INSTITUTE: National Cancer Institute

STUDY NUMBER: 12-C-0113 PRINCIPAL INVESTIGATOR: Kevin Conlon, MD

STUDY TITLE: A Phase I Study of A Continuous Intravenous Infusion of Recombinant Human IL-15 (rhIL-15) in Adults with Metastatic Cancers

Continuing Review Approved by the IRB on 07/23/18
Amendment Approved by the IRB on 07/14/18 (J) Date posted to web: 08/07/18

Standard

INTRODUCTION

We invite you to take part in a research study at the National Institutes of Health (NIH).

First, we want you to know that:

Taking part in NIH research is entirely voluntary**.**

You may choose not to take part, or you may withdraw from the study at any time. In either case, you will not lose any benefits to which you are otherwise entitled. However, to receive care at the NIH, you must be taking part in a study or be under evaluation for study participation.

You may receive no benefit from taking part. The research may give us knowledge that may help people in the future.

Second, 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). If you have such beliefs, please discuss them with your NIH doctors or research team before you agree to the study.

Now we will describe this research study. Before you decide to take part, please take as much time as you need to ask any questions and discuss this study with anyone at NIH, or with family, friends or your personal physician or other health professional.

Why is this study being done?

You are being invited to participate in a research study on the effects of an investigational new drug called recombinant human interleukin-15 (rhIL-15). rhIL-15 is not yet approved by the Food and Drug Administration (FDA). rhIL-15 is a man-made version of a small protein (cytokine) that is naturally produced in your body by certain white blood cells and increases the activity and strength of the immune system. Patients with cancer can have a weak immune system. This weakness can be caused by the cancer itself, or by treatments such as radiation, chemotherapy or other drugs that work against the immune system. It is hoped that rhIL-15 can "boost" or strengthen patients' immune systems and restore immune responses against cancer.

In this study, rhIL-15 will be given through a vein continuously (without a break) for 10 days (240 hours) or 5 days (120 hours). This is called a continuous intravenous infusion. In the first trial of rhIL-15 in humans, rhIL-15 was given through a vein for 30 minutes each day for 12 days in a row. This study will see if rhIL-15 given continuously for 10 or 5 days gives a better boost in the immune system.

Why are you being asked to take part in this study?

You are being asked to take part in this study because there are no treatments that are very effective for the cancer you have. We want to find out what effects; good and/or bad, rhIL-15 has on you and your cancer.

How many people will take part in this study?

Up to 52 patients may participate in this study.

Description of Research Study

The purpose of this study is to test the safety of different doses of rhIL-15 when given as a continuous infusion for 10 or 5 days. When you are enrolled in the study, you will be assigned to a Group of 3-6 patients and you will receive rhIL-15 treatment at the dose level assigned to that Group. The first group of patients entering the study will receive the lowest dose of rhIL-15 planned for this trial. If these patients tolerate the treatment well (no unacceptable side effects); then new groups of 3-6 patients will be enrolled and treated with higher doses of rhIL-15. Initial groups of patients will be treated with the 10-day schedule. After the group of patients on the 10-day schedule is finished then new groups of 3-6 patients will be treated with the 5-day schedule to identify the highest dose that can be safely given with this shorter schedule.

For the 10-day treatment groups, rhIL-15 will be given about every 42 days for Cycles 1 and 2, then every 28 days for Cycle 3 and beyond unless you have unacceptable side effects or your disease gets worse. CT scans will be performed before you start treatment and after each treatment cycle for the first 2 cycles to see if the treatment is shrinking your tumor. For the 5-day treatment groups, rhIL-15 will be given every 21 days and the first set of CT scans to check for response will be performed after the second cycle. If there is evidence of improvement in your scans and you do not have unacceptable side effects, you may continue rhIL-15 treatment. For the 10-day treatment group, the initial decision about whether to continue treatment will be made after 2 cycles of treatment and for the 5-day treatment group, the initial decision about whether to continue treatment will be made after 4 cycles so patients treated with both schedules will receive an equal number of doses to demonstrate their tumor is sensitive to rhIL-15.

If you continue treatment beyond Cycle 3 or 5, you will have CT scans after every other cycles (4, 6, 8 etc.). If your scans show worsening of your disease or the CT scans are unchanged after any 2 cycles of treatment in a row, rhIL-15 treatment will be stopped. Patients who stop treatment for side effects or no improvement in their disease will continue routine follow-up outpatient assessments unless they choose to start another treatment or withdraw from the trial. During treatment, we will perform routine blood tests to determine the effects of rhIL-15

treatment on your normal organ function and investigational tests to examine the effect of the treatment on your immune system. It is possible that you will be asked to have an additional CT scan to document a significant response to the rhIL-15 at least 28 days after the initial CT scan which showed the improvement. This is not a common practice and would expose you to slightly greater amount of radiation than normal. You are free to refuse this additional scan if you are concerned about the additional radiation exposure with this scan.

