Affix Patient Label Here

Title of Research Study: *Chimeric Antigen Receptor (CAR)-T Cell Therapy for Patients with B-cell Hematologic Malignancies, MT2017-45, CPRC #2017LS118*

Investigator Team Contact Information: *Veronika Bachanova MD, Ph.D*
For questions about research appointments, the research study, research results, or other concerns, call the study team at:

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If your doctor is also the person responsible for this research study, please note that she is interested in both your clinical care and the conduct of this research study. You have the right to discuss this study with another person who is not part of the research team before deciding whether to participate in the research.

Key Information About This Research Study

The following is a short summary to help you decide whether or not to be a part of this research study. More detailed information is listed later on in this form.

What is research?

Doctors and investigators are committed to your care and safety. There are important differences between research and treatment plans:

- The goal of research is to learn new things in order to help groups of people in the future. Investigators learn things by following the same plan with a number of participants, so they do not usually make changes to the plan for individual research participants. You, as an individual, may or may not be helped by volunteering for a research study.
- The goal of clinical care is to help you get better or to improve your quality of life. Doctors can make changes to your clinical care plan as needed.

Research and clinical care are often combined. One purpose of this informed consent document is to provide you clear information about the specific research activities of this study.

Why am I being asked to take part in this research study?

We are asking you to take part in this research study because you are being treated with a "CAR-T" cell therapy product, such as KYMRIAH (manufactured by Novartis), YESCARTA (manufactured by Kite Pharmaceuticals),TECARTUS (manufactured by Kite Pharmaceuticals) or BREYANZI or ABECMA (both manufactured by Bristol-Myers Squibb). This product has been FDA approved for clinical care for patients with your disease. The research aspect of this study is to allow us to collect data on patients who are being treated with this product. Patients will be followed throughout the course of their clinical care and for one year after their CAR-T infusion. This data will be saved and research may be performed on the data indefinitely.

What should I know about a research study?

- Someone will explain this research study to you.
- Whether or not you take part is up to you.
- You can choose not to take part.
- You can agree to take part and later change your mind.
- Your decision will not be held against you.
- You can ask all the questions you want before you decide.

Why is this research being done?

Although CAR-T products have been FDA approved for patients with your disease, we wish to save this data on your treatment course here at M Health. First, we want to confirm that the experiences with these products here conform to national and international research. In addition, the companies that manufacture these products have an agreement with the FDA to collect and report data on certain expected risks and overall outcomes of this therapy.

The purpose of this study is to collect information on CAR-T product treatment and provide a structure to save and report data on treatment using these products. Although you may or may not personally benefit from having your treatment course followed and your data saved, future patients may benefit from compiling knowledge and experience of these products.

How long will the research last?

We expect that your treatment course will last about 16 months, from screening through one year of follow up. However, the data we collect on your treatment will stay in our BMT Outcome database indefinitely.

What will I need to do to participate?

You will be asked to permit us to save your medical data and share it with the manufacturers of the CAR-T products, the FDA, and other agencies with regulatory oversight.

More information on your clinical care with CAR-T products is attached as ***Appendix A*** to this

document.

Is there any way that being in this study could be bad for me?

The main risk related to the research component of this study is the disclosure of private health information to unauthorized individuals. The study will be monitored twice yearly by the Masonic Cancer Center Data and Safety Monitoring Board.

More detailed information about the risks of this study can be found under ***"What are the risks of this study? Is there any way being in this study could be bad for me? (Detailed Risks)"***

More detailed information about the risks of CAR-T product treatment is attached as ***Appendix B*** to this document.

Will being in this study help me in any way?

There are no benefits to you from your taking part in this research. We cannot promise any benefits to others from your taking part in this research. The information we learn may benefit other patients with your disease that may be treated with CAR-T products in the future.

What happens if I do not want to be in this research?

There are no known alternatives, other than deciding not to participate in this research study.

