EFFECTIVE

7/9/2019

MCW/FH IRB

Medical College of Wisconsin and Froedtert Hospital
INTRODUCTION TO THE INFORMED CONSENT

Name of Subject: _____

Phase 1/1b Study of Redirected Autologous T Cells Engineered to Contain an Anti CD19 and Anti CD20 scFv Coupled to CD3ζ and 4-1BB Signaling Domains in Patients with Relapsed and/or Refractory CD19 or CD20 Positive B Cell Malignancies

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You are invited to take part in this research. You can decide whether to take part in this project or not. You are free to say yes or no. If there is anything that you do not understand, please ask questions.

Definitions

Chimeric Antigen Receptor (CAR) – a special receptor created in the laboratory that is designed to bind to certain proteins on the cancer cell.
T-Cells- are immune cells that fight infections and, in some cases, can also kill cancer cells.
Leukapheresis – the process of collecting your immune cells, these T cells will be used to make the CAR-20/19-T cells.

Purpose

This project is being done to find new ways to treat relapsed and/or refractory blood or lymph cancers.

Length

1. You will be in this research project for about 2 years from screening to the end of the study. If you progress you will be followed for survival, active CAR-T cells, and future treatments.

Procedures

The study is divided into two phases. Phase 1 and Phase 1b. In phase 1, it consists of 2 groups; dose escalation and dose expansion where the CAR-T cells were given over 2 days. The dose escalation group means finding the safest tolerated cell dose for the CAR-T 20/19. Once the safest dose has been identified we will move into the dose expansion group. In phase 1b CAR-T cells will be given as a single dose.

List of visits:

- Screening Visit
  - Total Number: 1
  - Total Time: approximately 2 hours to 8 hours
- Apheresis/Leukapheresis Visit
  - Total Number: 1
  - Total Time: approximately 4 hours to 8 hours
- Lymphodepletion Visit
  - Total Number: Daily for 3 days
- Total Time: approximately 2 hours to 4 hours
- CAR-T Infusion Visit
  - Total Number: 1-2 (depending on the phase you are enrolled to)
  - Total Time: approximately 1 hour
- Post-Treatment Visit
  - Total Number: 1 or more depending your disease is responding
  - Total Time: approximately 1 hour to 2 hours

Risks

This is a brief list of the most commonly seen side effects. The ***full consent form*** after this introduction contains a more complete list of potential research risks.

CAR-20/19-T Cell risks:

- Significant decrease in your B-cell count (type of white cell)
- Tumor Lysis Syndrome
- Cytokine release syndrome (CRS)
  - High fevers
  - Tiredness
  - Chills and shaking
  - Muscle aches
  - Joint aches
  - Sweating
  - Nausea
  - Vomiting
  - Diarrhea
  - Loss of appetite
- Neurotoxicity
  - Confusion and disorientation
  - Difficulty speaking or understanding speech
  - Prolonged or pronounce sleepiness
  - Tremor (shaky hand or other body part)
  - Facial droop
  - Seizures which may be prolonged
  - Inability to control bladder or bowel
- Infection
- Gene Transfer
- Graft-vs-Host Disease

Procedures that will occur at various visits:

Invasive Procedures

- CAR-T, blood sample collection, lymphodepleting chemotherapy, apheresis procedure, bone marrow collection and lumbar puncture

Non-invasive Procedures

- Full medical history exam, physical exam, urine sample collection, questionnaires, ECGs, MRI, MUGA/ECHO and PET/CT scan

Benefits

We don't know if this project will help you. Your condition may get better but it could stay the same or even get worse.

My Other Options

You do not have to join this project. Your other options may include:

- ⇨ Joining a different project
- ⇨ Routine care for this condition
- ⇨ Getting no treatment for this condition

If you have more questions about this project at any time, you can call Nirav Shah, MD at 414-805-6700.

If you have questions about your rights as a participant, want to report any problems or complaints, or offer input, you can call the MCW/Froedtert Hospital Research Subject Advocate at 414-955-8844.

CONSENT TO PARTICIPATE IN RESEARCH

A1. INTRODUCTION – WHY ARE WE ASKING YOU TO PARTICIPATE?

You are being invited to participate in this research study because you have a cancer of the blood, bone marrow or lymph nodes called Chronic Lymphocytic Leukemia {CLL}, Small Lymphocytic Leukemia {SLL} or Non-Hodgkin's Lymphoma {NHL}. Your lymphoma or leukemia has come back or has not gone away after treatment (relapsed and/or refractory.) There is no standard treatment for your cancer at this time, you are being asked to volunteer to be in a research study using special immune cells that have been modified using gene transfer. A gene transfer study places a new set of instructions (a new gene) in cells so that they start making a new component that recognizes the cancer.

A total of about 24 people are expected to participate in this research at the Medical College of Wisconsin/Froedtert Hospital/Blood Center of Wisconsin.

The Director of the project is Nirav Shah, MD in the Department of Medicine. A research team works with Dr. Shah. You can ask who these people are.

The Froedtert Foundation/Cancer Center, and Lentigen are supporting the study.

A2. DO I HAVE TO PARTICIPATE?

You can decide whether to take part in this research or not. You are free to say yes or no. If you say no, your regular medical care will not change. Even if you join this project, you do not have to stay in it. You may stop at any time.

A research project is different from routine medical care in three ways: 1) there are extra risks that we will tell you about in this form; 2) you may have some extra medical tests and visits; 3) the research procedures, tests and visits follow a set plan that must be kept.

A3. WHY IS THIS PROJECT BEING DONE?

This research study is being conducted to find new ways to treat relapsed and/or refractory blood or lymph cancers. In this study, a virus (lentivirus) is used to introduce a gene that creates a protein (called a chimeric antigen receptor or CAR) on the surface of T cells, a type of white blood cell (WBC) that fights infection and eliminates cancer cells. CAR-20/19-T cells are made from white blood cells that are removed from your blood by a procedure called apheresis. This research study will take some of your own white blood cells and modify them so that they can identify and possibly kill your cancerous cells. The hope is that the CAR on the T cells will bind to and kill cells that express CD20 and CD19 proteins that are found on blood cancer cells.

