PRINCIPAL INVESTIGATOR: James N. Kochenderfer, M.D.

STUDY TITLE: T Cells Expressing Fully- human Anti-CD19 and Anti-CD20 Chimeric Antigen Receptors for Treating B-cell malignancies and Hodgkin Lymphoma

STUDY SITE: NIH Clinical Center

Cohort: affected patient

Consent Version: June 12, 2020

WHO DO YOU CONTACT ABOUT THIS STUDY?

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KEY INFORMATION ABOUT THIS RESEARCH

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). This section provides the information we believe is most helpful and important to you to in making your decision about participating in this study. Additional information that may help you make a decision can be found in other sections of the document. Taking part in research at the NIH is your choice.

You are being asked to take part in this study because you have a B cell lymphoma or leukemia or Hodgkin lymphoma (such as: non-Hodgkin's lymphomas, Hodgkin lymphoma, and chronic lymphocytic leukemia), that has not been controlled with standard therapies.

The primary purpose of this study to determine if a personalized immune treatment is safe. This therapy has not been tested in humans before. We do not know if this therapy will make your cancer get any better.

The use of anti-CD19 and anti-CD20 CAR T cells used in this study are considered investigational, which means that it has not been approved by the U.S. Food and Drug Administration (FDA) to treat cancer. However, the FDA has given us permission to use anti-CD19 and anti-CD20 CAR T cells in this study. This is a phase 1 study and the purpose of a phase 1 study is to evaluate safety of these cells in humans. CD19 and CD20 are often found on lymphoma or leukemia (cancer) cells. If you have B cell lymphoma, your cancer cells usually have at least one of these proteins on the cell surface. This is why we believe these cells will work for B-cell lymphoma.

For Hodgkin lymphoma patients only: If you have Hodgkin lymphoma, your cancer cells often do not have CD19 or CD20 on the cell surface. The reason that Hodgkin lymphoma patients can participate in this clinical trial is because Hodgkin lymphoma is believed to come from B cells

that may possibly be killed by the anti-CD19 and anti-CD20 T cells that will be given to patients on this clinical trial. Also, your Hodgkin lymphoma must have had CD19 or CD20 expression at some time for you to be eligible for this clinical trial. Since your Hodgkin lymphoma cells themselves may not have CD19 or CD20 on the cell surface at this time, it is possible that your lymphoma will have low likelihood of response to this treatment. This therapy has not been tested except for the small number of patients treated on this clinical trial.

There are other drugs that may be used to treat your disease, and these can be prescribed/given by your regular cancer doctor, even if you are not in this study. These may include, for instance, chemotherapy or other treatments. While all the other therapies have their own side effects, CAR T-cell therapy can cause cytokine release syndrome (CRS) which causes high-fevers and makes you feel very sick, which may be different than most other therapies. It is expected that the CAR T-cells may cause cytokine-release syndrome. Patients sometimes need to go to the intensive care unit for close observation and intensive treatments for cytokine release syndrome.

If you decide to join this study, here are some of the most important things that you should know that will happen:

First, we will collect T cells from your blood thru a process called apheresis. Your whole blood will go through a machine that separates blood into different parts (this will take 3-4 hours). Your T cells will be grown with viruses that carry the CAR genes that lead cells to recognize CD19 and CD20. The viruses will put the CAR gene into your collected T cells. These CAR T cells will then be grown in a laboratory at the NIH for 7 to 9 days.

You will be given three days of low-dose standard chemotherapy before getting the CAR T cells. Chemotherapy creates an environment in your body where the T cells will be active and multiply. Three days after your chemotherapy ends, you will receive your CAR T cells by an intravenous (IV) infusion while in the hospital at the NIH.

You will be in the hospital for at least 14 days, if there are complications.

You may experience side effects from taking part in this study. Some can be mild or very serious, temporary, long-lasting, or permanent, any may include death. Some of the most important side effects that you may have include:

- Cytokine release syndrome (CRS): Cytokines are substances released from cells that can cause many side effects such as fever, fast heart rate, low blood pressure
- Tumor lysis syndrome (rapid breakdown of tumor that can cause side-effects such as fast heart rate, possible kidney damage that will most likely be temporary, shortness of breath)
- Headache
- Temporary muscle weakness or difficulty speaking
- Temporary decreased kidney function
- Tiredness, fever, chills
- Increased risk of infection
- Temporary changes in liver function tests

- Temporary abnormal heart rhythm
- Prolonged (a month or more) low blood counts including low white blood cells (leading to infection) and platelets (leading to bruising)

You will be seen often during the study. You will have laboratory, and imaging tests to see how you are doing and to see how your disease is responding. We will also collect required samples from you (such as: blood and bone marrow biopsies).