Detailed Information About This Research Study

The following is more detailed information about this study in addition to the information listed above.

How many people will be studied?

We expect about 180 people here will be in this research study.

What happens if I say "Yes", but I change my mind later?

You can leave the research study at any time and no one will be upset by your decision.

If you decide to leave the research study, contact the investigator so that the investigator can ensure that no more information is collected on your treatment course. We may not be able to remove previously collected data if it already been reported to the drug manufacturers and regulatory authorities, however no identifiable information will be sent outside the University of Minnesota.

Choosing not to be in this study or to stop being in this study will not result in any penalty to you or loss of benefit to which you are entitled. This means that your choice not to be in this study will not negatively affect your right to any present or future medical care.

What are the risks of being in this study? Is there any way being in this study could be bad for me? (Detailed Risks)

There is a risk that someone could get access to your stored data. There is a risk that someone not involved in the study could trace the information back to you. The chance that someone will identify you is very small, but the risk may grow in the future as people come up with new ways of tracing information.

The risks of the standard of care treatment are detailed in **Appendix B** of this document.

What do I need to know about reproductive health and/or sexual activity if I am in this study?

Although there are no risks to reproductive health for data collection, the standard of care treatment may hurt a pregnancy or fetus in ways that are unknown.

You should not be or become pregnant, "or father a baby" and/or "breastfeed" and/or "donate eggs/sperm" while on this treatment.

If you are sexually active, both men and women should use at least one effective means of birth control while participating in this research study. According to the World Health Organization and the United States Center for Disease Control and Prevention, the most effective forms of birth control include complete abstinence, surgical sterilization (both male and female), intrauterine devices (IUDs), and the contraceptive implant. The next most effective forms of birth control include injectables, oral contraceptive pills, the contraceptive ring, or the contraceptive patch. Acceptable, but least effective, methods of birth control include male condoms (with or without spermicide) and female condoms.

If you or your partner become pregnant while on this treatment or for 12 months after you complete the CAR-T therapy, it is important that you tell the study doctor or other research team member immediately. You might be required to stop participation in this study; however, other clinical care options will be discussed with you at that time if necessary.

If you or your partner [are/is] considered to be postmenopausal, you are not required to use contraception while on this treatment. If you or your partner become pregnant while on this treatment or for 12 months after you complete the treatment, it is important that you tell the study doctor or other research team member immediately. You may be required to stop the CAR-T therapy; however, other clinical care options will be discussed with you at that time if necessary.

Will it cost me anything to participate in this research study?

This treatment may lead to added costs to you. Costs associated with treatment and care will be

billed to you and/or your health insurance/health plan in the usual way. Prior to treatment, the Transplant Coordinator will verify your coverage with your insurance company to be sure that you are pre-authorized before beginning any part of this treatment. If you have concerns or questions regarding coverage or potential charges, you should contact the patient financial representative at (612) 273-2800.

What happens to the information collected for the research?

Efforts will be made to limit the use and disclosure of your personal information, including research study and medical records, to people who have a need to review this information. We cannot promise complete confidentiality. Organizations that may inspect and copy your information include the Institutional Review Board (IRB), the committee that provides ethical and regulatory oversight of research, and other representatives of this institution, including those that have responsibilities for monitoring or ensuring compliance.

Organizations that may look at and/or copy your medical records for research, quality assurance, and data analysis include:

