

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 (NIH CC)

Cohort: Assent Minors, 12-17 years old

Assent Version: 05/28/2024

What is a research study?

Research studies help us learn new things. We can test new ideas. First, we ask a question. Then we try to find the answer.

This paper talks about a research study that we are doing and the choice that you have to take part in it. You are being asked to join this research study because you have a type of B-cell leukemia or lymphoma. We want you to ask us any questions that you have. You can ask questions any time.

Important things to know...

- You get to decide if you want to take part.
- You can say ‘No’, or you can say ‘Yes’.
- No one will be mad at you if you say ‘No’.

Why are we doing this research?

We are doing this research to find out if a new therapy will be safe in children with your type of leukemia or lymphoma. This is called CAR therapy (CAR stands for Chimeric Antigen Receptor). CARs are genetically modified cells that are made from your own immune system. Normally your immune system can attack infection. What we are trying to do is to teach your immune system to attack your leukemia. During this study, we will take some of your cells (the kind of cells that help fight infection) and teach them how to fight leukemia. After these cells are grown in a lab, they will be given back to you.

This specific CAR is designed to recognize specific targets on your leukemia, called CD19 and CD22. We know that your cancer has CD19 and CD22 on it because we have tested your cancer cells for the CD19 and CD22. Some CARs have been tested in children and adults before. You may have received a prior CAR therapy. The CD19/CD22 CAR has not been tested in many children or adults and this is one of the first trials to use this therapy.

This is an investigational therapy. “Investigational” means that doctors are doing more research to learn more about it. We don’t know if the CAR therapy will work. The main purposes of the study are to see if the CD19/CD22 CAR T-cells are safe to use.

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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.

What would happen if I join this research?

The following will be done to see if you are eligible to participate in the treatment part of this study. If some of these tests were done recently, they may not need to be repeated.

- Medical records: We will look at your past doctor visits and use information about your care.
- Medical history: We will ask questions about your health, current medications, and any allergies.
- Physical exam: A doctor will look at your skin, listen to your heart, lungs, and stomach. You will also have your height, weight, temperature, blood pressure and how much oxygen you have in your blood checked.
- Performance status, which evaluates how you are able to carry on with your usual activities.
- Blood tests: You may need a needle poke so we could test some of your blood. If possible, we will try to get blood without a new poke.
- Other tests (to check your urine, liver)
- Pregnancy test (if you are female and able to get pregnant). You will not be able to participate if you are pregnant.
- Tests to check your heart:
 - Echocardiogram: Sometimes called an “echo” uses sound waves to create a picture of your heart.
 - Electrocardiogram: Sometimes called an “ECG” measures your heart’s electrical activity.
- Pulmonary Function Test: Sometimes called a “PFT” measures how well you can move air in and out of your lungs.
- Imaging with CT scan PET/CT or MRI
 - The CT scanner is a doughnut-shaped machine that uses x-rays to create computer pictures showing the inside of your body. You will need to lie still on a table inside the CT machine. The table will move you in and out of the machine during the scan and you will be told to hold your breath. The scan itself will only take a few minutes to complete, the entire visit will take about 30 minutes.
 - MRI creates pictures of the inside of your body using strong magnets instead of x-ray energy. You will also be asked to remove any metal objects you may be wearing (for example, watches, or earrings) and possibly to change into a hospital gown. Then you’ll be asked to lie on a narrow bed that will move into the MRI scanner. You will need to lie still on the table during the scan which will take about 30 minutes. You will have earplugs or earmuffs to lessen the noise.

