PRINCIPAL INVESTIGATOR: Kevin Conlon, M.D.

STUDY TITLE: Phase I/II Trial Evaluating the Safety and Efficacy of Ruxolitinib in Patients with Smoldering and Chronic Adult T-Cell Leukemia (ATL)

STUDY SITE: NIH Clinical Center

Cohort: Affected patient

Consent Version: 12/30/2020

WHO DO YOU CONTACT ABOUT THIS STUDY?

Principal Investigator: Kevin Conlon, M.D.
Phone: 240-760-6087
Email: conlonkc@mail.nih.gov

This consent form describes a research study and is designed to help you decide if you would like to be a part of the research study.

You are being asked to take part in a research study at the National Institutes of Health (NIH). Members of the study team will talk with you about the information described in this document. Some people have personal, religious, or ethical beliefs that may limit the kinds of medical or research treatments they would want to receive (such as blood transfusions). Take the time needed to ask any questions and discuss this study with NIH staff, and with your family, friends, and personal health care providers. Taking part in research at the NIH is your choice.

If the individual being asked to participate in this research study is not able to give consent for themselves, you, as the Legally Authorized Representative, will be their decision-maker and you are being asked to give permission for this person to be in this study. For the remainder of this document, the term "you" refers to you as the decision-maker and/or the individual being asked to participate in this research

IT IS YOUR CHOICE TO TAKE PART IN THE STUDY

You may choose not to take part in this study for any reason. If you join this study, you may change your mind and stop participating in the study at any time and for any reason. In either case, you will not lose any benefits to which you are otherwise entitled. However, to be seen at the NIH, you must be taking part in a study or are being considered for a study. If you do choose to leave the study, please inform your study team to ensure a safe withdrawal from the research.

WHY IS THIS STUDY BEING DONE?

Human T-cell leukemia virus 1 (HTLV-1) is a virus that causes Adult T-cell Leukemia (ATL). ATL is a complex disease that causes disruptions in your body's ability to control the HTLV-1 virus and the growth and reproduction of cells infected with the virus. Ruxolitinib was recently approved by the FDA for the treatment of patients with myelofibrosis (MF). Ruxolitinib is an oral

drug that has the ability to interfere with the regulatory proteins that are important to the development and growth of ATL cells. Experiments suggest that drugs like ruxolitinib can interrupt important activity in ATL cells. In addition, we have tested the ability of ruxolitinib to limit the growth and reproduction of ATL cells and we have shown that ruxolitinib is able to slow the growth of leukemic cells, indicating that this treatment could potentially be effective in treating ATL.

WHY ARE YOU BEING ASKED TO TAKE PART IN THIS STUDY?

You are being asked to take part in this study because you have HTLV-1 associated ATL which has or has not been treated. You may have been a patient who took part in this study before or who is being asked to take part again with a higher dose of study drug.

HOW MANY PEOPLE WILL TAKE PART IN THIS STUDY?

There will be up to 35 patients on this trial.

DESCRIPTION OF RESEARCH STUDY

WHAT WILL HAPPEN IF YOU TAKE PART IN THIS RESEARCH STUDY?

If the screening tests show that you are eligible to take part, you will receive ruxolitinib orally at a dose of 30, 40, or 50 milligrams (mg) twice daily. This will be given in cycles of 28 days, generally planned to be on an outpatient basis. This dose is higher than the currently FDA approved dose, but some other patients have been able to tolerate increased dosage and we believe that this increased dose will be more effective in treating ATL without causing patients to have too many bad side effect (also called unacceptable toxicity or side effects).

In order to confirm that the doses are safe, patients will be enrolled and start treatment on study in groups as follows:

- Dose escalation part: First, 3-6 study participants will receive ruxolitinib at the lowest dose. If the study drug does not cause serious side effects, the next group of 3-6 patients will receive ruxolitinib at the next highest dose, and so on. Each group of patients will be 3-6 each, with the study staff closely monitoring side effects for at least 4 weeks before enrolling the next group and/or moving on to the next dose.
- Dose expansion part: Once the highest safe dose of ruxolitinib is found, then at least a total of 9 patients will receive that dose to learn more about the drug and its effect on HTLV-1 associated ATL.