- The Masonic Cancer Center, University of Minnesota and/or their designee.
- M Health (Fairview Health Services), including University of Minnesota Medical Center, University of Minnesota Masonic Children's Hospital, and University of Minnesota West Bank Hospital.
- Any person who provides services or oversight responsibilities in connection with this study.
- Any member of the University of Minnesota workforce who provides services in connection with this study.
- Any laboratories, individuals, and organizations that use your health information in connection with this study.
- Any federal, state, or local governmental agency that regulates the study (such as the U.S. Food and Drug Administration (FDA), the U.S. Department of Health & Human Services (DHHS), and the Office for Human Research Protections (OHRP)).
- Center for International Blood and Marrow Transplant Research (CIBMTR) and National Marrow Donor Program (NMDP) for the Observational Research Database – this organization collects information on therapies involving donor cells.
- The designated Protocol Review and Monitoring Committees, Institutional Review Boards (IRB) such as the University of Minnesota IRB, Privacy Boards, Data and Safety Monitoring Council and their related staff that have oversight responsibilities for this study.
- Investigators at Novartis, Kite Pharmaceuticals and Bristol-Mysers Squibb, who will receive outcome and event-based information and copies of any product related reports submitted to the FDA.

- The Fairview BMT Outcome Database, a registry that compiles demographic and medical information related to hematopoietic cell transplant/cell therapy patients and donors

If you decide to participate, some private health information about you will be stored in OnCore, the computer database at the Masonic Cancer Center. This information will include your name and medical record number, date of birth, diagnosis, race/ethnicity, and the type of transplant you have. The purpose of storing this information is to assist the Cancer Center in creating reports about research and in making sure that research studies are being done correctly. Your information will not be used for any other purpose. There are no plans to erase information from the database. It will be stored indefinitely at the Masonic Cancer Center.

Whom do I contact if I have questions, concerns or feedback about my experience?

To reach the research team: Please see the "Investigator Contact Information" section at the beginning of this form.

To reach someone outside of the research team: This research has been reviewed and approved by an IRB within the Human Research Protections Program (HRPP). To share feedback privately with the HRPP about your research experience, call the Research Participants' Advocate Line at 612-625-1650 (Toll Free: 1-888-224-8636) or go to z.umn.edu/participants. You are encouraged to contact the HRPP if:

- Your questions, concerns, or complaints are not being answered by the research team.
- You are having difficulty reaching the research team.
- You want to talk to someone besides the research team.
- You have questions about your rights as a research participant.
- You want to get information or provide feedback about this research.

Will I have a chance to provide feedback after the study is over?

The HRPP may ask you to complete a survey that asks about your experience as a research participant. You do not have to complete the survey if you do not want to. If you do choose to complete the survey, your responses will be anonymous.

If you are not asked to complete a survey, but you would like to share feedback, please contact the study team or the HRPP. See the "Investigator Contact Information" of this form for study team contact information and "Whom do I contact if I have questions, concerns or feedback about my experience?" of this form for HRPP contact information.

What happens if I am injured while participating in this research?

In the event that this research activity results in an injury, treatment will be available, including first aid, emergency treatment and follow-up care as needed. Care for such injuries will be billed in the ordinary manner, to you or your insurance company. If you think that you have suffered a

research related injury let the study physicians know right away.

Use of Identifiable Health Information

We are committed to respect your privacy and to keep your personal information confidential. When choosing to take part in this study, you are giving us the permission to use your personal health information that includes health information in your medical records and information that can identify you. For example, personal health information may include your name, address, phone number or social security number. Those persons who get your health information may not be required by Federal privacy laws (such as the 1099 Rule) to protect it. Some of those persons may be able to share your information with others without your separate permission. Please read the HIPAA Authorization form that we have provided and discussed.

The results of this study may also be used for teaching, publications, or for presentation at scientific meetings.

Signature Block for Capable Adult:

Your signature documents your permission to take part in this research. You will be provided a copy of this signed document.

_____ _____

Signature of Participant Date

_____

Printed Name of Participant

_____ _____

Signature of Person Obtaining Consent Date

_____

Printed Name of Person Obtaining Consent

Affix Patient Label Here

Signature Block for Witness:

WITNESS STATEMENT:
The participant was unable to read or sign this consent form because of the following reason:

☐ The participant is illiterate

☐ The participant is visually impaired

☐ The participant is physically unable to sign the consent form. Please describe:

_____

☐ Other *(please specify)*:

_____

My signature below documents that the information in the consent document and any other written and information was accurately explained to, and apparently understood by, the participant, and that consent was freely given by the participant.