After you finish your CAR T cell treatment we would like to see you at the NIH Clinical Center monthly for 4 months then at 6, 9 and 12 months, every 6 months up to 3 years, and then annually to 5 years to see how you are doing and to determine what impact, if any, the cell therapy had on your disease.

After the study follow-up period has ended, long-term follow up will be requested. During the long-term follow-up, we would like to contact you one time each year until 15 years after your CAR T-cell infusion.

Just as we do not know what side-effects you might have, we cannot know if you may benefit from taking part in this study. If you do not benefit, this study and the results from our research may help others in the future.

We will cover the cost for some of your expenses, such as travel, lodging and/or meals. Someone will work with you to review your costs of taking part and what we will support.

You are free to stop participating in the trial at any time. If you decide to stop, the study doctor may ask you to agree to certain tests to make sure it is safe for you to stop.

The remaining document will now describe more about the research study. This information should be considered before you make your choice. 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.

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?

This is a research study. B cell cancers can be either lymphoma or leukemia. The purpose of this research study is to see if it is safe to give anti-CD19 and anti-CD20 CAR T cells T cells to people with a B cell cancer or Hodgkin lymphoma. We are asking you to join this research study because you have been diagnosed with a B cell cancer or Hodgkin lymphoma that has not been controlled with standard therapies, meaning that the cancer cells are growing despite your prior treatments or, if you did achieve a remission, the cancer has come back after your most recent treatment.

Anti-CD19 and Anti-CD20 CAR T cells are considered investigational, which means that they have not been approved by the U.S. Food and Drug Administration (FDA) to treat with a B cell cancer.

WHAT WILL HAPPEN DURING THE STUDY?

Before you begin the study

If you decide to take part in this study, before receiving treatment, you will have several tests performed to check whether the trial is suitable for you. This is called the Screening Period. Your doctor will review your medical history and the drugs that you are currently taking to determine whether you can participate in this trial.

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. If you have had some of these tests or procedures recently, they may or may not have to be repeated. These tests will be performed on a separate screening protocol # 01C0129 and include a medical history and physical examination, routine blood tests, pregnancy test in women who can have children (pregnant women are not allowed to take part), blood tests for viruses, taking a sample of your bone marrow, scans to assess your disease and tests of your heart function.

Before you begin the study treatment

Before you begin treatment on this protocol a bone marrow biopsy will be scheduled. This will allow us to see if you have lymphoma or leukemia in your bone marrow and if so, how much the bone marrow biopsy is required.

During the study therapy

Once it is determined that you are eligible to participate in the study, and you agree to participate by signing the study consent, you will undergo an apheresis procedure that will remove cells from your blood. Apheresis is a procedure for obtaining certain blood cells, such as white blood cells, without removing most other blood cells. It is a process people undergo for routine platelet donations. Some people need an IV (intravenous catheter, a small plastic tube that is put into a vein) inserted into each arm for this collection and some people need a temporary special apheresis "central line" just for the one-day collection.

After we collect your T cells, we will manipulate your cells in a laboratory so that they can recognize your lymphoma or leukemia.

We will use a type of virus (gamma-retrovirus) to permanently change the genes of your T cells. The virus will add a new gene to your T cells, so that your T cells will have 2 new receptors. The receptors will allow your T cells to target lymphoma cells that express the CD19 and CD20 proteins. Both your lymphoma cells and your normal B cells, which are a type of immune cell in your body, express CD19 and CD20. This means that your T cells, which have been changed to express the new receptor, may kill both your lymphoma cells and your normal B cells. We hope that your T cells will decrease the amount of cancer you have. However, it is possible that these cells will not have this effect on the cancer.

This study will be conducted as a "dose escalation". The purpose of dose escalation is to determine the safe dose of anti-CD19 and anti-CD20 T cells. There are five dose levels of anti-CD19 and anti-CD20 T cells. The first patients enrolled get the smallest dose and the dose is increased when a level has been determined to be safe. You can discuss this with the study doctors to find out which dose of anti-CD19 and anti-CD20 T cells you will be receiving.

