INSTITUTE: National Cancer Institute

STUDY NUMBER: 14-C-0168 PRINCIPAL INVESTIGATOR: James N. Kochenderfer, M.D.

STUDY TITLE: A Phase I Clinical Trial of T-Cells Targeting B-Cell Maturation Antigen for Previously Treated Multiple Myeloma

Continuing Review Approved by the IRB on 12/17/18
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Standard

INTRODUCTION

We invite you to take part in a research study at the National Institutes of Health (NIH).

First, we want you to know that:

Taking part in NIH research is entirely voluntary**.**

You may choose not to take part, or you may withdraw from the study at any time. In either case, you will not lose any benefits to which you are otherwise entitled. However, to receive care at the NIH, you must be taking part in a study or be under evaluation for study participation.

You may receive no benefit from taking part. The research may give us knowledge that may help people in the future.

Second, 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). If you have such beliefs, please discuss them with your NIH doctors or research team before you agree to the study.

Now we will describe this research study. Before you decide to take part, please take as much time as you need to ask any questions and discuss this study with anyone at NIH, or with family, friends or your personal physician or other health professional.

Why is this study being done?

The immune system plays many important roles in the body such as helping the body fight infections. The immune system is also known to affect cancer cells. “T” lymphocytes, or T cells, are a type of white blood cell and a major component of the immune system. T cells have been shown to be capable of recognizing and destroying a number of different cancers. Unfortunately, most cancers have developed ways of escaping the monitoring by the immune system for foreign or abnormal cells and continue to grow in an uncontrolled manner. Thus, we are looking at ways to manipulate the immune system, in particular the T cell component, so that it will more efficiently recognize and kill tumor cells. We have developed an experimental procedure for patients with

multiple myeloma that progressing despite standard therapies. This procedure uses your own blood cells. Specifically, it uses your own T cells which are manipulated in a research lab and then given back to you. The purpose of this study is to see if it is safe to administer these T cells to people with multiple myeloma. This T cell therapy is a type of "gene therapy" and is very closely monitored by the Food and Drug Administration (FDA) and other regulatory agencies. The risks of gene therapy will be described later in this document.

Why are you being asked to take part in this study?

You have been diagnosed with multiple myeloma that has not been controlled with standard therapies, meaning that the cancer cells are growing despite your prior treatments or, if you did achieve a remission, the cancer has recurred after your most recent treatment. Treatment for multiple myeloma that persists after standard therapies is primarily aimed at improving quality and perhaps length of life because multiple myeloma is almost never curable. Unfortunately, multiple myeloma usually develops resistance to standard treatment options and ultimately becomes completely resistant to conventional therapies. Thus, there is a need to find new approaches for the treatment of multiple myeloma.

How many people will take part in this study?

Up to 30 patients will take part in this research study.

Description of Research Study

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

Before you begin the study

You will need to have the following exams, tests or procedures to find out if you can be in the study. These exams, tests or procedures are part of regular cancer care and may be done even if you do not join the study. However, there are some extra exams, tests and procedures that you will need to have if you take part in this study. If you have had some of them recently, they may not need to be repeated.
These tests include:

- Physical examination
- Routine blood and urine tests
- Blood tests for viruses and other disease causing organisms
- Echocardiogram and EKG of your heart
- Bone marrow biopsy
- CT scan (chest, abdomen and pelvis) or PET scan, MRI of your head, and skeletal survey

During the study

First, you will undergo an apheresis procedure that will remove cells from your blood. Apheresis is a procedure for obtaining certain blood cells, such as white blood cells, without removing most blood cells. It is a process persons undergo when giving routine platelet donations.

Next, we will manipulate your cells in a laboratory so that they are capable of recognizing your multiple myeloma. Specifically, we will genetically modify your T cells and grow them in the laboratory. We hope that these T cells will decrease the amount of cancer you have. However, it is possible that these cells will not have this effect. We will be using a type of virus (retrovirus) that encodes a gene for an anti-B-cell maturation antigen (BCMA) receptor in making these anti-BCMA T cells. Your multiple myeloma cells express the BCMA protein on their surface. Multiple myeloma is a cancer of plasma cells. Normal plasma cells make antibodies, which play a role in fighting infections. Normal plasma cells also express the BCMA protein. This BCMA protein will serve as a target for the anti-BCMA T cells.