_____ _____
Signature of Witness to Consent Process Date

_____
Printed Name of Person Witnessing Consent Process

Appendix A: Treatment Calendar and Procedures

Below is a calendar of standard of care activities for treatment using CAR-T products.

Prior to treatment	Screening - routine tests and evaluation
3-4 weeks before CAR-T cell infusion	Your T-cells will be collected via leukapheresis
2-14 days before CAR-T cell infusion	Chemotherapy (the chemotherapy regimen will depend upon your disease, the CAR-T product used, and your physician's preference
Day 0	CAR-T cell infusion
Day 1-30	Monitoring your health and response to therapy (days 1 -7 may be inpatient)
Months 3, 6, 9 and 12	Follow up assessments

Screening

The following routine tests and evaluations may be done to determine if you can safely receive this treatment:

- Medical history and physical examination, including vital signs, height and weight
- Routine blood tests (requiring 2-3 tablespoons of blood) to evaluate hematologic, kidney, and liver function, as well as general health status
- Blood tests (requiring 1 tablespoon of blood) to check for exposure to hepatitis and HIV. If the results are positive, you will be notified and it will be recommended that a Blood Bank physician contact your personal physician regarding possible further testing. By law the Minnesota Department of Health must be notified if you test positive for hepatitis or HIV. Because of the sensitive nature of these tests, you have the right to review the results. If you test positive for some types of hepatitis or HIV, you will not be eligible for treatment.
- Urine test
- A pregnancy test (blood or urine) for women of childbearing potential.
- Tests to evaluate heart function including an electrocardiogram and an echocardiogram
- PET or CT scan
- Tests and procedures to evaluate your current disease status including a bone marrow biopsy
- Lumbar puncture (spinal tap)
- Any additional tests or evaluations, felt necessary by the medical staff, to evaluate your current health

The amount of blood that may be collected from you for routine labs is approximately 4 tablespoons.

Leukapheresis

T-cells will need to be collected from your body in order to make the CAR-T cells. In order to collect the T-cells, a procedure called leukapheresis is used.

In preparation for the leukapheresis procedure, two large needles will be placed in your veins near each elbow. Large diameter needles are commonly used, as they are needed to allow the free flow of blood into the leukapheresis machine – these are the same size needles used by the Red Cross when donating blood. The needles are collected by plastic tubing to a machine that will process a portion of your blood.

During the procedure, your blood will flow from one arm's vein into the machine, and back to the other arm. The leukapheresis machine, which performs the procedure described here, will remove some of your white blood cells and then return the rest of your blood back to your body.

Sometimes a single large catheter – called a central line – is placed in your neck or under your collarbone, and may be used for the procedure if your doctor believes it will be more effective and/or medically necessary for you.

Your blood is prevented from clotting within the machine tubing by adding a chemical called citrate. Some additional fluid (saline) will also be added to your blood. The amount of fluid will be determined by your blood pressure and the total time it takes to perform the leukapheresis procedure, which varies from person to person. The additional fluid (saline) is rapidly removed by your kidneys and will have no effect on you. The compound citrate may cause symptoms that include tingling in your lips and fingers. If this occurs, you will be given calcium (e.g. Tums) to reverse this effect.

Your pulse, blood pressure, and temperature will be checked before and after the procedure. You will be asked to report any new symptoms (e.g. lightheadedness, tingling in lips or extremities, shortness of breath, etc.). The leukapheresis procedure could last approximately 2-4 hours. At the end of the procedure, you will be monitored for at least one hour, depending on your condition and institutional guidelines. You will return to the clinic the next day for a check-up.

The T- cells taken from your body will then be modified (changed) by gene transfer to make them recognize your tumor cells. This modification takes approximately 3 to 4 weeks to complete. Once your modified T cells, or CAR-T cells, are made, they will be tested in a laboratory to make sure the modification was successful and the cells are safe to give to you. There is a chance that this

modification process will be unsuccessful (for instance if the cells do not grow) and you will not be able to receive them.