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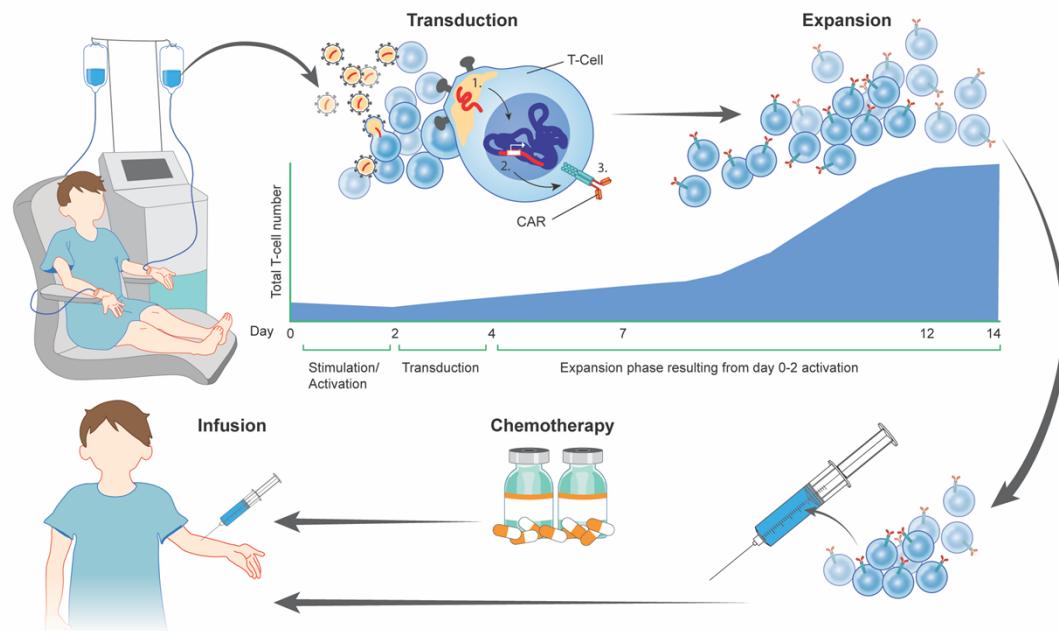


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- Before your PET-CT scan, you will get an injection of a small amount of a radioactive sugar (a tracer). The cells in your body absorb sugar. Areas that use more energy pick up more of the sugar. The PET scan shows where tracer is in your body. Your appointment will last 1 hour to 3 hours. Once the tracer gets to the right area through the IV, the scan itself usually only takes about 30 minutes. If the machine scans a large area, the test might take longer. The staff can tell you about how long it will take.
- Bone marrow aspiration/biopsy and lumbar puncture- Bone marrow aspiration is when we take a sample of the fluid from your lower back by your hip with a needle. A bone marrow biopsy is the removal of a small amount of solid tissue using a needle. Lumbar puncture takes a small amount of fluid that surrounds your spinal cord with a long needle that is inserted into our lower back.

If we think you can participate, you will first have to undergo an apheresis procedure. Apheresis is the process of how we collect cells from your immune system. This will be done by trained staff in the Department of Transfusion Medicine. For apheresis, either two intravenous lines, or a central line, will be placed in veins in your arms or groin or neck so blood can be removed through one needle and sent through a cell separator machine (a machine that divides your blood into red cells, plasma, and lymphocytes) to collect the lymphocytes (T-cells) which are used to make CAR cells, with the remaining cells sent back through the second needle. Blood thinning medications will be used to keep your blood from having blood clots during the procedure. The procedure takes about 4-6 hours. After the cells have been collected, they will be taken to the Research Laboratory to be made into CD19/CD22 CAR cells.



Before receiving the CD19/CD22 CAR cells, you will be given two chemotherapy drugs to help prepare your immune system to accept the CD19/CD22 CAR cells. These chemotherapy drugs are approved by the FDA to treat other diseases. The CD19/CD22 CAR will be given to you as an intravenous (IV) infusion, which means by a tube in one of your veins. A few weeks after the CAR

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cells are given, doctors will do some tests to see if the CAR cells worked. From the time that you start chemotherapy and receive the CAR cells, you will be in the hospital until the doctors feel that it is safe for you to stay outside the hospital.