This study will be conducted as a "dose escalation". The purpose of dose escalation is to determine the safe dose of anti-BCMA T cells. There are four dose levels of anti-BCMA T cells, but accrual has finished on the first 3 dose levels. The first patients enrolled get the smallest dose and the dose is increased when a level has been determined to be safe. You can discuss this with the study doctors to find out which dose of anti-BCMA T cells you will be receiving.

After you have had cells removed from your blood, you will receive 2 FDA approved drugs (chemotherapy) named cyclophosphamide and fludarabine, over a period of 3 days. The purpose of the chemotherapy is to enhance the activity of the anti-BCMA T cells. This is a standard chemotherapy regimen that is often used to treat certain types of leukemia. The chemotherapy can be administered on an outpatient basis, which means hospital admission is not necessary to receive this chemotherapy. If you have removed from the protocol BEFORE receiving any protocol therapy, you may be eligible for re-enrollment in the study.

Two days after the chemotherapy ends, you will be admitted to the hospital as an inpatient and receive the anti-BCMA T cells. The anti-BCMA T cells will be given to you as a single intravenous (IV) infusion. You will need to have a "central line", and IV catheter (or tube) placed in a large vein in your arm or chest for this infusion. If you have a catheter or a port-a-cath in place already, this could be used to receive the cell infusion. All patients that participate in this study will be required to stay in the hospital for close observation for at least 9 days after the cell infusion, and patients must stay within 60 minutes driving distance for 2 weeks after the cell infusion. This is because in our experience with similar treatments we have noticed side-effects including fevers, fatigue, low blood pressure, and others that have been most severe between 6 and 9 days after cell infusion.

You will be closely watched during the anti-BCMA cell infusion for signs of a reaction. While other types of genetically-modified T cells have been administered to many patients, infusion of anti-BCMA T cells is a new approach that is being evaluated in this protocol. There is always a

chance that we will not be able to genetically-modify your cells or be able to grow the cells in the laboratory. If we are not able to successfully prepare the minimal number of cells that we believe are needed to help control the tumor in our first attempt to produce the cells, we will make a second attempt to produce the cells if you give us permission to do so even if you have already received the chemotherapy part of the protocol at the time. This second attempt to produce cells will probably not be necessary.

For patients who still have disease after receiving anti-BCMA T cells the first time, repeated infusions might be possible. In order for a repeat infusion to be possible, you must not have experienced severe toxicities with their first infusion, and you must meet the original eligibility requirements for enrollment on the trial. Repeat treatments will also include the same chemotherapy as the first treatment.

When you are finished taking the drugs (treatment)

You will need to come for a clinic visit two weeks after your cell infusion, for blood work and a brief visit with one of our doctors. You will also need to return to clinic for evaluation of your overall health and your multiple myeloma 1, 2, 3, 4, 6, 9 and 12 months after the cell infusion.

After 12 months, follow up for patients with ongoing responses, which means the multiple myeloma has not progressed, will continue every 6 months for up to 5 years after your T-cell infusion. At the follow-up visits we will evaluate your general health, and we will assess your multiple myeloma. Blood will be drawn at all follow-up visits. Note that all of these follow-up visits are only required for patients with ongoing responses.

If your multiple myeloma progresses, you will be removed from the study to pursue other options. As long as your multiple myeloma does not progress, we ask that you do not take any other treatments. We also ask that you do not take any corticosteroid medications such as prednisone or dexamethasone. If you do take other treatments or if you take corticosteroids, we will not be able to interpret the results of the anti-BCMA T cells, and you will be removed from the study. You will also be followed by your home oncologist who will receive a detailed summary of your case and blood tests and other investigations that need to be performed and potential problems that may arise. We encourage early communication of any problems with us so that we can assist in deciding the best treatment approach.

