PRINCIPAL INVESTIGATOR: Kevin Conlon, M.D.

STUDY TITLE: Phase 1 Trial of Human IL-15 (rhIL-15) and Obinutuzumab for Relapsed and Refractory Chronic Lymphocyte Leukemia

INSTITUTE/CENTER: National Institutes of Health

Cohort: *Affected Patient*

Consent Version: 09/14/2021

WHO DO YOU CONTACT ABOUT THIS STUDY?

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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 to be in this study, you are being asked to give permission for this person as their decision-maker. The term "you" refers to you as the decision-maker and/or the individual being asked to participate in this research, throughout the remainder of this document.

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?

The general purpose of this study is to develop treatments for chronic lymphocytic leukemia (CLL) that have a shorter treatment period and are more effective than existing treatments. The experimental part of this treatment program is to test whether giving recombinant human

interleukin 15 (IL-15) in combination with obinutuzumab (also known as Gazyva) will improve the outcome of therapy for your disease.

IL-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. People 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 IL 15 can "boost" or strengthen persons' immune systems as they fight against cancer. In fact, in other clinical trials, all of the people who received IL-15 showed an increase in the number of their immune system cells. In some of the people, the growth was dramatic. We hope the same is true in this study.

Obinutuzumab is a monoclonal antibody that works by attaching to a protein on your tumor cells. Recent evidence shows that the effects of cancer therapy may be improved by combining other cancer therapies with monoclonal antibodies. Monoclonal antibodies are purified proteins that are specially made to attach to pieces of foreign substances (such as cancer cells) with the goal of inactivating them.

IL-15 is not approved by the US Food and Drug Administration (FDA). Obinutuzumab is approved by the FDA for the treatment of B-cell chronic lymphocytic leukemia (B-CLL) in combination with the chemotherapy drug chlorambucil. The FDA has given us permission to use IL-15 and obinutuzumab together in this study.

The goals of this study are to determine the safe dose of IL-15 when combined with obinutuzumab to be used in humans, to identify the side effects of the combination treatment and its effects on your immune system, and to determine if this treatment has activity against your cancer.

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

You are being asked to take part in this study because you have relapsed and/or refractory CLL for which standard therapy has failed.

HOW MANY PEOPLE WILL TAKE PART IN THIS STUDY?

Up to 24 participants will participate in this study.

DESCRIPTION OF RESEARCH STUDY

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

This trial is designed to test the safety of different doses of IL-15 when given as a continuous intravenous infusion (civ) over 24 hours on days 1-5 of a 28-day cycle, followed by intravenous infusion (IV) of obinutuzumab. Obinutuzumab will be given on days 4, 5, 11 and 18 of the first cycle at increasing doses to make sure participants are able to tolerate the drug. Then, it will be given on day 4 only on subsequent cycles. All participants will receive the same doses of obinutuzumab.

In order to confirm that the doses are safe, participants will be enrolled in groups:

- Dose escalation group: First, 3-6 study participants will receive IL-15 at the lowest dose, along with obinutuzumab. If the study drugs do not cause serious side effects, the next group of 3-6 participants will receive IL-15 at the next highest dose along with

obinutuzumab, and so on. Each group of participants 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 group: Once the highest safe dose of IL-15 with obinutuzumab is found, then up to 9 participants will receive that same IL-15 dose with obinutuzumab to learn more about the drugs and their effect on CLL.

All participants will be given treatment on an inpatient basis for the first week of the first cycle, and on an outpatient basis for subsequent weeks and cycles unless decided otherwise by the physician, based on clinical judgement. Treatment can continue for up to 6 (28-day) cycles. You will only be eligible for outpatient treatment if you have a caregiver to accompany you and help you manage the ambulatory infusion pump.

