RINCIPAL INVESTIGATOR: Scott Norberg, DO

STUDY TITLE: A Phase I Trial of T Cell Receptor Gene Therapy Targeting KK-LC-1 for Gastric, Breast, Cervical, Lung and other KK-LC-1 Positive Epithelial Cancers

STUDY SITE: National Institutes of Health (NIH) Clinical Center (CC)

Cohort: *Treatment, Affected Patient*

Consent Version: *12/20/2024*

WHO DO YOU CONTACT ABOUT THIS STUDY?

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KEY INFORMATION ABOUT THIS RESEARCH

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

You are being asked to take part in a research study at the National Institutes of Health (NIH). This section provides the information we believe is most helpful and important to you in making your decision about participating in this study. Additional information that may help you decide can be found in other sections of the document. Taking part in research at the NIH is your choice.

You are being asked to take part in this study because you have been diagnosed with metastatic or refractory/recurrent KK-LC-1 positive epithelial cancer. In addition, you completed the screening evaluation and were found to be eligible to take part in this research study.

The purpose of this study is to determine the safety of escalating doses of KK-LC-1 TCR T cells plus aldesleukin for the treatment of metastatic KK-LC-1 positive solid cancers.

The use of KK-LC-1 TCR T cells in this study is considered investigational, which means that it has not been approved by the U.S. Food and Drug Administration (FDA) to treat metastatic or recurrent/refractory solid epithelial cancers. However, the FDA has given us permission to use KK-LC-1 TCR T cells in this study.

There are other treatments that may be used to treat your disease, and these can be prescribed/given by your regular cancer doctor, even if you are not in this study. These treatments may include radiation, chemotherapy or immunotherapy.

The goal of this study is to find out if it is possible to treat patients with your type of cancer with the experimental KK-LC-1 TCR T Cell treatment. We hope it will shrink the cancer, but we do not know if this will be the case.

The way in which treatment is given in this study and the side effects may be different than if you were to receive standard care.

You will receive a chemotherapy regimen of cyclophosphamide and fludarabine followed by a single infusion of KK-LC-1 TCR T cells and high-dose aldesleukin.

Six escalating cell doses of KK-LC-1 TCR T Cells will be tested in this study. If the lower dose is found to be safe then subsequent patients will be treated with the next higher dose until the highest dose level is reached.

Participation in this study will require hospitalization, collection of a large volume of blood cells using a procedure called apheresis, optional biopsies of your tumor, and close follow up with visits to the NIH Clinical Center to monitor your cancer and the treatment side effects.

If your cells do not grow, you will not be able to receive the cell infusion. If we determine that your cells are not growing, we will inform you and discuss your options with you.

The single cycle of chemotherapy that is given as part of the experimental treatment has side effects that may include nausea, vomiting, diarrhea, hair loss, and decreased blood counts. These side effects are similar to the side effects you might experience from the standard chemotherapy you might receive even if you were not in this trial.

Also, as part of the experimental treatment, you will receive a drug called aldesleukin. The aldesleukin has side effects that may include fever, chills, low blood pressure, high heart rate, body swelling, and fatigue. Aldesleukin may have severe side effects that include lung failure, coma, and kidney failure. A complete list of side effects from the study medications is provided in this consent.

If you decide to join this study, here are some of the most important things that you should know that will happen:

- You may only participate in this study if you have been diagnosed with metastatic or refractory/recurrent KK-LC-1 positive solid epithelial cancer.
- The therapy used in this study is called T cell therapy. Immune cells from your blood will be genetically modified in the laboratory to give them the ability to attack the cancer that expresses the KK-LC-1 antigen.
- You completed the screening tests and you were found eligible for the study. If you decide to take part in this study, you will have a procedure to collect your T cells from the peripheral blood. These cells will be modified in the laboratory and will be given back to you by a one-time infusion into a vein. You will receive chemotherapy prior to getting the cells and a drug called aldesleukin afterwards. These drugs activate the gene-engineered T cells and help them proliferate. You will stay in the hospital for 2-3 weeks.

- You may experience side effects from taking part in this study. The most common side effects include decreased blood counts requiring transfusions, fevers, chills, nausea, low blood pressure and high heart rate. It is possible that you could develop more serious, temporary, long-lasting or permanent side effects including death.
- You will be seen regularly during the study. You will have clinical, laboratory, and imaging tests to see how you are doing and to assess your disease. We may draw your blood every day for research while you are in the hospital and we may ask you to have a biopsy of your cancer tumor for research.
- If you are a sexually active person capable of becoming pregnant, it is important that you do not become pregnant during your participation in this study. If you are a sexually active person with a partner able to become pregnant, it is important that your partner not become pregnant during the restricted period. You will need to practice an effective form of birth control before starting study treatment, during study treatment, and for twelve (12) months after you finish study treatment (the restricted period).
- After the study follow-up period has ended, we would like to talk with you for 5 years to see how you are doing. We will ask you to participate in a long-term follow-up study where we will follow you for 15 years from the time you receive the cells.

Just as we do not know what side effects you might have, we cannot know if you may benefit from taking part in this study. If you do not benefit, this study and the results from our research will help others in the future.

You are free to stop participating in the trial at any time. If you decide to stop, the study doctor may ask you to agree to certain tests to make sure it is safe for you to stop.