What will happen if you take part in this research study?

Before you begin the study

You will need to have examinations, tests and procedures to see if you qualify for the study. Many of these tests are performed as part of your regular medical care or during the prior treatments for your cancer. You will be asked to sign a separate consent describing the tests you will need to have done. These tests need to be performed within 28 days before you enroll in this study. After all of these examinations are performed and we determine you are eligible for the trial, you will be asked to sign this informed consent agreeing to participate in this research study.

During the study

You will be admitted to the inpatient unit for the rhIL-15 infusion. If you do not already have a functional implanted central venous catheter in place, we will insert a small, flexible tube known as a "PICC line" or a similar type of intravenous device into one or two of your veins for the drug to be given and for the multiple blood samples planned for this study.

Depending on your dosing schedule, you will spend approximately 12 or 6 days in the hospital for treatment and monitoring of your condition. You will be closely monitored during the treatment. If you develop side effects such as fever, chills, decreased blood pressure, blood test abnormalities, decrease in hemoglobin (red blood cells), rash or an allergic reaction, you will be treated as needed with IV fluids or solutions, transfusion, nausea and vomiting and diarrhea medications, ibuprofen (Motrin), acetaminophen (Tylenol) or antihistamines (Benadryl). If you tolerate the treatment well, you will be free to walk around the unit and the hospital building, but you will not be allowed outside the Clinical Center complex while you are being treated. While you are at the Clinical Center, we will also perform study tests and procedures to see how the study drug is affecting your body. Please see below for more details.

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
- Measurement of vital signs
- CT scans of the chest, abdomen and pelvis to identify your tumor locations and size
- EKG to check your heart

- Standard blood tests

Tests and procedures that are being done to see how the study is affecting your body:

- Blood tests to measure changes in the number and percentages of specific sets of white blood cells (lymphocytes) that make up your immune system and the production of other cytokines in your blood that result from the rhIL-15 treatment
- Blood tests to measure the amount of rhIL-15 in your blood over time; these will be collected during the first treatment cycle only
- Blood tests for antibodies to check whether your immune system is reacting against rhIL-15

When you are finished taking the drugs (treatment)

After you are done taking rhIL-15, we would like to do the following tests before you leave the study:

- History and physical exam
- Standard blood tests
- Research blood tests for antibodies against rhIL-15

If your treatment is stopped after 2 or 4 cycles because your disease remains unchanged, we would like to continue to follow you to see how long your disease remains stable. We will ask you to come to the Clinical Center for routine exams and x-rays every 2 months for the first 6 months after you stop taking rhIL-15 (3 visits) and then every 3 months thereafter for up to 2 years after your start of treatment. If your disease worsens or you start another treatment, the follow-up would end.

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 this medicine would affect your baby or your unborn child. If you are a woman who can become pregnant, or are the partner of 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 4 months after you finish study treatment. If you think that you or your partner is 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

Optional Biopsy

If you have a tumor that is easy to biopsy (remove a small piece of), you may be asked to have two biopsies to measure changes in the tumor itself as a result of the rhIL-15 treatment. The first biopsy would be done prior to beginning rhIL-15 treatment and the second biopsy would be performed at a convenient time sometime during the second or third week on treatment. These biopsies are done using a needle to collect the sample. Before the biopsies you will receive local anesthesia (numbing medicine similar to that used in the dentist's office) and there will be minimal discomfort. These biopsies are optional; they are exclusively for research purposes and will not benefit you. You do not have to agree to have them. You can still participate in the main study even if you decide not to have the biopsies.

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

Risks or Discomforts of Participation

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

You may have side effects while on the study. Everyone taking part in the study will be watched carefully for any side effects. However, doctors don't know all the side effects that may happen. Side effects may be mild or very serious. Your health care team may give you medicines to help lessen side effects. Some side effects may go away soon after you stop taking rhIL-15. In some cases, side effects can be serious, long lasting, may never go away, or may result in death.

rhIL-15 has been given to 19 patients as a short (30 minute) IV infusion in a trial that has been completed and to 25 patients participating in this trial as of April 2016. The treatment in this trial has been tolerated fairly well with some exceptions:

One patient whose cancer had spread to the lungs had breathing problems and required oxygen treatment.

