Official Title: Phase I Dose-Escalation Study of CPI-613, in Combination With Bendamustine, in Patients With Relapsed or Refractory T-Cell Non-Hodgkin Lymphoma or Classic Hodgkin Lymphoma
NCT02168140
IRB-Approved Date: 10/21/19

Wake Forest™
School of Medicine

Section on *Hematology and Oncology*

PHASE I DOSE-ESCALATION STUDY OF CPI-613, IN COMBINATION WITH BENDAMUSTINE, IN PATIENTS WITH RELAPSED OR REFRACTORY T-CELL NON-HODGKIN LYMPHOMA OR CLASSIC HODGKIN LYMPHOMA

Informed Consent Form to Participate in Research
Rakhee Vaidya, 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 Non-Hodgkin Lymphoma or Hodgkin Lymphoma that has either not responded (or has returned) despite standard treatment, and/or no further (non-investigational) therapies are left. 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.

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. In other studies, CPI-613 has been shown to kill cancer cells in some types of cancer.

Phase I studies are the first step in testing an investigational medication in humans. These studies look for the best way to give an investigational drug and also to try to find out if, and how, it can be given safely. Phase I studies also look for any harmful side effects that occur.

The purpose of this study is to find the highest dose of CPI-613 that can be given in combination with the drug Bendamustine without causing severe side effects. Bendamustine is routinely used for treatment of Non-Hodgkin Lymphoma and Hodgkin Lymphoma, but has not been approved by the FDA for the treatment of these conditions. In addition, this study will also test the safety

and effectiveness of CPI-613 when given in combination with Bendamustine.

HOW MANY PEOPLE WILL TAKE PART IN THE STUDY?

Approximately 20 people will take part in this study at two research sites. Approximately 12 people will take part at Wake Forest Baptist Health.

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.

Pre-Study Tests

The following tests may be completed over a four week period before receiving the investigational drug (CPI-613):

- You will undergo an imaging scan known as a CT scan. A CT scan uses computers and x-rays to take detailed pictures of areas inside your body.
- You will undergo a bone marrow biopsy
- Approximately four teaspoons of blood may be drawn to use for research purposes (only with your permission).

The following tests may be completed within two weeks before receiving the investigational drug (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.
- An electrocardiogram (ECG - a recording of the electrical activity of the heart) will be performed.
- Approximately 12 teaspoons of blood will be drawn for non-research related routine lab tests.

The following test must be completed within one week before receiving the investigational drug (CPI-613):

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

If the results of these tests show that you are eligible to enroll in this study, your participation on the study can begin.

Study Treatment and Procedures

This clinical research study consists of multiple four-week cycles of treatment with CPI-613 and Bendamustine. A cycle includes receiving treatment with CPI-613 four days during week one, followed by three weeks of rest (no treatment). Each cycle also includes treatment with Bendamustine on days four and five of week one. The number of cycles you receive will be determined by how well your cancer responds to the therapy. The maximum number of cycles you can receive is six.

The first table below shows the schedule of the treatment, tests, and procedures you will have during cycle one. The second table describes the schedule of treatment, tests, and procedures for all other cycles.

Procedures	**Cycle 1 (One Cycle = 4 weeks)**									
	Week 1					**Week 2**		**Week 3**		**Week 4**
	D1	**D2**	**D3**	**D4**	**D5**	**D1**	**D4**	**D1**	**D4**	**D1-D7**
Treatment with CPI-613	√	√	√	√						
Treatment with Bendamustine				√	√					
Neulasta					√					
Vital signs (if clinically indicated)	√	√	√	√					√	
Blood draw (12 teaspoons) for non-research related routine lab work	√	√	√	√					√	
Urinalysis	√	√								
Research Only Urinalysis	√									
Definitions of abbreviations used in this table: D1=Day 1; D2=Day 2; D3=Day 3; D4=Day 4; D5=Day 5; D7=Day 7										

Procedures	Cycles 2-6 (One Cycle = 4 weeks)									
	Week 1					Week 2		Week 3		Week 4
	D1	D2	D3	D4	D5	D1	D4	D1	D4	D1-D7
Treatment with CPI-613	√	√	√	√						
Treatment with Bendamustine				√	√					
Neulasta					√					
Vital signs (if clinically indicated)	√	√	√	√						
Blood draw (12 teaspoons) for non-research related routine lab work	√									
Urinalysis	√	√								
Research Only Urinalysis	√									
Definitions of abbreviations used in this table: D1=Day 1; D2=Day 2; D3=Day 3; D4=Day 4; D5=Day 5; D7=Day 7										

Additional Evaluations and Procedures
Within five days before the start of cycles two through six, you will have your vital signs and performance status evaluated. You will also be asked about any symptoms you may be experiencing and any medications you are taking and have an ECG.

After you have completed cycle two, you will have another CT scan to determine how well your cancer responded to treatment with CPI-613 with Bendamustine.

If the results of the CT scan indicate that your cancer has responded to the treatment, your doctor may decide that you can have two additional cycles of treatment with CPI-613 and Bendamustine. If you receive those additional cycles, you will again have a PET/CT scan at the end of cycle four.

If the results of the CT scan indicate your cancer is still responding to treatment and you receive two additional cycles of CPI-613 and Bendamustine, you will have a CT scan at the end of cycle six.
You will have a PET scan when you have completed all treatment on this protocol or when your doctor suspects relapse of disease. A positron emission tomography (PET) scan creates an image of your body's metabolic activity by injecting a small amount of a radioactive molecule into your blood through a vein. During a PET scan, a small amount of a radioactive chemical is

injected into your body through a vein in your arm. The radioactive chemical travels through your body and helps doctors see how the organs and tissues inside your body are functioning.