You will have to stay in the hospital if there are signs of fever or other side effects. We will ask you to stay close to NIH (i.e., at the Children's Inn) until Day 28. You will come to clinic at least twice a week so the doctors and nurses can keep watching to make sure that you are ok.

Throughout the study, to see how your disease is doing, you will come to the clinic to get some of the same tests repeated as you did to see whether you could join the study. Some of these tests include.

- Doctor's visit and physical exams
- Blood tests: You may need a needle poke so we could test some of your blood. If possible, we will try to get blood without a new poke
- Other tests (to check your urine, stool, and liver)
- Electrocardiogram: Sometimes called an "ECG" measures your heart's electrical activity.
- Imaging with CT scan, PET/CT, or MRI
- Bone marrow aspiration/biopsy and lumbar puncture- Bone marrow aspiration is when we take a sample of the fluid from your lower back by your hip with a needle. A bone marrow biopsy is the removal of a small amount of solid tissue using a needle. Lumbar puncture takes a small amount of fluid that surrounds your spinal cord with a long needle that is inserted into our lower back.
- If your central nervous system is involved, cognitive Tests (to see how you pay attention to things and think)

How long will I be in the study?

You will be involved in this study for about 5 years after you get the CAR cells. However, the FDA requires that we continue to follow you for up to 15 years to see how you are doing.

Could bad things happen if I join this research study?

Some of the tests or procedures might be uncomfortable. Doctors and nurses will try to reduce your discomfort and help explain what may happen and how you may feel. It is very important to tell your parents/guardians and doctors if you feel sick or have pain anywhere in your body. We will try to make sure that no bad things happen.

You can say 'no' to what we ask you to do for the research at any time and we will stop.

To turn your lymphocytes (T-cell) into CAR-T cells, we use a type of virus (lentivirus) to put the CD19/CD22 CAR gene into the T-cell. This process is called gene modification. Although this lentivirus is not active, there is a very small chance that it may cause infection. The cells could also cause you to develop another type of cancer in your blood cells, but this is rare, and we will be monitoring for it. There may be some risks that we don't know about.

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The main risk that we want you to know about is called “Cytokine Release Syndrome,” or, CRS, in short. Cytokines are proteins in the body that go up to high levels when the CAR-T cells are active and growing in your body. These cytokines will give you high fevers, body aches and make you feel very tired and sick. These cytokines cause inflammation, which is your body’s response to being sick. Sometimes people say this feels like having the flu. Usually, these symptoms start a few days after the CAR-T cells are given and will usually last 5-7 days.

For some people, CRS will be mild and they will quickly get better, but for others it may be very serious and you may have to go to the ICU (intensive care unit) so that the doctors can watch you more carefully. You may get special medications to help reduce the effects of the CRS (for instance steroids).

Symptoms of CRS may include:

- Fever, body aches and feeling tired
- Having a hard time breathing
- Rash
- Feeling sick to your stomach, vomiting or having diarrhea.
- Headaches, feeling confused or dizzy
- Changes in your lab tests (such as increases in lab tests that measure inflammation or other changes in the blood levels that measure the salt in the blood and other minerals or changes in your liver and kidney tests)
- Bleeding
- Swelling of your hands and feet
- Low blood pressure

For some people, after the CRS gets better, there may still be ongoing inflammation that will need to be monitored. Also, after getting the CAR-T cells and chemotherapy, you will be at increased risk for infection. You will receive blood and platelet transfusions or other related products to keep you safe through this therapy. Other risks could include allergic reaction (difficulty breathing, swelling, itching, rash) and you will be monitored for this.