Before you begin the study

Before you begin the study, you will have several tests performed to check whether the trial is suitable for you. This is called screening. 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 trial. A fresh blood sample will be drawn to confirm your diagnosis of CLL. Some of these tests or procedures are part of regular care and may be done even if you are not being considered to join the study. Some of these may be done on a separate screening protocol before signing the informed consent document for this study. If you have had some of these tests or procedures recently, they may or may not have to be repeated. The following tests and procedures will be performed prior to starting treatment:

- 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 and urine tests will be collected and tested, including:
    - To measure your liver, kidney, and thyroid function, red and white blood cells, platelets, electrolytes and others.
    - To measure how well your blood clots
    - Hepatitis B and C testing
    - As part of this study, we will also test you for infection with the human immunodeficiency virus (HIV), the virus that causes AIDS, if never done in the past or if not done recently. 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

  - To run routine tests done in people with your type of cancer to confirm the status of your disease

- If you have received a live vaccine within 30 days of starting study treatment, you will not be able to immediately participate. Examples of live vaccines include but are not limited to: the intranasal influenza vaccine known as Flu-Mist, measles, mumps, rubella, varicella/zoster, yellow fever, rabies, BCG, and typhoid vaccine.
- For females of child-bearing potential, a pregnancy test will be done (urine or blood sample). You will not be able to participate if you are pregnant.
- An electrocardiogram (EKG) to check your heart function.
- Bone marrow testing and imaging will be done to check your disease, as needed.
  - A bone marrow aspiration and/or biopsy will be done prior to starting treatment if not done within the last 3 months since completing the last treatment received to confirm the stage and course of your disease. These are done by numbing your hipbone using a small needle containing a 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. For participants with suspected involvement of disease in the central nervous system, an MRI of the brain will be taken.

During the study

If the screening process shows that you are eligible for the study, and you choose to be in it, you may need to have a few additional standard tests completed if not done recently. You will also have additional samples collected for research tests.

You will come to the NIH Clinical Center for treatment and procedures. The treatment will be given in the inpatient setting for the first week of the first cycle and then in the outpatient setting at the Clinical Center for the remainder of the study. You will be given IL-15 as a continuous intravenous infusion as described in section "What will happen if you take part in this research study?", over a 24-hour period. Your dose of IL-15 will be assigned depending on what dose level is open at the time of your enrollment (gradually increasing doses during the dose escalation or the maximum tolerated dose during the dose expansion portion). Obinutuzumab is also an IV infusion and will be given to you over about a 4-hour period.

A midline catheter may need to be inserted for each IL-15 infusion and maintained for the duration of the infusion. If you receive part of the treatment as an outpatient, you will get training on how to maintain the midline catheter and the ambulatory infusion pump before being discharged from the hospital. For the first five days of each cycle, you will need to report to the day hospital each day for an IL-15 bag change. Each IL-15 infusion is expected to start between 8am and 8pm, and bags will be replaced at the same time each day; however, if for any reason IL-15 infusion begins after hours (8pm-8am), you will need to come into the hospital during the night for nursing to manage the pump.

We will give you standard pre-medications before the IL-15 and obinutuzumab infusions. These may include acetaminophen (Tylenol), nonsteroidal anti-inflammatory drugs (NSAIDs such as ibuprofen), an antihistamine (Benadryl), steroids (IV glucocorticoids and dexamethasone or methylprednisolone). These are given to help prevent infusion related side effects. Your study doctor or a member of the study staff can explain these to you in more detail. You will also be asked to stay at the clinic for an additional 60 minutes after receiving obinutuzumab for monitoring.

Similar to the tests done at the beginning of the study, the following will be repeated during the study to see how you are doing and how the cancer may be responding to treatment:

- Review of medical history, and a physical exam (check weight and vitals), including obtaining information about how you function in your daily activities, side effects and symptoms, and review of medications
- Routine blood and urine tests
    - Bone marrow testing will be repeated (this is optional) after Cycle 3 and 6 on study if needed to confirm response, and at disease progression.
    - A CT neck, chest, abdomen and pelvis will be done after Cycle 6 of treatment to confirm response. Other body areas may be imaged if clinically indicated. If your disease does not progress, follow-up imaging may be done at 6 months after treatment, then annually, at the discretion of the clinical team. MRI of the brain is only required in participants with known suspected involvement of the central nervous system (CNS).

