INSTITUTE: National Cancer Institute

STUDY NUMBER: 12-C-0112 PRINCIPAL INVESTIGATOR: Terry Fry, M.D.

STUDY TITLE: Phase I Study of T Cells Expressing an Anti-CD19 Chimeric Receptor in Children and Young Adults with B Cell Malignancies

Continuing Review Approved by the IRB on 04/25/16
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Standard

INTRODUCTION

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

First, we want you to know that:

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

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

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

Second, some people have personal, religious or ethical beliefs that may limit the kinds of medical or research treatments they would want to receive (such as blood transfusions). If you have such beliefs, please discuss them with your NIH doctors or research team before you agree to the study.

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

If you are signing for a minor child, "you" refers to "your child" throughout the consent document.

Why is this study being done?

Although there have been significant strides in treating children with B-cell cancer, there are many children who develop recurrent disease or do not respond to the standard treatments for B-cell cancers. The NCI has developed an experimental procedure for patients with cancer that uses their own blood cells. We genetically modify these cells and grow them in the laboratory.

It is possible that these cells, when given back to the patient with cancer, will decrease the amount of cancer. However, these cells may not have this effect.

In this study, we will be using an anti-CD19 gene and a type of virus (retrovirus) in making these cells (anti-CD19 CAR cells). The Chimeric Antigen Receptor (CAR) is a genetically-engineered receptor made so that immune cells can recognize and respond to a specific molecule, which in this study is the CD19 protein. This uses a portion of an antibody to CD19 and a part of a molecule that activates the immune cell. We combine the CAR molecule with your T cells, a type of immune cell. Together, we hope the CAR will help these T cells find and kill the cancer in your body. Your cancer cells must express the CD19 protein in order for these experimental cells to find them. We have tested your cancer cells for the CD19 protein after you signed the screening consent.

If you decide to participate in this study we will grow these cells in the laboratory in large numbers and then the anti-CD19 CAR cells will be given to you as an intravenous (IV) infusion. The anti-CD19 CAR cells are considered experimental as they are not approved by the US Food and Drug Administration (FDA). Before giving the anti-CD19 CAR cells, you will be given chemotherapy, depending on the amount of tumor you have. If you have a lot of tumor cells in your blood (high tumor-burden, called Arm 2), you may be given standard chemotherapy treatment to decrease the amount of tumor. In the first 20 children treated on this study, those with high tumor-burden tended to have a greater risk of developing a potentially serious side effect called Cytokine Release Syndrome (CRS). If you do not have a lot of tumor cells in your blood when you enroll on this study or you cannot tolerate the intense chemotherapy required in Arm 2 (called Arm 1), you will be given two chemotherapy drugs, fludarabine and cyclophosphamide, to help prepare your immune system to accept the anti-CD19 CAR cells. These drugs are approved for use by the FDA.

This type of experimental therapy is called "gene therapy" and is very closely monitored by the Food and Drug Administration (FDA) and other regulatory agencies. The risks of gene therapy will be described later in this document. The main purposes of this study are:

1. To test the safety of giving the anti-CD19 CAR cells to children and young adults with B-cell cancer, and determine its side effects, including effects on the nervous system,
2. To test how your disease responds when you are given the anti-CD19 CAR cells after a chemotherapy regimen, and
3. To measure how long the anti-CD19 CAR cells live in your blood and/or bone marrow.

You will be given the highest safe dose of cells that was found after treating the first 20 people enrolled on this study.

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

You are being asked to take part in this research study because you have a form of leukemia such as acute lymphoblastic leukemia (ALL) or lymphoma, such as Non-Hodgkin's lymphoma (NHL) that has not been cured by standard therapy, including chemotherapy, surgery and/or radiation therapy. We have tested your cancer tissue and found that it expresses the CD19 protein, so we hope the specialized immune cells we grow in the lab will target your cancer cells.

How many people will take part in this study?

Up to 90 patients may take part in this study. You must have B cell leukemia or lymphoma that has CD19 expression to participate.

Description of R

Research Study

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

Before you begin the study

First we will test your cells to make sure they express CD19. If they do, you will need to have the following exams, tests or procedures to find out if you can be in the study. These exams, tests or procedures are part of regular cancer care and may be done even if you do not join the study. If you have had some of them recently, they may not need to be repeated. This will be up to your study doctor.