BEFORE YOU BEGIN THE STUDY

Before you begin the study, you will have several tests performed to check whether the study is suitable for you. This is called screening. Some of these will be done before signing the informed consent document for this study or as part of another screening study. Your doctor will review your medical history and the drugs that you are currently taking as well as the previous treatments of your disease to determine whether you can participate in this study.

- Your medical history, including previous cancer treatments, any current or previous medications (prescription, supplement, and over-the-counter medicines), will be reviewed.

If you have medical records from another clinic or hospital, you will be asked to get copies of these records, or your study doctor may be able to request them on your behalf.

- A complete physical examination will be performed that will include your vital signs (blood pressure, pulse, body temperature, and respiratory rate) and recording your height and weight, and evaluation of your ability to carry out daily activities.
- Blood tests will be collected to:
    - measure your liver, kidney, and other organ function, red and white blood cells, platelets, electrolytes and others;
    - test for certain viruses and infections (such as hepatitis)
    - test for human immunodeficiency virus (HIV) infection. This is the virus that causes AIDS. If you are infected with HIV you will not be able to participate in this study. We will tell you what the results mean, how to find care, how to avoid infecting others, how we report HIV infection, and the importance of informing your partners at possible risk because of your HIV infection.
    - run routine tests done in people with your type of cancer to confirm your diagnosis and the status of your disease.
- For females of child-bearing potential, a pregnancy test will be done (blood sample). You will not be able to participate if you are pregnant or you are breast feeding because we don't know how this medicine would affect your baby or your unborn child.
- Bone marrow testing will be done to check your disease (any time prior to treatment; one may not be needed if done in the past year). These are done by numbing your hipbone using a small needle containing local anesthesia, and then a needle will be put into the hipbone, and a small amount of bone marrow will be taken out through the needle
- Imaging will include a CT scan of neck, chest, abdomen and pelvis. Other body areas may be imaged if clinically indicated.

DURING THE STUDY

You should plan to stay at/near the Clinical Center during the first 2 weeks of treatment. You will be seen in the outpatient clinic on days 1, day 4 or 5, and day 8 to be examined by a doctor and get blood tests to monitor how you are doing and to evaluate your response to the treatment. If are doing well, you may be able to receive ongoing blood testing for the rest of cycle 1 closer to home, returning to the Clinical Center for cycle 2; otherwise, we may ask you to remain nearby for closer monitoring. After cycle 1 you will be seen at least once per cycle.

While ruxolitinib has been very well tolerated, if you have any significant side effects during treatment, you may have extra outpatient clinic visits. You will receive appropriate medications for relief of your particular symptoms and your ruxolitinib may be held. There are also medications that you should avoid while receiving ruxolitinib as these may interact with the study drug. The medications to avoid include some antibiotics, steroids, and hormones. Please talk with your study doctor before you take any new medication while you are on study. You should also avoid eating grapefruit or drinking grapefruit juice while taking ruxolitinib.

If there is evidence that your ATL is responding and there is a dose that does not cause unacceptable side effects for you, you may be given the option to continue ruxolitinib until there is evidence that the treatment has stopped working. If your ATL completely responds (no evidence of the disease), you will stop treatment and continue close monitoring only.

Standard procedures being done because you are in this study; these may be done more often because you are in the study:

- Medical history and physical exam
- Photographs of skin lesions or other visually-apparent signs of your disease (if present) at your initial and follow-up visits
- CT scans of the neck chest, abdomen and pelvis to identify your tumor locations and size
- Measurements of tumor markers in your blood
- Standard blood tests

Tests and procedures that are being done to see how the ruxolitinib is affecting your ATL:

- Blood tests to measure changes in the number and percentages of specific sets of ATL cells circulating in your blood
- Blood tests to measure the changes in the metabolic rate of ATL cells and markers of immune stimulation produced in your blood.
- Some patients with ATL skin lesions that are easily accessed may be asked to have additional biopsies to measure changes in the cell processes or genes induced by ruxolitinib treatment.
- CT scans may also be done, as needed, to identify your tumor locations and size

Optional Biopsy

We may request biopsies after you sign consent, with the first 28 days after the start of treatment and at disease progression. Some of the biopsies to be performed may be done using CT guidance and are to be used for research purposes and will not benefit you. It might help other people in the future. The decision to participate in this part of the research is optional, and no matter what you decide to do, it will not affect your care.

