PRINCIPAL INVESTIGATOR: James C. Yang, M.D.

STUDY TITLE: A Phase I/II Study Administering Peripheral Blood Lymphocytes Transduced with a Murine T-Cell Receptor Recognizing the G12D Variant of Mutated RAS in HLA-A*11:01 Patients

STUDY SITE: NIH Clinical Center (CC)

Cohort: Affected Patients

Consent Version: 06/13/2024

WHO DO YOU CONTACT ABOUT THIS STUDY?

James C. Yang, M.D. by phone at 240-760-6223 or email: JamesYang@mail.nih.gov

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

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

If the individual being asked to participate in this research study is not able to give consent to be in this study, you are being asked to give permission for this person as their decision-maker. The term "you" refers to you as the decision-maker and/or the individual being asked to participate in this research, throughout the remainder of this document.

IT IS YOUR CHOICE TO TAKE PART IN THE STUDY

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

WHY IS THIS STUDY BEING DONE?

We have developed an experimental therapy that involves taking white blood cells called lymphocytes from you, selecting a specific type of white blood cell to grow in the laboratory in large numbers, genetically modifying these specific cells using a type of virus (called a retrovirus), and then giving the cells back to you. By modifying the cells in this way, we hope to give them the ability to attack tumor cells. This type of therapy is called gene transfer. In this study, we are changing your white blood cells with a retrovirus to put in the gene for a specific anti-cancer

receptor called anti-KRAS G12D mTCR. KRAS G12D is a mutated protein in certain cancers including yours, and that is what is being targeted. We have given other cells modified with similar genes to patients with other types of cancer, but this is the first time we have investigated this gene therapy in several different cancers. Our laboratory studies show that these tumor-fighting cells work much like the cells we have given to patients in the past and should be just as safe, but as this is the first time these cells have been given to humans, we cannot predict all the side effects that may occur. Although mutated KRAS should only be present in cancerous tissues in your body, we cannot be certain that this receptor will not unpredictably react with any other similar tissue in the body and cause toxicity.

The first few patients enrolled will participate in the Phase I portion of the study, called the "dose escalation" phase. The purpose of dose escalation is to determine the highest dose of anti-KRAS G12D mTCR cells to give safely. There will be 7 dose levels of anti-KRAS G12D mTCR cells. The first patients enrolled get the smallest dose and the dose is increased when a level has been determined to be safe. If the first dose has too many side effects, patients enrolled may receive smaller doses. Once the maximum safe dose has been determined in the Phase I portion of this study, patients will be enrolled at the safe dose in the Phase II portion of the study. Discuss with your doctor which dose of anti-KRAS G12D mTCR cells you will be receiving.

Before receiving the anti-KRAS G12D mTCR cells, you will receive two 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 tumor-fighting cells stay alive longer. The purpose of this study is to see if these experimental anti-KRAS G12D mTCR cells can cause tumors to shrink, and to evaluate the safety and side effects of this treatment.

WHY ARE YOU BEING ASKED TO TAKE PART IN THIS STUDY?

You are being asked to participate in this study because you have been diagnosed with cancer that has a molecule on the surface of the tumors that can be recognized by the anti-KRAS G12D mTCR cells.

HOW MANY PEOPLE WILL TAKE PART IN THIS STUDY?

Up to 70 patients will be enrolled on this study.

DESCRIPTION OF RESEARCH STUDY

What will happen if you take part in this research study?

This study has several stages outlined below:

- Part of Stage 1 is performed under the screening protocol, 99C0128 (Evaluation for NCI Surgery Branch Clinical Research Protocols), to which you have already enrolled.
- Stages 1-2 are performed under the cell harvest protocol, 03C0277 (Cell Harvest and Preparation for Surgery Branch Adoptive Cell Therapy Protocols), to which you have already enrolled.
- Stages 3-7 are performed under this protocol.