- A medical history
- Physical exam, including measuring your height and weight
- Vital signs (blood pressure, pulse, temperature)
- Blood tests
- Urine tests
- Pregnancy test (if you are a woman who could have children)
- Electrocardiogram (ECG), and echocardiogram or MUGA, a test that checks the function of your heart
- We will also do whatever X-rays, CT or PET scans, or spinal fluid samples or bone marrow aspiration and biopsy, depending upon your type of cancer,

If you are eligible to participate in this study, the following procedures will be done (details follow in later sections):

During the study

Additional testing will be done before you start the chemotherapy to watch for any effects (good or bad) from this experimental regimen; this testing includes:

- Physical exam
- Eye exam, so we can check for vision changes
- Blood tests
- Urine tests
- Pregnancy test (if you are a woman who could have children)
- Neurologic evaluation: this includes questionnaires that take less than 1 hour to complete and a brief symptom checklist

- Cell collection: Some cells will be collected from your blood by a procedure known as "apheresis" (a procedure explained below). The anti-CD19 CAR gene will be incorporated into the cells and grown in the laboratory so that they can be given to you at a later date.
- Chemotherapy:
  - If you are in **Arm 1** you will receive three days of chemotherapy to weaken your immune system in order to accept the modified cells.
  - If you are in **Arm 2**, your doctor will discuss with you the type of chemotherapy you will be given and how long you will get chemotherapy. This will depend on what chemotherapy has already been used to treat your cancer, what kind of side effects you had before, and how your cancer responded to the chemotherapy. The most common chemotherapy treatment will be given over five days and will be followed by at least two days of rest before giving you the cells.
- Cell Infusion: You will then get the anti-CD19 CAR cell infusion.
- Follow up: When your condition is stable, you will be discharged from the hospital. You will be followed closely as an outpatient for the first six months, and then less frequently for at least five years. After that, you will be evaluated at home or at the NIH for follow-up visits.

Because we will be giving you so many drugs by IV and drawing blood for tests, you will need to have a central venous catheter (CVC) or a catheter in a large vein.

During the study in Detail

Apheresis

In order to collect the blood cells that we will use to make the anti-CD19 CAR cells, you will have a leukapheresis (apheresis to remove white blood cells) procedure. This will be done by trained personnel in the Department of Transfusion Medicine where two intravenous lines will be placed in veins in your arms or groin so blood can be removed through one needle and circulated though a cell separator machine (a machine that divides whole blood into red cells, plasma, and lymphocytes). The lymphocytes are sent to a collection bag and the remaining red cells and plasma, along with some salt solution (saline) and blood thinning medication (anticoagulant) are returned to you through the second IV line. Blood thinning medications, heparin and/or citrate anticoagulant, will be used to keep your blood from clotting during the

procedure. The procedure takes about 4 hours. After the lymphocytes have been collected, they will be taken to the Research Laboratory to be made into anti-CD19 CAR cells.

Chemotherapy in Arm 1

You will be given two chemotherapy drugs starting 4 days before the cell infusion (Day -4). These chemotherapy drugs are common drugs used in the treatment of cancer. In this study they will be used to lower your immune system's response to the anti-CD19 CAR cells. You will be given the following chemotherapy:

Fludarabine will be given into your IV over 30 minutes for 3 days (on Days -4, -3 and -2).

Cyclophosphamide will be given using a standard dose over 1 hour on Day -2.

While you are getting the chemotherapy, you will also be given fluids through your IV, and medications to help prevent the side effects from these chemotherapy drugs.

Chemotherapy in Arm 2

We cannot predict what kind of chemotherapy you will be given. Your doctor will discuss this with you in detail. The chemotherapy selected will depend on your past treatments and how you responded to them. The most common chemotherapy that will be prescribed are summarized below:

FLAG: **Fludarabine** will be given into your IV over 30 minutes for 5 days

Ara-C (cytarabine) will be given into your IV 4 hours after the fludarabine over 4 hours for 5 days

Filgrastim will be given as a shot under the skin starting the day before chemotherapy and continuing until your blood counts recover.

OR you may receive

Etoposide/Ifosfamide: **Etoposide** will be given into your IV over 1 hour for 5 days

Ifosfamide will be given into your IV with **Mesna** over 1 hour after the Etoposide, for 5 days, followed by 6 additional doses of Mesna

There will be at least 2 days of rest after the chemotherapy to allow you to recover before you receive the anti-CD19 CAR Cell infusion.

Anti-CD19 CAR Cell Infusion

If you were not admitted to the hospital to receive the chemotherapy, you will be admitted to the hospital before you are given the cell infusion. About 30 – 60 minutes before the cells, you will be given acetaminophen (Tylenol) and diphenhydramine (Benadryl) to help prevent any side effects from the cells. The anti-CD19 CAR cells will be given in your IV catheter over approximately 20- 30 minutes.

