INSTITUTE: National Cancer Institute

STUDY NUMBER: 14-C-0142 PRINCIPAL INVESTIGATOR: James L. Gulley, M.D., PhD.

STUDY TITLE: An Open-label Phase I Study to Evaluate the Safety and Tolerability of a Modified Vaccinia Ankara (MVA)-based Vaccine Modified to Express Brachyury and T-cell Costimulatory Molecules (MVA-Brachyury-TRICOM)

Continuing Review Approved by the IRB on 04/14/16

Amendment Approved by the IRB on 09/22/16 (C) Date posted to web: 09/24/16

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 NIH research team is studying an experimental vaccine made with yeast and designed to target cells expressing the brachyury protein. Brachyury is a 'transcription factor' within the T gene that regulates making proteins. Research shows that in some cancers, such as gastrointestinal, bladder, kidney, ovary, uterus and testicular cancers, brachyury is 'over expressed' and is thought to play a role in cancer growth and metastasis.

The vaccine is made with modified vaccinia Ankara (MVA) virus. This is a replication-deficient, attenuated derivative of vaccinia. The virus is genetically modified, made to express the brachyury protein, and deliver a combination of three human T-cell costimulatory molecules that stimulate the immune system, called TRICOM (B7.1, ICAM-1 and LFA-3). The goal is to "teach" the immune system to kill the tumor cells that express the brachyury protein, to help stop tumor cell growth and metastasis.

This study will test the safety of giving the MVA-brachyury-TRICOM vaccine to people with cancer. The vaccine is manufactured by Bavarian Nordic, Inc. and is known as MVA-brachyury-TRICOM. In previous studies, similar vaccines were found to be safe, well-tolerated, and had few side effects.

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

You are being asked to participate in this study because standard therapies have not been effective for your type of cancer and we are testing possible new agents for safety and to see if they are effective. Your participation is entirely voluntary.

How many people will take part in this study?

Up to 38 patients will take part in this study. There will be three groups of patients in the first part of the study to see what the best, safe dose is. Between 3--6 patients will be enrolled in the first group. If no serious side effects occur, the next set of 3--6 patients will get a higher dose of the MVA-brachyury-TRICOM vaccine. If the second dose level is found to be safe, an additional 3--6 patients will receive the highest dose level, until all three dose levels are tested.

The dose you receive is not based on what the doctor believes is best for you, but rather your dose level is based on the order in which you are enrolled in the study and how previous participants have reacted. Ask your doctor what dose level you will receive.

Up to an additional 10 patients will receive vaccine at the highest dose found to be safe (called the expansion cohort) and 10 more at the dose just below that dose level (the second highest dose).

Description of Research Study

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

Before you begin the study:

You will need to have the following exams, tests and procedures if you can be in the study. These exams, tests and procedures are part of regular cancer care and may be done even if you do not join the study. If you have had some of them done recently, they may not need to be repeated. This will be up to the study team.

- A complete medical history, including your cancer history and prior cancer treatments, all drugs that you may be taking, including over the counter drugs, vitamins and herbal supplements.
- Pathology review of your tumor sample.
- A complete physical examination, including assessing your ability to do physical activities and measuring your blood pressure, heart rate and breathing.
- Standard blood and urine tests to evaluate your organs' functioning (such as liver, kidneys, thyroid, blood sugar and blood electrolytes), including tests of your immune system and presence of infections.
- Evaluation of your cancer, which may include a CT (computed tomography) scan, a PET (positron emission tomography) scan, Bone scan and/or a Brain MRI (magnetic resonance imaging).
- A 12 lead ECG (electrocardiogram) to assess your heart.
- As part of this study, we will test you for infection with the human immunodeficiency virus (HIV), the virus that causes AIDS. If you are infected with HIV you will not be able to participate in this study because this cancer drug relies on the immune system to work. We will tell you what the results mean, how to find care, how to avoid infecting others, how we report newly diagnosed HIV infection, and the importance of informing your partners at possible risk because of your HIV infection.
- A pregnancy test will be performed in women who are able to have children. Women who are pregnant or breast-feeding will not be allowed to participate, as the effects of vaccine on a developing fetus or infant are not known.
- HLA typing: this blood test is done to see what protein is expressed by your blood cells, human leukocyte antigen (HLA).

During the study

If the initial exams and tests show that you can participate in this study, you will come to the NIH about every four (4) weeks for MVA-brachyury-TRICOM vaccines, exams and tests, for periodic visits.