In this study we want to evaluate the closed processing method for the production of CAR-20/19-T cells and determine the safety of administration of these cells. The entire manufacturing process will be performed by a computer-controlled program using the CliniMACS Prodigy device. We do not know all the ways that CAR-20/19-T cell infusion may affect people. The purpose of this study is to test and find out more about the side effects (problems and symptoms) of a CAR-20/19-T cell infusion for your type of blood cancer, and what doses are safe for people to take.

The study is divided into two phases. Phase 1 and Phase 1b. In phase 1, it consists of 2 groups; dose escalation and dose expansion where the CAR-T cells were given over 2 days. The dose escalation group means finding the safest tolerated cell dose for the CAR-T 20/19. Once the safest dose has been identified we will move into the dose expansion group.

In phase 1b CAR-T cells will be given as a single dose (instead of split-dose).

Based on results of the dose expansion group in Phase 1, you may be enrolled in the Phase 1b portion where the entire dose of CAR-T is administered as a single dose.

Everyone in this study will receive CAR-20/19-T cell infusion which is still experimental and is not approved by the U.S. Food and Drug Administration. All testing will be performed in accordance with FDA regulations. We do not know all the ways that CAR 20/19-T cell infusion may affect people.

B1. WHAT WILL HAPPEN IF I PARTICIPATE?

Prior to taking part in this study, you and your doctor should discuss the current standard treatments for your cancer. If you choose to take part in this research study; the study doctor will ask you to read and sign this informed consent after all or your questions have been answered.

Your study doctor will check your general health to assure that you are eligible to participate in the study. Many of the tests and procedures listed below are part of your regular care. You may have had some of them done already. Your study doctor will determine if any of these tests or procedures will need to be repeated for you to participate in the study.

Screening procedures- (completed prior to Apheresis):
Once you decide to participate and have signed this consent form, you will have to undergo a screening process to determine if you are able to join the study. You will be required to undergo the following tests and evaluations prior to Apheresis unless otherwise stated:

- Review of your medical history
- Physical Examination including review of your current medical conditions, height, weight and your performance status (your general strength and ability to carry out your daily activities)
- Vitals signs: Blood Pressure, Temperature, Respiratory rate, Heart rate and Oxygen level
- Review of your current medications and any specific side effects that you may be experiencing.
- Radiological evaluation: Depending on your type of disease, certain scans will be performed. You may have undergone one or more of the procedures listed below and, if done within the needed timeframe you will not be required to undergo the procedure again.
    - MRI of the brain, which uses radio waves and a powerful magnet to create detailed pictures of areas inside the body. These can be used to assess your disease as it can also measure disease inside the bone.

  - CT scan which uses a computer connected to an x-ray machine to make a series of detailed pictures of areas inside the body. This can be done from different angles to help assess your disease and look for tumors in your body

    OR

  - PET/CT scan will be done. This is a scan to look for tumors in your body

- An electrocardiogram (ECG) will be done. This test measures the electrical activity and health of the heart
- Heart Imaging:
  - An echocardiogram (ECHO)- an ultrasound generated images of the heart's structure and function

    OR
  - Multiple Gated Acquisition (MUGA) scan- images of the heart's structure and function generated by radioactive isotope injected prior to imaging
- Lumbar Puncture (removal of cerebrospinal fluid from your lower back) - to examine the fluid that surrounds your brain and spine to determine if your disease is affecting these areas - is required in patients with a prior history of blood cancer affecting the brain or spinal cord.
- Bone marrow Biopsy & Aspirate to measure the amount of disease that you have in your bone marrow – this will need to be repeated if your last one was completed greater than 8 weeks prior to the CAR-20/19/-T cell infusion.
- Collection of approximately 3 tablespoons of blood for routine laboratory tests.
- If you are a female and are able to have a child, you will have a pregnancy test (blood or urine)
- Urinalysis
- Baseline neurological assessment

Apheresis or Cell Collection (approximately 2-8 weeks prior to CAR-20/19-T cell infusion)

If the screening information shows that you meet the requirements, then you will be scheduled to undergo Apheresis. Apheresis is a process where blood is removed through a needle and passed through a special machine called a blood separator. The machine collects your white blood cells (T cells) and the rest of your blood is given back to you.

Your blood will be mixed with an anticoagulant to prevent it from clotting during your donation.

If the screening information shows that you cannot be in the research study, the study doctors will discuss other options with you and/or refer you back to your regular doctor.

Prior to your Apheresis procedure you will have:

- Physical Examination including review of your current medical conditions, weight and your performance status (your general strength and ability to carry out your daily activities)
- Vitals signs: Blood Pressure, Temperature, Respiratory rate, Heart rate and Oxygen level

- Review of your current medications and any specific side effects that you may be experiencing.
- Collection of approximately 2 tablespoons of blood for routine laboratory tests will be collected for analysis.
- Quality of Life Studies

Apheresis Donation-Standard
Before you donate, a needle will be placed in a vein in each of your arms. You will make one or two WBC donations, depending on the number of WBC that are collected during the first apheresis procedure. During the donation(s) you will need to lie fairly still in a recliner chair for four to six hours.

Apheresis Using a Central Line – Standard
Sometimes the needles used in the apheresis process are too big for a donor's arm veins. If it is discovered that the needles are too big for your arm veins, you may be asked to have a blood drawing tube called a "central line" placed in a larger vein in your body. The choice to use a central line may be made at your check-up, or on the day you donate. Placing a central line requires a surgical procedure under local anesthesia. Before a central line is placed, you will be asked to sign a separate consent form that explains the risks of central line placement.

If the collection team is not able to collect enough WBC from you on the first day of apheresis, you will be asked to do another collection the following day. You will be told if a second day of collection is needed. If that happens you will be asked to return to the collection center the next day.

After the collection, your white blood cells will be sent to the Froedtert Hospital Lymphocyte Propagation Laboratory within the BMT Laboratory to be genetically modified and grown. After the white blood cells are genetically modified and grown they will be stored in the BMT Laboratory until they are approved to be released and you are ready to receive them.