The doctors and nurses will watch you closely (taking your temperature, blood pressure, heart rate and breathing rate) during and after the cells; and will treat you immediately if you have any side effects. You will stay in the hospital until any bad effects of the cells are resolved. We will ask you to stay close to NIH (i.e. at the Children's Inn) until Day 28 so the doctors and nurses can check you frequently.

Research Blood Tests

As part of this study we will be looking at certain immune responses in your blood and how long the cells last in your blood. We will take about 4 mL of blood (less than 1 teaspoon) prior to giving you the cells and then on Day 1, 2, 3, 4, and 5 after the anti-CD19 CAR cell infusion. In addition about 10 mL (2 teaspoons) of blood will be taken just prior to the cell infusion and then on Day 1, 7, Day 14, Day 21 and 28. If your blood tests show that your cancer is improving, we may draw about 5 mL of blood on Day 28 and on the days we evaluate the status of your cancer to test for small amounts of leukemia left in your blood. This is called minimal residual disease testing (MRD) and is done at an outside laboratory. If you are given intrathecal chemotherapy as part of standard prevention or treatment of disease in the spinal fluid while participating on this study, we may also take a sample of your spinal fluid to test for anti-CD19 CAR cells. Patients with cancer in the bone marrow will also have a bone marrow sample sent for testing. If your cancer improves, about 2 mL of bone marrow may be sent to an outside lab for MRD testing. If your cancer improves after giving you the cells, we will continue to take about 14 mL (3 teaspoons) of blood each time you have a clinic visit (about every 2-3 months).

Some of the samples collected from you during the course of this study (including blood and bone marrow when available) may be sent to other institutions where the research testing is performed. Samples sent outside of NIH will be labeled with a code and will contain no information that could be used to identify you. Only the NIH investigators will be able to link the samples to your personal information.

When you are finished taking the drugs (Follow Up)

While you recover in the hospital you will be watched for any side effects; we will take standard blood tests every day for several days and then a couple times per week for the first 28 days.

After the first month, you will be asked to return to NIH for an evaluation every month for 2-3 months, then every 3 to 6 months, depending upon your condition. At these visits, you will have the following tests and procedures:

- History and physical exam, including neurologic symptoms
- Standard laboratory tests
- Evaluation of your disease, which may include a CT scan, bone marrow aspiration and biopsy and/or spinal tap.

Follow Up for Gene Therapy

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 collect a sample of your blood over the next several years, frequently at first and then less frequently. After receiving therapy we will ask you to have a physical exam and blood drawn for this testing either at NIH or by your local physician. This testing will determine if the cells have grown or changed in your body. We will test your blood immediately before the cells, and then at 3, 6 and 12 months (1-2 teaspoons each time). This testing will help us learn if the cells have grown or changed in your body. If all of the tests are normal and show no change, we will collect blood every year after that to store in case you develop symptoms later. According to FDA requirements, we need you to return annually to the NIH for a physical examination for five years after you receive the cells. After that time we will be sending you a questionnaire to get information regarding your health for the next ten years, for a total follow up time period of 15 years. 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. If you should die, 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. Given the long-term nature of this follow-up evaluation, if you are under 18 years old during your participation in this study and turn 18 during follow-up, you will be asked to sign a new informed consent form at the time you turn 18, granting us permission to continue with this long term follow-up.

Additional Doses of Anti-CD19 CAR Cells

If you benefitted from the first dose of anti-CD19 CAR cells (your cancer improved) and have enough cells left over, you may be eligible to receive additional doses of anti-CD19 CAR cells including some standard chemotherapy and research blood tests. The chemotherapy drugs will depend upon your past treatments, how you responded to them and what the doctor thinks will work best in your condition. The hospital procedures will be the same as those you underwent for the first dose. There must be least 28 days between doses of anti-CD19 CAR cells. The additional doses of cells will have been kept in the freezer with a special drug (DMSO) to preserve them.

Supportive Therapies

Chemotherapy into the Spinal Fluid

Subjects with ALL may also be given chemotherapy directly into the spinal fluid by spinal tap. This part of the therapy is not experimental and is done to decrease the risk that leukemia will spread to the spinal fluid. Three drugs, cytarabine (Ara-C), methotrexate and hydrocortisone (a corticosteroid like prednisone) will be given together into the spinal fluid. This will be done

approximately every 3 weeks at times when spinal taps are being performed to check for leukemia.