The remaining document will now describe the research study in more detail. This information should be considered before you make your choice. Members of the study team will talk with you about the information in this document. Some people have personal, religious, or ethical beliefs that may limit the kinds of medical or research interventions in which they would want to participate. Take the time you need to ask any questions and discuss this study with NIH staff, and with your family, friends, and personal health care providers.

IT IS YOUR CHOICE TO TAKE PART IN THE STUDY

You may choose not to take part in this study for any reason. If you join this study, you may change your mind and stop participating in the study at any time and for any reason. In either case, you will not lose any benefits to which you are otherwise entitled. However, to be seen at the NIH, you must be taking part in a study or are being considered for a study. If you do choose to leave the study, please inform your study team to ensure a safe withdrawal from the research.

WHY IS THIS STUDY BEING DONE?

The purpose of this research study is to determine the safety of escalating doses of KK-LC-1 TCR T cells plus aldesleukin for the treatment of metastatic or refractory/recurrent KK-LC-1 positive solid cancers.

We are asking you to join this research study because you have been diagnosed with metastatic or refractory/recurrent KK-LC-1 positive solid cancer.

KK-LC-1 TCR Transduced PBL is considered investigational, which means that it has not been approved by the U.S. Food and Drug Administration (FDA) to treat metastatic or recurrent/refractory solid epithelial cancers.

We have developed an experimental therapy that involves taking white blood cells called lymphocytes from you, growing them in the laboratory in large numbers, genetically modifying them to give them new genes (T Cell Receptor (TCR)), which help them recognize the cancer, and then giving the cells back to you. In this study, we are modifying your white blood cells with a retrovirus that has the gene for a TCR that recognizes the KK-LC-1 protein. This type of treatment is called cell therapy.

Before receiving the KK-LC-1 TCR cells, you will receive 2 FDA approved chemotherapy drugs to temporarily suppress the immune system to improve the chances that the experimental cells will be able to survive in the body. After the cells are given, you will receive aldesleukin (IL-2) to help these cells stay alive longer.

Once you have completed this therapy, you will be seen in our clinic 40 days after your cell infusion to evaluate how your cancer has responded to the treatment and whether you are recovering from any toxicities experienced during the trial. Depending on your response to the treatment, we will ask you to return to the NIH Clinical Center approximately every 3 months (x3), and every 6 months (x5 years), and then as determined by your physician. Some of your identifiable information will be shared with investigators at Rutgers University to assist with this assessment.

WHAT WILL HAPPEN DURING THE STUDY?

Before you begin the study

You will need to supply an updated complete list of your current medications to the study doctor. This includes over-the-counter medications and herbal supplements. Some medications may interfere with the study drugs and it is important that your study doctor and prescribing physician be aware of any potential risks so that they can prescribe alternative medications as necessary. If you do not already do so, please carry a list of your medications at all times.

This study has several stages after screening:

Stage	Timeframe	Location	Comments & Instructions
Baseline	Within 30 days prior to leukapheresis	Inpatient or outpatient	Complete physical examination, vein assessment, blood tests
Baseline	Within 4 weeks prior to starting	Inpatient or outpatient	Clinical staging (may include CT scan, MRI scan, PET scan), tumor measurements, tumor biopsy (any time prior to chemotherapy), ECG, Cardiac

Stage	Timeframe	Location	Comments & Instructions
	chemotherapy regimen		testing (cardiac stress test, ECHO) and/or pulmonary testing (PFT, 6MWT)
Leukapheresis before treatment	At least 11 days prior to cell infusion	Inpatient or outpatient	This is a half to full day appointment.
Chemotherapy (day -6 to -2)	1 week	Inpatient	Receive IV chemotherapy to prepare your immune system for the cells.
Cells and aldesleukin (Day 0-2)	1-3 days	Inpatient and possibly ICU	Receive KK-LC-1 TCR T cells IV and then high dose aldesleukin about every 8 hours for up to 12 doses.
Recovery	1-2 weeks	Inpatient unit	Recover from the effects of treatment.
Follow -up	First follow-up will be 40 days post cell infusion and then approximately every 3-6 months depending on response.	Outpatient	Return to clinic to evaluate how your cancer has responded to the treatment. You will have physical exam, laboratory blood tests, review of side effects, imaging procedures (may include CT scan, MRI scan, PET scan), and possible biopsy.

Baseline

Prior to receiving the experimental treatment, you will have additional tests. These may include imaging procedures, and laboratory tests. You will also have a large catheter inserted into a vein so that leukapheresis can be performed (see below). You may be admitted to the hospital for these tests and procedures.

During the study

Cell harvest and growth

You will have a procedure called leukapheresis to obtain white blood cells from you. These cells will be grown in the lab and genetically modified to recognize a protein on your tumor cells. It takes approximately 11-15 days to make the cells. You may have enrolled on protocol 16C0061

to undergo leukapheresis. If you had a leukapheresis procedure and we have collected cells, then you will not need to do it again.

If your cells do not grow, you will not be able to receive the cell infusion. If that happens, we will look at alternative experimental treatments at the NIH Clinical Center or refer you to the care of your referring home physician. At the time we determine that your cells are not growing, we will inform you and discuss your options with you.