You may be delayed getting your CAR-T cells if your doctor determines you are too sick to receive the therapy, and wants to wait until you get well enough to receive them.

Chemotherapy

Approximately 5 to 14 days before your scheduled CAR-T infusion, you may receive additional chemotherapy. The purpose of this chemotherapy is to help "make room" for the new genetically modified T-cells and allow them to grow, and to help treat your disease.

The chemotherapy you are given will depend on your disease, which CAR-T product you are receiving, and your physician's preference. You doctors will tell you which chemotherapy drugs you will receive and for how long. Generally, you will receive 3 or 4 days of chemotherapy.

CAR-T cell infusion

On the day of, but before your scheduled CAR-T infusion, your doctor will check to see how you are feeling. Your doctor will need to examine you and may choose to delay your CAR-T infusion until you feel better. You will be asked again about any medications you have been taking, your ability to perform every day activities and also how you are currently feeling. Prior to your CAR-T treatment, you will have the following tests done:

- Physical examination (a "check-up") and assessment of your ability to perform every day activities
- Blood tests for routine lab tests such as complete blood counts (CBCs) and other tests
- An electrical tracing of your heartbeat (electrocardiogram or ECG)
- Pulse oximetry (a test to measure your blood oxygen level)
- Measurement of your weight, temperature, blood pressure, respiratory and heart rate (pulse)

The amount of blood that may be collected from you for routine labs is approximately 4 tablespoons.

Once the doctor clears you, you will be ready to get your CAR-T infusion. The CAR-T cells that you will be given will be made from the same cells that were taken from your body during the leukapheresis procedure, but modified to recognize your tumor cells. These cells will have been tested to make sure that they are healthy and free from impurities before they are given to you. The amount, or dose, of cells given to you will depend on how much of your collected T-cells can be grown. You will receive your CAR-T cells intravenously (through a needle and tubing inserted

into your vein). In order to reduce potential side effects of CAR-T therapy, you may also receive acetaminophen or paracetamol (to reduce fever) and diphenhydramine (to avoid allergic reaction).

You will also undergo the following procedures:

- Measurement of your temperature, blood pressure, respiratory and heart rate (pulse) will be done before, during and after your CAR-T treatment.
- Blood tests for routine lab tests such as complete blood counts (CBCs) and other tests
- Blood tests to measure markers relevant to CAR-T therapy

The amount of blood that may be collected from you for routine labs is approximately 4 tablespoons.

Follow-Up

After receiving CAR-T, it you may be required to remain in the hospital next week, then close to the clinic for 3 more weeks so that the doctor can closely monitor your condition and reaction to the therapy.

You will need to return to M Health at 3, 6, 9 and 12 months after the CAR-T infusion so that your condition can be monitored.

At these visits you may undergo the following procedures to evaluate your disease status:

- Measurement of your temperature, blood pressure, respiratory and heart rate (pulse).
- Blood tests for routine lab tests such as complete blood counts (CBCs) and other tests
- Blood tests to measure markers relevant to CAR-T therapy
- CT or PET scan
- Bone marrow biopsy

The amount of blood that may be collected from you for routine labs is approximately 4 tablespoons.

Appendix B: Risks and Side Effects of CAR-T Therapy

Risks are possible side effects of treatment with CAR-T therapy. The list of side effects below contains the most common side effects from patients that have already received the CAR-T therapy. These events may happen any time within approximately 3-4 weeks after the therapy. This treatment may involve risks that are currently unforeseeable, so tell your doctor if you are experiencing any problems. It is very important that you contact your doctor immediately at any signs of fever or other new symptoms. Also problems or side effects that are not now known could also occur. You may be given any new information that may affect your willingness to start or continue treatment.