In addition, the following research samples will be collected, and some are optional:

- Blood Samples: Blood will be collected for research studies to learn more about how IL-15 and obinutuzumab affect your cancer at the beginning of the study prior to starting treatment, during the first cycle of treatment, and at about the same time as each imaging assessment. If at any time your doctor thinks you have responded or may have progressed during or after treatment, we will again collect samples. Optional blood samples may be obtained more frequently throughout the treatment cycles depending upon the days that you are seen in the clinic.
- Cheek Swab or Saliva Samples: A cheek swab and/or saliva sample to collect normal tissue will be done at the beginning of the study only. To obtain a cheek swab, a small brush is rubbed against the inside of the cheek to wipe off some cells. To obtain saliva, a special collection tube will be used, and it may take a few minutes to collect the saliva.
- Tumor Biopsies: These are an optional part of the study and you will only be asked to do so if it is felt to be safe. We will ask you to undergo a tumor biopsy at the beginning of the study, during the first Cycle of treatment and again if your disease should progress during or after treatment on this study. The tissue is being collected for special research tests. Your doctor or the study team will discuss the biopsies with you. The biopsies to be performed are exclusively for research purposes and will not benefit you. They might

help other people in the future. You may agree to biopsies now and change your mind later. If at any time you do not want to have a biopsy done, please tell us.

Usually tissue can be obtained safely and comfortably with local anesthesia. If you require sedation before undergoing a biopsy, you will be informed of the risks and you will be asked to sign an additional consent prior to undergoing the procedure. Biopsies will NOT be done on this study if they require general anesthesia. We may ask that you have ultrasound to help clearly locate your tumor when doing a biopsy.

The following sections describe studies to be done on your samples for research:

What tests will be done on my samples?

Your tissue (tumor and normal tissue) and samples that are collected will be used to look for specific changes in the DNA in tumors that could be used to develop new ways of diagnosing and treating cancer. DNA (also called deoxyribonucleic acid) are the molecules inside cells that carry genetic information and pass it from one generation of cells to the next – like an instruction manual. Normal tissue contains the DNA (instructions) that you were born with, DNA in tumor cells has changed – or mutated – and we think that change in the DNA is what causes tumors to form and to grow. To determine which parts of the DNA have mutated, we will compare the DNA in your tumor cells to DNA from your normal cells. We will then analyze the results from similar tumors to see if there are any changes in the DNA that are common to a particular type of tumor. To examine the tumor and normal tissue we may use several different techniques depending on the type of tissue we collect. These could include growing cell lines (cells which keep dividing and growing in the laboratory, sometimes for years allowing us to continually study those cells), xenograft studies (placing or growing cells in another animal, such as mice), and looking in detail at the parts of the genes that produce specific proteins. When we are examining these pieces of your DNA, it is possible that we could identify possible changes in other parts of your DNA that are not related to this research. These are known as “incidental medical findings”.

These include:

- Changes in genes that are related to diseases other than cancer
- Changes in genes that are not known to cause any disease. These are known as normal variations.
- Changes in genes that are new and of uncertain clinical importance. This means that we do not know if they could cause or contribute to a disease or if they are normal variations.

However, the analyses that we perform in our laboratory are for research purposes only; they are not nearly as sensitive as the tests that are performed in a laboratory that is certified to perform genetic testing. Changes that we observe unrelated to our research may or may not be valid. Therefore, we do not plan to inform you of the results of testing on your tissue and blood that is performed in our research lab. However, in the unlikely event that we discover a finding believed to be clinically important based on medical standards at the time we first analyze your results, we will contact you. This could be many years in the future. We will ask you to have an additional tube of blood drawn to verify the findings we have seen in our lab. If the results are verified, you will be re-contacted and offered a referral to a genetic healthcare provider to discuss the results.

Who else besides the investigators on this study will know the results of my sample testing?

Once we obtain any of the samples listed above, the investigators take all your personal information off those samples and label them with a study code number. Only the investigators on this study know who the sample came from. The key linking your personal information with the code number is kept in a secure computer data base, with access only to the limited research staff who will be discussing this study with you. Once the sample has been labeled with a code, it is sent to a variety of NIH laboratories for storage and testing. No one testing your samples will be able to link the results to you personally. Specimens obtained during your participation in this study may be sent for testing to investigators outside of the National Cancer Institute (NCI) or the NIH. All samples will be coded to protect your privacy and no personal information will be included. Other investigators on this study will have access to limited clinical and biologic data such as age, gender and disease status.