Gene-therapy-specific follow-up

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. We can obtain the blood needed for these studies at your regular follow-up visits as long as you are on the study. If you are removed from the study, we still need to conduct these gene-therapy follow-up visits according to FDA regulations. If you return to your referring physician after receiving therapy here, we will ask you to have your physician send your blood specimens here for this testing, which will decrease the inconvenience to you. This testing will determine if the cells have grown or changed in your body. We will test your blood immediately before you receive the cells, and then at 3, 6, and 12

months. If all of the tests are normal and show no change, we will collect blood from you every year after that to store in case you develop symptoms later. According to FDA requirements, we need you to return annually to the NIH for a physical examination for five years after your receive the cells. After that time we will be sending you a questionnaire 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 therapy approach. Please discuss this request with your family to inform them of your wishes.

Birth Control

If you are a woman who is breast feeding or pregnant, you may not take part in the study because we don't know how this therapy 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 at least 6 months after you finish the last cell infusion. If the anti-BCMA T cells are still detected in your blood longer than 6 months after your treatment, your doctors will recommend that you not become pregnant until the anti-BCMA T cells are not detectable in your blood. If you think that you or your partner is pregnant, you should tell your study doctor or nurse at once. If you are a man, you should not donate sperm during the study treatment and for 4 months after you finish the last cell infusion.

Effective forms of birth control include:

- abstinence
- intrauterine device (IUD)
- hormonal [birth control pills, injections, or implants]
- tubal ligation
- vasectomy

Tests for Research

An important part of this study is testing the effects of this treatment on your tumor and immune system. The following blood samples and tests will be done while you participate in this study:

How will my samples and data be used?

This study aims to perform laboratory studies (research) to better understand how the immune system fights cancer cells and to make more effective cell treatments. We plan to keep some of

your specimens and data that we collect while you are participating on this study to use in our research labs.

We will use some of the samples we collect (blood, tissue) to perform a number of genetic tests. This includes RNA sequencing on your samples. The human genome is the material in our cells that includes thousands of genes. Genes are the building blocks of our cells that make and maintain our body. A gene provides instructions to individual cells to make proteins through a middle step of making RNA. Proteins are the substances that are involved in all of our body's chemical processes.

The purpose of RNA sequencing is to learn about the expression of different genes in your cancer cells and in your CAR T cells. Our goal is not to look into genetic abnormalities that could be inherited by you or passed along to your children, but in the course of studying gene expression, there is a slight chance that we could find evidence of an inherited disorder or a genetic disorder that could be passed along to your children. The slight possibility of this happening is covered below under "Incidental and Secondary Findings".

Incidental and Secondary Findings

Because we might accidentally collect a small amount of normal tissue when we sample your tumor, it is possible, but unlikely, that we could identify possible changes in your RNA that are not related to this research. These are known as "incidental medical findings".

- Genetic changes that are related to diseases
- Genetic changes that are not known to cause any disease
- Genetic changes that are new and of uncertain clinical importance. This means that we do not know if they could cause or contribute to a disease or if they are normal variations.

The analyses that we perform in our laboratory are for research purposes only; they are not nearly as sensitive as the tests that are performed in a laboratory that is certified to perform genetic testing. Changes that we observe unrelated to our research may or may not be valid. Therefore, we do not plan to inform you of the results of testing on your samples that is performed in our research lab. However, in the unlikely event that we discover a finding that is believed to be clinically important based on medical standards at the time we first analyze your results, we will contact you if you still remain on the study. This could be many years in the future. We will ask if you would like to meet with a credentialed genetic healthcare provider for genetics education and counseling (either in clinic or via phone conference). The NIH will offer to pay for confirmation of the incidental genetic finding. You will have an additional tube of blood drawn to verify the findings we have seen in our lab. If the results are verified, you will be re-contacted and offered a referral to a genetic healthcare provider to discuss the results.

It is possible that none of the studies described above in this section will be performed.

