INSTITUTE: National Cancer Institute

STUDY NUMBER: 18-C-0074 PRINCIPAL INVESTIGATOR: Steven A. Rosenberg, M.D., Ph.D.

STUDY TITLE: A Phase I/II Trial to Evaluate the Safety and Immunogenicity of a Messenger RNA (mRNA)-Based, Personalized Cancer Vaccine Against Neoantigens Expressed by the Autologous Cancer

Continuing Review Approved by the IRB on 01/07/19
Amendment Approved by the IRB on 01/28/19 (E)
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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?

We are using a technique called exome sequencing. Exomes are the parts of your DNA that make proteins. Exome sequencing allows us to read the "letters" in the exome to see where the letters are correct (meaning normal proteins are being made) and where the letters are incorrect. Incorrect letters are called mutations and your tumor may contain specific mutations. By identifying specific mutations in your tumor, we can then use this information to make

experimental treatments. In this study, we plan to take a piece of your tumor and identify the tumor-specific mutations. We will then make intramuscular vaccines based upon these mutations. The vaccines, called mRNA vaccines, will be given as shots (or injections) in a muscle in arm or your thigh. You will receive the mRNA vaccines every 2 weeks for 8 weeks. Every dose is called a "cycle" and four cycles is considered a course of therapy. The purpose of this study is to see if the mRNA vaccine fighting cells are safe and can cause metastatic melanoma (skin cancer) or metastatic epithelial tumors to shrink. Epithelial cancer is cancer of cells that line or are found in parts of your body such as your intestines, lungs, reproductive organs, brain, and urinary tract.

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

You are being asked to participate in this study because you have been diagnosed with metastatic melanoma or metastatic epithelial cancer.

How many people will take part in this study?

Up to 64 patients will be enrolled on this study.

Description of Research Study

This study has several stages outlined below:

- Part of Stage 1 is performed under the screening protocol, 99-C-0128 (Evaluation for NCI Surgery Branch Clinical Research Protocols), to which you have already enrolled.
- Stages 1-2 are performed under the cell harvest protocol, 03-C-0277 (Cell Harvest and Preparation for Surgery Branch Adoptive Cell Therapy Protocols), to which you have already enrolled.
- Stages 3-4 are performed under this protocol.

Stage	Timeframe	Location	Comments & Instructions
1. Work-up	1-2 weeks	Inpatient and/or outpatient	Scans, x-rays, labs, leukapheresis, other tests as needed, and surgery to remove one of your tumors to obtain lymphocytes.
2. Sequencing your tumor then selecting specific cells	10-14 weeks	Home	You may resume care under your home oncologist and may or may not receive treatment depending on the status of your disease.
3. mRNA Vaccine	Days 0, 14, 28, and 42	Inpatient and/or outpatient	Receive the mRNA vaccines intramuscularly (IM)

4. Follow-up	Ongoing until disease progression	Outpatient	Return to clinic for physical exam, review of side effects, labs, and scans 2 weeks after final vaccine, then 1 month later x1, then every 1-2 months for the first year, and then annually for up to 5 years or until disease progression.

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

Before you Begin the Study

The following procedures are conducted under protocols 99-C-0128 or 03-C-0277.

Work-up

Prior to receiving the experimental treatment, you will undergo many tests. You may be admitted to the hospital for these 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 and urine tests. Patients who have a positive HIV blood test will not be eligible for this protocol because it may put them at higher risk of developing infections. If you are a woman, you will undergo a pregnancy test. However, you will be allowed to leave on pass on the days that you are not having tests performed.

Cell Harvest and Growth

You underwent either surgery or a biopsy to obtain pieces of your tumor, so we can grow TIL from your tumor cells in the laboratory while enrolled on our companion protocol 03-C-0277. Sometimes we are unable to successfully grow the cells needed for this procedure. If your cells do not grow, you will not be able to receive the vaccines. If that happens, we will look for alternative experimental treatments at the NIH Clinical Center or refer you to the care of your referring physician. We usually know after about four 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, so be sure to tell your doctor if you are allergic to any antibiotics.**

Leukapheresis

You also underwent a process called leukapheresis, possibly several times, while enrolled on our companion protocol 03-C-0277. 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 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. For this study, the white blood cells removed from your blood will be used to make your vaccines. Some of these cells will be grown in the lab and genetically modified to recognize a protein on your tumor cells. In addition to the leukapheresis before treatment, we will also ask you to undergo one additional apheresis procedure approximately two weeks after your last vaccine to see how the therapy has affected your immune system.

