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Wake Forest™ School of Medicine

Section on *Hematology and Oncology*

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)

Informed Consent Form to Participate in Research
Bayard Powell, MD Principal Investigator

INTRODUCTION

You are invited to be in a research study. Research studies are designed to gain scientific knowledge that may help other people in the future. You are being asked to take part in this study because you have acute myeloid leukemia (AML) that has either returned after a period of remission, or is no longer responding to treatment. Your participation is voluntary. Please take your time in making your decision as to whether or not you wish to participate. Ask your study doctor or the study staff to explain any words or information contained in this informed consent document that you do not understand. You may also discuss the study with your friends and family.

WHY IS THIS STUDY BEING DONE?

Phase II studies are an early step in testing an investigational medication in humans. These studies look to see how many people complete the planned therapy and which of them has a response. It is the first step to determine if the experimental therapy can be tested in a larger trial.

The purpose of this study is to test whether the combination of an investigational drug called CPI-613 ("study drug"), given at a high or low dose, with two other chemotherapy drugs: cytarabine and mitoxantrone is effective in controlling your leukemia and how many patients complete all planned therapy. The study team has become aware that similar response rates with less side effects are possible at lower doses. Because of this the study team has revised the induction dose as well as added a low dose study group. Whether you receive the high or low dose of CPI-613 will be determined before you start treatment. CPI-613 is thought to kill cancer cells by turning off their mitochondria. Mitochondria are used by cancer cells to produce energy and the building blocks needed to make more cancer cells. By shutting off these mitochondria, CPI-613 deprives the cancer cells of energy and other supplies that they need to survive and grow in your body. We want to find out what effects, good and/or bad, CPI-613 has on you and your cancer when given along with cytarabine and mitoxantrone. We also want to see if CPI-613 when given alone as a maintenance therapy can prolong remission for those patients who respond to this treatment.

An investigational drug is one that has not been approved by the U.S. Food and Drug Administration (FDA). CPI-613 is an investigational drug that has not been approved by the

FDA for any type of tumor or cancer, and it is currently being studied for the treatment of cancer.

HOW MANY PEOPLE WILL TAKE PART IN THE STUDY?

Approximately 67 people at Wake Forest Baptist Health will take part in this study.

WHAT IS INVOLVED IN THE STUDY?

After your study doctor has answered all your questions about this study and you have given written consent by signing this form, several tests will be done to be sure you are able to enter this study. Many of the tests are the same as those you have had in the past to diagnose and treat your disease. Some of these same tests will also be done during the study to follow your progress.

This clinical research study consists of several parts induction, consolidation and maintenance. The first part is induction and is a two-week cycle. During the first week, treatment is given as follows: CPI-613 (given on days one through five), cytarabine (given on days three through five), and mitoxantrone (given on days three through five). The second week of the cycle is a rest week (no treatment). On day 14 you will have another bone marrow biopsy to see if your disease has responded (just like you would if you were not on the study). If you need another cycle of induction therapy you may receive either a repeat of the first round or a shorter 3 day cycle depending on what your doctor thinks. For those patients who respond to the treatment they may be treated with the next phase called consolidation. This treatment usually starts after patients have recovered from induction therapy and uses the shorter 3 day treatment. Patients can have up to 2 cycles of consolidation therapy as recommended by their doctor. After a patient has received all the consolidation therapy that they or their doctor wants them to get they can go onto maintenance therapy. In this phase of the study patients just get CPI-613 once a day for 5 days every month. This will continue until your AML progresses, your doctor thinks you should not get more therapy or you decide you want to withdraw from the study.

Your participation in this study is divided into different visits:

Screening Visit (To see if you are eligible to participate in this study)
The following tests will be done during the Screening Visit. These tests may be completed over a four week period before receiving CPI-613.

- You will undergo a blood and bone marrow biopsy (if not already done by your doctor) to determine the extent of your cancer.
- Left Ventricular Ejection Fraction (by TTE, MUGA or cardiac MRI) sufficient to safely administer mitoxantrone as determined by the treating physician

The following tests may be completed within two weeks before receiving CPI-613.