Stage	Timeframe	Location	Comments & Instructions
1. Work-up	1-4 weeks	Inpatient and/or outpatient	Scans, x-rays, blood tests, and other tests as needed.
2. Leukapheresis	6-12 weeks	Outpatient then Home	Procedure will take 4-6 hours to complete.
3. Cell manufacturing	3 weeks	Home	
4. Chemotherapy (Days -7 to -3)	5 days	Inpatient	Receive IV chemotherapy to prepare your immune system for the cells.
5. Cells and aldesleukin (Days 0 to 3)	1-4 days	Inpatient and possibly ICU	Receive the anti-KRAS G12D mTCR cells IV, and then high-dose aldesleukin about every 8 hours for up to 9 doses.
6. Recovery	1-3 weeks	Inpatient	Recover from the effects of treatment.
7. Follow-up	Ongoing until disease progression	Outpatient	Return to clinic for physical exam, review of side effects, labs, and scans approximately 6 and 12 weeks following treatment, and then every 3 months x3, every 6 months for 2 years, and then as determined by your study doctor.

Before you Begin the Study

Before you begin the study, you will have had several tests performed to check whether the study is suitable for you. These will be done on another study before you can sign the informed consent document for this study. This is called screening. Your doctor will review your medical history and the drugs that you are currently taking as well as the previous treatments of your disease to determine whether you can participate in this study.

Some of these tests or procedures are part of regular care and may be done even if you are not being considered to join the study. If you have had some of these tests or procedures recently, they may or may not have to be repeated.

A. Cell Harvest and Growth

You underwent a process called “apheresis” while enrolled on protocol 03C0277. This process obtained certain types of blood cells from you. Some of these cells will be grown in the lab and genetically modified to recognize mutated KRAS on your tumor cells. If your cells do not grow, unfortunately you will not be able to receive the cell infusion. If that happens, we will look for an alternative experimental treatment at the NIH Clinical Center or refer you to the care of your referring physician. We usually know after about 4 weeks whether the cells will grow well enough to be used as an experimental treatment on this protocol. At the time we determine that your cells are not growing, we will inform you and discuss your options with you. **Several medications are**

used during the preparation of your cell product, be sure to tell your doctor if you are allergic to any antibiotics.

B. Central Venous Catheter Insertion

Prior to beginning the experimental treatment, you will have an intravenous (IV) catheter placed in your upper chest into a large vein. The area will be numbed with an anesthetic before the catheter is put in. Although rare, putting these catheters in can sometimes cause collapse of a lung or cause bleeding. Lung collapse is treated by putting a tube into your chest for a few days to allow your lungs 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.

During the Study

Similar to the tests done at the beginning of the study, the following will be repeated during the study to see how you are doing and how the cancer may be responding to treatment:

- Your medical history, any current or previous medications (prescription, supplement, and over-the-counter medicines), will be reviewed.
- A complete physical examination will be performed that will include your vital signs (blood pressure, pulse, body temperature, and respiratory rate) and recording your weight: before starting treatment and throughout treatment as needed.
- HIV Testing: As part of your study, we will test you for infection with the human immunodeficiency virus (HIV), the virus that causes AIDS. If you are infected with HIV, you will not be able to take part in this study. We will tell you what the results mean, how to find care, how to avoid infecting others, how we report HIV infections, and the importance of informing your partners at possible risk because of your HIV infection.
- Hepatitis B and C Testing: As part of your study, we will test you for infection with Hepatitis B and C. We will tell you what the results mean and how to find care. There may be some trials that you may not be able to participate in if you test positive for Hepatitis B and/ or C.
- Cytomegalovirus (CMV), Herpes Simplex Virus (HSV), Varicella Zoster Virus (VZV) and Epstein-Barr Virus (EBV) Testing: As part of this study, we will test you for these viruses. We will tell you what the results mean and how to find care if needed and how they may affect your participation in this study. You may need to take medicine such as Valtrex, an anti-viral, to prevent any type of herpes simplex virus.
- An evaluation of your ability to carry out daily activities: before and after treatment.
- Routine blood and urine samples will be collected: before starting treatment, during treatment and hospitalization, and during follow-up to measure:
    - your liver, kidney, and thyroid function, red and white blood cells, platelet counts, electrolytes and other blood values;
    - how well your blood clots;

- routine tests will be done in patients with your type of cancer to check the status of your disease.

The most amount of blood to be drawn during any study visit/cycle is expected to be about 8 tablespoons. This includes testing for standard of care tests (i.e., complete blood counts) as well as blood for research.

