INSTITUTE: National Cancer Institute

STUDY NUMBER: 11-C-0163 PRINCIPAL INVESTIGATOR: Steven A. Rosenberg, M.D., Ph.D.

STUDY TITLE: Phase II Study of Lymphocytes Generated with Engineered Cells for Costimulation Enhancement in Patients with Metastatic Melanoma Following Lymphodepletion

Continuing Review Approved by the IRB on 07/23/12
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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 purpose of this study is to determine whether we can treat melanoma by taking blood cells called lymphocytes from patients' tumors, and grow them in the laboratory in large numbers to then give the cells back to the patient. These cells are called Young Tumor Infiltrating Lymphocytes, or Young TIL and these Young TIL were prepared in the presence of another type of cell called Engineered Cells for Costimulation Enhancement (ECCE) that we hope will help us make the Young TIL cells grow easier and faster. We will test whether this experimental regimen can cause your tumor to shrink, as well as test the safety of this regiment and the effects on the immune system. Before giving the cells back to you, we will suppress (make it less able to fight) your immune system with two chemotherapy agents in order to create room for your cells and to prevent the immune system cells from working against the cells we give to you. After giving you the cells, we will give you aldesleukin (IL-2) for up to 5 days to help keep the cells alive.

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

Your doctor has told you that you have been diagnosed with melanoma. The only treatment available at this time that has been shown to cure melanoma is aldesleukin. We invite you to take part in this research study that is trying to find effective treatments for patients with melanoma.

How many people will take part in this Study?

As many as 63 patients may participate in this study. If you decide to participate, you will undergo a series of tests to make sure you are eligible, including blood tests and scans as described below.

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 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 four months after you finish study treatment. If you think that you or your partner is pregnant, you should tell your study doctor or nurse at once.

Effective forms of birth control include:

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

Description of Research Study

The cell therapy has 5 stages outlined below:

Stage	Timeframe	Location	Comments & Instructions
Work up	1-2 weeks	Inpatient and outpatient	Scans, x-rays, labs, leukapheresis other tests as needed
Chemotherapy (day -7 to -1)	1 week	Inpatient	Receive IV chemotherapy to prepare your immune system for the cells
Cells and IL-2 (Day 0)	1-5 days	Inpatient and possibly ICU	Receive Young TIL, and then IL-2 every 8 hours for up to 15 doses
Recovery	1-2 weeks	Inpatient unit	Recover from the effects of chemotherapy and IL-2
Follow -up	Ongoing unless disease progression	Outpatient	Return to clinic for physical exam, review of side effects, labs, scans every 1-4 months for the first year then every 3-4 months.

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

Cell harvest and growth

You will first have some tumors removed from your body so we can grow the TIL cells contained in the tumor in the laboratory. We will be obtaining the cells from a biopsy of your tumor or during surgery. Based on our previous experience growing Young TIL without the help of ECCE cells, at approximately 20% of the time we are unable to successfully grow the cells needed for this procedure. However, we have used ECCE cells in laboratory experiments and have shown that these ECCE cells help TIL have a better chance at growing. For this study, after obtain the cells from your tumor, we will try to grow them using two different methods. If your cells grow well using the original method to generate Young TIL, these are the TIL we will use to grow more cells for therapy. If your cells do not grow this way, we will check to see if your Young TIL are growing in the presence of ECCE cells. If your cells do not grow with either method, you will not be able to receive the cell infusion, you will be taken off this study, and we will look at alternative treatments for you or return you to the care of your referring physician. We usually know after about 2-4 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.

The procedure for converting your normal cells into cells that are able to recognize your tumor has been studied in the laboratory and although these cells can destroy tumor cells in the test tube, it is not clear that they will be able to destroy them inside a patient's body. We have grown young TIL cells similar to these and treated over 50 patients. The Young TIL cells in this study are different from others that we have given patients because they are grown in the presence of special ECCE cells that help stimulate the cells to grow. In previous studies we have used other cells from the patient's own blood or from a normal volunteer to stimulate the Young TIL to grow, but the process of collecting these extra cells is expensive, time-consuming and sometimes does not generate enough cells to help grow the Young TIL. This experimental study will test whether growing young TIL cells this way is effective in shrinking your cancer tumor(s). In our initial experience with Young TIL cells, of 45 patients treated and evaluated for response, 11 had some shrinkage.

Work up

Prior to receiving the experimental treatment you will undergo many tests. These include imaging procedures, heart and lung function tests, and laboratory tests. If you are a woman, you will undergo a pregnancy test. You will also have a large catheter inserted into a vein and leukapheresis (see description below) will be performed. 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 therapy, 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 to give you extra fluids, medicines, or nutrition.

