient does not Require immediate palliative treatment of any kind including surgery.  |  |
| 27 | Documentation that patient has not received a chemotherapy regimen with stem cell support in the previous 6 months.  |  |
| 28 | Documentation that patient does not have A history of additional risk factors for torsade de pointes (e.g., clinically significant heart failure, hypokalemia, family history of Long QT Syndrome).  |  |

## APPENDIX B – Safety and Toxicity Review Committee SAE Reporting Guidelines

|   |                         |
|---|-------------------------|
| <b>Safety and Toxicity Review Committee (STRC; previously known as CROC) Serious Adverse Event (SAE) Notification SOP</b> | <b>Date: 11/17/2016</b> |
|---|-------------------------|

### Mandatory STRC SAE Reporting Requirements

This document describes STRC reporting and use of the electronic submission form that is submitted for **unexpected grade 4 and any grade 5 (death during protocol intervention) SAEs on CCCWFU Institutional interventional trial patients**. There are multiple entities that require reporting of SAEs. Each entity has different rules for what is reported, and how it is reported.

Rules used by other entities (Institutional Review Board (IRB), AdEERS, MedWatch, etc.) should NOT be used to evaluate whether an event should be reported to STRC. Only the rules for reporting described in this document should be considered.

As defined in the NCI Data Table 4 reporting guidelines, **CCCWFU Institutional Interventional studies covered by these reporting requirements are defined as: In-house, internally reviewed trials, including those collaborative studies conducted with industry sponsorship in which the center is a primary contributor to the design, implementation, and monitoring of the trial, or participation in a multi-site trial initiated by an institutional investigator at another center.** Institutional trials are almost always authored by a researcher here at CCCWFU. Institutional protocols are labeled NCI Code="I" for Institutional on the protocol screen in ORIS. Cooperative group protocols are **not** considered Institutional, but Research Base trials **are** classified as Institutional.

The STRC is responsible for reviewing SAEs for CCCWFU Institutional Interventional studies, as defined above. STRC currently requires that unexpected grade 4 and all grade 5 SAEs on these trials be reported to the STRC for review. All Clinical Protocol and Data Management (CPDM) staff members assisting a PI in documenting and reporting an SAE that qualifies for STRC reporting are responsible for informing a clinical member of the STRC by phone (or in-person), followed by informing the entire committee via the required email notification.

**THESE REPORTING REQUIREMENTS APPLY TO any faculty or staff member on the study team for a CCCWFU Institutional Interventional trial. Once an event is observed, it is the responsibility of the person who observed the event to be sure that it is reported.**

### What is considered an SAE under this mandatory procedure?

Any **unexpected grade 4** event and **all grade 5 events** (death during protocol intervention) should be reported. These events should be reported if they occur while a patient is on study treatment or if they occur within 30 days of last study treatment (even if patient begins a new treatment during the 30 days). This window of 30 days should be the standard window to be used in all protocols unless a specific scientific rationale is presented to suggest that a shorter window can be used to identify events. In addition, if it is not clear whether the Grade 4 is unexpected it should be reported.

**Table 1: Summary of STRC Reporting Requirements for Institutional Pilot, Phase 1, Phase 2 and Phase 3 Interventional Trials**

STRC reporting may not be appropriate for specific expected adverse events for protocols. In those situations the adverse events that will not require STRC reporting **must be specified in**

|                  | ADVERSE EVENT             |              |                       |              |                       |                       |
|------------------|---------------------------|--------------|-----------------------|--------------|-----------------------|-----------------------|
|                  | Grade 1, Grade 2, Grade 3 |              | Grade 4               |              | Grade 5               |                       |
|                  | Unexpected                | Expected     | Unexpected            | Expected     | Unexpected            | Expected              |
| <b>Unrelated</b> | Not Required              | Not Required | <b>REPORT TO STRC</b> | Not Required | <b>REPORT TO STRC</b> | <b>REPORT TO STRC</b> |
| <b>Unlikely</b>  | Not Required              | Not Required | <b>REPORT TO STRC</b> | Not Required | <b>REPORT TO STRC</b> | <b>REPORT TO STRC</b> |
| <b>Possible</b>  | Not Required              | Not Required | <b>REPORT TO STRC</b> | Not Required | <b>REPORT TO STRC</b> | <b>REPORT TO STRC</b> |
| <b>Probable</b>  | Not Required              | Not Required | <b>REPORT TO STRC</b> | Not Required | <b>REPORT TO STRC</b> | <b>REPORT TO STRC</b> |
| <b>Definite</b>  | Not Required              | Not Required | <b>REPORT TO STRC</b> | Not Required | <b>REPORT TO STRC</b> | <b>REPORT TO STRC</b> |