Your individual genomic data and health information will be put in a controlled-access database. This means that only researchers who apply for and get permission to use the information for a specific research project will be able to access the information. Your genomic data and health information will not be labeled with your name or other information that could be used to identify you. Researchers approved to access information in the database have agreed not to attempt to identify you.

In the future, researchers will not be able to access specific information about you without prior approval from individuals or committees that monitor the use of the research information. However, researchers will be able to access summary information about all the participants included in the study (including you), or summary information combined from multiple studies, without applying for permission. This information may be shared through the scientific literature or through other public scientific resources, such as data repositories that provide unrestricted access to the information. Some examples of information that may be shared includes how different genes are associated with different traits or diseases across the many participants in a dataset, or how often certain gene changes are seen across participants from many studies. The risk of anyone identifying you with this information is very low.

How long will your samples be stored?

The samples collected during this study will be stored for as long as the study is open. When this study is closed, we will keep the samples for future research.

When you are finished taking the drugs (treatment)

When you finish taking the experimental therapy, we will ask you to come to the clinic for follow-up visits and assessments at about the following times after treatment: every three months for the first year and then every six months for up to five years. After 5 years, we may contact you by phone or by email to see how you are doing for the rest of your life. Only in certain cases, a participant may be asked to come in annually indefinitely. These clinic visits may include having blood samples collected for routine analysis and for research, and for CT scans to assess the status of your disease.

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 18 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

RISKS OR DISCOMFORTS OF PARTICIPATION

If you choose to take part in this study, there is a risk that the study treatment may not be as good as the usual approach for your cancer or condition at shrinking or stabilizing your cancer.

You also may have the following discomforts:

- Spend more time in the hospital or doctor's office.
- Be asked sensitive or private questions about things you normally do not discuss.
- May not be able to take part in future studies.

The study treatment used in this study may affect how different parts of your body work such as your liver, kidneys, heart, and blood. The study doctor will test your blood and will let you know if changes occur that may affect your health.

There is also a risk that you could have side effects from the study drug(s)/study approach.

Here are important things to know about side effects:

- The study doctors do not know who will or will not have side effects.
- Some side effects may go away soon, some may last a long time, and some may never go away.
- Some side effects may make it hard for you to have children.
- Some side effects may be mild. Other side effects may be very serious and even result in death.

You can ask your study doctor questions about side effects at any time. Here are important ways to make side effects less of a problem:

- If you notice or feel anything different, tell your study doctor. He or she can check to see if it is a side effect.
- Your study doctor will work with you to treat your side effects.
- Your study doctor may adjust the study drugs to try to reduce side effects.

The tables below show the most common and the most serious side effects doctors know about. Keep in mind that there might be other side effects doctors do not yet know about. If important new side effects are found, the study doctor will discuss these with you.

IL-15 Risks

You may have side effects from the IL-15 while on the study. We pay close attention to any side effects you have. However, we don't know all the side effects that may happen. Side effects may be mild or very serious. We may give you medicines to help lessen side effects. Many side effects go away soon after you stop taking the IL-15. In some cases, side effects can be serious, long lasting, or may never go away. It is possible that IL-15 could increase the growth of your leukemic cells, that is the IL-15 could make your CLL worse. There also is a risk of death.

Please talk to us about any symptoms you have while you are in the study.

In studies with humans, common and not very common risks and side effects related to the IL-15 included the following:

POSSIBLE, SOME MAY BE SERIOUS
• Anemia (low red blood cells) which may require blood transfusion • Abnormal heartbeat • Pain in belly • Diarrhea, nausea, vomiting • Chills, tiredness, fever • 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 • High blood pressure which may cause blurred vision • Low blood pressure which may cause feeling faint

Other risks seen with IL-15 that are possibly related to the drug include:

