INSTITUTE: National Cancer Institute

STUDY NUMBER: 13-C-0214 PRINCIPAL INVESTIGATOR: Steven A. Rosenberg, M.D., Ph.D.

STUDY TITLE: A Phase II Study of Metastatic Cancer that Expresses NY-ESO-1 Using Lymphodepleting Conditioning Followed by Infusion of Anti-NY ESO-1 Murine TCR-Gene Engineered Lymphocytes

Continuing Review Approved by the IRB on 10/09/19
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Assent (Ages 15-17 Years)

INTRODUCTION

We would like to invite you to take part in a research study at the National Institutes of Health (NIH). Before you decide about taking part in the study, we want you to know why we are doing the study and if it will help you. We also want you to know about any risks (what might go wrong) and what you will have to do. You can only be in the study if you and your parent(s) agree.

This form gives you information about the study. Your doctor will talk to you about the study and answer questions you have. If you would like to take part in this study, we will ask you to sign this form to show that you understand this study. We will give you a copy of this form to keep. It is important that you know:

- You do not have to join the study.
- You may change your mind and drop out of the study at any time.

If we make important changes to the study we will tell you about it and make sure you still want to be in the study.

Why is this study being done?

We have developed an experimental therapy for treating patients with cancer that involves taking white blood cells from the patient, growing them in the laboratory in large numbers, genetically modifying them, and then giving the cells back to the patient. In a previous study, we used the anti-ESO-1 gene and a type of virus (retrovirus) to make these special cells (anti-ESO-1 cells). About half of the patients who received this treatment experienced shrinking of their tumors. In this study, we are using a slightly different way of producing the cells which we hope will work better in making the tumors shrink. The purpose of this study is to see if these tumor-fighting cells (genetically modified cells) that express the receptor for the ESO-1 molecule on their surface cause tumors to shrink and to see if this treatment is safe.

What will I be asked to do? What are my requirements?

Before you Begin the Study

The following procedures are conducted under other Surgery Branch protocols, 99-C-0128 or 03-C-0277, to which you have already enrolled.

Cell Harvest and Growth

You underwent a process called "apheresis" while enrolled on our companion protocol 03-C-0277. This process obtained certain types of blood cells from you. Some of these cells (anti-ESO-1) will be grown in the lab and genetically modified to recognize a protein 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 at alternative experimental treatments at the NIH Clinical Center or refer you to the care of your doctor who referred you to the NIH. 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 study doctor if you are allergic to any antibiotics.**

Work-up

Prior to receiving the experimental treatment, you will undergo many tests. We will evaluate you for eligibility for participation on this trial with a physical examination, CT and/or MRI scans, x-rays, EKG, heart and lung function tests, and blood tests. If you have received ipilimumab (also called Yervoy, MDX-010) or ticilimumab, and have experienced any gastrointestinal toxicities, you will have a colonoscopy and biopsies to make sure your colon is normal since these drugs may have caused damage to your colon that may worsen with aldesleukin treatment. You may be admitted to the hospital for these tests. However, you will be allowed to leave on pass on the days that you are not having tests performed.

Catheter Insertion

Prior to beginning the experimental treatment, you will have an intravenous (IV) catheter placed in your upper chest. 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 lung to expand. Pressure is placed on any area that might bleed. Other IVs may be needed in one or both of your arms if we need to give you extra fluids, medicines, or nutrition.

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. The white blood cells collected before treatment may be used to help grow the 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 6 weeks after you receive the cell infusion to see the impact of this therapy on the immune system and see if the cells we gave you are still active.

The leukapheresis procedure takes between 4-5 hours to complete. Rarely, people may experience lightheadedness or dizziness. We ask that you eat prior to the procedure to prevent this.

During the Study

Chemotherapy Regimen (Day -7 through Day -3)

After we have grown the anti-ESO-1 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 suppress your immune system so the anti-ESO-1 cells can work without any interference from the cells in your immune system. (These medicines will not treat your cancer. They may cause your tumor to shrink some, but this shrinkage is anticipated to be only partial and only for a short time.) The main purpose of the chemotherapy is to see if we can make the cells more effective in fighting cancer tumors. Animal experiments have indicated that this can make the cells more effective in fighting cancer tumors, and we think this is true in humans. You will receive the cyclophosphamide through your catheter over 1 hour for two days (Day -7 and Day -6) and the fludarabine will be given through your catheter for 30 minutes every day for five days (Day -7 through Day -3). The side effects of these medicines are described on the following pages.