the text of the approved protocol.

**STRC notification responsibilities of the person handling the reporting/documenting of the SAE:**

1. Make a phone call (or speak in person) to the appropriate clinical member of the STRC as listed below (page if necessary)—see note 2 below
2. Submit the STRC Notification Form WITHIN 24 HOURS of first knowledge of the event. This form is found at either the ORIS main menu page or by going to <http://ccc.wfubmc.edu/oris/strc.aspx>.

This will ensure that all persons that need to be made aware of the event (i.e., study team members and STRC members) will be notified; remember to file a copy of your confirmation. (Form instructions will walk you through the required fields, consult the help page for further instructions.)

3. Ensure that you document that the appropriate person(s) on the STRC has been contacted. This documentation is placed on the STRC Notification form described above.
4. Follow up with/update the clinical member(s) of STRC regarding any new developments or information obtained during the course of the SAE investigation and reporting process.

**Elements to complete the electronic STRC form:**

**Please use 'reply to All' when responding with one of these terms: Definite, Probable, Possible, Unlikely, or Unrelated**

1. Patient ID (ORIS PID)
2. Patient Name
3. Patient MR#
4. CCCWFU(ORIS) Study Number
5. Title
6. PI Name
7. PI Contact Number
8. PI Comments
9. STRC Clinician notified by Phone
10. Notified Date
11. Notified Time
12. STRC Clinician Comments
13. Category [This is the Grade – Either Unexpected Grade 4 or Grade 5 should be entered]
14. Additional Information (IRB Reporting)(after discussion with PI or STRC Clinician)
  - i. Is This Event Related to Protocol Treatment?
  - ii. Is Suspension of the Protocol Needed?
  - iii. Any Changes to Consent or Protocol Needed?
  - iv. Was Nature or Severity of Event Unexpected?
15. Date of the event.
16. Brief description (include brief clinical history relevant to this event, including therapies believed related to event).
17. Date of Last Dose before event
18. Relevant tests/labs.
19. Other Relevant Treatment Information
20. Other Comments/Notes (include regimen of chemo and dates the patient received them if known).
21. Cc (email) (include treating Physician; separate email list with comma",")
22. Your Name
23. Your Email
24. Confirm Your Email

**The Clinical Members of STRC to Notify by Phone or Page:**

**Bayard Powell, MD** – Director-at-Large, CCCWFU; Section Head, Hematology/Oncology

6-7970 / 6-2701 / Pager 336-806-9308

**Glenn Lesser, MD** – Hematology Oncology 6-9527 / 6-7972 / Pager 336-806-8397

**Stefan Grant, MD, JD**-Hematology Oncology 3-5172/ 6-5772 Pager 336-806-6453

**Jimmy Ruiz, MD**-Hematology Oncology 6-0230/ Pager 336-806-9710

**Kathryn Greven, MD** – Vice Chair – Radiation Oncology

3-3600 / 3-6505 / Pager 336-806-8314

**Marissa Howard-McNatt, MD** – General Surgery 6-0545 / Pager 336-806-6438

**Mercedes Porosnicu, MD**- Hematology Oncology 6-7980 / 6-0230 / Pager 336-806-9150

**Definition of Unavailable:**

As a general guideline if the first clinician that is contacted does not respond to the phone call or page within a reasonable amount of time, then initiate contact with their backup. Give the back-up a reasonable amount of time to respond to a phone call or page before contacting another member. This is a general guideline. You must use your best judgment as a clinical research professional given the time of day, severity of the SAE, and other circumstances as to when it is appropriate to contact backup clinicians. If the event occurs near the end of day, then leave messages (voice or email) as appropriate and proceed with submitting your STRC notification form. The important criteria is that you have taken reasonable steps to notify and document that you have initiated some type of contact to one or more of the clinical members of STRC.