Storage and release of samples, genomic data, and health information

Portions of your samples, genomic data, and health information will be stored for an unlimited period of time to be used in future research.

Research blood samples

Blood will be drawn frequently during your treatment. Most of the blood draws will be to monitor your health during and after the cell infusion. In addition, some blood samples will be drawn for research purposes. Additional blood draws might be necessary to investigate T cell responses and serum cytokine levels in cases of clinical events such as rapid regressions of malignancy or toxicity. These samples will be used to study how your immune system is affected by the cell therapy. Some of the samples may be sent to investigators outside of the NIH for future research. In general, 4 tablespoons will be drawn at each clinic visit or every Monday, Wednesday, and Friday during the inpatient stay. On one occasion before the treatment a larger amount of blood (8 tablespoons) will be drawn. The NIH has set a limit on the maximum amount of blood that can be taken for research. This limit is based on your age. For adults, no more than 37 tablespoons can be taken over an 8-week period.

Bone Marrow Biopsies

Before you begin treatment on this protocol and at the time of the 2-month follow up appointment, bone marrow biopsies will be scheduled. Several patients have also required a bone marrow biopsy at the 1-month follow-up for clinical purposes. These biopsies are required for participation on the study to evaluate your tumor but also for research tests. A bone marrow biopsy will also be scheduled for the 6-month follow-up visit only for patients with ongoing responses.

Possible Additional Biopsies

In very rare instances, we may also ask your permission to perform an additional biopsy for research or clinical purposes. These additional biopsies could be bone marrow biopsies or biopsies of tumors that could be multiple myeloma. The tissue from this biopsy will be used for research purposes, to determine whether there is evidence of an immune response to the tumor or to determine if a newly discovered tumor is actually multiple myeloma. Any biopsies would only be performed with your permission, and if the biopsy is determined to be safe by the Principle Investigator of this trial and the additional physician or physicians that would actually perform the biopsy. Some of the samples may be used for other or future research conducted by the investigational team or other researchers. This future research might directly study malignancy of

the same type that you have, or it could focus on other areas of research. Your permission for this will be obtained at the time of the biopsy.

Risks or Discomforts of Participation

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

Because the BCMA protein is found on normal plasma cells as well as on your cancer, the anti-BCMA T cells might cause a fleeting or prolonged decrease in the number of normal plasma cells. A small number of B cells also express BCMA, so a slight decrease in B-cell counts might occur. Because plasma cells make antibodies that are involved in protection against infections, this decrease in plasma cell number might lead to a greater risk of infections because of low blood antibody levels. We do not know if a decrease in normal plasma cells will cause problems with infections and several steps can be taken to deal with an increased risk of infection or actual infections, such as giving antibodies intravenously, which is a standard treatment given to many patients with immune deficits.

The anti-BCMA T cells we will be giving you are exposed to a type of virus (retrovirus) in order to insert the anti-BCMA gene that gives the T cells the ability to recognize multiple myeloma. Although this retrovirus is not active, there is the rare possibility that it may cause infection. This has never happened to any of the hundreds of patients who received T cells that were modified with similar viruses. The anti-BCMA T cells could also cause you to develop another type of cancer in your blood cells, although we think this is very unlikely because it has never happened in the hundreds of patients who have received genetically-modified T cells.

Many patients have received similar cell infusions that are aimed at targets other than BCMA. In the studies that are most similar to this anti-BCMA T-cell study, patients have experienced a variety of side-effects. Most of these patients have developed fever and fatigue that can last for up to 2 weeks after cell infusion. Some patients that have received similar treatments have developed low blood pressure. In a minority of patients developing low blood pressure, a temporary decrease in kidney function also occurred. Several patients developed temporary confusion, headaches, or weakness. One patient developed severe, but temporary, muscle twitching. Three patients developed a temporary inability to speak, which resolved completely after a few days. One patient developed a temporary decrease in heart function. His heart function subsequently returned to normal levels. One patient developed tumor lysis syndrome, which is a release of toxic substances from tumor cells that are being destroyed. This tumor lysis syndrome was successfully treated and caused no long-term problems for the patient. Patients at risk of tumor lysis syndrome on the anti-BCMA T-cell study will receive medication to prevent this complication. Chemotherapy is part of this protocol. The chemotherapy part of this study can cause decreased blood count, nausea, and hair loss. The decreased blood counts due to chemotherapy can lead to infections and bleeding.

