PRINCIPAL INVESTIGATOR: Nirali Shah, MD

STUDY TITLE: Phase 1 Dose Escalation Study of CD19/CD22 Chimeric Antigen Receptor (CAR) T Cells in Children and Young Adults with Recurrent or Refractory CD19/CD22-expressing B Cell Malignancies

STUDY SITE: National Institutes of Health Clinical Center

Cohort: Standard, Parental or Guardian Permission for Minor

Consent Version: 05/28/2024

WHO DO YOU CONTACT ABOUT THIS STUDY?

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

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

If the individual being enrolled is a minor, then the term "you" refers to "you and/or your child" throughout the remainder of this document.

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?

Although there are well established treatments for B-cell leukemias and lymphomas, recurrent or resistant disease is often difficult to treat. Recent strides have occurred using the body's own immune cells to target B cell markers on malignant cells. In this research study, we will take some of your immune cells (called T cells) during a procedure called 'apheresis' and modify them in the laboratory to recognize markers on your cancer cells. These markers are CD19 and CD22 and are commonly found on B cell cancers. We call these cells CD19/CD22-CAR T-cells. The thought is that when these cells are given to people with cancer, they can attack the cancer cells. The CD19/CD22-CAR T cells attack cancer cells in mice studied in the laboratory.

In this study, we will be using a CD19/CD22 gene and a type of virus (lentivirus) in making these cells (CD19/CD22-CAR T cells). This Chimeric Antigen Receptor (CAR) is a genetically engineered receptor made so that immune cells can recognize and respond to two specific molecules, which in this study are the CD19 and CD22 proteins. This uses a portion of an antibody to CD19/CD22 and a part of a molecule that activates the immune cell (CD19/CD22-CAR molecule). We combine the CAR molecule with your T cells, a type of immune cell. Together, the CAR will help these T cells find the cancer in your body; it will be the experimental intervention in this study. Your cancer cells must express the CD19 and CD22 proteins for these experimental cells to find them. We have tested your cancer cells for the CD19 and CD22 proteins.

This is a phase I study. Phase I studies are small studies of an experimental intervention and are usually the first time the intervention has been tried in humans. As of January 2023, 29 patients with B-cell acute lymphoblastic leukemia (B-ALL) and 2 patients with B-cell non-Hodgkin lymphoma (NHL) have been treated on this study across three different dose levels and the results are described below.

Eighteen patients developed cytokine release syndrome (CRS), an inflammatory response seen with CAR T-cell therapy. Of the 18, in 3 patients, CRS was considered severe, but all patients were able to be effectively treated. Three patients experienced neurotoxicity which was considered a dose limiting toxicity in the first patient, and all completely resolved within 48 hours with treatment. In 20 patients, there was complete elimination of B-ALL. Based on the results to date, patients will be treated at dose level 3 which has been found to have a tolerable side effect profile and associated with anti-leukemia response.

Not all patients who receive CAR T cells will have a response. Some patients have not responded to CD19/CD22-CAR T cells. Additionally, one patient recently received CD19/CD22-CAR T cell and had progressive disease of the original leukemia, however the surface markers on the leukemia changed after treatment, which is called lineage switch. This means that even if CD19/CD22-CAR T cells were still present, they would be ineffective at targeting and killing the leukemia because the CAR T cells would not be able to recognize the leukemia because the surface markers have changed. This has been reported in the literature in patients receiving immunotherapy, specifically CAR T cells and blinatumomab.

Over time, we have learned that this CD19/CD22-CAR T cell has limited activity against targeting CD22 alone. Therefore, your team will discuss if you are a good candidate for this study based primarily on your CD19 expression. Also, we have learned that patients who have previously received CD19 or CD22 targeted CAR T-cells are less likely to respond to our CD19/CD22-CAR

T cells and thus you may receive a higher dose of chemotherapy prior to try to improve the response.

The CD19/CD22-CAR cells are considered experimental as they are not approved by the US Food and Drug Administration (FDA). Before giving the CD19/CD22-CAR T cells, you will be given two chemotherapy drugs, fludarabine (or pentostatin) and cyclophosphamide, to help prepare your immune system to accept the CD19/CD22-CAR cells. Fludarabine is approved by the FDA for use in adult patients with chronic lymphocytic leukemia who have not responded to other chemotherapies. Pentostatin is approved for use in adult patients with hairy cell leukemia.

This type of experimental therapy is called "gene therapy" and is very closely monitored by the 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 if it is feasible to grow the CD19/CD22-CAR T cells in the laboratory **COMPLETED**
2. To test the safety of giving the CD19/CD22-CAR T cells to children and young adults with B-cell cancer, and to determine its side effects,
3. To test how your disease responds when you are given the CD19/CD22-CAR T cells after a chemotherapy regimen, and
4. To measure how long the CD19/CD22-CAR T cells live in your blood and/or bone marrow, and the effects on your immune cells.

To test the safety of the CD19/CD22-CAR T cells we will give the first group of 3-6 patients a small dose of cells. If there are no unacceptable side effects, the next group of patients will get a higher dose. This is called 'dose escalation'. We will test up to 4 doses of cells in this manner. Dose escalation has been completed and participants are now being treated at dose level 3. Up to 60 patients will receive the highest safe dose tested. Ask your doctor which dose you will be receiving.