Some patients will have successful production of CAR-20/19-T cells but fail to make the adequate cell dose as required. If this should occur with your blood product, you will be allowed treatment as outlined in this consent. However, for the purposes of this Phase 1 study, your data will not be used. Patients will be followed as outlined in this consent with monitoring for safety, adverse events, and long-term survival. If there is excessive toxicity in patients receiving a non-specified dose, it is possible that this arm of the study is closed, and you will NOT be able to receive CAR-20/19-T cells if we cannot make the desired cell dose.

Lymphodepletion treatment (within approximately one week of your planned CAR-20/19-T cell infusion)
Lymphodepletion is the chemotherapy that you will receive prior to the CAR-20/19-T cell infusion starting on Day-4.

- Physical Examination including review of your current medical conditions, weight and your performance status (your general strength and ability to carry out your daily activities).

- Vitals signs: Blood Pressure, Temperature, Respiratory rate, Heart rate and Oxygen level
- Review of your current medications and any specific side effects that you may be experiencing.
- Radiological evaluation: Depending on how your disease was measured, you will be asked to provide information from a radiological evaluation that occurred at the time of initial diagnosis and/or at the time your disease has progressed. You may have undergone one or more of the procedures listed below and, if done within the needed timeframe you will not be required to undergo the procedure again.
    - CT scan which uses a computer connected to an x-ray machine to make a series of detailed pictures of areas inside the body. This can be done from different angles to help assess your disease and look for tumors in your body

      OR

    - PET/CT scan will be done. This is a scan to look for tumors in your body
- Urinalysis
- If you are a female and are able to have a child, you will have a pregnancy test (blood or urine)
- Respiratory Virus tests to check for viral infections if you are having symptoms concerning for an infection. If present, your CAR-20/19-T cell infusion will be delayed
- Collection of approximately 2 tablespoons of blood for routine laboratory tests will be collected for analysis.
- Bone marrow biopsy and aspirate to evaluate the extent of your disease if it has been more than 8 weeks since your screening biopsy and aspirate.
- Receive lymphodepleting chemotherapy for 5 days (3 days of chemotherapy with a day of rest) prior to CAR20/19-T cell infusion. You will receive the following chemotherapy regimen into your vein. You will get a combination of:
    - Fludarabine 30 mg/m^2
    - Cyclophosphamide-500mg/m^2

CAR-20/19-T Cell Infusion

Phase 1:
Once your white blood cells are genetically modified and grown and you are ready to receive them, the CAR-20/19-T cells will be administered by intravenous (IV) infusion in two doses back into your body. Typically, you will receive the CAR-20/19-T cell infusion 1-7 days after the completion of chemotherapy and will be administered over 2 days. It is possible that the second dose could be delayed, or you may not receive the second dose based on the side effects you experience from the first infusion. You will be admitted to Froedtert Hospital for the T-cell infusion. You will remain an inpatient for a minimum of 24 hours after the completion of the second dose of CAR-20/19-T cell infusion.

After you are discharged from the hospital, you are required to travel to the study site for each of the follow-up study visits. Given the risk of side effects, all patients who receive CAR-20/19-T cells must stay within 45 minutes of the study site for 28 days after the infusion. Once you have

had your CAR-20/19-T cell infusion, it is very important that the study doctor is able to monitor your health and safety.

The following procedures will be completed Day 0 and Day +1 prior to CAR-20/19-T Cell infusion unless otherwise stated:

- Physical Examination including review of your current medical conditions, height, weight and your performance status (your general strength and ability to carry out your daily activities), neurological exam (asking you questions)
- Vitals signs: Blood Pressure, Temperature, Respiratory rate, Heart rate and oxygen level will be taken before and after infusion of CAR-20/19-T cells, and every 15 minutes for approximately 1-hour post infusion.
- Review of your current medications and any specific side effects that you may be experiencing.
- An electrocardiogram (ECG) will be done. This test measures the electrical activity and health of the heart
- Collection of approximately 3 tablespoons of blood for routine laboratory tests will be collected for analysis.
- Research labs including test for detection of CAR-20/19-T cells prior to infusion. There will be additional clinical labs to monitor side effects of T-cells. This will require 3-5 tablespoons of blood.

Phase 1b:

Once your white blood cells are genetically modified and grown and you are ready to receive them, the CAR-20/19-T cells will be administered by intravenous (IV) infusion in a single dose back into your body. Typically, you will receive the CAR-20/19-T cell infusion 1-7 days after the completion of chemotherapy and will be administered over 1 days. You could be admitted to Froedtert Hospital or be seen in the outpatient day hospital in the cancer center for the T-cell infusion.

After your CAR-T infusion, you are required to travel to the study site for each of the follow-up study visits. Given the risk of side effects, all patients who receive CAR-20/19-T cells must stay within 45 minutes of the study site for 28 days after the infusion. Once you have had your CAR-20/19-T cell infusion, it is very important that the study doctor is able to monitor your health and safety.

The following procedures will be completed on the day of the CAR-20/19-T Cell infusion unless otherwise stated:

- Physical Examination including review of your current medical conditions, height, weight and your performance status (your general strength and ability to carry out your daily activities), neurological exam (asking you questions)
- Vitals signs: Blood Pressure, Temperature, Respiratory rate, Heart rate and oxygen level will be taken before and after infusion of CAR-20/19-T cells, and every 15 minutes for approximately 1-hour post infusion.
- Review of your current medications and any specific side effects that you may be experiencing.
- An electrocardiogram (ECG) will be done. This test measures the electrical activity and health of the heart

- Collection of approximately 3 tablespoons of blood for routine laboratory tests will be collected for analysis.
- Research labs including test for detection of CAR-20/19-T cells prior to infusion. There will be additional clinical labs to monitor side effects of T-cells. This will require 3-5 tablespoons of blood.