Two patients who were treated at the highest dose level of rhIL-15 (4 mcg/kg) had serious side effects including one patient who died from complications caused by blood vessel blockage. The first patient developed diarrhea, most likely due to a change in her liquid feeding tube preparation and treatment with antibiotics that were given for a suspected infection. The diarrhea led to an interruption of the patient's rhIL-15 treatment. The rhIL-15 was restarted after the patient's diarrhea decreased. Soon afterwards the patient developed abdominal pain and other problems that required the patient be taken to surgery. During the surgery the patient was discovered to have multiple areas of her stomach as well as her small and large bowel that had decreased blood flow. The area of involvement was too large to allow removal of all the damaged areas. At that time, the rhIL-15 treatment was permanently discontinued. The patient was given additional antibiotics, IV fluids and blood pressure medicine to support her during this period. The patient eventually died as a consequence of this event. In all the patients previously

treated in any of the rhIL-15 trials, we have had 2 or 3 patients with a few loose stools of short episodes (approximately 1 day) of diarrhea that did not appear related to or worsened by the rhIL-15 treatment. Although we do not entirely understand the exact cause of this event, it appears that rhIL-15 contributed to this serious toxicity. The second patient had periods of confusion related to the rhIL-15 treatment that eventually cleared up after the rhIL-15 was stopped. This patient had a large amount of cancer in his liver and we believe that added to his confusion. We will no longer treat patients with a large amount of cancer in their liver and we will stop treatment in any patient who has even mild diarrhea. We believe these changes will allow us to treat patients at higher dose levels for the upcoming patients.

There have been 2 patients who had significant bleeding episodes (the first patient bled from one of the airways in the lung and the second patient bled from the small bowel). In both cases, it is possible that the bleeding was caused by other factors, including tumor; but it is also possible that rhIL-15 was a contributing factor.

To reduce the chance that future patients will experience these events, changes have been made to the requirements that patients must meet in order to enroll on this study. The changes include performing extra blood tests and disappearance of side effects from previous cancer treatments.

The doctor going through this consent with you will describe these events and other toxicities seen in patients previously treated on this protocol in greater detail. Based on observations from all the rh IL-15 clinical trials to date, the known characteristics of this class of drug (interleukins) and the safety studies of rhIL-15 carried out in monkeys, the following side effects may be expected or theoretically possible:

Possible:

- Abnormal heartbeat
- Decreased red blood cells (anemia) which may require blood transfusion
- Pain in belly
- Low blood pressure which may cause feeling faint
- Chills
- Fatigue/Tiredness
- Fever
- Lowered numbers of a type of infection-fighting white blood cells (granulocytes)
- Increased or decreased numbers of blood immune cells (lymphocytes)
- Low albumin (blood protein)
- Liver blood test abnormalities
- Swelling of arms, legs

- Swelling and redness at the site of the medication injection
- Severe blood infection
- Bruising, bleeding
- Infection, especially when white blood cell count is low
- Muscle weakness
- Dizziness, headache
- Shortness of breath
- Dry skin
- Rash
- Fluid in the organs which may cause low blood pressure, shortness of breath, swelling of ankles
- Diarrhea
- Nausea and vomiting
- High blood pressure which may cause blurred vision
- Increased heart rate
- Decreased platelets (cells that help with blood clotting)
- Immune responses against rhIL-15
- Decreased blood oxygen level
- Blood chemistry (electrolyte) abnormalities

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 of a central line: In order to receive this therapy, you may need to have an intravenous catheter placed. This catheter is usually placed in the arm, chest or neck area into a major vein inside your chest. The catheter may be used for infusion of rhIL-15 and for drawing blood. It is usually inserted under local anesthesia. The risks associated with the procedure include pain, bleeding, infection, inflammation and puncture of the underlying lung. Lung puncture can result in lung collapse, which might require that a chest tube be placed into the chest cavity (usually for a day or two) to help the lung re-inflate. The long-term risks of the catheter include infection and clotting of the vein in which the catheter sits. If these occur, it may be necessary to remove the catheter. These risks will be explained to you in more detail at the time of the insertion.

Potential Benefits of Participation

Are there benefits to taking part in this study?

Taking part in this study may not have any effect on your disease or benefit for your general condition. We do not know if you will receive personal, medical benefit from taking part in this study. 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 stop your therapy for the following reasons:

- if he/she believes that it is in your best interest
- if your disease comes back during treatment and you need to have a different treatment
- if you have side effects from the treatment that your doctor thinks are too severe
- if new information shows that another treatment would be better for you
- if the study drug, rhIL-15 is no longer available
- if the FDA, other health authority, the NIH or the Biopharmaceutical Development Program (the makers of the study drug) 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 to 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 can**not** be recalled and destroyed.