Allopurinol (Aloprim™ or Zyloprim™) for Tumor Lysis Syndrome

Anti-cancer treatment sometimes kills leukemia or lymphoma cells so rapidly that the body cannot get rid of the waste products fast enough. This is known as tumor lysis syndrome and it requires special attention and treatment to decrease the chance of kidney damage and other side effects. If tests suggest that you might be at risk, we will watch closely for this problem. In addition, a medication called allopurinol may be given to try to prevent kidney problems from developing. It is a tablet that you swallow three times a day. You will need to keep taking allopurinol until the doctor says you are not at risk for tumor lysis syndrome. Allopurinol is usually well tolerated. Possible side effects are described in detail later in this consent.

Study Chart

Study Regimen	
DAY	**WHAT YOU DO**
Before starting study	A sample of your tumor will be tested for CD19 expression. Come into the clinic and do the following: • Physical exam by your doctor • Routine blood tests • ECG (electrocardiogram), echocardiogram or MUGA test (to check your heart) • Urine tests • Chest x-ray • Baseline neurologic assessment and symptom checklist • MRI, CT or PET scan, bone marrow biopsy, and/or spinal tap to check your cancer • Get a disease evaluation that will be done by your doctor. Depending on the results of this evaluation, your doctor will tell you whether or not you may begin this study.
Before chemotherapy	Come to NIH hospital and do the following: • Leukapheresis – to obtain the white blood cells to grow in the lab for the anti-CD19 CAR cells
Arm 1 Day -4 -3	• Get Fludarabine IV over 30 minutes

Arm 1 Day -2	• Routine blood tests • Get Fludarabine IV over 30 minutes • Get Cyclophosphamide IV over 60 minutes • Fluids will be given in your IV and Mesna (drug to prevent bladder problems from cyclophosphamide) will be given in your IV
Arm 2 before cell infusion	• Get chemotherapy according to type and schedule discussed with your doctor. • Chemotherapy will be followed by at least 2 days of rest.
Before Cell Infusion	Come to NIH hospital and do the following: • Eye exam (to check your eyes) • Physical exam • Routine blood and urine tests • If it has been longer than 14 days since your disease evaluation, it will be repeated.
Day 0 (may be delayed for 1-7 days)	• Take research blood samples (before the cells) • Get acetaminophen and diphenydramine 30-60 minutes before the cell infusion. • Get infusion of anti-CD19 CAR cells IV over 20-30 minutes
Daily for Days 1 to 7	• Physical exam • Routine blood tests • Research blood tests (except Day 6)
Once per Day until Day 14 and then twice per week until Day 28	Come into the clinic (if discharged from the hospital) and do the following: • Physical exam • Routine blood tests • Research blood tests (Day 7, 14, and 28 only). • Evaluation of cancer (between Day 14 - 21 only), may include scans, x-rays, bone marrow biopsy and/or lumbar puncture. • Neurologic symptom checklist (about Day 14) • Complete neurologic assessment and symptom checklist (between Day 21 and Day 28)
Month 2, 3, 6, 9 and 12, then every 6 months (2nd year), then annually (unless your cancer gets worse or you go to other therapies)	Come into the clinic and do the following: • Physical exam • Routine blood tests • Research blood tests • Evaluation of cancer, may include scans, x-rays, bone marrow biopsy and/or lumbar puncture. • Complete neurologic assessment and symptom checklist (about 3 months)

Long term follow up for gene therapy	Come into the clinic or go to your local health care provider every year for 5 years and do the following: • Physical exam • Routine blood tests • Research blood tests After 5 years, complete a questionnaire and have your doctor send a blood sample every year for 15 years.

Birth Control

Reproductive risks: You should not become pregnant or father a baby while on this study because the drugs in this study can affect an unborn baby. If you become pregnant on the study, you will be taken off of this regimen immediately. Further, if the pregnancy is taken to term, the outcome will also be recorded in study records. Women should not breastfeed a baby while on this study. It is important you understand that you need to use birth control while on this study and for at least four months after finishing the cell infusion. Check with your study doctor about what kind of birth control methods to use and how long to use them. Some methods might not be approved for use in this study.

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**:**

- In some cases, you might be eligible for a bone marrow transplant where your own stem cells are returned to you following high-dose chemotherapy.
- You could consider treatment with standard chemotherapy, radiation and/or surgery. You should discuss these alternatives including their possible risks, benefits, advantages, and disadvantages with your referring doctor and the NIH doctors.
- 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.