**STRC CLINICAN RESPONSIBILITY:**

It is the responsibility of the STRC clinician to review all reported events, evaluate the events as they are reported; and communicate a response to the Investigator, event reporter and the members of STRC. The review will include but not be limited to the information reported; there may be times when additional information is needed in order for an assessment to be made and further communication directly with the investigator may be warranted. STRC reserves the right to agree with the investigator's assessment if STRC does not agree with the investigator. STRC reserves the right to suspend the trial pending further investigation.

Is there any immediate danger or harm that could be present for a future patient based on the information provided in the STRC report – and if so an immediate suspension of enrollment should take place.

**AMENDMENTS TO PREVIOUS REPORTS**

If you are not able to supply all pertinent information with the initial submission, once the additional information is available **do not submit a new report**. Go to the original email that was received by STRC and others "reply to all" and entitle your email "**Amendment** for (list date of event and patient ID) this will avoid duplications of the same event. List the additional information which you are reporting.

**Acronyms and Definitions**

**STRC**-Safety and Toxicity Review Committee

CCCWFU 22215

Comprehensive Cancer Center of Wake Forest University

An Open Label Study to Evaluate the Feasibility of CPI-613 Given with High Dose Cytarabine and Mitoxantrone in Patients with Relapsed or Refractory Acute Myeloid Leukemia (AML)

NCT Clinicaltrials.gov: NCT02484391

**SAE**-Serious Adverse Event

**IRB**-Institutional Review Board

**CCCWFU**-Comprehensive Cancer Center Wake Forest University

**ORIS**-Oncology Research Information System

**NCI**-National Cancer Institute

**CPDM**-Clinical Protocol and Data Management

**Interventional Trials**-Therapeutic Level 1 and Level 2 trials

**Therapeutic Level 1**-A cancer treatment protocol aimed at directly treating/curing the patient's cancer.

**Therapeutic Level 2**-A therapeutic protocol not cancer treatment involves clinical activity to treat symptoms, improve the patient's quality of life, or prevent cancer.

## APPENDIX C- Response Criteria:

Table 5. Response criteria in AML

| Category                           | Definition   |
|------------------------------------|--|
| Complete remission (CR)*           | Bone marrow blasts < 5%; absence of blasts with Auer rods; absence of extramedullary disease; absolute neutrophil count $> 1.0 \times 10^9/L$ (1000/ $\mu$ L); platelet count $> 100 \times 10^9/L$ (100 000/ $\mu$ L); independence of red cell transfusions                                    |
| CR with incomplete recovery (CRI)† | All CR criteria except for residual neutropenia ( $< 1.0 \times 10^9/L$ [1000/ $\mu$ L]) or thrombocytopenia ( $< 100 \times 10^9/L$ [100 000/ $\mu$ L])   |
| Morphologic leukemia-free state‡   | Bone marrow blasts < 5%; absence of blasts with Auer rods; absence of extramedullary disease; no hematologic recovery required   |
| Partial remission (PR)             | Relevant in the setting of phase 1 and 2 clinical trials only; all hematologic criteria of CR; decrease of bone marrow blast percentage to 5% to 25%; and decrease of pretreatment bone marrow blast percentage by at least 50%  |
| Cytogenetic CR (CRc)§              | Reversion to a normal karyotype at the time of morphologic CR (or CRI) in cases with an abnormal karyotype at the time of diagnosis; based on the evaluation of 20 metaphase cells from bone marrow  |
| Molecular CR (CRm)                 | No standard definition; depends on molecular target  |
| Treatment failure                  |  |
| Resistant disease (RD)             | Failure to achieve CR or CRI (general practice; phase 2/3 trials), or failure to achieve CR, CRI, or PR (phase 1 trials); only includes patients surviving $\geq 7$ days following completion of initial treatment, with evidence of persistent leukemia by blood and/or bone marrow examination |
| Death in aplasia                   | Deaths occurring $\geq 7$ days following completion of initial treatment while cytopenic; with an aplastic or hypoplastic bone marrow obtained within 7 days of death, without evidence of persistent leukemia   |
| Death from indeterminate cause     | Deaths occurring before completion of therapy, or $< 7$ days following its completion; or deaths occurring $\geq 7$ days following completion of initial therapy with no blasts in the blood, but no bone marrow examination available   |
| Relapse¶                           | Bone marrow blasts $\geq 5\%$ ; or reappearance of blasts in the blood; or development of extramedullary disease   |