- For women who can have children, a pregnancy test will be done before starting treatment (urine or blood sample). You will not be able to participate if you are pregnant or breast feeding because we do not know how this medicine would affect your baby or your unborn child.
- An electrocardiogram (EKG) will be done to check the electrical activity of your heart. An electrocardiogram (EKG) is a test that is performed while you lie still for about 5 minutes. It involves placing electrodes (small stickers that are attached to wires that go to the machine) on the chest and arms/legs and recording the electrical activity of your heart. If you have a lot of hair on your chest, it may hurt a little bit when they remove these stickers.
- Scans

  CT, also called Computerized Tomography or Computerized Axial Tomography (CAT), also allows the doctor to view the organs inside your body in small sections. It can be done from different angles and allows a three-dimensional picture of the part of the body being studied. It may be done with or without contrast and may take between 30-90 minutes.

  MRI, also known as Magnetic Resonance Imaging, is a scan that allows the doctor to view parts of the body in small section views, so they can look closely at each part of the body. It does not use any radiation and can be done with or without contrast, called gadolinium, which is a dye-like material that helps make the picture clearer. Since the MRI uses large magnets to put the cells in a position so they can be seen more clearly, you must remove anything that is metal before having this test. This test takes between 35-50 minutes to complete and is entirely painless.

  PET, also called Positron Emission Tomography, which is a type of nuclear medicine scan, lets the doctor see the cell's activity in specific tissues of the body. It requires that you be given an intravenous (IV) fluid on which we have attached a radioactive particle that allows the fluid to be seen with a special gamma camera (usually a type of sugar fluid called fluorodeoxyglucose or FDG). The sugar fluid goes to cells that are most active, like cancer cells, and allows the doctors to see if you have a tumor.

  X-rays are single pictures taken of a body part by passing the X-rays through the body area. X-rays provide detailed information about bones but are not as good as CT or MRI scans for imaging other tissues or organs. Most X-rays only take a few minutes.

- Leukapheresis

  Leukapheresis, a specific type of "apheresis", is a procedure that allows us to remove certain types of blood cells from you and return the rest of your blood. It is a very common procedure that is done routinely here at the NIH with very few risks. During leukapheresis, blood is removed from you through a needle in your arm, circulated through a machine that divides whole blood into red cells, plasma (the liquid component of blood), and

lymphocytes (or white cells), and then the plasma and red cells are returned to you through a second needle in your other arm (or this might be done using a catheter if necessary). The white blood cells collected before treatment may be used to help grow the tumor-fighting cells. In addition to the leukapheresis you will undergo as part of your work-up, we will also ask you to undergo one additional apheresis procedure between 4 and 8 weeks after you receive the cell infusion to see the impact of this therapy on your immune system and see if the cells we gave you are still active.

The leukapheresis procedure takes between 3-6 hours to complete. Rarely, people may experience lightheadedness or dizziness. We ask that you eat prior to the procedure to prevent this.

A. Chemotherapy Regimen (Day -7 through Day -3)

After we have grown the anti-KRAS G12D mTCR 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 anti-KRAS G12D mTCR 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 for a short period of time. The main purpose of the chemotherapy is to see if we can help the cells be more effective in fighting cancer tumors. Animal experiments have indicated that chemotherapy can make the infused cells more effective in fighting cancer, but it is not known whether this is true in humans. The cyclophosphamide will be given into your catheter over one hour for two days (Day -7 and Day -6) and the fludarabine will be given approximately one to two hours after the cyclophosphamide into your catheter over 30 minutes for five days (Day -7 through Day -3). The side effects of these medicines are described on the following pages.

B. Cell Infusion and Aldesleukin (IL-2) Regimen (Day 0 through Day 3)

Two to four days after the last dose of chemotherapy, you will be given the anti-KRAS G12D mTCR cells. The anti-KRAS G12D mTCR cells will be given in your intravenous catheter over approximately 30 minutes. Within 24 hours after the anti-KRAS G12D mTCR cell infusion, you will be given high-dose aldesleukin through your intravenous catheter. Aldesleukin is approved by the FDA for treatment of metastatic melanoma and metastatic renal cell cancer. The purpose of giving aldesleukin with this therapy is to keep the cells we give you active for as long as possible so they will fight your tumor. Aldesleukin will be given as a 15-minute infusion approximately every 8 hours for up to three days after the cell infusion (maximum number of doses is 9). Doses may be skipped or delayed depending on how well you tolerate the infusion. The risks of the cells and aldesleukin are described on the following pages.

One day after you receive the anti-KRAS G12D mTCR cells, we may give you G-CSF (filgrastim) as a shot or injection under the skin to stimulate your blood cells until they increase to a sufficient number. This will continue until your white blood cell counts begin to return to normal.