After you have had cells removed from your blood, you will receive 2 FDA approved drugs (chemotherapy) named cyclophosphamide and fludarabine. These drugs will be given to you through a "central line" (or tube) placed in a large vein in your arm or chest once a day for 3 days. The two drugs are given one after the other with each infusion lasting about 30 minutes. The purpose of the chemotherapy is to improve the activity of the anti-CD19 and anti-CD20 T cells. This is a standard chemotherapy regimen that is often used to treat certain types of leukemia. The chemotherapy can be administered on an outpatient basis, which means hospital admission is not necessary. If you are removed from the protocol before receiving the CAR T cells, you may be eligible for re-enrollment in the study at a later date.

Three days after the chemotherapy ends, you will be admitted to the hospital as an inpatient where you will receive the anti-CD19 and anti-CD20 T cells. The anti-CD19 and anti-CD20 T cells will be given to you as a single intravenous (IV) infusion. You will need to have a "central line", an IV catheter (or tube) placed in a large vein in your arm or chest for this infusion. This may be the same "central line" that was used for the chemotherapy. You will receive the commercially-available, common drugs acetaminophen and diphenhydramine as premedication prior to the CAR T cells. All patients that participate in this study will be required to stay in the hospital for close observation and testing for at least 14 days after the cell infusion, and patients must stay within 60 minutes driving distance for 2 weeks after the cell infusion. This is because in our experience with similar treatments we have noticed side-effects including fevers, fatigue, low blood pressure, and others that have been most severe between 6 and 9 days after cell infusion. You may have to stay in the hospital longer to manage these side effects if they occur. During this time-period, it is very possible that you will need intensive care treatment that can include drugs that support your blood pressure, chest compressions, a machine to assist your kidneys, and being attached to a breathing machine.

You will be closely watched during the anti-CD19 and anti-CD20 cell infusion for signs of a reaction. While other types of genetically-modified T cells have been administered to many patients, infusion of anti-CD19 and anti-CD20 T cells is a new approach that is being evaluated in this protocol. There is always a chance that we will not be able to genetically-modify your cells or be able to grow the cells in the laboratory. If we are not able to successfully prepare the minimum number of cells that we believe are needed to help control the tumor in our first

attempt to produce the cells, we will make a second attempt to produce the cells if you give us permission to do so. This second attempt to produce cells will probably not be necessary. If a second attempt to produce cells is necessary, it might require a second apheresis.

For patients who still have disease after receiving anti-CD19 and anti-CD20 T cells the first time, repeated infusions might be possible. In order for a repeat infusion to be possible, you must not have experienced severe side effect with your first infusion, and you must meet the original eligibility requirements for enrollment on the trial. Repeat treatments will also include the same chemotherapy as the first treatment. A maximum of 2 total treatments can be given to any one patient.

Blood will be drawn frequently during your treatment. Most of the blood draws will be to monitor your health during and after the cell infusion. Additional blood draws might be necessary to investigate T cell responses and serum cytokine levels in cases of clinical events such as rapid regressions of malignancy or toxicity. These samples will be used to study how your immune system is affected by the cell therapy. If a cancer is suspected, but not definite, you may have subsequent evaluation here at NIH or at your home institution per standard of care. These might include additional testing (such as Lumbar Puncture), biopsies, or other imaging tests.

Lumbar Puncture

If you have a form of B cell lymphoma that has a tendency to spread to the lining of the brain or spinal cord (called the leptomeninges) or if there is any concern that this might have occurred, you may also require a lumbar puncture to determine whether you would require special therapy that should not be delayed while participating on an experimental protocol. The procedure is done with local anesthesia to numb the skin in the lower back, and a very thin needle is used to draw fluid from the area below the spinal cord. Approximately one-to-three teaspoons of the fluid that bathes the spinal cord (called the cerebrospinal fluid) would be removed and examined for tumor cells. There is very minor discomfort when the numbing medicine is injected into the skin, and a third or fewer patients may experience some headache while the body replaces the fluid that is removed.

Additional research testing

In addition to performing the tests described above, we will also do tests for purposes of research. These are being done to help us to find out if you have cancer, evaluate physical wellbeing, and to study possible markers in your blood.

The studies include:

- Imaging Assessments –
  - a computed tomographic scan (CT) that produces a picture of your body using a small amount of radiation (if you are not pregnant and do not have allergy to CT contrast)
  - Positron emission tomography (PET)/CT scans which combine two different types of scanners to get better image of your tumor before starting the study treatment, approximately 3 scans/year.