- Decreases in blood levels of albumin, phosphorus
- Low number of white blood cells, cells that help fight infection (lymphopenia, leukopenia, neutropenia)
- Low platelets, cells that help blood to clot (thrombocytopenia)
- Low blood oxygen – symptoms may include changes in skin color, confusion, cough, fast heartbeat, shortness of breath
- Chest pain
- Pneumonitis (inflammation of the lungs) - symptoms may include new or worsening cough, chest pain, shortness of breath.
- Kidney failure - signs of kidney problems may include: decrease in the amount of urine, blood in your urine, ankle swelling
- Liver damage which may cause yellowing of eyes and skin, swelling and may result in liver failure
- bronchopulmonary hemorrhage and diffuse alveolar hemorrhage
- Confusion, psychosis (i.e., delusions, hallucinations)
- Papilledema (changes in vision due to increased pressure in the brain)
- Uveitis (inflammation of the eye – symptoms may include redness, pain, blurred vision)
- Inflammation of the lining of the first part of the small intestine symptoms may include nausea, vomiting, stomach burning, pain, indigestion
- Immune related adverse events: hives, hypothyroidism and production of autoantibodies – symptoms made include joint pain, tiredness fever, rashes, allergy-type symptoms, muscle weakness

Obinutuzumab Risks

COMMON, SOME MAY BE SERIOUS In 100 people receiving obinutuzumab (Gazyva), more than 20 and up to 100 may have:
• Nausea • Tiredness, fever • Allergic reaction which may cause rash, low blood pressure, wheezing, shortness of breath, swelling of the face or throat • Low blood pressure which may cause feeling faint

OCCASIONAL, SOME MAY BE SERIOUS In 100 people receiving obinutuzumab (Gazyva), from 4 to 20 may have:
• Anemia which may require blood transfusion • Pain • Diarrhea, vomiting

OCCASIONAL, SOME MAY BE SERIOUS In 100 people receiving obinutuzumab (Gazyva), from 4 to 20 may have:
• A tear or hole in internal organs that may require surgery which may cause difficulty swallowing • Chills • Infection, especially when white blood cell count is low • Bruising, bleeding • Dizziness, headache • Painful urination • Inability to control urine • Cough, shortness of breath • Runny nose • Hair loss, itching, rash, hives • Flushing • High blood pressure which may cause headaches, dizziness, blurred vision

RARE, AND SERIOUS In 100 people receiving obinutuzumab (Gazyva), 3 or fewer may have:
• Chest pain • Heart failure which may cause shortness of breath, swelling of ankles, and tiredness • Abnormal heartbeat • Prior liver infection that returns which may cause yellow eyes and skin, tiredness • Kidney damage which may require dialysis • A type of skin cancer • A new skin cancer resulting from treatment of earlier cancer • Damage to the brain which may cause changes in thinking and may be life-threatening

Other risks of obinutuzumab:

- Allergic and infusion reactions: Sometimes people have allergic reactions to drugs. Serious allergic reactions can be life-threatening. If you have an allergic reaction, you might develop a rash, difficulty breathing, wheezing when you breathe, sudden low blood pressure with light-headedness, swelling around the mouth, throat or eyes, a racing heartbeat, and/or sweating. Before starting the study drug, you must tell your study doctor about any drug allergies. You should tell a member of the study team right away if you have any allergy symptoms listed above.
- Effects on the heart: Abnormal heartbeats (atrial fibrillation and/or atrial flutter) and worsening of heart conditions have been reported in participants treated obinutuzumab, especially when they also have a history of these and other heart conditions, including

increased blood pressure, infections, or had abnormal heartbeat in the past. Atrial fibrillation/flutter is a common type of abnormal heartbeat. The heartbeat may be fast or irregular causing symptoms such as a pounding or racing heart, dizziness, weakness, feeling light-headed or shortness of breath. If you develop any of these symptoms while on the study drug, you should tell your study doctor immediately.

- Hepatitis reactivation: In participants with a history of hepatitis B infection, taking obinutuzumab could cause it to return. You should not receive obinutuzumab or any of the study medications if you have active hepatitis B or C liver disease. We will screen you at baseline for hepatitis and monitor you during the study. You should tell your study doctor immediately if you have any of these symptoms which may suggest hepatitis: worsening of fatigue and yellow discoloration of the skin or eyes.

