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Wake Forest™
School of Medicine

Section on *Hematology and Oncology*

A Phase I Clinical Trial of Fluorouracil (5-FU) + CPI-613 Combination in previously treated Metastatic Colorectal Cancer Patients

Informed Consent Form to Participate in Research
Caio Max S. Rocha Lima, M.D., 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 colorectal, appendiceal or small bowel cancer that cannot be removed by surgery. 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?

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.

The purpose of this study is to test the safety and effectiveness of an investigational drug called CPI-613 ("study drug") when given at different dose levels in combination with Fluorouracil (5-FU) when used to treat colorectal cancer. 5-FU has been approved by the FDA for the treatment of colorectal cancer. CPI-613 is thought to kill cancer cells by turning off their mitochondria. Mitochondria are used by cancer cells to produce energy and are 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 5-FU. We also want to measure the amounts of CPI-613 in your blood after it has been given to you, as well as find the highest dose of CPI-613 that should be used in humans when given along with 5-FU .

HOW MANY PEOPLE WILL TAKE PART IN THE STUDY?

Eighteen people will take part in the initial portion of the study at Wake Forest Baptist Health in order to select the right dose of CPI-613. Once the right dose is found, another ten (10) people at Wake Forest Baptist Health will take part in this study. Over the course of the entire study, a minimum of 20 people to a maximum of 34 people will be enrolled.

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.

Your participation in this study is divided into different visits:

Pre-Study Screening Tests (To see if you are eligible to participate in this study)

The following tests will be done in order to determine if you are eligible to participate in this study. These tests may be completed over a four week period before receiving CPI-613.

- You will undergo an imaging scan of your chest, abdomen and pelvis to determine the extent of your cancer. This imaging scan, known as a computed tomography scan with contrast ("contrast CT scan" or "CAT scan with contrast"), uses computers and x-rays to take detailed pictures of areas inside your body. In addition, a small amount of a special dye called a "contrast material" will be used to help highlight the areas within your chest, abdomen, and pelvis. The contrast material will be injected into your body through a vein in your arm. The CT (Computed Tomography) scan is a study using x-rays to look at one part of your body. These scans are part of your routine cancer care and will be billed to your insurance.
- You will have approximately two teaspoons of blood drawn to test for the presence of a tumor marker known as CEA, which is often elevated in individuals with colorectal cancer.

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. This will measure how well you are able to carry on ordinary daily activities.
- A physical examination with your vital signs (heart rate, blood pressure, breathing rate, and body temperature), height, and body weight will be recorded. The physical exam traditionally includes an evaluation of your symptoms and side effects, discussion of results from recent tests and procedures and assessment of your body systems if needed. This may vary depending on the visit. Approximately 3 teaspoons of blood will be drawn for routine lab tests.

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.

Participants may receive different doses of the investigational drug CPI-613 depending on when they are enrolled onto the study. The highest possible dose of CPI-613 is 3,000mg/m^2 and was very well tolerated in another clinical trial done in patients with cancer. In this study, CPI-613 will be given at a lower dose and then gradually increased up to a maximum dose of 3,000mg/m^2.

You will be given CPI-613 on days one through four for one week and you will be given 5-FU on day two, followed by a continuous infusion through a portable pump over the next 46 hours, followed by a week of rest. 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).

Evaluation / Procedures for Cycle 1

Week 1, Day 1

- You will be given CPI-613
- Blood will be taken at certain time points for measurement of CPI-613 levels (pharmacokinetics) and/or other research. These time points are: just before you receive CPI-613; then at 30 minutes, 1, 1.5, 2, and 4 hours after the completion of CPI-613 infusion. The total amount of blood that will be withdrawn during this time is approximately one ounce.
- You will have a physical exam and your vital signs will be measured.
- Within 24 hours of receiving CPI-613 you will:
    - have your performance status determined. This will measure how well you are able to carry on ordinary daily activities.
    - have approximately 3 teaspoons of blood drawn for routine lab tests (unless you have had these labs drawn within the past 7 days)

Week 1, 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 followed by 5-FU given as a continuous infusion through a portable pump over the next 46 hours.
- You will have your vital signs measured

Week 1, Day 3

- 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 and your continuous infusion of 5-FU through a portable pump will be ongoing for 46 hours of treatment.
- You will have your vital signs measured

Week 1, Day 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 have your vital signs measured

- You will have your portable pump disconnected
- Within 24 hours of receiving CPI-613 you will:
    - have approximately 3 teaspoons of blood drawn for routine lab tests
- Blood will be taken just before you receive CPI-613 for measurement of CPI-613 levels (pharmacokinetics) and/or other research. The total amount of blood that will be withdrawn during this time is approximately one ounce.

Week 1, Days 5, 6 and 7

- Rest days (no treatment)

Week 2

- Rest week (no treatment)

Evaluation / Procedures for Cycles 2 and beyond

Week 1, Day 1

- You will have a physical exam and have your vital signs measured
- Within 24 hours of receiving CPI-613 you will:
    - have your performance status determined. This will measure how well you are able to carry on ordinary daily activities.
    - have approximately 3 teaspoons of blood drawn for routine lab tests

Week 1, 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 followed by 5-FU given as a continuous infusion through a portable pump over the next 46 hours.
    - You will have your vital signs measured

Week 1, Day 3

- 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 and your continuous infusion of 5-FU through a portable pump will be ongoing for 46 hours of treatment.
- You will have your vital signs measured

Week 1, Day 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 have your vital signs measured
- Your portable pump will be disconnected

Week 1, Days 5, 6 and 7

- Rest days (no treatment)

Week 2

- Rest week (no treatment)

Additional Evaluations and Procedures

After every fourth cycle of treatment, you will have the following performed:

- Contrast CT scan to evaluate the extent of your cancer
- You will have approximately two teaspoons of blood drawn to check your CEA levels

After your participation on the study is complete, you will be contacted every other month via telephone by the study nurse who will gather information related to any additional cancer treatments you have received, as well as your general health status.