- **Tumor Sampling:** Before or after of cell therapy, we may ask your permission to perform a biopsy of your cancer if we can safely perform a biopsy without general anesthesia or significant risk of danger or discomfort to you, a sample may be removed through a surgical procedure or with a needle biopsy. The specific details would be described to you by the surgeon and you will be asked to sign a separate consent for the procedure. The biopsy will be performed under sterile conditions to prevent infections. We may also ask your permission to perform a biopsy for research. The tissue from this biopsy will be used to determine whether there is evidence of an immune response to the tumor or to determine if a newly discovered tumor is actually B-cell cancer. Any biopsies would only be performed with your permission, and if the biopsy is determined to be safe by the Principal Investigator of this trial and the additional physician or physicians that would actually perform the biopsy. Some of the samples may be used for other or future research conducted by the investigational team or other researchers. This future research might directly study malignancy of the same type that you have, or it could focus on other areas of research.
- Blood samples will be collected to look at your RNA and to look at other markers in the blood that might suggest a cancer is present in your body.

Blood collected for research purposes on this study may be used to look for specific changes in the RNA in blood that could be used to develop new ways of diagnosing and treating cancer. RNA (called ribonucleic acid) carries the instructions from the DNA to the parts of your cells that make proteins. To look at your RNA, we may use do what is called "RNA sequencing." This where we will do special tests in the lab to look at the RNA sequence. The human genome is the material in our cells that includes thousands of genes. Genes are the building blocks of our cells that make and maintain our body. A gene provides instructions to individual cells to make proteins through a middle step of making RNA. Proteins are the substances that are involved in all of our body's chemical processes. This study aims to perform laboratory studies (research) to better understand how the immune system fights cancer cells and to make more effective cell treatments. However, you should know that 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 or testing for routine clinical care. For these reasons, we will not give you the results of the research tests done on your research samples in most cases.

The purpose of RNA sequencing is to learn about the expression of different genes in your cancer cells and in your CAR T cells.

When you are finished taking the drugs (treatment)

You will need to come for a clinic visit two weeks after your cell infusion, for blood work, urine tests, and a brief visit with one of our doctors. You will also need to return to clinic for evaluation of your overall health and your lymphoma or leukemia 1, 2, 3, 4, 6, 9 and 12 months after the cell infusion. These visits will also include a health and blood test, urine tests, and possible disease imaging. In addition, follow-up visits will be done at the NIH Clinical Center on days 16 and 21 after infusion for neurologic checks

After 12 months, follow up for patients with ongoing responses, which means the lymphoma or leukemia has not progressed, will continue every 6 months for up to 3 years then annually up to 5 years after your T-cell infusion. At the follow-up visits we will evaluate your general health, and we will assess your lymphoma or leukemia. Blood will be drawn at all follow-up visits. Note that all these follow-up visits are only required for patients with ongoing responses.

If your lymphoma or leukemia progresses, you will be removed from the study to pursue other options. As long as your lymphoma or leukemia does not progress, we ask that you do not take any other treatments. We also ask that you do not take any corticosteroid medications such as prednisone or dexamethasone unless instructed to do so by physicians at the NIH or if an emergency arises outside of the NIH. If you do take other treatments including corticosteroids, we will not be able to interpret the results of the anti-CD19 and anti-CD20 T cells, and you will be removed from the study. You will then be followed by your home oncologist who will receive a detailed summary of your case and blood tests and other investigations that need to be performed and potential problems that may arise. We encourage early communication of any problems with us so that we can assist in deciding the best treatment approach.

Gene Therapy Long Term Follow up (Retroviral Vectors)

You will be followed on a separate NCI protocol# 15C0141 if you leave the CAR protocol. There will be a consent process for the separate protocol. Because we do not know the long-term side effects of gene therapy, we will ask you to take part in long term follow up for the next 15 years. The Food and Drug Administration (FDA) requires that people who receive gene therapy be watched even after they complete the study. We will ask you questions about your health and ask you to have a physical exam every year. .If you return to your referring doctor after treatment here, we will ask you to have your doctor send us a copy of your physical exam and any needed blood samples. We will collect blood samples right after you receive the cells, and at 3, 6 and 12 months after treatment (2 teaspoons each time). This testing will help us learn if the cells have grown or changed in your body. We may also collect your blood over the next several years after 12 months if you have had any previous tests that show a retrovirus in your blood. For this reason, we ask that you continue to provide us with a current address and telephone number, even after you complete this research study. At the time of your death, no matter the cause, we may request permission for an autopsy in order to obtain vital information concerning the safety of this experimental therapy approach. Please discuss this request with your family to inform them of your wishes.

HOW LONG WILL THE STUDY TAKE?