Risks or Discomforts of Participation

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

This study includes a serious form of treatment with several possible risks. It is probable that you will experience some of the side effects listed, but it is unlikely that you will experience all of them. You will be watched closely and we will give you medicines to try and prevent or reverse the side effects. However, doctors don't know all the side effects that may happen. Side effects may be mild or very serious. In some cases, side effects can be serious, long lasting, or may never go away. There also is a risk of death. We will tell you if we learn any new information that may affect your health, welfare, or decision to stay in this study. You should talk to your study doctor about any side effects that you have while taking part in the study.

Risk of Anti-CD19 CAR Cells

The cells we will be giving you have a type of virus (retrovirus) put into them along with the anti-CD19 CAR gene. Although this retrovirus 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. Other gene-modified cells have been given only to a small number of individuals before so we do not have much information about the side effects. Potential risks include the following:

Risks associated with Anti-CD19 CAR Cells		
Common	Less Common	Rare
▪ Fever ▪ Chills ▪ Shortness of breath ▪ Lung congestion ▪ Rash	▪ Cytokine Release Syndrome	▪ Effects on the nervous system including difficulty speaking or confusion ▪ Autoimmunity ▪ Second cancer

- Cytokine Release Syndrome: Cytokine release syndrome (CRS) is a serious risk which has occurred in patients receiving gene modified cells, including CAR gene modified cells; one patient died at the NCI (not on this study) and one patient died at another hospital after receiving CAR modified cells (not on this study). CRS results from the release of cytokines (substances secreted by the immune cells) into the body's blood stream.

  On this study we have treated 16 patient and two patients have had significant CRS with high fever, chills and low blood pressure that was treated with fluids and supportive medicines. Three patients had severe, life-threatening CRS and required

treatment in the intensive care unit (ICU). One patient was intubated (required a tube passed through the nose or mouth to the lungs to support breathing), and all three required strong medicine to support blood pressure. One patient had heart failure and required a machine to support heart pumping. All patients on this study have recovered completely from the CRS.

Although the actual mechanism is not well understood it is thought that the cells 'turn on' the immune system causing the symptoms of CRS. CRS can initially cause nausea, headache, rash, difficulty breathing, low blood pressure, muscle aches, chills, fever, confusion, including hallucinations, and fast heart rate. If not treated adequately, CRS can cause liver, lung, heart and kidney failure, and possibly death. We will watch you very closely for any symptoms, taking blood samples frequently to test for cytokines. Symptoms have occurred in some patients up to 10 days after the cells are given. If you are discharged from the hospital before day 14, we will ask you to return to the clinic every day so you can have a physical exam and we can see how you feel. If you have any change in how you feel, let your doctors and nurses know immediately. If you develop symptoms of CRS you will be admitted to the hospital, if not already hospitalized, and treated immediately, which may include treatment in the Intensive Care Unit (ICU), treatment with a medicine called tocilizumab (also called Actemra®) to block IL-6 (one of the main cytokines released) or treatment with steroids. We will examine if treatment of CRS with toxilizumab is effective in reversing the symptoms. Tocilizumab is approved by the FDA for treatment of rheumatoid arthritis or juvenile idiopathic arthritis. It has been found to be effective though in reversing CRS in patients receiving cell therapy. Patients receiving tocilizumab for arthritis are at risk for some serious side effects, including hepatitis B infection, serious allergic reactions, infusion reactions (such as chills, fever, nausea, vomiting, headache or rash during or on the same day as tocilizumab), increased cholesterol or triglycerides, or other liver function tests. In this study you will receive 1-2 doses if needed, which is much less that the patients who developed toxicities.

- Autoimmunity As A Result Of Immunotherapy

Another risk of this experimental therapy is the development of immune reactions directed toward normal tissues, called "autoimmunity", which is expected to be rare. These reactions could range from mild effects without symptoms to severe reactions that could cause death. The most likely body organ for involvement is the bowel, but other areas of the body could also be involved, including (but not limited to) skin, liver, lungs, eyes, brain, etc. You will be watched closely for the development of autoimmunity and if you develop any symptoms, you will be treated with drugs designed to suppress the immune system, such as steroids, to stop the reaction. Please let your doctor know immediately of any changes in symptoms, including diarrhea, rash, stomach cramping, blurry vision, trouble breathing and headaches.

- Effects on the Nervous System

  At least 2 patients who received anti-CD19 CAR cells had reversible severe effects on their nervous system, including confusion and difficulty communicating. Additional possible risks to the nervous system include excessive sleepiness or other changes in the level of consciousness, seizures, headache, and weakness. If severe, this could require treatment in the ICU, which could possibly include breathing support by putting a tube through your mouth into your lungs to protect your airway.