- The study doctor or study nurse will ask you about your medical history, and obtain a list of all medications that you are currently taking.
- The study doctor or study nurse will examine you and determine your performance status.
- A physical examination with your vital signs (heart rate, blood pressure, breathing rate, and body temperature), height, and body weight will be recorded.
- Approximately 10 teaspoons of blood will be drawn for routine lab tests.
- Approximately two teaspoons of blood will be drawn to evaluate potential heart muscle

damage.

The following test must be completed within one week before receiving CPI-613:

- Pregnancy test for female subjects who can become pregnant. This must be done within one week of starting treatment.

Evaluation / Procedures:

Day 1

- You will be given CPI-613.
- Your vital signs will be measured immediately after receiving CPI-613 and you may have a physical exam if needed.

Day 2

- Approximately 10 teaspoons of blood will be drawn for routine lab tests within 24 hours before receiving CPI-613.
- You will be given CPI-613.
- You will be observed for one hour after receiving CPI-613. Your vital signs will be measured immediately after receiving CPI-613 and you may have a physical exam if needed.

Days 3 and 4

- Approximately 10 teaspoons of blood will be drawn for routine lab tests within 24 hours before receiving CPI-613.
- You will be given CPI-613.
- You will be given mitoxantrone and cytarabine.
- You will be observed for one hour after receiving CPI-613. Your vital signs will be measured immediately after receiving CPI-613 and you may have a physical exam if needed.

Day 5

- Prior to receiving treatment, you will undergo a blood test to determine how your cancer is doing
- Approximately 10 teaspoons of blood will be drawn for routine lab tests within 24 hours before receiving CPI-613.
- You will be given CPI-613.
- You will be given mitoxantrone and cytarabine.
- You will have a physical exam
- You will be observed for one hour after receiving CPI-613. Your vital signs will be measured immediately after receiving CPI-613 and you may have a physical exam if needed. One hour after completion of the CPI-613 infusion, you will have approximately two teaspoons of blood drawn to assess heart muscle damage.

Days 6, 7, and 8

- Approximately 10 teaspoons of blood will be drawn for routine lab tests.

- Approximately one teaspoon of blood will be drawn to monitor kidney function at 24, 48, and 72 hours after the last dose of CPI-613, mitoxantrone, and cytarabine (i.e., on days 6, 7, and 8)

Additional Evaluations and Procedures

Within 24 hours of every dose of CPI-613

- Approximately one teaspoon of blood will be taken to monitor kidney function

Day 14 of cycle 1

- You will undergo a bone marrow biopsy to evaluate your response to the therapy.
- Note: If your study doctor determines that the treatment is beneficial to you, additional cycles may be given (see "How Long Will I Be In The Study?" below). In the event that you receive more than one cycle, a bone marrow biopsy and blood test to determine the extent of your cancer will be performed at the end of every other cycle (i.e., cycles 3, 5, 7, etc.).

Maintenance Therapy

Patients who complete all planned consolidation therapy on this study may be treated with additional cycles of CPI-613 if their doctor feels this will be beneficial. If you are eligible and agree to receive maintenance therapy with CPI-613, you will have the following tests and procedures completed.

Day 1

- Approximately 10 teaspoons of blood will be drawn for routine lab tests within 24 hours before receiving CPI-613.
- You will be given CPI-613.
- Your vital signs will be measured immediately after receiving CPI-613 and you may have a physical exam if needed.

Days 2-5

- You will be given CPI-613.
- You will be observed for one hour after receiving CPI-613. Your vital signs will be measured immediately after receiving CPI-613 and you may have a physical exam if needed.
- Approximately one teaspoon of blood will be drawn to monitor kidney function

Days 6 and 7

- Rest days (no treatment)

You may receive maintenance therapy with CPI-613 until you are ready to have a stem cell transplant, your AML gets worse or you have an unacceptable side effect.

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.
Optional blood, plasma samples and bone marrow via biopsy will be 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 6 hours on days 1-5 and bone marrow sample to be obtained on day 14 of Cycle 1.