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

Vaccine Administration (Days 0, 14, 28, and 42)

You will receive the mRNA vaccine every 2 weeks for 8 weeks. The vaccine will be administered as an intramuscular injection in the day hospital. Before each vaccination cycle, the research nurse will review any side effects you might have experienced, and you will have blood drawn and a physical examination. The intramuscular injection will be given into the muscle of your upper arm. Alternating injection sites of the upper arm muscle will be used for each subsequent injection. Thigh muscles may also be used as an alternate injection site. We will watch you closely during this entire time for any side effects of this experimental regimen. We will discuss the side effects below and we will include in your care all the medicines and treatments to prevent as many of these side effects as we can and to make you as comfortable as we can. You will be able to go home about 2-3 hours following administration of the vaccine.

In addition to the laboratory tests to monitor your condition, we will remove about 14 teaspoons of blood before each cycle to study the effects of this regimen on your immune system. The maximum amount of blood for research during this course of four vaccines is approximately 1.2 cups.

Additional Vaccination Cycles (Second Course)

If the study doctor feels it would be helpful for you, you will also have the option of receiving a second course of four vaccines (four additional cycles) at the same vaccine dose at which you were previously vaccinated. The second course may start approximately 4 weeks (± 2 weeks) from your last vaccine dose. You will again receive the mRNA vaccine every 2 weeks for 8 weeks. The vaccine will be administered as an intramuscular injection, and the research nurse will continue to review any side effects you might have experienced.

We will conduct the same laboratory tests to monitor your condition. We will remove another approximately 14 teaspoons of blood before each cycle to study the effects of this regimen on

your immune system. The maximum amount of blood for research during this second course of four vaccines is approximately 1.2 cups.

The best course of action will be discussed with you, the study doctor and your local physician.

After you Receive the Final Vaccine (Treatment)

Follow-up and Evaluation of Experimental Regimen

We will ask you to return to the NIH Clinical Center frequently, approximately 2 weeks following the 4th cycle (or 8th cycle if you receive the second course of vaccines), then 1 month later x1, and then if you are responding to the treatment, every 1-2 months for the first year following treatment, and then annually for up to five years or until follow-up lab tests and imaging show your disease is worsening, whichever comes first. The follow up visits will take up to 2 days. At each visit you will have lab tests, imaging studies and a physical examination. At your 1st follow up visit (which is approximately 2 weeks after the 4th cycle), you may undergo leukapheresis, and then at subsequent visits you'll have about 9 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. You will not undergo leukapheresis on any other follow up visit after the 1st follow up visit. If you are unwilling or unable to travel to the NIH Clinical Center we will contact you by phone or e-mail 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 local physician.

Birth Control

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

Effective forms of birth control include a combination of any two of the following (unless method is abstinence or sterilization (i.e., tubal ligation or vasectomy), in which only one method is required):

- Abstinence
- Intrauterine device (IUD)

- Hormonal (birth control pills, injections, or implants)
- Barrier method (condom)
- Tubal ligation
- Vasectomy

Risks or Discomforts of Participation

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

Vaccines are generally well tolerated, however, this is the first treatment using this type of vaccine. It is likely that you will experience some mild side effects listed below. We will watch you carefully for any side effects that might occur, and we will ask you to keep track of any side effects you might experience at home.

Intramuscular (IM) Injection

The mRNA vaccination has potential side effects, and although the side effects of peptide vaccine injected under the skin are not completely known at this time, testing in our previous studies in humans has shown the following side effects:

- Local swelling and swelling of local lymph nodes
- Bruising, pain, and redness (inflammation) at the injection sites
- Rash, itchy skin, headache, and tiredness
- Fever, chills, and shortness of breath, which may last for a few hours (common)
- Metabolic laboratory abnormalities, such as changes in liver or kidney function tests, or other measurements in the blood
- Autoimmune reactions 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, 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.