If you agree to take part in this study, your involvement is expected to last for 5 years:

- You may be seen in the clinic two weeks after your cell infusion, for blood work, urine tests, and a brief visit with one of our doctors. Then to return to clinic for evaluation of your overall health and your lymphoma or leukemia 1, 2, 3, 4, 6, 9 and 12 months after the cell infusion
- After 12 months, follow up for patients with ongoing responses, which means the lymphoma or leukemia has not progressed, will continue every 6 months for up to 3 years and then annually up to 5 years after your T-cell infusion.

Your involvement on the Gene Therapy Long Term Follow Up Study will be 15 years once you are off treatment in this study.

HOW MANY PEOPLE WILL PARTICIPATE IN THIS STUDY?

We plan to have approximately 88 people participate in this study at the NIH.

WHAT ARE THE RISKS AND DISCOMFORTS OF BEING IN THE STUDY?

Risks of Study Drugs

Because the CD19 and CD-20 proteins are found on normal B cells as well as on your cancer, the anti-CD19 and CD-20 T cells might cause a short or long-term decrease in the number of normal B cells. Because B cells are involved in protection against infections, this decrease in B cell number might lead to a greater risk of infections. We do not know if a decrease in normal B cells will cause problems with infections. We will take steps to minimize the risk of infection or actual infections.

The anti-CD19 and anti-CD20 T cells we will be giving you have been modified to express the anti-CD19 and anti-CD20 part that targets the T cells to the cancer by using a virus (gamma-retrovirus). Although this virus is not active, there is the rare possibility that it may cause infection. The cells could also cause you to develop another type of cancer in your blood cells, although we think this is very unlikely. Other gene-modified T cells have been given to hundreds of individuals before, and in no patient receiving T-cell gene therapy has an infection or cancer developed that was shown to be caused by the lentivirus used.

Many patients receiving other types of CAR T cells at various institutions have developed fever and fatigue that can last for up to 2 weeks after cell infusion. Some patients that have received similar treatments have developed low blood pressure. A small number of patients developed a temporary decrease in heart function after participating in a similar study at this institute. Their heart function later returned to normal levels and the other participants in the study have not had decreased heart function. One participant on a different NCI anti-CD19 and anti-CD20 T-cell study developed tumor lysis syndrome, which is a release of toxic substances from tumor cells that are being destroyed. This tumor lysis syndrome was successfully treated and caused no long-term problems for the patient. Patients at risk of tumor lysis syndrome will receive medication to prevent this complication. Neurological toxicities such as a temporary loss of the ability to speak, temporary confusion, and temporary difficulty walking have occurred in several patients.

Chemotherapy is part of this protocol. The chemotherapy part of this study can cause decreased blood count, nausea, and hair loss. The decreased blood counts due to chemotherapy can lead to infections and bleeding.

The first patient treated on this protocol developed a neurologic disorder called Guillain-Bare syndrome in which your immune system attacks the peripheral nerves. This patient developed weakness of his arms and legs and tingling pain in his feet. Overall the patient's condition is improved so far but was not completely resolved 4 months after infusion of CAR T cells.

Potential risks of anti-CD19 and anti-CD20 T cells infusion include:

Likely:	**Less Likely:**	**Rare:**
• Fever • Chills • Fatigue • Low immunoglobulin levels (susceptibility to infection) • Abnormal blood tests such as low phosphorous	• Headache • General feeling of being unwell (malaise) • Temporary decreased kidney function • Temporary weakness or difficulty speaking • Low blood pressure • Fainting • Tumor lysis syndrome (rapid breakdown of tumor that can cause side-effects) • Possible intensive care unit admission • Fast heart rate • Possible kidney damage that will most likely be temporary • Possible breathing problems that might in rare cases require mechanical ventilation (breathing machine) • Cytokine release syndrome (release of substances from T cells that can cause many side-effects) including ➢ Fever ➢ Fast heart rate ➢ Low Blood Pressure ➢ Possible intensive care unit admission ➢ Rare cases, death. ➢ Temporary decreased cardiac function, or abnormal heart rhythms ➢ Prolonged (a month or more) low blood counts including low white blood cells and platelets ➢ Temporary changes in bleeding tests ➢ Temporary changes in liver function tests ➢ Temporary low calcium, phosphorous, albumin, or potassium in the blood	• Muscle pain, twitching • Death • Permanent kidney damage • Other neurologic problems • Coma • Temporary liver damage • Extreme weakness of the arms and legs • Muscle damage • Long-term debilitation • Difficulty breathing

