INSTITUTE: National Cancer Institute

STUDY NUMBER: 11-C-0013 PRINCIPAL INVESTIGATOR: Steven A. Rosenberg, M.D., Ph.D.

STUDY TITLE: Phase I/II Study of Metastatic Cancer Using Lymphodepleting Conditioning Followed by Infusion of Anti-VEGFR2 Gene Engineered CD8+ Lymphocytes

Continuing Review Approved by the IRB on 03/09/15
Amendment Approved by the IRB 07/15/15 (L) Date posted to web: 07/21/15

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

You have been diagnosed with metastatic cancer and the standard treatments available have not been effective. We have developed an experimental procedure for treating patients with cancer that uses blood cells found in their peripheral blood cells. We genetically modify these cells and

grow them in the laboratory. We will be using the anti-VEGFR2 gene and a type of virus (retrovirus) in making these special cells (anti-VEGFR2 CD8+ cells). The anti-VEGFR2 CD8+ cells target the vascular endothelial growth factor receptor 2. This receptor is located in cells in tumors that are involved in supplying blood to your tumor which may result in the growth of your tumor. By blocking VEGFR2, we hope that these cells when infused will decrease the size of your tumors. However, it is possible that these cells will not have this effect.

The anti- VEGFR2 CD8+ cells will be given to you as an intravenous (IV) infusion. This type of experimental regimen is called "gene transfer" and is very closely monitored by the Food and Drug Administration (FDA) and other regulatory agencies. The risks of gene transfer will be described later in this document.

This highly experimental regimen is explained below.

How many people will take part in this study?
Up to 118 patients may participate in this study.

Description of Research Study

This study has 5 stages outlined below:

What	Timeframe	Location	Comments & Instructions
Work up	1-2 weeks	Inpatient and out patient	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 anti-VEGFR2 CD8+ cells, and then IL-2 about 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 until disease progression	Outpatient	Return to clinic for physical exam, review of side effects, labs, scans every 1-6 months

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 most effective yet safe dose of anti-VEGFR2 CD8+ cells. There will be 11 dose levels of anti-VEGFR2 CD8+ cells. The first patients enrolled get the smallest dose and the dose is increased when a level has been determined to be safe. Discuss with your doctor which dose of anti- VEGFR2 CD8+ cells you will be receiving. The first twelve patients treated on this study received high dose IL-2 as part

of the treatment. However, in 3 of the 4 patients treated at the highest dose of cells, blood tests indicated that liver function was abnormal. Since high dose IL-2 can cause abnormal liver function, we have decided to reduce the dose of IL-2 to see if this prevents abnormal liver function. You will receive a low dose of IL-2 as part of your treatment.

The major side effects of this experimental regimen (described in detail on pages 8 and 9) 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, and high heart rate caused by the IL-2

We will discuss the side effects of this experimental regimen 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.

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

Before you begin the study

Cell harvest and growth

You will undergo apheresis to obtain certain types of blood cells from you. These cells (anti VEGFR2 CD8+ cells) will be grown in the lab and genetically modified to recognize a protein on your tumor cells. If your cells do not grow, you will not be able to receive the cell infusion. If that happens, we will look at alternative experimental treatments at the NIH Clinical Center or refer you to the care of your referring 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.

Work up

Prior to receiving the experimental regimen you will undergo many tests. These include imaging procedures, heart and lung function tests, eye exams, 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 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 regimen, 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 cells. In addition to the leukapheresis you will undergo as part of your work up, we will also ask you to undergo one additional pheresis procedure between 4 and 6 weeks after your cell regimen to see the impact of this therapy on the immune system and see if cells we gave you are still active.