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. To be eligible for treatment on this study, your cancer cells must have CD19 and CD22 proteins on their surface because these are the targets for treatment. Please be aware that the test that will be used in this study determine the CD19 and CD22 protein status of your tumor is experimental (Investigational Device) and is limited by United States law to experimental use. Experimental means that the test is not approved by the U. S. Food and Drug Administration (FDA) and is still being tested in research studies.

You may not be eligible for our study for several reasons, such as the presence of certain other diseases, infections, or problems with your organ function.

HOW MANY PEOPLE WILL TAKE PART IN THIS STUDY?

Up to about 115 patients may receive the study drug on this study.

DESCRIPTION OF RESEARCH STUDY

Before you begin the study

CD19 and CD22 Testing

Testing to see if your cancer cells carry these proteins, which is the first step in testing whether you are eligible for the research study with the CD19/CD22 CAR cells. We will collect or have a sample of your blood and/or bone marrow (or lymph node) to be sent to the NIH. This eligibility screening evaluation involves doing a flow cytometry on your blood or bone marrow, which is a special way of identifying proteins on your leukemia. We will use this sample to see if there are leukemia cells in your blood that have CD19 and CD22 on the surface. We will need about one teaspoonful of blood or bone marrow (depending on where the tumor cells are) for this test.

This test takes approximately one week for the results to be available. Your physician will be informed of the results and potential eligibility for the research study as soon as possible. If the results of this testing suggest that you may be eligible for the experimental cell therapy, additional information will be provided to you at that time. However, the results of this testing do not guarantee that you are eligible for the treatment study with CD19/CD22 CAR cells, as there are additional eligibility requirements. If you are interested in considering treatment on the CD19/CD22 CAR cell study, you will need to come to the NIH for additional eligibility testing. Your consent to allow further testing, and possibly to participate in the research study itself, will be discussed at that time.

Additional Eligibility Tests and Procedures

All of these tests or procedures are part of your 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. The following tests and procedures are needed to determine whether you are eligible for this trial.

- History and Physical Examination: A summary of your medical record will be requested from your physician when you are initially referred to the NIH. In addition, a physician or nurse practitioner at the NIH will review your medical history with you, and you will have a detailed physical examination, which may include a thorough neurological exam (an exam of the nervous system).
- Blood Draws: Blood will be drawn from either an arm vein or a central venous access device if you have one. This will be used for measurements of your blood counts, liver and kidney function, serum chemistries and other routine tests that determine whether you meet the requirements for participating in a specific protocol. Some of the blood may also be used for research tests that may not be available in other hospital clinical labs. These research tests may also be used to determine your eligibility for a research study, or they may be measured as a baseline for comparison of changes in the test result after treatment.
- HIV Testing: As part of this study, we will test you for infection with the human immunodeficiency virus (HIV), the virus that causes AIDS. If you are infected with HIV you will not be able to participate in this study. We will tell you what the results mean, how to find care, how to avoid infecting others, how we report HIV infection, and the importance of informing your partners at possible risk because of your HIV infection.

- Pregnancy Test: For women who could have children, a pregnancy test will be done (blood or urine sample). You will not be able to participate if you are pregnant.
- Urine Tests: A 24-hour urine collection to measure kidney function may be done if your blood tests show abnormal kidney function.
- Bone Marrow Aspiration / Biopsy: You will be asked to have a bone marrow biopsy and aspiration to collect bone marrow tissue and cells from your hip. Bone marrow is the soft material in the center of bones that produces new blood cells. The area will be numbed with lidocaine and, once numb, a large needle will be inserted through a small cut to draw about 4 tablespoons of marrow out of the bone and to possibly remove a small piece of bone. Your level of pain will be monitored throughout the procedure and you'll be encouraged to voice any concerns. Additional numbing medicine may be utilized if necessary. The entire procedure will take about 1 hour to complete. We will call you about 2 days after the procedure to see how you are doing.
- Lumbar Puncture: You will undergo a lumbar puncture (sometimes called a "spinal tap") to a obtain cerebral spinal fluid (CSF) sample. This procedure involves inserting a small needle into your lower back. The study staff will help position you either on your side or sitting up. The lower part of your back will first be cleaned with antiseptic, and then the study doctor will inject a small amount of local anesthetic to numb the area. Once numb, a very thin needle will be inserted into the spinal canal in your lower back [well below where the spinal cord ends]. About 2 teaspoons of spinal fluid will be removed for analysis and storage. Your body usually replaces this fluid within 1-2 hours.