Potential risks of anti-BCMA T cells infusion include:

Likely:	**Less Likely:**	**Rare:**
• Fever • Chills • Fatigue • Low immunoglobulin levels	• Headache • General feeling of being unwell (malaise) • Temporary decreased kidney function • Temporary weakness or difficulty speaking • Low blood pressure • Tumor lysis syndrome (rapid breakdown of tumor that can cause side-effects) o Possible intensive care unit admission o Fast heart rate o Possible kidney damage that will most likely be temporary o Possible breathing problems that might in rare cases require mechanical ventilation (breathing machine) • Cytokine release syndrome (release of substances from T cells that can cause many side-effects) including o Fever o Fast heart rate o Low Blood Pressure o Possible intensive care unit admission o Rare cases, death. • Decreased cardiac function • Prolonged (a month or more) low blood counts including low white blood cells and platelets	• Muscle pain, twitching • Death • Permanent kidney damage • Other neurologic problems • Coma • Temporary liver damage • Extreme weakness of the arms and legs • Muscle damage • Long-term debilitation

There are no data available at this time to guide us in how humans might respond to this type of cell infusion. As this is a new experimental therapy, side effects that we do not anticipate that may cause your condition to worsen may be encountered.

You will be treated on this gene transfer protocol with a viral vector that was manufactured at the NCI Surgery Branch Vector Production Facility before May 2016. An internal review of the facility that made the vector for this protocol determined that the facility needed to be closed due to manufacturing issues. We know of no additional risks related to the previously produced vector for patients who have received cells with vectors made in this facility as the vectors were extensively tested by outside experts. Therefore, the IRB has determined that the potential benefit to you outweighs the potential risks.

Potential risks of cyclophosphamide:

Likely:	Less Likely:	Rare:
• Low blood counts	• Nausea and vomiting • Painful and bloody urination • Sterility • Water retention • Hair Loss	• Heart damage • Secondary leukemia (a different type of cancer) • Skin rash • Bleeding

Potential risks fludarabine:

Likely:	Less Likely:	Rare:
• Low blood counts	• Long-term reduction of lymphocyte counts which could increase the risk of infection. • Infection	• Damage to the nervous system • Causing seizures, coma and even death • Inflammation in the lungs • Kidney damage

Gene Therapy Risk of Cancer and Other Diseases:

The risks of gene therapy causing new disease are unknown. It is possible that the gene therapy may cause an immune system, blood, or neurological disorder, or cause a new cancer in your blood cells to develop. It is unknown 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. In these children, stem cells were genetically modified, in contrast, during the research being offered to you, T cells will be genetically modified. Most of the children were cured, but 5 out of 22 children developed leukemia and one died. Experts who examined this case thought that the gene therapy caused the leukemia in these children. To monitor you for this risk we will be testing your blood as previously described.

Procedure Risks

Blood draws: Side effects of drawing blood include pain and bruising in the area where the blood was drawn, lightheadedness, or rarely fainting due to transient lowering of blood pressure. If you feel dizzy, you should lie down for a few minutes to avoid hurting yourself if you fall. Infection at the blood-drawing site could also occur.

Intravenous Catheter: In order to receive this treatment, you will need to have a central venous catheter. This catheter is placed under the skin of the chest wall and enters a major vein in the chest. There are several types of catheters including those which must be removed after each cycle of chemotherapy (temporary type) and those which may be kept for the duration of therapy (permanent type). These options will be discussed with you. The risks associated with placing some catheters include pain, bleeding, infection and collapsed lung. 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.