Leukapheresis

The procedure for obtaining blood cells through leukapheresis is a very common procedure that is done routinely here in the Clinical Center with very few risks. White blood cells (lymphocytes) are removed from you using a serum cell separator machine. This requires putting a needle into your arm to obtain blood to go into the machine. The machine divides whole blood into red cells, plasma (the liquid part) and lymphocytes (white cells). The lymphocytes will be taken out, and the plasma and red cells returned to you through a second needle in your other arm. The procedure takes between 4-6 hours to complete. If the procedure cannot be done through a needle in your arm, a central catheter may need to be placed. The white blood cells may be used to help grow your anticancer cells. In addition to the leukapheresis, we will also ask you to undergo one additional pheresis procedure around 6 weeks after your cell treatment to see how this therapy affects your immune system and see if cells we gave you are still active.

Intravenous Catheter

To receive this treatment, you may need to have a central venous catheter. We will place an intravenous catheter which is a small plastic tube inserted into a vein in your arm using a needle. The area will be numbed with an anesthetic before the catheter is put in. The procedure will be discussed with you in detail prior to the catheter placement.

Blood Draws

Blood will be drawn frequently during your treatment. Most of the blood draws will be to monitor your health during and after the lymphocyte infusion. During that time, we will remove between 1 and 9 teaspoons of blood daily to study the effects of the treatment regimen on your immune system. If you experience side effects in your kidneys, we will collect 1 additional teaspoon of blood. In addition, some blood samples will be drawn for research purposes. The maximum amount of blood for research is approximately 2.3 cups in 8 weeks. Additional blood draws might be necessary to investigate T cell responses and serum cytokine levels in cases of clinical events such as rapid progression of malignancy or side effects. These samples will be used to study how your immune system is affected by the cell therapy. Some of the samples may be used for other or future research conducted by the investigational team or other researchers.

Chemotherapy Regimen (Day -6 through Day -2)

After we have grown the KK-LC-1 TCR cells to large numbers in the laboratory, you will be admitted to the hospital to begin your experimental treatment. You will be given two chemotherapy medicines, cyclophosphamide and fludarabine, to make space in your immune system so the KK-LC-1 TCR cells can work without any interference from the cells in your immune system.

These medicines may cause your tumor to shrink some, but this shrinkage is anticipated to be only partial and of small duration. The main purpose of the chemotherapy is to see if we can make the

cells more effective in fighting cancer tumors. Animal experiments have indicated that chemotherapy can make the infused cells more effective in fighting your cancer, but it is not known whether this is true in humans.

The cyclophosphamide will be given into your catheter over 1 hour for two days (Day -6 and Day -2) and the fludarabine will be given into your catheter for 30 minutes every day for five days (Day -6 through Day -2). The side effects of these medicines are described on the following pages.

To decrease your risks for getting certain infections, we will treat you with medications that work against bacteria, virus, and, if needed, ones that work against fungal infections. You will have to take these for 6 months or longer, depending on the recovery of your infection fighting blood cells.

Cell Infusion and Aldesleukin Regimen (Day 0 through Day 2)

You will be given cells through the IV over 20-30 minutes two to four days after the last dose of chemotherapy. Within 24 hours after your cell infusion you will be given high dose aldesleukin through one of the IVs. It will be given as a 15-minute infusion about every 8 hours for up to four days after the cell infusion. Aldesleukin is a cell growth factor and it is thought that it will help the cells live longer in your body.

We will watch you closely during this entire time for any side effects of this experimental regimen. We will discuss the side effects below and we will include in your care all the medicines and treatments to prevent as many of these side effects as we can and to make you as comfortable as we can.

When you are finished with the T cell treatment

Recovery

You will recover in the hospital until you are well enough to go home. This will likely take 7-12 days after you have received cells; however, you may need to stay in the hospital longer until you are well enough to go home. We will continue to give you supportive medications, do laboratory tests, and watch you closely for any side effects until we feel your condition is stable.

In addition to the laboratory tests to monitor your condition, we will remove between 1 and 9 teaspoons of blood daily to study the effects of this regimen on your immune system. If you experience side effects in your kidneys, we will collect 1 additional teaspoon of blood and about 6 teaspoons of urine to help us determine the cause of these side effects. The maximum amount of blood for research is approximately 2.3 cups in 8 weeks.

Follow up and Evaluation of Experimental Regimen

You will need to come for a clinic visit approximately 40 days after cell administration for lab tests, imaging studies and a physical examination to evaluate how your cancer has responded to the treatment and whether you are recovering from any toxicities experienced during the trial. At this follow up visit, you may undergo apheresis or have about 8 tubes of blood drawn (4 tablespoons) so that we can see the effect this therapy had on your immune system and if the cells we gave you are still alive.

Depending on your response to the treatment, we will ask you to return to the NIH Clinical Center frequently after you are discharged approximately every 3 months (x3), and every 6 months (x5 years), and then as determined by your physician. The follow up visits take approximately 1-2

days. At each visit, you will have lab tests, imaging studies and a physical examination. If your tumor appears to be growing, we will look for other investigational therapies you may be eligible for or refer you back to the care of your local physician.

Retreatment

If you received a lower dose level and/or your tumor shrinks or disappears following the initial treatment and then recurs you may be able to receive one additional treatment if you tolerated the treatment well and if all the side effects have resolved. You must continue to meet the original eligibility criteria to be considered for retreatment. You will receive the same medications and cell infusion on the same schedule as with the first treatment, but your dose of KK-LC-1 cells may be at the higher dose if your first treatment was at one of the lower dose levels of the study. You will be allowed to have second treatment only if we have enough of your cells left over from the first treatment you had. The study doctors will review this with you. The second treatment will not begin prior to 6-8 weeks after your last dose of aldesleukin.