Urine samples will be collected from the first void after the first infusion of CPI-613 in the first induction cycle only.

HOW LONG WILL I BE IN THE STUDY?

You will be given CPI-613 five times a week for one week, followed by a week of rest. This two week period is considered "a cycle." CPI-613 will be given over a two-hour infusion into your vein through a central venous catheter (a catheter that is put into a larger vein in your body and will remain in place for the duration of the treatment). The study plans on one or two cycles of induction therapy, up to two cycles of consolidation therapy and then maintenance therapy for as long as you are willing and your doctors feels is beneficial to you.

You can stop participating at any time. It is important to tell the study doctor if you are thinking about stopping so that any risks from CPI-613 can be evaluated by your study doctor. Another reason to tell your study doctor that you are thinking about stopping is to discuss what follow-up care and testing could be most helpful for you.

WHAT ARE THE RISKS OF THE STUDY?

Being in this study involves some risk to you. You should discuss the risk of being in this study with the study staff.

Risks Related to CPI-613

The study drug is in the very early stages of development for use in humans. The main purpose of this study is to learn about the efficacy of the drug when given with mitoxantrone and cytarabine. Please carefully read the sections on risk and benefits below. Not all of the side effects are known at this time. If you choose to take part in this study, it is very important that you let the study team know of any symptoms you have.

Some potential risks associated with CPI-613 have been determined from previous animal studies. These side effects include vomiting and some temporary heart damage. CPI-613 has also caused inflammation around the area where the experimental drug is given, causing swelling, redness, and pain. To avoid this potential side effect, CPI-613 will be given to you through a central venous catheter. There may be other more severe side effects such as significant inflammation throughout your body. The study drug could cause changes in certain chemicals in your blood that could indicate liver problems. Significant side effects have also caused some deaths in test animals at dose levels that are higher than those to be used in this study. Many side effects may go away shortly after being given CPI-613 but in some cases, side effects may be

severe, long lasting, or may not go away. Although not yet reported in any human subjects, it remains possible that CPI-613 might cause your disease to progress or produce a fatal side effect. CPI-613 may also cause side effects that we have not yet seen and cannot predict.

The following describes events observed in patients who received one or more doses of CPI-613 in clinical trials. These side effects may be related to CPI-613, related to other drugs administered or related to activity of the cancer being treated.

COMMON, SOME MAY BE SERIOUS

In 100 cancer patients receiving CPI-613, more than 20 and up to 100 people may have experienced:

- nausea.

OCCASIONAL, SOME MAY BE SERIOUS

In 100 people receiving CPI-613, from 4 to 20 may have experienced:

- vomiting
- tiredness
- taste changes
- diarrhea
- anemia
- changes in liver function tests
- reactions at the place where they received CPI-613
- low sodium in the blood
- high levels of hemoglobin (a part of red blood cells)

RARE AND SERIOUS

In 100 people receiving CPI-613, 3 or fewer may have experienced:

- blockage of blood vessels
- heart failure
- heart attack
- chest pain not related to the heart
- death

In a study of patients with acute myeloid leukemia, who received CPI-613 combined with other chemotherapy, the most frequent (greater than 10%) side effects reported by people were:

- changes in liver function tests
- changes in components of the blood
- diarrhea
- nausea
- vomiting
- tiredness

- loss of appetite
- alterations in coagulation tests
- changes in kidney function
- fever of unknown origin
- sores on the gums

In previous animal studies, acute inflammation has been observed, however to date, no human subjects have experienced this side effect.

There may be other, more severe side effects, such as inflammation throughout your body. The study drug could cause changes in certain chemicals in your blood that could indicate liver problems.

Pregnancy Risks
The effects of CPI-613 on a fetus are unknown. You should not become pregnant or father a child while on this study. If you are able to become pregnant or father a child, BOTH you and your partner must use effective birth control methods during the study period. Effective birth control methods are outlined below.

Women subjects who have never been pregnant can use one of the following methods:
- Abstinence
- A barrier method (diaphragm, cervical cap, sponge, or condom with a spermicidal foam or jelly) plus hormonal birth control (oral, patch or injectable).
- A barrier method (diaphragm, cervical cap, sponge, or condom with a spermicidal foam or jelly) plus an intrauterine device (IUD).