Definitions of response criteria are based primarily on those given by Cheson et al.<sup>2</sup>

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

†The criterion of CRI is of value in protocols using intensified induction or double induction strategies, in which hematologic recovery is not awaited, but intensive therapy will be continued. In such protocols, CR may even not be achieved in the course of the entire treatment plan. In these instances, the overall remission rate should include CR and CRI patients. Some patients may not achieve complete hematologic recovery upon longer observation times.

‡This category may be useful in the clinical development of novel agents within phase 1 clinical trials, in which a transient morphologic leukemia-free state may be achieved at the time of early response assessment.

§Four studies showed that failure to convert to a normal karyotype at the time of CR predicts inferior outcome.<sup>112-115</sup>

||As an example, in CBF AML low-level PCR-positivity can be detected in patients even in long-term remission. Normalizing to  $10^4$  copies of *ABL1* in accordance with standardized criteria, transcript levels below 12 to 10 copies appear to be predictive for long-term remission.<sup>108-110</sup>

¶In cases with low blast percentages (5-10%), a repeat marrow should be performed to confirm relapse. Appearance of new dysplastic changes should be closely monitored for emerging relapse. In a patient who has been recently treated, dysplasia or a transient increase in blasts may reflect a chemotherapy effect and recovery of hematopoiesis. Cytogenetics should be tested to distinguish true relapse from therapy-related MDS/AML.

Blood. 2010;115:453-474

## Include hematologic response criteria listed below

Table 4. Proposed modified International Working Group response criteria for hematologic improvement<sup>7</sup>

| Hematologic improvement*                                   | Response criteria (responses must last at least 8 wk)†  |
|--|---|
| Erythroid response (pretreatment, < 11 g/dL)               | Hgb increase by $\geq 1.5$ g/dL<br>Relevant reduction of units of RBC transfusions by an absolute number of at least 4 RBC transfusions/8 wk compared with the pretreatment transfusion number in the previous 8 wk. Only RBC transfusions given for a Hgb of $\leq 9.0$ g/dL pretreatment will count in the RBC transfusion response evaluation‡ |
| Platelet response (pretreatment, < $100 \times 10^9/L$ )   | Absolute increase of $\geq 30 \times 10^9/L$ for patients starting with $> 20 \times 10^9/L$ platelets<br>Increase from $< 20 \times 10^9/L$ to $> 20 \times 10^9/L$ and by at least 100%†  |
| Neutrophil response (pretreatment, < $1.0 \times 10^9/L$ ) | At least 100% increase and an absolute increase $> 0.5 \times 10^9/L$ †   |
| Progression or relapse after HI‡                           | At least 1 of the following:<br>At least 50% decrement from maximum response levels in granulocytes or platelets<br>Reduction in Hgb by $\geq 1.5$ g/dL<br>Transfusion dependence   |

Deletions to the IWG response criteria are not shown.

To convert hemoglobin levels from grams per deciliter to grams per liter, multiply grams per deciliter by 10.

Hgb indicates hemoglobin; RBC, red blood cell; HI, hematologic improvement.

\*Pretreatment counts averages of at least 2 measurements (not influenced by transfusions)  $\geq 1$  week apart (modification).

†Modification to IWG response criteria.

‡In the absence of another explanation, such as acute infection, repeated courses of chemotherapy (modification), gastrointestinal bleeding, hemolysis, and so forth. It is recommended that the 2 kinds of erythroid and platelet responses be reported overall as well as by the individual response pattern.