Gene Therapy Long Term Follow up

You will be followed on a separate protocol once you finish the cell therapy. We will ask you to sign a separate consent for this other protocol. Because we do not know the long-term side effects of gene therapy, we will ask you to take part in long term follow up for the next 15 years. The Food and Drug Administration (FDA) requires that people who receive gene therapy be watched even after they complete the study. We will ask you questions about your health and ask you to have a physical exam every year. We will also collect your blood over the next several years. If you return to your home physician after treatment here, we will ask you to have them send us a copy of your physical exam and your blood samples. We will collect blood samples right after you receive the cells, and at 3, 6 and 12 months after treatment, and then every year after that (2 teaspoons each time) up to 5 years. This testing will help us learn if the cells have grown or changed in your body. For this reason, we ask that you continue to provide us with a current address and telephone number, even after you complete this research study.

At the time of your death, no matter the cause, we may request consent from your family for an autopsy. This will allow us to obtain important information about the safety of this experimental treatment. Please discuss this with your family to inform them of this potential request.

Additional research testing

In addition to the tests that we will conduct to determine whether you are having side effects or if you are responding to the study therapy, we will also collect samples from you for purposes of research only. The samples are being done to look at the effects of therapy on your immune system and markers of tumor activity, including collecting and testing tumor cells. The samples will be collected prior to treatment, during treatment while hospitalized and at subsequent follow-up visits.

HOW LONG WILL THE STUDY TAKE?

If you agree to take part in this study, your involvement is expected to last for up to 5 years:

- After you receive KK-LC-1 T cells, you will be seen in the clinic at 40 days post cell infusion for the first response assessment.

- Depending on your response to the treatment, we will ask you to return to the NIH Clinical Center approximately every 3 months (x3), and every 6 months (x5 years) and then as determined by your doctor.
- The follow up visits take approximately 1-2 days.
- Your involvement on the Gene Therapy Long Term Follow Up Study will last for 15 years from the time you receive the KK-LC-1 T cells.

HOW MANY PEOPLE WILL PARTICIPATE IN THIS STUDY?

Not everyone screened for this study will be eligible to receive treatment. It is expected that up to 35 people may receive treatment in this study.

WHAT ARE THE RISKS AND DISCOMFORTS OF BEING IN THE STUDY?

The risks and discomforts of this research study can be significant. This experimental treatment can lead to long-term decrease in your immune function. It is also possible that you may lose your fertility following this experimental treatment. It is possible, although unlikely, that this experimental treatment may cause your death.

We will discuss the side effects of this experimental treatment with you. You will be given medicines, transfusions, and treatments to prevent or treat the side effects including drugs to prevent and/or treat different types of infections. We will try to make you as comfortable as possible.

Blood Samples

Side effects of repeated blood sampling depend in part on how the blood is drawn. If through a central venous catheter, risks include contamination of the catheter which would result in a serious blood stream infection, requiring admission to the hospital and giving you antibiotics through the vein; if blood is drawn through a needle into your skin, side-effects could include pain and bruising in the area where the blood was drawn. Other side-effects can include bruising, redness, discomfort or bleeding at the site of the needle stick, and possible lightheadedness, or rarely, fainting. If you have too much blood taken over a prolonged period, your red blood cell count may drop (this is called "anemia"). As a precaution, we will check your red blood cell level, and give you iron treatment or a blood transfusion if needed.

Leukapheresis

The risks of leukapheresis include pain, bruising, lightheadedness or dizziness, nausea, vomiting and chills. Bruising may last up to 72 hours.

Tingling around the mouth, fingers, or toes and mild muscle cramps may develop from slight lowering of the blood calcium by the blood thinner used during the procedure. These symptoms can be treated by either temporarily stopping the procedure or by giving Tums. Leukapheresis uses a completely closed sterile system. The risk of infection is minimized by cleaning the skin before the needle stick. No infections from leukapheresis have been noted in thousands of such procedures performed over the last 10 years at the NIH.

Rarely, there can be a malfunction of the apheresis machinery that might prevent the return of your blood being processed in the machine. The amount of blood lost would be very small and

not harmful. It is also rare for people to faint, have seizures, or have air trapped in the bloodstream.

Temporary or permanent nerve damage may occur at the needle placement sites. This is very rare. At the NIH, to this point, there have been no cases of permanent nerve damage with leukapheresis.

During the leukapheresis procedure, your platelet count may decrease because platelets are collected with the white blood cells. Platelets are cells that help your blood to clot. Taking aspirin in combination with a lowered platelet count may increase your chance of developing bleeding. Therefore, you should not take aspirin or aspirin-containing drugs for 2 weeks after the procedure without physician approval.

Administration of KK-LC-1 T cells

The cells we will be giving you have a type of virus (retrovirus) put into them that recognizes the KK-LC-1 protein. Although this retrovirus is not active, there is the rare possibility that it may cause infection. The cells could also cause you to develop another type of cancer, such as leukemia or lymphoma. These specific gene-modified cells have not been given before and therefore we do not have information about the side effects.

Potential risks may include:

- Fever, chills and shortness of breath, which may last for a few hours (common)
- Lung congestion causing shortness of breath
- Severe reaction to the cells which would include very low blood pressure and damage to your heart, lung, and/or kidneys
- As this is a new experimental therapy, side effects that we do not anticipate that may cause your condition to deteriorate may be encountered. Any new information that becomes available during the course of this study will be shared with you.