Depending into which dose level you enroll, the MVA-brachyury-TRICOM vaccine will be given as 1, 2 or 4 small shots (injections), depending on which dose level you enroll into, under the skin into sites were of your body known to drain into a large number of lymph nodes. Lymph nodes contain large numbers of immune cells, which can potentially be activated (or turned on) by the vaccine to target cancer cells. In general, these sites will include upper thighs and the area around the armpits. The site may be dependent on the number of injections needed for each dose or other individual factors related to your body.

The following tests and procedures will be done during the time you are on this study. Many of them are part of regular cancer care; however, some tests and procedures may be done more often because you are on this study.

- **Clinic visit (physical exam):** we will ask you how you are feeling and do a physical examination. This exam will be done every 4 weeks if you are not having any problems.
- **Vital signs:** we will measure your blood pressure, temperature, pulse, breathing and weight each time you come to the clinic.
- **Routine blood tests:** lab tests of your organ functions (liver, kidneys, blood clotting, red and white blood cells, platelets, blood sugar and blood electrolytes) will be tested each time you come to clinic. In addition, there are some brachyury cells in the thyroid, so we will test your thyroid function at regular intervals to make sure the vaccine is not harming the thyroid gland
- **Urine test**: you will be asked to give a urine sample for testing each time you come for an outpatient visit.
- **CT scans or MRI** that detect the size of your tumor will be done at baseline (beginning therapy), after 3 months on study, and again 3 months later if you remain on study to that point. This is done so that any benefit of the vaccine can be determined or if your cancer is not responding to the vaccine, the study team can tell you and help you to seek other treatment options.
- **ECG**: this will be done to check your heart rhythm at 2-4 time points - once before starting vaccine and at the time of your last scheduled vaccine and on your final follow-up visit.

Research Blood Samples: It is important to understand the effects of this experimental vaccine on your body, particularly the immune system. To do this, blood samples (8 tubes of blood or about 5 tablespoons) will be taken at specific time points during your participation in this study.

How long will I receive vaccines?

You will receive MVA-brachyury-TRICOM vaccines every 4 weeks (or every 28 days) for 3 doses, as long as you do not have unacceptable side effects, your cancer does not get worse, and you are willing to continue participating. You will have follow-up visits for imaging and research blood draws at three months after enrollment and every three months until there is evidence of disease growth.

When you are finished getting the vaccine (treatment)

When you stop the MVA-brachyury-TRICOM vaccine, we will ask you to return to NIH for clinic visits at least every 3 months until you recover from any side effects and/or your cancer

worsens. At these visits you will have exams, tests and procedures that are part of regular cancer care, including physical exam, standard blood tests, scans and x-rays.

Study Chart

Day	**What to do and what will happen to you**
Before starting the vaccine	• Have a history taken of how you feel, undergo a physical examination by a health care provider • Get routine blood and urine tests • Get research blood drawn • Pregnancy test • Scans and X-rays • HLA blood typing • ECG to check your heart
Day 1	• Receive the first MVA-brachyury-TRICOM vaccine
Day 29	• Have a history taken of how you feel, undergo a physical examination by a health care provider • Get routine blood and urine tests • Get research blood drawn • Receive MVA-brachyury-TRICOM vaccine
Day 57	• Have a history taken of how you feel, undergo a physical examination by a health care provider • Get routine blood and urine tests • Get research blood drawn • Receive MVA-brachyury-TRICOM vaccine
Day 85	• Have a history taken of how you feel, undergo a physical examination by a health care provider • Get routine blood and urine tests • Get research blood drawn • Scans and X-rays
Day 169 and every 85 days thereafter until disease progression	• Have a history taken of how you feel, undergo a physical examination by a health care provider • Get routine blood and urine tests • Get research blood drawn • Scans and X-rays

Long Term Follow Up

At the end of this study, we would like to follow you for any late side effects, and see how you do on other treatments. We will request that at that time you enroll on our Long Term Follow-Up Study, 04-C-0274, which the study team will review with you.

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 4 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

Risks or Discomforts of Participation

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

You may have side effects while on the study. Everyone taking part in the study will be watched carefully for any side effects. However, doctors don't know all the side effects that may happen when taking the MVA-brachyury-TRICOM vaccine, so it is important to report changes that you notice, even if your study team does not ask you specifically about them. It is very important that you tell a member of the research team before starting any new medications. We do not know what side effects could happen when other drugs are given with the MVA-brachyury-TRICOM vaccine.

Side effects to the vaccine may be mild or very serious. Your health care team may give you medicines to help lessen side effects. Many side effects go away with those medicines, and others can go away soon after you stop receiving the vaccine. In some cases, side effects can be serious, long lasting, or may never go away, and may result in death. You should talk to your study team about all symptoms that you experience while taking part in the study.