Treatment with CAR-T therapy can result in a severe flu like syndrome that can include symptoms many of which are also mentioned below. This initially involves high fevers, chills, nausea and aching. This can also result in trouble breathing and difficulty getting enough oxygen as well as dangerously low blood pressure. This reaction could be mild or severe and could very rarely lead to death, which has been seen in a few adult patients. It is possible that you may need to be cared for in intensive care units for these severe reactions. Please notify your doctor if you experience any symptoms of the following side effects:

More Common

- Fatigue
- Chills and fever
- Decrease in blood pressure
- Shortness of breath
- Dizziness/lightheadedness
- Confusion
- Difficulty speaking or slurred speech
- Cough
- Fast heart rate.
- Significant decrease in blood counts, including neutropenia (low WBC count), anemia (low red blood cell count), and thrombocytopenia (low platelet counts). This will be related to the chemotherapy you receive prior to the CAR-T infusion (if given), and may be related to the CAR-T infusion as well. These decreases can last weeks or, much more rarely, months. These decreases will result in the need for transfusions (anemia and thrombocytopenia) and increase the risk of infection (neutropenia).
- Nausea and vomiting
- Diarrhea
- Decreased appetite
- Muscle and joint aches

- Headache
- Cytokine Release Syndrome/Neurotoxicity: When the CAR-T cells grow rapidly and become activated, they can release proteins called cytokines. Release of large amounts of certain cytokines can cause a "cytokine release syndrome" that can result in mild, moderate or severe reactions. Symptoms and problems can include high fevers, chills and shaking, sweating, nausea, vomiting, diarrhea, swelling, or skin rashes. Patients in whom the CAR-T cells have grown rapidly have occasionally become quite ill, with breathing difficulties and low blood pressure that can be life-threatening. Some patients have required use of a respirator (a breathing machine) and medications to keep blood pressure up. This cytokine release syndrome can lead to kidney and liver problems that can be severe, and several adult patients have required at least temporary dialysis. This reaction can be mild or severe and can lead to death. Additional organ system effects can include transient events of cardiac insufficiency and arrhythmia, hepatitis and jaundice. Some patients required intensive care at the hospital for several days. In addition, some patients developed confusion, disorientation, or have even become unresponsive, presumably from a complication of the cytokine release syndrome. Another reaction associated with the cytokine release syndrome is low blood counts as mentioned above. Fortunately, these side effects have gotten better with medications to reverse the cytokine release syndrome (steroid treatment or other medicines). The best time to administer medications to treat the cytokine release syndrome is at the onset of symptoms and you medical team has expertise and guidelines to treat side effects effectively and safely. If you experience cytokine release syndrome, blood samples will be collected during your treatment for these symptoms to track CAR-T cells and for research purposes. You will be closely monitored for signs or symptoms of these events and supported and treated for these events if they occur.
- Significant decrease in your B cell counts (type of white cell; expected with Kymriah). Your B cell count may already be low following treatments you have previously received for your cancer, since your tumor is comprised of B cells. Likewise, a decrease in your tumor B cell counts is the goal of this treatment and we expect the B cell counts that you have upon enrollment into this trial to decrease significantly after you receive the CAR-T cells. This decrease in B cells may continue for the period of time in which your body contains the CAR-T cells. The CAR-T cells cannot distinguish between your healthy and tumor B cells.
- If your B cell numbers decrease over time, you may experience an increase in viral (such as Cytomegalovirus "CMV") and bacterial infection because you have a decrease in the type of cells that fight these types of infections. Your doctor will be able to treat you with medications such as intravenous immunoglobulin (IVIG) which will reduce your chances of infection due to a lack of B cells. The decrease in these types of cells that fight infections minimizes the ability of your immune system and IVIG helps maintain your body's antibody levels to resist infection.

- Tumor Lysis Syndrome: If your tumor cells decrease quickly, you may experience Tumor Lysis Syndrome. This happens when the tumor 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 potassium level and calcium level and increase in your phosphate level.