If you agree to have the optional biopsy, you will be asked to sign a separate procedure consent before you have the procedure.

WHEN YOU ARE FINISHED TAKING THE STUDY DRUG

When you are finished taking the study therapy you will have a repeat physical exam, CT scans and blood tests within about 30 days after the last dose. We will continue to collect information from CT scans or other tests to monitor your disease if you come off treatment for a reason other than a worsening or progression of your disease. If you are having side effects related to the ruxolitinib, we may continue to follow you until these side effects improve or until you start another treatment. After this time, you will be taken off study.

BIRTH CONTROL

If you are a woman who is breast feeding or pregnant, you may not take part in the study because we don't know how ruxolitinib would affect your baby or your unborn child. If you are a woman who can become pregnant, you will need to practice an effective form of birth control before starting study treatment, during study treatment, and for 1 week after you finish study treatment. If you think that you are pregnant, you should tell your study doctor or nurse at once.

Effective forms of birth control include:

- abstinence
- intrauterine device (IUD)
- hormonal [birth control pills, injections, or implants]
- tubal ligation
- vasectomy

RISKS OR DISCOMFORTS OF PARTICIPATION

What side effects or risks can I expect from being in this study?

Ruxolitinib is generally well tolerated in patients with primary myelofibrosis. Below is a list of the side effects people have experienced who have taken this drug:

Likely:

- Anemia (lowered numbers of red blood cells) that may require blood transfusion
- Decreased platelets (aid in blood clotting)
- Lowered numbers of a type of infection-fighting white blood cells (leukocytes, granulocytes and lymphocytes)
- Dizziness

Unlikely:

- Headaches
- Infections (bacterial, viral, fungal)
- Weight gain
- Flatulence (increased bowel gas)
- Abnormal liver blood tests
- Elevation of blood cholesterol level
- Increased bruising

Rare:

- Drug infusion reactions

Risks of blood sampling:

The blood samples collected as part of this study are not expected to produce any important decrease in the total amount of blood in your body. Side effects may include pain and discomfort,

bruising, and rarely inflammation of the vein, bleeding or infection. Additionally, some patients can experience light-headedness or fainting.

Risks associated with biopsy of tumor, bone marrow and skin samples:

- Bone marrow: These procedures usually cause only brief discomfort at the site from which the biopsy is taken. Rarely, infection or bleeding may occur at the needle site. A numbing agent that can cause a stinging or burning sensation may be injected at the site of your bone marrow biopsy. The biopsy needle will go through the skin into the bone and may produce a brief, sharp pain. As the bone marrow liquid is taken from the bone, there may be a brief, sharp pain. Since the inside of the bone cannot be numbed, this procedure may cause some discomfort, however not all patients experience discomfort. The possible side effects associated with a bone marrow biopsy include pain, bleeding, bruising, and infection, as well as a reaction to the numbing agent.
- Optional Tumor biopsy: Once treatment is complete as part of follow-up assessments, you may agree to the biopsy now and change your mind later. If at any time you do not want to have a biopsy done, please tell us, it will not affect your care. If you agree to have the biopsy, you will be asked to sign a separate procedure consent before you have the procedure(s). The likely side effects include discomfort or pain, redness, swelling, and/or bruising at the site of the needle insertion. Bleeding from the site of the needle insertion is a less likely risk. Rarely, significant infection or bleeding from this procedure, allergic reaction to the anesthetic, or formation of a scar at the site of needle entry occurs. If you will have sedation with the procedure, these risks will be discussed with you prior to the procedure. You will be asked to sign a separate consent form prior to any biopsy procedure.
- Imaging/scans: CT scans are used to monitor your disease while you are in this study. CT scans expose you to radiation; the amount depends on the number of body areas scanned. In addition, scans involve use of contrast (oral and/or IV) that the cancer may be seen better on the images. You will have scans done (based on your disease at the discretion of your doctor) prior to treatment (if these need to be repeated from screening), at Day 29 Cycle 1, Day 29 Cycle 2 and every 2 Cycles thereafter during treatment.

  The below describes more information about the risks of the contrast and imaging:

  - Contrast Agents: There is a chance of developing an allergic reaction from the contrast material, which may cause symptoms ranging from mild itching or a rash to severe difficulty breathing, shock or rarely, death. The contrast material may also cause kidney problems. The study doctors will do a blood test prior to the test to confirm that it is safe you to receive the contrast.