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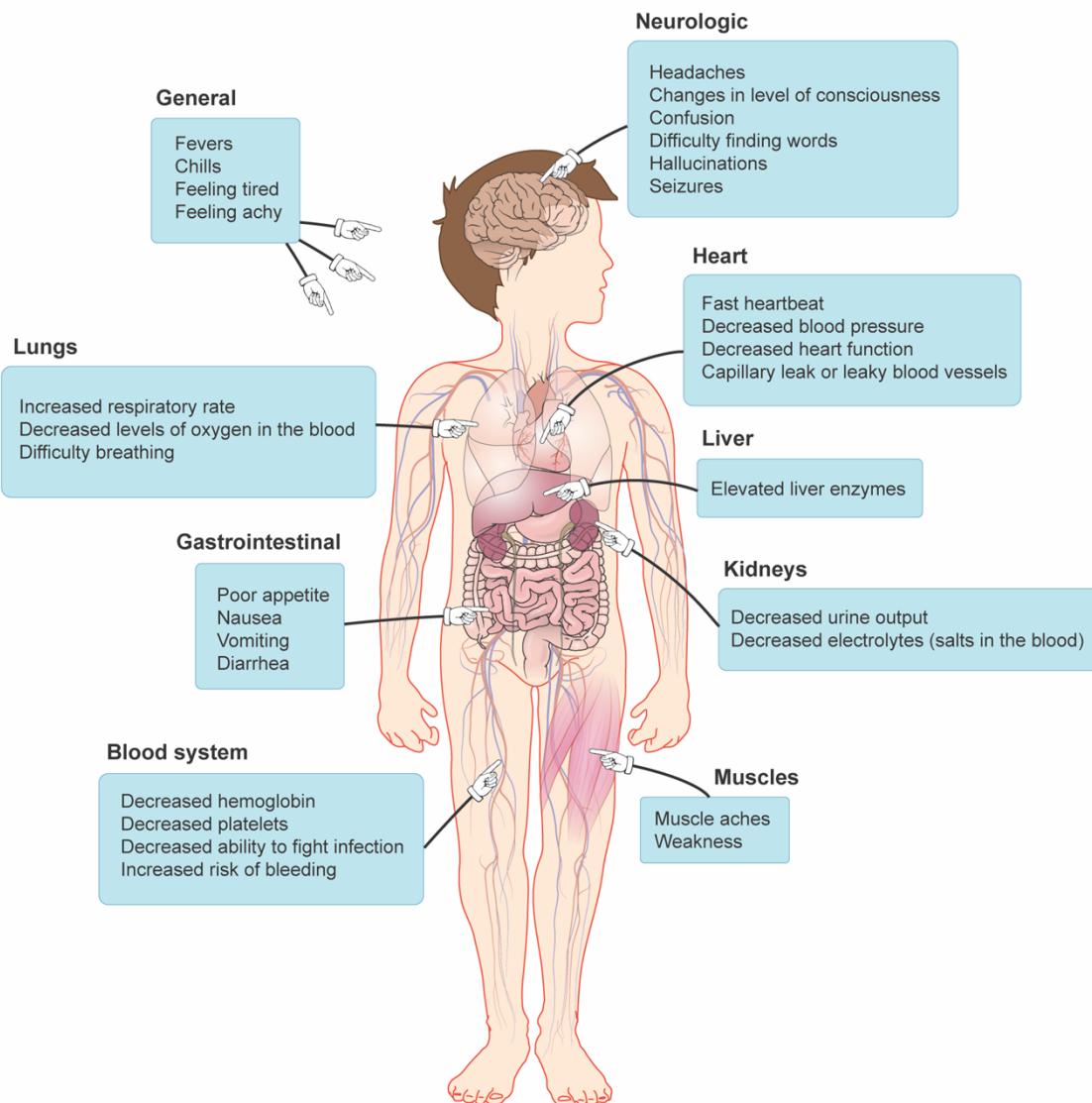
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Although we don't know the long-term effects of the CAR-T cells, one possible concern is that because these are immune cells, even though they are only supposed to get rid of the leukemia and other cells that have CD19 and CD22 on them, they could also trigger a reaction in your body that causes them to react against healthy parts of your body (like your skin or your eyes). If you have any concerns, you should let your doctor know.