**APPENDIX D – CCCWFU 22215 Pre-Study Data Collection Form****ORIS PID:** \_\_\_\_\_ **DATE COMPLETED:** (mm/dd/yy): \_\_\_\_\_ / \_\_\_\_\_ / \_\_\_\_\_**The following are required prior to registration:****CURRENT DISEASE STATUS AT REGISTRATION:** \_\_\_\_\_  
(1<sup>ST</sup> relapse, 2<sup>nd</sup> relapse, 3<sup>rd</sup> relapse, refractory etc., including allo or auto bone marrow transplant)

| Prior Therapies/<br>Protocol # if applicable | Start / End Date of<br>Prior Therapy | Best Response<br>(CR, Cri, PR,<br>Morph Leukemia-Free,<br>CRC, CRm, Treat Fail) | Date of<br>Best Response | Date of<br>Relapse | Duration of<br>Best Response<br>(in Months) |
|--|--------------------------------------|---|--------------------------|--------------------|---|
| #1 _____                                     | _____ / _____                        | _____   | _____                    | _____              | _____                                       |
| #2 _____                                     | _____ / _____                        | _____   | _____                    | _____              | _____                                       |
| #3 _____                                     | _____ / _____                        | _____   | _____                    | _____              | _____                                       |
| #4 _____                                     | _____ / _____                        | _____   | _____                    | _____              | _____                                       |

**COMMENT:** \_\_\_\_\_  
 \_\_\_\_\_  
 \_\_\_\_\_

**Date of original cancer diagnosis:** \_\_\_\_\_ / \_\_\_\_\_ / \_\_\_\_\_**Date of 1<sup>st</sup> Remission:** \_\_\_\_\_ / \_\_\_\_\_ / \_\_\_\_\_**Date of 1<sup>st</sup> Relapse:** \_\_\_\_\_ / \_\_\_\_\_ / \_\_\_\_\_**Date of 2nd Relapse:** \_\_\_\_\_ / \_\_\_\_\_ / \_\_\_\_\_**ECOG Performance Status:**

- Score 0** – Fully active, able to carry on all pre-disease performance without restriction
- Score 1** - Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light house work, office work
- Score 2** - Ambulatory and capable of all selfcare but unable to carry out any work activities. Up and about more than 50% of waking hours
- Score 3** - Capable of only limited selfcare, confined to bed or chair more than 50% of waking hours
- Score 4** - Completely disabled. Cannot carry on any selfcare. Totally confined to bed or chair

**MOLECULAR ABNORMALITIES:**

**Were Molecular Abnormality Tests Completed?**  Yes  No  Unknown  Not Done

**Date of Molecular Abnormality Report:** \_\_\_\_ / \_\_\_\_ / \_\_\_\_

**FLT-3:**  Yes  No

**NPM:**  Yes  No

**Cb alpha:**  Yes  No

**CYTOGENETICS:**

**Cytogenetics at Diagnosis:**

**Date of Cytogenetics Report:** \_\_\_\_ / \_\_\_\_ / \_\_\_\_

**Risk Category:**  Good  Intermediate  Poor  Unknown  Not Done

\*Enter descriptive text from Cytogenetic Report (3 categories) into REDCap database on Pre-Study Data Collection Form.

CCCFWFU 22215

Comprehensive Cancer Center of Wake Forest University

An Open Label Study to Evaluate the Feasibility of CPI-613 Given with High Dose Cytarabine and Mitoxantrone in Patients with Relapsed or Refractory Acute Myeloid Leukemia (AML)

NCT Clinicaltrials.gov: NCT02484391

## APPENDIX E - CCCWFU 22215 Day 14 Nadir Marrow Form

ORIS Assigned PID \_\_\_\_\_

Date Completed: \_\_\_\_ / \_\_\_\_ / \_\_\_\_

Visit Type:  Cycle 1  Cycle 2

- Progressive Disease (No effect or worsening of overall blast burden (cellularity x blasts %))
- Residual Disease (Presence of residual blasts but significant reduction from previous)
- Few Scattered blasts of unclear significance
- Hypoplastic Marrow / no evidence of disease