Other Study Drugs

The side effects of cyclophosphamide, fludarabine, high dose aldesleukin and some of the other medications you will receive are listed below:

Aldesleukin

Likely	Less Likely	Rare but Serious
• Fever, chills, and fatigue • Lowered platelet and red blood cell levels that may require transfusions • Significant fluid retention causing weight gain (as much as 20 pounds). • Low blood pressure • Increased heart rate	• Decrease in thyroid function that may require daily thyroid hormone replacement; • Abnormal kidney and liver function that can be severe; • Abnormal heartbeats or low blood pressure that	• Bowel perforation (a hole) requiring longer hospitalization or surgery. • Autoimmune disease, where your immune system attacks cells in organs of your body. Should this occur, you will be treated with steroids to stop the immune response.

Likely	Less Likely	Rare but Serious
• Low urine output • Swelling in your extremities • Fluid in your lungs that can require oxygen • Dry mouth, nausea, vomiting and diarrhea; • Rash, itching; and changes in skin or hair pigmentation, called vitiligo; • Changes in mental status, including confusion, difficulty sleeping or vivid dreams; this can be severe and require sedation and monitoring in the ICU	may require treatment in the ICU. • Breathing problems which may need monitoring in ICU and insertion of a breathing tube.	• Damage to the heart muscle or heart attack • Loss of blood flow to the extremities due to medicines used to treat very low blood pressure and shock. In one instance a patient had to have her lower arm amputated after treatment with these medicines. • Aldesleukin is mixed with human albumin which could cause an allergic reaction or potentially transmit viral infections, although we have not had this occur.

Cyclophosphamide

Likely, some may be serious	Less Likely, some may be serious	Rare, and Serious
• Fever • Infection, especially when white blood cell count is low • Anemia which may cause tiredness or may require transfusion • Brusing, bleeding • Blood in urine • Nausea, vomiting, diarrhea, loss of appetite, pain in belly • Hair loss, skins changes, rash, change in nails • Sores in mouth which may cause difficulty swallowing • Absence of menstrual period which may decrease the ability to have children • Blurred vision, vision changes	• Fluid around the heart • Damage to the bone marrow (irreversible) which may cause infection, bleeding, may require transfusions • Loss or absence of sperm which may lead to an inability to father children	• Damage to the heart or heart failure which may cause shortness of breath, swelling of ankles, cough or tiredness • Swelling of the body including the brain which may cause dizziness, confusion • Damage to the lungs or scarring of the lungs which may cause shortness of breath • Allergic reaction which may cause rash, low blood pressure, wheezing, shortness of breath, swelling of the face or throat • Hepatic veno-occlusive disease is a condition that is characterized by damage to blood vessels in the liver and

Likely, some may be serious	Less Likely, some may be serious	Rare, and Serious
		liver cells. Although it may be mild and not require further treatment, sometimes it may cause a severe decrease in liver function and may be life threatening or fatal. • Kidney damage which may cause swelling, may require dialysis • A new cancer (e.g., leukemia, lymphoma, sarcoma, etc.) resulting from treatment of a prior cancer • Impaired wound healing • Urinary tract and/ or kidney injury including blood in urine, painful urination, fever, urgency, inability to urinate, loss of bladder control and pain • Abnormal heartbeats: including atrial fibrillation and flutter and ventricular arrhythmias causing your heat to be fast or irregular resulting in a pounding or racing heart, dizziness, weakness, feeling light-headed or shortness of breath • Severe skin rash with blisters and peeling which can involve mouth and other parts of the body • Decreased levels of sodium in the blood, which can cause confusion, seizures, fatigue and low levels of consciousness.

In addition, because cyclophosphamide may contain alcohol, it may impair a person's ability to

drive or operate machinery immediately after the infusion.

Fludarabine

Likely	Less Likely	Rare but Serious
• Low blood counts	• Nausea, vomiting • Diarrhea • Long term reduction of lymphocyte counts which could increase risk of infection • Infection	• Coma, blindness, other neurologic toxicity and even death • Inflammation in the lungs • Kidney damage • Allergic reaction

Gene Therapy Risk of Cancer and Other Diseases

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

Study Procedures

Biopsies

Biopsy of the cancer tumor is optional and may be performed before getting the cells, approximately 6 weeks after T cell administration, and at the time of disease progression. Local anesthesia and conscious sedation may be used. Risks associated with the biopsies are pain and bleeding at the biopsy site. You will be asked to sign a separate consent prior to each procedure..

X-ray examination

An x-ray examination of your chest will be performed. The risk related to radiation exposure is discussed below under “What are the risks of radiation from being in the study?”

Cardiac Stress Test

A cardiac stress test may check for risks of a possible heart problem or diagnose an existing heart problem. During a cardiac stress test, you may be asked to walk or jog on a treadmill. While doing this, your heart will be watched on a monitor. Problems can happen during or after the test. Your blood pressure may decrease, and you may feel dizzy, lightheaded, and weak. You may feel your heart throbbing or have extra heartbeats. You may have a chest pain or heart attack. Doctors are there before, during, and after the test to help you.

Electrocardiogram (ECG)

An electrocardiogram or ECG is a test that records the electrical activity of the heart. It is used to measure the rate and regularity of heartbeats as well as the size and position of the heart chambers,

and the presence of any damage to the heart. For this test, you will be asked to lie down, and small patches that have an adhesive edge with a gel in the middle, called electrodes, will be placed on your arms, legs, and chest. The areas where the electrodes are placed will be cleaned and, if needed, some hair may be shaved or clipped to allow for better attachment of the electrodes. The adhesive from the patches may irritate your skin.