  After the lumbar puncture is complete, you will be monitored for about 30 minutes. To prevent side effects, it is important that you not do any strenuous physical activity for 24 hours following the procedure. This includes lifting, bending, doing housework and gardening, or exercising.
- Pulmonary Function Tests: Pulmonary Function Tests or PFTs measure the volume of air that a person can move into and out of the lungs in order to measure lung function. You will breathe into a machine that measures the air. This will only be done if you are on oxygen, or if you have a history of significant lung side effects from previous chemotherapy, radiation therapy, or bone marrow transplant.
- Electrocardiogram (ECG): An electrocardiogram (ECG) is a test that is performed while you lie still for about 5 minutes. It involves placing electrodes (small stickers that are attached to wires that go to the machine) on the chest and arms/legs and recording the electrical activity of your heart. If you have a lot of hair on your chest, it may hurt a little bit when they remove these stickers.
- Echocardiogram: An echocardiogram is used to evaluate the structure and function of your heart. It uses harmless sound waves which bounce off the heart structures as a series of echoes. The echoes are recorded on moving graph paper or a videotape.
- Imaging: The following scans may be done, as directed by your doctor and based upon your disease:

- MRI Scan: Magnetic resonance imaging (MRI) uses a strong magnetic field and radio waves to take pictures of the body. We will obtain pictures of your affected body area for this study. The MRI scanner is a metal cylinder surrounded by a strong magnetic field. During the MRI, you will lie on a table that can slide in and out of the cylinder. We will place soft padding or a coil around your affected body area. You will be in the scanner about 35-120 minutes. You may be asked to lie still for up to 120 minutes at a time. While in the scanner you will hear loud knocking noises, and you will be fitted with earplugs or earmuffs to muffle the sound. Younger patients and patients who have difficulty holding still or tolerating being placed in a scanner, can receive medications to make them sleep through the procedure by a doctor called an anesthesiologist. If you are awake for the procedure, you will be able to communicate with a technician at all times and can request to be removed from the scanner at any time.

  For cardiac MRIs, additional devices are used in order to generate high quality images of the heart. These devices require wire attachments to your body, primarily on your chest. On very rare occasions these wires have caused burns where they touched the skin, but this risk is rare and research staff has been trained to take the proper precautions to avoid this risk.

- CT Scan: A Computerized Tomography or CT scan provides multiple detailed pictures of the inside of the body, like an MRI scan, but the CT scan uses radiation, similar to an X-ray. CT scans may be done with or without oral or intravenous contrast. The scan may take between 30-90 minutes to complete depending on the areas of the body being scanned and the type of scanner.

- PET Scan: A Positron Emission Tomography scan or PET scan for short lets doctors see the activity of cells in specific tissues of the body. A sugar, which is attached to a chemical that gives off a signal, is injected into you intravenously before the scan. The scanner records the signals through the body. PET scans will be obtained only for clinical reasons and not as a research test.

During the Study

Additional Tests

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

- Physical exam
- Blood tests
- Urine tests
- Stool tests
- Pregnancy test (if you are a woman who could have children)
- Brain MRI (this will be up to the study doctor)
- Neurologic evaluation
- Neurocognitive assessments (performed in patients with isolated central nervous system (CNS) disease only): this includes cognitive tests that take less than 1 hour to complete and a brief symptom checklist

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.

Apheresis

Some cells will be collected from your blood by a procedure known as "apheresis". Apheresis is a standard procedure where a portion of your blood will be collected or removed. Apheresis is not an investigational procedure. During apheresis, blood will be drawn from you through a venous catheter (intravenous or IV), a needle in one arm, or through central venous catheter (CVC). Your blood will then pass through the apheresis machine and the blood components (red cells, plasma and lymphocytes) become separated by centrifugation (spinning). A small portion of your blood (the lymphocytes) will be collected into a storage bag and the remaining blood and some salt solution and blood thinning medicine (anticoagulant) will be returned to you through a second venous catheter or needle. Blood thinning medications, heparin and/or citrate anticoagulant, will be used to keep your blood from clotting during the procedure. The procedure usually takes about 4-6 hours. After the lymphocytes are collected, they will be taken to the laboratory where they will be prepared for your CD19/CD22-CAR T cell infusion or stored in a special freezer until you are ready to receive them.

If you have cells stored from another protocol that meet the requirements for this study, we may be able to use those to grow your cells on this study. The CD19/CD22 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. Your cells may be started in the laboratory within days of your cell collection. If growing your cells is delayed or you require cancer treatment between the time we take your cells and the start of the chemotherapy described here, you may be required to repeat the exams, tests or procedures described above to make sure it is safe for you to receive the study treatment described in this consent.

Lymphodepleting Chemotherapy

You will be given two chemotherapy drugs starting 4-5 days before the cell infusion. These chemotherapy drugs are common drugs used in the treatment of cancer. In this study, they will be used to weaken your immune system in order to accept to the CD19/CD22-CAR T cells. The exact regimen will be based on whether you have received prior CAR T-cells or not, and will be comprised of:

Fludarabine will be given into your IV over 30 minutes for 3-4 days. If fludarabine is not available, pentostatin will be given into your IV over 30 minutes or as a bolus for 1-2 days.

Cyclophosphamide will be given into your IV using a standard dose over 1 hour for 1-2 days.

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.

CD19/CD22-CAR T Cell Infusion

If you were not admitted to the hospital to receive the chemotherapy, you may be admitted to the hospital before you are given the cell infusion. Within 4 hours before the cells, you will be given acetaminophen (Tylenol) and diphenhydramine (Benadryl) to help prevent any side effects from the cells. The CD19/CD22-CAR T cells will be given in your IV catheter over a few 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.