    For IV contrast: You may feel discomfort when the contrast material is injected. You may feel warm, flushed, get a metallic taste in your mouth or, rarely, may make you vomit or feel sick to your stomach.

    For oral contrast: You may experience vomiting, nausea, cramping, bloating, constipation or diarrhea after drinking the contrast.
  - CT Scans: The CT scanner is a doughnut-shaped machine that uses x-rays to create computer pictures showing the inside of your body. During the procedure, you will need to lie still on a table inside the CT machine. The table will move you in and

out of the machine during the scan and you will be instructed to hold your breath. The scan itself will only take a few minutes to complete, the entire visit will take about 30 minutes. For the risks, see "Radiation" below & "Contrast Agent" above.

- Radiation – CT Scans: During your participation in this research study, you may be exposed to radiation from 8 CT Scans each year and up to 3 CT guided Biopsies. The amount of radiation exposure from these procedures is equal to approximately 12.8 rem. A rem is a unit of absorbed radiation.

  Every day, people are exposed to low levels of radiation that come from the sun and the environment around them. The average person in the United States receives a radiation exposure of 0.3 rem per year from these sources. This type of radiation is called "background radiation." This study will expose you to more radiation than you get from everyday background radiation. No one knows for sure whether exposure to these low amounts of radiation is harmful to your body.

  The CT scans that you get in this study will expose you to the roughly the same amount of radiation as 42.7 years' worth of background radiation. Being exposed to too much radiation can cause harmful side effects such as an increase in the risk of cancer. The risk depends on how much radiation you are exposed to. Please be aware that about 40 out of 100 people (40%) will get cancer during their lifetime, and 20 out of 100 (20%) will die from cancer. The risk of getting cancer from the radiation exposure in this study is 1.3 out of 100 (1.3%) and of getting a fatal cancer is 0.6 out of 100 (0.6%).

- Blood draws: The possible side effects of drawing blood include pain, bleeding, bruising, dizziness, light-headedness, fainting and, on rare occasions, local blood clot formation or infection with redness and irritation of the vein.
- Electrocardiogram (ECG/EKG): Some skin irritation can occur where the ECG/EKG electrodes are placed. Once the electrodes are placed, the test will begin, is completely painless, and generally takes less than a minute to perform. After the test, the electrodes are removed.

POTENTIAL BENEFITS OF PARTICIPATION

Are there benefits to taking part in this study?

Taking part in this study may or may not have any effect on your disease or benefit for your general condition. We hope that you will get personal medical benefit from taking part in this study, but we cannot be certain. These potential benefits could include shrinking of your tumor or lessening of your symptoms, such as the pain caused by your cancer. Because there is not much information about the drug's effect on your cancer, we do not know if you will benefit from taking part in this study, although the knowledge gained from this study may help others in the future who have cancer.

ALTERNATIVE APPROACHES OR TREATMENTS

What other choices do I have if I do not take part in this study?

Instead of being in this study, you have these options**:**

- Getting treatment or care for your cancer without being in a study
- Taking part in another study
- Getting comfort care, also called palliative care. This type of care helps reduce pain, tiredness, appetite problems and other problems caused by the cancer. It does not treat the cancer directly. Instead, it tries to improve how you feel. Comfort care tries to keep you as active and comfortable as possible.

Please talk to your doctor about these and other options.

STOPPING THERAPY

Your doctor may decide to take you off this study for the following reasons:

- if he/she believes that it is in your best interest
- if your disease comes back during treatment
- if you have side effects from the treatment that are your doctor thinks are too severe
- if new information shows that another treatment would be better for you
- if the study drug, ruxolitinib is no longer available
- if the FDA, other health authority, or the NIH decide to end the study
- If you do not follow the study requirements (for instance, if you are not coming for your study visits when scheduled).In this case, you will be informed of the reason therapy is being stopped.

You can stop taking part in the study at any time. However, if you decide to stop taking part in the study, we would like you to talk to the study doctor and your regular doctor first.