Likely	**Less Likely**	**Rare but Serious**
• Injection site reaction (including pain or discomfort, itching, redness, firmness, swelling, skin thickening, or bumps)	• Acute fever • Chills • Flu-like symptoms (including fatigue, soreness, general body pain, abdominal pain, cough, fever, headache) • Chest tightness • Shortness of breath • Leg pain and / or swelling • Headache • Loss of appetite • Weight loss • Diarrhea • Constipation • Rash • Nausea • Dizziness • Mild inflammation of the tissue lining the lung • Chronic inflammation of the skin • Insomnia • Open sores at the injection site (ulceration) • Enlargement of the lymph nodes • Low blood levels of sodium • Inflammation of the testicles (in men) • Inflammation of thyroid tissue, causing changes in thyroid function test results	• Difficulty breathing • Low blood pressure • Wheezing • Clots in the lung • Clots in the leg • Kidney damage • Decreased oxygen levels in the blood • Fluid around the lining of the lungs • Fluid around the lining of the heart

OTHER RISKS AND SIDE EFFECTS RELATED TO RESEARCH PROCEDURES:

Blood Sampling: Bruising or bleeding at the needle site; rarely infection. This is treated with bandages, pressure and, if infection, antibiotic medicines.

Risks of blood draws: Blood samples will be drawn from a vein in your inner arm. The risk of a blood draw may include fainting or pain. There could be bruising or infection at the site where blood is drawn. The risk is no greater than if you were having blood drawn for routine and normal healthcare.

Risks from X-rays and / or Scans: The risks of the contrast material used with the CT scan include rare allergic reactions, nausea, flushing, low blood pressure, asthma, stroke and organ damage. If the contrast material is given via your vein, it may make you feel flushed and give you a sensation of "pins and needles" for a few seconds.

Gene Therapy Risk of Cancer and Other Diseases

We are unsure if this type of gene therapy will cause you to become sick in the future. It is possible that it may cause your immune system or nerves not to work well or cause a sickness of your blood cells or even a cancer (for example leukemia). We do not know if you will develop any of these disorders, but you need to be aware of this possible risk. Children in France and England received gene therapy for a particular disease of the immune system. Most of the children were cured but 5 children out of 22 later developed leukemia and one died. Experts who looked at these cases thought that the gene therapy caused the leukemia in these children. To watch you for this risk we will be testing your blood as described before.

Potential Benefits of Participation

Are there benefits to taking part in this study?

The purpose of this study is to test the safety of the experimental vaccine MVA-brachyury-TRICOM, and to test whether it stimulates your immune system. Taking part in this study may or may not make your health better. 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 drug's effect on your cancer, we do not know if you will benefit from taking part in this study, although the knowledge gained from this study may help 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 these options:

- Getting treatment or care for your cancer without being in a study

- 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.

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
- Qualified representatives from Bavarian Nordic, Inc, the pharmaceutical company who produces MVA-brachyury-TRICOM.

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.

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 collaborators or designated representatives. If you withdraw your consent and leave the trial, any samples of yours that have been obtained for the study and stored at the NCI can be destroyed upon request. However, any samples and data generated from the samples that have already been distributed to other researchers or placed in the research databases can**not** be recalled and destroyed.

Conflict of Interest

The National Institutes of Health (NIH) reviews NIH staff researchers at least yearly for conflicts of interest. This process is detailed in a Protocol Review Guide. You may ask your research team for a copy of the Protocol Review Guide or for more information. Members of the research team who do not work for NIH are expected to follow these guidelines but they do not need to report their personal finances to the NIH.

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

Optional Biopsy and Archived Tissue use

In order to analyze brachyury expression in tissue samples, an optional on-study biopsy may be conducted as a means to obtain pathologic samples for correlation of clinical outcomes with brachyury expression. Additionally, the study team may request the use of pathology samples you may have had prior to this study for research purposes.

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 decide to have the biopsy you can change your mind at any time. You will be given the opportunity to decide whether you want to participate at the time of the procedure.

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.

Use of Specimens and Data for Future Research

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

We plan to keep some of your specimens and data that we collect and use them for future research and share them with other researchers. We will not contact you to ask about each of these future uses. These specimens and data will be stripped of identifiers such as name, address or account number, so that 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, James L. Gulley, M.D., PhD., Building 10, Room 12N226, Telephone: 301-496-4916. 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: 301-496-4251.

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 APRIL 14, 2016 THROUGH APRIL 13, 2017. _____ _____ _____ _____ Signature of Investigator Date Signature of Witness Date _____ _____ Print Name Print Name	