Less Common

- Severe breathing difficulties
- Increase in blood pressure
- Low heart rate
- Allergic reaction (itching, swelling of the tongue)
- Injection site reactions such as bruising, swelling, black and blue marks, fainting and/or infection at the site
- Kidney damage
- Unsuccessful manufacturing of CAR-T cells to be used for your treatment: It is important to understand that meeting eligibility does not guarantee that you will receive CAR-T. In order to modify T-cells taken from your body into “CAR-T cells”, your leukapheresed T-cells will need to be shipped to an outside manufacturing facility. There is a low possibility that during the transportation from the clinic to the manufacturing site your cells may become damaged, lost, or mislabeled. In addition, during the manufacturing, these T-cells may become contaminated, not grow properly, or not meet all required safety and quality criteria. If this happens you will not be able to receive CAR-T therapy, and you may be asked to consider a second attempt at manufacturing with a new collection of T-cells from your body
- Infectious Complications: Lymphodepleting chemotherapy cause lower numbers of white cells and this may increase your chances of getting infections. Your doctor will prescribe antibiotic medication to minimize the risk of bacterial and viral infections during this time. Infections such as pneumonia, bacteremia, urinary tract infections or other may occur.
- Macrophage activation syndrome (MAS) and hemophagocytic lymphohistiocytosis (HLH) are two potentially fatal syndromes. These syndromes cause malfunction of the immune system that results in wide spread inflammation and end-organ damage

Rare

- Shortly following CAR-T infusion (up to 7 days), you may experience changes in your thinking and alertness (i.e., altered mental status or confusion, unsteady balance, abnormal speech, seizures). These symptoms usually resolve within several days. In one case, an adult lymphoma patient treated with CAR-T showed progressive and non-reversible symptoms of altered mental status starting more than one month after

treatment. Before receiving CAR-T, this patient had increasing vision loss due to an inflammatory disorder called optic neuritis, which worsened following treatment with CAR-T. It is unknown whether this was related to previously chemotherapy drugs and/or CAR-T treatment. In another case, a child with leukemia treated with CAR-T developed encephalitis (inflammation of the brain) and passed away. It is unknown whether this was related to other events (virus infection, autoimmune reaction) and/or CAR-T therapy.

- You may be less likely to respond to similar gene therapy trials in the future because you may develop an immune response to the viral vector used for the gene transfer in your cells.

Very Rare and Unexpected

Certain long-term theoretical risks may be associated with CAR-T that would be rare and unexpected. These are listed below and will be monitored.

- Autoimmune disease:
- The use of CAR-T cells could theoretically 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 your own tissues by mistake and you can get sick. Autoimmune disease can affect many parts of your body, like your central or peripheral nervous system, muscles, the endocrine system (system that directs your body's hormones and other chemicals), and digestive system. There is no evidence in our current research to support this potential.
- Blood cancer: The treatment involves giving a person cells that have been modified by a lenti or retroviral vector used to deliver CAR-T. A retroviral vector is a gene delivery vehicle derived from the HIV virus. The retroviral vector is not infectious and does not cause disease. When viral vectors enter a cell in the body, the genetic material (deoxyribonucleic acid or DNA) of the vector inserts itself into the DNA in that cell. This process is called DNA integration. Most DNA integration is expected to cause no harm to the cell or to the patient. However, there is a theoretical chance that DNA integration might result in abnormal activity of other genes. In most cases, this effect will have no health consequences. Such integration has not been seen in this research program.
- There is a chance that there may be some regions of the normal human DNA where insertion of CAR-T DNA may result in activation of neighboring genes. For example, if the CAR-T inserts in a place in your DNA that tells your cell to start growing, this may cause uncontrollable growth of the cell, resulting in cancer. We do not know if the retro or lentivirus vector used in this protocol might cause a new cancer. However, you should be aware that the DNA contained in viral vectors will insert itself into your DNA and that under some circumstances; this has been known to cause malignant (cancerous) growth months to years later. It is important that you know about some cancers that occurred in