Research Subject's Rights

What are the costs of taking part in this study?

If you choose to take part in the study, the following will apply, in keeping with the NIH policy:

- 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.
- There are limited funds available to cover the cost of some tests and procedures performed outside the Clinical Center, NIH. 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 Clinical Center, NIH.
- Once you have completed taking part in the study, medical care will no longer be provided by the Clinical Center, NIH.

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 National Cancer Institute (NCI) and other government agencies, like the Food and Drug Administration (FDA), which are involved in keeping research safe for people.
- National Cancer Institute Institutional Review Board
- Regulatory agencies in the United States

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.

Certificate of Confidentiality

To help us protect your privacy, we have obtained a Certificate of Confidentiality. The researchers can use this Certificate to legally refuse to disclose information that may identify you in any federal, state, or local civil, criminal, administrative, legislative, or other proceedings, for example, if there is a court subpoena. The researchers will use the Certificate to resist any demands for information that would identify you, except as explained below.

You should also know that there are several circumstances in which the Certificate does not provide coverage. These include when information:

- will be used for auditing or program evaluation internally by the NIH; or
- must be disclosed to meet the legal requirements of the federal Food and Drug Administration (FDA).
- is necessary for your medical treatment and you have consented to this disclosure;
- is for other research.

In addition, identifiable, sensitive information protected by this Certificate cannot be admissible as evidence or used for any purpose in any action, suit, or proceeding without your consent.

You should understand that a Certificate of Confidentiality does not prevent you or a member of your family from voluntarily releasing information about yourself or your involvement in this research. If an insurer, employer, or other person obtains your written consent to receive research information, then the researchers will not use the Certificate to withhold that information.

The Certificate of Confidentiality will not protect against the required reporting by hospital staff of information on suspected child abuse, reportable communicable diseases, and/or possible threat of harm to self or others.

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, 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.

OTHER PERTINENT INFORMATION

1. Confidentiality. When results of an NIH research study are reported in medical journals or at scientific meetings, the people who take part are not named and identified. In most cases, the NIH will not release any information about your research involvement without your written permission. However, if you sign a release of information form, for example, for an insurance company, the NIH will give the insurance company information from your medical record. This information might affect (either favorably or unfavorably) the willingness of the insurance company to sell you insurance.

The Federal Privacy Act protects the confidentiality of your NIH medical records. However, you should know that the Act allows release of some information from your medical record without your permission, for example, if it is required by the Food and Drug Administration (FDA), members of Congress, law enforcement officials, or authorized hospital accreditation organizations.

2. Policy Regarding Research-Related Injuries. The 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 National Institutes of Health, the Clinical Center, or the Federal Government. However, you have the right to pursue legal remedy if you believe that your injury justifies such action.

3. Payments. The amount of payment to research volunteers is guided by the National Institutes of Health policies. In general, patients are not paid for taking part in research studies at the National Institutes of Health. Reimbursement of travel and subsistence will be offered consistent with NIH guidelines.

4. 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., Building 10, Room 4N115, Telephone: 240-760-6087. You may also call the Clinical Center Patient Representative at 301-496-2626. If you have any questions about the use of your specimens or data for future research studies, you may also contact the Office of the Clinical Director, Telephone: 240-760-6070.

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

COMPLETE APPROPRIATE ITEM(S) BELOW:

A. Adult Patient's Consent

I have read the explanation about this study and have been given the opportunity to discuss it and to ask questions. I hereby consent to take part in this study.

Signature of Adult Patient/ Legal Representative _____ Date _____

Print Name _____

B. Parent's Permission for Minor Patient.

I have read the explanation about this study and have been given the opportunity to discuss it and to ask questions. I hereby give permission for my child to take part in this study.
(Attach NIH 2514-2, Minor's Assent, if applicable.)

Signature of Parent(s)/ Guardian _____ Date _____

Print Name _____

C. Child's Verbal Assent (If Applicable)

The information in the above consent was described to my child and my child agrees to participate in the study.

Signature of Parent(s)/Guardian _____ Date _____ Print Name _____

THIS CONSENT DOCUMENT HAS BEEN APPROVED FOR USE FROM JULY 23, 2018 THROUGH JULY 22, 2019.

Signature of Investigator _____ Date _____

Print Name _____

Signature of Witness _____ Date _____

Print Name _____