If you decide at any time to withdraw your consent to participate in the trial, we will not collect any additional medical information about you. However, according to FDA guidelines, information collected on you up until that point may still be provided to designated representatives. If you withdraw your consent and leave the trial, any samples of yours that have been obtained for the study and stored at the NCI can be destroyed upon request. However, any samples and data generated from the samples that have already been distributed to other researchers or placed in the research databases **cannot** be recalled and destroyed.

CONFLICT OF INTEREST

The National Institutes of Health (NIH) reviews NIH staff researchers at least yearly for conflicts of interest. This process is detailed in a Protocol Review Guide. You may ask your research team for a copy of the Protocol Review Guide or for more information. Members of the research team who do not work for NIH are expected to follow these guidelines but they do not need to report their personal finances to the NIH.

Members of the research team working on this study may have up to $15,000 of stock in the companies that make products used in this study. This is allowed under federal rules and is not a conflict of interest.

USE OF SPECIMENS AND DATA FOR FUTURE RESEARCH

To advance science, it is helpful for researchers to share information they get from studying human samples. They do this by putting it into one or more scientific databases, where it is stored along with information from other studies. A researcher who wants to study the information must apply to the database and be approved. Researchers use specimens and data stored in scientific databases to advance science and learn about health and disease.

We plan to keep some of your specimens and data that we collect and use them for future research and share them with other researchers. We will not contact you to ask about each of these future uses. These specimens and data will be stripped of identifiers such as name, address or account number, so that they may be used for future research on any topic and shared broadly for research purposes. Your specimens and data will be used for research purposes only and will not benefit you. It is also possible that the stored specimens and data may never be used. Results of research done on your specimens and data will not be available to you or your doctor. It might help people who have cancer and other diseases in the future.

If you do not want your stored specimens and data used for future research, please contact us in writing and let us know that you do not want us to use your specimens and/or data. Then any specimens that have not already been used or shared will be destroyed and your data will not be used for future research. However, it may not be possible to withdraw or delete materials or data once they have been shared with other researchers.

COMPENSATION, REIMBURSEMENT, AND PAYMENT

Will you receive compensation for participation in the study?

Some NIH Clinical Center studies offer compensation for participation in research. The amount of compensation, if any, is guided by NIH policies and guidelines.

You will not receive compensation for participation in this study.

Will you receive reimbursement or direct payment by NIH as part of your participation?

Some NIH Clinical Center studies offer reimbursement or payment for travel, lodging or meals while participating in the research. The amount, if any, is guided by NIH policies and guidelines.

On this study, the NCI will cover the cost for some of your expenses. Some of these costs may be paid directly by the NIH and some may be reimbursed after you have paid. The amount and form

of these payments are determined by the NCI Travel and Lodging Reimbursement Policy. You will be given a summary of the policy which provides more information.

Will taking part in this research study cost you anything?

NIH does not bill health insurance companies or participants for any research or related clinical care that you receive at the NIH Clinical Center.

- You will receive study treatment at no charge to you. This may include surgery, medicines, laboratory testing, x-rays or scans done at the Clinical Center, National Institutes of Health (NIH), or arranged for you by the research team to be done outside the Clinical Center, NIH if the study related treatment is not available at the NIH.
- If some tests and procedures are performed outside the NIH Clinical Center, you may have to pay for these costs if they are not covered by your insurance company.
- Medicines that are not part of the study treatment will not be provided or paid for by the NIH Clinical Center.
- Once you have completed taking part in the study, medical care will no longer be provided by the NIH Clinical Center.

CLINICAL TRIAL REGISTRATION AND RESULTS REPORTING

A description of this clinical trial will be available on http://www.ClinicalTrials.gov, as required by U.S. Law. This Web site will not include information that can identify you. At most, the Web site will include a summary of the results. You can search this Web site at any time.

CONFIDENTIALITY PROTECTIONS PROVIDED IN THIS STUDY

Will your medical information be kept private?

We will do our best to make sure that the personal information in your medical record will be kept private. However, we cannot guarantee total privacy. Organizations that may look at and/or copy your medical records for research, quality assurance, and data analysis include:

- The NIH and other government agencies, like the Food and Drug Administration (FDA), which are involved in keeping research safe for people.
- National Institutes of Health Intramural Institutional Review Board

The researchers conducting this study and the NIH follow applicable laws and policies to keep your identifying information private to the extent possible. However, there is always a chance that, despite our best efforts, your identity and/or information about your participation in this research may be inadvertently released or improperly accessed by unauthorized persons.