Research 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 25 mL of blood (about 5 teaspoons) prior to giving you the cells and then frequently until around day 28. If you have disease in your spinal fluid, we may take a sample of your spinal fluid to test for CD19/CD22-CAR T cells. Patients with cancer in the bone marrow will also have a bone marrow sample sent for testing. If your cancer improves after giving you the cells, we may continue to take about 25 mL (5 teaspoons) of blood each time you have a clinic visit (about every 2-3 months). If your cancer responds to the CD19/CD22-CAR T cells and you continue to have CAR cells in your blood, we will continue to study your samples.

Samples may also be sent to a collaborator at Indiana University, to study the blood markers that might inform us about the safety and effectiveness of CAR cell therapies. Your samples will be sent with only a code, none of your personal identifiable information will be included, including your name, patient medical record number or date of birth. Only the investigators on this trial will know who the samples belong to. This information is solely for research and will not be returned to you as we do not know the meaning of the information at this time.

We may ask you to collect an optional stool sample in a container prior to starting lymphodepleting chemotherapy, prior to receiving the CAR T-cell infusion, and several times throughout the study if you develop side effects. We will use the stool for research studies to look at microbes in your intestines and learn the effects treatment may have on your intestines.

We may ask you to collect urine in a container prior to lymphodepleting chemotherapy, prior to receiving the CAR T-cell infusion, and then weekly until day 28. We will use the urine sample for research that will look at your metabolism and your body's immune response.

Care post CAR T-cell therapy infusion (Follow Up)

You may be admitted to the hospital for CAR T-cell infusion. When your condition is stable, you may be discharged from the hospital. After receiving cells, you will be monitored at least twice weekly until day 14 as inpatient or outpatient. You should plan to remain in close proximity to the NIH for around 28 days (+/- 4 days). During this time, you will have least twice weekly evaluations until you complete the Day 28 (+/- 4 days) restaging evaluations, unless restaging is done early in certain circumstances.

After the first month, you may be asked to return to clinic for an evaluation every month for 2-3 months depending upon your response to the therapy, then at 3, 6, 9 and 12 months for the first year, and then every 3 to 6 months, depending upon your condition, until about 5 years. If you are unable to come to the NIH for these evaluations, you may have them done at a local center and send them to us. Your study team can instruct you on how. We may also contact you by phone, email, or video chat (remotely) to speak with you directly and find out how you are doing. If you go onto other therapies these visits may or may not be necessary.

At these visits, you will have the following tests and procedures:

- History and physical exam

- Standard laboratory tests and research blood, stool, and urine tests
- Evaluation of your disease, which may include a CT scan, PET/CT scan, MRI, bone marrow aspiration and biopsy and/or spinal tap. Your doctor will tell you the best tests to evaluate your disease.

Study Chart

Study Regimen	
DAY	**WHAT YOU DO**
Prior to lymphodepleting chemotherapy	Come to NIH Clinical Center and do the following: • Apheresis – to obtain the white blood cells to grow in the lab for the anti-CD22 CAR cells (unless you have stored cells we can use) • Additional tests will be done before you start the chemotherapy which may include repeating some of the tests done to confirm eligibility • Neurologic evaluation • Neurocognitive assessments for patients with isolated CNS disease only: this includes questionnaires that take approximately 1 hour to complete and a brief symptom checklist • Collection of stool, blood, and urine research tests
Day -5 (if you have received prior CAR)	Come to NIH Clinical Center and do the following: • Get Fludarabine IV over 30 minutes; or • Get pentostatin IV over 30 minutes (alternative chemotherapy to fludarabine)
Day -4 and -3	Come to NIH Clinical Center and do the following: • Get Fludarabine IV over 30 minutes; or, • Get pentostatin IV over 30 minutes (alternative chemotherapy to fludarabine), one time dose on day -4 only • Get Cyclophosphamide IV over 60 minutes on day -3
Day -2	• Routine urine 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 or by mouth
Day 0	• Physical exam • Routine blood and urine tests • Research urine and stool tests • Take research blood samples (before the cells)

Study Regimen	
DAY	**WHAT YOU DO**
	• May have acetaminophen and diphenhydramine before the cell infusion. • Begin Keppra to help prevent neurotoxicity • Get infusion of anti-CD19/ anti-CD22 CAR cells IV over 5-20 minutes
At least twice weekly from Days 1-28; as an inpatient or outpatient	Come NIH Clinical Center and do the following: • Physical exam • Routine blood tests • Research blood, stool, and urine tests • Neurologic symptom checklist for patients with isolated CNS disease only: (about Day 10 and day 20) • Evaluation of cancer (Day 28 +/- 4 days), may include blood tests, scans, x-rays, bone marrow biopsy and/or lumbar puncture. In certain circumstances, disease evaluation post CAR T-cell therapy may be done earlier
Month 2 (if feasible)*	The following may be requested to be done at NIH or at home institution: • Medical History • Physical Exam (including vital signs-blood pressure, pulse, temperature, and weight) • Routine blood tests
Approximately Month 3, 6, and 12, then every 6 months (2nd year)	The following may be requested to be done at NIH or at home institution: • Physical exam • Routine blood tests • Research blood tests • Evaluation of cancer may include blood tests, scans, x-rays, bone marrow biopsy and/or lumbar puncture. • Complete neurologic assessment and symptom checklist for patients with isolated CNS disease only: (at 3 months only), if feasible

Additional Doses of CD19/CD22-CAR T Cells

If you benefitted from the first dose of CD19/CD22-CAR T cells (your cancer improved) without unacceptable side effects, and have enough cells left over, you may be eligible to receive additional dose(s) of CD19/CD22-CAR T cells. You may be given the same chemotherapy drugs and hospital procedures as you underwent for the first dose. In certain circumstances, your doctors may recommend giving you a higher dose of these same chemotherapy drugs prior to receiving the

cells. This may be done as we think it could help to improve your response to an additional dose of cells. You will have a discussion with your doctors regarding whether you should receive an additional dose of cells and how best to receive them. These cells will have been kept in the freezer with a special drug (DMSO) to preserve them.