Potential Benefits of Participation

Are there benefits to taking part in this study?

We do not know if you will receive personal, medical benefit from taking part in this study. These potential benefits could include shrinking of your tumor or lessening of your symptoms,

such as pain, that are caused by the cancer. Because there is not much information about the effect of this treatment on your type of cancer, we do not know if you will benefit from taking part in this study, although the knowledge gained from this study may benefit others in the future who have cancer.

Alternative Approaches or Treatments

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

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

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

Please talk to your doctor about these and other options.

Stopping Therapy

Your doctor may decide to stop your therapy if:

- He/she believes that it is in your best interest
- Your disease comes back during treatment
- You become pregnant
- You experience side effects from the treatment that your doctor thinks are too severe
- New information becomes available that shows that another treatment would be better for you
- You do not comply with study requirements

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

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

If you decide at any time to withdraw your consent to participate in the trial, we will not collect any additional medical information about you. However, according to FDA guidelines, information collected on you up to that point may still be provided to the Sponsor. If you withdraw your consent and leave the trial, any samples of yours that have been obtained for the study and stored at the NCI can be destroyed upon request. However, any samples and data generated from the samples that have already been distributed to other researchers or placed in the research databases cannot be recalled and destroyed.

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.
- NIH Intramural Institutional Review Board
- The study Sponsor, Center for Cancer Research, or their agents
- The company manufacturing the vaccine, ModernaTX, Inc. We will send the specific mutations that we identify from your tumor to ModernaTX so that they can manufacture your personalized vaccine. Since many of the sequences that make up your tumor mutations are specific to you, your tumor-specific mutations could possibly be identified

as belonging to you by others outside of NIH or ModernaTX. We will electronically transmit this information to ModernaTX in a highly secure manner which will help to make sure your personal information is only seen by those responsible for making your personalized vaccine.

A description of this clinical trial will be available on http://www.Clinicaltrials.gov, as required by U.S. Law. This website will not include information that can identify you. At most the website will include a summary of the results. You can search this website at any time.

Certificate of Confidentiality

To help us protect your privacy, we have obtained a Certificate of Confidentiality. The researchers can use this Certificate to legally refuse to disclose information that may identify you in any federal, state, or local civil, criminal, administrative, legislative, or other proceedings, for example, if there is a court subpoena. The researchers will use the Certificate to resist any demands for information that would identify you, except as explained below.

You should also know that there are several circumstances in which the Certificate does not provide coverage. These include when information:

- will be used for auditing or program evaluation internally by the NIH;
- must be disclosed to meet the legal requirements of the federal Food and Drug Administration (FDA);
- is necessary for your medical treatment and you have consented to this disclosure;
- is for other research.

In addition, identifiable, sensitive information protected by this Certificate cannot be admissible as evidence or used for any purpose in any action, suit, or proceeding without your consent.

You should understand 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. If an insurer, employer, or other person obtains your written consent to receive research information, then the researchers will not use the Certificate to withhold that information.

The Certificate of Confidentiality will not protect against the required reporting by hospital staff of information on suspected child abuse, reportable communicable diseases, and/or possible threat of harm to self or others.

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.

ModernaTX, Inc., a biotechnology company, is developing and providing the patient-specific cancer vaccines for this study to NIH without charge. No NIH investigator involved in this study receives any payment or other benefits from ModernaTX, Inc.

Use of Specimens and Data for Future Research

Blood and tissue collected during the course of this study will be used for future research and will be stored, tracked, and disposed of under our companion protocol 03-C-0277.

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

We plan to keep some of your specimens and data that we collect and use them for future research and share them with other researchers. We will not contact you to ask about each of these future uses. These specimens and data will be stripped of identifiers such as name, address or account number, so that they may be used for future research on any topic and shared broadly for research purposes. Your specimens and data will be used for research purposes only and will not benefit you. It is also possible that the stored specimens and data may never be used. Results of research done on your specimens and data will not be available to you or your doctor. It might help people who have cancer and other diseases in the future.

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

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: 240-760-6218. 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 JANUARY 07, 2019 THROUGH AUGUST 05, 2019.

Signature of Investigator — Date

Print Name

Signature of Witness — Date

Print Name