In most cases, the NIH will not release any identifiable information collected about you without your written permission. However, your information may be shared as described in the section of this document on sharing of specimens and data, and as further outlined in the following sections.

Further, the information collected for this study is protected by NIH under a Certificate of Confidentiality and the Privacy Act.

Certificate of Confidentiality

To help us protect your privacy, the NIH Intramural Program has received a Certificate of Confidentiality (Certificate). With this certificate, researchers may not release or use data or information about you except in certain circumstances.

NIH researchers must not share information that may identify you in any federal, state, or local civil, criminal, administrative, legislative, or other proceedings, for example, if requested by a court.

The Certificate does not protect your information when it:

1. is disclosed to people connected with the research, for example, information may be used for auditing or program evaluation internally by the NIH; or
2. is required to be disclosed by Federal, State, or local laws, for example, when information must be disclosed to meet the legal requirements of the federal Food and Drug Administration (FDA);
3. is for other research;
4. is disclosed with your consent.

The Certificate does not prevent you from voluntarily releasing information about yourself or your involvement in this research.

The Certificate will not be used to prevent disclosure to state or local authorities of harm to self or others including, for example, child abuse and neglect, and by signing below you consent to those disclosures. Other permissions for release may be made by signing NIH forms, such as the Notice and Acknowledgement of Information Practices consent.

Privacy Act

The Federal Privacy Act generally protects the confidentiality of your NIH medical records we collect under the authority of the Public Health Service Act. In some cases, the Privacy Act protections differ from the Certificate of Confidentiality. For example, sometimes the Privacy Act allows release of information from your medical record without your permission, for example, if it is requested by Congress. Information may also be released for certain research purposes with due consideration and protection, to those engaged by the agency for research purposes, to certain federal and state agencies, for HIV partner notification, for infectious disease or abuse or neglect reporting, to tumor registries, for quality assessment and medical audits, or when the NIH is involved in a lawsuit. However, NIH will only release information from your medical record if it is permitted by both the Certificate of Confidentiality and the Privacy Act.

POLICY REGARDING RESEARCH-RELATED INJURIES

The NIH Clinical Center will provide short-term medical care for any injury resulting from your participation in research here. In general, no long-term medical care or financial compensation for research-related injuries will be provided by the NIH, the NIH Clinical Center, or the Federal Government. However, you have the right to pursue legal remedy if you believe that your injury justifies such action.

PROBLEMS OR QUESTIONS

If you have any problems or questions about this study, or about your rights as a research participant, or about any research-related injury, contact the Principal Investigator, Kevin Conlon, M.D., conlonkc@mail.nih.gov, 240-760-6087. You may also call the NIH Clinical Center Patient Representative at 301-496-2626, or the NIH Office of IRB Operations at 301-402-3713, if you have a research-related complaint or concern.

CONSENT DOCUMENT

Please keep a copy of this document in case you want to read it again.

Adult Research Participant: I have read the explanation about this study and have been given the opportunity to discuss it and to ask questions. I consent to participate in this study.

Signature of Research Participant	Print Name of Research Participant	Date

Legally Authorized Representative (LAR) for an Adult Unable to Consent: I have read the explanation about this study and have been given the opportunity to discuss it and to ask questions. I am legally authorized to make research decisions on behalf of the adult participant unable to consent and have the authority to provide consent to this study. As applicable, the information in the above consent was described to the adult participant unable to consent who agrees to participate in the study.

Signature of LAR	Print Name of LAR	Date

Investigator:

Signature of Investigator	Print Name of Investigator	Date

Witness to the oral short-form consent process only:

Witness:

Signature of Witness*	Print Name of Witness	Date

***NIH ADMINISTRATIVE SECTION TO BE COMPLETED REGARDING THE USE OF AN INTERPRETER:**

____ An interpreter, or other individual, who speaks English and the participant's preferred language facilitated the administration of informed consent and served as a witness. The investigator obtaining consent may not also serve as the witness.

____ An interpreter, or other individual, who speaks English and the participant's preferred language facilitated the administration of informed consent but did not serve as a witness. The name or ID code of the person providing interpretive support is: _____.