Re-Treatment

Some patients who receive CAR-20/19-T cell therapy may initially have a benefit but then relapse of disease. For patients who are beyond 100 days after their CAR-T cell infusion but not greater than 2 years beyond therapy, and had a prior benefit to CAR-T cell therapy may be re-treated with CAR-T cells if they have CAR-T cells remaining from their initial production. Patients will have to meet the same eligibility criteria as they did for their first infusion. If you qualify for re-treatment, you will not need to repeat all of the research tests. This will be discussed with your treating physician.

Post infusion Monitoring up to Year 2

ONGOING RESPONSE

VISITS REQUIRED AT MCW/FH: After Day +28, you will have required visits at MCW/FH on Day +90 (+/- 7 days), Day+180 (+/- 14 days), Day 365 (+/- 1 month), +1.5 years (+/- 1 month) and 2 years (+/- 1 month). For any other visits that do not fall on those dates, you can be seen by your local oncologist and we will obtain your medical records.

Post Infusion Procedures - Days +1,-+7, 10, 14, 21, 28, 60, 90, 120, 150, 180, 270, 365, Follow-up year 1-2

- Physical Examination including review of your current medical conditions, height, weight and your performance status (your general strength and ability to carry out your daily activities), neurological exam (asking you questions)
- Vitals signs: Blood Pressure, Temperature, Respiratory rate, Heart rate and oxygen level
- Review of your current medications and any specific side effects that you may be experiencing
- Collection of approximately 3 tablespoons of blood for routine laboratory tests will be collected for analysis
- Urinalysis, Day 28 ONLY

Post Infusion Procedures – Days 28, 180, 365, Follow-up year 1-2

- Bone marrow biopsy and aspirate to evaluate the extent of your disease
- Radiological evaluation: Depending on how your disease was measured, you will be asked to provide information from a radiological evaluation that occurred at the time of initial diagnosis and/or at the time your disease has progressed. You may have undergone one or more of the procedures listed below and, if done within the needed timeframe you will not be required to undergo the procedure again.

- CT Scan which uses a computer connected to an x-ray machine to make a series of detailed pictures of areas inside the body. This can be done from different angles to help assess your disease and look for tumors in your body

  OR

- PET/CT scan will be done. This is a scan to look for tumors in your body

Post Infusion Research Labs - Days +1-+7, 10,14, 21, and 28, 60, 90, 180, 270, 365, Follow-up year 1-2

- Research labs including test for detection of CAR-20/19-T cells and to monitor side effects of T-cells. This will require 3-5 tablespoons of blood.

PROGRESSIVE DISEASE

If you develop **progressive disease** you will be placed in the follow-up plan as detailed below and you will be able to return to your local oncologist with your clinic visits scheduled every 6 months starting from CAR-T infusion date.

- Physical Examination including review of your current medical conditions and any subsequent treatments
- Vitals signs: Blood Pressure, Temperature, Respiratory rate, Heart rate and oxygen level
- Review of your current medications and any specific side effects that you may be experiencing
- Collection of approximately 3 tablespoons of blood for routine laboratory tests will be collected for analysis

Because you are a study participant, the study doctor will ask your family for permission to do an autopsy when you die, even though this may be years after the study. This may help the study team learn about the effects of gene transfer. By signing this consent form, you are not forcing your family to agree to this. You should talk about this request with your family and advise them of your wishes.

B2. HOW LONG WILL I BE IN THE PROJECT?

Your participation in this research study will be about 2 years from screening to the end of the study. If you progress you will be followed for survival, active CAR-T cells, and future treatments. It will be required that you participate in the separate mandatory 13 year follow up study that continues to assess your safety and well-being. You will receive additional information about the long-term follow-up study as you near completion of year 2. At that time, you will also be required to sign a separate consent form for the long- term follow up study. If you choose not to participate in the mandatory 13-year follow-up study, you may not be a part of this study. If you do agree to participate, you still have the option to withdraw at any time.

Do you agree to participate in the separate mandatory 13-year follow-up study?

☐ Yes ☐ No

Name: _____ Date: _____

B3. CAN I STOP BEING IN THE PROJECT?

You are free to withdraw from the project at any time. If you leave, your regular medical care will not change. If you are thinking about leaving, please tell the research doctor.

- The doctor can tell you about the effects of stopping, and you and the doctor can talk about what follow-up care would help you the most.
- You might be asked to come back for one more visit to check your health.
- If you received the CAR-20/19-T cells, you will still be followed for survival.

The research doctor may take you out of this project at any time. This would happen if:

- They think it is in your best interest.
- You do not follow the project rules.
- The whole project is stopped.

If this happens, the research doctor will tell you.

B4. ARE THERE ANY SPECIAL INSTRUCTIONS WHILE I AM IN THE PROJECT?

- You will be asked to receive all study-required treatments and complete all study-required procedures.
- You must stay within 45 minutes of the study site for 28 days after the CAR-20/19-T cell infusion
- You will be asked to return to the clinic at study specific visit dates and follow the doctor's directions throughout his/her participation in the study.
- While you are participating in this study (during treatment) you should not participate in other research studies that include experimental treatments, procedures, or devices.
- You will also be asked to share with your doctor what medications you are taking, as some medications should not be used while participating on the study.
- You should also report to your doctor any changes in your health or side effects that you may be experiencing.

C1. WHAT HEALTH RISKS OR PROBLEMS CAN I EXPECT FROM THE PROJECT?

There are risks to taking part in any research project. There is a risk that that the CAR-20/19-T cell infusion may not help your condition or may make it worse. There also may be problems (side effects) we do not know about yet, from CAR-20/19-T cell infusion itself, or how it combines with other drugs you are taking. If we learn about new important side effects, we will tell you.

We watch everyone in the project for problems (side effects). **You need to tell the research doctor or a member of the research team immediately if you experience any problems,**

side effects, or changes in your health. If you have any signs of fever or other new abnormal symptoms, call the providers listed on the contact card immediately. In an emergency, call 911. If you see a doctor other than you study doctor, please let them know that you are involved in a research study.

C2. RISKS OF THE RESEARCH STUDY

CAR-20/19-T Cell

The research CAR-20/19-T cells may cause problems (side effects). Side effects may be mild or very serious. Some can last a long time or never go away.