Risk of not being able to receive the anti-CD19 CAR cells

After receiving the chemotherapy, you will be evaluated to be sure that it is safe to proceed with the cell infusion. It is possible that your condition at that time would have changed so that the experimental cells would no longer be recommended. Possible reasons for this might include organ damage, severe infection, or worsening of your cancer. If something like this has occurred, this will be explained to you and you will be referred for appropriate medical attention.

In addition, if the cells are grown and do not meet the safety standards set by the FDA, we will not be able to give them to you. In either case, you will be taken care of in the hospital until your cell counts return to normal after which the doctors will discuss other treatment options with you.

Risks of Chemotherapy

If you are in Arm 1 you will be given fludarabine and cyclophosphamide.

Risks associated with chemotherapy in Arm 1		
Fludarabine side effects		
Common	**Less Common**	**Rare**
▪ Changes in blood counts	▪ Fever ▪ Loss of appetite, nausea, vomiting, ▪ Diarrhea, stomach pain ▪ Mouth sores ▪ Headache ▪ Fatigue or weakness ▪ Muscle or joint aches ▪ Swelling ▪ Skin rash ▪ Agitation ▪ Hearing loss ▪ Numbness and tingling (pins and needles)	▪ Bleeding bowel or stomach ▪ Organ damage: lung, kidney, liver ▪ Severe brain or spinal cord toxicity has occurred at very high doses, incl. blindness, deterioration of mental status, and death ▪ Transfusion associated GVHD (will be prevented by using irradiated blood products) ▪ Thrombotic thrombocytopenic purpura- a disorder that includes kidney damage

Cyclophosphamide side effects		
Common	**Less Common**	**Rare**
▪ Low blood counts ▪ Hair loss	▪ Loss of appetite, nausea, vomiting, ▪ Mouth sores ▪ Bladder irritation with bloody urine ▪ Water retention ▪ Loss of fertility	▪ Heart damage ▪ Secondary leukemia (a different type of cancer) ▪ Skin rash ▪ Headache ▪ Blurred vision or dizziness ▪ Swelling (edema) ▪ Allergic reaction

If you are in Arm 2, your doctor will discuss which chemotherapy drugs you will be given and the possible risks and side effects associated with those chemotherapy drugs. Some of those chemotherapy drugs may include the following:

FLAG: Fludarabine, **A**ra-C (also known as Cytarabine) and **G**M-CSF (also known as filgrastim)

Fludarabine side effects: See the list above		
Cytarabine side effects		
Common	**Less Common**	**Rare**
▪ Low in blood counts ▪ Loss of appetite, nausea, vomiting ▪ Abnormal liver tests ▪ Fever ▪ Rash ▪ Oral or anal ulcers	▪ Risk of infection ▪ Sore throat, or inflammation of the esophagus (swallowing tube) ▪ Headache ▪ Dizziness ▪ Hair loss ▪ Itchy rash ▪ Difficulty urinating ▪ Skin ulcer at the IV site	▪ Severe infection ▪ Pneumonia ▪ Allergic swelling (edema) ▪ Nerve damage ▪ Liver damage ▪ Severe allergic reaction (difficulty breathing/swelling)

Filgrastim, also called G-CSF (To increase production of white blood cells)		
Common	**Less common**	**Rare**
▪ Bone pain or muscle aches ▪ Pain or bruising from injections	▪ Severe headache ▪ Tiredness	▪ Severe breathing problems ▪ Rupture of your spleen ▪ Changes in certain laboratory tests

OR

Etoposide/Ifosfamide

Etoposide		
Common	**Less common**	**Rare**
▪ Nausea ▪ Vomiting ▪ Mouth sores ▪ Hair loss ▪ Decreased white blood cells (increasing risk of infection) ▪ Decrease platelets (increasing risk of bleeding)	▪ Loss of appetite ▪ Diarrhea ▪ Decrease red blood cells (can cause fatigue)	▪ Low blood pressure ▪ Allergic reaction ▪ Nerve toxicity ▪ Changes in liver function ▪

Ifosfamide		
Common	**Less common**	**Rare**
▪ Nausea ▪ Vomiting ▪ Hair loss ▪ Blood in urine ▪ Decreased white blood cells (increasing risk of infection) ▪ Decrease platelets (increasing risk of bleeding)	▪ Loss of appetite ▪ Nerve toxicity ▪ Infection ▪ Diarrhea ▪ Constipation ▪ Sleepiness	▪ Changes in liver function ▪ Changes in kidney function ▪ Blood clots

Some additional risks may occur and we may NOT know if they are caused by the chemotherapy or by the CAR modified cells, unless they occur before you are given the cells. These risks include a change in your body water (increased or decreased) causing swelling, abnormal levels of body electrolytes (high or low), including but not limited to sodium, potassium, chloride, magnesium, calcium, or glucose. We will be watching you closely and correct any of this abnormal levels if they occur.