Likely:	Less Likely:	Rare:
	➢ Increased risk of infection ➢ Shaking hands ➢ Confusion ➢ Temporary increase in markers of muscle damage • Guillain-Bare syndrome (your immune system attacks the peripheral nerves). including ➢ tingling or prickling sensations in your fingers and toes. ➢ muscle weakness in your legs that travels to your upper body and gets worse over time. ➢ difficulty walking steadily. ➢ Temporary difficulty moving your eyes or face, talking, chewing, or swallowing. ➢ Temporary severe lower back pain. ➢ Fainting or difficulty thinking ➢ Sudden paralysis	

There is no information available at this time to guide us in how humans might respond to this type of cell infusion. As this is a new experimental therapy, side effects that we do not anticipate that may cause your condition to worsen may be encountered.

Potential risks of cyclophosphamide:

Likely:	Less Likely:	Rare:
• Low blood counts	• Nausea and vomiting • Painful and bloody urination • Sterility • Water retention • Hair Loss	• Heart damage • Secondary leukemia (a different type of cancer) • Skin rash • Bleeding

Potential risks fludarabine:

Likely:	Less Likely:	Rare:

Likely:	Less Likely:	Rare:
• Low blood counts	• Long-term reduction of lymphocyte counts which could increase the risk of infection. • Infection	• Damage to the nervous system: Causing seizures, coma, vision loss, and even death • Inflammation in the lungs • Kidney damage

Gene Therapy Risk of Cancer and Other Diseases:

The risks of gene therapy causing new disease are unknown. It is possible that the gene therapy may cause an immune system, blood, or neurological disorder, or cause a new cancer in your blood cells to develop. It is unknown if you will develop any of these disorders, but you need to be aware of this possible risk. Children in France and England received gene therapy for a particular disease of the immune system. The disease these children had was very different from the disease that you have. These children did not receive CAR T cells, they received a different type of cells. In these children, stem cells were genetically modified (in contrast to the research offered in this trial where T cells are genetically modified). Most of the children were cured, but 5 out of 22 children developed leukemia and one died. Experts who examined this case thought that the gene therapy caused the leukemia in these children. To monitor you for this risk we will be testing your blood as previously described.

Procedure Risks

Apheresis

The risks of apheresis are similar to whole blood donation and include pain and bruising at the needle insertion site in the arms, lightheadedness, dizziness, nausea, and rarely fainting due to a rare reflex reaction to needle placement and to the temporary decrease in blood volume during apheresis. You may also feel tingling around your mouth or in your fingers caused by a blood thinner given during the procedure. The nurses will give you a calcium containing antacid to chew to reduce the tingling. All the symptoms usually go away within a few minutes of stopping the procedure. We ask that you eat a meal before coming to donate, and avoid caffeine, to prevent lightheadedness or dizziness that might occur. You will be asked to remain in the chair/bed for a few minutes after the donation is completed, and to sit down and relax for about 15 minutes after the donation. This is done so that staff can observe you to make sure that you feel entirely well before you leave our department.

Lumbar Puncture

The risks of Lumbar Puncture include headache from a persistent spinal fluid leak, brain herniation, bleeding, and infection. Each of these complications are uncommon with the exception of headache, which can appear from hours to up to a day after a lumbar puncture. Up to 25 % of patients will get headache after the procedure. You will be asked lying flat several hours after the procedure, so your headache occur less frequently.

Blood draws:

Side effects of drawing blood include pain and bruising in the area where the blood was drawn, lightheadedness, or rarely fainting due to transient lowering of blood pressure. If you feel dizzy, you should lie down for a few minutes to avoid hurting yourself if you fall. Infection at the blood-drawing site could also occur.

Central Intravenous Catheter:

In order to receive this treatment, you will need to have a central venous catheter. This catheter is placed under the skin of the chest wall and enters a major vein in the chest. There are several types of catheters including those which must be removed after each cycle of chemotherapy (temporary type) and those which may be kept for the duration of therapy (permanent type). These options will be discussed with you. The risks associated with placing some catheters include pain, bleeding, infection and collapsed lung. The long-term risks of the catheter include infection, and clotting of your veins. 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 insertion.

Bone marrow aspiration and biopsy:

A bone marrow biopsy is performed by inserting a needle into a bone of the hip. In the aspiration part of the procedure, a small amount of liquid bone marrow is removed, and in the biopsy part, a tiny solid piece of bone marrow is removed. You may feel a pressure sensation when the needle is being inserted and a pulling sensation and brief pain as the marrow is withdrawn. The amount of marrow taken is very small and will not change your body's ability to form blood cells. Potential complications of this procedure are local bleeding, pain at the site, and infection. Both are very rare. Bleeding can be stopped by applying local pressure and an infection can be treated with antibiotics.