Chemotherapy Regimen (Day -7 through Day -1)

After we have grown the anti-VEGFR2 CD8+ cells to large numbers in the laboratory, you will be admitted to the hospital to begin your experimental regimen. You will be given two chemotherapy medicines, cyclophosphamide and fludarabine, to suppress your immune system so the anti-CD8+ cells can work without any interference from the cells in your immune system. (These medicines will not treat your cancer.) Animal experiments have indicated that this can make the cells more effective in fighting cancer tumors, but it is not known whether this is true in humans. The cyclophosphamide will be given into your catheter over 1 hour for two days (Day -7 and Day -6) and the fludarabine will be given into your catheter for 30 minutes every day for the next five days (Day -5 through Day -1). The side effects of these medicines are described on the following pages.

After you have completed the chemotherapy regimen you will receive the cell infusion

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

One to four days after the last dose of chemotherapy, you will be given the anti-VEGFR2 CD8+ cells. The anti- VEGFR2 CD8+ cells will be given in your catheter over 20-30 minutes. Within 24 hours after the anti-VEGFR2 CD8+ cell infusion, you will be given low dose IL-2 through your catheter. High dose 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 keep the cells we give you active for as long as possible so they will fight your tumor. The IL-2 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 doses. The risks of the cells and IL-2 are described on the following pages.

The day after you receive the anti- VEGFR2 CD8+ cells, we will give you more 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.

We may ask you to allow us to perform a biopsy (remove a small piece) of your tumor or lymph node after receiving the regimen to look at the effects of the regimen on the immune cells in your tumor. However, this biopsy is not required for you to participate in this experimental study. 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 regimen. We will ask you to return to NIH 4 – 6 weeks after completing your regimen for evaluation. This visit will probably take 2 days. If your tumor shows evidence of shrinking, we will ask you to return for evaluation every month for several more months. 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. At some of your follow up visits, you may undergo leukapheresis 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.

Retreatment

If your tumor shrinks or disappears following the initial regimen and then recurs you may receive one additional regimen if you tolerated the regimen well and if all the side effects have resolved. If you are retreated, you will receive the same medications on the same schedule as with the first regimen.

Birth Control

If you are a woman who is breast feeding or pregnant, you may not participate in the study because we don't know how this medicine would affect your unborn child or your baby. 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 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

Gene Therapy Long Term Follow up (Retroviral Vectors)

Because we do not know the long term side effects of gene transfer, 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 the regimen 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 (2 teaspoons each time). 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 will ask you to return annually to the NIH for a physical examination for five years after you 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 regimen approach. Please advise your family of this request.

Alternative Approaches or Treatment

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

If there are effective salvage regimens (regimens used when standard regimens have failed), you will be directed to undergo these regimens before participating in this protocol.

Other options for treatment of your cancer include:

- Standard therapies (such as hormone therapy and/or systemic chemotherapy with or without Herceptin for treatment of metastatic breast cancer);
- experimental vaccines;
- experimental chemotherapies; or biotherapies (such as ipilimumab or tremelimumab);
- other combination therapies; or
- getting no treatment; getting comfort care, 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.

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 regimen can lead to long-term decrease in your immune function. It is also possible that you may lose your fertility following this experimental regimen. It is possible, although unlikely, that this experimental regimen may cause your death.

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, like TUMS 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 or bleeding.

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

Aldesleukin (IL-2)

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 the regimen, 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.

Anti-VEGFR2 CD8+ Cell Infusion (gene transfer)

The cells we will be giving you have a type of virus (retrovirus) put into them along with the anti-VEGFR2 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. We do not have much information about the specific side effects of the anti-VEGFR2 CD8+ cells since this is our first study using these cells. We have studied similar types of cells in patients with cancer in other studies, and have seen the following side effects:

- Fever, chills and shortness of breath, which may last for a few hours (common)
- Lung congestion
- Immune-type reaction.
    - In similar clinical trials with cells targeting a melanoma protein, we have observed the following immune-mediated toxicities: loss of skin pigment (known as vitiligo), inflammation of the eye (uveitis), hearing loss, and dizziness. The skin, the eye, and the ear are all sites where that targeted melanoma protein is known to exist.
    - In another clinical trial with a similar type of cell, a patient died due to an immune type reaction from the cells.