Women subjects who have previously been pregnant at least once can use one of the following methods:
- Abstinence
- A barrier method (diaphragm or condom with a spermicidal foam or jelly) plus hormonal birth control (oral, patch or injectable).
- A barrier method (diaphragm or condom with a spermicidal foam or jelly) plus an intrauterine device (IUD).

Male subjects can use one of the following methods:
- Abstinence
- Condom with spermicide

For male subjects, you should also advise your partner to use an effective birth control method such as those outlined above for women subjects.

If you suspect that you have become pregnant, you must notify the study doctor immediately.

Female subjects should avoid becoming pregnant for at least 10 weeks following completion of the study. Male subjects should avoid fathering a child for at least 10 weeks following study completion.

Risks Related to Mitoxantrone
Some common side effects observed in patients taking mitoxantrone include:

- Anemia
- Low white blood cells
- Low platelets
- Serious infections
- Nausea
- Hair loss
- Menstrual irregularities (female patients)
- Upper respiratory infection
- Urinary tract infection
- Irregular heart rhythm
- Inflammation of the mucus membranes lining the mouth
- Diarrhea
- Constipation
- Back pain
- Sinusitis
- Headache

Risks Related to Cytarabine
Some common side effects observed in patients taking cytarabine include:

- Anemia
- Low white blood cells
- Low platelets
- Serious infections
- Nausea
- Vomiting
- Diarrhea
- Stomach pain
- Loss of appetite
- Inflammation of the mucus membranes lining the mouth
- Hair loss
- Muscle or joint pain
- Tiredness
- Sore or red eyes
- Anemia
- Low levels of white blood cells
- Increased risk of infection
- Weight loss
- Decreased liver function
- Fever
- Increased risk of bleeding

Rarely, cytarabine has been associated with sepsis (whole-body infection and inflammation), pneumonia, difficulty urinating, decreased kidney function, nerve damage, sores in the throat, chest pain, inflammation of the lining that surrounds the heart, pancreatitis (inflammation of the pancreas), jaundice (temporary yellowing of the skin and eyes), eye infection, dizziness, shortness of breath, and headache.

Other Risks
It is possible that you could experience an allergic reaction to CPI-613 or to any combination of the drugs used in this study. An allergic reaction can be mild, or it can be serious, leading to shock with loss of consciousness, or it can be life-threatening.

Certain drugs, when taken together with the study drug, may increase side effects. It is possible that CPI-613 could increase the side effects of cytarabine or mitoxantrone. It is important that you inform your study doctor of any prescription, over-the-counter, or alternative medications you are taking while in this study.

Drawing blood may cause pain, bruising, lightheadedness, or, on rare occasions, infection.

Risks of a central venous catheter may include pain, bleeding, infection, and damage to lungs or other tissue.

Your condition may not get better or may become worse during this study.

If you have questions about risks and side effects, ask your study doctor. **You should talk to your study doctor about any side effects that you have while taking part in this study.** The study doctor will take steps to try to treat any side effects, if they appear. If the study drug causes severe side effects or if your disease worsens, the study drug will be discontinued. In that case, your study doctor will discuss treatment options with you.

Taking part in this research study may involve providing information that you consider confidential or private. Efforts, such as coding research records, keeping research records secure and allowing only authorized people to have access to research records, will be made to keep your information safe.

ARE THERE BENEFITS TO TAKING PART IN THE STUDY?
If you agree to take part in this study, there may or may not be direct benefit to you. We hope the information learned from this study will benefit other people in the future. The benefits of participating in this study may be: improvement in your cancer.

WHAT OTHER CHOICES ARE THERE?
You do not have to be in this study to receive treatment. You should talk to your doctor about all the choices you have. Instead of being in this study, you have these options:

- Other chemotherapies
- Comfort care, which is an option if you decide that you do not want any more active treatment for your cancer. Comfort care includes pain medication and other types of

support. It aims to maintain your comfort and dignity rather than cure disease. Usually this care can be provided at home. If you think you might prefer comfort care, please discuss this with your family, friends, and your doctor.