Echocardiogram (ECHO)

An echocardiogram is an ultrasound to evaluate your heart structure and function. This test is very safe and is performed using a probe with gel placed on your chest.

Pulmonary (lung) Function Test (PFT)

These tests measure how well your lungs work. They are usually safe for most people. However, because the test may require you to breathe in and out quickly, you may feel dizzy. There's a small risk that you might faint. If you have asthma, this test could cause you to have an asthma attack. In very rare cases, pulmonary function tests may cause a collapsed lung. If you have asthma or feel lightheaded during the test, tell your doctor.

6 ***Minute Walk Test (6MWT)***

This is a low risk medical assessment that measures how far you can walk in 6 minutes. If you experience chest pain or breathing trouble during the assessment, tell you doctor.

Intravenous Catheter

The risks associated with placing some catheters include pain, bleeding, infection and collapsed lung. Lung collapse is treated by putting a tube into your chest for a few days to allow your lung to expand. Pressure is placed on any area that might bleed. Other IVs may be needed in one or both of your arms if we need to give you extra fluids, medicines, or nutrition. The long-term risks of the catheter include infection and clotting of your veins. If these occur, it may be necessary to remove the catheter. These risks will be explained to you in more detail at the time of insertion.

CT Scan

The CT scanner is a donut-shaped machine that uses x-rays to make computer pictures of the inside of your body. During the procedure, you will need to lie still on a table inside the CT machine. The table will move you in and out of the machine during the scan, and you will be told to hold your breath. The scan itself will only take a few minutes, and the entire visit will take about 30 minutes. The risk related to radiation exposure is discussed below under "What are the risks of radiation from being in the study?"

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

You could have an allergic reaction to the contrast, which may cause side effects ranging from mild itching or a rash, to severe trouble breathing, shock or rarely, death. The contrast may also cause kidney problems. The study doctors will do a blood test to make sure it is safe for you to get the contrast.

You may also drink oral contrast. You may have vomiting, nausea, cramping, bloating, constipation, or diarrhea after drinking the contrast.

***Magnetic Resonance Imaging (*MRI)**

An MRI makes pictures of the inside of your body using strong magnets instead of x-ray energy. At the time of each scan, you will be asked to fill out a screening form to verify that it is safe for you to have the scan. You will also be asked to remove any metallic objects you are wearing (for example, watches, earrings, or piercings). We may ask you to change into a hospital gown.

Then you'll be asked to lie on a narrow bed that will move into the MRI scanner. The scanner is a long, narrow tube that is open at each end. Once you are comfortable, the table will be moved into the scanner. You will need to lie still on the table during the scan. You will hear normal "hammering" or clicking and squealing noises during the scan. We will give you earplugs or earmuffs to muffle the sound. You will be able to communicate with the technician running the scan the entire time. We will also give you an emergency button to squeeze at any time if you want the scan to stop.

Risks for MRI:

You might be at risk for injury from the MRI magnet if you have some kinds of metal in your body. It may be unsafe for you to have an MRI scan if you have:

- pacemakers or other implanted electrical devices,
- brain stimulators,
- some types of dental implants,
- aneurysm clips (metal clips on the wall of a large artery),
- metal prostheses (including metal pins and rods, heart valves, and cochlear implants),
- permanent eyeliner,
- tattoos,
- an implanted delivery pump,
- or shrapnel fragments. Welders and metal workers may have small metal fragments in the eye.

You will be screened for these conditions before having any MRI scan. If you have a question about metal in your body, you should tell us. You will be asked to fill out an MRI screening form before each MRI scan you have.

If you are afraid of confined (small, cramped) spaces, you may get anxious during an MRI. If you have back problems, you may have back pain or discomfort from lying in the scanner.

The noise from the scanner is loud enough to damage your hearing, especially if you already have hearing loss. We will give you hearing protection. If the hearing protection comes loose during the scan, you should let us know right away.

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

Gadolinium

During part of the MRI we will give you gadolinium, a contrast agent, through an intravenous (IV) catheter (small tube).

Mild symptoms from gadolinium happen in less than 1% of people who get it. Symptoms usually go away quickly. Mild symptoms may include:

- your arm being cold during the injection,
- a metallic taste,
- headache, and
- nausea.

More severe symptoms have been reported in an extremely small number of people (fewer than 1 in 300,000 people). These symptoms include:

- shortness of breath,
- wheezing,
- hives, and
- lowering of blood pressure.

You should not get gadolinium if you ever had an allergic reaction to it. We will ask you about any allergic reactions before giving you gadolinium.

People with kidney disease are at risk for a serious reaction to gadolinium contrast called "nephrogenic systemic fibrosis (NSF)." NSF always involves the skin and can also involve the muscles, joints, and internal organs. NSF has resulted in a very small number of deaths. We may do a blood test of your kidney function within 30 days before an MRI scan with gadolinium contrast. You will not get gadolinium for a research MRI scan if your kidney function is below the safe level.

Most of the gadolinium contrast will leave your body in the urine. However, the FDA has issued a safety alert that says small amounts of gadolinium may stay in your body for months or years. The long-term effects of the gadolinium that stays in your body are unknown. Some types of gadolinium are less likely to remain in the body than others. In this study, we will use the gadolinium contrast that is less likely to remain in your body, whenever we can. We will also give you additional information called a "Medication Guide." If you ask, we will also give you individual information about any remaining gadolinium we see on your scans.