- Several drugs and antibodies which target VEGFR2 have been used to treat patients in other studies. Some of the side effects seen in these studies include high blood pressure, blood clots, stroke, increased bleeding, abdominal pain, hoarseness, and fatigue.

There is 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 deteriorate may be encountered. Any new information that becomes available during the course of this study will be shared with you.

Gene Therapy Risk of Cancer and Other Diseases: When retroviral vectors enter a normal cell in the body, the DNA of the vector inserts itself into the normal DNA in that cell; this process is called integration. Most integration is expected to cause no harm to the cell or to the patient. However, there is a chance that there may be some regions of the normal human DNA where integration of the viral vector's DNA may result in activation of neighboring genes. For example, if one of these genes were a growth factor, this may cause uncontrolled division of the cell, resulting in a cancer. This type of event has occurred in one animal study in mice where the vector integration site correlates with the occurrence of cancer in these mice. Five instances of a similar event have been reported in five children out of 22 who received a retroviral vector in two experimental gene transfer studies for X-linked Severe Combined Immunodeficiency (SCID) conducted in Europe, not under the jurisdiction of the U.S. Food and Drug Administration (FDA). While most of the children who participated in this clinical trial appear to have been cured of their disease, five children developed leukemia (a form of cancer of the blood) approximately 2-6 years after receiving the gene transfer regimen. The first patient had

extensive testing done to determine the cause of the leukemia. A group of experts in this field have looked at all the test results, and concluded that the gene transfer caused the leukemia in the first child. One of the children died as a result of their leukemia. The risk of another cancer developing in you, including leukemia, is unknown, but you need to be aware of this possible risk. To monitor you for this risk we will be testing your blood 3 months after cell infusion, then at 6 and 12 months, and then annually thereafter. If we find that the cells we have given you grow out of control, chemotherapy will be given to you to kill the cells, given their risk of causing leukemia or a second cancer.

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 both 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 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

Low dose Aldesleukin Risks and Discomforts	
Common	Unlikely
• Local swelling at site of injection • Low blood pressure • Tiredness • Swelling in hands and feet • Rash	• Nausea • Vomiting • Diarrhea • Infection • Laboratory changes including kidney blood tests • Decreased urine • Changes in consciousness • Infections

Prior to and throughout this study you will undergo many tests to determine the size and extent of your tumor, as well as the impact of the regimen. Multiple blood tests will be performed and some of your serum and lymphocytes will be stored for future testing. Blood and tissue samples collected from you may be stored and used in the future to study scientific questions related to this protocol. If there are any risks to you or your family associated with these future scientific studies which are not covered in this consent form, your consent will be obtained before such studies are performed.

If your disease progresses, or recurs after this experimental regimen and you are not eligible for retreatment, then you will no longer receive the regimen in this protocol, though you may be eligible to be considered for other protocols at the National Cancer Institute, NIH or referred elsewhere for treatment.

Potential Benefits of Participation

Are there benefits to taking part in this study?

It is possible that your tumors may shrink as a result of this experimental regimen, but it is not possible to predict whether this will occur. It is likely that there will be no long-term benefit for participating in this study but that the information derived from this study could benefit future patients.

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 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 (*Steven A. Rosenberg, M.D., Ph.D.*)

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.

Stopping the Study

Your doctor may decide to take you off this study under the following circumstances:

- if he/she believes that it is in your best interest
- if your disease comes back during treatment
- if you experience side effects from the treatment that are considered too severe
- if new information becomes available that shows that another treatment would be better for you

In this case, you will be informed of the reason for that decision.

You can stop participating at any time. However, if you decide to stop participating in the study, we encourage 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 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.

Conflict of Interest

The National Institutes of Health 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 additional information or a copy of the Protocol Review Guide. 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.

The National Institutes of Health and the research team for this study have developed the cell product being used in this study. This means it s 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 the cell product.

Optional Biopsy

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 biopsy for research tests in this study

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. 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 MARCH 9, 2015 THROUGH MARCH 8, 2016

Signature of Investigator _____ Date _____ Signature of Witness _____ Date _____

Print Name _____ Print Name _____