SAMPLES FOR FUTURE STUDIES

The researchers would like your permission to use blood, plasma and/or bone marrow samples collected for the study for future health research related to the purposes of the CCCWFU-22215 study.

My blood/tissue samples and related information may be kept in a Biobank for use in future health research.

YES ____ NO ____

Your blood/tissue samples will be stored de-identified, which means that no identifying information will be stored with it. Researchers will not know the name, date of birth, medical record number, social security number, etc., of the person who donated the sample.

The research that may be performed with your blood/tissue sample is not designed to help you specifically. There is no personal benefit to you from taking part in this aspect of the research study. It might help people who have diseases at some point in the future, but it is not known if this will happen. The results of the research performed with your blood will not be given to you or your doctor. The results will not be put in your medical record. The research using your blood/tissue sample will not affect your care.

Your blood/tissue sample will be used only for research and will not be sold. The findings from this research may result in the future development of products that are of commercial value. There are no plans to share any of the profits with you which may occur as a result of the research.

What About My Health Information?

In this research study, any new information we collect from you about your health or behaviors is considered Protected Health Information. The information we will collect for this research study includes: your health history, how you respond to study procedures, laboratory and other test results, and physical examinations.

If this research study involves the diagnosis or treatment of a medical condition, then Protected Health Information collected from you during this study will be placed in your medical record, and may be used to help treat you, arrange payment for your care, or assist with Medical Center operations.

We will make every effort to keep your Protected Health Information private. We will store records of your Protected Health Information in a cabinet in a locked office or on a password protected computer. Only the following people or organizations will be granted access to your Protected Health Information:

1) The study investigator and his/her staff, or others at Wake Forest University Health Sciences who oversee research

2) Other people or laboratories providing services for this research project on behalf of Wake Forest University Health Sciences and Wake Forest University Baptist Medical Center

3) The U.S. Food and Drug Administration (FDA); Rafael Pharmaceuticals, Inc.

If required by law or court order, we might also have to share your Protected Health Information with a judge, law enforcement officer, government agencies, or others. If your Protected Health Information is shared with any of these groups it may no longer be protected by federal or state law.

Any Protected Health Information collected from you in this study that is maintained in the research records will be kept for an indeterminate period of time. This authorization does not expire. Any research information entered into your medical record will be kept for as long as your medical record is kept by the Medical Center. You will not be able to obtain a copy of your Protected Health Information in the research records until all activities in the study are completely finished.

You can tell Dr. Bayard Powell that you want to take away your permission to use and share your Protected Health Information at any time by sending a letter to this address:

Bayard Powell, MD
[redacted]

However, if you take away permission to use your Protected Health Information you will not be able to be in the study any longer. We will stop collecting any more information about you, but any information we have already collected can still be used for the purposes of the research study.

By signing this form you give us permission to use your Protected Health Information for this study.

If you choose to participate in this study, your medical record at Wake Forest University Baptist Medical Center will indicate that you are enrolled in a clinical trial. Information about the research and any medications or devices you are being given as a participant may also be included in your medical record. This part of the medical record will only be available to people who have authorized access to your medical record. If you are not a patient at this Medical Center, a medical record will be created for you anyway to ensure that this important information is available to doctors in case of an emergency.

A description of this clinical trial will be available on http://www.ClinicalTrials.gov, as required

by U.S. Law. This website will not include information that can identify you. At most, the website will include a summary of the results. You can search this Web site at any time.

Laboratory test results and other medical reports created as a result of your participation in the research study may be entered into the computer systems of Wake Forest University Health Sciences and North Carolina Baptist Hospital. These will be kept secure, with access to this information limited to individuals with proper authority, but who may not be directly involved with this research study.

A North Carolina Baptist Hospital (NCBH) medical record will be created for all study participants. Information about your participation in the study will be placed in the NCBH medical record, along with any routine medical test results that were obtained at NCBH as part of this study.

WHAT ARE THE COSTS?