CT-Guided Biopsies:

You may be asked to undergo a biopsy if needed for protocol eligibility and in some cases for research only if you have progressive lymphoma after treatment. Tumor biopsies can be performed as an outpatient surgical procedure or can be done by a specialist using the CT scanner or ultrasound machine to guide the biopsy needle into the tumor to ensure accuracy. There are risks associated with the biopsies, which can include pain and bleeding at the biopsy site. You will be asked at the time of the procedure if you are willing to have this biopsy.

Risks from PET, and CT scan

You may have allergic reaction to contrast used to perform CT scan.

For radiation risk associated with CT scans and PET scans, please, see next paragraph.

What are the risks of radiation from being in the study?

During your participation in this research study, you will be exposed to radiation from CT scans of your neck, chest, abdomen and pelvis, CT-Guided biopsies and 18FDG-PET/CT scans. The amount of radiation exposure you will receive from these procedures is equal to approximately 19.1 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, CT-Guided biopsies and 18FDG-PET/CT scans that you get in this study will expose you to the roughly the same amount of radiation as 63.7 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 1.9 out of 100 (1.9%) and of getting a fatal cancer is 1.0 out of 100 (1.0%).

Please tell your doctor if you have had any radiation exposure in the past year, either from other research studies or from medical tests or care, so we can make sure that you will not receive too much radiation. Radiation exposure includes x-rays taken in radiology departments, cardiac catheterization, and fluoroscopy as well as nuclear medicine scans in which radioactive materials were injected into your body.

You may not participate in this study if you are pregnant. If you can become pregnant, we will perform a pregnancy test before exposing you to radiation. You must tell us if you may have become pregnant within the previous 14 days because the pregnancy test is unreliable during that time

What are the risks related to pregnancy?

If you are able to become pregnant, we will ask you to have a pregnancy test before beginning this study. You will need to practice an effective form of birth control before starting study treatment, during study treatment, and for at least 4 months after your last research treatment (the restricted period). If you become pregnant, there may be unknown risks to the fetus or unborn child, or risks that we did not anticipate. There may be long-term effects of the treatment being studied that could increase the risk of harm to a fetus. You must tell the study doctor if your birth control method fails during the restricted period. If you think or know you have become pregnant during the restricted period, please contact the research team member identified at the top of this document as soon as possible.

If you are a sexually active person with a partner capable of becoming pregnant, it is important that your partner not become pregnant during the restricted period. There may be unknown risks to a fetus or risks we did not anticipate. You and your partner must agree to use birth control if you want to take part in this study. If you think your partner has become pregnant during the restricted period, please contact the research team member identified at the top of this document as soon as possible. If you and your partner plan for your partner to become pregnant after the restricted period, please discuss this with the study team.

WHAT ARE THE BENEFITS OF BEING IN THE STUDY?

You might not benefit from being in this study. However, the potential benefit could include shrinking of your lymphoma or leukemia if the cell infusion is accepted by your body or lessening of your symptoms, such as pain, that is caused by the cancer.

Are there any potential benefits to others that might result from the study?

In the future, other people might benefit from this study because the knowledge gained from this study may help in developing treatments for those who have this cancer.

WHAT OTHER OPTIONS ARE THERE FOR YOU?

Before you decide whether or not to be in this study, we will discuss other options that are available to you. Instead of being in this study, you could:

- choose to be treated with other forms of chemotherapy, antibody-drug therapy, radiation, stem cell or bone marrow transplantation, or immune therapies.
- choose to take part in a different study, if one is available
- choose not to be treated for cancer but you may want to receive comfort care to relieve symptoms.

You should discuss with your doctor your other choices and their risks and benefits.

DISCUSSION OF FINDINGS

New information about the study

If we find out any new information that may affect your choice to participate in this study, we will get in touch with you to explain what we have learned. This may be information we have learned while doing this study here at the NIH or information we have learned from other scientists doing similar research in other places.

Return of research results

Results of imaging evaluations (CT or PET) and laboratory analyses will be shared with you.

The analyses that we perform in our laboratory regarding genetic studies 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 participants of the results of testing on the tissue and blood that is performed in our research lab.