PET Scans

The PET (Positron Emission Tomography) scanner is a donut-shaped machine that uses x-rays combined with a dose of a radioactive material (tracer) to make computer pictures showing the inside of your body.

Before the scan, we will give you an injection (shot) of radioactive material into a vein your arm. After the shot, you will need to wait for about 1 -2 hours for the material to be absorbed in your body. After this time, you'll lie on a narrow, padded table. We will position your body for the scan. The scan itself is painless and won't make noise. During the scan, you will need to lie very still. The scan will take about another 30 minutes to complete.

The risk related to radiation exposure is discussed below under "What are the risks of radiation from being in the study?"

What are the risks related to pregnancy?

If you are able to become pregnant, we will ask you to have a pregnancy test before starting this study. You will need to practice an effective form of birth control before starting study treatment, during study treatment, and for twelve (12) months after you finish study treatment (the restricted period). If you become pregnant, there may be unknown risks to the fetus or unborn child, or risks that we did not anticipate. There may be long-term effects of the treatment being studied that could increase the risk of harm to a fetus. You must tell the study doctor if your birth control method fails during the restricted period. If you think or know you have become pregnant during the restricted period, please contact the study team as soon as possible.

If you are a sexually active person with a partner able to become pregnant, it is important that your partner not become pregnant during the restricted period. There may be unknown risks to a fetus or risks we did not anticipate. You and your partner must agree to use birth control if you want to take part in this study. If you think your partner has become pregnant during the restricted period, please contact the study team as soon as possible. If you and your partner plan for your partner to become pregnant after the restricted period, please discuss this with the study team.

What are the risks of radiation from being in the study?

During your participation in this research study, you may be exposed to radiation from chest x-ray, CT and PET scans, or CT-guided biopsies. The amount of radiation exposure from these procedures is equal to approximately 8.1 rem. A rem is a unit of absorbed radiation.

Every day, people are exposed to low levels of radiation that come from the sun and the environment around them. The average person in the United States receives a radiation exposure of 0.3 rem per year from these sources. This type of radiation is called "background radiation." This study will expose you to more radiation than you get from everyday background radiation. No one knows for sure whether exposure to these low amounts of radiation is harmful to your body.

The chest x-ray, CT scans, PET scans, or CT-guided biopsies that you get in this study will expose you to the roughly the same amount of radiation as 27 years' worth of background radiation. Being exposed to too much radiation can cause harmful side effects such as an increase in the risk of cancer. The risk depends on how much radiation you are exposed to. Please be aware that about 40 out of 100 people (40%) will get cancer during their lifetime, and 20 out of 100 (20%) will die from cancer. The risk of getting cancer from the radiation exposure in this study is 0.8 out of 100 (0.8%) and of getting a fatal cancer is 0.4 out of 100 (0.4%).

WHAT ARE THE BENEFITS OF BEING IN THE STUDY?

You might not benefit from being in this study.

However, the potential benefit to you might include the shrinking of your tumor or lessening of your symptoms, such as pain, that are caused by the cancer.

Are there any potential benefits to others that might result from the study?

In the future, other people might benefit from this study because the knowledge gained from this study may help in developing treatments for those who have KK-LC-1 positive cancers.

WHAT OTHER OPTIONS ARE THERE FOR YOU?

Before you decide whether or not to be in this study, we will discuss other options that are available to you. Instead of being in this study, you could:

- choose to be treated with surgery, radiation or with drugs already approved by the FDA for your disease
- choose to take part in a different study, if one is available
- choose not to be treated for cancer but you may want to receive comfort care to relieve symptoms.

DISCUSSION OF FINDINGS

New information about the study

If we find out any new information that may affect your choice to participate in this study, we will get in touch with you to explain what we have learned. This may be information we have learned while doing this study here at the NIH or information we have learned from other scientists doing similar research in other places.

Return of research results

We do not plan to return research results to you. A summary of the research results will be posted on Clinicaltrials.gov at completion of the study.

EARLY WITHDRAWAL FROM THE STUDY

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

- if he/she believes that it is in your best interest
- if your disease worsens or comes back during treatment and you are not eligible for retreatment
- if you have side effects from the treatment that your doctor thinks are too severe
- if you become pregnant
- if new information shows that another treatment would be better for you
- if you do not follow the study rules
- if the study is stopped for any reason

In this case, you will be informed of the reason therapy is being stopped.

After therapy is finished, we would like to see you for a safety visit 40 days after your cell infusion.

You can stop taking part in the study at any time. However, if you decide to stop taking part in the study, we would like you to talk to the study doctor and your regular doctor first.

If you decide at any time to withdraw your consent to participate in the trial, we will not collect any additional medical information about you. However, according to FDA guidelines, information collected on you up to that point may still be provided to our collaborators or designated representatives.

STORAGE, SHARING AND FUTURE RESEARCH USING YOUR SPECIMENS AND DATA

Will your specimens or data be saved for use in other research studies?

As part of this study, we are obtaining specimens and data from you. We will remove all the identifiers, such as your name, date of birth, address, or medical record number and label your specimens and data with a code so that you cannot easily be identified. However, the code will be linked through a key to information that can identify you. We plan to store and use these specimens and data for studies other than the ones described in this consent form that are going on right now, as well as studies that may be conducted in the future. These studies may provide additional information that will be helpful in understanding KK-LC-1 positive cancers or other diseases or conditions. This could include studies to develop other research tests, treatments, drugs, or devices, that may lead to the development of a commercial product by the NIH and/or its research or commercial partners. There are no plans to provide financial compensation to you if this happens. Also, it is unlikely that we will learn anything from these studies that may directly benefit you.