Other Study Risks

- 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.
- EKG: Some skin irritation can occur where the EKG (also referred to as ECG) 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.
- Imaging/scans: CT and/or MRI scans are used to monitor your disease while you are in this study. CT scans expose you to radiation and the amount depends on the number of body areas scanned. In addition, CT scans involve use of contrast (oral and/or IV) so that the cancer may be seen better on the images. Please ask the study doctor if you have questions about the risks of these scans. If done, MRI scans do not involve radiation risk but may involve a special dye or contrast agent may have to be injected into you intravenously. The scans that you will receive during this study are considered standard for your type of disease.
- Bone marrow: 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 people 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.
- Tumor biopsy: 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.

Radiation Exposure from Imaging

During your participation in this research study, you will be exposed to radiation from CT of the chest, abdomen, and pelvis. The amount of radiation exposure you will receive from these procedures is equal to approximately 5.2 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 17 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 0.5 out of 100 (0.5%) and of getting a fatal cancer is 0.3 out of 100 (0.3%).

MRI Risks

Your doctor may want you to get a magnetic resonance imaging (MRI) scan. MRI uses a strong magnetic field and radio waves to take pictures of the body. We will obtain pictures of your brain for this study. The MRI scanner is a metal cylinder surrounded by a strong magnetic field. During the MRI, you will lie on a table that can slide in and out of the cylinder. We will place soft padding or a coil around your head. You will be in the scanner about 45 minutes. You may be asked to lie still for up to 15 minutes at a time. While in the scanner you will hear loud knocking noises, and you will be fitted with earplugs or earmuffs to muffle the sound. You will be able to communicate with the MRI staff at all times during your scan, and you may ask to be moved out of the machine at any time.

It is very important for the experiment that you do not move your head or body inside the scanner. We will use padding around your head to help keep it in place.

We may place a bar in your mouth to help keep your head still.

People are at risk for injury from the MRI magnet if they have some kinds of metal in their body. It may be unsafe for you to have an MRI scan if you have pacemakers or other implanted electrical devices, brain stimulators, some types of dental implants, aneurysm clips (metal clips on the wall of a large artery), metal prostheses (including metal pins and rods, heart valves, and cochlear implants), permanent eyeliner, tattoos, an implanted delivery pump, or shrapnel fragments. Welders and metal workers may have small metal fragments in the eye. You will be screened for these conditions before having any MRI scan. If you have a question about metal in your body, you should inform the staff. You will be asked to complete an MRI screening form before each MRI scan you have.

In addition, all magnetic objects (like watches, coins, jewelry, and credit cards) must be removed before entering the MRI scan room.

People with fear of confined spaces may become anxious during an MRI. Those with back problems may have back pain or discomfort from lying in the scanner. The noise from the scanner is loud enough to damage hearing, especially in people who already have hearing loss. Everyone having a research MRI scan will be fitted with hearing protection. If the hearing protection comes loose during the scan, you should let us know right away.

There are no known long-term risks of MRI scans.

Risks for gadolinium enhanced MRI scans:

Procedure

During part of the MRI you may receive gadolinium, a contrast agent, through an intravenous (iv) catheter. It will be done for medical purposes.

Risks

The risks of an IV catheter include bleeding, infection, or inflammation of the skin and vein with pain and swelling.

Mild symptoms from gadolinium infusion occur in fewer than 1% of those who receive it and usually go away quickly. Mild symptoms may include coldness in the arm during the injection, a metallic taste, headache, and nausea. In an extremely small number, fewer than one in 300,000 people, more severe symptoms have been reported including shortness of breath, wheezing, hives, and lowering of blood pressure. You should not receive gadolinium if you previously had an allergic reaction to it. You will be asked about such allergic reactions before gadolinium is given.

People with kidney disease are at risk for a serious reaction to gadolinium contrast called "nephrogenic systemic fibrosis" which has resulted in a very small number of deaths. A blood test of your kidney function may be done within the month before an MRI scan with gadolinium contrast. You will not receive gadolinium for a research MRI scan if your kidney function is not normal or if you received gadolinium within the previous month.

Most of the gadolinium contrast leaves the body in the urine. However, the FDA recently issued a safety alert that indicates small amounts of gadolinium may remain in the body for months to years. The effects of the retained gadolinium are not clear. At this time, retained gadolinium has not been linked to health risks in people whose kidneys work well.