SUPPORTIVE THERAPIES

Antimicrobial Prophylaxis

Subjects with ALL or lymphoma are at high-risk for developing many types of infection, which include, but are not limited to bacterial, viral and fungal infection. You may already be on medications to help prevent infections. These medications may be continued or changed based on you and the clinical situation. Medication to help prevent infection will be determined on a case-by-case basis, with plans for starting medications to prevent fungal infection and bacterial infection during periods of neutropenia (decreased ability to fight infection).

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. Any combination of standard chemotherapy drugs including cytarabine (Ara-C), methotrexate and hydrocortisone (a corticosteroid like prednisone) will be given either alone or together into the spinal fluid and your team will review the specific plan with you. This will be done approximately every 3-4 weeks at times when spinal taps are being performed to check for leukemia.

BIRTH CONTROL

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 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 up to 12 months if you are a woman who can become pregnant, and for at least four months after finishing the cell infusion if you are a man with a partner who can become pregnant. 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.

GENE THERAPY LONG TERM FOLLOW UP (LENTIVIRAL VECTORS)

Because we do not know the long-term side effects of gene therapy, we will collect a sample of your blood over the next several years, frequently at first and then less frequently. If you return to your referring physician after treatment here, we will ask you to have your physician send your blood specimens here for this testing. This testing will determine if the cells have grown or changed in your body. We will collect your blood immediately before the cells, and then at 3, 6 and 12 months (3-4 teaspoons each time), and we may test these samples at a future date to help us learn if the cells have grown or changed in your body. We will continue to collect blood every year and store samples in case you develop symptoms later. Your study team will discuss this with you.

According to FDA requirements, we need you to have an annual physical examination for five years after you receive the cells. After that time, we will contact you yearly via mail, phone, or email 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, telephone number, and email address, even after you complete this research study.

If you should die, no matter the cause, we may request permission for an autopsy to obtain vital information concerning the safety of this experimental therapy approach. Please discuss this with your family to inform them of this request.

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.

These long-term follow-up evaluations will be conducted under our companion protocol 15-C-0028, "Follow-Up Evaluation for Gene-Therapy Related Delayed Adverse Events after Participation in Pediatric Oncology Branch Clinical Trials", to which we will ask you to enroll in.

RISKS OR DISCOMFORTS OF PARTICIPATION

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

There are risks, discomforts, and inconveniences associated with any research study. These deserve careful thought. You should talk with the Investigator if you have any questions.

The potential risks of CD19/CD22-CAR T cells may be significant. These risks are due to the drugs used to prepare the body for the cell infusion, as well as side effects associated with the CD19/CD22-CAR T cell infusion itself.

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.

Possible Side Effects of CD19/CD22-CAR T cells

Since the purpose of this study is to see how well the CD19/CD22-CAR T cells are tolerated, we do not know if there will be any side effects.

The cells we will be giving you have a type of virus (lentivirus) put into them along with the CD19/CD22 CAR gene. Although this lentivirus 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. CD19-CAR T gene-modified cells have been given to hundreds of individuals and CD22-CAR T cells have been given to about 70 individuals before, but there is still a lot we may not know and there may be risks that we cannot predict. The CD19/CD22-CAR T cells have been given to at least 26 patients before and risks described below is based on our experience to date.

Potential risks, based on experiences on the CD19 and CD22 CAR T-cell trials, include:		
Common In 100 people, more than 20 and up to 100 may have:	**Less Common** In 100 people from 4 to 20 may have:	**Rare** In 100 people 3 or fewer may have:
• Fever, chills and shortness of breath, which may last for several days • Tiredness • Elevated white blood cell count • Pain, which may be worse at sites of disease • Rash • Cough • Increase in blood levels of C-reactive protein, which may indicate inflammation • Decreased B cells (a type of white blood cell) that may increase your risk of infection • Low blood pressure • Cytokine release syndrome (CRS): nausea, headache, fast heartbeat, low blood pressure, rash and shortness of breath • Changes in blood levels of liver that may indicate damage to the liver • Electrolytes changes (changes to the salts and minerals in your body)	• Nausea or vomiting • Lung congestion • Autoimmune reaction such as loss of skin pigment (known as vitiligo) or inflammation of the eye (uveitis) which may require the use of steroid eye drops. • Neurologic toxicity which may include pain, headache, confusion, delirium, hallucinations seizures and a temporary inability to speak • Changes in the kidney function • Inflammation that extends beyond the initial cytokine release syndrome (CRS—see below) and may lead to other problems including macrophage activation syndrome (MAS) or hemophagocytic lymphohistiocytosis (HLH) which requires additional anti-inflammatory therapy • Increase risk of bleeding/bruising throughout the body including development of disseminated intravascular coagulation (DIC), nosebleeds, bleeding from bladder	• Allergic reaction (including wheezing, difficulty breathing, fast heartbeat, low blood pressure, rash) • Capillary leak syndrome (CLS): swelling of hands and feet, lowered blood pressure, fast heartbeat, weight gain, low oxygen blood levels. • Graft-versus-host disease (GVHD): inflammation that could occur in different organs after CAR T-cell infusion in patients who have received a stem cell transplant or donor lymphocyte infusions. Symptoms can include skin rash, nausea, abdominal pain, diarrhea, and changes in blood levels of the liver