I give permission for my coded specimens and data to be stored and used for future research as described above.

_____ Yes _____ No

Initials Initials

Will your specimens or data be shared for use in other research studies?

We may share your coded specimens and data with other researchers. If we do, while we will maintain the code key, we will not share it, so the other researchers will not be able to identify you. They may be doing research in areas that are similar to this study or in other unrelated areas. These researchers may be at NIH, other research centers and institutions, or commercial entities.

I give permission for my coded specimens and data to be shared with other researchers and used by these researchers for future research as described above.

_____ Yes _____ No

Initials Initials

If you change your mind and do not want us to store and use your specimens and data for future research, you should contact the research team member identified at the top of this document. We will do our best to comply with your request but cannot guarantee that we will always be able to destroy your specimens and data. For example, if some research with your specimens and data has already been completed, the information from that research may still be used. Also, for

example, if the specimens and data have been shared already with other researchers, it might not be possible to withdraw them.

In addition to the planned use and sharing described above, we might remove all identifiers and codes from your specimens and data and use or share them with other researchers for future research at the NIH or other places. When we or the other researchers access your anonymized data, there will be no way to link the specimens or data back to you. We will not contact you to ask your permission or otherwise inform you before we do this. We might do this even if you answered "no" to the above questions. If we do this, we would not be able to remove your specimens or data to prevent their use in future research studies, even if you asked, because we will not be able to tell which are your specimens or data.

It is required that your clinical and other study data be placed in an internal NIH database that is accessible to other NIH researchers for future research. Usually, these researchers will not have access to any of your identifiers, such as your name, date of birth, address, or medical record number; and your data will be labeled with only a code. We cannot offer you a choice of whether your data to be placed in this database or not. If you do not wish to have your data placed in this database, you should not enroll in this study.

How long will your specimens and data be stored by the NIH?

Your specimens and data may be stored by the NIH indefinitely.

Risks of storage and sharing of specimens and data

When we store your specimens and data, we take precautions to protect your information from others that should not have access to it. When we share your specimens and data, we will do everything we can to protect your identity, for example, when appropriate, we remove information that can identify you. Even with the safeguards we put in place, we cannot guarantee that your identity will never become known or someone may gain unauthorized access to your information. New methods may be created in the future that could make it possible to re-identify your specimens and data.

PAYMENT

Will you receive any type of payment for taking part in this study?

You will not receive any payment for taking part in this study.

REIMBURSEMENT

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

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

If your travel to the NIH Clinical Center (e.g. flight, hotel) is arranged and paid for by the NIH, the agency making the reservations and their representatives will have access to your identifiable information.

COSTS

Will taking part in this research study cost you anything?

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

- If some tests and procedures are performed outside the NIH Clinical Center, you may have to pay for these costs.

CONFLICT OF INTEREST (COI)

The National Institutes of Health (NIH) reviews NIH staff researchers at least yearly for conflicts of interest. This process is detailed in a COI Guide. You may ask your research team for a copy of the COI Guide or for more information. Members of the research team who do not work for NIH are expected to follow these guidelines or the guidelines of their home institution, but they do not need to report their personal finances to the NIH.

The NIH and the research team for this study are using KK-LC-1 TCR Transduced PBL developed by Center for Cancer Research through a joint study with your study team and the company. This means it is possible that the results of this study could lead to payments to NIH. By law, the government is required to share such payments with the employee inventors. You will not receive any money from the development of KK-LC-1 TCR Transduced PBL.

The company also provides financial support for this study.

CLINICAL TRIAL REGISTRATION AND RESULTS REPORTING

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

CONFIDENTIALITY PROTECTIONS PROVIDED IN THIS STUDY

Will your medical information be kept private?

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

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

The researchers conducting this study and the NIH follow applicable laws and policies to keep your identifying information private to the extent possible. However, there is always a chance that, despite our best efforts, your identity and/or information about your participation in this research may be inadvertently released or improperly accessed by unauthorized persons.

In most cases, the NIH will not release any identifiable information collected about you without your written permission. However, your information may be shared as described in the section of this document on sharing of specimens and data, and as further outlined in the following sections.

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

Certificate of Confidentiality

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

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

The Certificate does not protect your information when it:

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

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

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

Privacy Act

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

involved in a lawsuit. However, NIH will only release information from your medical record if it is permitted by both the Certificate of Confidentiality and the Privacy Act.

RESEARCH-RELATED INJURIES

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

PROBLEMS OR QUESTIONS

If you have any problems or questions about this study, or about your rights as a research participant, or about any research-related injury, contact the Principal Investigator, Scott Norberg, DO, scott.norberg@nih.gov, 301-275-9668. You may also call the NIH Clinical Center Patient Representative at 301-496-2626, or the NIH Office of IRB Operations at 301-402-3713, if you have a research-related complaint or concern.

CONSENT DOCUMENT

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

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

Signature of Research Participant	Print Name of Research Participant	Date

Investigator:

Signature of Investigator	Print Name of Investigator	Date

Witness should sign below if either:

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

Signature of Witness	Print Name of Witness	Date

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

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

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