Treating Physician Signature: \_\_\_\_\_ Date: \_\_\_\_\_

PI Signature: \_\_\_\_\_ Date: \_\_\_\_\_

**APPENDIX F - CCCWFU 22215 Data Collection Form – FOLLOW-UP Form**  
**Response Evaluation Criteria for Acute Myeloid Leukemia**

PID: \_\_\_\_\_

Date: \_\_\_\_ / \_\_\_\_ / \_\_\_\_

Please check the response that applies to this patient:

- Complete Remission (CR)
- Complete Remission with Incomplete Recovery (CRi)
- Morphological Leukemia-Free State
- Partial Remission (PR)
- Cytogenetic Complete Response (CRc)
- Molecular Complete Response (CRm)

Treatment Failures

- Treatment Failure due to Resistant Disease (TFRD)
- Treatment Failure due to Complications of Aplasia (TFCA)
- Treatment Failure of Indeterminate Cause (TFIC)
- Induction Death
- Relapse

Hematologic Response Criteria

- Erythroid Response (pretreatment, <11g/dL)
- Platelet Response (pretreatment, < 100 x 10<sup>9</sup>/L)
- Neutrophil Response (pretreatment, <1.0 x 10<sup>9</sup>/L)
- Progression or Relapse after (HI) Hematologic Improvement

\*If the patient has experienced relapse please record cytogenetics and molecular abnormalities at the time of relapse on next page. (not required per protocol)

Treating Physician Signature: \_\_\_\_\_ Date: \_\_\_\_\_

PI Signature: \_\_\_\_\_ Date: \_\_\_\_\_

**MOLECULAR ABNORMALITIES (AT RECOVERY MARROW ON STUDY):**

**Were Molecular Abnormality Tests Completed?**  Yes  No  Unknown  Not Done

**Date of Molecular Abnormality Report:** \_\_\_\_ / \_\_\_\_ / \_\_\_\_

**FLT-3:**  Yes  No

**NPM:**  Yes  No

**Cb alpha:**  Yes  No

**CYTOGENETICS:**

**Cytogenetics at Relapse:**

**Was Cytogenetic Testing Completed?**  Yes  No  Unknown  Not Done

**Date of Cytogenetics Report :** \_\_\_\_ / \_\_\_\_ / \_\_\_\_

**Relapse Time:**  1<sup>st</sup> Relapse  2<sup>nd</sup> Relapse  3<sup>rd</sup> Relapse

**Risk Category:**  Good  Intermediate  Poor

\*Enter descriptive text from Cytogenetic Report (3 categories) into REDCap database on Data Collection Form FOLLOW-UP Form.

**APPENDIX G – CCCWFU 22215 Urine Collection****OPTIONAL URINE COLLECTION FORM**

This form is for the collection of research urine samples collected from the first void after the first infusion of CPI-613 on day 1 of the first induction cycle only to be stored for future use.

**Sample Handling:** Once collected 5-10 ml of urine should be placed in a 15 ml conical tube and placed at 4 degrees Celsius until it can be sent to the tumor tissue core facility (see below).

Samples should be frozen and stored in the Tumor Tissue Core at -80 until use.

**Tumor Tissue Core**

Wake Forest Baptist Comprehensive Cancer Center

Tumor Tissue Core Facility  
Care of Dr. Greg Kucera  
Hanes Building Rm 4049  
Medical Center Blvd  
Winston-Salem NC 27157

|                                       |                                    |
|---------------------------------------|------------------------------------|
| <b>ORIS PID:</b> _____                | <b>Date:</b> _____ / _____ / _____ |
| <b>PI:</b> <u>Bayard Powell, M.D.</u> | <b>Study Number: _____</b>         |

**Urine Sample**

Sample ID: \_\_\_\_\_

Time of Collection

Time of CPI infusion completion \_\_\_\_\_ am/pm

Time of urine collection \_\_\_\_\_ am/pm

Time urine placed in freezer storage \_\_\_\_\_ am/pm

Location of Sample

Freezer ID: \_\_\_\_\_ Shelf: \_\_\_\_\_ Box: \_\_\_\_\_

Person Processing sample \_\_\_\_\_ Date \_\_\_\_\_