Some types of gadolinium contrast drugs are less likely to remain than others. In this study, we will use the gadolinium contrast drugs that are less likely to remain.

We will also give you additional information called a "Medication Guide." Upon request, we will give you individual information about retained gadolinium we see on your studies.

Psychological or Social Risks Associated with Loss of Privacy

As part of the research study, it is possible that you could learn that you have genetic risks for another disease or disability. This may be upsetting and, depending on what you learn, might create a need to make challenging decisions about how to respond.

Although your genomic information is unique to you, you share some genomic similarities with your children, parents, brothers, sisters, and other blood relatives. Therefore, learning your research results could mean something about your family members and might cause you or your

family distress. Before joining the study, it may be beneficial to talk with your family members about whether and how they want you to share your results with them.

Privacy Risks Associated with Return of Incidental or Secondary Findings

Although your genetic information is unique to you, you do share some genetic information with your children, parents, brothers, sisters, and other blood relatives. Consequently, it may be possible that genetic information from them could be used to help identify you. Similarly, it may be possible that genetic information from you could be used to help identify them. Patterns of genetic variation also can be used by law enforcement agencies to identify a person or his/her blood relatives.

Protections against misuse of genetic information

This study involves genetic testing on samples. Some genetic information can help predict future health problems of you and your family and this information might be of interest to your employers or insurers. The Genetic Information Nondiscrimination Act (GINA) is a federal law that prohibits plans and health insurers from requesting genetic information or using genetic information. It also prohibits employment discrimination based on your health information. However, GINA does not address discrimination by companies that sell life insurance, disability insurance, or long-term care insurance. GINA also does not protect you against discrimination based on an already-diagnosed condition or disease that has a genetic component.

POTENTIAL BENEFITS OF PARTICIPATION

Are there benefits to taking part in this study?

The aim of this study is to see if this combination of treatment of IL-15 and obinutuzumab is safe to give to people with relapsed/refractory CLL. We also hope to learn more about how effective or not this combination of medications may be in treating people. These potential benefits could include shrinking of your tumor or lessening of your symptoms, such as pain, that are caused by the 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. Talk to your doctor about other approved agents and treatments that are available to you and that may provide clinical benefit without taking part in this study. If you do choose to take part, 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 worsens or comes back during 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

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 Division of Cancer Treatment and Diagnosis (DCTD) or 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.

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.

Genomic Data Sharing

As part of this research study, we will put your genomic data in a large database for broad sharing with the research community. These databases are commonly called data repositories. The information in this database will include but is not limited to genetic information, race and ethnicity, and sex. If your individual data are placed in one of these repositories, they will be labeled with a code and not with your name or other information that could be used to easily identify you, and only qualified researchers will be able to access them. These researchers must receive prior approval from individuals or committees with authority to determine whether these researchers can access the data.

Summary information about all of the participants included in this study (including you) is being placed in a database and will be available through open access. That means that researchers and non-researchers will be able to access summary information about all the participants included in the study, or summary information combined from multiple studies, without applying for permission. The risk of anyone identifying you with this information is very low.

NIH policies require that genomic data be placed in a repository for sharing. Therefore, we cannot offer you a choice of whether your data will be shared. If you do not wish to have your data placed in a repository, you should not enroll in this study.

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.

DCTD is providing IL-15 for this study to NIH without charge. No NIH investigator involved in this study receives payments or other benefits from any company whose drug, product or device is being tested. However, there are some non-NIH collaborators on this study who may receive payments or benefits, limited by the rules of their workplace.

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. Someone will work with you to provide 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.

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

- 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 Clinical Center, NIH.
- Once you have completed taking part in the study, medical care will no longer be provided by the Clinical Center, NIH.

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 study Sponsor (Center for Cancer Research) or their agents
- Qualified representatives from DCTD, the manufacturer of IL-15.

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.

If we share your specimens or data with other researchers, in most circumstances we will remove your identifiers before sharing your specimens or data. You should be aware that there is a slight possibility that someone could figure out the information is about you.

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., Telephone: 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 should sign below if either:

1. **A short form consent process has been used to enroll a non-English speaking subject or**
2. **An oral presentation of the full consent has been used to enroll a blind or illiterate subject**

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: _____.