Taking part in this study may lead to added costs to you or your insurance company. We will give you an estimate of what the added cost may be based on your particular situation and insurance coverage.

WILL YOU BE PAID FOR PARTICIPATING?

The investigational study drug, CPI-613, is being provided to you at no cost from the pharmaceutical company (Rafael Pharmaceuticals, Inc.). Parking validation will be provided for study-related visits.

WHO IS SPONSORING THIS STUDY?

This study is being sponsored by Wake Forest University Health Science. Rafael Pharmaceuticals, Inc. is providing the investigational drug (CPI-613) to Wake Forest University Health Sciences to help conduct this study. Dr. Timothy Pardee, a Co-investigator on this study, has a relationship with Rafael Pharmaceuticals and receives compensation, separate from this study, for consulting services. Rafael has also provided some lab materials for Dr. Pardee's research. Dr. Powell and the other researchers do not, however, hold a direct financial interest in Rafael Pharmaceuticals, Inc. or the product being studied.

WHAT HAPPENS IF YOU EXPERIENCE AN INJURY OR ILLNESS AS A RESULT OF PARTICIPATING IN THIS STUDY?

Should you experience a physical injury or illness as a direct result of your participation in this study, Wake Forest University School of Medicine maintains limited research insurance coverage for the usual and customary medical fees for reasonable and necessary treatment of such injuries or illnesses. To the extent research insurance coverage is available under this policy the reasonable costs of these necessary medical services will be paid, up to a maximum of $25,000. Wake Forest University Baptist Medical Center holds the insurance policy for this coverage. It provides a maximum of $25,000 coverage for each claim and is limited to a total of $250,000 for all claims in any one year. The Wake Forest University School of Medicine, and the North Carolina Baptist Hospitals, Incorporated do not assume responsibility to pay for these medical services or to provide any other compensation for such injury or illness. Additional information may be obtained from the Medical Center's Director of Risk and Insurance

Management, at [redacted].

If you are injured, the insurer may require information such as your name, social security number, and date of birth in order to pay for your care. This is because the insurer is required by law to report any payments made to cover the care of any persons who are members of a government insurance plan to the Department of Health and Human Services.

You do not give up any legal rights as a research participant by signing this consent form. For more information on medical treatment for research related injuries or to report a study related illness, adverse event, or injury you should call Dr. Bayard Powell at [redacted].

WHAT ARE MY RIGHTS AS A RESEARCH STUDY PARTICIPANT?

Taking part in this study is voluntary. You may choose not to take part or you may leave the study at any time. Refusing to participate or leaving the study will not result in any penalty or loss of benefits to which you are entitled. If you decide to stop participating in the study we encourage you to talk to the investigators or study staff first to learn about any potential health or safety consequences. The investigators also have the right to stop your participation in the study at any time. This could be because it is in your best interest, you do not follow the study rules, the study is stopped, you do not later consent to any future changes that may be made to the study plan, or your become pregnant.

You will be given any new information we become aware of that would affect your willingness to continue to participate in the study.

WHOM DO I CALL IF I HAVE QUESTIONS OR PROBLEMS?

For questions about the study or in the event of a research-related injury, contact the study investigator, Dr. Bayard Powell at [redacted].

The Institutional Review Board (IRB) is a group of people who review the research to protect your rights. If you have a question about your rights as a research participant, or you would like to discuss problems or concerns, have questions or want to offer input, or you want to obtain additional information, you should contact the Chairman of the IRB at [redacted].

You will be given a copy of this signed consent form.

SIGNATURES

I agree to take part in this study. I authorize the use and disclosure of my health information as described in this consent and authorization form. If I have not already received a copy of the Privacy Notice, I may request one or one will be made available to me. I have had a chance to ask questions about being in this study and have those questions answered. By signing this consent and authorization form, I am not releasing or agreeing to release the investigator, the sponsor, the institution or its agents from liability for negligence.

Subject Name (Printed):_____

Subject Signature: _____ Date: _____Time:_____ am pm

Person Obtaining Consent (Printed):_____

Person Obtaining Consent:_____ Date:_____ Time:_____ am pm