Many go away soon after the infusion of CAR-20/19-T cells is complete. Complications of some of the side effects below may lead to life-threatening events such as infections, kidney failure, bleeding, disabilities and possibly death.

The side effects in the small number of people that have received other types of CAR-T cells have experienced so far:

More Common

Significant decrease in your B-cell counts (type of white cell)

CAR-T cells kills cancerous B-cells but can also kill normal B-cells. This happens because CAR-T cells cannot tell the difference between cancerous B-cells and normal B-cells. Normal B-cells fight viral and bacterial infections by producing antibodies know as immunoglobulins. Decreasing the number of normal B-cells puts you at risk of potentially life-threatening viral and bacterial infections. If your immunoglobulins are too low, your doctor may give you intravenous immunoglobulin (IVIG). It is possible that your B-cells may never return, in which case you may have life-long risk for viral and bacterial infections and need repeated doses of IVIG.

This risk could possibly be greater since this study targets CAR-T-CD19 cells and CAR-T-CD20 cells together rather than targeting each separately.

- Tumor Lysis Syndrome

  If your B-cells decrease quickly, you may experience Tumor Lysis Syndrome. This happens when cells in your body are killed quickly and the body doesn't have enough time to get rid of the dead cells. If this happens, you will be monitored closely for the following side effects:
  - Acute renal failure (kidney damage)
  - Increase in your blood potassium level
  - Increase in your blood phosphate level
  - Decrease in your blood calcium level
  - Elevation in your blood uric acid level

- Cytokine release syndrome (CRS)/macrophage activation syndrome

Rapidly growing activated CAR-T cells release proteins and chemical called cytokines. Macrophage activation syndrome is an activation of your immune system associated with the cytokine release syndrome. CRS can affect many different parts of the body, and most patients will have at least some of the symptoms listed below. Cytokine release syndrome can cause a sever flu-like syndrome. The symptoms include:

- High fevers
- Tiredness
- Chills and shaking
- Muscle aches
- Joint aches
- Sweating
- Nausea
- Vomiting
- Diarrhea
- Loss of appetite
- Fatigue
- Headache
- Heart: Rapid or irregular heart rate, decreased heart function, cardiac arrest, heart muscle injury
- Very low blood pressure
- Swelling in arms and legs
- Electrolyte changes (changes in your blood sodium calcium, phosphate)
- Liver problems
- Kidney problems: low urine output and kidney failure sometimes requiring dialysis
- Lungs: shortness of breath and low oxygen supply sometimes requiring supplemental oxygen. Some people need to be treated with a ventilator (a breathing machine)
- Blood vessels: vascular leak syndrome (in which the fluid in your blood stream leaks out of circulation into other areas of your body)

This reaction can be mild or severe and can lead to death. Many patients with severe flu-like syndromes have had to be cared for in an intensive care unit at the hospital.

These side effects may or may not be reversible. Medications are available to potentially reverse the cytokine release syndrome and macrophage activation syndrome (steroid treatment or other medicines). Unfortunately, these medicines could get rid of the CAR-T cells and prevent them from working. The best time to administer medications to treat the cytokine release syndrome and macrophage activation syndrome is not currently known.

Neurotoxicity

Neurotoxicity is a group of symptoms involving the brain and spinal cord associated with the use of CAR-T cells. Most patients will have a least some of the symptoms listed below. Specific symptoms have included:

- Confusion and disorientation (unaware of who they are and/or where they are, not recognizing family and friends, unaware of the date and unaware of their health problems).
- Difficulty speaking or understanding speech
- Prolonged or pronounce sleepiness

- Tremor (shaky hand or other body part)
- Facial droop
- Seizures which may be prolonged
- Inability to control bladder or bowel
- Weakness in arms and /or legs
- Difficulty or inability to walk
- Anxiety
- Dizziness

Neurotoxicity can lead to difficulty breathing and low oxygen levels, requiring insertion of a breathing tube and placement on a ventilator (breathing machine) and be potentially life-threatening.

Infection
As a result of lymphodepletion of CAR-T cell therapy patients may have a weakened immune system and be at higher risk of infection. For patients who develop signs/symptoms of infection, appropriate work-up and anti-infective agents will be used. Additionally, for patients who receive CAR-T cells fresh after production, there is a risk that further testing later reveals that the cells were infected. If that happens, patients will be checked for infection and treated with appropriate anti-infective agents as needed.

Gene Transfer
To get the antibody to attach to the surface of the T cell, we must deliver the gene for the antibody into the T cells. This is done with a virus called a lentivirus that has been made for this study. The lentivirus has been altered so it should not be able to come out of the T cells and infect other cells. When lentiviral vectors enter a normal cell in the body, the gene it carries goes into the DNA (genetic material) of the cell. Human DNA contains thousands of genes. When the lentivirus adds the gene, it carries into the human DNA this is called integration. Integration can occur anywhere in DNA and most integration does not harm the cell or the study subjects. However, there is a chance that there may be some parts of human DNA where integration may turn on other genes. For example, if it turned on a gene that made a substance that caused the cell to grow it might cause uncontrolled increase in the numbers of cells, which could potentially result in cancer.

Graft-vs-Host Disease (GVHD)
You may be familiar with the risk of GVHD, which was a major anticipated side effect of your allogeneic hematopoietic stem cell transplant (HSCT). Whenever additional donor T-cells are given to you as "donor lymphocyte infusions" or "DLI", they can cause GVHD. In patients who get a similar dose of unmodified donor T-cells (donor T-cells or white blood cells that do not have the gene put in them to target CD20 and CD19), approximately 40-50% develop GVHD.

If you are enrolled in this research study, the amount of your original donor cells remaining will be determined and you will be monitored closely throughout the research study for signs of GVHD. It is not known if putting the gene for CD20 and CD19 into the donor T-cells will increase, decrease or not change the risk of GVHD.
The severity of GVHD ranges from very mild to severe and life-threatening. If you develop GVHD you will be treated initially with steroids and possibly other medications as your condition warrants. These medications will suppress your immune system and may also make you susceptible to serious infections.