Risks of the Support Medications

You will get several medicines to prevent the side effects of this experimental regimen. All medicines carry some risk of side effects. The support medicines we expect to give you and their side effects are listed in the table(s) below:

Support Medications – side effects		
Common	**Less common**	**Rare**
Mesna (To prevent bleeding in the bladder from cyclophosphamide)		
	▪ Bad taste in mouth ▪ Pain in vein where drug is given	▪ Stomach pain ▪ Nausea or vomiting ▪ Headache ▪ Limb or joint pain ▪ Sleepiness ▪ Rash ▪ Diarrhea ▪ Low blood pressure

Trimethoprim/Sulfamethoxazole, also called Bactrim (To prevent a certain lung infection, pneumocystis)		
Common	**Less common**	**Rare**
	▪ Fever ▪ Nausea, vomiting, ▪ Skin rash with itching ▪ Reduced number of white blood cells ▪ Allergic reaction	

Allopurinol (To prevent Tumor Lysis Syndrome)		
Common	**Less common**	**Rare**
▪ Skin rash or sores ▪ Hives ▪ Itching	▪ Drowsiness (patient should not drive or use machines until they feel alert again)	▪ Chills ▪ Fever ▪ Joint pain ▪ Muscle aches or pains ▪ Sore throat ▪ Nausea or vomiting

Risks associated with drugs used in the spinal fluid for ALL

When cytarabine (Ara-C) methotrexate and hydrocortisone are given by spinal tap they can cause nausea, vomiting, fever, headaches, irritation of tissues in the brain/spinal cord, stiff neck, increase in the number of cells in the spinal fluid, rash, or drowsiness. Rarely, cytarabine and methotrexate can cause weakness and seizures. Cytarabine and methotrexate usually do not

cause other toxicities when given into the spinal fluid, but you will be watched for low blood counts and liver function changes, which can occur when they are given by vein. In order to decrease the risk of methotrexate side effects, a vitamin called leucovorin will be administered in a tablet form. Learning disabilities have developed in children treated for leukemia. Possible rare side effects of leucovorin include nausea, vomiting and allergic reactions (rash, itching, and flushing). The chemotherapy is put into the spinal fluid with a procedure called a spinal tap, also known as a lumbar puncture. This procedure is commonly done and risks are rare. The most common side effect is a 'post spinal' headache with nausea. You may also have some slight numbness or tingling in your leg during the procedure which will go away after the procedure. Serious risks are rare but include bleeding or damage to the spinal cord causing weakness or loss of sensation.

Risks associated with routine procedures:

- Blood Drawing: Side effects of blood draws include pain and bruising in the area where the needle was placed, lightheadedness, and rarely, fainting. When a large amount of blood is drawn, the red blood cell count may drop causing anemia. We will check your red blood cell count frequently during the study.
- Apheresis: The most common side effects of apheresis are pain and bruising at the IV needle sites. Mild side effects from the blood thinning medication citrate used in the apheresis procedure are common and include:
    - chills,
    - numbness and tingling sensations ("pins and needles") especially around the mouth,
    - anxiety,
    - muscle cramps, and
    - nausea.

  These rapidly go away when the collection is slowed down or stopped. More serious side effects due to citrate-induced low calcium levels are uncommon and include:

    - low blood pressure,
    - seizures,
    - weakness, and
    - muscle stiffness.

  If this happens, the apheresis procedure will be stopped, in which case these side effects quickly go away. If you require calcium to be given through your I.V., there is a small risk of damage to your skin and veins around the I.V., slowed heart rate or changes in blood pressure. Some people have a low number of blood platelets for a short period of time after donation. Platelets help the blood to clot. However, low platelet counts from apheresis have not caused an increased risk of bleeding. To be safe, your platelet count will be checked during and after the apheresis procedure.

- Bone Marrow: This procedure usually causes temporary pain and bruising at the needle site. Pain can usually be managed with acetaminophen (Tylenol). Very rarely, infection or bleeding may occur at the needle site. Serious risks are very rare but include fat embolism (fat from the bone marrow enters the blood and goes to another part of the body, blocking the blood flow), and the risks of anesthesia. You will be given these risks and another consent document to sign if you require anesthesia.
- Central Venous Catheter (CVC): Risks include bleeding, bruising, blood clot or infection at the site where the catheter is put in. In rare cases, placing a CVC has resulted in collapse of a lung. If this happens, the lung would be quickly re-inflated using a tube put into your chest. If the catheter becomes clogged or infected, it may need to be replaced. The CVC will be flushed once a day to prevent it from becoming clogged. The nursing staff will show you how to do this yourself when you return home.