STORAGE OF BIOLOGICAL TISSUE

If you agree to participate in this study, you will have the option to provide blood and blood plasma samples to use for future research. If you choose to provide these samples, we will draw two teaspoons of blood and two teaspoons of blood plasma from a vein in your arm at the following time points: up to four weeks before the start of treatment with CPI-613, and prior to the last dose of CPI-613 on Day 4 of cycle one. These samples will be kept and may be used in future research to learn more about other diseases. Your samples will be obtained in the Hematology and Oncology clinic at Wake Forest University Baptist Medical Center. The sample will be sent to Rafael Pharmaceuticals, Inc for storage. We would also like to draw two teaspoons of blood up to four weeks before the start of treatment with CPI-613 to be stored at Wake Forest University Baptist Medical Center for future research by Dr. Rakhee Vaidya. It will be given only to researchers approved by Dr. Rakhee Vaidya. An Institutional Review Board (IRB) must also approve any future research study using your samples.

Your blood and blood plasma samples 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 and study staff 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 blood plasma samples 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 blood plasma samples will not be given to you or your doctor. The results will not be put in your medical record and will not affect your care.

Your blood and blood plasma samples 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.

Please choose one of the following to indicate your desire to provide blood and blood plasma samples for use in future research:

_____ YES, I would like to provide blood and blood plasma samples for use in future research, provided they are kept secure and any future study will be reviewed by an IRB. I understand that there is no benefit to me from taking part in this aspect of this study.

____ NO, I would not like to provide blood and blood plasma samples for use in future research. I understand that there is no penalty for choosing not to provide these samples, and I understand that I can still participate in this study and that my decision not to provide the samples will not affect my care.

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. All participants will be in the study until it is determined that your cancer is no longer responding to treatment with CPI-613, up to a maximum of six cycles. If you have had treatment with Bendamustine in the past, you will only receive a maximum of six cycles of treatment with this drug (including treatment before this study and during this study). Once you have had six cycles of treatment with Bendamustine, you will only receive treatment with CPI-613 for the remainder of the study.

For example, if the PET/CT scan that is performed at the end of cycle two shows that your cancer has responded to treatment, you will receive two more cycles of treatment. If the scan shows that your cancer has stopped responding, you will not receive any further treatment.

Once you have finished treatment as part of this study, you will receive a phone call from the research nurse once every two months to check and see how you are doing if you do not return to the clinic for follow-up. These phone calls will continue long term as long as you give permission.

In addition, 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 and Bendamustine 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. One goal of this study is to learn about the safety and effectiveness of the drug when used together with Bendamustine to treat Non-Hodgkin Lymphoma and Hodgkin Lymphoma. 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.

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

- Allergic reaction 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 levels of white blood cells
- Low levels of platelets (blood cells that help to form clots)
- Electrolyte imbalance
- Blood in urine

Rarely, there may be other, more severe side effects, such as inflammation throughout your body. In addition, 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.

Risks and side effects related to bendamustine include those which are:

Likely

- Lowered white blood cell count (neutrophils) that may lead to infection
- Lowered platelets, which may lead to an increase in bruising or bleeding
- Lowered red blood cells, which may cause anemia, tiredness or shortness of breath
- Fatigue
- Nausea
- Vomiting
- Infection
- Side effects during or shortly after the infusion: fever, chills

Less Likely:

- Diarrhea
- Constipation
- Loss of appetite
- Difficulty sleeping or falling asleep
- Rash
- Dehydration
- Heartburn
- Irritation or sores in the lining of the throat
- Nosebleed
- Fever with dangerously low white blood cell count
- Blood infection
- Pneumonia

Rare but Serious:

- Tumor lysis syndrome, a rapid decline in the number of leukemia/lymphoma cells. This may result in kidney failure or chemical imbalances that may have an effect on other organs like your heart. If this were to occur, you would receive close monitoring and laboratory tests, as well as appropriate medical treatment.
- Severe side effects during the infusion or shortly after, or severe allergic reactions including shortness of breath, swelling of the throat, and low blood pressure.
- Development of a second cancer such as leukemia
- A potentially life-threatening condition, affecting less than 10% of the skin, in which the skin separates and peels off.
- A life-threatening condition, affecting more than 30% of the skin, in which the skin separates and peels off.

Other Risks

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 bendamustine and other drugs. 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.

You may experience discomfort, bruising and/or bleeding where the needle is inserted. Occasionally some people become dizzy lightheaded or feel faint. Infection may occur on rare occasions.

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 drugs cause 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.

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:

For female participants:

- 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).

For male participants:

- Abstinence
- Condom with spermicide

Males should also advise their partner to use an effective birth control method such as those outlined above for females.

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.

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

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. Rakhee Vaidyathat 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:

Rakhee Vaidya, 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 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.

WHAT ARE THE COSTS?

There are no costs to you for taking part in this study. Rafael Pharmaceuticals, Inc. is providing the investigational drug (CPI-613), for all participants. Costs for your regular medical care, which are not related to this study, will be your own responsibility.

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?

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. The researchers do not, however, hold a direct financial interest in Rafael Pharmaceuticals, Inc. or the product being studied. Dr. Timothy Pardee, a co-investigator for this study, was compensated by Rafael Pharmaceuticals, Inc. for his time and travel to present clinical trial data at an advisory panel meeting in 2014 and at medical conferences from 2011-2012. Rafael has also provided some lab materials for Dr. Pardee's research.

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. Rakhee Vaidyaat [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 not in your best medical interest, your condition worsened, new information becomes available, you had an unexpected reaction, or because the entire study has been stopped.

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. Rakhee Vaidya, 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