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; which can be associated with severe symptoms requiring intensive care unit (ICU) level care or even death. Several patients have been intubated (required a tube passed through the nose or mouth to the lungs to support breathing) or were given strong medicine to support blood pressure. Although the cause behind this 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, high fever, confusion and fast heart rate. If not treated, CRS can cause liver, lung and kidney failure and possibly death. On this study, 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 an outpatient, we will ask you to return to the clinic at least twice a week until you reach day 28. This is so you can have a physical exam and we can see how you feel. We will be testing your blood frequently and watching you closely for CRS. We will give you medicines to treat the effects of CRS, but if they become severe or life-threatening, you will be treated in the Intensive Care Unit (ICU).

As of April 2023, we will use a different first line medication to treat symptoms of CRS called siltuximab. Siltuximab is FDA approved for use in multicentric Castlemans disease; however, siltuximab is considered experimental for treating CRS. It has been used at other centers in clinical trials to prevent or treat CRS or neurotoxicity associated with CAR T-cells and early results have shown that this treatment can be effective. There is a chance that this medication does not help treat CRS and you could get sicker. If this happens, we have additional medications that can be used to treat CRS. One of the other medicines we may give you is called tocilizumab, a different antibody that could block the effects of the CRS. Tocilizumab is approved by the FDA for treating CRS.

Risk Associated with Siltuximab		
Common	**Less common**	**Rare**
• Upper respiratory tract infections (common cold) • Skin rash • Swelling • Weight gain	• Low blood pressure • Headache • Increased risk of infection • Kidney problems • Increased levels of cholesterol	• Severe allergic reaction – may include rash, hives, fever, difficulty breathing, and low blood pressure. • Gastrointestinal perforation – hole in the intestines which may possibly cause contents to leak into the abdomen

Risk Associated with Tocilizumab (to block cytokines)		
Common	**Less common**	**Rare**
• Upper respiratory tract infections (common cold) • Headache • High blood pressure • Increased levels of blood cholesterol	• Dizziness • Increased risk of infection • Skin rash • Stomach irritation • Sores in the mouth	• Stomach or intestinal ulcers • Severe allergic reaction

Hemophagocytic lymphohistiocytosis (HLH)/ macrophage activation syndrome (MAS)

HLH/MAS is an inflammatory response which may be related to CAR-T cell therapy, but the mechanism is poorly understood. This may present with liver function test abnormalities, low blood cell counts, fevers, elevated ferritin and/or elevated triglycerides. HLH/MAS may be genetic (inherited) or acquired (secondary), but in the setting of CAR-therapy we believe it is acquired. This can spontaneously resolve or be treated with steroids, anakinra or other immunosuppressive therapies including chemotherapy. Anakinra is approved by the FDA for rheumatologic conditions in adults and children but is considered experimental for treating HLH/MAS.

Disseminated Intravascular Coagulation (DIC)

DIC generally refers to a state when there is an imbalance in the body's ability to maintain normal bleeding/clotting function. DIC is a known complication of CAR therapy. In DIC, patients may develop blood clots or have bleeding symptoms. DIC can be without symptoms (lab abnormalities only), or be associated with bleeding (nose bleedings, easy bruising) and can be quite serious. Patients are monitored for this routinely and treated with supportive care measures, which may include steroids, and transfusion support with blood, platelet and coagulation factors.

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

Several patients who received CD19 CAR cells had reversible severe effects of their nervous system, including confusion and difficulty communicating. In severe cases, this nervous system toxicity led to death. 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.

You will be given a medication (levetiracetam or Keppra) to help prevent neurotoxicity. If you show signs or symptoms of neurotoxicity, we will give you additional therapies (i.e. steroids).

In 2019, one subject on the CD22 CAR T-cell trial developed a hemorrhagic stroke in the setting of infection, but this had not previously been seen. All subjects will continue to be closely monitored for neurotoxicity. Of the at least 28 patients receiving this CD19/22 CAR at the time this consent text was written, 2 patients developed neurotoxicity which included weakness, difficulty talking and confusion. This was able to be appropriately treated and fully resolved.

Any new information that becomes available during the course of this study that may impact your willingness to participate will be shared with you.

Risk of not being able to receive the CD19/CD22-CAR T 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.

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 children out of 22 later developed leukemia and one died. Experts who looked at these cases thought that the gene therapy caused the leukemia in these children. To watch you for this risk we will be collecting your blood samples as described before, and will test at a future date if clinically indicated.