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 Treatment

A. Recovery

You will recover in the hospital until you are well enough to go home. This usually takes 7-21 days after you have received the cells or your last dose of aldesleukin; however, you may need to stay in the hospital for longer than this before you are well enough to go home. We will continue to give you support 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 collect blood to study the effects of this regimen on your immune system. Between 1-11 teaspoons may be collected on a single day. 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.

B. Follow-up and Evaluation of Experimental Regimen

You will need to continue taking Bactrim (or equivalent), an antibiotic, for at least 6 months following your treatment to prevent you from catching a certain type of pneumonia seen in patients who have low white blood cell counts. You may also need to take Valtrex, an anti-viral, for at least 6 months following your treatment to prevent any type of herpes simplex virus, like shingles.

After you are discharged, we will ask you to return to the NIH Clinical Center approximately 6 weeks and 12 weeks following treatment, and then if you are responding to the treatment, every 3 months x3, then every 6 months for 2 years, and then as determined by your physician. The follow-up visits will probably take 1-2 days. At each visit, you will have lab tests, imaging studies (i.e., CT, MRI, PET scans), and a physical examination. At some of your follow-up visits, you may undergo leukapheresis or have about 12 tubes of blood drawn (6.5 tablespoons) so that we can see the effect this therapy has had on your immune system and if the cells we gave you are still alive. If you are unwilling or unable to travel to the NIH Clinical Center, we will contact you by phone or email and we may ask you to send us lab, imaging, and physical exam reports from your local physician. 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.

Gene Therapy Long-Term Follow-up (Retroviral Vectors)

Because we do not know the long-term side effects of gene therapy, we will collect your blood over the next several years, frequently at first and then less frequently. If you return to your referring physician after treatment here, we will ask you to have your physician send your blood specimens here for this testing. This testing will determine if the cells have grown or changed in your body. We will test your blood immediately after you receive the cells, and then at 3, 6, and 12 months (approximately 8-10 teaspoons each time) after cell administration. If all the tests are normal and show no change, we may not need to continue to collect your blood every year. Your study team will discuss this with you.

According to FDA requirements, you need to have a physical examination for five years after you receive the cells. It is preferred that you return to the NIH Clinical Center for these appointments. If you cannot return, then copies of your medical records will need to be sent from your healthcare provider. Information will also be obtained from you via phone/ email and added to your medical

record. After that time, we will be calling you to get information regarding your health for the next ten years, for a total follow-up time-period of 15 years. For this reason, we ask that you continue to provide us with a current address and telephone number, even after you complete this research study. At the time of your death, no matter the cause, we may request permission for an autopsy in order to obtain vital information concerning the safety of this experimental treatment approach. Please discuss this with your family to inform them of the possibility of this request. These long-term follow-up evaluations will be conducted under the long-term follow-up protocol, 09C0161 (Follow-up Protocol for Subjects Previously Enrolled on NCI Surgery Branch Studies), to which you will be enrolled following treatment.

RISKS OR DISCOMFORTS OF PARTICIPATION

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

The risks and discomforts of this research study can be significant. This experimental treatment can lead to a long-term decrease in your immune function; for example, you may be more likely to get infections including certain viral infections like shingles. 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, blood and platelet 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. You should talk to your study doctor about any symptoms that you experience while taking part in the study.

You may experience side effects that we do not expect that may cause your condition to worsen. Any new information that becomes available during the course of this study will be shared with you.

A. Risks from Blood Collection

The amount of blood to be drawn at any one visit is up to about 8 tablespoons. This includes testing for standard of care tests (i.e., complete blood counts) as well as blood for research. The maximum amount of blood for research is approximately 11 tablespoons over 8 weeks.

Each time a blood sample is needed, a needle will be put into a vein in your arm (or into your central venous catheter, if you have one). You may feel pain when the needle goes through the skin. Other side effects associated with drawing your blood for blood tests may include infection, bruising, redness, discomfort, or bleeding at the site of the needle stick, and possible lightheadedness and fainting.