Leukapheresis

Leukapheresis 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 serum part), 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 may be used to help grow the Young TIL and after the experimental therapy, you will have leukapheresis so that we can test your cells.

Chemotherapy Regimen (Day -7 through Day -1)

You will be admitted to the hospital. For the seven days prior to receiving your cells you will be given two chemotherapy medicines to suppress your immune system so the cells we give you can work without any interference from the cells in your immune system. There is evidence in animal experiments and human studies that this can increase how effective the cells we give are in fighting cancer cells, but it is not known whether this is true for your cells.

The two chemotherapy medicines are called cyclophosphamide and fludarabine. The cyclophosphamide will be given into your IV over 1 hour for two days and the fludarabine will be given into your IV for 30 minutes every day for the five days following the cyclophosphamide. These chemotherapies will not treat the tumor and are given only to see if the suppression of the immune system improves the functioning of the experimental cells we will be giving you.

Cell Infusion and IL-2 Regimen (Day 0 to Day 4)

One to four days after the last dose of chemotherapy, you will be given the TIL. The TIL will be given in your catheter over 20-30 minutes. Within 24 hours after the TIL infusion, you will be given high dose aldesleukin (IL-2) through your catheter. IL-2 is approved by the FDA for treatment of metastatic melanoma and metastatic renal cell cancer. The purpose of giving the IL-2 with this therapy is to help the cells live longer in your body. The IL-2 will be given as a 15-minute infusion 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 doses. The risks of the cells and IL-2 are described on the following pages.

The day after you receive the TIL, we will give you G-CSF (filgrastim) as a shot or injection under the skin. This will continue until your white blood cell counts begin to return to normal.

Recovery

After your last dose of IL-2, you will recover in the hospital until you are well enough to go home. This usually takes 5 to 10 days; however, you may need to stay in the hospital for longer than 10 days 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 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.

Optional Biopsy

We may ask you to allow us to perform a biopsy (remove a small piece) of your tumor or lymph node after receiving the treatment to look at the effects of the treatment on the immune cells in your tumor. The biopsy to be performed is exclusively for research purposes and will not benefit you. It might help other people in the future. Even if you sign "yes" to have the biopsy you can change your mind at any time. Please read each sentence below and think about your choice. After reading each sentence, circle and initial the answer that is right for you. The decision to participate in this part of the research is optional, and no matter what you decide to do, it will not affect your care.

I agree to have the tumor or lymph node biopsy for the research tests in this study.

Yes No Initials_____

To obtain cells by a biopsy, a small area of skin is numbed with an anesthetic and a small piece of your tumor is removed, either with a needle or by a small cut in the tumor. The area is covered with a bandage for a day or two, during which time we will ask you to keep it dry.

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. We will ask you to return to NIH approximately 4-6 weeks after receiving the Young TIL. This will probably take 2 days. You will have scans and x-rays to evaluate your tumor and blood tests. We will also take some blood from you through leukapheresis to see the impact of this therapy on the immune system and see if cells we gave you are still alive. If your tumor shows evidence of shrinking, we will ask you to return for evaluation every month for the first 3 months, then every 3-4 months for the next 5 years, and yearly thereafter. 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.

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 treatment or care for your cancer without being in a study
    - One of the few therapies that have been approved by the US Food and Drug Administration (FDA) for the treatment of melanoma is interleukin-2 (IL-2), also called aldesleukin. IL-2 can shrink tumors in approximately 16% of patients with metastatic melanoma.
    - Chemotherapy, such as dacarbazine or temozolomide, is also used to treat melanoma.
- 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.

Please talk to your doctor about these and other options.

Risks or Discomforts of Participation
The major side effects of this treatment (described in detail below) that are most severe include:

- Infection and low blood counts caused by the chemotherapy
- Confusion and changes in mental status caused by the IL-2
- Fluid retention, low blood pressure, shortness of breath, and high heart rate caused by the IL-2. Other side effects of IL-2 are listed below.

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.

During the leukapheresis procedure, you may have some tingling in your face and lips due to the medicine used to keep your blood from clotting during the procedure. The nurses may give you a calcium-containing antacid to chew that takes away this tingling. Rarely, people may experience lightheadedness or dizziness. We ask that you eat prior to the procedure to prevent this. Rare complications of this procedure are lowered blood pressure, bleeding or bruising where the needles are put in your arms.

Discomfort due to a biopsy may include pain at the site of the biopsy, swelling, bruising, and infection.

When IL-2 is given through a 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 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.

TIL Cell Infusion

All TIL cells will be given through your catheter while we keep you in the patient care unit so we can watch you closely.

Potential risks include:

- shortness of breath, or
- an 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.
- As this is a new experimental therapy, side effects that we do not anticipate that may cause your condition to deteriorate may be encountered. Any new information that becomes available during the course of this study will be shared with you.