GVHD usually involves the following symptoms:

Skin: ranges from a mild rash to severe blistering.

Liver: ranges from mild abnormalities in liver function detected by blood testing to severe liver failure. This can lead to nausea, vomiting, loss of appetite, fluid retention, bleeding problems, and severe liver failure, and can be fatal.

Intestine: ranges from mild diarrhea, nausea and vomiting to severe diarrhea, abdominal pain, paralysis of the bowel, bleeding from the bowel, and inability to eat.

Bone marrow: The infused lymphocytes may attack your bone marrow cells. It is possible that all normal bone marrow cells can be irreversibly destroyed (bone marrow aplasia). These cells are necessary to produce red blood cells, white blood cells, and platelets. If your red blood counts become very low, you can develop weakness, fatigue, shortness of breath and other symptoms related to anemia. This may be treated with red blood cell transfusions. If your white blood count becomes too low, you may be susceptible to serious infections. This may require hospitalization for antibiotics and other treatment. If the platelets are too low, you may be risk for serious bleeding problems. Platelet transfusions can be given as well.

Potential risk of autoimmune disease (very rare, unexpected):
The use of CAR-20/19-T cells could potentially result in an illness which doctors call "autoimmune disease." Our bodies have an immune system that protects us from disease and infection. When you have an autoimmune disease, your immune system attacks itself by mistake and you can get sick. Autoimmune disease can affect many parts of your body, like your nerves, muscles, the endocrine system (system that directs your body's hormones and other chemicals, and digestive system.

Potential risk of blood cancer (very rare, unexpected):
There is a chance that the insertion of the CAR-20/19-T cells into some gene regions of your DNA may activate a neighboring gene or genes. Depending on the type(s) of neighboring gene(s) activated, there may be a risk of uncontrolled cell growth that could result in cancer. We do not know if and what specific genes may be activated by integration of the lentivirus vector used in this protocol and if these would cause a new cancer.

While this risk is rare, you will be monitored for development of any new cancer throughout the scheduled protocol visits. If a new cancer develops while you are on study, you will be treated by standard of care clinical procedures, and the cancer will be investigated to determine if the lentiviral vector contributed to its development.

Cyclophosphamide
Common

- Hair loss
- Nausea, Vomiting, loss of appetite
- Sores in mouth
- Infection, especially when white blood count is low
- Absence of menstrual period which may decrease the ability to have children
- Blood in urine

Occasional
- Damage to the bone marrow (irreversible) which may cause infection, bleeding, may require transfusions
- Loss of absence of sperm which may lead to an inability to father children
- Stuffy nose
- Fluid around the heart

Rare
- Severe skin rash with blisters and peeling with can involve mouth and other parts of the body
- Damage to the heart or heart failure which may cause shortness of breath, swelling of ankles, cough or tiredness
- A new cancer including cancer of bone marrow caused by chemotherapy
- Swelling of the body including the brain which may cause dizziness, confusion
- Scarring of the lungs

Fludarabine
Common
- Low blood counts
- Infection
- Nausea
- Vomiting
- Fatigue
- Diarrhea

Occasional
- Rash

Rare
- Vision Problems
- Numbness
- Confusion
- Pneumonia
- Nerve damage
- Hemolytic Anemia
- Secondary Cancers

C3. OTHER RISKS OF THIS RESEARCH PROJECT

Other procedures that are part of the research also involve some risks:

Apheresis
During the apheresis procedure, you may experience chilliness, some tingling sensations in your face and lips, numbness, muscle cramping, nausea and vomiting, allergic reactions and headache. This could be due to the medicine that keeps your blood from clotting during the procedure.

Additional risks during the apheresis collection; chemical imbalance in the blood, fatigue, allergic reactions, low platelet count or red blood cell count requiring a transfusion, infection for the central venous catheter, clotting of the central venous catheter or the peripheral needles, low blood pressure and nausea.

Blood drawing

Blood sampling and needle punctures carry some risk. Possible side effects include, but are not limited to fainting, bleeding, bruising, discomfort, dizziness, and infection and/or pain at the puncture site.

Bone marrow biopsy/bone marrow aspirate

Risks associated with the procedure include pain, discomfort, soreness, redness, swelling, bleeding (may be excessive), bruising, and/or drainage (such as pus) at the needle site.

- Rare: Infection, fever, and allergic reaction to the medication used to numb the skin over the biopsy site.

CT Scan/PET scan

A CT scan is a test that uses a small amount of radiation (x-ray) to make pictures of the inside of your body. For this test, the study doctor or research staff may give you a contrast dye, either by mouth or with a needle. You may feel a sharp sting when the needle is placed in your vein followed by a feeling of warmth throughout the body. There is a slight risk of developing an allergic reaction to the contrast material. Be sure to tell your study doctor if you have allergies of any kind, such as hay fever, iodine allergy, eczema, hives, or food allergies. There is always a slight risk from being exposed to any radiation, including the low levels of x-rays used for a CT scan. However, the risk from the x-rays is usually very low compared with the potential usefulness of the test to manage your treatment. Confinement and claustrophobia may be experienced during the scan.

A PET scan uses a small amount of radioactive material (tracer). The tracer is given through a vein (IV). The needle is most often inserted on the inside of your elbow. The tracer travels through your blood and collects in organs and tissues. This helps the radiologist see certain areas more clearly. You may feel a sharp sting when the needle with the tracer is placed into your vein. Rarely, people may have an allergic reaction to the tracer material. Some people have pain, redness, or swelling at the injection site.

Electrocardiogram (ECG)

There are very few risks associated with an ECG. To perform the test, stickers (called leads or electrodes) will be placed on your skin to record your heart's activity. You may have irritation where the adhesive pads are applied or if they have to shave the area where the adhesive pads are applied. A slight redness or inflammation may appear due to an allergic reaction to the adhesive used to attach the electrodes to the skin.

Heart Scans:
Echocardiogram (ECHO):
The ECHO involves placing a gel on the skin of the chest and rubbing the ultrasound wand over your heart to see the blood pumping out of your heart. There are no known complications from the ECHO procedure.