OPTIONAL BLOOD AND PLASMA SAMPLES

We are asking that you provide samples of your blood and plasma to the study team for future research. If you agree to participate in the optional blood and plasma banking portion of this study, we will draw approximately four teaspoons of blood and plasma to use for future research during pre-study screening and before each restaging scan. This sample will be kept and may be used in future research to learn more about how CPI-613 works. Your sample will be obtained in the department of Hematology and Oncology at Wake Forest University Baptist Medical Center. The sample will be stored in the Tumor Tissue Core Facility of Wake Forest and it will be given only to researchers approved by Dr. Caio Max S. Rocha Lima. An Institutional Review Board (IRB) must also approve any future research study using your blood and plasma samples. You do not have to provide blood and plasma samples for future research to be able to participate in this study.

Your blood and plasma sample will be stored with a unique identifier and will not include any identifiable information about you such as your name, address, telephone number, social security number, medical record number or any of the identifiers outlined in the HIPAA Privacy Rule. The unique identifier will be a randomly assigned number and only the principal investigator will have access to the code that links the unique identifier to you. Your name, address, social security number, etc., will never be disclosed to future researchers and neither will the code that links your identifiers to the sample.

The research that may be performed with your blood and plasma 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 and plasma will not be given to you or your doctor. The results will not be put in your medical record. The research using your blood and plasma sample will not affect your care.

Your blood and plasma 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.

____YES I would like to allow for collection and storage of my blood and plasma samples
____NO I would not like to allow for collection and storage of my blood and plasma samples

HOW LONG WILL I BE IN THE STUDY?

The length of participation in this study will vary for each person and will be determined by the number of treatment cycles you receive. You are expected to be in the study for at least 3 to 6 months.

Your treatment with CPI-613 will continue if you receive benefit from the CPI-613, until you have an unacceptable side effect to the drug or your cancer gets worse.

Once you have completed treatment with CPI-613, you will be contacted once every two months by telephone to see how you are doing and to see if you have started any new treatment for your cancer.

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 safety and effectiveness of the drug when used to treat colorectal cancer. 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. However, we have not witnessed any heart damage in the patients we have treated to date. 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.

Some common side effects observed in patients taking CPI-613 include:

- Allergic reaction (such as redness, swelling and pain)at the place where you receive your drug
- Vomiting
- Diarrhea
- Fatigue
- Headache
- Constipation
- Nausea
- Light-headedness
- Abdominal pain
- Changes in liver function
- Changes in kidney function
- Jaundice (temporary yellowing of the skin and eyes)
- Too much or too little calcium in the blood
- Flushing
- Anemia (low red cells that can contribute to fatigue)
- Low levels of white blood cells
- Low levels of platelets (red blood cells that help to form clots)
- Electrolyte imbalance

There may be other, more severe side effects, such as inflammation throughout your body.

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 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 and 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 5-Fluorouracil (5-FU)

More Likely:

- Loss of appetite
- Soreness or painful ulcers of the mouth or throat
- Pain when swallowing
- Diarrhea (loose and frequent stools)
- Constipation
- Nausea (feeling sick to the stomach)
- Vomiting (throwing up)
- Temporary hair loss
- Decreases in the blood cells produced in bone marrow, leading to decreased white blood cells, red blood cells and platelets
- Metallic taste in the mouth

Less Likely:

- Swelling and pain of the hands and feet
- Thinning of the skin, or dry, flaking or cracking skin
- Fingernail changes
- Redness or increased skin coloring over the veins
- Skin rash
- Increased sensitivity to the sun

Rare:

- Irritation of the eyes with watery eyes and a scratchy feeling
- Unsteadiness in walking
- Dizziness
- Confusion
- Chest pain
- Changes in the heart rhythm

Risks Related to Continuation of CPI-613 Treatment for Two More Cycles After Imaging Scans Indicate Disease Progression

For some patients, even when imaging scans indicate that you have progression in your disease, your doctor may feel that you are still benefiting (feeling better on treatment) from the combination treatment. If you agree, you can continue to receive CPI-613 for two more cycles as long as you still meet eligibility criteria and you do not have symptoms of disease progression. There is no evidence that this will benefit you and continued treatment may expose you to toxicities of CPI-613 that are described above. The reason for that is because CPI-613 can cause first swelling of your tumor that cannot be easily distinguished with the first standard scan.

Other Risks

It is possible that you could experience an allergic reaction to CPI-613. 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 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.

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, medical images, 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); Cornerstone 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. Caio Max S. Rocha Lima 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:

Caio Max S. Rocha Lima, M.D.
[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?

The investigational study drug, CPI-613, is being provided to you at no cost from the pharmaceutical company (Cornerstone Pharmaceuticals, Inc.). However, 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 carrier.

WILL YOU BE PAID FOR PARTICIPATING?

You will receive no payment or other compensation for taking part in this study. Parking validation will be provided for all study-related visits.

WHO IS SPONSORING THIS STUDY?

Cornerstone Pharmaceuticals, Inc. is providing the investigational drug to Wake Forest University Health Sciences to help conduct this study. The researchers do not, however, hold a direct financial interest in the sponsor 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. Caio Max S. Rocha Limaat [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. Caio Max S. Rocha Lima 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:_____ Date:_____ Time:_____ am pm