Cell Infusion and Aldesleukin (IL-2) Regimen (Day 0 through Day 5)

Two to four days after the last dose of chemotherapy, you will be given the anti-ESO-1 cells. The anti-ESO-1 cells will be given through your catheter over 20-30 minutes. Within 24 hours after the anti-ESO-1 cell infusion, you will be given high-dose aldesleukin through your 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 about every 8 hours for up to five days after the cell infusion (maximum number of doses is 15). 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.

The day after you receive the anti-ESO-1 cells, we may give you G-CSF (filgrastim) as a shot or injection under the skin every day 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 and to make you as comfortable as we can.

When you are Finished with Treatment

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 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 remove approximately 1-9 teaspoons of blood three times per week to study the effects of this regimen on your immune system. The maximum amount of blood for research is approximately 2.3 cups in 8 weeks.

Follow-up and Evaluation of Experimental Regimen

You will need to continue to take Bactrim, 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 and 12 weeks following treatment, and then if you are responding to the treatment, every 3 months x3, every 6 months for 2 years, and then as determined by your study doctor.

The first follow-up visit will probably take 2 days; the following visits may only take one day. At each visit you will have lab tests, imaging studies, and a physical examination. At some of your follow-up visits, you may undergo leukapheresis or have about 8 tubes of blood drawn (4 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. 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 doctor who referred you to the NIH.

Sometimes things that don't feel good happen in research studies.

Some things that could happen, called side effects, may hurt you or make you feel upset. Some of the things might happen to you or they might not. Or things might happen that we don't know about yet.

This experimental treatment can lead to long-term decrease in your immune function, which means it can lower your body's ability to fight infections. It is also possible that you may lose

your fertility following this experimental treatment, meaning it may be harder for you to make a baby. It is possible, although unlikely, that this experimental treatment may cause your death.

We will discuss the side effects of this experimental treatment with you. You will be given medicines, transfusions, and treatments to prevent or treat the side effects including drugs to prevent and/or treat different types of infections. We will try to make you as comfortable as possible. You should talk to your study doctor about any symptoms that you experience while taking part in the study.

As this is a new experimental therapy, 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.

Anti-ESO-1 Cell Infusion (Gene Transfer)

The cells we will be giving you have a type of virus (retrovirus) put into them along with the anti-ESO-1 protein. Although this retrovirus is not active, there is the rare possibility that it may cause infection. The cells could also cause you to develop another type of cancer, such as leukemia or lymphoma. These specific gene-modified cells have been given only to a few individuals before so we do not have much information about the side effects. Potential risks include:

- Fever, chills and shortness of breath, which may last for a few hours (common)
- Lung congestion causing shortness of breath, which may progress to needing insertion of a breathing tube and treatment in the ICU.
- Mental status changes
- Abnormal kidney or liver function
- Breathing problems, which may be severe
- Decreased heart function
- Electrolyte imbalances
- Changes in your blood pressure
- Autoimmune reaction, such as loss of skin pigment (known as vitiligo) or inflammation of the eye (uveitis) which may require the use of steroid eye drops.

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.

Aldesleukin (IL-2)

When IL-2 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. In our experience giving IL-2 to over 2,000 patients, we have found that these side effects go away within a few days of stopping the IL-2.

Medications

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

Cyclophosphamide and Fludarabine Side Effects

Common	Less Common	Rare
▪ Changes in blood counts including: low red cell count (causing fatigue and shortness of breath), low platelet count (increasing the risk of bleeding and bruising), decrease in white blood cells (increasing the risk of infection and the need for treatment with antibiotics or other treatment) ▪ Loss of appetite, nausea, vomiting ▪ Diarrhea, stomach pain ▪ Mouth sores ▪ Hair loss ▪ Fatigue ▪ Muscle or joint aches	▪ Bleeding ▪ Infection ▪ Bladder irritation with bloody urine ▪ Severe allergic reaction (difficulty breathing/swelling) ▪ Headache or dizziness ▪ Sweating ▪ Swelling of arms or legs ▪ Skin changes, rash, blisters ▪ Weakness ▪ Hearing loss	▪ Heart damage ▪ Lung damage ▪ Kidney damage ▪ Inflammation of the eye resulting in blindness ▪ Inflammation of nervous system resulting in death ▪ Epstein Barr Virus Lymphoma. This can be fatal. (Two patients on other studies in the Surgery Branch developed EBV lymphoma, and both died as a result of this disease.) ▪ Loss of fertility ▪ Complications resulting from suppression of immune function, which can result in a severe infection and can be fatal.