DMSO Risk (if frozen doses of CD19/CD22-CAR T cells are given)

As previously noted, any extra cells from the first infusion of the Anti-CD19/CD22 CAR Cells are frozen and stored with a preservative called DMSO. Side effects may include nausea, vomiting, and diarrhea. Most commonly it causes an unpleasant taste and smell (like garlic). Other side effects that have been reported include facial flushing, loss of appetite and flu-like symptoms.

Risks of Lymphodepleting Chemotherapy

Fludarabine side effects		
Common	**Less Common**	**Rare**
• Changes in blood counts (may be serious and life-threatening)	• 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, including 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**
• Infection, especially when white blood cell count is low • Hair loss, skin changes, rash, change in nails • Mouth sores which may cause difficulty swallowing • Fever • Nausea, vomiting, diarrhea, loss of appetite, pain in belly	• Loss or absence of sperm which may lead to an inability to father children • Fluid around the heart • Damage to the bone marrow (irreversible) which may cause infection, bleeding, may require transfusions	• Damage to the heart or heart failure which may cause shortness of breath, swelling of ankles, cough or tiredness • A new cancer (e.g., leukemia, lymphoma, sarcoma etc.) resulting from treatment of a prior cancer • Swelling of the body including the brain which may cause dizziness, confusion • Allergic reaction which may cause rash, low blood pressure, wheezing, shortness of breath, swelling of the face or throat • Damage to the lungs or scarring of the lungs which may cause shortness of breath • Hepatic veno-occlusive disease is a condition that is characterized by damage to blood vessels in the

• Anemia which may cause tiredness, or may require transfusion • Bruising, bleeding • Absence of menstrual period which may decrease the ability to have children • Blurred vision, vision changes		liver and liver cells. Although it may be mild and not require further treatment, sometimes it may cause a severe decrease in liver function and may be life threatening or fatal. • Severe skin rash with blisters and peeling which can involve mouth and other parts of the body. • Impaired wound healing • Urinary and/ or kidney including blood in urine, painful urination, fever, urgency, inability to urinate, loss of bladder control and pain. • Kidney damage which may cause swelling, which may require dialysis. • Decreased levels of sodium in the blood, which can cause confusion, seizures, fatigue and low levels of consciousness. • Abnormal heartbeats: including atrial fibrillation and flutter and ventricular arrhythmias causing your heart to be fast or irregular resulting in a pounding or racing heart, dizziness, weakness, feeling light-headed or shortness of breath.

In addition, because cyclophosphamide may contain alcohol, it may impair a person's ability to drive or operate machinery immediately after the infusion.

Pentostatin side effects		
Common	**Less Common**	**Rare**
• Infection • Nausea/ Vomiting • Diarrhea • Fatigue • Fever • Headache	• Skin Rash • Allergic Reaction • Thrombocytopenia – low platelet count which may cause bleeding and bruising.	• Damage to the central nervous system causing seizures, coma, and even death • Inflammation of the lungs • Kidney damage

• Leukopenia – low white blood cell count that may increase the risk of infection, which may be serious or life-threatening • Anemia – low red blood cell count • Myalgia - muscle pain	• Abdominal pain • Stomatitis - inflammation of the mouth • Hepatic disorder/elevated liver enzymes – can cause fatigue and jaundice (yellowing of the skin and eyes)	

Mesna (To prevent bleeding in the bladder from cyclophosphamide)		
Common	**Less common**	**Rare**
	• 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

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 these 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. Any risks associated with a support medication that is prescribed to will be explained to you prior to receiving the first dose.

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.

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. During screening, we will collect about 4 tablespoons of blood. We will not collect more than 6 ½ tablespoons of blood during any day on study or 30 tablespoons within an 8-week period. If you are under the age of 18, the amount collected may be less as it will be based on your weight.

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 Aspiration / Biopsy

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.

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.

Pulmonary Function Tests

These tests are safe and side effects are unlikely. During the test you will be asked to breathe deeply or rapidly, which may occasionally cause brief light headedness or slight soreness of the chest.

Electrocardiogram (ECG) / Echocardiogram

Other than possibly experiencing some minor skin irritation from the electrodes there are no anticipated risks related to complete the electrocardiogram and/or the echocardiogram.

Cognitive Testing

You may experience feelings of frustration while taking the tests. These tests are meant to be challenging. You will be able to take breaks as necessary.

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. Sometimes catheters may become infected or clogged. If this happens the catheter 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.

Stool and urine collections

Collecting your stool and urine may be embarrassing but it should not hurt and there are no risks.

CT Scan and PET Scan

In addition to the radiation risks from the scans discussed above there is a chance of developing an allergic reaction from the contrast material, which may cause symptoms ranging from mild itching or a rash to severe difficulty breathing, shock or rarely, death. The contrast material may also cause kidney problems. The study doctors will do a blood test prior to the test to confirm that it is safe you to receive the contrast.

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

For oral contrast: You may experience vomiting, nausea, cramping, bloating, constipation or diarrhea after drinking the contrast.

Risk of Radiation

During your participation in this research study, you may be exposed to radiation from up to 6 CT Scans and 6 PET scans each year. The amount of radiation exposure from these procedures is equal

to approximately 13.8 rem. A rem is a unit of absorbed radiation. This amount of radiation is greater than the NIH Radiation Guidelines of 0.5 rem per year for participants less than 18 years old.