another gene transfer research study. The study, conducted in France in 2002, involved a disease called X-linked Severe Combined Immunodeficiency (SCID). Years after receiving cells that were modified by a viral vector, a significant number of the children in this small study developed leukemia- like malignant disease (cancer). At least one child died from the cancer. However, most of the children with X-linked SCID who have received experimental gene transfer have not been found to have a leukemia-like disease at this time. Although they appear healthy, we still do not know whether they, too, will develop a malignant growth.

- Replication Competent Lentivirus or "RCL:" There is a risk that the vector used to deliver the CAR-T to your cells could mutate (change) and grow once it has been inserted into T cells taken from your body. This would be called a replication competent lentivirus, or "RCL". The risks of an RCL are unknown, but it is possible that it could make you sicker than you are now. To date, no patient has developed an RCL.
- Risks associated with HIV: The retroviral vector that is used to transfer the CAR-T genetic material to T cells taken from your body is made up of parts of the human immunodeficiency virus (HIV). The vector does not behave like HIV and it cannot cause acquired immune deficiency syndrome (AIDS). The lentiviral vector is washed away during the manufacturing process of T cells taken from your body, however there is a possibility that a small amount of parts of the lentiviral vector may remain with the T cells and cause your body to generate antibodies to the HIV proteins. Although generation of antibodies to HIV does not pose a risk to you, it may cause a positive test result in some antibody-based tests for HIV. If you become positive for HIV antibodies, you can have a more sensitive test done to determine whether or not you are HIV positive.
- Risk of Progressive Multifocal Leukoencephalopathy (PML): Patients with low B cells rarely develop PML. If you develop PML, you may develop weakness, speech difficulties, unsteady walking, and difficulty seeing. You may develop headaches or seizures, but this is uncommon. Dementia in the form of difficulties in cognition, personality changes, and issues in memory are also common. Death can occur. Your doctor will monitor you regularly for any new or worsening signs or symptoms associated with the appearance of PML.
- Hepatitis B reactivation: If you have a previous history of inactive or resolved hepatitis B, you may have reactivation or abrupt increase in growth of the virus. This can either occur spontaneously, but more often occurs in patients who have received treatment that has suppressed the immune system, in this case the medicine that has been used to treat your cancer (CAR-T cells). This may cause severe liver failure. In most cases, this will resolve naturally, but in cases where the virus persists, it can lead to worsening liver injury and death.
- Antibody formation: The white blood cells taken from your body during the leukapheresis procedure will be processed to separate the T cells (a type of white blood cell) needed for your treatment. The separation requires the use of mouse antibodies. Residual mouse

antibodies, which are proteins that are foreign to your body, can result in the formation of antibodies in your body that may cause an immune response against the CAR-T cells. If this occurs it may result in the loss of the CAR-T cells you were given. The loss of CAR-T cells is not expected to be harmful to you. Furthermore, it is also possible that you may develop antibodies to other residual proteins used during the preparation of CAR-T cells that may not have been completely removed during the manufacturing process. The result of this is that your body could develop antibodies to the "foreign" proteins, which could lead to an allergic reaction, such as skin rash, itching and fever. Testing during the manufacturing of CAR-T therapy is in place to make sure that foreign residual proteins are completely removed but it is possible that some residual protein could remain.

- If you develop a secondary malignancy you may be asked to submit a biopsy for further investigation.
- While we test the CAR-T cells for impurities and presence of infectious agents, it is still possible that you could acquire an infection from the material being infused

Patients receiving CAR-T are at risk for altered or decreased consciousness or coordination in the 8 weeks following CAR-T infusion. You are advised to refrain from driving and engaging in hazardous occupations or activities, such as operating heavy or potentially dangerous machinery, during this initial period.