Bone marrow aspiration and biopsy: A bone marrow biopsy is performed by inserting a needle into a bone of the hip. In the aspiration part of the procedure, a small amount of liquid bone marrow is removed, and in the biopsy part, a tiny solid piece of bone marrow is removed. You may feel a pressure sensation when the needle is being inserted and a pulling sensation and brief pain as the marrow is withdrawn. The amount of marrow taken is very small and will not change your body's ability to form blood cells. Potential complications of this procedure are local bleeding, pain at the site, and infection. Both of these are very rare. Bleeding can be stopped by applying local pressure and an infection can be treated with antibiotics.

Non-physical risks of genetic research

Psychological or Social Risks Associated with Return of Incidental or Secondary Findings

As part of the research study, it is possible that you could learn that you have genetic risks for another disease or disability. Although your genomic information is unique to you, you share some genomic similarities with your children, parents, brothers, sisters, and other blood relatives. Therefore, learning your research results could mean something about your family members and

their risk for certain illnesses. Before joining the study, it may be beneficial to talk with your family members about whether and how they want you to share your results with them.

Privacy Risks Associated with Return of Incidental or Secondary Findings

Your privacy is very important to us and we will use many safety measures to protect your privacy. However, in spite of all of the safety measures that we will use, we cannot guarantee that your identity will never become known. While neither the public nor the controlled-access databases developed for this project will have information such as your name, address, telephone number, or social security number, it may be possible to identify you based on the information in these databases and other public information (including information you tell people or post about yourself). The risk of this happening is currently very low.

Although your genetic information is unique to you, you do share some genetic information with your children, parents, brothers, sisters, and other blood relatives. Consequently, it may be possible that genetic information from them could be used to help identify you. Similarly, it may be possible that genetic information from you could be used to help identify them. Patterns of genetic variation also can be used by law enforcement agencies to identify a person or his/her blood relatives.

It is possible also that someone could get unauthorized access or break into the system that stores information about you. Every precaution will be taken to minimize this risk. There also may be other privacy risks that we have not foreseen.

Certificate of Confidentiality

We have obtained a Certificate of Confidentiality from the Department of Health and Human Services. The Certificate is designed to prevent us from being forced to disclose identifying information for use in any federal, state, or local civil, criminal, administrative, legislative, or other court proceeding, even if faced with a court subpoena. You should understand, however, that a Certificate of Confidentiality does not prevent you or a member of your family from voluntarily releasing information about yourself or your involvement in this research. We may not withhold information if you give your insurer or employer or a law enforcement agency permission to receive information about your participation in this project. This means that you and your family must also actively protect your own privacy.

The Certificate does not prevent us from taking steps, including reporting to authorities, to prevent serious harm to yourself or others. We will also share information as described in item 1 on page 16.

Potential Benefits of Participation

It is unknown at this time whether anti-BCMA T cell infusions will improve survival or have any benefit for patients with multiple myeloma. If accepted by your body, the cell infusion may decrease the amount of your cancer. Your participation in this experimental treatment may also help us advance the understanding and treatment of multiple myeloma.

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 these options:

- Getting care for your cancer without being in a study such as other forms of chemotherapy, radiation, stem cell or bone marrow transplantation, or immune therapies.
- Taking part in another study
- Getting comfort care, also called palliative care. This type of care helps reduce pain, tiredness, appetite problems and other problems caused by the cancer. It does not treat the cancer directly. Instead, it tries to improve how you feel. Comfort care tries to keep you as active and comfortable as possible.

You should discuss with your referring doctor and the NIH doctors whether any of these treatments might represent a reasonable treatment option for your disease.

Research Subject's Rights

What are the costs of taking part in this study?

If you choose to take part in the study, the following will apply, in keeping with the NIH policy:

- You will receive study treatment at no charge to you. This may include surgery, medicines, laboratory testing, x-rays or scans done at the Clinical Center, National Institutes of Health (NIH), or arranged for you by the research team to be done outside the Clinical Center, NIH if the study related treatment is not available at the NIH.
- There are limited funds available to cover some travel expenses for travel to appointments required by this clinical trial.
- There are limited funds available to cover the cost of some tests and procedures performed outside the Clinical Center, NIH. 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 Clinical Center, NIH.
- Once you have completed taking part in the study, medical care will no longer be provided by the Clinical Center, NIH.