B. Risks from Leukapheresis

The risks of apheresis are similar to whole blood donation and include pain and bruising at the needle insertion site in the arms, lightheadedness, dizziness, nausea, and rarely fainting due to a rare reflex reaction to needle placement and to the temporary decrease in blood volume during apheresis. You may also feel tingling around your mouth or in your fingers caused by a blood thinner given during the procedure. The nurses will give you a calcium containing antacid to chew to reduce the tingling. All the symptoms usually go away within a few minutes of stopping the

procedure. We ask that you eat a meal before coming to donate, and avoid caffeine, to prevent lightheadedness or dizziness that might occur. You will be asked to remain in the chair/bed for a few minutes after the donation is completed, and to sit down and relax for about 15 minutes after the donation. This is done so that staff can observe you to make sure that you feel entirely well before you leave our department.

C. IV Catheter Insertion

A non-tunneled central catheter is a soft tube a doctor puts into a vein in your arm or in a vein leading to your heart. It is a way to take blood samples or give you fluids, medicines, or nutrients over a long period of time. Possible side effects include pain, bleeding, bruising, and, on rare occasions, swelling in your arm, chest, neck, or face on the same side as your catheter or infection.

D. EKG

Other than possibly experiencing some minor skin irritation from the electrodes there are no anticipated risks.

E. Photography

There are no known risks to having photographs of your skin lesions. Any identifying features, such as your face, will not be included in the photographs.

F. Urine Collection

There are no known physical risks of collecting urine.

G. Risks Due to Cell Infusion (Gene Transfer)

The receptor against cancer we put into your cells is introduced with a type of virus called a retrovirus. Although this retrovirus has been made non-contagious, there is the rare possibility that it could cause an infection. The cells could also cause you to develop another type of cancer, such as leukemia or lymphoma, although this has not yet been seen in trials similar to this one. These specific gene-modified cells have not been given to patients and thus we do not have information about their side effects, although we do have information about similar gene-modified cells.

Potential risks include:

- Fever, chills, and shortness of breath, which may last for a few hours (common)
- Lung congestion causing shortness of breath
- Flu-like symptoms, and fluid retention (common)
- Severe reaction to the cells which would include very low blood pressure and damage to your heart, lung, and/or kidneys
- Severe diarrhea, which could lead to hospitalization

H. 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. The gene therapy was done on the bone marrow of these children and similar problems have not been seen when the blood was used (as it will be for you). We will monitor you for this risk as described above (*Gene Therapy Long-Term Follow-up* section), under protocol 09C0161.

I. Aldesleukin (IL-2)

When aldesleukin is given through an intravenous catheter, it can make you feel like you have the flu. It can also cause confusion and mental status changes making you unable to make sound decisions. Prior to beginning treatment, we will ask you to complete a Durable Power of Attorney so that a person of your choosing can make health care decisions for you in case you develop these side effects. In our experience giving aldesleukin to over 2,000 patients, we have found that these side effects go away within a few days of stopping the aldesleukin.

COMMON, SOME MAY BE SERIOUS In 100 people receiving aldesleukin, more than 20 and up to 100 may have:
• Fever • Chills • General feeling of discomfort • Fatigue • Low blood pressure • Abnormal heart rate • Swelling in the hands, feet, ankles, legs • Diarrhea • Vomiting • Nausea • Inflammation of the mouth and lips • Loss of appetite • Confusion • Drowsiness • Difficult breathing • Collection of liquid in the lungs • Rash • Itching • Low blood counts • High liver and kidneys enzymes level in blood • Kidney problems

OCCASIONAL, SOME MAY BE SERIOUS In 100 people receiving aldesleukin, from 4 to 20 may have:
• Infection • Pain • Abdominal pain • Abdomen enlarged • High blood pressure • fluctuations in blood pressure • Weight gain • Accumulation of carbon dioxide in the blood • Low magnesium level in blood • Low calcium level in blood • Dizziness • Anxiety • Cough • Rhinitis • Peeling of the skin over large areas of the body

RARE, AND SERIOUS In 100 people receiving aldesleukin, 3 or fewer may have:
• Getting worse of pre-existing autoimmune disease • Leaking of fluid out of tiny blood vessels into surrounding tissues • Anaphylaxis (severe, potentially life-threatening allergic reaction) • High level of several kinds of blood cells • Overactive thyroid • Diseases of the heart muscle • Damage to the stomach and colon lining • Death of tissue near injection site • Hepatitis (liver disease) • Gallbladder problems • Disease of muscles • Brain lesions • Altered mental state