EARLY WITHDRAWAL FROM THE STUDY

Your doctor may decide to stop your therapy for the following reasons:

- if he/she believes that it is in your best interest
- if you have side effects from the treatment that your doctor thinks are too severe
- if you develop problems such as an infection or other severe illness during or after the protocol chemotherapy before the CAR T-cell infusion
- if you become pregnant

- if you need to receive any other treatment for your disease
- if the study doctor decides to end the study
- if new information shows that another treatment would be better for you.
- if you do not follow the study rules

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. 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.

WILL YOUR SPECIMENS OR DATA BE SAVED FOR USE IN OTHER RESEARCH STUDIES?

As part of this study, we are obtaining specimens and data (such as: blood and bone marrow biopsies) from you. We plan to use these specimens and data for studies going on right now, as well as studies in the future. These studies may provide additional information that will be helpful in understanding cancer, or other diseases or conditions. This could include studies to develop other research tests, treatments, drugs, or devices, that may lead to development of a commercial product by the NIH and/or its research or commercial partners. There are no plans to provide financial compensation to you if this happens. Also, it is unlikely that we will learn anything from these studies that may directly benefit you. By agreeing to let us use your specimens and data, you give the NIH any rights you may have in the specimens and data.

We may share your specimens and data with other researchers. They may be doing research in areas similar to this research or in other unrelated areas. These researchers may be at NIH, other research centers and institutions, or industry sponsors of research.

We may put your research data in a large database for broad sharing with the research community. These databases are commonly called data repositories. These data repositories might or might not be located at the NIH. The information in this database could include but is not limited to genetic information, ethnicity and sex. If your individual research data is placed in one of these repositories, it will not be labeled with your name or other information that could be used to easily identify you, and only qualified researchers will be able to look at your data. These researchers must receive prior approval from individuals or committees to access the data.

Your summary genomic data is being placed *in an* unrestricted database , so 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. The risk of anyone identifying you with this information is very low.

In addition to the use and sharing of your specimens and data described above, we might remove any information from your specimens and data that can identify you such as name, address, or medical record number, and then use the specimens and data for additional research studies at the NIH or other places. If we do this, we might not contact you to ask your permission or otherwise inform you.

If you change your mind and do not want us to store and use your specimens and data for future research, you should contact the research team member identified at the top of this document. We will do our best to comply with your request but cannot guarantee that we will always be able to destroy your samples. For example, if some research with your specimens and data has already been completed, the information from that research may still be used. Also, for example, if the specimens and data have been shared already with other researchers, it might not be possible to withdraw the samples and data.

Please place your initials in the blank next to Yes or No for each of the questions below:

My specimens and data may be stored and used for future research as described above.

_____ Yes _____ No

Initials Initials

My specimens and data may be shared with other researchers and used by these researchers for future research as described above.

_____ Yes _____ No

Initials Initials

How Long Will Your Specimens and Data be Stored by the NIH?

Your specimens and data will be stored at NIH indefinitely.

Risks of Storage and Sharing of Specimens and Data

When we store your specimens and data, we take precautions to protect your information from others that should not have access to it. When we share your specimens and data, we will do everything we can to protect your identity, for example, when appropriate, we remove information that can identify you. Even with the safeguards we put in place, we cannot guarantee that your identity will never become known or someone may gain unauthorized access to your information. New methods may be created in the future that could make it possible to re-identify your specimens and data.

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?

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.

- 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.

CONFLICT OF INTEREST (COI)

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

The National Institutes of Health and the research team for this study have developed anti-CD19 and anti-CD20 being used in this study. This means it is possible that the results of this study could lead to payments to NIH. By law, the government is required to share such payments with the employee inventors. You will not receive any money from the development of anti-CD19 and anti-CD20.

The NIH and the research team for this study are using anti-CD19 and anti-CD20 developed by Dr. Kochenderfer and the National Institutes of Health through a joint study with Kite Pharma, Inc. The company also provides financial support for this study.

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

Some of your health information, and/or information about your specimen, from this study will be kept in a central database for research. Your name or contact information will not be put in the database. Your test results will be identified by a unique code and the list that links the code to your name will be kept separate from your sample and health information. Your information may be given out if required by law. For example, certain states require doctors to report to health boards if they find a disease like tuberculosis. However, the researchers will do their best to make sure that any information that is released will not identify you.

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
- Qualified representatives from Kite Pharma, Inc., the pharmaceutical company who is collaborating on this study and providing financial support.

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 identifier before sharing your specimens and 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 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 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 information 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 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, Jim Kochenderfer, M.D., Building 10, Room 12C121, Telephone: 240-760-6062.You may also call the 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: _____.