In the first 24 patients treated on the initial Young TIL study, we have observed an increase in the number of patients who have experienced some of the side effects of cells and aldesleukin. One out of three these patients were intubated (a tube was placed in the throat to help them breath), and two patients were put on dialysis due to abnormalities in kidney function.

Medications

The side effects of cyclophosphamide, fludarabine, IL-2 and some of the other medications you will receive are listed in 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 one died as a result of this disease.) ▪ Loss of fertility

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	▪ Skin rash, hives, itching ▪ Tremors, dizziness, Confusion, seizures

	not cause any symptoms ▪ Nausea, vomiting, diarrhea, constipation ▪ Pain and irritation at place of injection	▪ Fatigue ▪ Blood in the urine

IL-2 (aldesleukin) side effects		
Common	Less common	Rare
▪ Fever, chills, and fatigue ▪ Lowered platelet and red blood cell levels that may require transfusions ▪ Significant fluid retention causing weight gain (as much as 20 pounds). ▪ Low blood pressure ▪ Increased heart rate ▪ Low urine output ▪ Swelling in your extremities, ▪ Fluid in your lungs that can require oxygen ▪ Dry mouth, nausea, vomiting and diarrhea; ▪ Rash, itching; and changes in skin or hair pigmentation, called vitiligo; ▪ Changes in mental status, including confusion, difficulty sleeping or vivid dreams; this can be severe and require sedation and monitoring in the ICU	▪ Decrease in thyroid function that may require daily thyroid hormone replacement; ▪ Abnormal kidney and liver function that can be severe; ▪ Abnormal heartbeats or low blood pressure that may require treatment in the ICU. ▪ Breathing problems which may need monitoring in ICU and insertion of a breathing tube	▪ Bowel perforation (a hole) requiring longer hospitalization or surgery. ▪ Autoimmune disease, where your immune system attacks cells in organs of your body. Should this occur, you will be treated with steroids to stop the immune response. ▪ 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.

Potential Benefits of Participation

Are there benefits to taking part in this study?

One aim of this study is to see if this experimental young TIL will cause your tumors to shrink. We hope that you will get personal medical benefit from taking part in this study, but we cannot be certain. These potential benefits could include shrinking of your tumor or lessening of your symptoms, such as pain, that are caused by the cancer.

Research Subject's Rights

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 that it would not be safe for you to continue. Any significant new findings that relate to this protocol will be discussed with you.

The sponsor of this study is Dr. Steven A. Rosenberg. Your records may be reviewed by NIH organizations and by organizations outside the National Institutes of Health, such as representatives of the US Food and Drug Administration. Every effort will be made to protect your privacy in any recording or reporting of this information.

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 the cost of some tests and procedures performed outside the Clinical Center, NIH. You may have to pay for these costs even 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.

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 comes back during treatment
- 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

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

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.

Conflict of Interest

The National Institutes of Health (NIH) reviews NIH staff researchers at least yearly for conflicts of interest. The following link contains details on this process *http://ethics.od.nih.gov/procedures/COI-Protocol-Review-Guide.pdf*. 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.

The National Institutes of Health and the research team for this study have developed the Young TIL being used in this study. This means it is possible that the results of this study could lead to payments to NIH scientists and to the NIH. By law, government scientists are required to receive such payments for their inventions. You will not receive any money from the development of Young TIL.

Optional Studies

We would like to keep some of the specimens and data that are collected for future research. These specimens and data will be identified by a number and not your name. The use of your specimens and data will be 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 decide now that your specimens and data can be kept for research, you can change your mind at any time. Just contact us and let us know that you do not want us to use your specimens and data. Then any specimens that remain will be destroyed and your data will not be used for future research.

Please read each sentence below and think about your choice. After reading each sentence, circle and initial the answer that is right for you. No matter what you decide to do, it will not affect your care.

1. My specimens and data may be kept for use in research to learn about, prevent, or treat cancer.

Yes No Initials_____

2. My specimens and data may be kept for use in research to learn about, prevent or treat other health problems (for example: diabetes, Alzheimer's disease, or heart disease).

Yes No Initials_____

3. Someone may contact me in the future to ask permission to use my specimen(s) and data in new research not included in this consent.

Yes No Initials_____

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, Steven A. Rosenberg, M.D., Ph.D., Building 10 CRC, Room 3-3940, Telephone: 301-496-4164. If you have any questions about the use of your tissue for future research studies, you may also contact the Office of the Clinical Director, Telephone: 301-496-4251.

You may also call the Clinical Center Patient Representative at 301-496-2626.

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 JULY 23, 2012 THROUGH JANUARY 22, 2013.

Signature of Investigator _____ Date _____

Print Name _____

Signature of Witness _____ Date _____

Print Name _____