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 National Cancer Institute (NCI) and other government agencies, like the Food and Drug Administration (FDA), which are involved in keeping research safe for people.
- National Cancer Institute Institutional Review Board
- The study Sponsor or his agent(s)

Controlled access databases:

Your individual genomic data and health information will be put in a controlled-access database. This means that only researchers who apply for and get permission to use the information for a specific research project will be able to access the information. Your genomic data and health information will not be labeled with your name or other information that could be used to identify you. Researchers approved to access information in the database have agreed not to attempt to identify you.

Stopping Therapy

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 progresses or comes back after a remission
- if you have side effects from the treatment that your doctor thinks are too severe
- if new information shows that another treatment would be better for you.
- if the study doctor decides to end the study
- if you become pregnant

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

You may stop your participation 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 the Center for Cancer Research, NCI or designated representatives. 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 can**not** be recalled and destroyed.

Conflict of Interest

The National Institutes of Health (NIH) reviews NIH staff researchers at least yearly for conflicts of interest. This process is detailed in a Protocol Review Guide . You may ask your research team for a copy of the Protocol Review 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.

Members of the research team working on this study may have up to $15,000 of stock in the companies that make products used in this study. This is allowed under federal rules and is not a conflict of interest.

Use of Specimens and Data for Future Research

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 it 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

OTHER PERTINENT INFORMATION

1. Confidentiality. When results of an NIH research study are reported in medical journals or at scientific meetings, the people who take part are not named and identified. In most cases, the NIH will not release any information about your research involvement without your written permission. However, if you sign a release of information form, for example, for an insurance company, the NIH will give the insurance company information from your medical record. This information might affect (either favorably or unfavorably) the willingness of the insurance company to sell you insurance.

The Federal Privacy Act protects the confidentiality of your NIH medical records. However, you should know that the Act allows release of some information from your medical record without your permission, for example, if it is required by the Food and Drug Administration (FDA), members of Congress, law enforcement officials, or authorized hospital accreditation organizations.

2. Policy Regarding Research-Related Injuries. The 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 National Institutes of Health, the Clinical Center, or the Federal Government. However, you have the right to pursue legal remedy if you believe that your injury justifies such action.

3. Payments. The amount of payment to research volunteers is guided by the National Institutes of Health policies. In general, patients are not paid for taking part in research studies at the National Institutes of Health. Reimbursement of travel and subsistence will be offered consistent with NIH guidelines.

4. 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, Jim Kochenderfer, M.D., Building 10, Room 12C121, Telephone: 240-760-6062. You may also call the Clinical Center Patient Representative at 301-496-2626. If you have any questions about the use of your specimens or data for future research studies, you may also contact the Office of the Clinical Director, Telephone: 240-760-6070.

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

COMPLETE APPROPRIATE ITEM(S) BELOW:

A. Adult Patient's Consent

I have read the explanation about this study and have been given the opportunity to discuss it and to ask questions. I hereby consent to take part in this study.

Signature of Adult Patient/ Legal Representative _____ Date _____

Print Name _____

B. Parent's Permission for Minor Patient.

I have read the explanation about this study and have been given the opportunity to discuss it and to ask questions. I hereby give permission for my child to take part in this study.
(Attach NIH 2514-2, Minor's Assent, if applicable.)

Signature of Parent(s)/ Guardian _____ Date _____

Print Name _____

C. Child's Verbal Assent (If Applicable)

The information in the above consent was described to my child and my child agrees to participate in the study.

Signature of Parent(s)/Guardian _____ Date _____ Print Name _____

THIS CONSENT DOCUMENT HAS BEEN APPROVED FOR USE FROM DECEMBER 17, 2018 THROUGH JANUARY 7, 2020.

Signature of Investigator _____ Date _____

Print Name _____

Signature of Witness _____ Date _____

Print Name _____