RARE, AND SERIOUS In 100 people receiving aldesleukin, 3 or fewer may have:
• Stabbing, burning, and often severe pain due to an irritated or damaged nerve • Insomnia • Internal loss of blood that can cause death • Stupor, coma • Heart problems that can cause sudden death • Headache, paranoid reaction, psychosis • Blood clotting problems • Kidney failure • Blindness (transient or permanent)

J. Cyclophosphamide

COMMON, SOME MAY BE SERIOUS
• Fever • Infection, especially when white blood cell count is low • Anemia which may cause tiredness, or may require transfusion • Bruising, bleeding • Blood in urine • Nausea, vomiting, diarrhea, loss of appetite, pain in belly • Sores in mouth which may cause difficulty swallowing • Absence of menstrual period which may decrease the ability to have children • Hair loss, skin changes, rash, change in nails • Blurred vision, vision changes

OCCASIONAL, SOME MAY BE SERIOUS
• 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

RARE, AND SERIOUS
• 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

RARE, AND SERIOUS
• 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 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 • Severe skin rash with blisters and peeling which can involve mouth and other parts of the body. • 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 heart to be fast or irregular resulting in a pounding or racing heart, dizziness, weakness, feeling light-headed or shortness of breath. • 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.

K. Fludarabine

COMMON, SOME MAY BE SERIOUS In 100 people receiving fludarabine, more than 20 and up to 100 may have:
• Infection, especially when white blood cell count is low • Vomiting, loss of appetite • Tiredness, fever • Pain • Bruising, bleeding • Cough • Increased risk of unusual infections lasting more than 6 months

OCCASIONAL, SOME MAY BE SERIOUS In 100 people receiving fludarabine, from 4 to 20 may have:
• Anemia, kidney problems which may cause tiredness, bruising, or swelling

OCCASIONAL, SOME MAY BE SERIOUS In 100 people receiving fludarabine, from 4 to 20 may have:
• Nausea, chills • Feeling of "pins and needles" in arms and legs • Damage to organs (brain, lungs, others) which may cause tiredness, changes in thinking or shortness of breath • Confusion

RARE, AND SERIOUS In 100 people receiving fludarabine, 3 or fewer may have:
• Kidney damage which may require dialysis

Risks from Scans and Radiation

X-rays, CT, MRI, and PET scans are common standard imaging tests used in the diagnosis of cancer. The most common discomfort is the length of time a patient must lay still during a scan. Occasionally, a patient may become uncomfortable with the closed space of the machines, particularly the MRI. If this occurs, your doctor can order a medicine to help you relax during this scan. If a contrast agent (the special dye) is given with the scan, there is a small risk of having a reaction to the contrast. In that small group of patients who have a reaction, the most common symptoms are nausea, pain in the vein where the contrast was given, a metallic or bitter taste in the mouth, and a warm or flushing feeling that lasts from 1-3 minutes. Rarely do these symptoms require any treatment. In very rare cases, people have had severe reactions that affect their breathing and heart rhythm. If you have had a reaction in the past, be sure to tell you doctor or nurse about it.

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.

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.

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

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

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

Radiation risk from all scans: During your participation in this treatment study, you will be exposed to radiation from X-rays, CT, and PET scans. The amount of radiation exposure you will receive from these procedures is equal to approximately 6.11 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 X-rays, CT, and PET scans that you get in this study will expose you to roughly the same amount of radiation as approximately 20 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 0.6 out of 100 (0.6%) and of getting a fatal cancer is 0.3 out of 100 (0.3%).

You may not participate in this study if you are pregnant. If you are able to become pregnant, we will perform a pregnancy test before exposing you to radiation. You must tell us if you may have become pregnant within the previous 14 days because the pregnancy test is unreliable during that time.

What are the risks related to pregnancy?

If you are a woman who is breastfeeding or pregnant, you may not take part in the study because we do not know how this medicine would affect your baby or your unborn child. If you are a woman who can become pregnant or are the partner of a woman who can become pregnant, you will need to practice an effective form of birth control before starting study treatment, during study treatment, and for up to 12 months if you are a woman who can become pregnant or for 4 months after you finish treatment if you are a man with a partner who can become pregnant. In addition, men should not donate sperm during this time-period. If you think that you or your partner is pregnant, you should tell your study doctor or nurse as soon as possible.