Gene Therapy Risk of Cancer and Other Diseases

We are unsure if this type of gene therapy will cause you to become sick in the future. It is possible that it may cause your immune system or nerves not to work well or cause a sickness of your blood cells or even a cancer (for example leukemia). We do not know 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. Most of the children were cured but 5 out of 22 children later developed leukemia and one died. Experts who looked at these cases thought that the gene therapy caused the leukemia in these children. Since then, many improvements have been implemented to minimize this risk. To watch you for this risk we will be testing your blood as described before.

DMSO Risk (if frozen doses of Anti-CD19 CAR Cells are given)

As previously noted, any extra cells from the first infusion of the Anti-CD19 CAR Cells are frozen and stored with a preservative called DMSO. The most common side effect is an odd odor, akin to garlic on your breath shortly after the infusion. Other side effects include nausea, vomiting, stomach cramps, skin flushing, coughing, shortness of breath, or chest tightness. We will monitor you carefully, especially during the first hour after the cells, and treat any side effects with a steroid (hydrocortisone), IV antihistamine (Benadryl®), and/or by slowing down the rate of the cell infusion the rate of transfusion.

Potential Benefits of Participation

Are there benefits to taking part in this study?

The aim of this study is to see if this experimental treatment is safe and if it will decrease the amount of your cancer. It is possible that this experimental treatment could reduce the amount of cancer you have or related symptoms. Because there is not much information about the effects of this treatment on your cancer, we do not know if you will benefit from taking part in this

study, although the knowledge gained from this study may help others in the future who have cancer.

Research Subject's Rights

What are the costs of taking part in this study?

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

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

Will your medical information be kept private?

The sponsor of this study is Dr. Terry Fry. Your records may be reviewed by NIH organizations and by organizations outside the National Institutes of Health, such as representatives of the US Food and Drug Administration. Every effort will be made to protect your privacy in any recording or reporting of this information.

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.

Stopping Therapy

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

- if he/she believes that it is in your best interest
- if your disease comes back during treatment (unless you are eligible to receive another dose of cells)
- 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 used in this study. In addition, if you have received the anti-CD19 CAR cells, FDA regulations require that periodically check your blood and your condition, to watch for any long-term safety concerns. 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.

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.

It is possible that the information obtained from your child's participation on this study may become valuable for commercial research and development purposes (including patentable inventions), which may be of significant benefit to society, the sponsor of this study, individual researchers or other third parties. You or your child will not receive direct financial benefit from such research and development. The NIH and 1 of the investigators on the research team have developed the cell process being used in this research and have a patent pending. This means that it is possible that the results of this study could lead to payments to NIH scientists and to the NIH. By law, government scientists are required to receive such payments for their inventions. If you refuse your child's participation or withdraw from the protocol or at the completion of the protocol, we will attempt to offer your child participation in other NIH protocols if these are available, or will refer your child to their home physician for further management.

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 the specimens and data that we collect and use them for future research and share them with other researchers. 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 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 remain will be destroyed and your data will not be used for future research. However, it may not be possible to withdraw or delete materials or data once they have been shared with other researchers.

OTHER PERTINENT INFORMATION

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

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

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

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

4. Problems or Questions. If you have any problems or questions about this study, or about your rights as a research participant, or about any research-related injury, contact the Principal Investigator, Terry Fry, M.D., Building 10, Room 1W-3750, Telephone: 301-402-0215. You may also call the Clinical Center Patient Representative at 301-496-2626. If you have any questions about the use of your specimens or data for future research studies, you may also contact the Office of the Clinical Director, Telephone: 301-496-4251.

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

COMPLETE APPROPRIATE ITEM(S) BELOW:

A. Adult Patient's Consent

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

Signature of Adult Patient/ Legal Representative _____ Date _____

Print Name _____

B. Parent's Permission for Minor Patient.

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

Signature of Parent(s)/Guardian _____ Date _____

Print Name _____

C. Child's Verbal Assent (If Applicable)

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

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

THIS CONSENT DOCUMENT HAS BEEN APPROVED FOR USE FROM APRIL 25, 2016 THROUGH OCTOBER 24, 2016.

Signature of Investigator _____ Date _____

Print Name _____

Signature of Witness _____ Date _____

Print Name _____