Aldesleukin (IL-2) Side Effects

Common	Less Common	Rare
▪ Fever, chills, and fatigue	▪ Decrease in thyroid	▪ Bowel perforation (a

▪ Lowered platelet and red blood cell levels that may require transfusions ▪ Significant fluid retention causing weight gain (as much as 20 pounds) ▪ Low blood pressure ▪ Increased heart rate ▪ Shortness of breath ▪ Low urine output ▪ Swelling in your extremities ▪ Fluid in your lungs that can require oxygen ▪ Dry mouth, nausea, vomiting, diarrhea ▪ Rash, itching ▪ Changes in skin or hair pigmentation, called vitiligo ▪ Changes in mental status, including confusion, difficulty sleeping or vivid dreams; this can be severe and require sedation and monitoring in the ICU.	function that may require daily thyroid hormone replacement ▪ Abnormal kidney and liver function that can be severe ▪ Abnormal heartbeats or low blood pressure that may require treatment in the ICU ▪ Breathing problems which may need monitoring in ICU and insertion of a breathing tube	hole) requiring longer hospitalization or surgery. This is more common in patients who have previously received anti-CTLA-4 antibody (i.e., ipilimumab). You will have a colonoscopy and biopsy before treatment if you have previously received anti-CTLA-4 antibody. ▪ Autoimmune disease, where your immune system attacks cells in organs of your body. Should this occur, you will be treated with steroids to stop the immune response. ▪ Damage to the heart muscle or heart attack. ▪ Loss of blood flow to the extremities due to medicines used to treat very low blood pressure and shock. In one instance, a patient had to have her lower arm amputated after treatment with these medicines. ▪ IL-2 is mixed with human albumin which could cause an allergic reaction or potentially transmit viral infections, although we have not had this occur.
Support Medications – Side Effects		

Common	Less Common	Rare
Filgrastim (To increase production of white blood cells)		
▪ Bone pain	▪ Severe headache	▪ Severe breathing problems ▪ Rupture of your spleen
Bactrim (To prevent a specific type of pneumonia)		
	▪ Fever ▪ Nausea, vomiting ▪ Skin rash with itching ▪ reduced number of white blood cells ▪ Allergic reaction	
Fluconazole (To prevent fungal infections)		
▪ Headache ▪ Nausea, vomiting, diarrhea, abdominal pain ▪ Itching		▪ A skin disorder called Stevens Johnson Syndrome, which can be fatal ▪ Liver damage, which may be permanent
Acyclovir and Valacyclovir		
	▪ Temporary decrease in kidney function, which may not cause any symptoms ▪ Nausea, vomiting, diarrhea, constipation ▪ Pain and irritation at place of injection	▪ Skin rash, hives, itching ▪ Tremors, dizziness, Confusion, seizures ▪ Fatigue ▪ Blood in the urine

What benefit can I expect?

People may also have good things happen to them when they are in research studies. The good things may be 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 receive personal, medical benefit from taking part in this

study, although what we learn from this study may help others in the future who also have cancer.

Can I refuse to be in the study?

Please talk to your parents about this before you decide whether or not to be in this research study. We will also ask your parents to give their permission for you to be in this study. But even if your parents say "yes," you can still decide not to be in this research study.

If you don't want to be in this study, you don't have to.

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

If you don't want to be in this study, there are other options for treatment of your cancer including:

- 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 study doctor about these and other options.

You may stop being in this any time.

Remember, being in this study is up to you and no one will be upset if you don't want to take part in this study or even if you change your mind later and want to stop. If you don't want to take part in this study, you will be free to return to the care of your doctor who referred you to the NIH.

Consenting

Once you have turned 18, we will contact you to find out if you would still like to participate in the study.

You can ask any questions that you have about the study.

If you have a question later that you didn't think of now, you can call me or ask me next time.

Putting your name at the bottom means that you have decided to be in this study. You and your parents will be given a copy of this form after you have signed it.

I have had this study explained to me in a way that I understand, and I have had the chance to ask questions. I agree to take part in this study.

Signature of Minor Patient:_____Date:_____

Print Name:_____

Signature of Investigator:_____Date:_____

Print Name:_____