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 and PET scans that you get in this study will expose you to the roughly the same amount of radiation as 46 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 1.4 out of 100 (1.4%) and of getting a fatal cancer is 0.7 out of 100 (0.7%).

Risk of MRI

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

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

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

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

Risks of gadolinium enhanced MRI

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

People with kidney disease are at risk for a serious reaction to gadolinium contrast called "nephrogenic systemic fibrosis (NSF)". This condition always involves the skin and can also involve the muscles, joints and internal organs. NSF has resulted in a very small number of deaths. A blood test of your kidney function may be done within the month before an MRI scan with gadolinium contrast. You will not receive gadolinium for a research MRI scan if your kidney function is below the safe level.

Most of the gadolinium contrast leaves the body in the urine. However, the FDA has issued a safety alert that indicates small amounts of gadolinium may remain in the body for months to years. The long-term effects of the retained gadolinium are not unknown. Some types of gadolinium contrast drugs are less likely to remain in the body than others. In this study, we will use the gadolinium contrast drugs that are less likely to remain in the body. In this study, we will use the gadolinium contrast drugs that are less likely to remain in the body, whenever possible. We will also give you additional information called a "Medication Guide." Upon request, we will give you individual information about retained gadolinium we see on your studies.

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 able to be given safely. We do not know if you will receive personal, medical benefit from taking part in this study. These potential benefits could include shrinking of your tumor/decrease in leukemia or lessening of your symptoms, such as pain, that are caused by the cancer. Because there is not much information about the drug's effect on your cancer, we do not know if you will benefit from taking part in this study, although the knowledge gained from this study may help others in the future who have cancer.

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.

STOPPING PARTICIPATION

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
- 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. 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 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 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 CD19/CD22-CAR T cells being used in this study. This means 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. You will not receive any money from the development of CD19/CD22-CAR T cells.

USE OF SPECIMENS AND DATA FOR FUTURE RESEARCH

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

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

If you do not want your stored specimens and data used for future research, please contact us in writing and let us know that you do not want us to use your specimens and/or data. Then any

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

COMPENSATION, REIMBURSEMENT, AND PAYMENT

Will you receive compensation for participation in the study?

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

Children/participants will be paid $20 for each stool sample collected for research, up to $100. For minors, payment will be given to a parent or legal guardian.

If you receive payment using a bankcard, the bank will have access to identifiable information. The bank will not have access to any medical information.

If you receive payment by direct deposit, we will need your social security number. You do not have to give it to us, but you may not be able to receive payment if you do not.

If you are unable to finish the study, you will receive payment for the stool samples that were collected. If you have unpaid debt to the federal government, please be aware that some or all of your compensation may be automatically reduced to repay that debt on your behalf.

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

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

On this study, the NCI will cover the cost for some of your expenses. Some of these costs may be paid directly by the NIH and some may be reimbursed after you have paid. The amount and form of these payments are determined by the NCI Travel and Lodging Reimbursement Policy. You will be given a summary of the policy which provides more information.

Will taking part in this research study cost you anything?

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

- If some tests and procedures performed outside the NIH Clinical Center, you may have to pay for these costs if they are not covered by your insurance company.
- Medicines that are not part of the study treatment will not be provided or paid for by the NIH Clinical Center.
- Once you have completed taking part in the study, medical care will no longer be provided by the NIH Clinical Center.

CLINICAL TRIAL REGISTRATION AND RESULTS REPORTING

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

CONFIDENTIALITY PROTECTIONS PROVIDED IN THIS STUDY

Will your medical information be kept private?

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

- The NIH and other government agencies, like the Food and Drug Administration (FDA), which are involved in keeping research safe for people.
- National Institutes of Health Intramural Institutional Review Board
- The study Sponsor (Center for Cancer Research) or their agent(s)

In most cases, the NIH will not release any identifiable information collected about you without your written permission. However, if you sign a release of information form, for example, for an insurance company, the NIH will give the insurance company information from your medical record. This information might affect (either favorably or unfavorably) the willingness of the insurance company to sell you insurance.

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

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

Certificate of Confidentiality

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

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

The Certificate does not protect your information when it:

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

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

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

Privacy Act

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

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, about your rights as a research participant, or about any research-related injury, contact the Principal Investigator, Nirali Shah, M.D., at 240-760-6199. You may also call the NIH Clinical Center Patient Representative at 301-496-2626, or the NIH Office of IRB Operations at 301-402-3713, if you have a research-related complaint or concern.

CONSENT DOCUMENT

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

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

Signature of Research Participant	Print Name of Research Participant	Date

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

Signature of LAR	Print Name of LAR	Date

Parent/Guardian of a Minor Participant: I have read the explanation about this study and have been given the opportunity to discuss it and to ask questions. I give permission for my child to take part in this study.

Signature of Parent/Guardian	Print Name of Parent/Guardian	Date
Signature of Parent/Guardian	Print Name of Parent/Guardian	Date

Assent: I have had this study explained to me in a way that I understand, I have been given the opportunity to discuss it, and I have had the chance to ask questions. I agree to take part in this study.

Assent of Minor:

Signature of Minor	Print Name of Minor	Date

Investigator:

Signature of Investigator	Print Name of Investigator	Date

Witness should sign below if either:

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

Signature of Witness	Print Name of Witness	Date

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

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

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