MUGA:
The MUGA involves injecting a small amount of imaging agent (radioactive tracer) into a vein in your arm and then scanning. The tracer and the scan let the doctor see how well the chambers of your heart pump blood. The level of radiation is very low. You may have an allergic reaction to the tracer.

Intravenous (IV) infusion Access
Some therapies will be given through a needle inserted into a vein in your arm and/or a central vein. If the drugs or CAR-20/19-T cells leak into your tissue, it can be uncomfortable and painful. You may also have the following problems:

- Irritation of the vein; your skin near the vein could become warm, swell, hurt, or get red
- Damage to your vein
- Damage to the skin or tissue around the injection site

Lumbar Puncture
Prior to the lumbar puncture, you may be given a local anesthetic to numb the area. The procedure may cause headache, local pain or discomfort, or bleeding. After the procedure, you may develop a headache that may be accompanied by nausea, vomiting, and dizziness. A lumbar puncture can also cause infection including meningitis, although rare.

Magnetic Resonance Imaging (MRI)
Risks of MRI include claustrophobia, discomfort due to lying still for a prolonged period of time, and other factors which will be described to you and discussed with you at the MRI center.

C4. REPRODUCTIVE RISKS

Risks to women who could become pregnant
The chemotherapy and the genetically modified CAR-20/19-T cells in this project might affect a baby, before or after the baby is born. We do not know if the modified CAR-20/19-T cells cause(s) harm to a baby, so we do not want anyone who might be pregnant to enter the project. You should not become pregnant or nurse a baby while in this project. You must tell the research doctor right away if you think you are pregnant. You will be asked to have a pregnancy test to be sure you are not pregnant at the start of the project and during the project.

If you become pregnant during the project, you will be dropped from participation for safety reasons. If you become pregnant while you are taking this experimental drug, we ask that you inform the research doctor immediately. The research doctor will ask you for written permission to obtain information from you or your obstetrician on your pregnancy and the health of the baby.

Risks of fathering a child
You should not father a baby while taking part in this project because it is unknown if the chemotherapy and genetically modified CAR-20/19-T cells in this project could affect a baby. If your partner is able to become pregnant, one or both of you must use some form of effective birth control. You must tell the research doctor right away if you think your partner is pregnant.

Birth control methods for all subjects
Check with the research doctor about the birth control methods needed for this project and how long to use them. Some methods might not be good enough for this project. If you are having sex that could lead to pregnancy, you should use birth control while you are in this project. This may include:

- Not having vaginal sex (abstinence)
- Taking birth control pills orally
- Having birth control shots or patches such as Depo-Provera
- Surgical sterilization (hysterectomy or tubal ligation)
- Use of an intrauterine device (IUD)
- Use of diaphragm with contraceptive jelly
- Use of condoms with contraceptive foam
- Use of diaphragm with condoms ("double barrier")
- Limiting sexual activity to a male partner who has had a vasectomy

You should continue using birth control until the CAR-20/19-T cells are no longer present in your blood.

Risks of harm from this study include the possibility that the genes in some of your sperm (men) or eggs (women) may be permanently changed. Some of these changes could lead to miscarriage or birth defects in your future children. Other changes may have no apparent effects but could still be passed on to future generations. The likelihood of such outcomes is currently unknown.

C5. ARE THERE ANY BENEFITS TO TAKING PART IN THE PROJECT?

This study is not likely to help you, but we hope the information from this study will help us develop better treatments for blood cancers.

D1. ARE THERE ANY COSTS TO BEING IN THE PROJECT?

Most of the medical care that you will receive in this study is considered routine care for your condition and would be recommended whether you join the study or not. Costs for routine care will be billed to you or your insurance carrier.

Activities / costs that are part of the study will not be billed to you or your insurance company. These are the apheresis procedure, preparation or manufacture of process of cells for infusion, research samples and the processing and shipping of the research samples. Some insurers will not pay for drugs, tests or hospitalization that are part of research studies, so check with your insurer before you join this study. If you have questions regarding study costs, please contact Dr. Shah.

If you participate in this research, the costs of any necessary emergency medical treatment in the event of a research-related injury will be billed to you or your health insurance.

D2. WILL I BE PAID FOR PARTICIPATING IN THE PROJECT?

There is no payment for being in this study.

D3. WHAT OTHER HEALTHCARE CHOICES DO I HAVE?

You do not have to join this project. You are free to say yes or no. If you do not join this project, your research doctor can discuss other healthcare choices with you.
Your other choices may include:

- Joining a different research study
- Other chemotherapies, cancer treatments, or combination of treatments without being in a study
- Getting no treatment

The research doctor can explain both the possible benefits and the risks of other options that are available to you.

D4. WILL I BE GIVEN NEW INFORMATION ABOUT THE PROJECT?

If we learn any important new information chemotherapy and the genetically modified CAR-20/19-T cells that might change your mind about being in the project, we will tell you about it right away. You can then decide if you want to stay in the project.

When research data/biospecimens/images are collected and analyzed, there is the chance of finding something clinically relevant. There may be benefits to learning such results (such as early detection and treatment of a medical condition), but there are risks as well (such as feeling worried about a finding for which no treatment is required or appropriate).

The results from the data/biospecimens/images we collect in this research study are not the same quality as what you would receive as part of your health care, so you will not be informed of any clinically relevant research findings. The results of your research data/biospecimens/images will not be placed in your medical record.

D5. WHAT HAPPENS IF I AM INJURED BECAUSE I TOOK PART IN THE PROJECT?

Emergency medical treatment for injuries directly related to your participation in this research project will be provided to you. You or your health insurance will be billed for the costs of this emergency treatment. MCW will decide on a case by case basis if they will reimburse you or your insurer for emergency treatment costs. If your research-related injury requires medical care beyond this emergency treatment, you or your insurer will be responsible for the costs of this follow-up care.

At this time, there is no plan for any additional financial payments.