Some of the things might happen to you or they might not. Or things might happen that we don't know about yet.

You may have some, all, or none of the following, as part of the tests done to see if you are able to be a part of the study:

- The poke to test your blood can hurt. Sometimes the needle can leave a bruise on the skin. We can put a cream on your skin before we take blood. This cream can help so it won't hurt as much
- Discomfort from small stickers that go on your chest and arms/legs. These stickers are attached to wires that go to the EKG machine that tests to see how your heart is working
- Pain, bruising and bleeding and sometimes infection from the bone marrow biopsy, lumbar puncture, or apheresis needles
- After a lumbar puncture you may have a headache or if you already had a headache it may get worse.
- It may be embarrassing to have urine and stool samples collected but should not hurt.
- During the apheresis, you may also feel chills, pins and needles and muscle cramps, which will be temporary.
- The chemotherapy given to prepare your body for the CAR cells may make you feel sick or nauseous. You may experience hair loss, mouth sores, blurred vision, pain when you pee, belly pain, hearing loss. There is a rare chance that you could develop a new cancer from the chemotherapy.
- CT Scan (computerized tomography): CT scans expose you to radiation. You could have an allergic reaction to the dye (contrast) that is used to make the images clear, and have a rash or trouble breathing, and feel uncomfortable when the contrast is injected.
- MRI (magnetic resonance imaging): Being in the small space and hearing the loud noise can sometimes make people feel nervous and scared.
- PET Scan (positron emission tomography): A PET scans expose you to radiation. A PET-CT scan does not hurt. But some positions might be uncomfortable or tiring. You need to lie still for the entire scan. You might also need to keep your arms above your head. The staff might ask you to hold your breath sometimes. Motion from breathing can cause blurry pictures. The staff might also raise, lower, or tilt the table during the scan. This gets pictures from different angles. Ask them to tell you when the table will move. You can expect to hear whirring or clicking sounds from the machine. Some machines are noisier than others.

The study therapy may hurt an unborn child. If you are sexually active, the study doctor will talk with you about using birth control while participating in this study. If you or your partner becomes

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pregnant while you're in the study, you must tell the study doctor immediately. If you are able to become pregnant, you will have a urine pregnancy test completed before starting chemotherapy. You must avoid getting pregnant or making someone pregnant while taking these medicines for at least 12 months after receiving the CAR cells if you are able to become pregnant and for 4 months after receiving the CAR cells if you are able to father a child.

Your medical team will talk to you about all of this and any concerns that you have. They will continue to tell you about what will happen or what is happening. If you have any concerns, you should always talk to your care team.

Could the research help me?

We think being in this research may help you because that the amount of cancer in your body may decrease. We hope that information we learn will benefit people with blood cancers in the future.

What else should I know about the research?

Please talk to your parents about this before you decide whether or not to be in this research study. We will also ask your parents to give their permission for you to be in this study. But even if your parents say "yes," you can still decide not to be in this research study.

If you don't want to be in this study, you don't have to.

Remember, being in this study is up to you and no one will be upset if you don't want to take part in this study.

It is also OK to say 'yes' and change your mind later. You can stop being in the research at any time. If you want to stop, please tell the research doctors. If you do stop, we may ask you to come back to see us at least one more time to see how you are doing.

You will not receive anything for being in the study.

Once you have turned 18, we will contact you to find out if you would still like to participate in the study.

What if I have any questions?

You can ask questions any time. You can talk to me, Dr. Shah, at 240-760-6199. Ask us any questions you have. Take the time you need to make your choice.

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Is there anything else?

If you want to be in the research study after we talk, please write your name below. We will write our name too. This shows we talked about the research and that you want to take part.

Assent of Minor:

Signature of Minor

Print Name of Minor

Date

Investigator:

Signature of Investigator

Print Name of Investigator

Date