Effective forms of birth control include:

- Abstinence
- Intrauterine device (IUD)
- Hormonal [birth control pills, injections, or implants]
- Tubal ligation
- Vasectomy

POTENTIAL BENEFITS OF PARTICIPATION

Are there benefits to taking part in this study?

The aim of this study is to see if this experimental treatment will cause your tumors to shrink. We do not know if you will receive personal, medical benefit from taking part in this study. These potential benefits could include shrinking of your tumor or lessening of your symptoms, such as pain, that are caused by the cancer. Because there is not much information about the effect of this treatment on cancer, we do not know if you will benefit from taking part in this study, although the knowledge gained from this study may help others in the future who have cancer.

ALTERNATIVE APPROACHES OR TREATMENTS

What other choices do I have if I do not take part in this study?

Instead of being in this study, you have the following options:

- Taking part in another study
- Getting treatment or care for your cancer without being in a study
- Getting no treatment or getting comfort care, which is also called palliative care. This type of care helps reduce pain, tiredness, appetite problems, and other problems caused by cancer. It does not treat the cancer directly, but instead tries to improve how you feel. Comfort care tries to keep you as active and comfortable as possible.

Please talk to your doctor about these and other options.

STOPPING THERAPY

Your doctor may decide to stop your therapy if:

- He/she believes that it is in your best interest
- Your disease comes back during treatment
- You become pregnant
- You experience side effects from the treatment that your doctor thinks are too severe
- New information shows that another treatment would be better for you

In this case, you will be informed of the reason for the decision to take you off the study.

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 refuse to participate, withdraw from the protocol, or at the completion of the protocol, we will attempt to offer you participation in other NIH protocols if these are available, or will refer you to your home physician for further management.

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 the Sponsor. If you withdraw your consent and leave the trial, any samples of yours that have been obtained for the study and stored at the NCI can be destroyed upon request. However, any samples and data generated from the samples that have already been distributed to other researchers or placed in the research databases cannot be recalled and destroyed.

You should understand that this study involves research and that your participation is voluntary. Unexpected or unforeseeable side effects may also occur. Your participation in this protocol may be terminated without your consent if your physician feels it would not be safe for you to continue. Any significant new findings that relate to this protocol will be discussed with you.

USE OF SPECIMENS AND DATA FOR FUTURE RESEARCH

Blood and tissue collected during the course of this study will be used for future research and will be stored, tracked, and disposed of under protocol 03C0277.

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

We plan to keep some of your specimens and data that we collect and use them for future research and share them with other researchers. We will not contact you to ask about each of these future uses. These specimens and data will be stripped of identifiers such as name, address, or account number, so that they may be used for future research on any topic and shared broadly for research purposes. Your specimens and data will be used for research purposes only and will not benefit

you. It is also possible that the stored specimens and data may never be used. Results of research done on your specimens and data will not be available to you or your doctor. It might help people who have cancer and other diseases in the future.

If you do not want your stored specimens and data used for future research, please contact us in writing and let us know that you do not want us to use your specimens and/or data. Then any specimens that have not already been used or shared will be destroyed and your data will not be used for future research. However, it may not be possible to withdraw or delete materials or data once they have been shared with other researchers.

COMPENSATION, REIMBURSEMENT, AND PAYMENT

Will you receive compensation for participation in the study?

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

You will not receive compensation for participation in this study.

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

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

On this study, the NCI will cover the cost for some of your expenses. Some of these costs may be paid directly by the NIH and some may be reimbursed after you have paid. Someone will work with you to provide more information.

Will taking part in this research study cost you anything?

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

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

CONFLICT OF INTEREST (COI)

The 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, but they do not need to report their personal finances to the NIH.

The NIH and the research team for this study have developed the anti-KRAS G12D mTCR being used in this study. 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 anti-KRAS G12D mTCR.

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)

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

POLICY REGARDING 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, James C. Yang, M.D., JamesYang@mail.nih.gov, 240-760-6223. You may also call the NIH Clinical Center Patient Representative at 301-496-2626, or the NIH Office of IRB Operations at 301-402-3713, if you have a research-related complaint or concern.

CONSENT DOCUMENT

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

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

Signature of Research Participant	Print Name of Research Participant	Date

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

Signature of LAR	Print Name of LAR	Date

Investigator:

Signature of Investigator	Print Name of Investigator	Date

Witness should sign below if either:

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

Signature of Witness*	Print Name of Witness	Date

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

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

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