If you believe that you have been injured because of your participation in this project, contact the research doctors right away. Contact information:

Nirav Shah MD
Froedtert & the Medical College of Wisconsin
Division of Hematology and Oncology
9200 W. Wisconsin Avenue
Milwaukee WI 53226
414-805-6700

Nothing in this consent form affects any legal rights you may have nor does it release the investigator, the sponsor, the institution, or its agents from liability for negligence.

D6. WHO CAN ANSWER MY QUESTIONS ABOUT THE PROJECT?

- If you have more questions about this project at any time, you can call Dr. Shah at 414-805-6700.
- If you have questions about your rights as a research participant, want to report any problems or complaints, or offer input, you can call the MCW/Froedtert Hospital Research Subject Advocate at 414-955-8844.

E. PERMISSION TO COLLECT, USE AND SHARE HEALTH INFORMATION

E1. What health information will be collected and used for this project?

To be in this research project, the research team needs your permission to access, collect and use some of your health information. If you say no, you cannot be in the project. This information may come from questions we ask, forms we ask you to fill out, or your medical record, as described below. We will only collect and use information needed for the project.

The protected health information (PHI) originates from services you will or have received at one or more of the following locations: the Medical College of Wisconsin (MCW); BloodCenter of Wisconsin (BCW); Children's Hospital of Wisconsin (CHW); any Froedtert Health Affiliate-Froedtert Memorial Lutheran Hospital (FMLH), Inc.; Community Memorial Hospital (CMH) Menomonee Falls, Inc.; St. Joseph's Community Hospital (SJH) West Bend, Inc.; Froedtert & The Medical College of Wisconsin Community Physicians Clinics, Inc. (FMCWCP); the West Bend Surgery Center, LLC; and the Froedtert Surgery Center, LLC.

The health information to be collected and used for this project is:

- Hospital/Medical Records
- Physician/Clinical Records
- Lab and/or Pathology Reports
- Radiology Reports
- Biological Samples
- Health Questionnaires

E2. Who will see the health information collected for this project?

The only MCW/Froedtert Hospital employees allowed to handle your health information are those on the research team, those on the Institutional Review Board (IRB) and those who check on the research activities to make sure the hospital's rules are followed.

If the costs of any necessary emergency medical treatment in the event of a research-related injury are billed to your health insurance, your health information may need to be disclosed to the insurer for billing purposes.

The research team may share your information with people who don't work at MCW/Froedtert Hospital because they planned, pay for, or work with us on this project. The federal Privacy Rule may no longer protect your health information once it leaves MCW/Froedtert Hospital. For this project, we plan to share information with those doctors, researchers or government representatives working with us on this project at the institutions or companies listed here:

- The U.S. Food and Drug Administration (FDA)
- Federal agencies such as the Department of Health and Human Services (the DHHS), the National Cancer Institutes / National Institutes of Health (the NCI/NIH) and the Office of Human Research Protections (the OHRP)
- Other regulatory agencies and/or their Designated Representatives
- Lentigen Technology, Inc
- Miltenyi Biotech
- Any independent ethics committee, which approved this study
- Those required by law

Because this project involves the use of drugs and/or devices, the FDA also has the right to inspect all project records.

We may record your research information, including results of tests and procedures done for research, in your Froedtert Hospital and/or Medical College of Wisconsin medical record. As a result, this research information may be seen by people allowed to see your medical records for healthcare operations or treatment, by those you allow to see your medical records by giving written permission, and by others when required by law.

We will not use your personal health information for a different project without your permission or the permission of a hospital research review board (IRB). Once all personal identification is removed from your health information and/or biospecimens, the information and/or biospecimens may be used for future research or distributed to another investigator for future research without additional informed consent from you or your legally authorized representative. The information might also be used or released for other purposes without asking you. Results of the project may be presented in public talks or written articles, but no information will be presented that identifies you.

E3. What are the risks of sharing this health information?

One risk of taking part in a research project is that more people will handle your personal health information collected for this project. The research team will make every effort to protect the information and keep it confidential, but it is possible that an unauthorized person might see it. Depending on the kind of information being collected, it might be used in a way that could embarrass you or affect your ability to get insurance. If you have questions, you can talk to the research doctor about whether this could apply to you.

E4. How long will you keep the health information for this project?

If you sign this form, we plan to keep your information without any end-date in case we need to check it again for this project.

E5. Can I cancel my permission to share this health information?

If you change your mind later and do not want us to collect or share your health information, you need to send a letter to

Nirav Shah MD
Froedtert & the Medical College of Wisconsin
Division of Hematology and Oncology
9200 W. Wisconsin Avenue
Milwaukee WI 53226

The letter must say that you have changed your mind and do not want the researcher to collect and share your health information. At that time, we may decide that you cannot continue to be part of the project. We may still use the information we have already collected.

F1. FOR MORE INFORMATION ABOUT THE PROJECT

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.

You can look up this project by referring to the ClinicalTrials.gov number (NCT03019055) or by asking the research team for a printed copy.

CONSENT TO PARTICIPATE

By signing my name below, I confirm the following:

- I have read (or had read to me) this entire consent document. All of my questions have been answered to my satisfaction.
- The project's purpose, procedures, risks and possible benefits have been explained to me.
- I agree to let the research team use and share the health information and other information gathered for this project.
- I voluntarily agree to participate in this research project. I agree to follow the procedures as directed. I have been told that I can stop at any time.

IMPORTANT: You will receive a signed and dated copy of this consent form. Please keep it where you can find it easily. It will help you remember what we discussed today.

Subject's Name *please print*	**Subject's Signature**	**Date**
Name of Witness (if applicable**)** *please print*	**Signature of Witness**	**Date**
Rationale for Use of Witness ☐ Subject has limited/no literacy ☐ Subject has limited English proficiency ☐ Subject has limited/no vision	☐ Sponsor requirement ☐ Other _____	
*** Name of person discussing/ obtaining consent** *please print*	**Signature of person discussing/obtaining consent**	**Date**

** A member of the research team trained and authorized by the Principal Investigator to act on her/his behalf in obtaining informed consent according to the protocol. The Principal Investigator is responsible and accountable for the research project.*